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Review

The complex functions of microRNA-150 in allergy, autoimmunity and immune tolerance

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Abstract: At present, special efforts are being made to develop the strategies allowing for activation of long-lasting antigen-specific immune tolerance in therapy of allergic and autoimmune diseases. Some of these therapeutic approaches are aimed at modulating cell functions at genetic level by using miRNA-based and miRNA-targeting treatments. Simultaneously, the crucial role of extracellular vesicles as natural miRNA conveyors is highlighted for induction of antigen-specific immune tolerance, especially that they appear to be easily manipulatable for therapeutic applications. Among other immune-related miRNAs, miR-150 is getting special attention as it is differently expressed by immune cells at various stages of their maturation and differentiation. In addition, miR-150 is involved in different signaling cascades orchestrating humoral and cell-mediated mechanisms of both innate and adaptive immune responses. Therefore, miR-150 is considered a master regulator of immunity in mammals. Currently, physiological miR-150-dependent regulatory circuits and causes of their malfunctioning that underlie the pathogenesis of allergic and autoimmune disorders are being unraveled. Thus, present review summarizes the current knowledge of the role of miR-150 in the pathogenesis and complications of these diseases. Furthermore, the involvement of miR-150 in regulation of immune responses to allergens and self-antigens and in induction of antigen-specific immune tolerance is discussed with the special emphasis on the therapeutic potential of this miRNA.

Keywords: miR-150; immune tolerance; immune suppression; allergy; autoimmunity; hypersensitivity; self-tolerance; exosomes; extracellular vesicles

1. Introduction

To function properly, the immune system requires balanced reactivity of immune cells. In particular, the ability to distinguish between danger and neutral signals allows immune cells to activate immune responses to invading pathogens and tumor antigens or maintain immune tolerance to self- and nonpathogenic antigens. Breaking of the mechanisms that provide the latter function causes autoimmune-, allergic- or hypersensitivity-related diseases.

When compared to other classes, microRNAs (miRNAs) are likely the most evolutionarily conserved type of non-coding RNA molecules. After discovery in *Caenorhabditis elegans*, miRNAs have been shown to down-regulate gene expression post-transcriptionally. Mature miRNA strands are around 22 nucleotides in length and in most cases bind to 3′ untranslated region (3′ UTR) of target mRNAs to induce their degradation. However, in certain circumstances, miRNAs may also regulate transcription or activate translation processes [1]. There is a growing evidence that miRNAs are a part of cell secretome that, when released to extracellular milieu, could be protected by either association with proteins, such as argonaute-2, or packaging into extracellular vesicles (EVs). In both forms, circulating miRNAs could be easily detected in various biological fluids and seem to be extremely stable both *in vivo* and *in vitro* [1]. These features emphasize the essential regulatory role played by miRNAs in homeostasis of the organism [2]. The complex biogenesis of miRNAs and their sophisticated biological functions have recently been outlined by Dexheimer and Cochella [3]. It is worth noting that recent advances in understanding of the latter make miRNAs promising candidates for various clinical applications, including treatment of immune-related disorders.

Along these lines, therapeutic activation of long-lasting antigen-specific immune tolerance is a critical point in allergic and autoimmune diseases that is extremely hard to achieve. One can speculate that such therapeutic maneuvers would be the most efficient when modulating cell functions at genetic level. Thus, miRNA-based and miRNA-targeting strategies deserve special attention. Simultaneously, the crucial role of EVs as natural miRNA conveyors is emphasized for induction of antigen-specific immune tolerance [4], especially that EVs could likely be quite easily manipulated for therapeutic applications [5]. However, physiological miRNA-dependent regulatory circuits and causes of their malfunctioning, which underlies the pathogenesis of particular disorder, have to be unraveled at first.

