AIMS Medical Science

AIMS Medical Science, 7(3): 122–203.
DOI: 10.3934/medsci.2020011
Received: 16 July 2020
Accepted: 18 August 2020
Published: 25 August 2020

http://www.aimspress.com/journal/medicalScience

Review

Sensitization to cell death induced by soluble Fas ligand and agonistic antibodies with exogenous agents: A review

Michiro Muraki*

Biomedical Research Institute, National Institute of Advanced Industrial Science and Technology (AIST), Central 6, 1-1-1 Higashi, Tsukuba, Ibaraki 305-8566, Japan

*** Correspondence:** Email: m-muraki@aist.go.jp.

Abstract: Specific binding of either soluble Fas ligand extracellular domain (sFasL) or agonistic anti-Fas receptor extracellular-domain monoclonal-antibodies (FasR-mAb) can trigger apoptotic death of emerging harmful cells in the human body. However, the efficient cell-death induction through the action of these executors are often prevented by the resistance mechanisms equipped with the target cells. Hence, strengthening their cell-death inducing activity by sensitization with the help of exogenous agents will contribute to the development of advanced treatment strategies for many serious diseases caused by impaired cell death, including cancers and autoimmune diseases. This review gives an overview focusing on the sensitization of the cell-death induction via either sFasL- or FasR-mAb-primed signal transduction system with exogenous agents. In the beginning section, the structural and functional characteristics of cell-death induction using these soluble agonistic proteins were briefly introduced. In the following sections, the studies on the sensitization of Fas signaling system with the exogenous agents, classified into two groups, were investigated, based on an extensive survey of the relevant literatures. First, the sensitization with non-cytokine agents was described, where the effects of representative low molecular-weight clinical anticancer drugs were highlighted. Then, the potency of exogenous cytokine agents was depicted, while centering on the sensitization with interferon-γ. The survey revealed that the agents examined here were effective for the sensitization against various malignant tumors-derived and other types of cells by upregulating pro-apoptotic molecular machinery and/or downregulating anti-apoptotic factors. However, in the demanding instances, this strategy still remained dysfunctional in completing the target cell-killing process due to resistance mechanisms, such as overexpression of intracellular inhibitory proteins. Finally, it is proposed that the sensitization of cell-death induction with exogenous agents, combined with empowerment regarding the targeting specificity by protein engineering techniques, is a promising approach to potentiate the soluble agonists for translating them into clinical protein pharmaceuticals.

Keywords: agonistic antibody; anti-cancer drugs; cell death; exogenous agents; Fas ligand; Fas receptor; interferon-γ; soluble protein; sensitization

Abbreviations: FasL: Fas ligand; FasLECD: Fas ligand extracellular domain; FasR: Fas receptor; FasRECD: Fas receptor extracellular domain; FasR-mAb: anti-Fas receptor extracellular-domain monoclonal-antibody; sFasL: soluble Fas ligand; mFasL: cell-surface membrane-bound Fas ligand

1. Introduction

1.1. Cell-death induction by soluble Fas ligand

The implementation of the cell-death induction against emerging malignant cells is one of the most important defensive actions for the maintenance of health in the human body. The failures in the controlled execution of cell-death processes via death ligand—death receptor systems including Fas ligand (FasL)—Fas receptor (FasR) result in the onset of many serious diseases, caused by either abnormal proliferation of malignant cells or excessive death of normal cells, such as cancers, various autoimmune diseases including rheumatoid arthritis, and type-I diabetes [1–3]. The apoptotic cell-death triggered by the binding of FasL to FasR is considered to play a central role for both the anti-pathogenic elimination of emerging harmful cells and the pathogenic destruction of beneficial cells [4]. Thus, from a medical viewpoint, if it is possible to devise an effective means for controlling the execution of Fas signaling system-mediated cell death at will, that will directly lead to the development of advanced therapeutic treatment strategy for such serious diseases.

Human Fas ligand extracellular domain (FasLECD) consists of 178 amino-acid residues located at the carboxyl-terminal side of whole human FasL protein molecule [5]. In human, the soluble, homo-trimeric extracellular-domain fragment called sFasL, comprised of the almost full region of FasLECD, is generated from cell-surface membrane-bound FasL (mFasL) by the processing with a cell-surface matrix-associated metalloproteinase, MMP7 (also called matrilysin), under many physiological and pathological circumstances [6,7]. The relative cell-death inducing activity of human sFasL to that of mFasL was reported to be less than one thousandth [8], but sFasL still showed the significant activity against *in vitro* activated human peripheral blood T-cells [9]. The cytotoxic activity of human sFasL was greater than murine sFasL, and the difference was ascribed to the existence of a stalk region (Gln103–Pro136) at the N-terminal side of human FasLECD [10]. The cleaved bond in human mFasL by MMP7 was initially suggested to be the bond between Lys129 and Gln130 [11], but was corrected to that between Ser126 and Leu127 later [8].

Many diseases have been investigated in relation to the roles of sFasL during the onset processes of their pathological conditions. sFasL and mFasL can exert opposite biological functions with regard to the occurrence of diseases [12]. Because of the marginal cell-death inducing activity and the comparable affinity with mFasL toward Fas receptor extracellular domain (FasRECD), sFasL is generally considered to work as an antagonist of the mFasL-mediated cell-death induction [13]. Indeed, sFasL is known to stimulate the proliferation of fibroblast like synoviocytes of the patients suffered from rheumatoid arthritis by inhibiting the action of mFasL [14]. Also, the MMP7-mediated cleavage of mFasL to sFasL was pointed out to protect tumor cells from the cell-death induction by an anti-cancer drug, doxorubicin [7]. However, in contrast, many instances suggesting sFasL to play a role of

the potent cell-death inducer in diseases have been reported, which include the host lymphocyte apoptosis by colon adenocarcinoma cells [15], the damage of ciliated epithelial cells in severe asthma patients [16], the acute kidney injury in cisplatin-treated mice [17], and also blister formation in pemphigus [18].

1.2. Two alternative methods for triggering the cell-death via Fas signaling system by soluble agonistic proteins

It is possible to trigger the cell-death via Fas signaling system by the action of soluble agonistic proteins using two alternative methods. One way is the binding of the extracellular domain of the natural cognitive ligand, FasLECD, to FasRECD, and the other way is the binding of the specific monoclonal antibody (mAb) directed to FasRECD as the artificial substitute for FasLECD. The FasRECD-specific mAb are classified into two categories. One is cytotoxic, agonistic antibodies, represented by CH-11 (subclass IgM) and DX-2 (subclass IgG1), and the other is neutralizing, antagonistic antibodies, such as ZB4 [19]. Historically, the more frequently used reagents for triggering cell-death induction via the Fas signal transduction pathway were the FasR-mAbs in basic research, partly due to their better availability as a variety of commercial products at reasonable prices. It was revealed that the affinity strength was not always positively correlated to the potency of the cell-killing activity through the analysis of a series of IgG type monoclonal antibody [20].

From the viewpoint of therapeutic agents, it is possible to say that soluble proteins are more favorable than membrane proteins due to their uncomplicatedness in handling. However, as mentioned above, sFasL is functionally impaired in regard to the cell-killing activity as compared with mFasL. Therefore, if we intend to convert this soluble, but less potent as it is, protein molecule into effective cell-death inducing agents, employment of some engineering tactics would be required for obtaining the enough ability to induce the efficient death of target cells. One promising way is the application of the techniques for empowerment of sFasL molecule itself. This includes a further multimerization of self-trimeric FasLECD with the help of either additional domains for spontaneous oligomerization [21,22] or crosslinking antibodies directed to the pre-attached peptide-tags in sFasL derivatives [23,24]. Another potential approach for the enhancement of cell-death inducing activity will be the concentration of sFasL molecules around the surface of target cells by the use of binding domains to the target cells. Promising techniques have been developed for this purpose, where the affinity-providing protein domains toward target cells were engaged in. Methodologically, this can be accomplished by the conjugation to the N-terminal side of sFasL with antibody fragments, using either gene fusions with the single-chain Fv [25] or site-specific chemical modifications with Fab' fragments [26], as well as by construction of bispecific antibodies [27].

2. Literature survey

The initial process of literature survey in this study was performed by collecting the candidate papers for the references extensively, by applying combinations of the selection key-words, "Fas", "cell-death", "sensitization", "cisplatin/CDDP", "5-fulorouracil/5-FU", "doxorubicin/adriamycin", "camptothecin", "gemcitabine", "interferon-gamma", "interferon-alpha", "interferon-beta", "tumor necrosis factor-alpha", and "cytokines", to the searching engines including PubMed, Web of Science and Google scholar, using the literature information retrieval system available. Final selection of

appropriate literatures from the original hits was conducted based on a judging criteria for inclusion, which primarily depended on close relation to the scientific aim and scope of this survey and also the free-accessibility to whole paper contents for obtaining detailed experimental conditions as well. In Tables 1 to 3, the summarized results of the finally selected, relevant studies in terms of the target cells, the sensitization method, the cell-death induction method, and the primary findings in each study are listed in chronological order. The cell-death, directly caused by the administration of exogenous non-cytokine or cytokine agent independent of the soluble FasR agonists, was generally outside the scope of this review.

3. Sensitization of Fas signaling system with exogenous non-cytokine agents

3.1. Low molecular-weight anticancer drugs

It has been pointed out that malignant tumor cells escape from host's immune-surveillance system by suppressing cell-death arising from the immunocompetent mechanisms, including FasR-mediated apoptosis [4,28]. The pharmaceutically important anti-proliferative agents, represented by anticancer drugs used for chemotherapies, are considered to primarily depend their therapeutic potentials on the cell-death inducing ability against diseased cells, where the Fas signaling system plays a key role in the implementation processes [29]. Therefore, it would be reasonable to expect cumulative therapeutic effects for the combination of an agonist against FasR with other substances or physical treatment. So far, a number of methods using exogenous non-cytokine agents, including clinical or non-clinical low-molecular weight compounds, non-cytokine macromolecules, virus or bacteria-derived factors, physical stresses, *etc*. have been examined for the sensitization to the cell-death inducing activity of sFasL or agonistic FasR-mAb.

Among them, numerous researchers' efforts have been especially devoted to seek the possibility that the clinically available low molecular-weight anticancer drugs, which are mainly considered to work as apoptosis inducers via intrinsic pathways, sensitize the tumor cells for making them more susceptible to Fas signaling system-mediated cell-death, known as a typical apoptotic event via an extrinsic pathway. A summary of the examination results concerning commonly used five representative clinical chemotherapeutics, namely cisplatin, doxorubicin (also called adriamycin), 5-fluorouracil (5-FU), camptothecin (including its derivatives) and gemcitabine, is presented in Table 1 [29–88]. As shown in Table 1, the level of sensitizing efficiency to Fas signaling system substantially depended on both the cell types and the nature of each sensitizing agent, which reflected the difference in the intracellular molecular-machineries required for the implementation of an efficient cell-death induction in individual target cells. The survey results suggested that the sensitization was frequently achieved by upregulation of either cell-surface FasR or intracellular pro-apoptotic proteins, such as initiator or effector caspases, Fas-associated death domain (FADD), oncogene B-cell lymphoma (Bcl)-extra-small protein (Bcl-X_S), Bcl-2-like protein 4 (Bax), or by downregulation of intracellular anti-apoptotic factors including Bcl-2, Bcl-extra-large protein (Bcl-X_L), Fas-associated death domain-like interleukin (IL)-1-converting enzyme inhibitory protein-long form ($FLIP_L$), as well as by simultaneous operation of these processes.

Table 1. Sensitization of cell-death induction via Fas signaling system with five representative low molecular-weight clinical anti-cancer drugs.

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Primary findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Ovarian cancer (A-2780, AD-10, C-30)	f-FR and f-CD (Pre and Co), CDDP (0.1–10 μg/ml) ± BHA (200 μM), 2–18 h (f-FR); 24 h (f-CD, Pre); 48 h (f-CD, Co)	FR-mAb (nd, IgM), 100–1000 ng/ml, Pre, 24 h; Co, 48 h	Up-FR and synergistic up-CD by either Pre or Co with CDDP. No inhibition in the synergism by coexistence of BHA.	[55]
hu, Colon cancer (HT-29, HCT-8R, HCT-116); leukemia (U937)	f-FR, and f-CD (Pre), CDDP (10 μM) ± ActD (5 μg/ml), 5FU (260 μM), DXR (10 μM) or CPT (0.3 μM), 3–6 h (f-FR, mRNA); 4 h (f-FR, protein and f-CD)	FR-mAb (CH-11, IgM), 5–100 ng/ml ± antagonistic FR-mAb (ZB-4, IgG1), 2 μg/ml or muFL-N2A, 0.5 U/ml (1 U: 1 μl of 100-fold conc), 72 h; PBL, E/T ratio: 25–100:1, 24 h	Up-FR with clinically relevant conc of CDDP, 5FU, DXR and CPT. Up-FR and up-CD with CDDP in agonistic FR-mAb-, sFL in muFL-N2A- or PBL-mediated cytotoxicity, blocked by ActD or antagonistic FR-mAb.	[30]
hu, Prostate cancer (PC-3, DU-145, LnCAP); mu, lymphoma (DT-140, LF^-)	f-FR and f-CD (Pre and Co), CDDP (0.1–10 μg/ml), 18 h (f-FR); o/n (f-CD, Pre); 24 h (f-CD, Co)	muCTL, hybridoma (PMMI), TIL (kidney tumors), LAK (whole blood), E/T ratio: 0.3–30:1, 5–7 h; FR-mAb (CH-11, IgM), 100 ng/ml, 24 h	Up-FR in all cell lines except LF^- and up-CD by CDDP treatment using PMMI cells or TIL/LAK cells in PC-3, DU-145, but not in LnCAP, associated with attenuation by coexistence of EGTA / $MgCl_2$ and FR-mAb.	[61]
hu, Prostate cancer (PC-3, DU-145, LnCAP); ovarian cancer (AD-10)	f-FR and f-CD (Pre and Co), CDDP (1–10 μg/ml) or ADR (0.1–1 μg/ml), 18–24 h (f-FR and f-CD, Pre); 48 h (f-CD, Co)	FR-mAb (CH-11, IgM), 10–1000 ng/ml, Pre, 24 h; Co, 48 h; muCTL hybridoma (PMMI), E/T ratio: 0.3–10:1, Co, 7 h	Minimal effect on FR by CDDP treatment in all cell lines. Synergistic up-CD by either Pre with CDDP or Co with CDDP / ADR in PC-3 and DU-145, but much less in LnCAP.	[56]
hu, Glioma (T-98G, LN-229)	f-CD (Co), CPT (1 μM), 16–24 h	muFL-N2A, 100 U/ml, 16–24 h	Synergistic up-CD by Co with CPT and sFL, possibly mediated by enhanced Bax and decreased Bcl-2.	[48]
hu, Neuroblastoma (SHEP Tet-21/N)	f-FR and f-CD (Pre), DOX (100 ng/ml), 24 h	FR-mAb (nd, IgG3), 1 μg/ml, 24 h	Up-FR by treatment with DOX. Up-CD and up-FL by DOX Pre with cooperation by MycN oe.	[49]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Primary findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Colon cancer (HT-29, HCT-116); leukemia (U-937)	f-FL and f-FR, CDDP (10 μM) or DXR (10 μM), 4 h	None	No modification of cell-surface FL and up-reg of FR clustering with CDDP. Recruitment of FADD to FR by treatment with either drug.	[31]
hu, Colon cancer (HT-29, HCT-116, HCT-8R); myeloblastoma (U-3A, U-3A-STAT1)	f-FR, CDDP (10 μM) or DXR (10 μM), 72 h	None	Up-FR and up-reg of Bax in HT-29 cells by treatment with either drug. STAT1 independent up-reg of FADD, procasp-3 and -8.	[32]
hu, Prostate cancer (DU-145, LnCAP)	f-FL, f-FR and f-CD (Co), CPT (100 ng/ml) or CDDP (1.0 μg/ml),	FR-mAb (CH-11, IgM), 200 ng/ml, 24 h	No up-reg of FL and FR, and overcoming of CD resistance only in DU-145 cells by CPT treatment via activation of casp.	[62]
hu, Leukemia (CEM, REH, Nalm-6, KM-3, Nalm-6-RD)	f-FR and f-CD (Pre), DOX (10–500 ng/ml), 9–24 h (f-FR); 12 h (f-CD)	FR-mAb (nd, IgG3), 1 μg/ml plus Protein A (10 ng/ml), 1–48 h; LAK (peripheral blood), E/T ratio: 1:4, 24 h	Up-FR and up-CD in resistant pre-B-ALL cell lines by DOX Pre, associated with loss of Bcl-X_L and up-reg of PARP cleavage.	[70]
hu, Breast cancer (MCF-7, EVSA-T)	f-FR, f-FL and f-CD (Co), DOX (100–500 μg/ml), 8–24 h (f-FR and f-FL); 48 h (f-CD)	FR-mAb (CH-11, IgM), 500 ng/ml, 48 h	Up-FR, but not up-FL, and up-CD by DOX Co in MCF-7 cells alone.	[66]
hu, Colon cancer (HT-29, HCT-8, HCT-116, VRC_5/c1, RKO)	f-FR and f-CD (Co), 5FU (0.3–10 μM) plus LV (1 μM) ± dThd (20 μM), 48 h (f-FR); 72 h (f-CD)	FR-mAb (CH-11, IgM), 200 ng/ml, 72 h	Up-FR in wt p53 expressing cell lines with 5FU plus LV. Cl-dep reversal in up-CD by coexistence of dThd.	[33]
hu, Osteogenic sarcoma (MG-63)	f-FR and f-CD (Co), CDDP (0.5–5 μg/ml), 48 h	FR-mAb (CH-11, IgM), 100 ng/ml, 48 h	Up-CD by CDDP Co, associated with dn-reg of FLIP-$_L$ without up-FR.	[76]
hu, Head and neck cancer (HSC-2, HSC-3, HSC-4)	f-FR and f-FL, CDDP (5 μg/ml), 24 h	None	No up-FR, no up-FL, but up-reg of casp, in particular casp-9 by CDDP treatment.	[83]
hu, Non-small cell lung cancer (NCI-H-292, NCI-CorL-23, NCI-Colo-699)	f-FR and f-CD (Pre), GEM (0.005–0.5 μM), 24–72 h	FR-mAb (CH-11, IgM), 200 ng/ml, 3 h	Cl-dep and tm-dep up-FR and up-CD by GEM treatment. Synergistic effects on CD between GEM and FR-MAb in H-292 cells.	[41]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Primary findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Prostate cancer (DU-145)	f-CD (Co), CPT (100 ng/ml), 1–24 h	FR-mAb (CH-11, IgM), 200 ng/ml, 1–24 h	Tm-dep activation of SAPK / JNK activity for up-CD by CPT treatment, concomitant with c-Jun induction.	[63]
hu, Kidney cancer (ACHN, Caki-1, Caki-2, A-704, NC-65, fresh cells from patients' surgical specimens)	f-FR and f-CD (Pre and Co), ADR (0.1–10 μg/ml), 2–24 h	FR-mAb (CH-11, IgM), 0.01–1 μg/ml, 2–24 h	Up-FR and synergistic up-CD irrespective of cell types by ADR treatment.	[82]
hu, Breast cancer (MCF-7)	f-FR and f-CD (Co), DOX (10 ng/ml), 48 h	FR-mAb (CH-11, IgM), 500 ng/ml, 48 h	Marked up-FR, but insignificant up-CD by DOX treatment.	[67]
hu, Colon cancer with Val^{12}-*ras* mutation (SW480, SW620)	f-FR and f-CD (Pre), 5FU (30 μg/ml), CPT-11 (1 μg/ml) or CDDP (0.1 μg/ml), 24 h	FR-mAb (CH-11, IgM), 500 ng/ml; anti-Val^{12}-*ras* CTL, E/T ratio: 1.25–10:1, 18–20 h	Significant up-FR and up-CD by either inducer in SW480 cells, but much less FR and CD induction only with CTL in SW620 cells, after treatments with anti-cancer drugs.	[34]
hu, Melanoma (M-202, M-207, M-238, T-2); prostate cancer (DU-145, PC-3)	f-FR and f-CD (Pre), CDDP (0.1–10 ng/ml), 18 h	mu PMMI CTL or MART-1-specific CTL, E/T ratio: 1–30:1, 5–6 h	Up-FR and up-CD in M-202, T-2, DU-145 and PC-3, but M-207 and M-238 remained resistant to up-FR and up-CD, after CDDP treatment.	[64]
hu, Small cell lung cancer (POGB)	f-FR, DOX (200 ng/ml), 24 h	None	Up-FR similar to γ-ray treatment by DOX treatment, associated with marked up-reg of c-Myc.	[42]
hu, Glioblastoma (GBM)	f-FR and f-CD (Pre), topotecan (0.01 μg/ml), CPT-83 (0.1 μg/ml) or CDDP (0.3 μg/ml), 24 h	FR-mAb (nd), 1 μg/ml, 24–72 h	Up-FR by treatments with either CPT derivatives or CDDP, but synergistic up-CD with CPT derivatives alone.	[50]
hu, Cervical cancer (HeLa)	f-FR and f-FL, CDDP (0.25 μg/ml), 48–72 h	None	No up-reg in mRNAs of FR and FL by CDDP treatment.	[72]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Primary findings related to sensitization of cell-death induction via Fas signaling system	Refs.
mu, Thymoma (EL-4)	f-FR and f-CD (Pre and Co), DOX (0.001–200 μM) or CPT (0.001–200 μM), 0.5–20 h (f-FR); 24 h (f-CD, Co)	Crosslinked-sFL (2–200 ng/ml), 5 h (Pre); 24 h (Co)	Marked up-FR and up-CD by treatments with either DOX or CPT without any influence on FLIP-$_L$.	[84]
hu, Liver/cervical cancer (Chang/HeLa)	f-FR and f-FL, ADR (0.5 μg/ml) ± Palgin (15.6 μg/ml), 2–10 h	None	Tm-dep up-FR and up-FL, associated with increase in casp-3 activity by combined treatment with ADR and an herb drug.	[73]
hu, Colon cancer (Caco-2, Colo-320, SW-948)	f-FR, 5FU (5–25 μM), CDDP, (5–25 μM), 24 h	None	Significant up-FR by CDDP treatment in Colo-320 alone.	[35]
hu, Oral squamous cell cancer (NA, HSC-4)	f-FR and f-CD (Pre), CDDP (1 μg/ml) and/or 5FU (2.5 μg/ml), 8–24 h	FR-mAb (CH-11, IgM), 100 ng/ml, 12 h	Marked up-FR and up-CD by CDDP and/or 5FU treatment with dn-reg of cFLIP. Increasing effect on CD by combined treatment.	[85]
hu, Colon cancer (HT-29)	f-CD (Pre), 5FU (100 μg/ml), CDDP (5 μg/ml) or DXR (2.5 μg/ml), 24 h	sFL, nd, 16 h	Marked up-CD by Pre with non-toxic conc of 5FU, CDDP or DXR.	[36]
hu, Ovarian cancer (2008, 2008-C13)	f-FR and f-FL, CDDP (20–40 μM) ± Z-VAD-fmk (50 μM), 6–24 h	None	Up-FL mRNA in CDDP-sensitive cells by the treatment, insensitive to coexistence of pan-casp inhibitor.	[57]
hu, Colon cancer (RKO, SW620)	f-FR and f-FL, CPT (5–40 nM) ± Ad-E2F-1 infection, 48–72 h	None	No change in FR and FL by CPT alone or a combined treatment with G1/S cell-cycle transition regulator.	[37]
ra, Cardiac myocytes (ventricles of 0-1 d-old Wister-Imamichi)	f-FR and f-CD (Pre), DOX (0.5–5 μM), 6–24 h	sFL, 10–1000 ng/ml, 12 h	Significant up-CD by DOX Pre, concomitant with tm-dep ROS-controlled FLIP-$_L$ dn-reg.	[88]
hu, Melanoma (UACC-903, DM-13, A-375)	f-FR and f-CD (Pre), 5FU (25 μg/ml), 48 h	FR-mAb (CH-11, IgM), 67–1800 ng/ml, 5–16 h; CD95L$^+$-G209 specific-CTL, E/T ratio: 30–1:1, 6 h; ± FR-mAb (ZB4, IgG1), 2–10 g/ml	Significant up-FR and cl-dep up-CD by 5FU treatment. Almost complete block of FR-mAb-induced, but not CTL-induced, up-CD in the presence of antagonistic FR-mAb.	[81]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Primary findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Stromal-type neuroblastoma (SH-EP1, SK-N-AS)	f-FR, f-FL and f-CD (Co), DOX (0.5 μg/ml), 4–24 h	FR-mAb (CH-11, IgM), 1 μg/ml; sFL, 10 ng/ml, 24 h	Significant up-FR and up-CD by DOX Co, associated with tm-dep up-reg of casp-3, -8 and -9.	[51]
hu, Colon cancer (HT-29)	f-FR and f-CD (Co), CDDP (5 μg/ml), 4h (f-FR); 24 h (f-CD) ± nystatin (10 μg/ml) or imipramine (50 μM), 1 h pretreated	FR-mAb (CH-11, IgM), 100 ng/ml, 24 h	Marked clustering of FR in plasma membrane-raft and up-CD by CDDP treatment, associated with aSMase activation and ceramide production	[38]
hu, Epidemoid lung cancer (49-year-old man patient at stage $T_3N_1M_0$)	f-FR and f-FL, *in vivo*: CDDP (10 mg/kg), 1–7 times; *in vitro*: CDDP (2 μg/ml), 24–48 h	None	Strong up-FR and up-FL in the beginning, followed by dn-reg *in vivo*, and dn-reg of FR mRNA *in vitro* by CDDP treatment.	[43]
hu, Testicular germ cell cancer (Tera)	f-FR and f-CD (Pre), CDDP (0.25–1.0 μM), 24 h	FR-mAb (7C11, IgM), 2 μg/ml, 20 h	Up-FR and up-CD by CDDP treatment without up-reg of p21 expression.	[86]
hu, Breast cancer (MCF-7, MCF-6/E6)	f-FR, CDDP (5 μM) ± Bcl2 specific AS-ODN (1 μM), 48 h	None	Up-FR by CDDP treatment irrespective of the presence of Bcl-2 specific AS-ODN or p53 activation status.	[68]
hu, Cervical cancer (HPV-18 positive and wt p53: HeLa; HPV-16 positive and wt p53: CaSki, SiHa; HPV negative and mut p53: C-33A)	f-FR, f-FL and f-CD (Pre), CDDP (0.5–5 μM), 24 h (f-FR); 2 h (f-CD)	FR-mAb (7C11, IgM), 50–1000 ng/ml, 24 h	Up-FR in all HPV positive cells, but not in C-33A, without major change in p53 levels by CDDP treatment. Strong up-CD only in HeLa and insignificant up-CD in other cells.	[74]
hu, Astrocytoma (U-373MG)	f-FR and f-CD (Pre), CDDP (25 μM), 2 h	FR-mAb (7C11, IgM), 200 ng/ml, 24 h	Up-FR and up-CD by CDDP treatment with requirement of active p73 protein.	[52]
hu, Glioblastoma (U-87, U-373, A-172, SNB-19)	f-FR, f-FL and f-CD (Co), CPT (1–100 μM), ADR (0.1–20 μM), 24 h	FR-mAb (CH-11, IgM), 50–1000 ng/ml, 24 h	No change in FR and FL by CPT alone treatment, but significant up-CD by Co with CPT or ADR regardless of p53 status.	[53]
hu, Colon cancer (HCT-116 with wt, null or mut p53, H630, RKO)	f-FR and f-CD (Pre), 5FU (5 μM), CPT-11 (5 μM), 24–48 h	FR-mAb (CH-11, IgM), 25–100 ng/ml, 12–48 h	p53 status independent up-FR by CPT-11, but not by 5FU treatment. Up-CD only in wt p53 cells by Pre with 5FU.	[39]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Primary findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Urinary bladder cancer (T-24, RT-4)	f-FR, f-FL and f-CD (Co), ADM (0.1–10 μg/ml), 24 h	FR-mAb (CH-11, IgM), 1–1000 ng/ml, 24 h	No up-FR, cl-dep change in FL and synergistic up-CD by ADM treatment.	[87]
mu, Lewis lung cancer (3LL)	f-FR, f-CD (Pre and Co), *in vitro*: DOX (0.03–3 μg/ml), 24–48 h; *in vivo*: DOX (1–4 mg/kg), 24 h	muFR-mAb (Jo2, IgM), 1 μg/ml, 48 h; splenic CTL, E/T ratio: 40–80:1, 20 h	Up-FR and ds-dep up-CD by DOX treatment *in vitro*. Up-FR mRNA with anti-tumor therapeutic effect on solid tumor *in vivo*.	[44]
hu, Ovarian cancer (OVCAR-3, advanced -stage patient's ascitic fluid)	f-FR and f-CD (Pre), CDDP (IC_{30} or 3 μM), 24 h	FR-mAb (CH-11, IgM), 300 ng/ml, 24 h	Up-FR and up-CD by CDDP treatment both with cell line sample and with the patient's ascitic sample.	[58]
hu, Osteosarcoma (U-2-OS, MG-63)	f-FR, CDDP (5 μM), 24–72 h	None	No significant change in FR and Bax expression by CDDP treatment in cells with either wt p53 or mut p53.	[77]
mu, Ovarian cancer (ID-8)	f-FR and f-CD (Pre), liposomal DOX (Doxil) (0.1–3 μg/ml), 6 h	muFR-mAb (Jo2, IgM), nd, plus Protein G, 2 μg/ml, 24 h; splenic CTL, E/T ratio: 10–20:1, 4h	Significant ds-dep up-FR, associated with MHC class1 up-reg and up-CD by liposomal DOX treatment.	[59]
hu, Lung cancer (ASTC-A-1)	f-FR and f-FL, CDDP (20 μM), 16 h ± ursolic acid (100 μM), 8 h preceded	None	Insignificant up-FR and up-FL by CDDP treatment alone or after preceding treatment with ursolic acid.	[45]
hu, Ovarian cancer (OVCAR-3)	f-FR, CDDP (1 μM) ± AT-101 (0.5 μM), 72 h	None	Up-reg of FR, Bax, Bad and dn-reg of Bcl-2 by CDDP treatment, augmented by combining with Mcl-1 inhibitor.	[60]
hu, Non-small cell lung cancer (H-292, COLO-699); immortalized normal bronchial (16-HBE)	f-FL and f-CD (Pre and Co), GEM (0.05 μM), 24–96 h	mAb (CH-11, IgM), 200 ng/ml, 3 h (Pre); LAK / MPL, E/T ratio: 5:1, 16 h (Co)	Significant up-FL mRNA level by GEM treatment in all cell lines. Up-reg of LAK / MPL-induced CD in H-292 cells by Pre with GEM.	[46]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Primary findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Colon cancer (Lovo)	f-FR and f-FL, CDDP (10 μM) ± andrographolide (10 μM), 24 h	None	Up-FR, up-FL and up-reg of FR-FL complex formation by andrographolide treatment, augmented by combination with CDDP.	[40]
hu, Non-small cell lung cancer (A-549, NCI-H-460)	f-FR, CDDP (22-26 μM), 24 h ± followed by gambogic acid (3.5–4 μM), 24 h	None	Augmented up-FR, up-reg of Bax and dn-reg of Bcl-2, but no effect on Bcl-X_L by sequential treatments with CDDP and then with gambogic acid.	[47]
hu, Osteosarcoma (MG-63)	f-FR, DOX (1 μg/ml) ± MTE (50 mg/ml), 72 h	None	Up-FR by DOX treatment, augmented by combination with MTE.	[78]
hu, Monocytic leukemia (U-937)	f-FR, DOX (1 μM) ± MG132 (1 μM), 3 h	None	Up-reg of FR and Bax mRNAs and dn-reg Bcl-X_L mRNA by combined treatment with DOX and MG132.	[71]
hu, Neuroblastoma (SK-N-AS)	f-FR and f-FL, CDDP (30 μM), 6–24 h ± TNF-α (100 ng/ml) followed, 24 h	None	Tm-dep up-reg of FL mRNA by CDDP treatment. Significant up-FR only after post-treatment with TNF-α.	[54]
hu, Cervical cancer (HeLa)	f-FL, CDDP (50-250 μg/ml) ± LPA (20 μM), 4 h	None	Ds-dep up-FL and up-reg of Bax and dn-reg of Bcl-2 by CDDP treatment, all negatively affected by LPA.	[75]
hu, Prostate cancer (DU-145)	f-FR, DOX (0.5 μM) ± sildenafil (10 μM), 48 h	None	Up-reg of surface localization of FR, by DOX treatment, enhanced with sildenafil. Dn-reg of increased FLIP-$_L$ and FLIP-$_S$ by DOX alone treatment after combination with sildenafil.	[65]
hu, Breast cancer (MCF-7); mu, Liver cancer (Hepa-1-6)	f-FR and f-FL, DOX (1 μM) ± MCD (5 mM) ± PFT-α (20 μM), 24 h ± *p53* siRNA transfection, 18 h preceded	None	Up-FR, up-FL, up-reg of Bax, but dn-reg of Bcl-2, by DOX treatment. Up-FR and up-FL were augmented by combination with MCD, but attenuated with PFT-α or p53 siRNA transfection.	[69]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Primary findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Pancreatic cancer (SW-1990, Panc-1)	f-FR and f-CD (Pre), GEM (0.025–25 μM), 48 h	FR-mAb (CH-11, IgM), 200 ng/ml, 4 h; pancreatic cancer specific CTL, E/T ratio: 20–100:1 ± FR-mAb (ZB4), 500 ng/ml, 4 h	Ds-dep up-FR and up-CD with either pancreatic cancer specific CTL or agonistic FR-mAb by GEM treatment, attenuated by the presence of neutralizing FR-mAb.	[79]
hu, Pancreatic cancer (SUIT-020)	f-FR and f-CD (Pre and Co), GEM (1–10000 ng/ml), 24 h ± zVAD-fmk (50 μM) /NEC (50 μM) / SP600125 (10 μM), 30 m preceded	FR-mAb (nd, IgG3), 333 ng/ml, 30 m (Pre); 1.5–25 ng/ml, 24 h (Co)	Undetectable up-FR, but marked up-CD by GEM treatment, mediated through dn-reg of cFLIP and Mcl-1. Induction of apoptosis and necroptosis by combination of FL and GEM.	[80]
hu, Lung cancer (A-549); colon cancer (HCT-116); breast cancer (MCF-7)	f-FR and f-CD (Co), GEM (5–5000 nM) ± U0126 (1–10 μM) or SP600125 (1–10 μM), 24 h	Poly-His-tagged sFL, 50 ng/ml plus tag-crosslinking mAb, 3 μg/ml ± antagonistic FR-mAb 1-10 μg/ml, 24 h	Up-FR in all cells and up-CD in HCT-116 cells by GEM treatment at subtoxic doses. Reduction of up-FR by coexistence of JNK or ERK inhibitor.	[29]

So far, the most and the second frequently employed anticancer drugs for the sensitization experiments were cisplatin and doxorubicin (adriamycin), respectively. The above mentioned low molecular-weight anti-cancer drugs have been examined with the malignant tumor cells derived from various kinds of organs, including colon [29–40], lung [29,41–47], central nervous system [48–54], ovary [55–60], prostate [56,61–65], breast [29,66–69], blood cells [30,31,61,70,71], uterus [72–75], bone [76–78], pancreas [79,80], skin [64,81], kidney [82], head and neck [83], thymus [84], oral cavity [85], testis [86], bladder [87], and liver [69]. The sensitizing effects significantly depended on the kind of not only originated organs but also cell lines, and marked differences were observed even among the tumor cells originated from the same organs in some cases. For instances, upregulation of cell-death induction using the same FR-mAb were reported to be largely affected by the difference in cell lines of prostate cancer [56,62] as well as that of colon cancer [34]. As for the intracellular factors which can critically influence the sensitization effects, the difference in either the mutation status or the expression level of other apoptosis execution-related proteins, such as p53 [33,39,53,68,77], p21 [86] and p73 [52], have been repeatedly investigated from the viewpoint regarding upregulation of the cell-death induction and that of cell-surface FasR expression. It is reasonable that the sensitization effects largely depended on the kind of anticancer drugs, since each group of anticancer drugs possesses its own specific interference mechanism different from others with proliferation of tumor cells. For example, the significant sensitization of cell-death induction was observed in the pretreatments with camptothecin, CPT-11 (a synthetic analog of camptothecin) or doxorubicin regardless of p53 mutation status of the target cells [39,53], however the pretreatment with 5-fluorouracil was effective for the enhanced death of the cells with wild-type p53 alone [39]. Also, it is interesting to note that the pharmaceutical substances used in traditional medicines [47,78] or that in treatment of non-tumor diseases [65] have been reported to augment the FasR expression in the target cells by combining with the anti-cancer drugs in some instances. With respect to non-tumor target cells, a large increase in the cell-death induction by sFasL treatment was observed for cardiac myocytes after the pretreatment with doxorubicin, accompanied by marked down-regulation of $FLIP_L$ [88].