In 2005, studies on the regulation of mammalian hematopoiesis by miRNAs identified predominant miR-150 expression in resting T and B lymphocytes [6]. Two years later the crucial role of miR-150 in the development of mature T and B cells was confirmed by another group [7]. In addition, prematurely expressed miR-150 was found to block early B cell development [7]. Detailed analysis revealed the transcription factor c-Myb, targeted by miR-150 while controlling B cell maturation [8]. Further comprehensive studies outlined functions of miR-150 in normal and malignant hematopoiesis, which vary by cell lineage and differentiation stages [9]. Besides, miR-150 was also found to be rather exported than retained by immune cells [10], implying its involvement in communication between immune and neighboring cells. Moreover, increased serum concentration of EV-associated miR-150 is considered a biomarker of T and B cell activation [11,12]. Therefore at present, the complex and ambiguous role of miR-150 in physiological and pathological conditions is widely studied with the special focus on tumorigenesis and mutual interactions of immune and tumor cells [13,14]. However, the importance of miRNA-mediated immune regulation in allergic diseases has recently emerged [15–17], and miR-150 appears to be involved not only in regulation of allergic

responses but also in autoimmunity and maintenance of immune tolerance, as summarized in the current review.

2. miR-150 in type I allergic reactions

Balanced mechanisms of immune responses and tolerance remain under control of multifactorial circuits, including dynamic regulation of gene expression by miRNAs. At present, there is growing body of evidence that breaking the immune tolerance to allergens and development of allergic reactions are strictly associated with dysregulation of miRNA-mediated signaling cascades [16–18]. Thus, understanding of these aspects would greatly benefit the development of treatment strategies aiming at amelioration of imbalanced cellular interactions at genetic level.

In sensitized individuals, allergen-specific IgE antibodies trigger mast cell and basophil degranulation and release of proinflammatory mediators responsible for the development of type I hypersensitivity reactions. Those include but are not limited to allergic asthma and rhinitis, food allergy and urticaria.

Some of the first studies that focused on miR-150 involvement in allergic inflammation demonstrated its increased expression levels in lung tissue harvested from asthmatic mice sensitized to ovalbumin (OVA) [19], and then in CD4+ T lymphocytes collected from spleen of similarly sensitized animals [20]. Other studies showed that miR-150 is abundantly expressed in human CD8+ T cells isolated from peripheral blood of both asthmatic patients and healthy individuals [21]. Conversely, preliminary report suggested that miR-150 is down-regulated in mouse CD4+ T cells during OVA-induced allergic inflammation, and that transgenic mice, which overexpress miR-150, are resistant to asthma induction [22], suggesting that miR-150 may prevent the development of hypersensitivity. This could be due to the indirect regulation of GATA3, which is controlled by c-Myb, a crucial target of miR-150 [23]. GATA3 is a transcription factor that controls type 2 helper T (Th2) cell development, and thus modulates the induction of humoral and allergic responses. In addition, miR-150 is supposed to inhibit airway smooth muscle cell hypertrophic remodeling [24], which may improve asthmatic patient condition. Furthermore, down-regulated expression of miR-150 has recently been detected in colon tissue collected from symptomatic mice allergic to β-lactoglobulin [25]. The latter finding suggests that miR-150 may down-regulate type I allergy to bovine milk proteins. As discussed below, our observations imply that non-IgE-mediated allergy to casein from cow's milk could also be suppressed by EV-enclosed miR-150 [26]. Altogether, miR-150 appears to be involved in regulation of allergic reactions and thus could be considered very interesting candidate for various therapeutic applications.

3. miR-150 in delayed-type hypersensitivity (DTH) reactions

In humans, delayed-type hypersensitivity reaction underlies allergic contact dermatitis, non-IgE-mediated food allergies and celiac disease [27], as well as some autoimmune diseases, as discussed below. The first report that compared miRNA expression patterns in healthy and lesional skin revealed four different miRNAs (namely miR-21, miR-223, miR-142-3p, and miR-142-5p) that are significantly up-regulated after allergen sensitization both in human and mouse samples. Interestingly, all of them are related to T cell activation, which is observed in the pathogenesis of allergic contact dermatitis. However, miR-150 was found up-regulated in skin biopsies from patients

with contact allergy to diphenylcyclopropenone, while it was down-regulated in skin samples from mice sensitized with dinitrofluorobenzene [28]. These observations were related to the function of miR-150 in CD1d-restricted invariant NKT cell development [29], which is disrupted in miR-150 knock out mice [30]. However, invariant NKT cells seem to play a dual role in mouse contact hypersensitivity (CHS) reaction. These cells were shown, on the one hand, to regulate CHS in dinitrofluorobenzene-sensitized mice by controlling CD8+ T cell effector functions [31], while, on the other hand, to support CHS elicitation by providing IL-4 for activation of B1a lymphocytes [32]. Additionally, it was assumed that observed differences in miR-150 expression may result from its impact on antigen-presenting cell (APC) functions [29]. Accordingly, epidermal Langerhans cells from miR-150 knock out mice were found to express reduced capacity to cross-present soluble exogenous antigens to CD8+ T cells [33]. This suggests that miR-150 can drive the presentation of haptenated proteins to cytotoxic T lymphocytes in CHS. However, these aspects require further investigation.

It is worth noting that subsequent studies confirmed significant upregulation of miR-150 in lesional skin biopsies collected 3 days after hapten challenge when compared to placebo-challenged skin of dinitrofluorobenzene-sensitized human volunteers. However, miR-150 was only slightly upregulated at day 14 after challenge. Accordingly, it was postulated that the preferential expression of miR-150 at the peak of DTH reaction could promote resolution of cutaneous inflammation later on [34]. This assumption seems to be in line with our research findings.

In early 1970s the newly discovered population of suppressor CD8+ T (Ts) cells was shown to antigen-specifically suppress CHS reaction in mice. Further studies revealed that Ts cells are induced in mice by intravenous administration of a high dose of haptenated syngeneic red blood cells [35]. However, the exact mechanism of Ts cell-mediated immune suppression was uncovered by our recent studies [4]. We have demonstrated that Ts cells release miR-150 in EVs that are coated with B1 cell-secreted, antigen-specific antibody light chains [36]. These EVs with enclosed miR-150 were then proved to suppress mouse CHS reaction in a hapten-specific manner ensured by antibody light chains [37]. Analogously, we have recently found that Ts cell-derived, EV-carried miR-150 suppresses DTH to ovalbumin and casein [26,38]. Interestingly, when compared to intraperitoneal, intradermal and intravenous routes, the highest therapeutic effect of miR-150-carrying EVs was achieved after oral administration [26,38] (Figure 1). These miR-150-carrying EVs target APCs, which in turn inhibit the proliferation of CHS and DTH effector T cells [39] by inducing their apoptosis and reducing activation at the immune synapse [40]. Our current findings suggest that miR-150-carrying EVs target APCs antigen-specifically due to the surface coating of light chains that bind antigenic determinants presented by major histocompatibility complex (MHC) molecules on the surface of APCs [38]. We assumed that miR-150 stimulates APCs to release secondary EVs that inhibit DTH effector T cells [4,41]. However, this aspect remains under investigation, as discussed below.