The other low molecular-weight clinical anticancer drugs already examined include daunorubicin [89], decitabine [90,91], carboplatin [92], oxaliplatin [29], arsenic trioxide [93], bortezomib [94], mitoxantrone [95], and sorafenib [96]. In several cases, combinations of clinical anticancer drugs with other low-molecular weight pharmaceuticals, each of which exhibited limited efficiency in the sensitization as a sole agent, have been reported to show an improved efficacy by synergizing effects, resulting in a considerable level of cell-death induction associated with up-regulated FasR or FasL expression [40,60,91,97].

3.2. Other non-cytokine agents

Except for the clinical anti-cancer drugs, many low molecular-weight compounds including sodium butyrate [98,99], enzyme inhibitors [100,101], ceramides [23,102], edelfosine [103,104] and perillyl alcohol [105] have been examined for the sensitizing effect. Apart from the low molecular-weight agents, the components or the inactivated whole cells, derived from the virus and bacteria including human immunodeficiency virus [106], hepatitis C virus [107], *Propionibacterium acnes* [108] and *Helicobacter pylori* [109], have been also used for the sensitization experiments. The typical physical stress employed for the investigation was irradiation [110,111].

4. Sensitization of Fas signaling system with exogenous cytokine agents

4.1. Interferon-γ (IFN-γ)

The number of studies on the sensitization of Fas signaling system-mediated cell-death induction using cytokine agents have fairly exceeded that employing non-cytokine agents described above. Among various clinically relevant cytokines responsible for the immune system, IFN-γ has been most extensively used exogenous agents for this purpose to date. This protein is the sole cytokine belonging to type-II interferon, and shows multifaceted important immune-modulatory biological functions including antiviral, cell-differentiative, and anti-proliferative activities via various mediators, in particular Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signal transduction pathway [112,113]. Activation of STAT-1 signaling system directed by IFN-γ-primed signaling is known to be responsible for the enhancement of FasR and FasL as an important mechanism of tumor suppression [114]. IFN-γ is also suggested to be critically involved in tumor immunity in the human body by exerting pleiotropic overcoming of immunosuppression effects [115,116].

Table 2 presents a summary of the survey results concerning the sensitization studies using exogenous agents containing IFN-γ as the component [117–283]. The concentration of exogenous IFN-γ, applied for the sensitization experiments, ranged from 0.1 to 10000 U/ml, however it fell within 10–1000 U/ml in most cases. Of note, nearly half of the studies listed in this Table were targeted to non-tumor cells. It was considered that one of the major reasons for the wide usage of IFN-γ by quite a few researchers of broad medical disciplines might come from the remarkable up-regulation effects on the surface FasR expression not only in various types of tumor cells but also in many types of other target cells, derived from patients with non-tumor diseases or healthy donor. An interesting feature about the investigations targeted to tumor cells using exogenous IFN-γ-containing agents is that a relatively large number of studies (approximately 40% of malignant tumor cases) have been conducted with colon cancer using a variety of cell-lines as the target cells [30,35,98,117–146]. The primary organs of examined malignant tumors except for colon covered blood cells [117,138,147–162], central nervous system [54,163–168], lung [169–174], breast [67,174–177], uterus [74,141,144,178–180], soft tissue [117,124,164,181,182], kidney [183–186], skin [187–189], bone [164,190,191], ovary [147,192], stomach [109,193,194], liver [195], bile duct [196], pancreas [197], and prostate [198]. The samples of peripheral blood mononuclear cells from stage-IV cancer patients were also subjected to the analysis [133,139].

As for non-tumor and benign tumor targets, many kinds of cells derived from human patients and animal models suffering from the diseases, including type-I diabetes [199,200], insulinoma [201–204,283], Graves' disease [205,206], non-toxic and multi-nodular goiter [206,267], Hashimoto's thyroiditis [206], epilepsy [207], asthma [208], Down syndrome [209], Sjögren's syndrome [210,272], Simpson-Golabi-Behmel syndrome [211], Sézary syndrome [212], *Leishmania major* infection [213,214], cardiac transplantation [215], keratoplasty [216], atherosclerosis [217,218], peritoneal dialysis [219], glaucoma [220], and dry-eye [221], have been used for the studies. Also, normal or immortalized cells derived from healthy donors, including the samples of bone-marrow cells [222,224–231]; mononuclear [223,224], eosinophil [232,233], basophil [235], monocyte [234], and erythroid progenitor [236] cells from blood; Kupffer [237], parenchymal [237], hematopoietic progenitor [238], and stellate [239] cells from liver; spleen cells [225]; small intestine lamina propria T-lymphocytes [240]; pancreas β-islet cells [200,241,242]; corpus luteum [243–247] and granulosa [248,249] cells from

ovary; placenta trophoblast cells [250,251]; testis Sertoli cells [252]; mesangial [253,254] and tubular [255] cells from kidney; microglia [256,257], cortical astrocyte [258], and motoneuron [259] cells from central nervous system; keratinocyte [260,261] and hair follicle [262] cells from skin; vasculature smooth muscle cells [153]; endothelial cells from umbilical vein [153,263,264], dermal microvasculature [263], and lung microvasculature [265]; epithelial cells from thyroid gland [266–270], salivary gland and duct [210,271,272], intestine [132,273,274], eye conjunctiva [275,276], lung alveolus [265], small airway [277], bronchus [277], and uterus endometrium [278]; fibroblast and myofibroblast cells from lung [279], cardiac [280]; and uterus endometrial stromal cells [281,282], have been employed for the sensitization experiments as the target cells.

In majority of the instances, the concomitant up-regulation of cell-death induced with sFasL or agonistic FR-mAb were observed for the cases that exhibited up-regulation of FasR expression at protein or mRNA level in cell line-, dose-, and treatment time-dependent manners. However, it should be pointed out that the increase in cell-surface expression of FasR by the sensitization with IFN-γ did not always directly correspond to the enhancement in death-induction level of the target cell. The existence of numerous, endogenous limiting-obstacles, which mainly consisted of up-regulation of anti-apoptotic factors and down-regulation of pro-apoptotic factors, has been suggested with respect to the demanding target cells. The representative former and the latter factors include enhanced expression or activation of Bcl-2, FLIP, STAT-3, and decoy receptor-3 (DcR3), and reduced expression or activation of caspase-1, -3, -8, and STAT-1, respectively. As a noteworthy example for the discrepancy between the responses to up-regulation of FasR expression and that to the augmentation of cell-death induction, the primary (SW-480) and the metastatic (SW-620) colon cell-lines harboring a mutation in Ras protein, originated from the same patient, exhibited significantly different responses to the sensitization under the identical experimental conditions [123,127–129,136]. In spite of the similar behavior in the up-regulation of cell-surface FasR, the metastatic cell-line emerged *in vivo* showed fairly delayed or largely diminished up-regulation in the cell-death induction by the treatment with either an agonistic FR-mAb or sFasL [123,128], possibly due to the absence of cell-surface FasR capping [123] as well as the presence of intracellular expression of strong constitutive Bcl-2 [129] and IFN-γ inducible interferon consensus sequence-binding protein [136].

Further, it is important to note that the sensitization to the cell-death via Fas signaling system with IFN-γ was often synergistically or additively augmented by the combined treatment either with other exogenous cytokines such as tumor necrosis factor (TNF)-α [54,122,142,163,165,180,184,190, 194,203,207,211,216,219,222,231–233,244,245,247,248,252,255,256,258,261,267,270,273,274,276, 278,279,281,282], IL-1α, -1β [180,199,201–204,258,261,267–269,282] and transforming growth factor (TGF)-β1, -β2 [163,180,216,282], or with non-cytokine agents including 5-FU [139,146], 5-aza-2'-deoxycytidine [173], cycloheximide [35,129,177], lipopolysaccharide [161,255], all-*trans* retinoic acid [177], and mAb specific to CD40 [210,265]. As an exceptional case, TGF-β2 has been reported to show substantial inhibitory effects against sensitization to the apoptosis of murine microglia cells by IFN-γ treatments in combination with or without TNF-α, where an intense induction of cellular FLIP expression was observed [257]. Also, in some instances, the up-regulation of cell-death was further enhanced by the coexistence of p44/p42 mitogen-activated protein-kinase kinase inhibitors [268], *Helicobacter pylori* extract [109], trichostatin A [182], tosyl lysine or phenylalanine chloromethyl ketone [144], and constitutive intracellular expression of interferon regulatory factor (IRF) [181]. In contrast, the event was significantly attenuated by exogenous addition of mAbs specific to human leukocyte antigen (HLA)-2 or intercellular adhesion molecule (ICAM) [127]; inhibitors to

relevant caspases (general and caspase-1, -3, -7, -8, -9, -10) [141,168,201,241], related kinases (phosphatidylinositol-3 kinase, protein kinase B, Janus kinase 2) [171,215], intracellular FasR trafficking [215], and nitric monoxide synthase [192]; antisense-oligodeoxyribonucleotides (AS-ODN) to IRF-1 [185]; small interfering RNA (siRNA) targeted to activator subunits of immune-proteasome-8 [217], human apolipoprotein L6 [218] and autoantigens found in Sjögren's syndrome and systemic lupus erythematosus [179], as well as exogenously applied thyroid gland stimulating hormone [205,266], IL-3, -5 [232], IL-4, -10 [206,250,274], granulocyte macrophage colony-stimulating factor (GM-CSF) [156,232], phorbol 12-myristate 13-acetate [123], and dexamethasone [169,216,272].

An important topic except for the cell-death inducing effects on tumor cells is the sensitization to the cells concerning reproduction of animals including human origin [243–251,278,281,282]. Several types of the cells, including those originated from ovary corpus and placenta trophoblast, have been supplied for the examination. Although the influence of the pretreatments with exogenous IFN-γ depended on the cases, the sensitization efficiency to the up-regulation of cell-death or cell-surface FasR was often significantly augmented by the combination with the cytokines, especially TNF-α. [244,247,248,278,281,282]. Another topical issue that has been targeted would be the sensitization effects on the cells of cardiovascular and lung alveolar systems [153,215,217,263,265]. In this case, the treatment efficiency tended to largely depend on the structural position of the cells, i.e. endothelial, smooth muscle or epithelial cells, and IFN-γ was mostly employed as the single cytokine agent, rather combined not with other cytokines but with non-cytokine agents, represented by low-molecular weight kinase inhibitors [215], so far.

Table 2. Sensitization of cell-death induction via Fas signaling system with exogenous agents containing IFN-γ.

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Lymphoma (U-937, Dauji), leukemia (HL-60, MOLT-4B), rhabdomyosarcoma (A-673), amnion-derived (FL), colon cancer (HT-29), foreskin fibroblast (FS-7, TM-11)	f-CD (Pre), IFN-γ (200 U/ml), 24 h	FR-mAb (nd, IgM), 10–100 ng/ml, 5–15 h	Up-CD in FR-mAb-primed cell-killing, indistinguishable from that primed with TNF-α, by IFN-γ Pre. Marked up-CD except for MOLT-4B and Daudi.	[117]
hu, Ovarian cancer (222, 222TR, SKOV-3, A-2780, AD-10, C-30), lymphoma (U-937, Raji)	f-CD (Pre), IFN-γ (50–150 U/ml), 24 h	FR-mAb (nd, nd), 0.1–10 μg/ml ± DTX, 10 pM–10 nM ± ADM, 1 μg/ml ± CDDP, 3 μg/ml, 24 h	Cl-dep up-CD of the target cells including multi-drug resistant cells by IFN-γ Pre, in synergy with DTX, ADM or CDDP.	[147]
hu, Lymphoma [U-937: uninfected (commercially obtained, cloned); HIV-infected (U1)]	f-CD (Co), IFN-γ (1000 U/ml), 72 h	FR-mAb (nd, IgM), 1 μg/ml, 72 h	Synergistic up-CD of several uninfected clones and HIV-infected cells by Co with IFN-γ and FR-mAb.	[148]
hu, Foreskin keratinocyte (non-lesional epidermis)	f-FR and f-CD (Pre), IFN-γ (10–10000 U/ml), 24 h	FR-mAb (CH-11, IgM), 1 μg/ml, 48 h	Marked up-FR and up-CD, associated with large increase in ICAM-1.	[260]
hu, Glioma (T-98G, LN-18, LN-215, LN-229, LN-308, LN-319, LN-405)	f-FR and f-CD (Pre), IFN-γ (100 U/ml) ± TNF-α (10 ng/ml) ± TGF-β2 (nd), 24 h	FR-mAb (CH-11, IgM), 0.1–1 μg/ml, 24 h	Cl-dep up-FR and up-CD by IFN-γ treatment, associated with synergistic effects of TNF-α or TGF-β2.	[163]
hu, Retinal pigment epithelium (keratoplasty donor eyes)	f-FR and f-CD (Pre), IFN-γ (100 U/ml) ± [TNF-α (10 ng/ml) or TGF-β2 (10 ng/ml)] ± DEX (10 μM), 24 h	FR-mAb (nd, IgM), 1 μg/ml, 16 h	Up-FR and synergistic up-CD by combined treatment with IFN-γ and TNF-α or TGF-β2, accompanied by significant dn-reg effect of DEX	[216]
hu, Multiple myeloma (RPMI-8226, ARH-77, KMM-1, U-266, Hs)	f-CD (Pre), IFN-γ (200 U/ml), 24 h	FR-mAb (nd, IgM), 100 ng/ml, 10 m-18 h	Cl-dep up-CD by IFN-γ Pre. No correlation between Bcl-2 expression and the sensitivity.	[149]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Bone marrow hematogenic $CD34^+$ progenitor (normal volunteers)	f-FR and f-CD (Pre), IFN-γ (1–10000 U/ml) ± TNF-α (10 U/ml) ± SCF (100 ng/ml), 48 h, (f-FR); 36 h (f-CD)	FR-mAb (CH-11, IgM), 1 μg/ml, 12 h	Ds-dep up-FR by IFN-γ treatment in synergy with TNF-α, but not with SCF. Insignificant effects on up-CD by IFN-γ Pre alone or in combination with TNF-α.	[222]
hu, Peripheral blood mononuclear (HIV-seronegative healthy donors)	f-FR, IFN-γ (1000 U/ml) ± TNF-α (1 μg/ml) ± VES (50 μg/ml), 48 h	None	No blocking effect of VES on up-FR by IFN-γ treatment alone or in combination with TNF-α.	[223]
hu, Primitive hematopoietic progenitor ($CD34^+CD38^{+/-}$ fetal liver)	f-FR and f-CD (Co): selected combinations of IFN-γ, KL, GM-CSF (20 ng/ml each) and TNF-α (100 ng/ml), 3–5 d	FR-mAb (CH-11, IgM), 2 μg/ml, 3–5 d	Augmented up-FR by treatment with TNF-α and/or KL plus GM-CSF in the presence of IFN-γ. No up-CD, but reduction in hematopoietic potential.	[238]
hu, Cervical cancer cells (HeLa)	f-CD (Pre), IFN-γ (50 U/ml) ± pepstatin A (10^{-4} M), 20 h	FR-mAb (nd, IgG3), 50 ng/ml, 40 h	Suppression of up-CD by IFN-γ Pre with an inhibitor of cathepsin D.	[178]
hu, Leukemia (drug sensitive: K-562/WT, HL-60; multidrug-resistant: KG-1a, K-562/ADM)	f-FR and f-CD (Pre and Co), IFN-γ (100 U/ml), 24 h (f-FR and f-CD, Pre); IFN-γ (100 U/ml) ± DNR (10 ng/ml), VCR (3 ng/ml), CBDCA (1 mg/ml), ARC (1 ng/ml), DEX (4 ng/ml) or IR (1 Gy), 48 h (f-CD, Co)	FR-mAb (CH-11, IgM), 0.01–10 μg/ml, 48 h	Up-FR and up-CD by IFN-γ treatment alone and in combination with anticancer-drugs, IR or DEX in multidrug-resistant and sensitive cells, correlated with reduction of intracellular glutathione contents.	[150]
hu, Kidney mesangial (cadaver glomeruli)	f-FR and f-CD (Pre), IFN-γ (1000 U/ml), 48 h	FR-mAb (CH-11, IgM), 0.1–500 ng/ml, 24 h	Significant p-FR and up-CD by IFN-γ treatment.	[253]
hu, Colon cancer (HT-29, COLO-205)	f-CD (Pre), IFN-γ (100 U/ml), 72 h	FR-mAb (nd, IgG3), 500 ng/ml, 1–3 h	Up-CD by IFN-γ Pre, associated with de-adhesion from hyaluronate-coated plate and shedding of CD44.	[118]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Thyrocytes (normal thyroid glands)	f-FR and f-CD (Pre), IFN-γ (500 U/ml) ± boTSH (10 mU/ml), 48 h	FR-mAb (nd, IgM), 1000 ng/ml, 18 h	Up-FR and up-CD by IFN-γ treatment, associated with significant inhibition by coexistence of TSH.	[266]
hu, Breast normal (MCF-10A), cancer (MCF-7, ZR75-1, T-47D, MB-231, MB-468, SKBr-3)	f-FR and f-CD (Pre), IFN-γ (20–2000 U/ml), 96 h	FR-mAb (CH-11, IgM), 1 μg/ml, 16 h	Up-CD in 4 of 5 resistant cell lines IFN-γ Pre, associated with up-reg of ICE. No or small up-FR in all cell-lines.	[175]
hu, Kidney cancer (OUR-10)	f-FR and f-CD (Pre), IFN-γ (nd) ± IFN-α (nd), 24 h	FR-mAb (CH-11, IgM), 330 ng/ml, 48 h	Up-FR and up-CD by treatment with IFN-γ, not augmented by coexistence of IFN-α.	[183]
mu, Pancreas islet-β (β-TC-1)	f-FR, muIFN-γ (10^5 U/l) ± muIL-1α (10^3–10^4 U/l), 6 h	None	Significant up-reg of FR mRNA by combined treatment with IFN-γ and IL-1α.	[283]
hu, Bone osteosarcoma (HOS/TE-85, MG-63, Saos-2)	f-FR and f-CD (Pre), IFN-γ (250–500 U/ml) ± TNF-α (250 U/ml), 24 h	FR-mAb (nd, nd), 1 μg/ml, 24 h	Synergistic up-FR and up-CD of resistant cells by combined treatment with IFN-γ and TNF-α.	[190]
hu, Thyroid gland epithelium (GD patients)	f-FR and f-CD (Pre), IFN-γ (500 U/ml) ± [healthy donors', GD patients' or IME patients' IgG (5mg/ml) or boTSH (5 mU/ml)], 48 h	FR-mAb (nd, IgM), 1000 ng/ml, 18 h	Up-FR and up-CD by IFN-γ treatment, associated with significant inhibition by coexistence of GD patients' IgG or TSH, but not of healthy donors' or IME patients' IgG.	[205]
hu, Colon cancer (HT-29)	f-FR, f-CD (Pre), IFN-γ (200 U/ml or 25 ng/ml) ± ActD (5 μg/ml), 3–6 h (f-FR, mRNA); 24–48 h (f-FR, protein and f-CD)	FR-mAb (CH-11, IgM), 5–100 ng/ml or muFL-N2A, 0.25–0.5 arbitrary U/ml ± antagonistic FR-mAb (ZB4, IgG1), 2 μg/ml, 72 h	More or equivalent up-FR and up-CD by treatment with IFN-γ, compared to clinical cytotoxic drugs. Blockade of the enhancing effects in the presence of ActD or antagonistic FR-mAb.	[30]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Colon cancer (HT-29)	f-FR, f-CD (Pre), IFN-γ (200 U/ml), 16 h	FR-mAb (nd, nd), 10–50 ng/ml, 24 h	p53-state independent up-CD by IFN-γ Pre, linked with up-FR and up-reg of other many apoptosis-related gene products including Bak but not Bax.	[119]
mu, Ovary surface epithelium (OSE) [corpora lutea (CL) of pseudo-pregnant CD1 mice]	f-FR and f-CD (Pre), muIFN-γ (1–1000 U/ml), 24 h	muFR-mAb (Jo2, IgG2), 1 μg/ml, 8 h	Up-FR mRNA and marked up-CD by 10-1000 U/ml IFN-γ Pre. No effect on other cell types except OSE in CL culture.	[243]
hu, Bone marrow (mononuclear, $CD34^+$) (posterior iliac crest of healthy volunteers)	f-FR and f-CD (Pre, colony- formation), IFN-γ (20–2000 U/ml), 48 h; (f-FR); 24 h (f-CD)	FR-mAb (CH-11, IgM), 1 μg/ml, 24 h	Ds-dep up-FR and up-CD by IFN-γ treatment, without significant change in IFN-γR expression.	[224]
hu, Stomach cancer (HM-02)	f-CD (Co), IFN-γ (10 ng/ml) plus TNF-α (20 ng/ml) ± *H. p.* extract (10^6 cfu/ml), 24 h	FR-mAb (nd, nd), 20 ng/ml, 24 h	Significant up-CD by IFN-γ plus TNF-α treatment, enhanced by the addition of *H. p.* extract.	[109]
hu, Lung cancer (A-549)	f-FR and f-CD (Pre), IFN-γ (250 U/ml) ± DEX (1mM), 24 h (f-FR); 12h (f-CD, Pre)	FR-mAb (nd, IgM), 100 ng/ml, 36–60 h	Up-FR and up-CD by IFN-γ treatment, associated with induction of ICE and IRF-1 expression. An inhibitory effect of DEX due to expression of CIAP-2.	[169]
hu, Colon cancer (HT-29, HCT-116, HCT-8)	f-FR and f-CD (Pre), IFN-γ (100 U/ml), 24 h	FR-mAb (CH-11, IgM), 50–200 ng/ml, 72 h	Up-FR in all cell lines and marked up-CD of HT-29 by IFN-γ treatment.	[120]
hu, Colon cancer (HT-29)	f-FR, IFN-γ (200 U/ml), 24 h	None	Up-FR by IFN-γ treatment.	[98]
mu, Bone marrow Mϕ (infected with *Leishmania major*) (mice: wt, lpr-mut, gld-mut)	f-FR and f-CD (Pre), muIFN-γ (50 U/ml), 48 h	muFL-N2A, 20% (v/v), 4 h	Up-FR and up-CD in wt and gld-mut, but not in lpr-mut, Mϕ infected with *L. major* by IFN-γ treatment.	[213]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Colon cancer (COLO-205, HT-29)	f-FR and f-CD (Pre), IFN-γ (1–2000 U/ml), 24 h	muCTL cells (F3H, MD45), E/T ratio: 40:1–1:5, 16 h; sFL in COS cells supernatant, 1:2 dilution, 16 h	Marked up-FR and up-CD in COLO-205, but not in HT-29, by IFN-γ treatment, associated with enhanced cell-surface CEA expression.	[121]
hu, Colon cancer (COLO-201)	f-FR, f-FL and f-CD (Co), IFN-γ (3–100 U/ml) ± TNF-α (0.3 μg/ml), 3–5 d (f-FR and f-CD, Co); 3–12 h (f-FL)	FR-mAb (nd, nd), 100 ng/ml, 3d	Synergistic ds-dep up-FR and up-CD by combined treatment with IFN-γ and TNF-α, associated with dn-reg of Bcl-2 and up-reg of Bax.	[122]
hu, Blood eosinophils (peripheral blood of normal healthy volunteers)	f-FR and f-CD (Pre), IFN-γ ± TNF-α (1–100 ng/ml each) ± [IL-3 (0.0001–10 ng/ml), IL-5 or GM-CSF (10 ng/ml each)], 0.5–24 h	sFL in 293T cells (transfected with FL expression vector) supernatant, equal volume, 12 h	Tm-dep, ds-dep up-FR and significant up-CD by combined treatment with IFN-γ and TNF-α, associated with some inhibition against the up-FR by coexistence of IL-3, IL-5 and GM-CSF.	[232]
mu, Ovary granulosa (pregnant mare serum gonadotropin treated)	f-FR and f-CD (Pre or Pre plus Co), muIFN-γ (200 U/ml) ± muTNF-α or TNF-α (10 ng/ml), 24 h (Pre) ± following 24 h (Co)	muFR-Ab (Jo2, IgG2), 2 μg/ml ± muTNF-α, 10 ng/ml, 24 h ± CHX, 0.5 μg/ml, 2 h preceded	Synergistic up-reg of FR mRNA and up-CD by IFN-γ treatment combined with muTNF-α, but not with huTNF-α, in the presence or absence of CHX.	[248]
mu, Central nervous system microglia (primary)	f-FR and f-CD (Pre), muIFN-γ (100 U/ml) ± muTNF-α (10 ng/ml), 24–48 h	muFL-N2A, 20% (v/v), 20 h ± [FR-Fc (0.05–30 μg/ml) ± Protein A enhancer], 30 m preceded	Up-FR and synergistic up-CD by combined treatment with IFN-γ and TNF-α, associated with marked dn-reg of Bcl-X_L expression and ds-dep inhibition by coexistence of FR-Fc.	[256]
hu, Multiple myeloma (IL-6 dependent: U-266-1970, U-1958; IL-6 independent: U-266-1984)	f-FR and f-CD (Pre), IFN-γ (1–1000 U/ml) + IL-6 (20–100 U/ml), 96 h	FR-mAb (CH-11, IgM), 100 ng/ml, 24 h	Significant ds-dep up-CD only in IL-6 dependent cells by IFN-γ treatment, without substantial change in FR.	[151]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Colon cancer (COLO-205, SW-480, SW-620, HT-29)	f-FR and f-CD (Pre), IFN-γ (100 U/ml), 6–72 h ± PMA (5 ng/ml); SSP (35 μM) or Goe6983 (l μM), 0.5–1 h preceded	FR-mAb (nd, IgG3), 500 ng/ml, 3–24 h	Up-FR and up-CD by IFN-γ treatment, counteracted by presence of PMA. Delayed apoptosis of SW-620 as compared with SW-480, associated with the absence of FR capping.	[123]
hu, Colon cancer (HT-29), fibrosarcoma (U-3A, STAT-1 transfected U-3A)	f-FR, f-FL and f-CD (Pre), IFN-γ (0.1–500 U/ml), 3–48 h (f-FR and f-FL); 40 h (f-CD, Pre)	FR-mAb (CH-11, IgM), 500 ng/ml, 20 h	Ds- and tm-dependent, marked up-FR, modest up-FL and up-CD in HT-29 cells by IFN-γ treatment. Up-FR and up-FL in STAT-1 transfected U-3A, but not in STAT-1-deficient U-3A cells.	[124]
hu, Ovarian cancer (A-2780, AD-10)	f-FR and f-CD (Pre), IFN-γ (10–1000 U/ml) ± L-NMA (1.0 mM), 18–24 h	FR-mAb (CH-11, IgM), 10–1000 ng/ml, 24 h	Cl-dep, ds-dep up-FR and up-CD by IFN-γ treatment, associated with dn-reg effects by iNOS inhibitor co-treatment.	[192]
hu, Breast cancer (T-47D, MCF-7, BT-20)	f-FR and f-CD (Pre), IFN-γ (1000 U/ml), 24 h	Anti-ErbB-2 scFv transfected MD45 murine CTL cells, E/T ratio: 1–40:1, 16 h	Up-CD in two (T-47D, BT-20) of three ErbB-2 positive cells without up-FR, but not in MCF-7, by IFN-γ Pre.	[176]
hu, Myeloblastic leukemia (EoL-1)	f-FR and f-CD (Pre), IFN-γ (1000 U/ml), 72 h	FR-mAb (CH-11, IgM), 50–1000 ng/ml, 24 h	Up-FR and up-CD by IFN-γ treatment, but marked inhibition of TNF-α induced apoptosis.	[152]
hu, Stomach cancer (AGS)	f-FR, IFN-γ (12.5 ng/ml), 24 h	None	Up-FR comparable to *H. p.* infection by IFN-γ treatment.	[193]
ra, Liver Kupper Mϕ (KC), parenchymal (PC) (male Wister rats)	f-FR, f-FL and f-CD (Co), raIFN-γ (100 U/ml) ± CsA (1 μM), 3–48 h (f-FR, f-FL); 24 h (f-CD, Co)	FR-mAb (CH-11, IgM), 10–100 ng/ml, 24 h	Up-FL in KC cells, up-FR in KC and PC cells, and up-CD in PC cells by IFN-γ treatment, all associated with a small inhibitory effect of CsA.	[237]
hu, Colon cancer (HT-29)	f-CD (Pre), IFN-γ (1000 U/ml), 24 h	FR-mAb (CH-11, IgM), 100 ng/ml, 17 h	Up-reg of α-1, 3 fucosyltransferase activity by IFN-γ treatment.	[125]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Small intestinal epithelium (non-tumoral fatal crypt); colonic organ cultures	f-FR and f-CD (Co), INF-γ (1–1000 U/ml) ± TNF-α (0.01–10 ng/ml), 24–48 h	FR-mAb (CH-11, IgM), 1–500 ng/ml, 24–48 h	Synergistic up-FR and up-CD by combined treatment with IFN-γ and TNF-α, both in cell and organ cultures.	[273]
mu, Bone marrow (femurs and tibiae), spleen (C57BL/6 mice)	f-FR and f-CD (Co, colony formation), muIFN-γ (100 U/ml), 24 h	muFR-mAb (Jo2, IgG2), 5 μg/ml, 24 h	Up-FR and up-CD by IFN-γ treatment, evaluated by *in vitro* and *in vivo* colony-formation assays.	[225]
hu, Colon cancer (HT-29, Caco-2, HCT-8, HCT-116, GC_3/c1, VRC_5/c1)	f-FR, f-FL and f-CD (Co), IFN-γ (25–100 U/ml) ± 5-FU (3 μM) and LV (1 μM); IFN-γ (25–100 U/ml) ± anti-FR mAb (ZB4, IgG1) (100 ng/ml), 24–96 h	FR-mAb (CH-11, IgM), 10–200 ng/ml, 24–96 h	Cl-dep, tm-dep up-FR and up-FL, associated with some augmentation with 5-FU and LV, and up-CD, associated with inhibitory effect of antagonistic FR-mAb, by IFN-γ treatment.	[126]
hu, Melanoma (A-375, BLM, BS-1251, Colo-38, M-518, Me1Ju, Me1Juso, MeWo, SK-Mel-25, SK-Mel-28, W+); leukemia (Jurkat); lymphoma (Raji)	f-FR and f-CD (Co), IFN-γ (100–2500 U/ml), 48 h	FR-mAb (7C11, IgM), 50 ng/ml, 48 h	Cl-dep up-CD of melanoma cell-lines, associated with up-FR and/or up-reg of Bcl-X_S, by IFN-γ treatment. No apparent correlation of up-FR degree with up-CD level.	[187]
mu, Pancreas islet ($RAG2^{-/-}$ NOD transgenic mice: wt and lpr-mut)	f-FR and f-CD (Co), muIFN-γ (250 U/ml) ± muIL-1α or muIL-1β (10–100 U/ml) ± Z-VAD-FMK (nd), 16 h	NOD mice-derived spleen $CD4^+$-CTL, E/T ratio: 10:1, o/n; muFR-mAb (Jo2, IgG2), 1 μg/ml plus ActD, 30 μg/ml, 16 h	Up-FR and up-CD by treatment with IFN-γ, associated with enhancement by coexistence of IL-1α or IL-1β, and partial dn-reg with pan-casp inhibitor, in NOD mice islet cells with wt FR, but not in lpr-mut FR.	[199]
hu, Colon cancer with Val^{12}-*ras* mutation (SW-480)	f-FR and f-CD (Pre), IFN-γ (250 U/ml), 24 h	Anti-Val^{12}-*ras* CTL, E/T ratio: 1.25–10:1, nd; FR-mAb (CH-11, IgM), 1–1000 ng/ml, 24 h	Up-FR, associated with HLA-2 and ICAM-1 up-reg, up-CD induced with CTL or FR-mAb, and abrogation of CMA-inhibited CD, by IFN-γ treatment.	[127]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
mu, Kidney cancer (Renca)	f-FR and f-CD (Pre), muIFN-γ (100 U/ml) ± muTNF-α (100 U ml), 3–24 h	muFR-mAb (Jo2, IgG2), 0.002–1 μg/ml plus mAb- crosslinking P815 cells, 1×10^5 cells/200 μl, 18 h	Some up-FR in the constitutively resistant cells by IFN-γ treatment, but significant up-CD only after combination with TNF-α.	[184]
hu, Colon cancer with Val^{12}-*ras* mutation (SW-480, SW-620)	f-FR and f-CD (Pre), IFN-γ (250 U/ml), 18–24 h	Anti-Val^{12}-*ras* CTL, E/T ratio: 2.5–20:1 ± CMA, 10 μM, 12 h; FR-mAb (CH-11, IgM), 1–2000 ng/ml or sFL, 0.1–100 ng/ml, 18 h	Significant up-FR and up-CD with CTL by IFN-γ treatment in both SW-480 and SW-620 cells, but associated with stronger CD-inhibition with CMA in SW-640 than in SW-480 cells. Marked up-CD by IFN-γ Pre, associated with either FR-mAb or sFL only in SW-480 cells.	[128]
hu, Eye conjunctival (Chang conjunctiva clone 1-5c-4)	f-CD (Pre), IFN-γ (30 U/ml), 24 h	FR-mAb (CH-11, IgM), 500 ng/ml, 1–24 h	Tm-dep up-CD by non-toxic dose of IFN-γ Pre, associated with up-reg of STAT-1.	[275]
mu, Brain neuron [euploid and Down syndrome model trisomy 16 (Ts16) fatal mice]	f-FR, muIFN-γ (67–600 U/sample), 48 h	None	Significant ds-dep up-FR in Ts16 cells with higher sensitivity, compared to euploid cells by IFN-γ treatment.	[209]
mu, Kidney cultured tubular epithelium (primary)	f-FR and f-CD (Pre plus Co), IFN-γ (300 U/ml), muTNF-α (30 ng/ml) and LPS (10 μg/ml), 48 h (f-FR); 24 h (f-CD, Pre), and then 24 h (f-CD, Co)	sFL, 1–100 ng/ml with 10-fold excess crosslinking antibody, 24 h	Up-FR and marked up-CD in the serum-deprived resistant cells by combined treatments with a mixture of IFN-γ, TNF-α and LPS.	[255]
hu, Peripheral blood eosinophils (normal non-atopic donors)	f-FR and f-CD (Pre), IFN-γ (1–100 ng/ml) ± TNF-α (1–100 ng/ml), 6–24 h	sFL, 100 ng/ml, 12 h	Synergistic up-FR and positive correlation of up-FR with up-CD in combined treatment with IFN-γ and TNF-α.	[233]
hu, Salivary duct epithelium (HSG)	f-FR and f-CD (Pre), IFN-γ (1–100 U/ml), 4–48 h (f-FR); 24 h (f-CD, Pre)	FR-mAb (DX-2, IgG1), 500 ng/ml, 3 h	Ds-dep, tm-dep up-FR and up-CD by INF-γ treatment.	[271]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Colon cancer (HT-29, SW-620)	f-CD (Pre), IFN-γ (50–2000 U/ml), 16 h	FR-mAb (CH-11, IgM), 100 ng/ml ± CHX, 1 μg/ml, 24 h	Correlation of up-CD degree with constitutive expression level of Bcl-2. Necessity of CHX for maximal up-CD of SW-620 cells.	[129]
hu, Brain oligodendrocyte (adult intractable epilepsy patients)	f-FR and f-CD (Pre), IFN-γ (100 U/ml) ± TNF-α (100 U/ml), daily over 72 h	FR-mAb (nd, nd), 10 μg/ml, 24 h ± Z-VAD, 0.02 %, 1h preceded	Significant up-FR and up-CD by IFN-γ treatment, associated with augmentation by coexistence of TNF-α and inhibition with pan-casp inhibitor.	[207]
hu, Colon cancer (HT-29-D4)	f-CD (Pre), IFN-γ (40 ng/ml), 5 m pulse	FR-mAb (CH-11, IgM), 500 ng/ml ± des-(1-3)-IGF-1, 50 ng/ml, 24 h	Up-CD by IFN-γ Pre, associated with insignificant inhibition by coexistence of N-terminally truncated IGF-1.	[130]
mu, Testis seminiferous epithelium (Sertoli)	f-FR, f-FL and f-CD (Pre), muIFN-γ (500 U/ml) ± muTNF-α (20 ng/ml), 24 h	muFL-N2A, E/T ratio: 1–10:1, 7 h	Up-FR and up-CD by treatment with IFN-γ alone and synergistic up-reg of them after combination with TNF-α, without up-reg of FL mRNA.	[252]
hu, Breast cancer (MCF-7: wt p53, MDA-MB231: mut p53)	f-FR, f-FL and f-CD (Pre or Co), IFN-γ (10 ng/ml), 24–48 h (f-FR); 24–36 h (f-CD, Pre); 48–72 h (f-CD, Co)	FR-mAb (CH-11, IgM), 500 ng/ml, 24–72 h; sFL, 100 ng/ml plus 200 ng/ml sFL-crosslinker, 48 h	Up-FR without induction of FL mRNA, up-CD independent of p53 status by IFN-γ treatment, associated with casp-8 activation and prevented by intracellular Bcl-2 oe.	[67]
hu, Umbilical vein endothelial (HUVEC), vascular smooth muscle (hVSMC) (internal mammary artery), leukemia (Jurkat E6-1)	f-FR and f-CD (Co), IFN-γ (100 ng/ml), 24 h (f-FR); 48 h (f-CD, Co)	Ad-muFL, multiplicity of infection: 300, 48 h	Marked up-FR in HUVEC cells, but not in hVSMC and Jurkat cells, and significant up-CD in hVSMC cells, but not in HUVEC cells, after Ad-muFL infection, by IFN-γ treatment.	[153]
hu, Thyroid gland follicular [nontoxic goiter (NTG), Hashimoto's thyroiditis (HT) and Grave's disease (GD) patients]	f-CD (Pre), IFN-γ (1000 U/ml) ± [IL-4 (20 ng/ml) or IL-10 (40 ng/ml)], 24 h	FR-mAb (CH-11, IgM), 200 ng/ml, 24 h	Small up-CD by IFN-γ Pre in HT and NTG cells. Enhanced Bcl-X_L and cFLIP in GD cells. Abolition of the sensitizing effect by coexistence of IL-4 or IL-10.	[206]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Stomach cancer (Kato-III, AGS-NY-2, N-87)	f-FR and f-CD (Pre), IFN-γ (100 U/ml) ± *H. p.* (300 bacteria/epithelial cell) ± TNF-α (40 ng/ml), 24–48 h (f-FR), 6–48 h (f-CD)	FR-mAb (CH-11, IgM), 50–100 ng/ml, 12 h	Synergistic up-FR by IFN-γ treatment in combination with *H. p.* and TNF-α. Up-FR and up-CD in all cell lines by IFN-γ Pre alone.	[194]
mu, Central nervous system microglia (primary)	f-FR, muIFN-γ (100 U/ml) ± muTNF-α (10 ng/ml) ± TGF-β2 (20 ng/ml), 24 h	None	Up-FR by IFN-γ ± TNF-α treatment, associated with significant reduction by coexistence of TGF-β2 in the case of treatment with IFN-γ alone.	[257]
hu, Salivary gland epithelium cells (non-neoplastic primary derived from SS patients and control individuals)	f-FR and f-FL, IFN-γ (500 U/ml), 48 h ± DEX (500 nM), 60 h	None	Significant up-FR and up-FL by IFN-γ treatment, associated with complete inhibition by coexistence of DEX.	[272]
hu, Lung cancer (A-549)	f-CD (Pre), IFN-γ (40 ng/ml), 6 h	FR-mAb (CH-11, IgM), 100 ng/ml, 24 h	Up-CD by IFN-γ Pre, associated with significant up-reg casp-1 and -3.	[170]
hu, Colon cancer (HT-29)	f-CD (Pre), IFN-γ (10 ng/ml), 16 h	FR-mAb (CH-11, IgM), 5–200 ng/ml or TNF-α, 0.05–2.0 ng/ml, 24 h	Up-CD by IFN-γ Pre via FR-mAb stimulation similar to that via TNF-α stimulation, but through different NF-κB activation mechanism in IκB-α degradation.	[131]
hu, Liver normal (Chang liver), cancer (SK-HEP-1, HEP-G2, -3B, -G2.2.15, PLC/PRF/5, SNU-182, -354, -387, -398, -423, -449, -475)	f-FR and f-CD (Pre), IFN-γ (250 U/ml), 24 h (f-FR); 36 h (f-FR and f-CD)	FR-mAb (CH-11, IgM), 250 ng/ml, 36 h	Insignificant up-CD in most cell lines except three (SNU-354, 387 and 423) by IFN-γ Pre. Significant up-FR in the strongly sensitized cell lines.	[195]
hu, Lymphoma (U-937), myeloid leukemia (HL-60, THP-1)	f-CD (Pre), IFN-γ (10 U/ml), 24 h	FR-mAb (CH-11, IgM), 20 ng/ml, 24–36 h	Up-CD by IFN-γ Pre, associated with dn-reg of Bcl-2 and up-reg of casp-8.	[154]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Bile duct cancer (Sk-ChA-1)	*In vitro*: f-FR and f-CD (Pre), IFN-γ (250 U/ml), 12–18 h; *in vivo* (5×10^6 tumor cells-injected athymic 6–8 w age female mice): 5×10^4 U/d/mouse, (3 daily injections in 4 d) × 3 in 2 w	FR-mAb (CH-11, IgM), 250 ng/ml, 15–20 h	Up-FR and up-CD in either FR level-low or -high subpopulation cells *in vitro* by IFN-γ treatment, associated with up-reg of casp-3, -4, -8, -7 -10a and Bak. Decreased tumorigenicity of FR level-low cells in nude mice.	[196]
bo, Ovary corpus luteum (midluteal stage of estrous cycle)	f-FR and f-CD (Pre plus Co), boIFN-γ (50 ng/ml) ± TNF-α (50 ng/ml), 24 h, (f-FR; f-CD, Pre) followed by 24 h (f-CD, Co)	sFL, 100 ng/ml, 24 h	Significant up-reg of FR mRNA and up-CD by IFN-γ treatment, associated with augmentation by coexistence of TNF-α.	[244]
hu, Placenta trophoblast (A-3, HTR/8)	f-FR, f-FL and f-CD (Pre and Co), IFN-γ (5–10 ng/ml) ± IL-10 (10 ng/ml), 12–24 h (f-FR, f-FL); 24 h (f-CD)	FR-mAb (nd, nd), 20–500 ng/ml, 24 h	Up-FR without up-FL, and up-CD by IFN-γ treatment, associated with inhibition against up-CD by coexistence of IL-10.	[250]
hu, Lung cancer (A-549)	f-FR and f-CD (Pre), IFN-γ (250 U/ml) ± IL-1β (50 pg/ml), 24 h ± LY294002 (10 μM), 30 m preceded	FR-mAb (CH-11, IgM), 10–100 ng/ml, 4–24 h	Up-FR and up-CD by IFN-γ treatment. Sequence-dependent opposing effects to IFN-γ regarding up-CD by IL-1β treatment, associated with reversal by Pre with PI3K inhibitor.	[171]
hu, Leukemia (B-lineage: SEM, RS-4;11, REH, Nalm-6; T-lineage: Jurkat, CEM), lymphoma (Raji, Ramos)	f-FR and f-CD (Pre), IFN-γ (500 U/ml) ± [castanospermine (1.06 mM), 1-deoxymannojirimycin (2 mM) or swainsonine (57.7 μM)], 48 h	FR-mAb (CH-11, IgM), 200 ng/ml, 48 h	Up-reg of high molecular-weight form FR in B-lineage cell lines, except Nalm-6, by IFN-γ treatment. Change in CD-sensitivity, but not in up-FR, by treatments with N-linked glycosylation inhibitors.	[155]
hu, Neuroblastoma (CHP-126, KAN, SH-SY5Y, Kelly), medulloblastoma (D283Med), Ewing's sarcoma (CADO-ES-1, STA-ET-2.1, 6647, RDES), fibrosarcoma [2fTGH, U-3A, U-3A-STAT-1]	f-FR and f-CD (Co), IFN-γ (1000 U/ml) ± [Z-VAD-FMK (50 μM) or Z-IETD-FMK (50 μM)], 24–72 h	FR-mAb (nd, IgG3), 0.1 μg/ml, 24–72 h	Up-FR and up-reg of casp-8 in various neuroblastoma, Ewing's sarcoma and medulloblastoma cells. Blockade of up-CD by Co with pan-casp or casp-8 specific inhibitor, or by deficiency in STAT-1 protein.	[164]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Lung cancer (A-549)	f-CD (Co), IFN-γ (500 U/ml) ± [Z-VAD-FMK (20 μM) or IETD-FMK (50 μM)], 1–3 d (Co)	FR-mAb (nd, nd), 200 ng/ml, 1–3 d (Co)	Up-CD by IFN-γ Co via up-reg of casp-8, and selective increase in casp-7 and -8, by treatment with IFN-γ alone.	[172]
hu, Umbilical vein endothelium (HUVEC), dermal microvasculature endothelium (HDMEC)	f-FR and f-CD (Pre), IFN-γ (4–300 ng/ml), 3–22 h (f-FR); IFN-γ (100 ng/ml), 20 h (f-CD, Pre)	CTL (preincubated with PMA, 10ng/ml plus ionomycin, 0.5 μM, 1 h), E/T ratio: 15:1, 5 h	Ds-dep, tm-dep up-FR in both types of normal endothelial cells. Up-CD of HUVEC cells by IFN-γ Pre.	[263]
hu, Normal intestine crypt epithelium (primary, colon and jejunum) (HIPEC); colon cancer (HT-29), leukemia (Jurkat)	f-FR and f-CD (Pre), IFN-γ (200 U/ml) ± TNF-α (10 ng/ml), 18–20 h	FR-mAb (CH-11, IgM), 100–300 ng/ml, 1–24 h ± Z-IETD-FMK, Z-LEHD-FMK or Z-DEVD-FMK (5 μM each), 15 m preceded	Insignificant up-FR, but significant up-CD of HIPEC cells by IFN-γ Pre, to the level of Jurkat cells with delay, associated with considerable degree of reduction by coexistence of casp-3, -8 and -9 inhibitors.	[132]
hu, Thyroid gland epithelium (primary, normal and multinodular goiter patients' thyroid tissues)	f-CD (Pre), IFN-γ (100 U/ml) ± TNF-α (50 ng/ml) ± IL-1β (50 U/ml), 4 d	FR-mAb (CH-11, IgM), 1 μg/ml, 20 h	Up-CD in goitrous cells, much less than normal cells, by Pre with IFN-γ in combination with IL-1β and/or TNF-α.	[267]
hu, Colon cancer (HT-29, *in vitro*), peripheral mononuclear blood (PBMC, *in vivo*) (stage-IV cancer patients)	f-FR, *in vitro*: IFN-γ (1-10 U/ml), 2 h; *in vivo*: IFN-γ (25–100 μg/m^2), administered at days 1 and 3	None	Tm-dep up-FR with the maximum of 3-fold in HT-29 *in vitro*, and 2.5-fold in CD15$^+$ PBMC from cancer patients *in vivo*, by IFN-γ treatment.	[133]
hu, Colon cancer (HT-29)	f-CD (Co), IFN-γ (80 U/ml, for HT-29 cells only), ± Z-VAD-FMK (50 μM)	FR-mAb (CH-11, IgM), 0.2–200 ng/ml, 3–4 d	Up-CD by IFN-γ Co in HT-29, not blocked by coexistence of pan-casp inhibitor.	[134]
mu, Bone marrow Mϕ (*Leishmania major* infected)	f-CD (Co), IFN-γ (10 ng/ml), 48 h	sFL, 100 ng/ml, 48 h	Requirement of Co with IFN-γ and sFL for leishmanicidal activity in the infected bone marrow Mϕ.	[214]
hu, Blood erythroid colony-forming (normal donors)	f-CD (Co), IFN-γ (400 U/ml) ± SCF (100 ng/ml), 24-120 h	sFL, 10–50 ng/ml, 24–120 h	Protective effect of SCF from up-CD by IFN-γ Co via inhibition of casp-3 and -8 activation and up-reg of FLIP.	[236]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Colon cancer (HT-29, HCT-116, HCT-116 p53-/-)	f-FR, IFN-γ (100 U/ml) ± ZD9331 (50–100 nM), 24 h	None	p53-state dependent enhancing effect of thymidylate synthase inhibitor on up-FR by IFN-γ treatment.	[135]
hu, Small cell lung cancer (SCLC) (N-417)	f-FR and f-CD (Co), IFN-γ (2500 U/ml) ± 5dAzaC (1 μM), 72 h	muFL-N2A, 10%, 72 h	Enhanced up-FR and up-CD in SCLC cells by IFN-γ treatment after combination with 5dAzaC.	[173]
hu, Acute myeloid leukemia (GM-CSF-dependent) (AML-193)	f-FR and f-CD (Co), IFN-γ (1000 U/ml), 24–40 h, after pre-cultivation with GM-CSF (20 ng/ml), at least 2 w	FR-mAb (FAS18, IgG2a), 5 μg/ml, 24–40 h	No difference in FR and 2.5-fold median up-CD by IFN-γ treatment in the absence of GM-CSF, associated with selective reduction of G1 cell-cycle state.	[156]
hu, Colon cancer [SW-480, SW-620, both original and IFN-consensus binding protein (ICSBP)-gene transfected]	f-FR and f-CD (Pre), IFN-γ (250 U/ml), 4–24 h	FR-mAb (CH-11, IgM), 1 μg/ml, 18–24 h ± casp-1 inhibitor (Z-YVAD-FMK or Z-LEVD-FMK), 20 μM, 30 m preceded	Marked up-FR in both primary and metastatic cells by IFN-γ treatment. Significant up-CD by IFN-γ Pre in SW-480 cells and ICSBP-gene transfected SW-620 cells.	[136]
hu, Colon cancer [SW-480 (parent), SW-480sell (metastatic subline selected *in vitro*), SW-480spl (metastatic subline obtained *in vivo*, SW-620 (primary metastatic tumor)]	f-FR and f-CD (Pre), IFN-γ (250 U/ml), 18–24 h	FR-mAb (CH-11, IgM), 1 μg/ml, 18–24 h	Resemblance of SW-480sell and SW-480spl cells to SW-620 cells regarding CD resistance in spite of significant up-FR by IFN-γ treatment and morphology, associated with identical genome-wide gene expression profiles.	[137]
hu, Peritoneum mesothelial (effluents from peritoneal dialysis patients)	f-FR and f-CD (Pre), IFN-γ (300 U/ml) ± TNF-α (5000 U/ml), 24 h	sFL (aggregated), 10–100 ng/ml, 24 h	Up-FR, associated with additive effect of TNF-α, and significant up-CD, by IFN-γ treatment.	[219]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu and mu, Prostate cancer (hu: LNCaP, PC-3; mu: RM-1)	f-CD (Pre), IFN-γ (100 U/ml) or muIFN-γ (25–200 U/ml), 24 h	FR-mAb (nd, nd) or muFR-mAb (nd, nd), 10 μg/ml each, 1 d; sFL in 30x conc. TC268 cell culture medium, 1:1 (v/v), 18 h; Ad-muFL, moi: 3.125-25, 1h exposure plus 24 h incubation	Synergistic up-CD in all prostate cancer cells, irrespective of the induction via either exogenously provided FR-mAb or sFL, as well as via transfection with Ad-muFL, by IFN-γ Pre.	[198]
hu, Kidney cancer (ACHN)	f-CD (Pre plus Co), IFN-γ (400 U/ml) ± [DEVD-CHO, YVAD-CHO (10 mM each), IRF-1 AS-ODN (2.5–20 μM) or random ODN (10 μM)], 31 h (Pre) followed by 17 h (Co)	FR-mAb (CH-11, IgM), 800 ng/ml, 17 h	Up-CD by IFN-γ treatment without up-FR, inhibited strongly either by casp-3/7 inhibitor or by IRF-1 AS-ODN, weakly by casp-1 inhibitor, but not by random ODN.	[185]
hu, Pancreas cancer (AsPC-1, BxPC-3, Capan-2, CFPAC-1, HPAC, MIAPaCa-2, PANC-1)	f-FR and f-CD (Pre plus Co), IFN-γ (40 U/ml), 48 h (f-FR); 24 h (f-CD, Pre) followed by 48 h (f-CD, Co)	FR-mAb (CH-11, IgM) or sFL, 1–100 ng/ml, 24–72 h; mFL-transfected murine L5178 lymphoma cells (mFL), E/T ratio: 10:1, 48 h	Up-CD in 5 of 7 cell lines induced with FR-mAb, 4 in 7 cell lines with mFL, by IFN-γ treatment without up-FR. Significant correlation of mFL-, but not FR-mAb-, mediated growth inhibition with endogenous DcR3 level.	[197]
hu, Colon cancer (Caco-2, Colo-320, SW-948)	f-FR and f-CD (Pre), IFN-γ (1–1000 U/ml), 24 h ± CHX (5 μg/ml), 1 h preceded to FR-mAb addition	FR-mAb (7C11, IgM), 50–1000 ng/ml, 24 h	Marked up-FR and up-CD by IFN-γ treatment, augmented by coexistence of CHX, in SW-948 cells, less in Colo-320 cells, but not significant in Caco-2 cells.	[35]
hu, Spontaneously transformed umbilical vein endothelium (ECV-340)	f-FR and f-CD (Pre), IFN-γ (100 U/ml), 6–48 h (f-FR); 12 h (f-CD, Pre)	sFL, 50–5000 ng/ml or FR-mAb (CH-11, IgM), 50–500 ng/ml, 20 h	Tm-dep up-reg of FR mRNA and ds-dep up-CD, associated with enhancement of IL-8 and MCP-1 secretion.	[264]
hu, Placenta villus trophoblasts and explanted tissues (woman with uncomplicated pregnancies)	f-FR, f-FL and f-CD (Co, explant tissues), IFN-γ (0.1–50 ng/ml), 24 h ± FR-Fc (2 ng/ml), 1 h preceded	Endogenous FR-mediated CD inducer in explanted tissues	No up-FL, insignificant up-FR, and up-CD by IFN-γ treatment, associated with suppression by FR-Fc Pre.	[251]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
mu, Pancreas β-cells insulinoma (NIT-1) (autoimmune diabetes-prone NOD mice)	f-FR and f-CD (Co), IFN-γ (1000 U/ml) plus IL-1β (100 U/ml) ± Z-VAD, 100 μM, 24 h	Super-FL, 100 ng/ml, 24 h	Significant up-FR and up-CD by IFN-γ treatment, associated with up-reg of casp-3 activity and prevention with pan-casp inhibitor.	[201]
hu, Oligodendroglioma (HOG, MO-3.13)	f-FR, f-FL and f-CD (Pre), IFN-γ (1–500 ng/ml) ± TNF-α (25–100 ng/ml), 24 h	sFL, 1–10 ng/ml, 24–72 h	Significant up-FR and up-CD by IFN-γ treatment, associated with up-reg of MHC-I expression and augmented up-FR in combination with TNF-α.	[165]
hu, Astrocytoma (CRT-J, U-373-MG, U-87-MG, U-251-MG, CH-235-MG)	f-FR and f-CD (Pre), IFN-γ (20–1000 U/ml), 0–72 h	FR-mAb (CH-11, IgM), 100–1000 ng/ml, 24 h	Up-FR in all cell lines, associated with cl-dep up-reg of casp-1, but up-CD by IFN-γ treatment, limited to CRT-J, U251-MG and CH235-MG.	[166]
mu, Brain cortical astrocytes (primary) (1 to 2 d old mice)	f-FR and f-CD (Pre), muIFN-γ (5 U/ml) and/or muTNF-α (10 ng/ml) and/or muIL-1β (10 ng/ml) ± SB203580 or SB202190 (0.1–20 μM each), 0.5–24 h ± W1400 (10–50 μM) or indomethacin (10 μM), prior addition	muFR-mAb (Jo2, IgG2), 1–10^4 μg/ml, sFL,10^{-2}–10^2 ng/ml plus enhancer, 1 μg/ml or muFL-N2A, 2%, 24 h	Tm-dep up-FR mRNA and up-CD in resistant cells by Pre with complete cytokines (IFN-γ, TNF-α and IL-1β) mix, accompanied by ds-dep inhibition of CD with p38 mitogen activated protein kinase inhibitor, but neither with iNOS inhibitor or COX-2 inhibitor.	[258]
hu, Proximal lung epithelium [normal bronchus (NHBE), small airway (DLEC)]	f-FR and f-CD (Pre and Co), IFN-γ (100 U/ml), 18 h	sFL, 25–500 ng/ml, 18h (Pre); last 16 h (Co)	No up-CD in DLEC cells, but significant up-CD in NHBE cells, without significant up-FR, by IFN-γ Pre. No up-CD in both types of cells by IFN-γ Co.	[277]
hu, Colon cancer (HT-29, DLD-1), monocyte leukemia (THP-1)	f-CD (Pre plus Co), IFN-γ (10 pM), o/n-9 d (Pre), followed by 24 h (Co)	FR-mAb (APO-1-3, IgG3), 60–600 pM, 24 h; sFL, 3.1 nM, 24 h	Significant up-CD in HT-29 and DLD-1, but not THP-1, by Pre with 10 pM IFN-γ o/n. Decrease in CD response by prolonged IFN-γ Pre.	[138]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Melanoma [HeLa, cell death inhibiting RNA (CDIR) oe or control vector transfected]	f-CD (Pre), IFN-γ (200 U/ml), 24 h	FR-mAb (CH-11, IgM), 100 ng/ml, 10–30 h	Inhibition of up-CD caused by IFN-γ Pre in HeLa cells, transfected with CDIR oe vector.	[188]
hu, Kidney mesangial (glomeruli from normal portion of renal tissue)	f-FL, IFN-γ (1000 U/ml) ± lactacystin (20 μM), 24 h	None	Significant up-FL by IFN-γ treatment, associated with complete reversal by coexistence of NFκB blocker.	[254]
hu, Colon cancer (HT-29, *in vitro*); peripheral blood mononuclear (PBMC, *in vivo*) (stage-IV cancer patients)	f-FR, *in vitro*: IFN-γ (1–10 U/ml), 6.5 h ± 5FU (38.5 μM) and LV (1 μM), 2 h preceded; *in vivo*: IFN-γ (10–100 μg/m^2), at days 1, 3 and 5 of a 28 d cycle with LV (200 mg/m^2) and 5FU (370 mg/m^2), at days 1–5 daily	None	Up-FR in PBMC from cancer patients *in vivo* and HT-29 *in vitro* by treatment with clinically achievable IFN-γ conc. Positive correlation of up-FR with the area under conc–time curve and time above 33.3 pg/ml in several compartments of PBMC.	[139]
ra, Colon cancer (CC-531s)	f-CD (Pre), IFN-γ (100 U/ml), 24 h	sFL, 1–100 ng/ml ± crosslinking antibody, 1 μg/ml, 18 h; LSEC cells, E/T ratio: 2.5–10:1 ± anti-FL mAb, 20 μg/ml, NMA, 1 mM or DEX, 10 μg/ml, 18 h	Up-CD induced with either sFL or co-cultured LSEC cells by IFN-γ Pre. No effect of anti-FL mAb and suppression effects on CD with nitric monoxide inhibitors	[140]
hu, Breast cancer (MCF-7)	f-FR and f-CD (Pre), IFN-γ (10–1000 U/ml) ± AT (0.1–1000 nM) ± CHX (20 μM), 6–72 h (f-FR); 48 h (f-CD, Pre)	FR-mAb (CH-11, IgM), 500 ng/ml ± CHX, 5 μM, 12–48 h	Ds-dep, tm-dep up-FR and modest up-CD by synergistic treatment with IFN-γ and AT, associated with up-reg of STAT-1, TR1 and PKR. Enhanced up-CD in the presence of CHX.	[177]
hu, Multiple myeloma (U-266-1970, U-1958; both IL-6 dependent)	f-FR, f-FL and f-CD (Pre), IL-6 (20 U/mL) ± IFN-γ (1000 U/ml) and, 0.5–96 h	FR-mAb (CH-11, IgM), 100 ng/ml, 6–24 h	Significant up-FR and up-CD by IFN-γ treatment without large change in Bcl-2 family members' expression, associated with enhancement of STAT-1 activation and attenuation of STAT-3 activation.	[157]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Cervical cancer (HPV-18 positive and wt p53: HeLa; HPV-16 positive and wt p53: CaSki, SiHa; HPV negative and mut p53: C-33A)	f-FR, f-FL and f-CD (Pre), IFN-γ (10–100 U/ml), 24 h (f-FR); 2 h (Pre)	FR-mAb (7C11, IgM), 50–1000 ng/ml, 24 h	Up-FR in all HPV positive cells, but not in C-33A, without major change in p53 levels by IFN-γ treatment. Strong up-CD only in HeLa and insignificant up-CD in other cells.	[74]
hu, Thyroid epithelium (primary, contralateral lobes of normal thyroid tissues)	f-FR and f-CD (Pre), IFN-γ (100 U/ml) plus IL-1β (50 U/ml), 4 d	FR-mAb (CH-11, IgM), 0.1–1 μg/ml, 1 h - o/n ± U0126, 10–50 μM, 30 m preceded	Significant up-FR and up-CD by IFN-γ treatment, associated with significant up-reg of many pro-apoptotic molecules, including Bid. Enhanced up-CD by coexistence of a p44/p42 MAPK kinase inhibitor.	[268]
hu, Salivary gland epithelium (healthy donors, Sjögren's syndrome patients)	f-FR and f-CD (Pre), IFN-γ (1000 U/ml), 72 h	FR-mAb (CH-11, IgM), 1 μg/ml ± anti-CD40 mAb, 1 μg/ml, 24 h	Up-FR and marked up-CD by IFN-γ treatment, only under cooperated stimulation with anti-CD40 mAb.	[210]
hu, Cervical cancer (KB: original, Bcl-2, FLIP-$_L$ or FLIP-$_S$ gene-transfected); Colon cancer (HT-29)	f-FR and f-CD (Pre), IFN-γ (20 ng/ml), 24 h	[FLAG-tagged sFL, 0.01–1000 ng/ml + Anti-FLAG mAb (M2, IgG1), 0.5–1 μg/ml, or Fc-sFL, 500 ng/ml] ± Z-VAD-FMK, 20 μM, 30 m-18 h	Up-FR and up-CD in both KB and HT-29 cells by IFN-γ treatment, associated with up-reg of IκBα, IL-6 and IL-8 expression. Inhibition of up-CD by coexistence of pan-casp inhibitor or FLIP-$_{L/S}$ oe, and less by Bcl-2 oe.	[141]
hu, Neuroblastoma (Paju)	f-FR and f-CD (Pre), IFN-γ (100 ng/ml), 16 h (f-FR); 24 h (f-CD, Pre)	FR-mAb (CH-11, IgM), 3 μg/ml, 24 h	Up-FR, but insignificant up-CD, by IFN-γ treatment, associated with neurite outgrowth.	[167]
mu, Small intestine epithelium (immortalized by SV-40 large T-gene transfection) (MODE-K, IEC-4.1)	f-FR and f-CD (Pre), [IFN-γ ± TNF-α (2–10 ng/ml each)] ± IL-10 (5–50 ng/ml), 24–48 h	muFR-mAb (Jo2, IgG2), 1 μg/ml, 24 h	Marked up-FR and up-CD by synergistic treatment with IFN-γ and TNF-α, associated with suppression by coexistence of IL-10.	[274]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Skin pre-adipocyte and adipocyte (primary, SGBS patients)	f-FR and f-CD (Co), IFN-γ (1000 U/ml) ± TNF-α (10 nM), 6–72 h	FR-mAb (nd, IgG3), 1 μg/ml, 6–72 h	Tm-dep synergistic up-FR and up-CD by combined treatment with IFN-γ and TNF-α, associated with increased DISC formation.	[211]
hu, Lung fibroblast (fatal, MRC-5; primary, undifferentiated from normal lung tissue), myofibroblast (both, differentiated with TGF-β)	f-FR and f-CD (Pre), IFN-γ (50 U/ml) ± TNF-α (20 ng/ml), 36–48 h	FR-mAb (CH-11, IgM), 250 ng/ml, 4–12 h	Marked up-FR and up-CD, associated with efficient DISC formation, by synergistic combined treatment with IFN-γ and TNF-α, but not by IFN-γ treatment alone.	[279]
mu, Mastocytoma (P-815), lymphoma (LS-102.9); wc, hepatocytes (WCM-260)	f-FL and f-CD (Pre), wcIFN-γ (1.5–1500 U/ml) ± muFR-mAb (Jo2, IgG2) (nd), 18 h	Wc hepatocytes (IFN-γ pretreated WCM-260), E/T ratio: 1.5–12:1, 18 h	Significant up-FL and up-reg of MHC-I expression in wc hepatocytes by IFN-γ Pre. Ds-dep up-CD of mu cells by treatment with IFN-γ-sensitized wc hepatocytes, associated with inhibition by muFR-mAb Pre.	[158]
hu, Oral mucosa melanoma (MMN9)	f-CD (Co), IFN-γ (1000 U/ml), 24 h	FR-mAb (mHFE7A, IgG), 0.1 μg/ml, 4 h, then with cross-linking antibody, 1.0 μg/ml, 24 h,	Weaker Up-CD by IFN-γ Co using an IgG subclass FR-mAb than that using an IgM subclass FR-mAb as the agonistic for CD-induction.	[189]
hu, Aorta vascular smooth muscle (cardiac transplantation patients)	f-FR and f-CD (Pre), IFN-γ (500 U/ml), 24 h ± LY2940002 (10 μM), BFA (5 μg/ml), ActD (1 μg/ml), tyrphostin AG490 (10 μM) or SH5 (20 μM), 30 m preceded	mFL, 1:2000, 6–24 h	Up-reg of cell-surface FR without increase in total FR and up-CD by IFN-γ treatment, associated with abrogation by coexistence of inhibitors to intracellular trafficking, PI3K, Akt, and Jak2.	[215]
mu, Colon cancer (C-15-4.3: MC-38 transfected with hu CEA gene)	f-FR and f-CD (Pre), muIFN-γ (1000 U/ml) ± muTNF-α (250 U/ml), o/n	CEA-mimicking epitope (3H1)-specific CTL, E/T ratio: 50:1 ± [CMA (500 nM), anti-FL mAb or anti-TRAIL mAb (10 μg/ml each)], 8 h	Marked up-FR and up-CD by synergistic treatment with IFN-γ and TNF-α, associated with inhibition by additional combination of CMA, anti-FL mAb and anti-TRAIL mAb.	[142]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Uterus endometrial stroma (ESC: undifferentiated, decidualized) (benign hysterectomy tissue from pre-menopausal woman)	f-FR and f-CD (Pre), IFN-γ (50 ng/ml) ± TNF-α (25 ng/ml) ± hCG (1 U/ml), 24–48 h	FR-mAb (CH-11, IgM), 100 ng/ml, 24 h	Up-FR and up-CD irrespective of differentiation state by combined Pre with IFN-γ and TNF-α without strong influence by coexistence of hCG, associated with up-reg of FLIP mRNA.	[281]
hu, Thyroid gland epithelium (primary, contralateral lobes of normal thyroid tissues)	f-CD (Pre), IFN-γ (100 U/ml) plus IL-1β (50 U/ml), 3 d ± Z-VAD, Inhibitor for casp- (IC)1, IC3, IC4, IC8, IC10, SB203580 or MG132 (singly or in pairs), 60 m preceded	FR-mAb (CH-11, IgM), 1 μg/ml, o/n	Up-CD by IFN-γ plus IL-1β Pre, associated with significant prevention with inhibitors of pan-casp or specific to casp-3/7, -10 and p38 MAPK kinase, but not with proteasome inhibitor.	[269]
hu, Eye subconjunctival Tenon fibroblast (biopsy specimen from glaucoma patients)	f-FR, IFN-γ (100 U/ml) ± IFN-α (5000 U/ml), 48 h	None	Significant up-FR by IFN-γ treatment, associated with augmentation by coexistence of IFN-α and up-reg of sensitivity to MMC-mediated CD.	[220]
mu, Soft tissue sarcoma (CMS-4: parental; transfectant with empty-control, K79E-mut or R289E-mut IRF-8 gene)	f-FR and f-CD (Pre), IFN-γ (100 U/ml), o/n-24 h	sFL, 200 ng/ml, 24 h	Up-FR and marked up-CD by IFN-γ treatment in wt IRF-8 expressing cells, associated with enhanced STAT-1 activation and significant inhibition by oe of functionally-impaired mut IRF-8.	[181]
hu, Peripheral blood $CD4^+$ leukocyte [healthy donors (HD) and Sézary syndrome (SzS) patients]	f-FR and f-CD (Pre), IFN-γ (100 U/ml), o/n	Super-FL, 100 ng/ml, 6–8 h	Significant up-FR and up-CD in both $CD4^+$ leukocytes from HD and SzS patients by IFN-γ treatment.	[212]
mu, Thyroid gland epithelium [primary, parental (Tg^-) and FLIP transgenic (Tg^+) mice]	f-FR, f-FL and f-CD (Pre), IFN-γ (100 U/ml) and TNF-α (50 U/ml), 4 d	muFR-mAb (Jo2, IgG2), 1 μg/ml, o/n	Up-reg of FR and FL mRNAs in both FLIP Tg^+ and Tg^- cells and up-CD only in Tg^- cells by combined treatment with IFN-γ and TNF-α.	[270]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Astroglioma (ADF, LN-229, U-373)	f-FR, f-FL and f-CD (Pre), IFN-γ (500 U/ml) ± lactacystin (1.25–10 μM), 24–72 h	FR-mAb (CH-11, IgM), 500 ng/ml, 24 h ± casp inhibitor (Z-VAD-, IETD-, AEVD- or LEHD-FMK) (50 μM each), 2 h preceded	Tm-dep up-FR, up-reg of sFL release, associated with up-reg of Bax, Bak expression. Marked up-CD by IFN-γ treatment, associated with ds-dep up-reg by a proteasome-specific inhibitor, but with attenuation by coexistence of casp-specific inhibitors.	[168]
hu, Heart vascular fibrous cap (atherosclerotic lesion)	f-FR and f-CD (Pre), IFN-γ (5 ng/ml), 20–24 h ± siRNA (non-targeted and targeted to PSME-1, PSME-8 or PSME-1 and -8 mix) (total 50 nM), 24–48 h preceded	FR-mAb (CH-11, IgM), 50–100 ng/ml, 24 h	Up-FR without block by siRNA Pre and up-CD by IFN-γ treatment, associated with inhibition by Bcl-X_L oe or Pre with siRNA targeted to PSME-8 component for immunoproteasome.	[217]
mu, Convoluted-type T-cell lymphoma (ST4: wild-type and $LI^{255-256}$ to AA mutation in IFN-γ receptor 2)	f-FR and f-FL, IFN-γ (1000 U/ml), 24 h	None	Marginal up-FR in both types of cells by IFN-γ treatment. Significant up-FL only in cells expressing mut IFN-γ receptor, associated with more persisted STAT-1 phosphorylation.	[159]
eq, Ovary corpus luteum (midluteral stage of estrous cycle)	f-CD (Co), IFN-γ plus TNF-α (10 ng/ml each), 24 h	sFL, 10 ng/ml, 24 h	Modest up-CD by Co with IFN-γ and TNF-α, associated with up-reg in PARP 1 activity, P_4 production, and dn-reg of $PGF_{2\alpha}$ production.	[245]
bo, Ovary corpus luteum (midluteral stage of estrous cycle)	f-CD (Co), boIFN-γ (2.5 nM) plus TNF-α (2.9 nM), 48 h	sFL, 2.9 nM, 48 h	Insignificant change in CD and cFLIP levels by treatment with IFN-γ plus TNF-α, after combination with sFL.	[246]
hu, Lung cancer (A-549); breast cancer (MCF-7) (parental and Rel A-kd with both cells)	f-FR, IFN-γ (50 ng/ml) plus TNF-α (20 ng/ml) ± anti-IFN-γRα mAb (nd) plus anti-TNF-α mAb (nd), 24 h	None	Up-FR by IFN-γ treatment, associated with reduction by either blocking IFN-γ and TNF-α or kd of main member of NF-κB family.	[174]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
mu, Bone marrow lymph-node (inguinal, axillary and lateral axillary from normal B6 mice)	f-FR, muIFN-γ (20-60 ng/ml), 18–72 h	None	Up-FR in total and residual cells after body γ-ray irradiation by IFN-γ treatment, accompanied by up-reg expression and co-localization of FR with MHC-class II.	[226]
hu, Colon cancer (HT-29)	f-FR and f-CD (Co), *in vitro*: IFN-γ (250 U/ml) or Let-7 inhibitors (50 nM), 24 h; *in vivo*: IFN-γ (1000 U) or Let-7 inhibitors (20 μg), intra-tumoral injections at days 4, 6 and 8 in 18 d period	FR-mAb (CH-11, IgM), 1 μg/ml (*in vitro*), 24 h; 20 μg/injection (*in vivo*)	Up-FR by IFN-γ treatment and its enhancement in the presence of FR-mAb. Enhancing effect of inhibitor against micro RNA targeting to FR mRNA, similar to IFN-γ, on up-CD both *in vitro* and *in vivo*.	[143]
ra, Pancreas insulinoma (INS-1E: uninfected, infected with Ad expressing Bcl-6 or control luciferase)	f-FR, raIFN-γ (100 U/ml) plus IL-1β (10 U/ml), 6–24 h	None	Marked up-reg of FR mRNA by combined-cytokines treatment in either uninfected or control Ad-infected cells, but significant attenuation in Bcl-6-expressing Ad-infected cells.	[202]
mu, Bone marrow (tibiae and femurs of 8-w-old mice)	f-FR and f-FL, muIFN-γ (100 ng/ml) plus M-CSF (100 ng/ml), 4 d	None	Up-FL in non-adherent cells, but no significant up-FR, irrespective of cell-adherence by IFN-γ treatment.	[227]
hu, Bone osteosarcoma (HOS, U-2OS)	f-FR and f-CD (Pre and Co), IFN-γ (500 U/ml), 48 h (f-FR and f-CD, Pre for CH-11 treatment; f-CD, Co for γδ-T cells treatment)	FR-mAb (CH-11, IgM), 100 ng/ml, 24 h; γδ-T cells ± [CMA (15 nM) or anti-FL mAb (10 μg/ml)], 30 m preceded, E/T ratio: 1.5–12:1, 4–18 h	Significant up-FR and up-CD by IFN-γ treatment, associated with reduction of CD after IFN-γ Pre induced with γδ-T cells Co by coexistence of FR-mediated pathway inhibitor, but weaker effects than perforin-mediated pathway inhibitor.	[191]
hu, Pancreas islet β [βLox5: wild type, mitochondria (mt)-depleted mutant (ρ^0), cybrid of ρ^0 with platelet cells holding normal mt DNA]	f-FR and f-CD (Co), IFN-γ (250–1000 U/ml), o/n (f-FR); IFN-γ (1000 U/ml) ± Z-VAD-FMK (50 μM × 2), 48 h (f-CD, Co)	FR-mAb (CH-11, IgM), 500 ng/ml, 48 h	Significant up-FR and up-CD in wt cells, and up-CD in ρ^0 and cybrid cells by IFN-γ Co, associated with complete suppression by coexistence of pan-casp inhibitor.	[241]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
mu, Bone marrow mesenchymal stem (bone cavity of tibiae and femurs)	f-FR, IFN-γ (50 ng/ml) ± TNF-α (20 ng/ml), 24 h ± Fas siRNA treatment (nd), nd	None	Up-FR by combined treatment with IFN-γ and TNF-α, associated with suppression by Fas siRNA treatment. Significant up-FR, but insignificant activation of casp-3 and -8, by treatment with IFN-γ alone.	[228]
mu, Pancreas islets (wild-type and Bid deficient NOD mice)	f-CD (Co), IFN-γ (100 U/ml) plus IL-1β (10 U/ml) ± TNF-α (1000 U/ml), 3–5 d	sFL, 100 nM, 3–5 d	Significant protection of Bid-deficient islet cells from sFL-induced CD under Co with IFN-γ plus IL-1β ± TNF-α.	[200]
mu, Eye conjunctiva epithelium (dry-eye model mice; wild-type and IFN-γ gene-kd)	f-FR, *in vivo*: muIFN-γ (10000 U/eye/injection), before, at 2nd and 4th d in 5 d desiccating stress period	None	More enhanced up-FR mRNA level in wt mice as compared with IFN-γ-gene- kd mice by IFN-γ treatment, associated with up-reg of casp-3, -8, -9 activities.	[221]
hu, Blood vessel smooth muscle cells-like myofibroblast (carotid artery atherosclerotic lesion)	f-CD (Pre), IFN-γ (50 U/ml), 8 h ± ApoL6 siRNA (10 nM), o/n preceded	FR-mAb (CH-11, IgM), 10–25 ng/ml, 20 h	Significant up-CD by IFN-γ Pre, associated with partial suppression by Pre with ApoL6 siRNA.	[218]
ra, Pancreas islet-β (primary); insulinoma (INS-1E); (either transfected with CHOP-kd or control siRNA)	f-FR, raIFN-γ (100 U/ml) plus [IL-1β (10 U/ml) or TNF-α (1000 U/ml)], 8 h (INS-1E); raIFN-γ (1000 U/ml) plus [IL-1β (50 U/ml) or TNF-α (1000 U/ml)], 24 h (primary)	None	Up-reg of FR-mRNA by combined-cytokines treatment. Suppression by siRNA-kd of CHOP, associated with decrease in NF-kB activity and in degradation of Bcl-2 and Mcl-1.	[203]
mu, Soft tissue sarcoma (CMS-4: wild-type, mutant IRF-8-expressing or IRF-8-deficient via shRNA transfection)	f-CD (Pre), IFN-γ (200 U/ml), 24 h ± TSA (20–100 nM), 4 h preceded	sFL, 100 ng/ml, 24 h	Up-CD by IFN-γ Pre, associated with augmentation by coexistence of TSA and attenuation by either deficiency or impaired function of IRF-8 using shRNA transfection.	[182]
hu, Multiple myeloma (U-266-1970, U-266-1970-STAT-1C)	f-CD (Pre), IFN-γ (1000 U/ml), 96 h	FR-mAb (CH-11, IgM), 100 ng/ml, 24 h	Insignificant enhancement in up-CD by IFN-γ Pre after stable expression of a constitutively active mut STAT-1 alone.	[160]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Cervical cancer (HeLa: Ro52 siRNA or control siRNA transfected)	f-CD (Pre), IFN-γ (50 ng/ml), 24h	FR-mAb (nd, nd), 250 ng/ml, 3 h	Up-CD by IFN-γ Pre, associated with significant suppression after Ro52-siRNA transfection.	[179]
mu and hu, lung alveolar wall (normal lung tissue from healthy mice) (mu, *in vivo*); normal microvascular endothelium (HPMVEC) and alveolar epithelium (HPAEpiC) (hu, *in vitro*)	f-FR and f-CD (Co), *in vivo*: [muIFN-γ (100 μg) ± anti-muCD40 mAb (30 μg)] per intratracheal injection, every 3 d × 8; *in vitro*: IFN-γ (1000 U/ml) ± anti-CD40 mAb (0.2–20 μg/ml), 12 h	muFR-mAb (Jo2, IgG2), *in vivo*: 0.1 μg/g/injection, every 3 d × 8; *in vitro*: FR-mAb (nd, nd), 2.0 μg/ml, 12 h	Up-FR and up-CD specific to HPMVEC by treatment with IFN-γ alone either *in vivo* or *in vitro*. More pronounced up-CD in HPMVEC than in HPAEpiC by IFN-γ treatment alone or combination with anti-CD40 mAb.	[265]
mu, Airway $CD4^+$ T lymphocytes (lung tissue and peri-bronchial lymph nodes of OVA-sensitized asthma model mice); spleen CD4+ T lymphocytes (naïve)	f-FR and f-FL, *in vivo*: IFN-γ (10–1000 U/mouse/d), 6 d, 5 m preceding each OVA inhalation ± anti-FL mAb (MFL-3, IgG) (100 μg/mouse), at day 2; *in vitro*: IFN-γ (0.1–10 U/ml) ± anti-FL mAb (MFL-3, IgG) (10 μg/ml), 6–24 h	None	Ds-dep dn-reg of cell-surface FR and FL in OVA-sensitized airway T-cells *in vivo*, and up-reg of cell-surface FL in naïve and OVA-treated spleen T-cells *in vitro*, by IFN-γ treatment. Both occurred without significant effect of anti-FL mAb.	[208]
hu, Eye conjunctiva epithelium (IOBA-NHC) (normal, spontaneously immortalized)	f-FR and f-FL, IFN-γ (500 U/ml) ± TNF-α (25 ng/ml), 24-48 h ± CsA (10 μM), 24 h-pre-, co- or 24 h-post-treatment	None	Up-FR and up-FL by combined treatment with IFN-γ and TNF-α, but only up-FR with IFN-γ alone, associated with treatment procedures- dependent reduction by coexistence of CsA.	[276]
ra, Pancreas islet β (RINm5F; wild-type and plasmid vector for SOCS1-oe transfected)	f-FR, IFN-γ (1000 U/ml) ± IL-1β (50 U/ml) ± TNF-α (1000 U/ml)	None	No alteration in FR mRNA level by treatments with IFN-γ alone or in combination with other cytokines, irrespective of SOSC1 oe.	[242]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Epidermal keratinocyte (HEK) (primary from normal neonatal foreskin)	f-FL, IFN-γ (20 ng/ml) ± TNF-α (75 ng/ml) ± IL-1β (500 pg/ml), 24–72 h ± NMA (3 mM), 2 h preceded	None	Significant up-FL mRNA by combined-cytokines treatment containing IFN-γ, accompanied by up-reg of NO production with suppression by coexistence of iNOS inhibitor.	[261]
bo, Ovary corpus luteum (midluteal stage of estrous cycle)	f-FR and f-FL, IFN-γ (50 ng/ml) plus TNF-α (50 ng/ml) ± LPA (435 ng/ml), 6–12 h	None	Up-FR and up-FL by combined treatment with IFN-γ and TNF-α, associated with suppression by coexistence of LPA and up-reg of Bax, but not of Bcl-2, expression.	[247]
hu, Blood monocytes, Mϕ (buffy coats of healthy donors)	f-FR, IFN-γ (10 ng/ml) ± IL-10 (50 ng/ml) + DEX (100 nM), 3 d (for monocytes); 8 d (for Mϕ, IL-10 and DEX added on day 5)	None	Up-FR by IFN-γ treatment, associated with significant augmentation by coexistence of IL-10 or DEX and reduction of MerTK expression.	[234]
bo, Uterus endometrium epithelial and stromal (intercaruncular endometrial tissues form healthy Holstein cows, 2–5 d after ovulation)	f-FR and f-CD (Pre plus Co or Co alone), boIFN-γ (50 ng/ml) plus TNF-α (100 ng/ml), 24 h (f-FR, Co); 24 h plus 24 h (Pre plus Co)	sFL, 50–100 ng/ml, 24 h	Marked up-reg of FR mRNA and up-CD by Pre with IFN-γ and TNF-α in both types of cells. More prominent CD in stromal cells than in epithelial cells by the combined treatment.	[278]
hu, Uterus endometrial epithelium cancer (RL95-2: wild-type, Sdc-1-kd)	f-FR and f-CD (Pre), IFN-γ, IL-1β (10 ng/ml each), TNF-α (5 ng/ml) plus TGF-β1 (0.5 ng/ml), 24 h	FR-mAb (EOS9.1, IgM), 5 μg/ml, 7 h	Up-FR and up-CD in both types of cells by combined-cytokines Pre plus FR-mAb treatment, associated with up-reg of Bad, FADD and XIAP.	[180]
mu, Blood Mϕ-like leukemia (RAW264)	f-CD (Pre), IFN-γ (10 ng/ml) plus LPS (1 μg/ml), 24 h	mu auricular chondrocytes (wt, gld mut), E/T ratio: 1.25–10:1, 4 h	Ds-dep more up-CD by Pre with IFN-γ plus LPS induced with wt effector cells than that with gld mut cells.	[161]
hu, Kidney cortex / proximal tubule epithelium (HK-2) (transformed with HPV-16)	f-CD (Co), IFN-γ (50 ng/ml) ± TNF-α (25 ng/ml), 48 h	FR-mAb (CH-11, IgM), 0.5 μg/ml, 48 h	No up-CD by Co with either IFN-γ alone or combination of IFN-γ and TNF-α.	[186]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
mu, Small intestine lamina propria $CD4^+$ T-lymphocytes (naïve and peanuts-derived allergen sensitized 6-8-w-old mice)	f-FL, IFN-γ (20 ng/ml), nd	None	Significant up-FL by treatment with IFN-γ alone in cells from either naïve or allergen-sensitized mice, associated with increased unmethylation of FL gene.	[240]
hu, Uterus immortalized endometrial stromal (St-T1: wild-type, Sdc-1-kd: both non-differentiated, decidualized)	f-FR and f-CD (Pre), IFN-γ (10 ng/ml) ± [IL-1β (10 ng/ml), TNF-α (5 ng/ml) plus TGF-β1 (0.5 ng/ml)], 24 h	FR-mAb (EOS9.1, IgM), 5 μg/ml, 24 h	Up-FR and significant up-CD by treatment with all combined-cytokines containing IFN-γ, associated with sdc-1-kd or differentiation state dependent difference in up-reg degree.	[282]
mu, Bone marrow hematopoietic stem and progenitor (KSL, KL, $KLCD150^+$, $KLCD150^+$ $CD48^-$) (tibiae and femurs)	f-FR and f-CD (Co), *in vitro*: muIFN-γ (25–50 ng/ml) plus [IL-3, IL-6, SCF and Flt-3 L (10 ng/ml each)], 24 h - 6 d; *in vivo*: IFN-γ (10 ng/mouse), 20 h - 2 d	muFR-mAb (nd, nd), 0.5–2.0 μg/ml, 24 h	Significant up-FR in all types of cells by treatments with IFN-γ either *in vitro* or *in vivo*, and reduced recovery of total KSL or BM cells by Co with IFN-γ and FR-mAb.	[229]
hu, Neuroblastoma [SH-SY5Y, SK-N-BE (2)]	f-FR and f-CD (Pre), IFN-γ (100 ng/ml), 24 h ± TNF-α (100 ng/ml), 24 h followed	Fc-sFL, 100 ng/ml, 24 h	Significant up-FR and up-CD in both cells by IFN-γ treatment, associated with enhanced CD in highly resistant cells by additional Pre with TNF-α.	[54]
hu, Cervical cancer (HeLa), colon cancer (HT-29)	f-FR and f-CD (Pre), IFN-γ (100–1000 U/ml), 2–24 h ± [TLCK, TPCK or EI (10–100 μM)], 30 m preceded	FR-mAb (nd, nd), 5–1000 ng/ml, 2–4 d	Significant up-FR and up-CD by IFN-γ treatment, associated with augmentation by Pre with TLCK or TPCK, but not with EI.	[144]
hu, Blood basophils (venous EDTA-blood of healthy non-selected donors)	f-CD (Pre), IFN-γ (1000 U/ml), 24–48 h	Super-FL, 5–100 ng/ml, 24 h	No up-CD by IFN-γ Pre, in spite of STAT-1 activation.	[235]
ra, Ovary granulosa [diethylstilbestrol-primed (relatively undifferentiated); eCG-primed (differentiated)]	f-FR and f-CD (Pre plus Co), raIFN-γ (10–1000 U/ml), 18 h (Pre) plus 6 h (Co)	muFR-mAb (Jo2, IgG2), 1 μg/ml, 6 h	Up-reg of FR mRNA, requiring a higher IFN-γ dose in differentiated cells, and more prominent up-CD in relatively undifferentiated cells, by Pre with IFN-γ.	[249]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
mu, Bone marrow mesenchymal stem (bone cavity of tibiae and femurs of pathogen-free mice)	f-FR, IFN-γ (200 ng/ml) ± IL-17 (200 ng/ml), 24–72 h	None	Tm-dep synergistic up-reg of FR mRNA by combined treatment with IFN-γ and IL-17, associated with STAT-1 and casp-8 activation.	[230]
mu, Skin hair follicle (alopecia areata mice)	f-FR, [IFN-γ (50 ng/ml) plus TNF-α (25 ng/ml)] ± SOCS3 (nd), 48 h	None	Marked suppression of up-FR mRNA by IFN-γ plus TNF-α treatment in the presence of SOCS3, associated with concomitant dn-reg of MHC-I mRNA.	[262]
hu, Liver hepatic stellate (hTERT-immortalized)	f-FR, IFN-γ (100 ng/ml) ± 1MT (0.5 mM), 3–72 h	None	Tm-dep up-FR by IFN-γ treatment, associated with up-reg of STAT-1, IDO-1, -2 and dn-reg of α-SMA as well as up-reg of IFN-γRβ1 in the presence of 1MT.	[239]
hu, Leukemia (K-562)	f-FR and f-FL, IFN-γ (10–1000 U/ml), 12–48 h	None	Ds-dep, tm-dep up-FR and up-FL by IFN-γ treatment.	[162]
hu, Colon cancer (HT-29)	f-CD (Pre), IFN-γ (0.1–100 U/ml), 24–72 h	SSCC of sFL with fluorescein or avidin, 0.001–1000 ng/ml, 4–72 h	Ds-dep and tm-dep up-CD of resistant colon cancer cells by Pre with IFN-γ.	[145]
ra, Pancreas islet-β insulinoma (INS-1E)	f-FR, raIFN-γ (1000 U/ml) plus IL-1β (10 U/ml), 48 h ± PRL (0.5 μg/ml), 24 h preceded	None	Marked up-FR by combined treatment with IFN-γ plus IL-1β, associated with significant attenuation, concomitant with dn-reg Iκ-Bα, MCP-1, A20 and Cxcl-10 expression, by Pre with PRL.	[204]
mu, Spinal cord motoneuron (wt mice)	f-CD (Pre), muIFN-γ (10 ng/ml), 24 h	$CD8^+$ T-lymphocyte cells (wt, E/T ratio: 10:1, 72 h	Insignificant up-CD in co-culture together with wt T-cells by Pre with IFN-γ.	[259]
hu, Cardiac myofibroblast (normal adult ventricles)	f-FR and f-FL, IFN-γ (100 ng/ml) ± 1MT (0.5 mM), 3–72 h	None	Tm-dep up-FR and up-FL by treatment with IFN-γ, associated with significant augmentation by coexistence of IDO inhibitor.	[280]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Colon cancer (HT-29)	f-CD (Pre), IFN-γ (10–1000 U/ml) ± 5FU (25–100 U/ml), 24 h	SSCC of sFL with biotin, 100 ng/ml, 72 h	Enhanced up-CD by IFN-γ Pre in combination with 5FU.	[146]
mu, Mesenchymal stem / stromal (tibia and femur bone marrow from wt, $FR^{-/-}$ lpr-mut, iNOS-deficient mice)	f-FR and f-CD (Co), [IFN-γ (10 ng/ml) ± TNF-α (10 ng/ml)] ± SNAP (20 μM), 3–48 h	muFR-mAb (Jo2, IgG2), nd, 48 h	Tm-dep significant up-reg of FR mRNA and CD-induction in wt cells, less in iNOS-deficient cells and no in $FR^{-/-}$ lpr-mut cells, by synergistic treatment with IFN-γ and TNF-α.	[231]