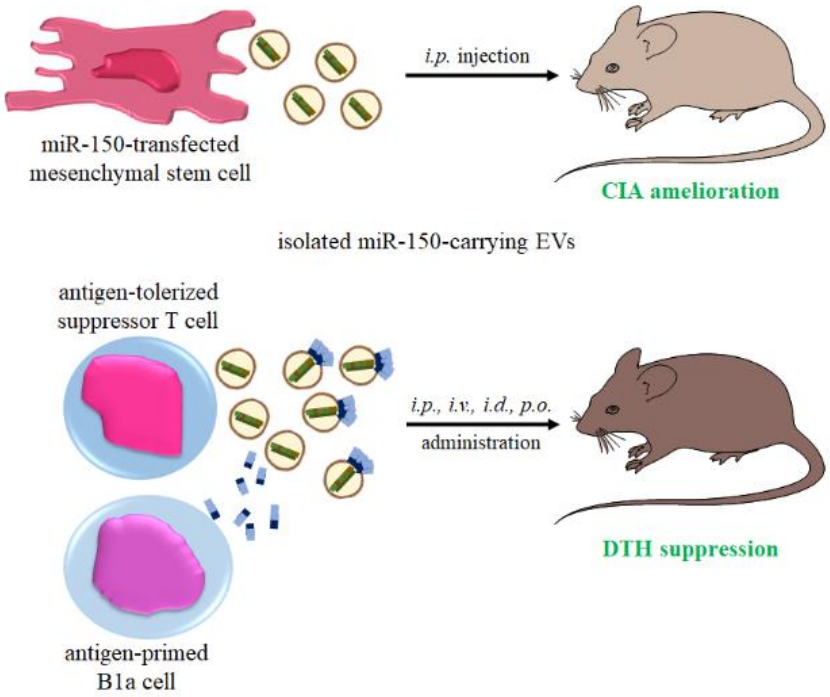

Figure 1. Postulated therapeutic activity of extracellular vesicle (EV)-transmitted miR-150. Studies in animal models showed that miR-150 delivered by EVs released by miR-150-transfected mesenchymal stem cells ameliorates the course of collagen-induced arthritis (CIA) in DBA/1 mice after intraperitoneal (*i.p.*) injection. Moreover, suppressor T cells induced by intravenous administration of antigen-conjugated syngeneic erythrocytes release miR-150-carrying EVs that are coated with B1a cell-derived antibody light chains, and then suppress delayed-type hypersensitivity (DTH) when administered *i.p.*, intravenously (*i.v.*), intradermally (*i.d.*) or *per os* (*p.o.*) to actively immunized CBA or C57BL/6 mice.

Furthermore, we have demonstrated that miR-150 can be associated with B1 cell-derived EVs to induce CHS suppression in mice [32,42]. This allowed us to propose an alternate pathway of transmission of freely circulating miRNAs to acceptor cells [42]. In addition, these findings brought an evidence for the possibility to load EVs with selected miRNAs by passive incubation, which has a very low impact on the quality of EVs [5]. In parallel, our research revealed a possible role of miR-150 in induction of self-tolerance and regulation of DTH-based autoimmune responses [40], on which our ongoing studies are focused. However, as discussed below, the role of miR-150 in autoimmunity is ambiguous (Figure 2).

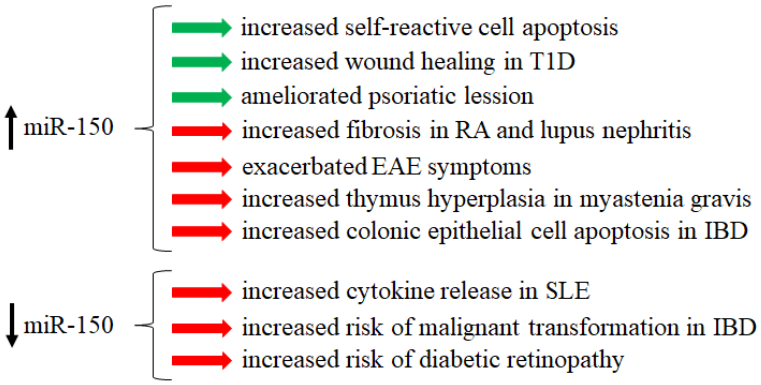

Figure 2. Effects of the changes in miR-150 expression on autoimmune responses. Scheme summarizes the beneficial (green arrows) or deleterious (red arrows) effects of either increased/induced expression of miR-150 or its knocking-out/silencing/antagonizing.

4. miR-150 in autoimmune disorders

Numerous studies imply a complex role of miR-150 in autoimmunity. As mentioned above, it is involved in regulation of B and T cell differentiation, and thereby could modulate both the induction and effector phases of autoimmune responses [43]. Moreover, depending on the targeted organ and its cellular source, miR-150 was suggested to either promote [44–47] or inhibit [48,49] the fibrosis process. Furthermore, another study showed the dysregulated miR-150 expression in inflamed but not fibrostenotic areas of intestinal mucosa collected from patients with Crohn's disease [50], implying its immune regulatory function in this disorder. In addition, miR-150 was found to play a protective role in tissue injury [51]. Moreover, our studies suggest that EV-derived miR-150 from self-antigen-activated Ts cells suppress self-reactive Th1 lymphocytes [40]. Accordingly, one can speculate that miR-150 might both prevent the progression and attenuate symptoms of various autoimmune diseases (Figure 2). Thus, we summarize below the already uncovered functions of miR-150 in particular systemic and organ-specific autoimmune disorders. It should be noted, however, that classification of autoimmune diseases as systemic and organ-specific provides a simple conceptual framework, not taking into account the diversity of their pathophysiologies.

4.1. Systemic autoimmune diseases

Systemic lupus erythematosus (SLE) is a very complex systemic autoimmune disease with variable clinical manifestations and usually severe complications, including lupus nephritis [52]. In addition, patients can develop cutaneous lupus erythematosus (CLE) that may not be associated with systemic disease [53]. Dysregulation of multiple immune cell functions in both innate and adaptive immunity leads to autoimmune responses underlying the pathogenesis of SLE. On the one hand, breaking of the tolerance to nuclear and cytoplasmic self-antigens induces autoantibody production by B cells interacting with various helper T cell populations, which is followed by immune complex formation, and multiorgan damage [54]. On the other hand, neutrophils have recently gained special attention due to their increased capacity to form extracellular traps (NETs) that can both retain autoantigens to trigger autoimmunity and induce endothelial damage to favor thrombosis, and thus

exacerbate the course of the disease [54]. These mechanisms are accompanied by dysregulation of cytokine signaling cascades. In addition, the involvement of self-reactive T cells [54] and proinflammatory macrophages [55] cannot be excluded as well. Thus, due to such multifactorial pathogenesis, SLE treatment requires holistic approach, including novel strategies allowing immune regulation at genetic level. These could be based on RNA interference technology [56], for instance with the use of miRNA mimics or inhibitors, that seem to be well suited for treating patients with systemic autoimmune diseases [56,57]. At first, however, both gene dysregulation patterns and miRNA expression profiles have to be identified for each autoimmune disorder.

Accordingly, since miR-150 modulates B cell differentiation, its possible role in SLE has already been investigated in several studies. While assessing the potential biomarker value of the B cell-related circulating microRNAs in the differential diagnosis and monitoring of SLE progression, miR-150 expression in plasma was found significantly decreased when compared to healthy controls [58–61] (Table 1). Similar decrease was observed in serum-derived EVs from SLE patients [62], and in serum of patients with CLE [63]. However, another study involving plasma samples showed that miR-150 expression was slightly upregulated [64]. These discrepancies may result from the differences in stages and manifestations of the disease between enrolled cohorts. For instance, vascular complications could increase blood cell and platelet counts and activation, which in turn was suggested to contribute to the elevated expression of miR-150 [65]. Similar elevation may likely be observed in patients with fibrotic complications, lupus nephritis especially, since miR-150 was suggested to promote renal fibrosis by reducing the antifibrotic activity of the suppressor of cytokine signaling 1 (SOCS1) and enhancing the synthesis of profibrotic proteins in both proximal tubular and mesangial cells [47]. Furthermore, combined assessment of miR-21, miR-29c, and miR-150 expression in EVs collected from urine is considered very interesting candidate for non-invasive detection and monitoring of renal fibrosis in lupus nephritis in adults [66], while assessing miR-125a, miR-150, and miR-155 in the urine supernatant may complement the current strategy for estimating the activity of lupus nephritis in children [67]. Besides, miR-150 expression could be considered a potential biomarker of histological changes in the progression of lupus nephritis [68]. In addition, miR-150 levels seem to correlate with peripheral blood plasmacytoid dendritic cell and skin CD4+IL-4+ T cell counts in patients with CLE [63]. Finally, the expression of miR-150 appears to correlate positively with the ratios of CD19+IgD−CD27− B cells and plasmablasts in peripheral blood of SLE patients [69]. Altogether, changes in miR-150 expression were included to the signature of a SLE-related miRNA profile by analyzing the Gene Expression Omnibus repository [68]. On the other hand, one can speculate that therapeutic silencing of miR-150 activity could ameliorate renal fibrosis. This could likely be achieved by inhibiting miR-150 with various types of anti-sense inhibitors or by sponging it with the use of circular RNAs containing complementary binding sites to particular miRNA strand [70]. Accordingly, Luan et al. have already identified circHLA-C as a candidate sponge RNA for miR-150 by examining human kidney tissue samples from subjects with lupus nephritis [71], and showed that locked nucleic acid (LNA)-anti-miR-150; i.e. antisense oligonucleotide that binds to miR-150 to inhibit its function, ameliorates the course of lupus nephritis in a mouse model [45].

Expression of particular miRNA in peripheral blood can be measured not only in total plasma/serum, plasma/serum-derived EVs and EV-depleted plasma/serum, but also in isolated cell populations. Accordingly, miR-150 was found down-regulated in purified T cells of SLE patients when compared to healthy individuals [72]. Furthermore, various mouse models of SLE are

characterized by an increased frequency of an atypical NK cell subset that expresses significantly less miR-150 than conventional NK cells [73]. These atypical NK cells found in lupus-prone mice may refer to CD56+ NK cell subpopulation, which number increases in SLE patients even though the general counts of NK cells seem to decrease. Interestingly, this NK cell subpopulation generates cytokines efficiently at inflamed sites [73], which implies its possible involvement in SLE pathogenesis. Altogether, these findings suggest that decreased miR-150 activity in immune cells may underlie their proinflammatory activation in SLE. Therefore, one can assume that up-regulation of miR-150 expression in these cells would produce beneficial effects.