4.2. Other cytokine agents

In addition to the combined treatments with IFN-γ, many exogenous cytokine agents independent of IFN-γ have been applied for the sensitization studies. The summarized results of them are listed in Table 3 [54,122,124,132,138,142,151,153,156,157,158,161,163,165,171,181,183,184,186,187,190, 194,199,205,207,211,212,216,219,220,224,227,228,230–235,238,240,244,248,250–252,254,256–258,261,266,267,271–274,276,277,279,281–310]. As compared to the agents containing IFN-γ, the number of the studies employing the other cytokine agents lacking IFN-γ as a component is still rather limited. Among them, TNF-α and IFN-α, -β are the representative molecules, which have been frequently used for the sensitization experiments to date. TNF-α is a protein that belongs to the same TNF ligand-superfamily as is the case for FasL. However, unlike FasL, TNF-α is known to exert primarily not only pro-apoptotic but also anti- or non-apoptotic biological activities, such as proliferation, angiogenesis and metastasis, on the target cells, due to the presence of a pair of receptors, TNFR-I and TNFR-II. These receptors are responsible for the mediation of several distinct signaling pathways including nuclear factor-kappa B (NF-κB) and c-Jun N-terminal kinase (JNK) signaling pathways, which can give negative feedbacks against the apoptosis pathway [311]. On the other hand, IFN-α and IFN-β belong to the Type-I interferon family, which regulates many cellular functions by activating signaling processes, including the JAK-STAT pathway that closely crosstalk to each other with apoptosis-priming cytokines, represented by IFN-γ [112,312]. Thus, the sensitization effects caused by TNF-α or IFN-α, -β to Fas signaling system can be less straightforward in transmitting the signals received at each responsible receptor than the cases primed with IFN-γ, because of the presence of rather complicated regulation mechanisms arising from many crosstalk between each signaling system and the IFN-γ signaling system. Nevertheless, in majority of the cases, the up-regulation of cell-death induction concomitant with the enhancement of cell-surface FasR expression was also observed in the treatment with the exogenous agents, containing TNF-α or IFN-α, -β, but lacking IFN-γ, which accompanied intracellular pro-apoptotic events, such as the activation of caspases-3, -7, -8, or STAT-1; increase in poly (ADP-ribose) polymerase cleavage; and decrease in STAT-3 activation. The sensitization degrees were often significantly correlated with the intracellular expression levels of FLIP, Bcl-2, Bcl-X_L, Bax, Bcl-2 homologous antagonist / killer protein (Bak), Bcl-2 like protein 11 (Bim) and Bcl-2 homology domain 3 interacting-domain death agonist (Bid). In the treatments with TNF-α-containing agents, IL-1β or TGF-β exhibited the enhancing [216,258] and suppressing [257,298] action to TNF-α in multiple studies. Also, the inhibition of NF-κB signaling pathway reversed the up-regulation effects on cell-surface FasR and cell-death of the target cells, caused by TNF-α treatment [54,292,310]. The TNF-α treatment combined with ribavirin synergistically up-regulated the cell-death of hepatoma [293]. As for IFN-α and IFN-β, the combined treatments with other low molecular weight compounds, such as epigallocatchin-gallate [304] or methotrexate [305], and post-treatment with temozolomide [307], have been identified as the enhancing factors for the sensitization in some cases.

Apart from TNF-α and IFN-α, -β, a variety of other cytokines and hormones, including IL-1α, -1β [163,171,199,205,251,254,258,261,266,267,271–273,277,282,283,287,309], IL-2 [183,271,287, 303], IL-3 [238,235], IL-12 [285,294], IL-17, -18 [230,234,240,289,294], other ILs [161,163,232,234,250,271,274,287,298], TGF-β1, -β2 [163,186,257,282,298], TNF-β [163], TNF related apoptosis-inducing ligand (TRAIL) [302], macrophage inflammatory protein (MIP)-1α, -1β, -2, IFN-γ-inducible protein-10 (IP-10), keratinocyte-derived chemokine (KC) [161], kit ligand

(KL) [238], GM-CSF [132,232,238,271,298], granulocyte colony-stimulating factor (G-CSF) [161], macrophage colony-stimulating factor (M-CSF) [163], platelet-derived growth factor (PDGF), epidermal growth factor (EGF), fibroblast growth factor (FGF) [124], and thyroid stimulating hormone (TSH) [205,266], have been examined for sensitization to target cells as the exogenous agents individually. Among them, IL-1α and IL-1β constitute the most frequently used cytokines after TNF-α and IFN-α, -β. IL-1 are known to exert pleiotropic biological functions including the augmentation of IFN-γ-mediated cytolytic activity of natural killer cells [112,313] and anti-tumor activity of macrophages [314], where Fas signaling system is expected to have profound connections with them. However, the actual actions of IL-1 in the sensitization to FasR-mediated cell-death largely depended on the cases, and even significant down-regulation of FasL expression was observed in an instance [272]. This may be closely related to the mechanism that the signal transduction by IL-1 is implemented through the modulation of NF-κB [315], which is also a major transcription factor for cell-proliferation, and to the phenomenon that IL-1β was released by the action of FasL during the events in inflammation [316]. Further extensive studies in relation to Fas signaling system would be required for making discussion about general mechanistic characteristics of the sensitization to cell-death via FasR-mediated signaling by exogenous treatments with other cytokine agents.