Along these lines, approximately 4-fold decrease in miR-150 expression was found in splenocytes collected from lupus-prone mice. This was accompanied by the up-regulation of triggering receptor expressed on myeloid cells 1 (TREM-1) on splenic conventional dendritic cells of mice with SLE, which was found responsible for amplification of TLR4-dependent proinflammatory cytokine release. Bioinformatic analysis revealed that miR-150 may target TREM-1 mRNA, and further analysis confirmed significant reduction of TREM-1 protein level in miR-150-transfected dendritic cells [74]. These findings suggest that miR-150 down-regulation in immune cells and circulating blood plasma promotes SLE development and progression. Thus, miR-150 could be considered a promising candidate for cell-directed therapeutic applications in SLE. Conversely, as mentioned above, its tissue-targeted therapeutic silencing could offer therapeutic benefit in the case of lupus nephritis.

Similarly to SLE, enhanced B cell activity characterized by autoantibody production is the hallmark of primary Sjögren's syndrome, a common systemic autoimmune disease affecting mainly the exocrine glands. In some patients, the decreased lacrimal and salivary secretion could be accompanied by a variety of extraglandular manifestations [75]. In addition, secondary Sjögren's syndrome can also develop in individuals with other autoimmune connective tissue diseases, such as SLE and rheumatoid arthritis [75]. While other miRNAs have been widely studied in this disease, the decreased miR-150 expression was confirmed so far in one study [69] (Table 1). Interestingly, this decrease seems to be more pronounced than in SLE patients. However, no difference in miR-150 levels was shown between patients with glandular symptoms only and those with accompanying extraglandular manifestations [69]. Thus, down-regulation of this miRNA in immune cells appears to favor the development of Sjögren's syndrome, thereby implying its therapeutic potential. However, another study implied the increase in miR-150 expression in serum from patients enrolled to discovery cohort, but this observation was not repeated in validation cohort [76]. Thus, the role of miR-150 in Sjögren's syndrome requires further investigation.

Scleroderma (systemic sclerosis, SSc) is an autoimmune connective tissue disease of unknown etiology with a chronic and quite unpredictable course with prominent inflammatory and vascular manifestations, which are thought to trigger the activation of fibroblasts and excessive production of extracellular matrix. As a result, SSc affects skin and multiple internal organs due to the occurrence of widespread parenchymal fibrosis that is its distinguishing characteristic feature.

The large cross-sectional study, aimed at validating selected miRNAs for the highest diagnostic accuracy, made miR-150 strong classifier for SSc in comparison to SLE [59], thereby suggesting the possible usefulness of miR-150 as biomarker for differential diagnosis of these diseases (Table 1). However, this study showed no significant correlation of circulating miRNA profiles with clinical variables, including autoantibody presence [59]. Another research demonstrated the increased miR-150 expression in peripheral blood mononuclear cells from patients with SSc. However,

miR-150 transcript levels negatively correlated with mRNA for survivin, one of the apoptosis inhibitors [77]. The latter indicates that up-regulated miR-150 expression may promote apoptosis of self-reactive lymphocytes, and thus ameliorate the course of SSc.

Additionally, another study conducted in Japan suggested that miR-150 may likely also alleviate the symptoms of SSc. Along these lines, this research demonstrated significant decrease of miR-150 levels both in fibroblasts obtained by lesional skin biopsy and in serum [49]. Further analysis revealed that normal fibroblasts transfected with miR-150 inhibitor were characterized by an increased integrin β3 and type I collagen expression, which resembles fibroblasts from SSc patients. Molecular examination of the latter cells showed that their transfection with miR-150 mimic diminished the up-regulated expression of integrin β3, phosphorylated Smad3, and type I collagen. Finally, *in vivo* visualization demonstrated reduced miR-150-emitted signal detected in SSc fibroblasts located between the thickened collagen bundles, when compared to normal skin fibroblasts with no differences between other cell types [49]. Altogether, these results imply that miR-150 prevents fibroblast overactivation that characterizes SSc. This assumption appears to be supported by experimentally observed anti-fibrotic effect of miR-150. Interestingly, its direct cleaving by IRE1α kinase seems to mediate fibrosis in SSc [78]. On the other hand, serum miR-150 levels seemed to correlate with the prevalence of pitting scars or ulcers and the incidence of anti-topoisomerase I autoantibody [49,79]. In this regard, miR-150 could be considered an epigenetic biomarker of disease severity [80].

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease predominantly driven by CD4+ Th cells and autoantibody-producing B lymphocytes and affecting mainly the joints [81]. Some studies have already suggested the role of miR-150 in this disease [82].

Experimental approaches demonstrated that miR-150 inhibits SOCS1 and promotes the growth of MH7A cell line, i.e. RA synovial fibroblasts [83]. Since inflammatory-activated synovial fibroblasts play a deleterious role in the course of RA, these observations implied the detrimental role of miR-150 in disease progression. Accordingly, miR-150 sponging by long non-coding RNA LINC01197 was found to inactivate the TLR4/NF-κB signaling pathway, and thus to alleviate inflammation in experimental RA model [84].

Along these lines, IL-17-producing CD4+ Th17 lymphocytes drive tissue inflammation and thus exacerbate the symptoms of RA [81]. Interestingly, miR-150 was found significantly up-regulated in IL-17-producing T cells expanded from peripheral blood of healthy subjects, when compared to unexpanded T cells. Furthermore, this study showed a significant increase in miR-150 level in peripheral blood mononuclear cells of RA patients, compared to healthy controls and patients suffering from osteoarthritis. When compared to synovium from subjects with osteoarthritis, increased miR-150 expression was observed in synovial tissues characterized by hyperplasia and infiltration of inflammatory cells, including Th17 cells, that were collected from RA patients with severe joint destruction [85]. These findings seem to be in line with abovementioned experimental observations, and suggest the possible deleterious role of miR-150 in the course of RA, especially in enhancing its severity. A significantly increased miR-150 expression was also detected in peripheral blood mononuclear cells from RA patients [86] (Table 1). Subsequent study also showed the significant up-regulation of serum miR-150 level, suggesting simultaneously that serum concentration of miR-150 cannot be used to discriminate between “good” and “poor” responders to the conventional therapy [87]. However, prior study demonstrated no significant changes in miR-150 levels analyzed in RNA samples extracted from the whole blood obtained from Canadian patients

with RA, their seropositive first-degree relatives and matched healthy controls [88]. In addition, lower miR-150 levels in serum, synovial tissue homogenates as well as in isolated fibroblast-like synoviocytes were shown in samples obtained from Chinese patients with RA who underwent synovectomy or joint replacement, when compared with subjects with osteoarthritis [89]. In addition, this research evaluated the putative therapeutic potential of miR-150 derived by EVs released by miR-150-transfected mesenchymal stem cells, and showed that it down-regulates the expression of matrix metalloproteinase-14 (MMP14) and vascular endothelial growth factor (VEGF) in fibroblast-like synoviocytes from RA patients as well as significantly alleviates the course of collagen-induced arthritis (CIA) in DBA/1 mice [89] (Figure 1). These observations imply that EV-enclosed miR-150 could be therapeutically used for suppressing autoimmune responses in RA, which seems to be in line with our findings that this miRNA may induce immune tolerance to self-antigens [40].

Cigarette smoking has recently been considered an environmental factor that exacerbates the course of RA [90]. One can speculate that this effect could at least partly result from the impact on miRNA expression profile. Interestingly, in the case of Swedish RA patients, miR-150 level was found increased in peripheral blood CD8+ T cells in smokers compared to non-smoking patients. In addition, *in vitro* stimulation of smoker's CD8+ T cells with nicotine appeared to enhance miR-150 expression in these cell population, which was suggested to block the formation of memory lymphocytes [91]. Thus, one can assume that smoking may also impair development of acquired anti-viral and anti-tumor immunity by RA patients through enhancing miR-150 activity.

miR-150 was down-regulated in all of the plasma samples from patients with radiographic axial spondyloarthritis [92]. Furthermore, Spanish research group reported the lower level of miR-150 in plasma samples from patients with ankylosing spondylitis. In addition, this miRNA was also found decreased in patients with psoriatic arthritis, another subtype of spondyloarthritis. Therefore, plasma level of miR-150 was suggested a suitable biomarker for the prediction of both spondyloarthritis and severe structural joint damage [93] (Table 1).