Table 3. Sensitization of cell-death induction via Fas signaling system with exogenous cytokine agents independent of IFN-γ.

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Glioma (T-98G, LN-18, LN-215, LN-229, LN-308, LN-319, LN-405)	f-FR and f-CD (Pre), TNF-α and/or TGF-β2, IL-10, IL-13 (10 ng/ml each), TNF-β, IL-8 (20 ng/ml each), IL-1β (2.5 ng/ml), IL-4 (5 ng/ml), IL-6 (100 U/ml), or M-CSF (10 U/ml), 24 h	FR-mAb (CH-11, IgM), 0.1–1 μg/ml, 24 h	Cl-dep up-FR and up-CD by treatment with TNF-α, TGF-β2, IL-1β or IL-8, and up-CD of only T-98G cells by Pre with IL-10 or -13. Correlation of CD sensitivity with cell-surface FR expression level after TNF-α treatment.	[163]
hu, Retinal pigment epithelium (keratoplasty donor eyes)	f-FR and f-CD (Pre), TNF-α (10 ng/ml) ± TGF-β2 (10 ng/ml) ± DEX (10 μM), 24 h	FR-mAb (nd, IgM), 1 μg/ml, 16 h	Up-FR by treatment with TNF-α alone, Synergistic up-CD by combination of TNF-α with TGF-β2, associated with inhibition by coexistence of DEX.	[216]
mu, Pancreas islet (primary, β-TC-1)	f-FR and f-CD (Pre), muIL-1α (10^2–10^5 U/l) ± NMA 0.2–1.0 mM) or minus L-arginine, 1–12 h	muFR-mAb (RK8, nd), 0.5–5 mg/l, 12–72 h	Tm-dep up-reg of FR and FR-mRNA, and ds-dep up-CD by treatment with IL-1α alone, without inhibition by coexistence of iNOS inhibitor and dependence on L-arginine.	[283]
hu, Primitive hematopoietic progenitor ($CD34^+CD38^{+/-}$ fetal liver)	f-FR, f-CD (Co), selected combinations of KL, IL-3, GM-CSF (20 ng/ml each) or TNF-α (100 ng/ml), 3–5 d	FR-mAb (CH-11, IgM), 2 μg/ml, 3–5 d	Up-FR by treatment with KL plus GM-CSF ± TNF-α. No up-CD, but reduction in hematopoietic potential by treatment with TNF-α alone.	[238]
hu, Kidney cancer (OUR-10)	f-FR and f-CD (Pre), IFN-α (nd) or IL-2 (nd), 24 h	FR-mAb (CH-11, IgM), 330 ng/ml, 48 h	Insignificant up-FR or up-CD by treatment with IFN-α or IL-2 alone.	[183]
hu, Thyrocytes (normal thyroid gland)	f-FR and f-CD (Pre), IL-1β (10 U/ml) and/or boTSH (0.1–20 mU/ml), 24–72 h	FR-mAb (nd, IgM), 1000 ng/ml, 18 h	Tm-dep, ds-dep dn-reg of FR by treatment with TSH alone. Up-FR and up-CD by IL-1β treatment, associated with significant inhibition by coexistence of TSH.	[266]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Thyroid gland epithelium (GD patients)	f-FR and f-CD (Pre), IL-1β (10 U/ml) ± [healthy donors', GD patients' or IME patients' IgG (5mg/ml) or boTSH (5 mU/ml)], 48 h	FR-mAb (nd, IgM), 1000 ng/ml, 18 h	Up-FR and up-CD by IL-1β treatment, associated with significant inhibition by coexistence of GD patients' IgG or TSH, but not of healthy donors' or IME patients' IgG.	[205]
hu, Osteosarcoma (HOS/TE-85, MG-63, Saos-2)	f-FR, TNF-α (250–500 U/ml), 24–48 h	None	Significant up-FR by treatment with TNF-α alone, associated with much weaker up-reg of soluble FR.	[190]
hu, Bone marrow (mononuclear, $CD34^+$) (posterior iliac crest of healthy volunteers)	f-FR, f-CD (Pre, colony formation) TNF-α (2–20 ng/ml), 48 h (f-FR); 24 h (f-CD)	FR-mAb (CH-11, IgM), 1 μg/ml, 24 h	Ds-dep up-FR and marked up-CD by TNF-α treatment, without significant change in TNFR-I and -II expression.	[224]
hu, Brain glioma (LN-229, LN-308, T-98G)	f-FR and f-CD (Pre), IFN-α (100–2500 U/ml), 48 h	muFL-N2A, 125-250 U/ml (1 U: half-maximal CD activity against LN-18 cell line), 24 h	No modulation of FR, but ds-dep significant up-CD, unaffected by ectopic expression of Bcl-2 or FR.	[284]
hu, Blood eosinophils (peripheral blood of normal healthy volunteers)	f-FR and f-CD (Pre), TNF-α (1–100 ng/ml), IL-3, IL-5 or GM-CSF (10 ng/ml each), 2–24 h	sFL in 293T cells (transfected with FL expression vector) supernatant, equal volume, 12 h	Small up-FR by TNF-α treatment alone. No up-reg of FR mRNA, but augmentation of early apoptosis by treatment with IL-3, IL-5 or GM-CSF.	[232]
mu, Ovary granulosa (pregnant mare serum gonadotropin treated)	f-FR and f-CD (Pre or Pre plus Co), TNF-α or muTNF-α (10 ng/ml), 24 h (Pre) ± following 24 h (Co)	muFR-Ab (Jo2, IgG2), 2 μg/ml, 24 h ± CHX, 0.5 mg/ml, 2 h preceded	Up-reg of FR mRNA by muTNF-α treatment, but not by huTNF-α treatment. Insignificant up-CD by Pre with muTNF-α alone.	[248]
mu, Central nervous system microglia (primary, BV-2)	f-FR and f-CD (Pre), muTNF-α (0.01–100 ng/ml), 24–48 h	muFL-N2A, 20% (v/v), 20 h	Up-FR and ds-dep up-CD by treatment with TNF-α alone, associated with marked dn-reg of Bcl-X_L expression and up-reg of FLIP mRNA.	[256]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Multiple myeloma (IL-6 dependent: U-266-1970, U-1958; IL-6-independent: U-266-1984)	f-FR and f-CD (Pre), IFN-α (1–1000 U/ml) ± IL-6 (20-100 U/ml), 96 h	FR-mAb (CH-11, IgM), 100 ng/ml, 24 h	Significant ds-dep up-CD by IFN-α treatment, irrespective of IL-6 dependency, without substantial change in FR.	[151]
hu, Colon cancer (HT-29), fibrosarcoma (U-3A, STAT-1 transfected U-3A)	f-FR, f-FL and f-CD (Pre), TNF-α (1000 U/ml), PDGF, EGF or FGF (20 ng/ml each), 3–48 h (f-FR and f-FL); 40 h (f-CD, Pre)	FR-mAb (CH-11, IgM), 500 ng/ml, 20 h	Up-FR by TNF-α or FGF, up-FL by TNF-α, and up-CD by TNF-α, PDGF, or EGF treatment in HT-29 cells, and No up-FR and no up-FL by TNF-α treatment, in U-3A or STAT-1 U-3A cells.	[124]
mu, Spleen ($CD4^+$) , (received in GVHD mice)	f-FR, *in vivo*: IL-12 (4900 IU at day 0, 2400 IU at days 3, 5 and 7 of BM transplantation by injection)	None	Up-FR in lethally irradiated GVHD mice after BM transplantation, by IL-12 treatment.	[285]
hu, Colon cancer (COLO-201)	f-FR, f-FL and f-CD (Co), TNF-α (0.01–0.3 μg/ml), 3–5 d (f-FR); 3 d (Co); 3–12 h (f-FL)	FR-mAb (nd, nd), 100 ng/ml, 3d	Up-FR and up-CD by TNF-α treatment alone in ds-dep, tm-dep manner, associated with dn-reg of Bcl-2 and up-reg of Bax expression.	[122]
hu, Melanoma (A-375, BLM, BS-1251, Colo-38, M-518, Me1Ju, Me1Juso, MeWo, SK-Mel-25, SK-Mel-28, W+)	f-CD (Co), IFN-α-2b (500 U/ml), 48 h	FR-mAb (7C11, IgM), 50 ng/ml, 48 h	Insignificant up-CD in any melanoma cell-line by treatment with IFN-α alone.	[187]
hu, Small intestinal epithelium (non-tumoral fatal crypt); colonic organ cultures	f-FR and f-CD (Co), TNF-α (1–100 ng/ml) or IL-1β (0.1–100 ng/ml), 24–48 h	FR-mAb (CH-11, IgM), 1–500 ng/ml, 24–48 h	Ds-dep significant up-FR in cell culture, slight up-FR in organ culture, and modest up-CD, by treatment with TNF-α alone, but not with IL-1β alone.	[273]
hu, Synovial (osteoarthritis patients' tissue)	f-FR and f-CD (Pre), TNF-α (5–10 ng/ml), 2–5 d	FR-mAb (CH-11, IgM), 1 μg/ml ± Z-IETD-FMK, Ac-DEVD-CHO or Ac-YVED-CHO, 5–500 μM, 24 h	Insignificant up-FR and tm-dep up-CD by TNF-α treatment, associated with inhibition by coexistence of casp-3, 8 inhibitors.	[286]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
mu, Pancreas islet ($RAG2^{-/-}$ NOD transgenic mice: wt and lpr-mut)	f-FR and f-CD (Co), muIL-1α or muIL-1β (10–100 U/ml each), 16 h-o/n	NOD mice-derived spleen $CD4^{+}$-CTL, E/T ratio: 10:1, o/n; muFR-mAb (Jo2, IgG2), 1 μg/ml plus ActD, 30 μg/ml, 16 h	Significant up-FR and up-CD by treatment with IL-1α, and less with IL-1β, in NOD mice islet cells possessing wt FR, but not in cells possessing lpr-mut FR.	[199]
mu, Kidney cancer (Renca)	f-FR and f-CD (Pre), muTNF-α (100 U ml), 3–24 h	muFR-mAb (Jo2, IgG2), 0.002–1 μg/ml plus mAb- crosslinking P815 cells, 1×10^5 cells/200 μl, 18 h	Some up-FR, but no up-CD, in the constitutively resistant cells by treatments with TNF-α alone.	[184]
hu, Peripheral blood eosinophils (normal non-atopic donors)	f-FR, TNF-α (1–100 ng/ml), 6–24 h	None	Small up-FR by treatment with TNF-α alone.	[233]
hu, Salivary duct epithelium (HSG)	f-FR and f-CD (Pre), TNF-α (1–100 U/ml), IL-1β, IL-2 (0.001–0.1 U/ml), IL-4 (3–30 U/ml) or GM-CSF (0.01–1 mg/ml), 6–48 h (f-FR); 24 h (f-CD, Pre)	FR-mAb (DX-2, IgG1), 500 ng/ml, 3 h	Ds-dep up-FR and up-CD by TNF-α treatment, but no significant up-FR by treatment with other cytokines.	[271]
hu, Brain oligodendrocyte (adult intractable epilepsy patients)	f-CD (Pre), TNF-α (100 U/ml), daily over 72 h	FR-mAb (nd, nd), 10 μg/ml, 24 h	Insignificant up-CD by Pre with TNF-α alone.	[207]
hu, Umbilical vein endothelial (HUVEC), vascular smooth (hVSMC) (internal mammary artery), leukemia (Jurkat E6-1)	f-FR and f-CD (Co), TNF-α (25 ng/ml), 24 h (f-FR); 48 h (f-CD, Co)	Ad-muFL, multiplicity of infection: 300, 48 h	Modest up-FR in HUVEC, but not in hVSMC and Jurkat cells, by TNF-α treatment. Modest up-CD in hVSMC, but no up-CD in HUVEC after Ad-muFL treatment	[153]
ra, Non-transformed gastric mucosal (RGM-1)	f-FR, muIL-1β (1 ng/ml), raIL-2 (20 U/ml), IL-8 (50 ng/ml) or TNF-α (300 U/ml), 2–24 h	None	Up-reg of FR mRNA by treatment with IL-1β or TNF-α, but not with other cytokines.	[287]
hu, Stomach cancer (Kato-III)	f-FR, TNF-α (40 ng/ml), 48 h	None	Significant up-FR by TNF-α treatment alone.	[194]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
mu, Testis seminiferous epithelium (Sertoli)	f-FR, f-FL and f-CD (Pre), muTNF-α (0.5–250 ng/ml), 24 h	muFL-N2A, E/T ratio: 1–10:1, 7 h	Ds-dep up-FR and up-CD by TNF-α treatment alone, associated with up-reg of soluble FR, and without up-reg of FL mRNA.	[252]
hu, Prostate cancer (LNCap)	f-FR, f-FL and f-CD (Co), TNF-α (0.4–40 ng/ml) ± TLCK (20-50 μM), 6–48 h ± Z-VAD (50 μM), 1 h preceded	FR-mAb (CH-11, IgM), 0.4–4 μg/ml ± γ-ray IR, 8–20 Gy, 20–24 h	Up-FR and ds-dep synergistic f-CD by TNF-α treatment combined with IR, associated with complete inhibition by coexistence of pan-casp inhibitor.	[288]
mu, Central nervous system microglia (primary, BV-2)	f-FR, f-CD (Pre), muTNF-α (10 ng/ml) ± TGF-β2, muIL-4 or muIL-10 (20 ng/ml), 24 h; TGF-β2 (0.02–100 ng/ml) 1–24 h	muFL-N2A, 0.5–20% (v/v), 1–24 h	Marked up-FR and up-CD by TNF-α treatment, associated with significant protection from CD by coexistence of TGF-β2 via up-reg of FLIP expression.	[257]
mu, Spleen T-lymphocyte (acute GVHD model by bone-marrow transplantation; donors: wt, lpr-mut, IFN-γ-kd mice)	f-FR and f-CD (Co), *in vivo*: muIL-18 (1 μg *i.p.* injection/d/mouse), each d at day -2 to 2 (day 0: transplantation day)	Endogenous FR-mediated CD inducer in recipient mouse	Up-FR and up-CD by IL-18 treatment, resulting protection from GVHD in wt donor, but not in functional FR-deficient donor and IFN-γ-kd donor.	[289]
hu, Salivary gland epithelium cells (non-neoplastic primary derived from SS patients and control individuals)	f-FR and f-FL, TNF-α, IFN-α (500 U/ml each) or IL-1β (5 ng/ml), 48 h	None	Significant up-FR and up-FL by treatment with TNF-α, but not with IFN-α, and dn-reg of FL with IL-1β.	[272]
mu, T-cell hybridoma (DO11.10); $CD8^{-/-}$ spleen (primary, $CD4^{+}$ 85%-enriched)	f-CD (Pre), TNF-α (1-100 ng/ml), 6 h	muFR-mAb (Jo2, IgG2), immobilized with 5 μg/ml of anti-goat Ab, 16 h; FLAG-tagged sFL (100 ng/ml) plus anti-FLAG mAb (2 μg/ml), 24 h	Ds-dep up-CD by TNF-α treatment in both types of cells without significant up-FR, accompanied by dn-reg of FLIP and up-reg of Bax mRNA expression.	[290]
hu, Peripheral blood activated T-lymphocyte (relapsing- remitting multiple sclerosis patients)	f-FR, *in vivo*: IFN-β-1a, 22 μg × 3/w, 44 μg × 3/w, 30 μg × 1/w or 2.5–6.5 y (mean: 4.8 y)	None	Insignificant change in FR and Bcl-2, and dn-reg of surviving, by long-term IFN-β treatment.	[291]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
bo, Ovary corpus luteum (midluteal stage of estrous cycle)	f-FR and f-CD (Pre plus Co), TNF-α (50 ng/ml), 24 h, (f-FR; f-CD, Pre) followed by 24 h (f-CD, Co)	sFL, 100 ng/ml, 24 h	Insignificant up-reg of FR mRNA and up-CD by treatment with TNF-α alone.	[244]
hu, Placenta trophoblast (A-3, HTR/8)	f-FR, f-FL and f-CD (Pre and Co), TNF-α, IL-6 or IL-10 (10 ng/ml each), 1–24 h (f-FR, f-FL); 24 h (f-CD)	FR-mAb (nd, nd), 20–500 ng/ml, 24 h	Tm-dep up-FR by TNF-α treatment. Proliferation by IL-6 treatment after FR-mAb stimulation. Ds-dep, tm-dep up-FL by IL-10 treatment, associated with up-reg of FLIP expression.	[250]
hu, Lung cancer (A-549)	f-FR and f-CD (Pre), IL-1β (50 pg/ml), 24 h	FR-mAb (CH-11, IgM), 10–100 ng/ml, 4–24 h	No up-FR and inhibition of CD by treatment with IL-1β alone.	[171]
hu, Normal intestine crypt epithelium (primary, colon and jejunum) (HIPEC)	f-FR and f-CD (Pre), TNF-α (10 ng/ml) or GM-CSF (20 ng/ml), 18–20 h	FR-mAb (CH-11, IgM), 100 ng/ml, 18–24 h	Insignificant up-FR and no up-CD of HIPEC cells by Pre with either TNF-α or GM-CSF alone, not due to absence of each receptor expression.	[132]
hu, Thyroid gland epithelium (primary, normal and multinodular goiter patients' thyroid tissues)	f-CD (Pre), TNF-α (50 ng/ml) and/or IL-1β (50 U/ml), 4 d	FR-mAb (CH-11, IgM), 1 μg/ml, 20 h	Up-CD in goitrous cells by Pre with TNF-α and/or IL-1β, in much less extent than normal cells.	[267]
hu, Acute myeloid leukemia (GM-CSF-dependent) (AML-193)	f-FR and f-CD (Co), IFN-α-2b (500 U/ml), 24–40 h, after pre-cultivation with GM-CSF (20 ng/ml), at least 2 w	FR-mAb (FAS18, IgG2a), 5 μg/ml, 24–40 h	No difference in FR and 2.5-fold median up-CD by IFN-α treatment in the absence of GM-CSF, associated with selective reduction of G1 cell-cycle state.	[156]
hu, Peritoneum mesothelial (effluents from peritoneal dialysis patients)	f-FR and f-CD (Pre), TNF-α (500–5000 U/ml), 24 h	sFL (aggregated), 10–100 ng/ml, 24 h	Insignificant up-FR and significant up-CD only by treatment with high conc of TNF-α.	[219]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Placenta villus trophoblasts and explanted tissues (woman with uncomplicated pregnancies)	f-FR, f-FL and f-CD (Co, explant tissues), TNF-α or IL-1β (0.1–50 ng/ml each), 24 h ± FR-Fc (2 ng/ml), 1 h preceded	Endogenous FR-mediated CD inducer in explanted tissues	No up-FL, insignificant up-FR and up-CD by treatment with either TNF-α or IL-1β, associated with inhibition by Pre with FR-Fc in the case of TNF-α treatment alone.	[251]
hu, Follicular dendritic cell-like (HK from 2 different donors' tonsils)	f-FR and f-CD (Pre), TNF-α (20 ng/ml), 24 h ± ALLN (20 μM), 30 m preceded	sFL containing culture supernatant of CHO-K1-sFL cells, 10% (v/v), ± CHX (2 μg/ml), 16 h	Up-FR and up-CD by TNF-α treatment, associated with up-reg of CD by coexistence of CHX as well as diminished up-FR by inclusion of NF-κB inhibitor.	[292]
hu, Hepatoma (HepG-2)	f-CD (Pre), IFN-α (5–100 kU/ml) ± ribavirin (250–100 μM), 24 h	FR-mAb (nd, nd), 0.25 μg/ml, 12 h	Ds-dep synergistic up-CD by combined Pre with IFN-α and ribavirin, accompanied by up-reg of casp-3, -7, -8 activation and PARP cleavage.	[293]
hu, Kidney mesangial (glomeruli from normal portion of renal tissue)	f-FL, IL-1β (20 ng/ml) ± lactacystin (20 μM), 24 h	None	Up-FL by treatment with IL-1β than that with IFN-γ, associated with strong NF-κB induction and complete inhibition with NF-κB blocker.	[254]
hu, Oligodendroglioma (HOG, MO-3.13)	f-FR, f-FL and f-CD (Pre), TNF-α (1–100 ng/ml), 24 h	sFL, 1 ng/ml, 48 h	Cl-dep significant up-FR and up-CD by treatment with TNF-α alone, associated with up-reg of MHC-I expression.	[165]
mu, Basophil precursor-enriched splenocytes (wt, depleted of mature cells, c-*kit*$^-$ fraction); Lymphocytic leukemia (L1210: non-transfected, FR-transfected)	f-FR and f-CD (Pre), *in vitro*: muIL-12 (10 ng/ml) and/or muIL-18 (100 ng/ml), 24 h; *in vivo*: muIL-12 (0.2 μg/mouse) plus muIL-18 (0.25 μg/mouse), single *i.v.* injection, 2 h	Splenocytes (total and NK1.1$^+$) cells, E/T ratio: 0.75–12 (*in vitro* Pre cells); 3–24 (*in vivo* Pre cells), 18 h	Up-FR in immature basophil precursor splenocytes, and up-reg of FR-mediated-CD via splenocytes in leukemia cells, by IL-12 and IL-18 treatment with synergistic effects.	[294]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Proximal lung epithelium [normal bronchus (NHBE), small airway (DLEC)]	f-FR and f-CD (Pre and Co), TNF-α or IL-1β (10 ng/ml each), 18 h	sFL, 25–500 ng/ml, 18h (Pre); last 16 h (Co)	No up- FR in both types of cells by either cytokine. Up-CD in NHBE by Pre with TNF-α or IL-1β, but in DLEC only by Pre with IL-1β.	[277]
mu, Brain cortical astrocytes (primary) (1 to 2 d old mice)	f-CD (Pre), muTNF-α (10 ng/ml) and/or muIL-1β (10 ng/ml) ± SB203580 or SB202190 (0.1–4 μM each), 0.5–24 h	muFR-mAb (Jo2, IgG2), 1–10^4 μg/ml, 24 h	Up-CD in resistant cells by synergistic Pre with TNF-α and IL-1β, associated with ds-dep inhibition of CD by coexistence of p38 mitogen activated protein kinase inhibitor.	[258]
hu, Colon cancer (HT-29, DLD-1); leukemia (THP-1, Jurkat)	f-CD (Pre plus Co), TNF-α (100 pM), 1–7 d (Pre), followed by 24 h (Co)	FR-mAb (APO-1-3, IgG3), 180 pM or sFL, 3.1 nM, 24 h	Up-CD in HT-29 cells, but not in DLD-1, THP-1 or Jurkat cells, by o/n Pre with TNF-α, associated with decrease in CD response by prolonged Pre.	[138]
hu, T-lymphocyte (naïve $CD4^+$ from neonates)	f-FR and f-CD (Pre), IFN-α2 (1 nM), 20 h ± additional 48–72 h	FR-mAb (CH-11, IgM), 50 ng/ml, 16 h	Significant up-FR, and up-CD, as judged by casp-3, -8 activation, by Pre with IFN-α, associated with up-reg of Bcl-2 expression and dn-reg of active Bax expression.	[295]
hu, Renal cell cancer (SK-RC-44, SK-RC-07)	f-FR and f-CD (Pre plus Co), IFN-α (300–3000 U/ml) ± G3139 (300 nM), 48 h (f-FR and f-CD, Pre) plus 24 h (f-CD, Co)	FR-mAb (CH-11, IgM), 12.5–100 ng/ml, 8–24 h ± antagonistic FR-mAb (ZB4, IgG1), 1 μg/ml, 1 h preceded	Significant up-FR and up-CD by Pre with IFN-α, associated with enhancement by coexistence of Bcl-2 AS-ODN, but abolition by Pre with antagonistic mAb.	[296]
hu, Multiple myeloma (U-266-1970, U-1958; both IL-6 dependent; primary, BM from newly diagnosed or relapsed MM patients)	f-FR, F-FL and f-CD (Pre), IL-6 (20 U/mL) ± IFN-α-2b (1000 U/ml), 0.5–96 h	FR-mAb (CH-11, IgM), 100 ng/ml, 6–24 h	Up-FR and up-CD by IFN-α treatment, associated with enhancement of STAT-1 activation, but attenuation of STAT-3 activation.	[157]
mu, Bone marrow osteoclast progenitor (RAW-264.7); differentiated osteoclast (from RAW-264.7)	f-FR and f-CD (Pre), RANKL (1.1–3.3 nM) plus M-CSF (10 ng/ml), 6 d	muFR-mAb (Jo2, IgG2), 1 μg/ml, 24 h	Ds-dep, tm-dep up-reg of FR and CD in osteoclast progenitor, and ds-dep dn-reg of FR and CD in differentiated osteoclast, by treatment with RANKL	[297]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Follicular dendritic cell-like (HK)	f-FR and f-CD (Pre), TNF-α (20 ng/ml) and/or TGF-β1 (10 ng/ml); IL-4 (20 ng/ml), GM-CSF (50 ng/ml) or LT-α (10 ng/ml), 6–48 h	sFL in culture supernatant of CHO-K1-sFL cells, 10% (v/v) plus CHX, 2 mg/ml, 18 h	Significant up-FR and up-CD by Pre with TNF-α, associated with tm-dep counteraction and dn-reg of casp-8 expression by coexistence of TGF-β.	[298]
hu, Synovial fibroblasts (RA-SF, synovial tissues from rheumatoid arthritis patients)	f-FR and f-CD (Pre), TNF-α (10–100 ng/ml) ± [Ad-TIMP-3 transduction (100–1000 pfu) or TIMP-3 (10–1000 ng/ml)], 24 h	sFL, 100 ng/ml, 16 h	Up-FR and ds-dep up-CD in Ad-TIMP-3 transduced cells, but not in cells co-treated with exogenous TIMP-3, by TNF-α treatment.	[299]
hu, Multiple myeloma (U-266-1970, IL-6 dependent)	f-CD (Pre), IFN-α (1000 U/ml) plus IL-6 (20 U/mL), 24 h	FR-mAb (CH-11, IgM), 100 ng/ml, 24 h	Up-CD by Pre with IFN-α, associated with reduction of telomerase activity repressed at mRNA level.	[300]
mu, Small intestine epithelium (immortalized by SV-40 large T-gene transfection) (MODE-K, IEC-4.1)	f-FR and f-CD (Pre), TNF-α (2–10 ng/ml) or IL-10 (5–50 ng/ml), 24 h	muFR-mAb (Jo2, IgG2), 1 μg/ml, 24–48 h	Significant up-FR and up-CD by treatment with TNF-α alone, but dn-reg of CD by Pre with IL-10 alone.	[274]
hu, Prostate cancer (PC-3)	f-FR and f-CD (Pre), TNF-α (1–100 U/ml) ± sTNF-RI (0.3 μg/ml), 12–24 h	FR-mAb (CH-11, IgM), 30 ng/ml, 12 h	Dn-reg of FR and CD by TNF-α treatment, associated with partial reversal by co-existence of sTNF-RI.	[301]
hu, Skin pre-adipocyte and adipocyte (primary, SGBS patients)	f-FR and f-CD (Co), TNF-α (10 nM), 6–72 h	FR-mAb (nd, IgG3), 1 μg/ml, 6–72 h	Tm-dep up-FR and up-CD by treatment with TNF-α alone, associated with increased DISC formation.	[211]
mu, Liver hepatocytes (primary from wt and *Bim*-deficient mice)	f-CD (Pre), TRAIL (30 ng/ml), nd	muFL-N2A, E/T ratio: 10–90:1, nd; Fc-sFL, 0.15–5 ng/ml, nd	Up-CD by TRAIL treatment, associated with activation of JNK and Bim.	[302]
hu, Lung fibroblast (fetal, MRC-5; primary, undifferentiated from normal lung tissue), myofibroblast (both, differentiated with TGF-β)	f-FR and f-CD (Pre), TNF-α (0.01–20 ng/ml), 36–48 h	FR-mAb (CH-11, IgM), 250 ng/ml, 4–12 h	Up-FR and ds-dep up-CD, irrespective of differentiation state, by treatment with TNF-α alone, associated with efficient DISC formation.	[279]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
wc, Hepatocytes (WCM-260)	f-FL, wcTNF-α (35 U/ml), 18 h	None	Insignificant up-FL mRNA, but associated with increased MHC-I expression, by Pre with TNF-α.	[158]
mu, Colon cancer (C-15-4.3: MC-38 transfected with hu CEA gene)	f-FR, muTNF-α (250 U/ml), o/n	None	Significant up-FR by treatment with TNF-α alone.	[142]
mu, Soft tissue sarcoma (CMS-4: parental; transfectant with empty-control, K79E-mut or R289E-mut IRF-8 gene)	f-CD (Pre), TNF-α (100 U/ml), o/n	sFL, 200 ng/ml, 24 h	Up-CD by TNF-α treatment alone in wt IRF-8 expressing cells, associated with significant inhibition by oe of functionally-impaired mut IRF-8.	[181]
hu, Eye subconjunctival Tenon fibroblast (biopsy specimen from glaucoma patients)	f-FR, IFN-α-2b (5000 U/ml), 48 h	None	Slight up-FR by IFN-α treatment alone, accompanied by up-reg of sensitivity to MMC-mediated CD.	[220]
hu, Uterus endometrial stroma (ESC: undifferentiated, decidualized) (benign hysterectomy tissue from pre-menopausal woman)	f-FR and f-CD (Pre), TNF-α (25 ng/ml) ± hCG (1 U/ml), 24–48 h	FR-mAb (CH-11, IgM), 100 ng/ml, 24 h	Small effect on both FR and CD by TNF-α treatment alone, without significant influence by coexistence of hCG.	[281]
hu, Periphral blood mononuclear [healthy donors, T-large-granular lymphocyte (LGL) patients]	f-CD (Pre), IL-2 (500 U/ml) ± anti-CD3 mAb (0.01–10 μg/ml), 24 h	FR-mAb (Apo-1, IgG3), 500–1000 ng/ml, 45 m-24 h	Up-CD only in LGL patients' cells, associated with enhancement of DISC formation, and up-reg c-FLIP$_{L/S}$ only in healthy donors' cells, by Pre with IL-2.	[303]
hu, Peripheral blood CD4$^+$ leukocyte [healthy donors (HD) and Sézary syndrome (SzS) patients]	f-FR and f-CD (Pre), IFN-α (100 U/ml), o/n	Super-FL, 100 ng/ml, 6–8 h	Significant up-FR and up-CD in either CD4$^+$ leukocytes from HD or SzS patients by IFN-α treatment.	[212]
hu, Melanoma (Hs-294T)	f-FR and f-CD (Pre), IFN-α-2b (1000 U/ml) ± EGCG (10 μg/ml), 48 h	FLAG-tagged sFL (50 ng/ml) plus anti-FLAG mAb (1 μg/ml), 16 h	Up-FR and up-CD by treatment with IFN-α ± EGCG, associated with marked decrease in NF-κB expression.	[304]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Cutaneous T-cell lymphoma (HH, SZ-4, MyLa, Hut-78); SzS blood tumor (SS1)	f-FR and f-CD (Pre), IFN-α (100 U/ml) ± MTX (10 μM), nd	FLAG-tagged sFL (50 ng/ml) plus anti-FLAG mAb (1 μg/ml), 16 h	Up-FR and up-CD by IFN-α treatment, associated with enhancement by coexistence of MTX.	[305]
mu, Bone marrow (tibiae and femurs of 8-w-old mice)	f-FR and f-FL, muTNF-α (100 ng/ml) plus M-CSF (100 ng/ml), 4 d	None	Up-FR in adherent cells, but no significant up-FL, irrespective of cell-adherence.	[227]
mu, Bone marrow mesenchymal stem (tibiae and femurs)	f-FR, TNF-α (20 ng/ml), 24 h	None	Insignificant up-FR and casp-3 activation by treatment with TNF-α alone.	[228]
mu, Hepatocyte (*in vitro*: primary from wt, $Bid^{-/-}$ mut, $XIAP^{-/-}$ mut, $FR^{-/-}$ mut, FL gld-mut; *in vivo*: wt mice of 8-12-w-old mice)	f-CD (Pre), *in vitro*: TNF-α (25 ng/ml), 0.2–48 h ± SP600125 (25 μM), preceded ± Bim siRNA treatment (10 nM); *in vivo*: TNF-α (40 μg/kg), 2 h	*in vitro*: muFL-N2A, 50 ng/ml, 6 h; *in vivo*: muFR-mAb (Jo2, IgG2), 80 μg/kg, 5 h	Tm-dep significant up-CD, both *in vitro* and *in vivo*, by TNF-α treatment, associated with abolition by loss of FR or Bid, but not of XIAP or mut of FL, and with suppression by Pre with JNK inhibitor or Bim siRNA.	[306]
hu, Melanoma (wt p53: D05, A375: both parent and transfected with DN-FADD gene; mut p53: D14)	f-CD (Pre plus Co), IFN-β-1a (300 U/ml), 24 h (Pre) ± TMZ (50 μM), 72 h (Pre) plus 24 h (Co) followed	FR-mAb (APO-1-3, IgG3), 25 ng/ml plus Protein A, 25 ng/ml, 24 h	Up-CD, irrespective of p53 state, by Pre with IFN-β, associated with enhancement by TMZ treatment and reduction by DN-FADD transfection.	[307]
hu, Peripheral blood T-lymphocyte ($CD4^+$, $CD8^+$) (healthy donors, at least 1 y HIV-I positive patients)	f-FR and f-CD (Pre), IFN-α or IFN-β (1000 U/ml each) plus plate-bound anti-CD3 mAb (OKT-3, IgG2a) (0.1 μg/ml), 3 d	Plate-bound FR-mAb (CH-11, IgM), 5 μg/ml, 14 h	Up-FR and up-CD in healthy donors' cells and up-CD in HIV patients' cells by treatment with type-I IFNs, associated with up-reg of Bak expression alone among many Bcl-2 family members.	[308]
hu, Eye conjunctiva epithelium (IOBA-NHC) (normal, spontaneously immortalized)	f-FR and f-FL, TNF-α (25 ng/ml), 24–48 h	None	Insignificant up-FR or up-FL by treatment with TNF-α alone.	[276]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Epidermal keratinocyte (HEK) (primary from normal neonatal foreskin)	f-FL, TNF-α (75 ng/ml) and/or IL-1β (500 pg/ml), 24–72 h	None	Significant up-reg of FL mRNA by treatment with TNF-α and/or IL-1β, associated with modest up-reg of NO production.	[261]
hu, Blood monocytes, Mϕ (buffy coats of healthy donors)	f-FR, [IL-4 (20 ng/ml) or IL-17 (100 ng/ml)] ± IL-10 (50 ng/ml) ± DEX (100 nM), 3 d (for monocytes); 8 d (for Mϕ, IL-10 and DEX added on day 5)	None	Up-FR by treatment with IL-10, but not with IL-4 or IL-17, associated with significant augmentation by coexistence of DEX and inverse correlation between FR and MerTK.	[234]
mu, Hepatocyte (primary from wt, $Bid^{-/-}$ mut, $Bim^{-/-}$ mut, or $XIAP^{-/-}$ mut 8-14-w-old mice)	f-CD (Pre), IL-1β (1–20 ng/ml) or TNF-α (25 ng/ml), 12–24 h ± Q-VD-Oph (25 μM), 30 m preceded	muSFL-N2A, 50 ng/ml, 6 h	Protection from CD by Pre with IL-1β, without influence from deficiency in Bid or Bim, associated with further dn-reg of CD by coexistence of pan-casp inhibitor.	[309]
hu, Auricular chondrocytes (remnant cartridge of microtia patients)	f-FL mRNA, G-CSF, IL-6, IP-10, KC, MIP-1α, -1β, -2 (0.1–10 × ED_{50} each), ± AG490 (nd), 5 d	None	Enhanced FL mRNA by G-CSF, IL-6, KC, MIP-1α /-1β treatment, associated with dn-reg by coexistence of JAK-2 inhibitor.	[161]
hu, Kidney cortex / proximal tubule epithelium (HK-2) (transformed with HPV-16)	f-CD (Co), TNF-α (25 ng/ml) or TGF-β1 (1 ng/ml), 48 h	FR-mAb (CH-11, IgM), 0.5 μg/ml, 48 h	No up-CD by Co with either TNF-α or TGF-β1 alone.	[186]
mu, Small intestine lamina propria $CD4^+$ T-lymphocytes (naïve and peanuts-derived allergen sensitized 6-8-w-old mice)	f-FL, IL-18 (100 ng/ml) ± anti-CD3/CD24 mAb (2 μg/ml) ± anti-IFN-γ mAb (200 ng/ml), 3 d	None	Insignificant up-FL by treatment with IL-18 alone in both types of cells, but associated with increase in FL by coexistence of anti-CD3 / CD24 mAb and its complete reversal with anti-IFN-γ mAb.	[240]

Continued on next page

Target cells: species, cell type (cell line/origin)	Sensitization method: type (mode), sensitizer (conc), treatment time	Cell-death induction method: inducer (name, subclass), conc, treatment time	Main findings related to sensitization of cell-death induction via Fas signaling system	Refs.
hu, Neuroblastoma [MYCN amplified: LAI-5S, SK-N-BE (2), IMR-32, Tet-21-N; MYCN non-amplified: SK-N-AS, SK-N-SH, CHLA-90, SH-SY5Y]	f-FR and f-CD (Pre and Co), TNF-α (100 ng/ml), 0.5–24 h ± prior treatment with BAY11-7082 (10-25 μM)	Fc-sFL, 1–100 ng/ml, 24 h	Cl-dep, tm-dep up-FR and up-CD by TNF-α treatment, associated with full abrogation of up-FR by coexistence of NF-κB inhibitor and positive correlation of up-CD with up-FR.	[54]
hu, Uterus immortalized endometrial stromal (St-T1: wt, Sdc-1-kd: both non-differentiated, decidualized)	f-CD (Pre), IL-1β (10 ng/ml), TNF-α (5 ng/ml) or TGF-β1 (0.5 ng/ml), 24 h	FR-mAb (EOS9.1, IgM), 5 μg/ml, 24 h	Greater up-CD in Sdc-1-kd-cells than wt cells, irrespective of differentiation state, by treatment with individual cytokine alone .	[282]
hu, Blood basophils (venous EDTA-blood of healthy non-selected donors)	f-CD (Pre), IFN-α (1000 U/ml) and/or IL-3 (50 ng/ml), 24–48 h	Super-FL, 5–100 ng/ml, 24 h	Insignificant up-CD by Pre with IFN-α, associated with enhanced Bcl-2 cleavage and protection from CD by coexistence of IL-3	[235]
mu, Bone marrow mesenchymal stem (bone cavity of tibiae and femurs of pathogen-free mice)	f-FR, IL-17 (200 ng/ml), 24–72 h	None	Tm-dep small up-reg of FR mRNA by treatment with IL-17 alone.	[230]
mu, hepatoma (Hepa-1-6, 3T3); hepatocytes (primary from 14-w-old mice, AML-12); embryo fibroblasts (3T3); hu, Hepatoma (HepG-2)	f-FR and f-CD (Pre), *in vitro*: TNF-α (20 ng/ml), 2–14 h; *in vivo*: TNF-α (200 μg/kg), 14 h; either ± NF-κB p65-subunit shRNA treatment	Fc-sFL, 20 ng/ml, 1–5 h	Marked up-FR and up-CD in all types of cells except HepG-2 by either *in vitro* or *in vivo* treatment with TNF-α, associated with inhibition by NF-κB p65-subunit shRNA treatment.	[310]
mu, Mesenchymal stem / stromal (tibia and femur bone marrow from iNOS-deficient mice)	f-CD (Co), TNF-α (10 ng/ml) plus SNAP (20 μM), 48 h	muFR-mAb (Jo2, IgG2), nd, 48 h	Insignificant up-CD in iNOS-deficient cells by treatment with TNF-α alone, in the presence of NO donor.	[231]

Annotations on the abbreviated words and the substance names used in Tables 1-3:

***Fas ligand and Fas receptor-related derivatives*: Ad-muFL**: adenovirus vector expressing mouse FL; **Fc-sFL**: an agonistic fusion protein of sFL with IgG-Fc domain; **FL**: Fas ligand; **FR**: Fas receptor; **FR-Fc**: a fusion protein of FR extracellular domain with IgG-Fc domain; **FR-mAb**: Anti-Fas receptor extracellular-domain monoclonal antibody; **sFL**: soluble FL extracellular-domain; **mFL**: cell-surface membrane-bound FL; **muFL-N2A**: soluble mouse FL-containing supernatant of neuroblastoma N2A cells; **super-FL**: sFL fused with an activity-enhancing peptide-tag.

Species, treatment conditions and effects: **bo**: bovine; **CD**: cell death / apoptosis; **f-CD**: for CD induction; **cfu**: colony forming unit; **cl-dep**: cell-line dependent; **Co**: cotreatment; **d**: day(s); **conc**: concentration; **dn-reg**: down-regulation; **ds-dep**: dose-dependent; **eq**: equine; **f-FR**: for cell-surface FR expression (protein, mRNA); **f-FL**: for cell-surface FL expression (protein, mRNA); **h**: hour(s); **E/T ratio**: effector to target cell ratio; **hu**: human (omitted from protein names of human origin); **i.p.**: intraperitoneal: **i.v.**: intravenous; **kd**: knockdown; **m**: minute(s); **moi**: multiplicity of infection; **mu**: murine; **mut**: mutant; **nd**: not described; **oe**: over-expression; **o/n**: overnight; **Pre**: pretreatment; **ra**: rat; **tm-dep**: time-dependent; **up-FR**: up-reg of surface FR expression in the target cells; **up-FL**: up-reg of sFL / mFL; **up-CD**: up-reg of FR mediated CD-induction; **up-reg**: up-regulation; **w**: week(s); **wc**: woodchuck; **wt**: wild type.

Others: **ActD**: actinomycin D; **Ad**: adenovirus; **ADM / ADR**: adriamycin; **AG490**: a JAK 2/3 inhibitor; **Akt**: protein kinase B; **ALL**: acute lymphocytic leukemia; **ALLN**: *N*-acetyl-L-leucyl-L-leucyl-L-norleucinal; **ALS**: amyotrophic lateral sclerosis; **ApoL6**: human apolipoprotein L6; **ARC**: arabinocytosine; **aSMase**: acid sphingomyelinase; **AS-ODN**: antisense-oligodeoxyribonuclotide; **AT**: all-*trans* retinoic acid; **AT-101**: an inhibitor of Mcl-1; **A20**: TNF-α-induced protein 3; **Bad**: Bcl-2 associated agonist of cell death protein; **Bak**: Bcl-2 homologous antagonist / killer protein; **Bax**: Bcl-2-like protein 4; **BAY11-7082**: an NF-κB inhibitor; **Bcl-2**: oncogene B-cell lymphoma 2; **Bcl-$X_{L/S}$**: B-cell lymphoma extra-large / -small protein; **BFA**: brefeldin A; **BHA**: butylated hydroxyanisole; **Bid**: Bcl-2 homology domain 3 interacting-domain death agonist; **Bim**: Bcl-2 like protein 11; **BM**: bone marrow; **casp**: caspase(s); **CBDCA**: carboplatin; **CDDP**: cisplatin; **CEA**: carcinoembryonic antigen; **C/EBP**: CCAAT/enhancer binding protein; **cFLIP**: cellular FLICE inhibitory protein; **CHOP**: C/EBP transcription factor homologous protein; **CHX**: cycloheximide; **CIAP**: cellular inhibitor of apoptosis protein; **c-Jun**: an oncogenic transcription factor; **CMA**: concanamycin A; **COX**: cyclooxygenase; **CPT**: camptothecin; **CPT-11 / CPT-83 / topotecan**: analogs of CPT; **CsA**: cyclosporine A; **CTL**: cytotoxic T-lymphocyte cells; **CXCL10**: C-X-C motif chemokine 10; **-D-CHO**: - L-aspart-1-al; **DcR3**: decoy receptor 3; **DEX**: dexamethasone; **DISC**: death-inducing signaling complex; **DN**: dominant negative; **DNR**: daunorubicin; **DOX / DXR**: doxorubicin; **dThd**: thymidine; **DTX**: diphtheria toxin: **eCG**: equine chorionic gonadotropin; **EGCG**: (-)-epigallocatechin-3-gallate; **EGF**: epidermal growth factor; **EI**: elastase inhibitor; **ErbB-2**: human epidermal growth factor receptor; **ERK**: extracellular signal-regulated kinase; **FADD**: Fas-associated death domain; **FGF**: fibroblast growth factor; **FLAG**: DYKDDDDK peptide sequence; **FLICE**: FADD-like IL-1β-converting enzyme / procaspase-8; **FLIP-$_{L/S}$**: long / short form FLIP protein; **Flt-3 L**: Fms-related kinase 3 ligand; **FMK**: fluoromethyl ketone; **GD**: Graves' disease; **gld**: generalized lymphoproliferative disease; **GM-CSF**: granulocyte Mϕ colony-stimulating factor; **Goe6983**: a protein kinase C inhibitor; **GVHD**: graft-versus-host diseases; **G3139**: a phosphorothioate, Bcl-2-targeting AS-ODN; **hCG**: human chorionic gonadotropin; **HLA**: human leukocyte antigen; ***H. p.***: *Helicobacter pylori*; **HIV**: human immunodeficiency virus; **HPV**: human papilloma virus; **hTERT**: human telomerase reverse transcriptase; **ICAM**: intercellular adhesion molecule; **ICE**: interleukin-1 converting enzyme; **IDO**: indoleamine 2,3-dioxygenase; **IFN**: interferon; **IFN-γR**: INF-γ receptor; **IGF**: insulin-like growth factor; **IκB-α**: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor-alpha; **IL**: interleukin; **IME**: idiopathic myxoedema; **iNOS**: inducible nitric oxide synthase; **IP-10**: IFN-γ-inducible protein-10; **IR**: ionizing radiation; **IRF**: IFN regulatory factor; **JAK**: Janus kinase; **JNK**: c-Jun N-terminal kinase; **KC**: keratinocyte-derived chemokine; **KL**: kit ligand / SCF; **KL cells**: Kit^+Lin^- cells; **KSL cells**: $c\text{-}Kit^+Sca1^+Lin^-$ cells; **LAK**: lymphokine activated killer cells; **Let-7**: a microRNA considered important in development and cancer; **LPA**: lysophosphatidic acid; **lpr**: lymphoproliferation; **LPS**: lipopolysaccharide; **LSEC**: liver sinusoidal endothelial cells; **LT**: lymphotoxin; **LV**: leucovorin; **LY294002**: a phosphatidylinositol 3 kinase inhibitor; **Mϕ**: macrophage cells; **MAPK**: mitogen-activated protein kinase; **MCD**: methyl β-cyclodextrin; **Mcl-1**: an anti-apoptotic Bcl-2 family protein; **MCP**: monocyte chemoattractant protein; **M-CSF**: Mϕ colony stimulating factor; **MerTK**: Mer receptor tyrosine kinase; **MG132**: a proteasome inhibitor Z-L-leucyl-L-leucyl-L-leucinal; **MHC**: major histocompatibility complex; **MIP**: Mϕ inflammatory protein; **MM**: multiple myeloma; **MMC**: mitomycin C; **MPL**: malignant pleural lymphocytes; **MTE**: *Marsdenia*

tenacissima extract; **MTX**: methotrexate; **Myc (incl. c-Myc, n-Myc / MYCN)**: a family of oncogenic transcription factors; **NEC**: an RIPK-1 inhibitor necrostatin-1; **NF-κB**: nuclear factor-kappa B; **NMA**: γ-*N*-methyl-L-arginine; **NO**: nitric monoxide; **NOD**: non-obese diabetic; **OVA**: chicken egg-white ovalbumin; **P_4**: progesterone; **p21**: a cyclin-dependent kinase inhibitor involved in p53-dependent cell cycle arrest; **p53**: a tumor suppressor transcription factor involved in apoptosis induction; **p73**: a p53-resembled tumor suppressor involved in cell cycle regulation; **PARP**: poly (ADP-ribose) polymerase; **PBL**: peripheral blood leukocyte cells; **PDGF**: platelet-derived growth factor; **PFT-α**: a p53 inhibitor pifithrin-α; **$PGF_{2\alpha}$**: prostaglandin 2α; **PI3K**: phosphatidylinositol-3 kinase; **PKR**: double-strand RNA-dependent protein kinase; **PMA**: phorbol 12-myristate 13-acetate; **PRL**: prolactin; **PSME**: activator subunits of immune-proteasome; **Q-VD-Oph**: a pan-casp inhibitor; **RAG2**: recombination activating gene 2; **RANKL**: receptor activator of NF-κB ligand; **RelA**: NF-κB p65 subunit A; **RIPK-1**: receptor interacting protein 1 kinase; **Ro52**: an antigen found in various autoimmune diseases including Sjögren's syndrome and systemic lupus erythematosus; **ROS**: reactive oxygen species; **SAPK**: stress-activated protein kinase; **SB203580 / SB202190**: a p38 mitogen activated protein kinase inhibitor; **SCF**: stem cell factor; **Sdc**: syndecan; **SGBS**: Simpson-Golabi-Behmel syndrome; **shRNA**: short hairpin RNA; **siRNA**: small interfering RNA; **SMA**: smooth muscle actin; **SNAP**: *S*-nitroso-*N*-acetyl-penicillamine; **SOCS**: suppressor of cytokine signaling; **SP600125**: a JNK inhibitor; **SS**: Sjögren's syndrome; **SSCC**: site-specific chemical conjugate; **SSP**: staurosporine; **STAT**: signal transducer and activator of transcription; **sTNF-RI**: soluble extracellular domain of TNF receptor-I, **SzS**: Sézary syndrome; **TGF**: transforming growth factor; **TIL**: tumor infiltrated cells; **TIMP-3**: tissue inhibitor of metalloproteinases-3; **TLCK**: tosyl lysine chloromethyl ketone; **TMZ**: temozolomide; **TNF**: tumor necrosis factor; **TPCK**: tosyl phenylalanine chloromethyl ketone; **TRAIL**: TNF related apoptosis-inducing ligand; **TR1**: thioredoxin reductase; **TSA**: trichostatin A; **TSH**: thyroid gland stimulating hormone; **U0126**: a p44/p42 MAPK / ERK kinase inhibitor; **VCR**: vincristine; **VES**: vesnarinone; **W1400**: an iNOS inhibitor; **XIAP**: X-linked inhibitor of apoptosis protein; **Z-**: benzyloxycarbonyl-; **ZD9331**: a thymidylate synthase inhibitor; **Z-VAD-fmk**: a pan-caspase inhibitor;**1MT**: 1-methyl-L-tryptophan; **3H1**: an anti-idiotype mAb which mimics a specific epitope of CEA; **5dAzaC**: 5-aza-2'-deoxycytidine; **5FU**: 5-fluorouracil.

5. Conclusions and perspectives

The present survey clarified that many non-cytokines represented by clinical anticancer drugs and cytokines such as interferon-γ are effective in sensitizing the death of a wide range of target cells through FasR-mediated signaling, as the exogenous agents. The cell-death induction via death receptors such as FasR has been repeatedly suggested to become a possible alternative strategy to the conventional chemo- and radio-therapies for the treatment of various tumors [317,318]. An artificially planned implementation of the death of a wide range of target cells, including various types of malignant tumor cells, could be attained by treatments with soluble cell-death inducers. Soluble FasL and agonistic FasR-mAb are the promising candidates for this purpose. However, despite of their great potentials, the development of the treatment strategy using these agonistic proteins in clinical medicine remains still on the way. There are two important problems that have to be overcome for making these proteins more powerful as the cytotoxic pharmaceuticals. One is the impaired cell-death inducing activity as compared to the natural mFasL protein, existing on the surface of immune cells. Hence, the development of effective sensitization methods is essential for the efficient cell-death induction using the soluble agonists. Once effectively potentiated with any appropriate method, the lesser cell-death inducing activity of the soluble agonists can turn out to be a merit, since this property is beneficial for the avoidance of unwanted, potential adverse effects, which might be caused by the too strong action of membrane-bound agonists. Also, the treatment with soluble agonists is in principle free of the possible problems derived from the cell-killing processes through the direct contact between the immune cells and the target cells, represented by tumor cells' counter-attack against infiltrating lymphocytes [319]. Moreover, soluble proteins will be manufactured in a large amount much more easily at reasonable costs, as compared with either water-insoluble membrane proteins or delicate immune cells, since the former is generally more stable and easier to handle than the latter.

As also suggested from the literature survey conducted in this study, it is obviously important to pay attentions to the possible induction of toxicity caused by the death of the cells constituting normal or non-targeted organs, particularly the liver [108,320], which may be substantially augmented by the exogenous agents. The toxicity induction can raise a serious problem, especially in the cases that we plan to apply the soluble FasR-agonists for the systemic, therapeutic treatments depending on the selective death execution against malignant cells in the future. Nevertheless, it is fair to speculate that the greater activity of mFasL in the surface membrane of the immune cells as compared to sFasL at least partly derives from the coexistence of other molecules, which specifically recognizes the target cells. Hence, it is reasonable to expect that the increase in the specificity of the soluble FasR agonists to the target cells using protein-engineering technologies will significantly contribute to the reduction of this unwanted adverse effect. Further, at present, it is still difficult to draw a complete mechanistic picture of each experimental result in all the studies surveyed in this paper, however the basic researches striving for the understanding of detailed mechanisms would also continue to shed useful, informative lights on the solution of critical problems in the practical applications. The specific issues, which have already been investigated, include the connection of the apoptosis system via extrinsic FasR-mediated pathway to that via intrinsic mitochondrial pathway involving Bid [321], the stimulation of FasR by singlet oxygen [322], the interaction of the activated Fas signaling system with the activation of NADPH oxidase [323,324], and also that with the enhancement of inducible nitric oxide synthase [325].

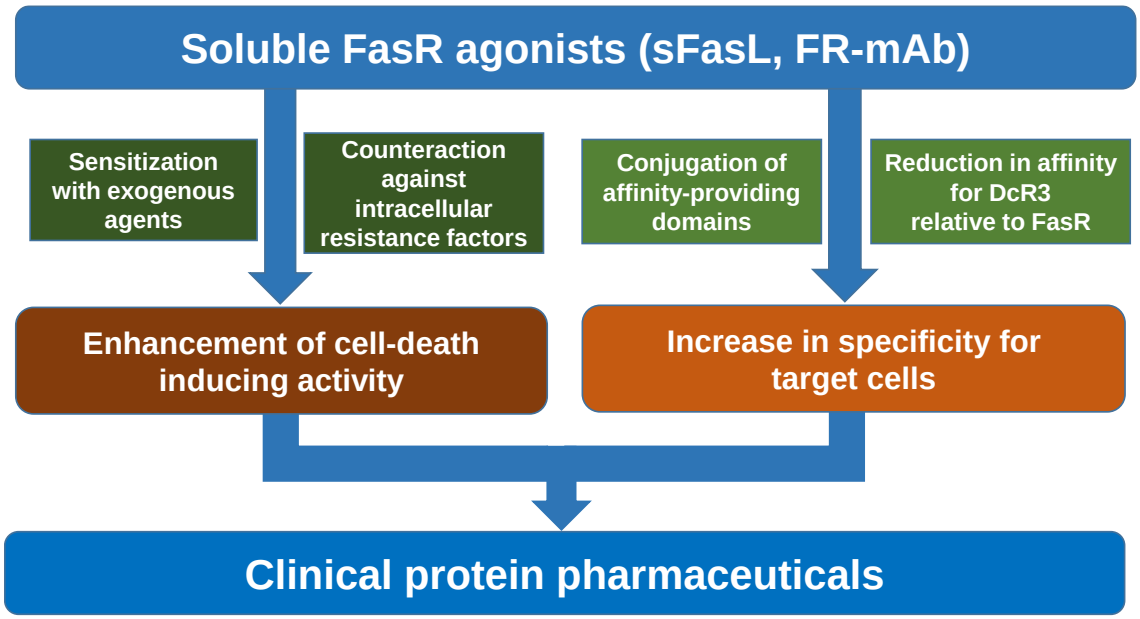

Figure 1. A strategy for translating soluble agonists at Fas receptor into clinical protein pharmaceuticals.

In Figure 1, a possible strategy for the translation of the soluble agonists at FasR into practical protein pharmaceuticals is shown. In addition to finding of the solution using the sensitization with exogenous agents, further in-depth characterization studies aimed at overcoming the resistance problems in the demanding targets, which are often mediated by intracellular anti-apoptotic factors represented by Bcl-2 and Bcl-X_L [326] as well as the functional modulation caused by post-translational modifications of FasR molecule [327], are also essential for the development of advanced strategies in the enhancement of cell-death induction. As shown in Tables 2 and 3, owing to the recent progress in the synthetic technology of oligonucleotides, multiple versatile tools to interfere with specific genes involved in the counteractions against the effective cell-death, such as AS-ODN [185,296], siRNA [179,203,217,218,228], and short hairpin RNA (shRNA) [182], have already been employed for the sensitization studies in combination with exogenous cytokine agents. However, at the moment, it seems that they have been mainly used as the evaluation aid for analytical purposes. Further technical advancements in the treatment efficacy would be required for safe clinical applications of these tools. Additional finding of the unexplored compounds including repositioning of the existing drugs may also significantly contribute to the effective sensitization in the future.

As mentioned above, apart from the enhancement of cell-death inducing activity, another critical problem to be solved with regard to the medical applications of sFasL or agonistic FR-mAb is the lack of specificity. Thus, multiple protein engineering techniques have been devised to empower the targeting ability by conjugations of affinity-providing domains, represented by single-chain antibody fragment, to date [5,25]. The coexistence of a decoy receptor can be a serious obstacle to efficient implementation of the death against the target cells. Thus, the achievement of affinity reduction for a decoy receptor, DcR3, relative to the genuine receptor, FasR, is an another important targetable issue worth to be tackled in finding the good solution, since FasR and DcR3 share a comparable affinity for sFasL to each other in spite of considerably weak homology (17%) in the primary structures [328,329]. The sensitization of cell-death induction using exogenous agents in combination with increase in the

targeting specificity using protein engineering techniques, which can be assisted by suitable preventions against the endogenous resistance in refractory cells using co-treatments with function-masking molecules, is proposed to be a valuable approach for improving the efficacy of the soluble agonistic proteins reviewed in this paper as the therapeutic substances. It is hoped that this strategy will ultimately contribute toward translating them into novel pharmaceuticals for curative treatments in clinical medicine.

Acknowledgements

This work was supported by a grant for operating expenses from the Ministry of Economy, Trade and Industry, Japan. The author thanks all of the members of National Institute of Advanced Industrial Science and Technology, Japan, especially Dr. Kiyonori Hirota, for their assistance in publishing this paper.

Conflict of interest

The author declares no conflict of interest in this paper.

References

1. Walczak H (2013) Death receptor-ligand systems in cancer, cell death, and inflammation. *Cold Spring Harb Perspect Biol* 5: a008698.
2. Calmon-Hamaty F, Audo R, Combe B, et al. (2015) Targeting the Fas/FasL system in rheumatoid arthritis therapy: promising or risky? *Cytokine* 75: 228–233.
3. Franke DDH, Yolcu ES, Alard P, et al. (2007) A novel multimeric form of FasL modulates the ability of diabetogenic T cells to mediate type 1 diabetes in an adoptive transfer model. *Mol Immunol* 44: 2884–2892.
4. Nagata S (1997) Apoptosis by death factor. *Cell* 88: 355–365.
5. Muraki M (2018) Development of expression systems for the production of recombinant human Fas ligand extracellular domain derivatives using *Pichia pastoris* and preparation of the conjugates by site-specific chemical modifications: A review. *AIMS Bioengineer* 5: 39–62.
6. Powell WC, Fingleton B, Wilson CL, et al. (1999) The metalloproteinase matrilysin proteolytically generates active soluble Fas ligand and potentiates epithelial cell apoptosis. *Curr Biol* 9: 1441–1447.
7. Mitsiades N, Yu WH, Poulaki V, et al. (2001) Matrix metalloproteinase-7-mediated cleavage of Fas ligand protects tumor cells from chemotherapeutic drug cytotoxicity. *Cancer Res* 61: 577–581.
8. Schneider P, Holler N, Bodmer JL, et al. (1998) Conversion of membrane-bound Fas (CD95) ligand to its soluble form is associated with downregulation of its proapoptotic activity and loss of liver toxicity. *J Exp Med* 187: 1205–1213.
9. Tanaka M, Suda T, Takahashi T, et al. (1995) Expression of functional soluble form of human Fas ligand in activated lymphocytes. *EMBO J* 14: 1129–1135.
10. Herrero R, Kajikawa O, Matute-Bello G, et al. (2011) The biological activity of FasL in human and mouse lungs is determined by the structure of its stalk region. *J Clin Invest* 121: 1174–1190.

11. Tanaka M, Itai T, Adachi M, et al. (1998) Downregulation of Fas ligand by shedding. *Nature Med* 4: 31–36.
12. Matsumoto H, Murakami Y, Kataoka K, et al. (2015) Membrane-bound and soluble Fas ligands have opposite functions in photoreceptor cell death following separation from the retinal pigment epithelium. *Cell Death Dis* 6: e1986.
13. Suda T, Hashimoto H, Tanaka M, et al. (1997) Membrane Fas ligand kills human peripheral blood T lymphocytes, and soluble Fas ligand blocks the killing. *J Exp Med* 186: 2045–2050.
14. Audo R, Calmon-Hamaty F, Papon L, et al. (2014) Distinct effects of soluble and membrane-bound Fas ligand on fibroblast-like synoviocytes from rheumatoid arthritis patients. *Arthritis Rheum* 66: 3289–3299.
15. Song E, Chen J, Ouyang N, et al. (2001) Soluble Fas ligand released by colon adenocarcinoma cells induces host lymphocyte apoptosis: an active mode of immune evasion in colon cancer. *Br J Cancer* 85: 1047–1054.
16. Wadsworth SJ, Atsuta R, McIntyre JO, et al. (2010) IL-13 and TH2 cytokine exposure triggers matrix metalloproteinase 7-mediated Fas ligand cleavage from bronchial epithelial cells. *J Allergy Clin Immnunol* 126: 366–374.
17. Soni H, Kaminski D, Gangaraju R, et al. (2018) Cisplatin-induced oxidative stress stimulates renal Fas ligand shedding. *Renal Failure* 40: 314–322.
18. Lotti R, Shu E, Petrachi T, et al. (2018) Soluble Fas ligand is essential for blister formation in pemphigus. *Front Immunol* 9: 370.
19. Komada Y, Inaba H, Li QS, et al. (1999) Epitopes and functional responses defined by a panel of anti-Fas (CD95) monoclonal antibodies. *Hybridoma* 18: 391–398.
20. Chodorge M, Züger S, Stirnimann C, et al. (2012) A series of Fas receptor agonist antibodies that demonstrate an inverse correlation between affinity and potency. *Cell Death Differ* 19: 1187–1195.
21. Shiraishi T, Suzuyama K, Okamoto H, et al. (2004) Increased cytotoxicity of soluble Fas ligand by fusing isoleucine zipper motif. *Biochem Biophys Res Comm* 322: 197–202.
22. Daburon S, Devaud C, Costet P, et al. (2013) Functional characterization of a chimeric soluble Fas ligand polymer with *in vivo* anti-tumor activity. *Plos One* 8: e54000.
23. Cremesti A, Paris F, Grassme H, et al. (2001) Ceramide enables Fas to cap and kill. *J Biol Chem* 276: 23954–23961.
24. Muraki M (2014) Improved production of recombinant human Fas ligand extracellular domain in *Pichia pastoris*: yield enhancement using disposable culture-bag and its application to site-specific chemical modifications. *BMC Biotechnol* 14: 19.
25. Wajant H, Gerspach J, Pfizenmaier K (2013) Engineering death receptor ligands for cancer therapy. *Cancer Lett* 332: 163–174.
26. Muraki M, Hirota K (2017) Site-specific chemical conjugation of human Fas ligand extracellular domain using trans-cyclooctene–methyltetrazine reactions. *BMC Biotechnol* 17: 56.
27. Herrmann T, Große-Hovest L, Otz T, et al. (2008) Construction of optimized bispecific antibodies for selective activation of the death receptor CD95. *Cancer Res* 68: 1221–1227.
28. Kaplan DH, Shankaran V, Dighe AS, et al. (1998) Demonstration of an interferon γ-dependent tumor surveillance system in immunocompetent mice. *Proc Natl Acad Sci USA* 95: 7556–7561.
29. Gravett AM, Dalgleish AG, Copier J (2019) *In vitro* culture with gemcitabine augments death receptor and NKG2D ligand expression on tumour cells. *Sci Rep* 9: 1544.

30. Micheau O, Solary E, Hammann A, et al. (1997) Sensitization of cancer cells treated with cytotoxic drugs to Fas-mediated cytotoxicity. *J Natl Cancer Inst* 89: 783–789.
31. Micheau O, Solary E, Hammann A, et al. (1999) Fas ligand-independent, FADD-mediated activation of the Fas death pathway by anticancer drugs. *J Biol Chem* 274: 7987–7992.
32. Micheau O, Hammann A, Solary E, et al. (1999) STAT-1-independent upregulation of FADD and procaspase-3 and -8 in cancer cells treated with cytotoxic drugs. *Biochem Biophys Res Comm* 256: 603–607.
33. Petak I, Tillman DM, Houghton JA (2000) p53 dependence of Fas induction and acute apoptosis in response to 5-fluorouracil-leucovorin in human colon carcinoma cell lines. *Clin Cancer Res* 6: 4432–4441.
34. Bergmann-Leitner ES, Abrams SI (2001) Treatment of human colon cell lines with anti-neoplastic agents enhances their lytic sensitivity to antigen-specific $CD8^+$ cytotoxic T lymphocytes. *Cancer Immunol Immunother* 50: 445–455.
35. van Geelen CMM, de Vries EGE, Le TKP, et al. (2003) Differential modulation of the TRAIL receptors and the CD95 receptor in colon carcinoma cell lines. *Br J Cancer* 89: 363–373.
36. Lacour S, Micheau O, Hammann A, et al. (2003) Chemotherapy enhances TNF-related apoptosis-inducing ligand DISC assembly in HT29 human colon cancer cells. *Oncogene* 22: 1807–1816.
37. Dong YB, Yang HL, McMasters KM (2003) E2F-1 overexpression sensitizes colorectal cancer cells to camptothecin. *Cancer Gene Ther* 10: 168–178.
38. Lacour S, Hammann A, Grazide S, et al. (2004) Cisplatin-induced CD95 redistribution into membrane lipid rafts of HT29 human colon cancer cells. *Cancer Res* 64: 3593–3598.
39. McDermott U, Longley DB, Galligan L, et al. (2005) Effect of p53 status and STAT1 on chemotherapy-induced, Fas-mediated apoptosis in colorectal cancer. *Cancer Res* 65: 8951–8960.
40. Lin HH, Shi MD, Tseng HC, et al. (2014) Andrographolide sensitizes the cytotoxicity of human colorectal carcinoma cells toward cisplatin via enhancing apoptosis pathways *in vitro* and *in vivo*. *Toxicol Sci* 139: 108–120.
41. Pace E, Melis M, Siena L, et al. (2000) Effects of gemcitabine on cell proliferation and apoptosis in non-small-cell lung cancer (NSCLC) cell lines. *Cancer Chemother Pharmacol* 46: 467–476.
42. Supino R, Perego P, Gatti L, et al. (2001) A role for *c-myc* in DNA damage-induced apoptosis in a human *TP53*-mutant small-cell lung cancer cell line. *Eur J Cancer* 37: 2247–2256.
43. Okouoyo S, Herzer K, Ucur E, et al. (2004) Rescue of death receptor and mitochondrial apoptosis signaling in resistant human NSCLC *in vivo*. *Int J Cancer* 108: 580–587.
44. Yoshimoto Y, Kawada M, Ikeda D, et al. (2005) Involvement of doxorubicin-induced Fas expression in the antitumor effect of doxorubicin on Lewis lung carcinoma *in vivo*. *Int Immunopharmacol* 5: 281–288.
45. Li Y, Xing D, Chen Q, et al. (2010) Enhancement of chemotherapeutic agent-induced apoptosis by inhibition of NF-κB using ursolic acid. *Int J Cancer* 127: 462–473.
46. Siena L, Pace E, Ferraro M, et al. (2013) Gemcitabine sensitizes lung cancer cells to Fas/FasL system-mediated killing. *Immunology* 141: 242–255.
47. Wang LH, Li Y, Yang SN, et al. (2014) Gambogic acid synergistically potentiates cisplatin-induced apoptosis in non-small-cell lung cancer through suppressing NF-κB and MAPK/HO-1 signaling. *Br J Cancer* 110: 341–352.

48. Weller M, Winter S, Schmidt C, et al. (1997) Topoisomerase-I inhibitors for human malignant glioma: differential modulation of p53, p21, bax, and bcl-2 expression and of CD95-mediated apoptosis by camptothecin and β-lapachone. *Int J Cancer* 73: 707–714.
49. Fulda S, Lutz W, Schwab M, et al. (1999) MycN sensitizes neuroblastoma cells for drug-induced apoptosis. *Oncogene* 18: 1479–1486.
50. Ciusani E, Perego P, Carenini N, et al. (2002) Fas/CD95-mediated apoptosis in human glioblastoma cells: a target for sensitization to topoisomerase I inhibitors. *Biochem Pharmacol* 63: 881–887.
51. Bian X, Giordano TD, Lin HJ, et al. (2004) Chemotherapy-induced apoptosis of S-type neuroblastoma cells requires caspase-9 and is augmented by CD95/Fas stimulation. *J Biol Chem* 279: 4663–4669.
52. Terrasson J, Allart S, Martin H, et al. (2005) p73-dependent apoptosis through death receptor: impairment by human cytomegalovirus infection. *Cancer Res* 65: 2787–2794.
53. Xia S, Rosen EM, Laterra J (2005) Sensitization of glioma cells to Fas-dependent apoptosis by chemotherapy-induced oxidative stress. *Cancer Res* 65: 5248–5255.
54. Galenkamp KMO, Carriba P, Urresti J, et al. (2015) TNFα sensitizes neuroblastoma cells to FasL-, cisplatin- and etoposide-induced cell death by NF-κB-mediated expression of Fas. *Mol Cancer* 14: 62.
55. Uslu R, Jewett A, Bonavida B (1996) Sensitization of human ovarian tumor cells by subtoxic CDDP to anti-Fas antibody-mediated cytotoxicity and apoptosis. *Gynecol Oncol* 62: 282–291.
56. Uslu R, Borsellino N, Frost P, et al. (1997) Chemosensitization of human prostate carcinoma cell lines to anti-Fas-mediated cytotoxicity and apoptosis. *Clin Cancer Res* 3: 963–972.
57. Mansouri A, Ridgway LD, Korapati A, et al. (2003) Sustained activation of JNK/p38 MAPK pathways in response to cisplatin leads to Fas ligand induction and cell death in ovarian carcinoma cells. *J Biol Chem* 278: 19245–19256.
58. Bagnoli M, Balladore E, Luison E, et al. (2007) Sensitization of p53-mutated epithelial ovarian cancer to CD95-mediated apoptosis is synergistically induced by cisplatin pretreatment. *Mol Cancer Ther* 6: 762–772.
59. Alagkiozidis I, Facciabene A, Carpenito C, et al. (2009) Increased immunogenicity of surviving tumor cells enables cooperation between liposomal doxorubicin and IL-18. *J Transl Med* 7: 104.
60. Karaca B, Atmaca H, Bozkurt E, et al. (2013) Combination of AT-101/cisplatin overcomes chemoresistance by inducing apoptosis and modulating epigenetics in human ovarian cancer cells. *Mol Biol Rep* 40: 3925–3933.
61. Frost P, Ng CP, Belldegrun A, et al. (1997) Immunosensitization of prostate carcinoma cell lines for lymphocytes (CTL, TIL, LAK)-mediated apoptosis via the Fas-Fas-ligand pathway of cytotoxicity. *Cell Immunol* 180: 70–83.
62. Costa-Pereira AP, Cotter TG (1999) Camptothecin sensitizes androgen-independent prostate cancer cells to anti-Fas-induced apoptosis. *Br J Cancer* 80: 371–378.
63. Costa-Pereira AP, McKenna SL, Cotter TG (2000) Activation of SAPK/JNK by camptothecin sensitizes androgen-independent prostate cancer cells to Fas-induced apoptosis. *Br J Cancer* 82: 1827–1834.
64. Frost PJ, Butterfield LH, Dissette VB, et al (2001) Immunosensitization of melanoma tumor cells to non-MHC Fas-mediated killing by MART-1-specific CTL cultures. *J Immunol* 166: 3564–3573.

65. Das A, Durrant D, Mitchell C, et al. (2015) Sildenafil (Viagra) sensitizes prostate cancer cells to doxorubicin-mediated apoptosis through CD95. *Oncotarget* 7: 4399–4413.
66. Ruiz-Ruiz MC, López-Rivas A (1999) p53-mediated up-regulation of CD95 is not involved in genotoxic drug-induced apoptosis of human breast tumor cells. *Cell Death Differ* 6: 271–280.
67. Ruiz-Ruiz C, Muñoz-Pinedo C, López-Rivas A (2000) Interferon-γ treatment elevates caspase-8 expression and sensitizes human breast tumor cells to a death receptor-induced mitochondria-operated apoptotic program. *Cancer Res* 60: 5673–5680.
68. Basma H, El-Refaey H, Sgagias MK, et al. (2005) Bcl-2 antisense and cisplatin combination treatment of MCF-7 breast cancer cells with or without functional p53. *J Biomed Sci* 12: 999–1011.
69. Mohammad N, Singh SV, Malvi P, et al. (2015) Strategy to enhance efficacy of doxorubicin in solid tumor cells by methyl-β-cyclodextrin: involvement of p53 and Fas receptor ligand complex. *Sci Rep* 5: 11853.
70. Posovszky C, Friesen C, Herr I, et al. (1999) Chemotherapeutic drugs sensitize pre-B ALL cells for CD95- and cytotoxic T-lymphocyte-mediated apoptosis. *Leukemia* 13: 400–409.
71. Ortiz-Lazareno PC, Bravo-Cuellar A, Lerma-Díaz JM, et al. (2014) Sensitization of U937 leukemia cells to doxorubicin by the MG132 proteasome inhibitor induces an increase in apoptosis by suppressing NF-kappa B and mitochondrial membrane potential loss. *Cancer Cell Int* 14: 13.
72. Duverger V, Sartorius U, Klein-Bauernschmitt P, et al. (2002) Enhancement of cisplatin-induced apoptosis by infection with adeno-associated virus type 2. *Int J Cancer* 97: 706–712.
73. Lim YS, So HS, Kim MS, et al. (2002) Palgin sensitizes the Adriamycin-induced apoptosis via the enhancement of Fas/Fas ligand expression. *Life Sci* 71: 2391–2401.
74. Hougardy BMT, van der Zee AGJ, van den Heuvel FAJ, et al. (2005) Sensitivity to Fas-mediated apoptosis in high-risk HPV-positive human cervical cancer cells: relationship with Fas, caspase-8, and Bid. *Gynecol Oncol* 97: 353–364.
75. Sui Y, Yang Y, Wang J, et al. (2015) Lysophosphatidic acid inhibits apoptosis induced by cisplatin in cervical cancer cells. *BioMed Res Int* 2015: 598386.
76. Kinoshita H, Yoshikawa H, Shiiki K, et al. (2000) Cisplatin (CDDP) sensitizes human osteosarcoma cell to Fas/CD95-mediated apoptosis by down-regulating FLIP-L expression. *Int J Cancer* 88: 986–991.
77. Yuan XW, Zhu XF, Huang XF, et al. (2007) p14ARF sensitizes human osteosarcoma cells to cisplatin-induced apoptosis in a p53-independent manner. *Cancer Biol Ther* 6: 1074–1080.
78. Huang T, Gong WH, Zou CP, et al. (2014) *Marsdenia tenacissima* extract sensitizes MG63 cells to doxorubicin-induced apoptosis. *Genet Mol Res* 13: 354–362.
79. Pei Q, Pan J, Ding X, et al. (2015) Gemcitabine sensitizes pancreatic cancer cells to the CTLs antitumor response induced by BCG-stimulated dendritic cells via a Fas-dependent pathway. *Pancreatology* 15: 233–239.
80. Pietkiewicz S, Eils R, Krammer PH, et al. (2015) Combinatorial treatment of CD95L and gemcitabine in pancreatic cancer cells induces apoptotic and RIP1-mediated necroptotic cell death network. *Exp Cell Res* 339: 1–9.
81. Yang S, Haluska FG (2004) Treatment of melanoma with 5-fluorouracil or dacarbazine *in vitro* sensitizes cells to antigen-specific CTL lysis through perforin/granzyme- and Fas-mediated pathways. *J Immunol* 172: 4599–4608.

82. Wu XX, Mizutani Y, Kakehi Y, et al. (2000) Enhancement of Fas-mediated apoptosis in renal cell carcinoma cells by adriamycin. *Cancer Res* 60: 2912–2818.
83. Kuwahara D, Tsutsumi K, Kobayashi T, et al. (2000) Caspase-9 regulates cisplatin-induced apoptosis in human head and neck squamous cell carcinoma cells. *Cancer Lett* 148: 65–71.
84. Kataoka T, Ito M, Budd RC, et al. (2002) Expression level of c-FILP versus Fas determines susceptibility to Fas ligand-induced cell death in murine thymoma EL-4 cells. *Exp Cell Res* 273: 256–264.
85. Iwase M, Watanabe H, Kondo G, et al. (2003) Enhanced susceptibility of oral squamous cell carcinoma cell lines to Fas-mediated apoptosis by cisplatin and 5-fluorouracil. *Int J Cancer* 106: 619–625.
86. Spierings DCJ, de Vries EGE, Stel AJ, et al. (2004) Low $p21^{Waf1/Cip1}$ protein level sensitizes testicular germ cell tumor cells to Fas-mediated apoptosis. *Oncogene* 23: 4862–4872.
87. Yamana K, Bilim V, Hara N, et al. (2005) Prognostic impact of Fas/CD95/APO-1 in urothelial cancers: decreased expression of Fas is associated with disease progression. *Br J Cancer* 93: 544–551.
88. Nitobe J, Yamaguchi S, Okuyama M, et al. (2003) Reactive oxygen species regulate FLICE inhibitory protein (FLIP) and susceptibility to Fas-mediated apoptosis in cardiac myocytes. *Cardiovasc Res* 57: 119–128.
89. Labroille G, Dumain P, Lacombe F, et al. (2000) Flow cytometric evaluation of fas expression in relation to response and resistance to anthracyclines in leukemic cells. *Cytometry* 39: 195–202.
90. Fulda S, Küfer MU, Meyer E, et al. (2001) Sensitization for death receptor- or drug-induced apoptosis by re-expression of caspase-8 through demethylation or gene transfer. *Oncogene* 20: 5865–5877.
91. Yang D, Torres CM, Bardhan K, et al. (2012) Decitabine and vorinostat cooperate to sensitize colon carcinoma cells to Fas ligand-induced apoptosis *in vitro* and tumor suppression *in vivo*. *J Immunol* 188: 4441–4449.
92. Mishima K, Nariai Y, Yoshimura Y (2003) Carboplatin induces Fas (APO-1/CD95)-dependent apoptosis of human tongue carcinoma cells: sensitization for apoptosis by upregulation of FADD expression. *Int J Cancer* 105: 593–600.
93. Woo SH, Park IC, Park MJ, et al. (2004) Arsenic trioxide sensitizes CD95/Fas-induced apoptosis through ROS-mediated upregulation of CD95/Fas by NF-kappaB activation. *Int J Cancer* 112: 596–606.
94. Hallett WH, Ames E, Motarjemi M, et al. (2008) Sensitization of tumor cells to NK cell-mediated killing by proteasome inhibition. *J Immunol* 180: 163–170.
95. Symes JC, Kunin M, Fleshner NE, et al. (2008) Fas-mediated killing of primary prostate cancer cells is increased by mitoxantrone and docetaxel. *Mol Cancer Ther* 7: 3018–3028.
96. Llobet D, Eritja N, Yeramian A, et al. (2010) The multikinase inhibitor sorafenib induces apoptosis and sensitizes endometrial cancer cells to TRAIL by different mechanisms. *Eur J Cancer* 46: 836–850.
97. Zhang G, Park MA, Mitchell C, et al. (2008) Vorinostat and sorafenib synergistically kill tumor cells via FLIP suppression and CD95 activation. *Clin Cancer Res* 14: 5385–5399.
98. Bonnotte B, Favre N, Reveneau S, et al. (1998) Cancer cell sensitization to Fas-mediated apoptosis by sodium butyrate. *Cell Death Differ* 5: 480–487.

99. Rivkin I, Cohen K, Bod T, et al. (2014) Cancer cell sensitization and improved treatment efficacy by combined sodium butyrate and paclitaxel formulations is cancer-type specific. *Int J Pharm* 461: 437–447.
100. Kondo G, Iwase M, Watanabe H, et al. (2006) Enhancement of susceptibility to Fas-mediated apoptosis in oral squamous cell carcinoma cells by phosphatidylinositol 3-kinase inhibitor. *Oral Oncol* 42: 745–752.
101. Rao-Bindal K, Zhou Z, Kleinerman ES (2012) MS-275 sensitizes osteosarcoma cells to Fas ligand-induced cell death by increasing the localization of Fas in membrane lipid rafts. *Cell Death Dis* 3: e369.
102. Castro BM, de Almeida RF, Goormaghtigh E, et al. (2011) Organization and dynamics of Fas transmembrane domain in raft membranes and modulation by ceramide. *Biophys J* 101: 1632–1641.
103. Gajate C, Del Canto-Jañez E, Acuña AU, et al. (2004) Intracellular triggering of Fas aggregation and recruitment of apoptotic molecules into Fas-enriched rafts in selective tumor cell apoptosis. *J Exp Med* 200: 353–365.
104. Mollinedo F, de la Iglesia-Vicente J, Gajate C, et al. (2010) *In vitro* and *in vivo* selective antitumor activity of Edelfosine against mantle cell lymphoma and chronic lymphocytic leukemia involving lipid rafts. *Clin Cancer Res* 16: 2046–2054.
105. Rajesh D, Stenzel RA, Howard SP (2003) Perillyl alcohol as a radio-/chemosensitizer in malignant glioma. *J Biol Chem* 278: 35968–35978.
106. Westerndorp MO, Frank R, Ochsenbauer C, et al. (1995) Sensitization of T cells to CD95-mediated apoptosis by HIV-1 Tat and gp120. *Nature* 375: 497–500.
107. Ruggieri A, Harada T, Matsuura Y, et al. (1997) Sensitization to Fas-mediated apoptosis by hepatitis C virus core protein. *Virology* 229: 68–76.
108. Tanaka M, Suda T, Yatomi T, et al. (1997) Lethal effect of recombinant human Fas ligand in mice pretreated with *Propionibacterium acnes*. *J Immunol* 158: 2303–2309.
109. Wagner S, Beil W, Westermann J, et al. (1997) Regulation of gastric epithelial cell growth by *Helicobacter pylori*: evidence for a major role of apoptosis. *Gastroenterology* 113: 1836–1847.
110. Chakraborty M, Abrams SI, Camphausen K, et al. (2003) Irradiation of tumor cells up-regulates Fas and enhances CTL lytic activity and CTL adoptive immunotherapy. *J Immunol* 170: 6338–6347.
111. Park IC, Woo SH, Park MJ, et al. (2003) Ionizing radiation and nitric oxide donor sensitize Fas-induced apoptosis via up-regulation of Fas in human cervical cancer cells. *Oncol Rep* 10: 629–633.
112. Schroder K, Herztog PJ, Ravasi T, et al. (2004) Interferon-γ: an overview of signals, mechanisms and functions. *J Leukoc Biol* 75: 163–189.
113. Zaidi MR, Merlino G (2011) The two faces of interferon-γ in cancer. *Clin Cancer Res* 17: 6118–6124.
114. Meissl K, Macho-Maschler S, Müller M, et al. (2015) The good and the bad faces of STAT1 in solid tumors. *Cytokine* 89: 12–20.
115. Showalter A, Limaye A, Oyer JL, et al. (2017) Cytokines in immunogenic cell death: applications for cancer immunotherapy. *Cytokine* 97: 123–132.
116. Burke JD, Young HA (2019) IFN-γ: a cytokine at the right time, is in the right place. *Semin Immunol* 43: 101280.

117. Yonehara S, Ishii A, Yonehara M (1989) A cell-killing monoclonal antibody (anti-Fas) to a cell surface antigen co-downregulated with the receptor of tumor necrosis factor. *J Exp Med* 169: 1747–1756.
118. Günthert AR, Sträter J, von Reyher U, et al. (1996) Early detachment of colon carcinoma cells during CD95 (APO-1/Fas)-mediated apoptosis. I. de-adhesion from hyaluronate by shedding of CD44. *J Cell Biol* 134: 1089–1096.
119. Ossina NK, Cannas A, Powers VC, et al. (1997) Interferon-γ modulates a p53-independent apoptotic pathway and apoptosis-related gene expression. *J Biol Chem* 272: 16351–16357.
120. Tillman DM, Harwood FG, Gibson AA, et al. (1998) Expression of genes that regulate Fas signaling and Fas-mediated apoptosis in colon carcinoma cells. *Cell Death Differ* 5: 450–457.
121. Darcy PK, Kershaw MH, Trapani JA, et al. (1998) Expression in cytotoxic T lymphocytes of a single-chain anti-carcinoembryonic antigen antibody. Redirected Fas ligand-mediated lysis of colon carcinoma. *Eur J Immunol* 28: 1663–1672.
122. Koshiji M, Adachi Y, Sogo S, et al. (1998) Apoptosis of colorectal adenocarcinoma (COLO 201) by tumour necrosis factor (TNF-α) and/or interferon-gamma (IFN-γ), resulting from down-modulation of Bcl-2 expression. *Clin Exp Immunol* 111: 211–218.
123. von Reyher U, Sträter J, Kittstein W, et al. (1998) Colon carcinoma cells use different mechanisms to escape CD95-mediated apoptosis. *Cancer Res* 58: 526–534.
124. Xu X, Fu XY, Plate J, et al. (1998) IFN-γ induces cell growth inhibition by Fas-mediated apoptosis: requirement of STAT1 protein for up-regulation of Fas and FasL expression. *Cancer Res* 58: 2832–2837.
125. Rapoport E, Pendu JL (1999) Glycosylation alterations of cells in late phase apoptosis from colon carcinomas. *Glycobiology* 9: 1337–1345.
126. Tillman DM, Petak I, Houghton JA (1999) A Fas-dependent component in 5-fluorouracil/leucovorin-induced cytotoxicity in colon carcinoma cells. *Clin Cancer Res* 5: 425–430.
127. Bergmann-Leitner ES, Abrams SI (2000) Influence of interferon γ on modulation of Fas expression by human colon carcinoma cells and their subsequent sensitivity to antigen-specific CD8+ cytotoxic T lymphocyte attack. *Cancer Immunol Immunother* 49: 193–207.
128. Bergmann-Leitner ES, Abrams SI (2000) Differential role of Fas/Fas ligand interactions in cytolysis of primary and metastatic colon carcinoma cell lines by human antigen-specific $CD8^+$ CTL. *J Immunol* 164: 4941–4954.
129. O'connell J, Bennett MW, Nally K, et al. (2000) Interferon-γ sensitizes colonic epithelial cell lines to physiological and therapeutic inducers of colonocyte apoptosis. *J Cell Physiol* 185: 331–338.
130. Remacle-Bonnet MM, Garrouste FL, Heller S, et al. (2000) Insulin-like growth factor-I protects colon cancer cells from death factor-induced apoptosis by potentiating tumor necrosis factor α-induced mitogen-activated protein kinase and nuclear factor κB signaling pathways. *Cancer Res* 60: 2007–2017.
131. Manos EJ, Jones DA (2001) Assessment of tumor necrosis factor receptor and Fas signaling pathways by transcriptional profiling. *Cancer Res* 61: 433–438.
132. Martin CA, Panja A (2002) Cytokine regulation of human intestinal primary epithelial cell susceptibility to Fas-mediated apoptosis. *Am J Physiol Gastrointest Liver Physiol* 282: G92–G104.

133. Schwartzberg LS, Petak I, Stewart C, et al. (2002) Modulation of Fas signaling pathway by IFN-γ in therapy of colon cancer: phase I trial and correlative studies of IFN-γ, 5-fluorouracil, and leucovorin. *Clin Cancer Res* 8: 2488–2498.
134. Wilson CA, Browning JL (2002) Death of HT29 adenocarcinoma cells induced by TNF family receptor activation is caspase-independent and displays features of both apoptosis and necrosis. *Cell Death Differ* 9: 1321–1333.
135. Geller J, Petak I, Szucs KS, et al. (2003) Interferon-γ-induced sensitization of colon carcinomas to ZD9331 targets caspases, downstream of Fas, independent of mitochondrial signaling and the inhibitor of apoptosis survivin. *Clin Cancer Res* 9: 6504–6515.
136. Liu K, Abrams SI (2003) Coordinate regulation of IFN consensus sequence-binding protein and caspase-1 in the sensitization of human colon carcinoma cells to Fas-mediated apoptosis by IFN-γ. *J Immunol* 170: 6329–6337.
137. Liu K, McDuffie E, Abrams SI (2003) Exposure of human primary colon carcinoma cells to anti-Fas interactions influences the emergence of pre-existing Fas-resistant metastatic subpopulations. *J Immunol* 171: 4164–4174.
138. Seidelin JB, Jäättelä M, Nielsen OH (2004) Continuous interferon-γ or tumor necrosis factor-α exposure of enterocytes attenuates cell death responses. *Cytokine* 27: 113–119.
139. Turner PK, Houghton JA, Petak I, et al. (2004) Interferon-gamma pharmacokinetics and pharmacodynamics in patients with colorectal cancer. *Cancer Chemother Pharmacol* 53: 253–260.
140. Vekemans K, Braet F, Muyllaert D, et al. (2004) Nitric oxide from rat liver sinusoidal endothelial cells induces apoptosis in IFN γ-sensitized CC531s colon carcinoma cells. *J Hepatol* 41: 11–18.
141. Siegmund D, Wicovsky A, Schmitz I (2005) Death receptor-induced signaling pathways are differentially regulated by gamma interferon upstream of caspase-8 processing. *Mol Cell Biol* 25: 6363–6379.
142. Saha A, Chatterjee SK, Foon KA, et al. (2006) Anti-idiotype antibody induced cellular immunity in mice transgenic for human carcinoembryonic antigen. *Immunology* 118: 483–496.
143. Geng L, Zhu B, Dai BH, et al. (2011) A let-7/Fas double-negative feedback loop regulates human colon carcinoma cells sensitivity to Fas-related apoptosis. *Biochem Biophys Res Comm* 408: 494–499.
144. Shadrin N, Shapira MG, Khalfin B, et al. (2015) Serine protease inhibitors interact with IFN-γ through up-regulation of FasR; a novel therapeutic strategy against cancer. *Exp Cell Res* 330: 233–239.
145. Muraki M, Hirota K (2018) Confirmation of covalently-linked structure and cell-death inducing activity in site-specific chemical conjugates of human Fas ligand extracellular domain. *BMC Res Notes* 11: 395.
146. Muraki M, Hirota K (2019) Site-specific biotin-group conjugate of human Fas ligand extracellular domain: preparation and characterization of cell-death-inducing activity. *Curr Top Pep Prot Res* 20: 17–24.
147. Morimoto H, Yonehara S, Bonavida B (1993) Overcoming tumor necrosis factor and drug resistance of human tumor cell lines by combination treatment with anti-Fas antibody and drugs or toxins. *Cancer Res* 53: 2591–2596.

148. Biswas P, Poli G, Orenstein JM, et al. (1994) Cytokine-mediated induction of human immunodeficiency virus (HIV) expression and cell death in chronically infected U1 cells: do tumor necrosis factor alpha and gamma interferon selectively kill HIV-infected cells? *J Virol* 68: 2598–2604.
149. Shima Y, Nishimoto N, Ogata A, et al. (1995) Myeloma cells express Fas antigen/APO-1 (CD95) but only some are sensitive to anti-Fas antibody resulting in apoptosis. *Blood* 85: 757–764.
150. Efferth T, Fabry U, Osieka R (1996) Anti-Fas/Apo-1 monoclonal antibody CH-11 depletes glutathione and kills multidrug-resistant human leukemic cells. *Blood Cell Mol Dis* 22: 2–9.
151. Spets H, Georgii-Hemming P, Siljason J, et al. (1998) Fas/APO-1 (CD95)-mediated apoptosis is activated by interferon-γ and interferon-α in interleukin-6 (IL-6)-dependent and IL-6-independent multiple myeloma cell lines. *Blood* 92: 2914–2923.
152. Horie T, Dobashi K, Iizuka K, et al. (1999) Interferon-γ rescues TNF-α-induced apoptosis mediated by up-regulation of TNFR2 on EoL-1 cells. *Exp Hematol* 27: 512–519.
153. Sata M, Suhara T, Walsh K (2000) Vascular endothelial cells and smooth muscle cells differ in expression of Fas and Fas ligand and in sensitivity to Fas ligand-induced cell death. Implications for vascular disease and therapy. *Arterioscler Thromb Vasc Biol* 20: 309–316.
154. Varela N, Muñoz-Pinedo C, Ruiz-Ruiz C, et al. (2001) Interferon-γ sensitizes human myeloid leukemia cells to death receptor-mediated apoptosis by a pleiotropic mechanism. *J Biol Chem* 276: 17779–17787.
155. Dörrie J, Sapala K, Zunino SJ (2002) Interferon-γ increases the expression of glycosylated CD95 in B-leukemic cells: an inducible model to study the role of glycosylation in CD95-signalling and trafficking. *Cytokine* 18: 98–107.
156. Jedema I, Barge RMY, Willemze R, et al. (2003) High susceptibility of human leukemic cells to Fas-induced apoptosis is restricted to G_1 phase of the cell cycle and can be increased by interferon treatment. *Leukemia* 17: 576–584.
157. Dimberg LY, Dimberg AI, Ivarsson K, et al. (2005) Ectopic and IFN-induced expression of Fas overcomes resistance to Fas-mediated apoptosis in multiple myeloma cells. *Blood* 106: 1346–1354.
158. Guy CS, Wang J, Michalak TI (2006) Hepatocytes as cytotoxic effector cells can induce cell death by CD95 ligand-mediated pathway. *Hepatology* 43: 1231–1240.
159. Boselli D, Ragimbeau J, Orlando L, et al. (2010) Expression of IFNγR2 mutated in a dileucine internalization motif reinstates IFNγ signaling and apoptosis in human T lymphocytes. *Immunol Lett* 134: 17–25.
160. Dimberg LY, Dimberg A, Ivarsson K, et al. (2012) Stat1 activation attenuates IL-6 induced Stat3 activity but does not alter apoptosis sensitivity in multiple myeloma. *BMC Cancer* 12: 318.
161. Fujihara Y, Takato T, Hoshi K (2014) Macrophage-inducing FasL on chondrocytes forms immune privilege in cartilage tissue engineering, enhancing *in vivo* regeneration. *Stem Cell* 32: 1208–1219.
162. Xia HL, Li CJ, Hou XF, et al. (2017) Interferon-γ affects leukemia cell apoptosis through regulating Fas/FasL signaling pathway. *Eur Rev Med Pharmacol Sci* 21: 2244–2248.
163. Weller M, Frei K, Groscurth P, et al. (1994) Anti-Fas/APO-1 antibody-mediated apoptosis of cultured human glioma cells. Induction and modulation of sensitivity by cytokines. *J Clin Invest* 94: 954–964.
164. Fulda S, Debatin KM (2002) IFNγ sensitizes for apoptosis by upregulating caspase-8 expression through the Stat1 pathway. *Oncogene* 21: 2295–2308.

165. Buntinx M, Gielen E, van Hummelen P, et al. (2004) Cytokine-induced cell death in human oligodendroglial cell lines. II: alterations in gene expression induced by interferon-γ and tumor necrosis factor-α. *J Neurosci Res* 76: 846–861.
166. Choi C, Jeong E, Benveniste EN (2004) Caspase-1 mediates Fas-induced apoptosis and is up-regulated by interferon-γ in human astrocytoma cells. *J Neuro-oncol* 67: 167–176.
167. Song JH, Wang CX, Song DK, et al. (2005) Interferon γ induces neurite outgrowth by up-regulation of p35 neuron-specific cycline-dependent kinase 5 activator via activation of ERK1/2 pathway. *J Biol Chem* 280: 12896–12901.
168. Giammarioli AM, Vona R, Gambardella L, et al. (2009) Interferon-γ bolsters CD95/Fas-mediated apoptosis of astroglioma cells. *FEBS J* 276: 5920–5935.
169. Wen LP, Madani K, Fahrni JA, et al. (1997) Dexamethasone inhibits lung epithelial cell apoptosis induced by IFN-γ and Fas. *Am J Physiol* 273: L921–L929.
170. Maeyama T, Kuwano K, Kawasaki M, et al. (2001) Upregulation of Fas-signaling molecules in lung epithelial cells from patients with idiopathic pulmonary fibrosis. *Eur Respir J* 17: 180–189.
171. Coulter KR, Doseff A, Sweeney P, et al. (2002) Opposing effect by cytokines on Fas-mediated apoptosis in A549 lung epithelial cells. *Am J Respir Cell Mol Biol* 26: 58–66.
172. Kim KB, Choi YH, Kim IK, et al. (2002) Potentiation of Fas- and TRAIL-mediated apoptosis by IFN-γ in A549 lung epithelial cells: enhancement of caspase-8 expression through IFN-response element. *Cytokine* 20: 283–288.
173. Hopkins-Donaldson S, Ziegler A, Kurtz S, et al. (2003) Silencing of death receptor and caspase-8 expression in small cell lung carcinoma cell lines and tumours by DNA methylation. *Cell Death Differ* 10: 356–364.
174. Crescenzi E, Pacifico F, Lavorgna A, et al. (2011) NF-κB-dependent cytokine secretion controls Fas expression on chemotherapy-induced premature senescent tumor cells. *Oncogene* 30: 2707–2717.
175. Keane MM, Ettenberg SA, Lowrey GA, et al. (1996) Fas expression and function in normal and malignant breast cell lines. *Cancer Res* 56: 4791–4798.
176. Haynes NM, Smyth MJ, Kershaw MH, et al. (1999) Fas-ligand-mediated lysis of erbB-2-expressing tumour cells by redirected cytotoxic T lymphocytes. *Cancer Immunol Immunother* 47: 278–286.
177. Danforth DN, Zhu Y (2005) Conversion of Fas-resistant to Fas-sensitive MCF-7 breast cancer cells by the synergistic interaction of interferon-γ and all-*trans* retinoic acid. *Breast Cancer Res Treat* 94: 81–91.
178. Deiss LP, Galinka H, Beriss H, et al. (1996) Cathepsin D protease mediates programmed cell death induced by interferon-γ, Fas/APO-1 and TNF-α. *EMBO J* 15: 3861–3870.
179. Jauharoh SNA, Saegusa J, Sugimoto T, et al. (2012) SS-A/Ro52 promotes apoptosis by regulating Bcl-2 production. *Biochem Biophys Res Comm* 417: 582–587.
180. Boeddeker SJ, Baston-Buest DM, Altergot-Ahmad O, et al. (2014) Syndecan-1 knockdown in endometrial epithelial cells alters their apoptotic protein profile and enhances the inducibility of apoptosis. *Mol Hum Reprod* 20: 567–578.
181. Yang D, Thangaraju M, Browing DD, et al. (2007) IFN regulatory factor 8 mediates apoptosis in nonhemopoietic tumor cells via regulation of Fas expression. *J Immunol* 179: 4775–4782.
182. Banik D, Khan ANH, Walseng E, et al. (2012) Interferon regulatory factor-8 is important for histone deacetylase inhibitor-mediated antitumor activity. *Plos One* 7: e45422.

183. Nonomura N, Miki T, Yokoyama M, et al. (1996) Fas/APO-1-mediated apoptosis of human renal cell carcinoma. *Biochem Biophys Res Comm* 229: 945–951.
184. Lee JK, Sayers TJ, Brooks AD, et al. (2000) IFN-γ-dependent delay of *in vivo* tumor progression by Fas overexpression of murine renal cancer cells. *J Immunol* 164: 231–239.
185. Tomita Y, Bilim V, Hara N, et al. (2003) Role of IRF-1 and caspase-7 in IFN-γ enhancement of Fas-mediated apoptosis in ACHN renal cell carcinoma cells. *Int J Cancer* 104: 400–408.
186. García-Sánchez O, López-Novoa JM, López-Hermández FJ (2014) Interferon-γ reduces the proliferation of primed human renal tubular cells. *Nephron Extra* 4: 1–7.
187. Ugurel S, Seiter S, Pappl G, et al. (1999) Heterogeneous susceptibility to CD95-induced apoptosis in melanoma cells correlates with bcl-2 and bcl-x expression and is sensitive to modulation by interferon-γ. *Int J Cancer* 82: 727–736.
188. Shchors K, Yehiely F, Deiss LP (2004) Cell death inhibiting RNA (CDIR) modulates IFN-γ-stimulated sensitization to Fas/CD95/Apo-1 and TRAIL/Apo2L-induced apoptosis. *Cell Cycle* 3: 1606–1611.
189. Hiramoto K, Inui M, Kamei T, et al. (2006) mHFE7A, a newly identified monoclonal antibody to Fas, induces apoptosis in human melanoma cells *in vitro* and delays the growth of melanoma xenotransplants. *Oncol Rep* 15: 409–415.
190. Fellenberg J, Mau H, Scheuerpflug C, et al. (1997) Modulation of resistance to anti-APO-1-induced apoptosis in osteosarcoma cells by cytokines. *Int J Cancer* 72: 536–542.
191. Li Z, Xu Q, Peng H, et al. (2011) IFN-γ enhances HOS and U2OS cell lines susceptibility to γδ T cell-mediated killing through the Fas/Fas ligand pathway. *Int Immnonopharmacol* 11: 496–503.
192. Garbán HJ, Bonavida B (1999) Nitric oxide sensitizes ovarian tumor cells to Fas-induced apoptosis. *Gynecol Onco*l 73: 257–264.
193. Jones NL, Day AS, Jennings HA, et al. (1999) *Helicobacter pylori* induces gastric epithelial cell apoptosis in association with increased Fas receptor expression. *Infect Immun* 67: 4237–4242.
194. Wang J, Fan X, Lindholm C, et al. (2000) *Helicobacter pylori* modulates lymphoepithelial cell interactions leading to epithelial cell damage through Fas/Fas ligand interactions. *Infect Immun* 68: 4303–4311.
195. Shin EC, Shin WC, Choi Y, et al. (2001) Effect of interferon-γ on the susceptibility to Fas (CD95/APO-1)-mediated cell death in human hepatoma cells. *Cancer Immunol Immunother* 50: 23–30.
196. Ahn EY, Pan G, Vickers SM, et al. (2002) IFN-γ upregulates apoptosis-related molecules and enhances Fas-mediated apoptosis in human cholangiocarcinoma. *Int J Cancer* 100: 445–451.
197. Tsuji S, Hosotani R, Yonehara S, et al. (2003) Endogenous decoy receptor 3 blocks the growth inhibition signals mediated by Fas ligand in human pancreatic adenocarcinoma. *Int J Cancer* 106: 17–25.
198. Selleck WA, Canfield SE, Hassen WA, et al. (2003) IFN-γ sensitization of prostate cancer cells to Fas-mediated death: a gene therapy approach. *Mol Ther* 7: 185–192.
199. Amrani A, Verdaguer J, Thiessen S, et al. (2000) IL-1α, IL-1β, and IFN-γ mark β cells for Fas-dependent destruction by diabetogenic $CD4^+$ T lymphocytes. *J Clin Invest* 105: 459–468.
200. Mollah ZUA, Wail J, McKenzie MD, et al. (2011) The pro-apoptotic BH3-only protein Bid is dispensable for development of insulitis and diabetes in the non-obese diabetic mouse. *Apoptosis* 16: 822–830.

201. Augstein P, Bahr J, Wachlin G, et al. (2004) Cytokines activate caspase-3 in insulinoma cells of diabetes-prone NOD mice directly and via upregulation of Fas. *J Autoimmun* 23: 301–309.
202. Igoillo-Esteve M, Gurzov EN, Eizirik DL, et al. (2011) The transcription factor B-cell lymphoma (BCL)-6 modulates pancreatic β-cell inflammatory responses. *Endocrinology* 152: 447–456.
203. Allagnat F, Fukaya M, Nogueira TC, et al. (2012) C/EBP homologous protein contributes to cytokine-induced pro-inflammatory responses and apoptosis in β-cells. *Cell Death Differ* 19: 1836–1846.
204. Nardelli TR, Vanzela EC, Benedicto KC, et al. (2018) Prolactin protects against cytokine-induced beta-cell death by NFκB and JNK inhibition. *J Mol Endocrinol* 61: 25–36.
205. Kawakami A, Eguchi K, Matsuoka N, et al. (1997) Modulation of Fas-mediated apoptosis of human thyroid epithelial cells by IgG from patients with Graves' disease (GD) and idiopathic myxoedema. *Clin Exp Immunol* 110: 434–439.
206. Stassi G, Di Liberto D, Todaro M, et al. (2000) Control of target cell survival in thyroid autoimmunity by T helper cytokines via regulation of apoptotic proteins. *Nat Immunol* 1: 483–488.
207. Pouly S, Becher B, Blain M, et al. (2000) Interferon-γ modulates human oligodendrocyte susceptibility to Fas-mediated apoptosis. *J Neuropathol Exp Neurol* 59: 280–286.
208. Yao Y, Lu S, Li H, et al. (2012) Low doses of exogenous interferon-γ attenuated airway inflammation through enhancing Fas/FasL-induced $CD4^+$ T cell apoptosis in a mouse asthma model. *J Interferon Cytokine Res* 32: 534–541.
209. Hallam DM, Capps NL, Travelstead AL, et al. (2000) Evidence for an interferon-related inflammatory reaction in the trisomy 16 mouse brain leading to caspase-1-mediated neuronal apoptosis. *J Neuroimmunol* 110: 66–75.
210. Ping L, Ogawa N, Sugai S (2005) Novel role of CD40 in Fas-dependent apoptosis of cultured salivary epithelial cells from patients with Sjögren's syndrome. *Arthritis Rheum* 52: 573–581.
211. Fischer-Posovszky P, Hebestreit H, Hofmann AK, et al. (2006) Role of CD95-mediated adipocyte loss in autoimmune lipodystrophy. *J Clin Endocrinol Metab* 91: 1129–1135.
212. Contassot E, Kerl K, Roques S, et al. (2008) Resistance to FasL and tumor necrosis factor-related apoptosis-inducing ligand-mediated apoptosis in Sézary syndrome T-cells associated with impaired death receptor and FLICE-inhibitory protein expression. *Blood* 111: 4780–4787.
213. Conceição-Silva F, Hahne M, Schröter M, et al. (1998) The resolution of lesions induced by *Leishmania major* in mice requires a functional Fas (APO-1, CD95) pathway of cytotoxicity. *Eur J Immunol* 28: 237–245.
214. Chakour R, Guler R, Bugnon M, et al. (2003) Both the Fas ligand and inducible nitric oxide synthase are needed for control of parasite replication within lesions in mice infected with *Leishmania major* whereas the contribution of tumor necrosis factor is minimal. *Infect Immun* 71: 5287–5295.
215. Rosner D, Stoneman V, Littlewood T, et al. (2006) Interferon-γ induces Fas trafficking and sensitization to apoptosis in vascular smooth muscle cells via a PI3K- and Akt-dependent mechanism. *Am J Pathol* 168: 2054–2063.
216. Esser P, Heimann K, Abts H, et al. (1995) CD95 (Fas/APO-1) antibody-mediated apoptosis of human retinal pigment epithelial cells. *Biochem Biophys Res Comm* 213: 1026–1034.

217. Yang Z, Gagarin D, St. Laurent III G, et al. (2009) Cardiovascular inflammation and lesion cell apoptosis. A novel connection via the interferon-inducible immunoproteasome. *Arterioscler Thromb Vasc Biol* 29: 1213–1219.
218. Zhaorigetu S, Yang Z, Toma I, et al. (2011) Apolipoprotein L6, induced in atherosclerotic lesions promotes apoptosis and blocks Beclin 1-dependent autophagy in atherosclerotic cells. *J Biol Chem* 286: 27389–27398.
219. Catalan MP, Subirá D, Reyero A, et al. (2003) Regulation of apoptosis by lethal cytokines in human mesothelial cells. *Kidney Int* 64: 321–330.
220. Wang XY, Crowston JG, Zoellner H, et al. (2007) Interferon-α and interferon-γ sensitize human tenon fibroblasts to mitomycin-C. *Invest Ophthalmol Vis Sci* 48: 3655–3661.
221. Zhang X, Chen W, De Paiva CS, et al. (2011) Interferon-γ exacerbates dry eye-induced apoptosis in conjunctiva through dual apoptotic pathways. *Invest Ophthalmol Vis Sci* 52: 6279–6285.
222. Nagafuji K, Shibuya T, Harada M, et al. (1995) Functional expression of Fas antigen (CD95) on hematopoietic progenitor cells. *Blood* 86: 883–889.
223. Oyaizu N, Mc Closkey TW, Than S, et al. (1996) Inhibition of CD4 cross-linking-induced lymphocytes apoptosis by vesnarinone as a novel immunomodulating agent: vesnarinone inhibits Fas expression and apoptosis by blocking cytokine secretion. *Blood* 87: 2361–2368.
224. Sato T, Selleri C, Anderson S, et al. (1997) Expression and modulation of cellular receptors for interferon-γ, tumour necrosis factor, and Fas on human bone marrow $CD34^+$ cells. *Br J Haematol* 97: 356–365.
225. Schneider E, Moreau G, Arnould A, et al. (1999) Increased fatal and extramedullary hematopoiesis in Fas-deficient C57BL/6-*lpr/lpr* mice. *Blood* 94: 2613–2621.
226. Erie AJ, Samsel L, Takaku T, et al. (2011) MHC class II upregulation and colocalization with Fas in experimental models of immune-mediated bone marrow failure. *Exp Hematol* 39: 837–849.
227. Kohara H, Kitaura H, Fujimura Y, et al. (2011) IFN-γ directly inhibits TNF-α-induced osteoclastgenesis *in vitro* and *in vivo* and induces apoptosis mediated by Fas/Fas ligand interactions. *Immunol Lett* 137: 53–61.
228. Liu Y, Wang L, Kikuiri T, et al. (2011) Mesenchymal stem cell-based tissue regeneration is governed by recipient T lymphocytes via IFN-γ and TNF-α. *Nat Med* 17: 1594–1601.
229. Chen J, Feng X, Desierto MJ, et al. (2015) IFN-γ-mediated hematopoietic cell destruction in murine models of immune-mediated bone marrow failure. *Blood* 126: 2621–2631.
230. Xu, J, Wang Y, Li J, et al. (2016) IL-12p40 impairs mesenchymal stem cell-mediated bone regeneration via $CD4^+$ T cells. *Cell Death Differ* 23: 1941–1951.
231. Li X, Shang B, Li YN (2019) IFNγ and TNFα synergistically induce apoptosis of mesenchymal stem/stromal cells via induction of nitric oxide. *Stem Cell Res Ther* 10:18.
232. Luttmann W, Opfer A, Dauer E, et al. (1998) Differential regulation of CD95 (Fas/APO-1) expression in human blood eosinophils. *Eur J Immunol* 28: 2057–2065.
233. Luttmann W, Dauer E, Schmidt S, et al. (2000) Effects of interferon-γ and tumour necrosis factor-α on CD95/Fas ligand-mediated apoptosis in human blood eosinophils. *Scand J Immunol* 51: 54–59.
234. Zizzo G, Cohen PL (2013) IL-17 stimulates differentiation of human anti-inflammatory macrophages and phagocytosis of apoptotic neutrophils in response to IL-10 and glucocorticoids. *J Immunol* 190: 5237–5246.

235. Hagmann BR, Odermatt A, Kaufmann T, et al. (2016) Balance between IL-3 and type I interferons and their interrelationship with FasL dictates lifespan and effector functions of human basophils. *Clin Exp Allergy* 47: 71–84.
236. Chung IJ, Dai C, Krantz SB (2003) Stem cell factor increases the expression of FLIP that inhibits IFN-γ-induced apoptosis in human erythroid progenitor cells. *Blood* 101: 1324–1328.
237. Müschen M, Warskulat U, Peters-Regehr T, et al. (1999) Involvement of CD95 (Apo-1/Fas) ligand expressed by rat Kupffer cells in hepatic immunoregulation. *Gastroenterology* 116: 666–677.
238. Bárcena A, Park SW, Banapour B, et al. (1996) Expression of Fas/CD95 and Bcl-2 by primitive hematopoietic progenitors freshly isolated from human fetal liver. *Blood* 88: 2013–2025.
239. Oh JE, Shim KY, Lee JI, et al. (2017) 1-Methyl-L-tryptophan promotes the apoptosis of hepatic stellate cells arrested by interferon-γ by increasing the expression of IFN-γRβ, IRF-1 and Fas. *Int J Mol Med* 40: 576–582.
240. He W, Yang C, Xia L, et al. (2014) $CD4^+$ T cells from food allergy model are resistant to TCR-dependent apoptotic induction. *Cytokine* 68: 32–39.
241. Lightfoot YL, Chen J, Mathews CE (2011) Role of the mitochondria in immune-mediated apoptotic death of the human pancreatic β cell line βLox5. *Plos One* 6: e20617.
242. Sun Q, Xiang RL, Yang YL, et al. (2013) Suppressor of cytokine signaling 1 protects rat pancreatic islets from cytokine-induced apoptosis through Janus kinase/signal transducers and activators of transcription pathway. *Chin Med J* 126: 4048–4053.
243. Quirk SM, Cowan RG, Huber SH (1997) Fas antigen-mediated apoptosis of ovarian surface epithelial cells. *Endocrinology* 138: 4558–4566.
244. Taniguchi H, Yokomizo Y, Okuda K (2002) Fas-Fas ligand system mediates luteal cell death in bovine corpus luteum. *Biol Reprod* 66: 754–759.
245. Galvao AM, Ramilo DW, Skarzynski DJ, et al. (2010) Is Fas/Fas ligand system involved in equine corpus luteum functional regression? *Biol Reprod* 83: 901–908.
246. Hojo T, Al-zi'abi O, Komiyama J, et al. (2010) Expression and localization of FLIP, an anti-apoptotic factor, in the bovine corpus luteum. *J Reprod Dev* 56: 230–235.
247. Woclawek-Potocka I, Kowalczyk-Zieba I, Tylingo M, et al. (2013) Effects of lysophosphatidic acid on tumor necrosis factor α and interferon γ action in the bovine corpus luteum. *Mol Cell Endrocrinol* 377: 103–111.
248. Quirk SM, Porter DA, Huber SC, et al. (1998) Potentiation of Fas-mediated apoptosis of murine granulosa cells by interferon-γ, tumor necrosis factor-α, and cycloheximide. *Endocrinology* 139: 4860–4869.
249. Lee HJ, Kim JY, Park JE, et al. (2016) Induction of Fas-mediated apoptosis by interferon-γ is dependent on granulosa cell differentiation and follicular maturation in the rat ovary. *Dev Reprod* 20: 315–329.
250. Aschkenazi S, Straszewski S, Verwer KMA, et al. (2002) Differential regulation and function of the Fas/Fas ligand system in human trophoblast cells. *Biol Reprod* 66: 1853–1861.
251. Balkundi DR, Ziegler JA, Watchko JF, et al. (2003) Regulation of FasL/Fas in human trophoblasts: possible implications for chorioamnionitis. *Biol Reprod* 69: 718–724.
252. Riccioli A, Starace D, D'Alessio A, et al. (2000) TNF-α and IFN-γ regulate expression and function of the Fas system in the seminiferous epithelium. *J Immunol* 165: 743–749.
253. González-Cuadrado S, López-Armada MJ, Gómez-Guerrero C, et al. (1996) Anti-Fas antibodies induce cytolysis and apoptosis in cultured human mesangial cells. *Kidney Int* 49: 1064–1070.

254. Tsukinoki T, Sugiyama H, Sunami R, et al. (2004) Mesangial cell Fas ligand: upregulation in human lupus nephritis and NF-κB-mediated expression in cultured human mesangial cells. *Clin Exp Nephrol* 8: 196–205.
255. Lorz C, Ortiz A, Justo P, et al. (2000) Proapoptotic Fas ligand is expressed by normal kidney tubular epithelium and injured glomeruli. *J Am Soc Nephrol* 11: 1266–1277.
256. Spanaus KS, Schlapbach R, Fontana A (1998) TNF-α and INF-γ render microglia sensitive to Fas ligand-induced apoptosis by induction of Fas expression and down-regulation of Bcl-2 and Bcl-xL. *Eur J Immunol* 28: 4398–4408.
257. Schlapbach R, Spanaus KS, Malipiero U, et al. (2000) TGF-β induces the expression of the FLICE-inhibitory protein and inhibits Fas-mediated apoptosis of microglia. *Eur J Immunol* 30: 3680–3688.
258. Falsig J, Latta M, Leist M (2004) Defined inflammatory states in astrocyte cultures: correlation with susceptibility towards CD95-driven apoptosis. *J Neurochem* 88: 181–193.
259. Coque E, Salsac C, Espinosa-Carrasco G, et al. (2019) Cytotoxic $CD8^+$ T lymphocytes expressing ALS-causing SOD1 mutant selectively trigger death of spinal motoneurons. *Proc Natl Acad Sci USA* 116: 2312–2317.
260. Sayama K, Yonehara S, Watanabe Y, et al. (1994) Expression of Fas antigen on keratinocytes *in vivo* and induction of apoptosis in cultured keratinocytes. *J Invest Dermatol* 103: 330–334.
261. Viard-Leveugle I, Gaide O, Jankovic D, et al. (2013) TNF-α and IFN-γ are potential inducers of Fas-mediated keratinocyte apoptosis through activation of inducible nitric oxide synthase in toxic epidermal necrolysis. *J Invest Dermatol* 133: 489–498.
262. Gao Z, Jin YQ, Wu W (2017) SOCS3 treatment prevents the development of alopecia areata by inhibiting $CD8^+$ T cell-mediated autoimmune destruction. *Oncotarget* 8: 33432–33443.
263. Li JH, Kluger MS, Madge LA, et al. (2002) Interferon-γ augments CD95 (APO-1/Fas) and pro-caspase-8 expression and sensitizes human vascular endothelial cells to CD95-mediated apoptosis. *Am J Pathol* 161: 1485–1495.
264. Yamaoka-Tojo M, Yamaguchi S, Nitobe J, et al. (2003) Dual response to Fas ligation in human endothelial cells: apoptosis and induction of chemokines, interleukin-8 and monocyte chemoattractant protein-1. *Coron Artery Dis* 14: 89–94.
265. Shigeta A, Tada Y, Wang JY, et al. (2012) CD40 amplifies Fas-mediated apoptosis: a mechanism contributing to emphysema. *Am J Physiol Lung Cell Mol Physiol* 303: L141–L151.
266. Kawakami A, Eguchi K, Matsuoka N, et al. (1996) Thyroid-stimulating hormone inhibits Fas antigen mediated apoptosis of human thyrocytes *in vitro*. *Endocrinology* 137: 3163–3169.
267. Mezosi E, Yamazaki H, Bretz JD, et al. (2002) Aberrant apoptosis in thyroid epithelial cells from goiter nodules. *J Clin Endocrinol Metab* 87: 4264–4272.
268. Mezosi E, Wang SH, Utsugi S, et al. (2005) Induction and regulation of Fas-mediated apoptosis in human thyroid epithelial cells. *Mol Endocrinol* 19: 804–811.
269. Wang SH, van Antwerp M, Kuick R, et al. (2007) Microarray analysis of cytokine activation of apoptosis pathways in the thyroid. *Endocrinology* 148: 4844–4852.
270. Fang Y, Braley-Mullen H (2008) Cultured murine thyroid epithelial cells expressing transgenic Fas-associated death-like interleukin-1β converting enzyme inhibitory protein are protected from Fas-mediated apoptosis. *Endocrinology* 149: 3321–3329.

271. Marsumura R, Umemiya K, Goto T, et al. (2000) Interferon gamma and tumor necrosis factor alpha induce Fas expression and anti-Fas mediated apoptosis in a salivary ductal cell line. *Clin Exp Rheumatol* 18: 311–318.
272. Abu-Helu RF, Dimitriou ID, Kapsogeorgou EK, et al. (2001) Induction of salivary gland epithelial cell injury in Sjogren's syndrome: *in vitro* assessment of T cell-derived cytokines and Fas protein expression. *J Autoimmun* 17: 141–153.
273. Ruemmele FM, Russo P, Beaulieu JF, et al. (1999) Susceptibility to Fas-induced apoptosis in human nontumoral enterocytes: role of costimulatory factors. *J Cell Physiol* 181: 45–54.
274. Bharhani MS, Borojevic R, Basak S, et al. (2006) IL-10 protects mouse intestinal epithelial cells from Fas-induced apoptosis via modulating Fas expression and altering caspase-8 and FLIP expression. *Am J Physiol Gastrointest Liver Physiol* 291: G820–G829.
275. De Saint Jean M, Debbasch C, Rahmani M, et al. (2000) Fas-and interferon γ-induced apoptosis in Chang conjunctival cells: further investigations. *Invest Ophthalomol Vis Sci* 41: 2531–2543.
276. Gao J, Sana R, Calder V, et al. (2013) Mitochondrial permeability transition pore in inflammatory apoptosis of human conjunctival epithelial cells and T cells: effect of cyclosporine A. *Invest Ophthalmol Vis Sci* 54: 4717–4733.
277. Nakamura M, Matute-Bello G, Liles WC, et al. (2004) Differential response of human lung epithelial cells to Fas-induced apoptosis. *Am J Pathol* 164: 1949–1958.
278. Arai M, Yoshioka S, Nishimura R, et al. (2014) Fas/FasL-mediated cell death in the bovine endometrium. *Anim Reprod Sc*i 151: 97–104.
279. Frankel SK, Cosgrove GP, Cha SI, et al. (2006) TNF-α sensitizes normal and fibrotic human lung fibroblasts to Fas-induced apoptosis. *Am J Respir Cell Mol Biol* 34: 293–304.
280. Lee JW, Oh JE, Rhee KJ, et al. (2019) Co-treatment with interferon-γ and 1-methyl tryptophan ameliorates cardiac fibrosis through cardiac myofibroblasts apoptosis. *Mol Cell Biochem* 458: 197–205.
281. Fluhr H, Krenzer S, Stein GM, et al. (2007) Interferon-γ and tumor necrosis factor-α sensitize primarily resistant human endometrial stromal cells to Fas-mediated apoptosis. *J Cell Sci* 120: 4126–4133.
282. Boeddeker SJ, Baston-Buest DM, Fehm T, et al. (2015) Decidualization and syndecan-1 knock down sensitize endometrial stromal cells to apoptosis induced by embryonic stimuli. *Plos One* 10: e0121103.
283. Yamada K, Takane-Gyotoku N, Yuan X, et al. (1996) Mouse islet cell lysis mediated by interleukin-1-induced Fas. *Diabetologia* 39: 1306–1312.
284. Roth W, Wagenknecht B, Dichgans J, et al. (1998) Interferon-α enhances CD95L-induced apoptosis of human malignant glioma cells. *J Neuroimmunol* 87: 121–129.
285. Dey BR, Yang YG, Szot GL, et al. (1998) Interleukin-12 inhibits Graft-Versus-Host disease through a Fas-mediated mechanism associated with alterations in donor T-cell activation and expansion. *Blood* 91: 3315–3322.
286. Kobayashi T, Okamoto K, Kobata T, et al. (1999) Tumor necrosis factor α regulation of the Fas-mediated apoptosis-signaling pathway in synovial cells. *Arthritis Rheum* 42: 519–526.
287. Houghton J, Macera-Bloch LS, Harrison L, et al. (2000) Tumor necrosis factor alpha and interleukin 1β up-regulate gastric mucosal Fas antigen expression in *Helicobacter pylori* infection. *Infect Immun* 68: 1189–1195.

288. Kimura K, Gelmann EP (2000) Tumor necrosis factor-α and Fas activate complementary Fas-associated death domain-dependent pathways that enhance apoptosis induced by γ-irradiation. *J Biol Chem* 275: 8610–8617.
289. Reddy P, Teshima T, Kukuruga M, et al. (2001) Interleukin-18 regulates acute graft-versus-host disease by enhancing Fas-mediated donor T cell apoptosis. *J Exp Med* 10: 1433–1440.
290. Elzey BD, Griffith TS, Herndon JM, et al. (2001) Regulation of Fas ligand-induced apoptosis by TNF. *J Immunol* 167: 3049–3056.
291. Sharief MK, Semra YK (2002) Down-regulation of survivin expression in T lymphocytes after interferon beta-1a treatment in patients with multiple sclerosis. *Arch Neurol* 59: 1115–1121.
292. Park SM, Park HY, Lee TH (2003) Functional effects of TNF-α on a human follicular dendritic cell line: persistent NF-κB activation and sensitization for Fas-mediated apoptosis. *J Immunol* 171: 3955–3962.
293. Schlosser SF, Schuler M, Christoph PB, et al. (2003) Ribavirin and alpha interferon enhance death receptor-mediated apoptosis and caspase activation in human hepatoma cells. *Antimicrob Agents Chemother* 47: 1912–1921.
294. Schneider E, Tonanny MB, Lisbonne M, et al. (2004) Pro-Th1 cytokines promote Fas-dependent apoptosis of immature peripheral basophils. *J Immnunol* 172: 5262–5268.
295. Dondi E, Roué G, Yuste VJ (2004) A dual role of IFN-α in the balance between proliferation and death of human $CD4^+$ T lymphocytes during primary response. *J Immunol* 173: 3740–3747.
296. Kelly JD, Dai J, Eschwege P, et al. (2004) Downregulation of Bcl-2 sensitizes interferon-resistant renal cancer cells to Fas. *Br J Cancer* 91: 164–170.
297. Wu X, Pan G, McKenna MA, et al. (2005) RANKL regulates Fas expression and Fas-mediated apoptosis in osteoclasts. *J Bone Mineral Res* 20: 107–116.
298. Park SM, Kim S, Choi JS, et al. (2005) TGF-β inhibits Fas-mediated apoptosis of a follicular dendritic cell line by down-regulating the expression of Fas and caspase-8: counteracting role of TGF-β on TNF sensitization of Fas-mediated apoptosis. *J Immunol* 174: 6169–6175.
299. Drynda A, Quax PHA, Neumann M, et al. (2005) Gene transfer of tissue inhibitor of metalloproteinases-3 reverses the inhibitory effects of TNF-α on Fas-induced apoptosis in rheumatoid arthritis synovial fibroblasts. *J Immunol* 174: 6524–6531.
300. Lindkvist A, Ivarsson K, Jernberg-Wiklund H, et al. (2006) Interferon-induced sensitization to apoptosis is associated with repressed transcriptional activity of the hTERT promoter in multiple myeloma. *Biochem Biophys Res Comm* 341: 1141–1148.
301. Huerta-Yepez S, Vega M, Garban H, et al. (2006) Involvement of the TNF-α autocrine-paracrine loop, via NF-κB and YY1, in the regulation of tumor cell resistance to Fas-induced apoptosis. *Clin Immunol* 120: 297–309.
302. Corazza N, Jakob S, Schaer C, et al. (2006) TRAIL receptor-mediated JNK activation and Bim phosphorylation critically regulate Fas-mediated liver damage and lethality. *J Clin Invest* 116: 2493–2499.
303. Yang J, Epling-Burnette PK, Painter JS, et al. (2008) Antigen activation and impaired Fas-induced death-inducing signaling complex formation in T-large-granular lymphocyte leukemia. *Blood* 111: 1610–1616.
304. Nihal M, Ahsan H, Siddiqui IA, et al. (2009) (-)-Epigallocatechin-3-gallate (EGCG) sensitizes melanoma cells to interferon induced growth inhibition in a mouse model of human melanoma. *Cell Cycle* 8: 2057–2063.

305. Wu J, Wood GS (2011) Reduction of Fas/CD95 promoter methylation, upregulation of Fas protein, and enhancement of sensitivity to apoptosis in cutaneous T-cell lymphoma. *Arch Dermatol* 147: 443–449.
306. Schmich K, Schlatter R, Corazza N, et al. (2011) Tumor necrosis factor α sensitizes primary murine hepatocytes to Fas/CD95-induced apoptosis in a Bim- and Bid-dependent manner. *Hepatology* 53: 282–292.
307. Roos WP, Jöst E, Belohlavek C, et al. (2011) Intrinsic anticancer drug resistance of malignant melanoma cells is abrogated by IFN-β and valproic acid. *Cancer Res* 71: 4150–4160.
308. Fraietta JA, Mueller YM, Yang G, et al. (2013) Type I interferon upregulates Bak and contributes to T cell loss during human immunodeficiency virus (HIV) infection. *Plos Pathog* 9: e1003658.
309. Lutz A, Sanwald J, Thomas M, et al. (2014) Interleukin-1β enhances FasL-induced caspase-3/-7 activity without increasing apoptosis in primary mouse hepatocytes. *Plos One* 9: e115603.
310. Faletti L, Peintner L, Neumann S, et al. (2018) TNFα sensitizes hepatocytes to FasL-induced apoptosis by NFκB-mediated Fas upregulation. *Cell Death Dis* 9: 909.
311. Aggarwal BB, Gupta SC, Kim JH (2012) Historical perspectives on tumor necrosis factor and its superfamily: 25 years later, a golden journey. *Blood* 119: 651–655.
312. van Boxel-Dezaire AHH, Rani MRS, Stark GR (2006) Complex modulation of cell type-specific signaling in response to type I interferons. *Immunity* 25: 361–372.
313. Hunter CA, Timans J, Pisacane P, et al. (1997) Comparison of the effects of interleukin-1α, interleukin-1β and interferon-γ-inducing factor on the production of interferon-γ by natural killer. *Eur J Immunol* 27: 2787–2792.
314. Bonta IL, Ben-Efraim S (1993) Involvement of inflammatory mediators in macrophage antitumor activity. *J Leukoc Biol* 54: 613–626.
315. Stylianou E, Saklatvala J (1998) Interleukin-1. *Int J Biochem Cell Biol* 30: 1075–1079.
316. Miwa K, Asano M, Horai R, et al. (1998) Caspase 1-indenendent IL-1β release and inflammation induced by the apoptosis inducer Fas ligand. *Nat Med* 4: 1287–1292.
317. Linkermann A, Qian J, Lettau M, et al. (2005) Considering Fas ligand as a target for therapy. *Expert Opin Ther Targets* 9: 119–134.
318. Villa-Morales M, Fernández-Piqueras (2012) Targeting the Fas/FasL signaling pathway in cancer therapy. *Expert Opin Ther Targets* 16: 85–101.
319. Michael-Robinson JM, Pandeya N, Cummings MC, et al. (2003) Fas ligand and tumour counter-attack in colorectal cancer stratified according to microsatellite instability status. *J Pathol* 201: 46–54.
320. Ogasawara J, Watanabe-Fukunaga R, Adachi M, et al. (1993) Lethal effect of the anti-Fas antibody in mice. *Nature* 26: 806–809.
321. Tsujimoto Y, Shimizu S (2000) Bcl-2 family: life-or-death switch. *FEBS Lett* 466: 6–10.
322. Zhuang S, Dermirs JT, Kochevar IE (2001) Protein kinase C inhibits singlet oxygen-induced apoptosis by decreasing caspase-8 activation. *Oncogene* 20: 6764–6776.
323. Suzuki Y, Ono Y, Hirabayashi Y (1998) Rapid and specific reactive oxygene species generation during Fas-mediated apoptosis. *FEBS Lett* 425: 209–212.
324. Reinehr R, Becker S, Eberle A, et al. (2005) Involvement of NADPH oxidase isoforms and Src family kinases in CD95-dependent hepatocyte apoptosis. *J Biol Chem* 280: 27179–27194.
325. Selleri C, Sato T, Raiola AM, et al. (1997) Induction of nitric oxide synthase is involved in the mechanism of Fas-mediated apoptosis in heamopoietic cells. *Br J Heamatol* 99: 481–489.

326. Solano-Gálvez SG, Abadi-Chiriti J, Gutiérrez-Velez L, et al. (2018) Apoptosis: activation and inhibition in health and disease. *Med Sci* 6: 54.
327. Seyrek K, Lavik IN (2019) Modulation of CD95-mediated signaling by post-translational modifications: towards understanding CD95 signaling networks. *Apoptosis* 24: 385–394.
328. Pitti RM, Marsters SA, Lawrence DA, et al. (1998) Genomic amplification of a decoy receptor for Fas ligand in lung and colon cancer. *Nature* 396: 699–703.
329. Liu W, Ramagopal U, Cheng H, et al. (2016) Crystal structure of the complex of human FasL and its decoy receptor DcR3. *Structure* 24: 2016–2023.

AIMS Press