A study conducted in Israel that examined miRNA profiles in normal skin and both uninvolved and lesional skin biopsies collected from patients with psoriasis revealed the significant under expression of miR-150 in uninvolved psoriatic skin, compared to normal and psoriatic lesion skin [94]. Thus, it was speculated that miR-150 down-regulation may promote the development of psoriatic lesions. In addition, *in situ* hybridization demonstrated that miR-150 was mostly expressed in the upper part of the epidermis in normal skin, while was either not found in uninvolved skin, or found evenly distributed in psoriatic epidermis. These observations suggested that this miRNA could regulate keratinocyte proliferation and differentiation [94], thereby preventing psoriasis development. Along these lines, subsequent research demonstrated that experimentally-induced overexpression of miR-150 in HaCaT cell line and primary human keratinocytes results in reduced viability and proliferation of both cell populations, while miR-150 inhibition exerts the opposite effect. Detailed analysis revealed that this miRNA affects keratinocyte viability by regulating hypoxia-inducible factor (HIF)-1α and vascular endothelial growth factor A (VEGFA) protein expression, with the strongest effect induced in hypoxic conditions. In addition, expression of HIF-1α and VEGFA negatively correlated with miR-150 level in psoriatic skin [95]. Based on these, one can assume that hypoxia-induced under expression of miR-150 may increase the proliferation of keratinocytes by up-regulating HIF-1α activity [96]. Thus, these findings imply the therapeutic potential of miR-150 in active psoriasis. In contrast to previously mentioned study [94], Li et al. [95] found that the

expression of miR-150 was significantly down-regulated in lesional skin tissues, compared to uninvolved skin, while examining paired lesional and non-lesional psoriatic skin biopsies collected from Chinese psoriatic patients. However, they found that lower miR-150 expression significantly correlated with disease severity, which seems to validate miR-150 therapeutic potential in psoriasis. Furthermore, based on the findings of Italian research group, the relative quantities of serum miR-150 were proposed for use as a readout of the inflammatory state in psoriatic patients before and after effective treatment with an anti-TNF-α biologics [97] (Table 1). Remarkably, Torri et al. [97] also reported that miR-150 is significantly enriched in regulatory T (Treg) cell-derived EVs, when compared to EVs released by CD4+ Th1 and Th17 lymphocyte populations, and that it is able to down-regulate c-Myb mRNA. Accordingly, it is worth noting that Treg cell-released EVs were proposed to suppress Th1 cell function [98], and we demonstrated that Ts cell EV-contained miR-150 suppresses Th1 cell-driven DTH reaction to self-antigens [40]. Thus, since Th1 lymphocytes are involved in psoriasis pathogenesis, one can speculate that EV-carried miR-150 may be successfully used for treatment of psoriatic patients in the future.

Inflammatory bowel disease (IBD) is associated with chronic relapsing inflammation in the gastrointestinal tract and comprises Crohn's disease affecting different areas of the digestive tract and often spreading into the deeper layers of mucosal tissue, ulcerative colitis that affects colon and rectum, and IBD-unclassified disorders. Intestinal epithelial barrier malfunctioning plays a critical role in the pathophysiology of IBD, and miR-150 appears to be involved in this process [99]. Namely, levels of miR-150 in colon tissue were found to increase following treatment of mice with colitis-inducing dextran sulphate sodium (DSS), when compared to normal colon samples. Similarly, elevated miR-150 levels were detected in human colon tissues collected from patients with active ulcerative colitis, compared to samples obtained from healthy subjects. In both cases, increased miR-150 expression was accompanied with c-Myb down-regulation, which was suggested to induce the colonic epithelial cell apoptosis and thus to drive epithelial barrier dysfunction and increase its permeability [100]. Interestingly, elevation of miR-150 could be reduced by administering probiotics, such as *Escherichia coli* Nissle 1917 [101], *Bifidobacterium bifidum* ATCC 29521 [102], or *Lactobacillus fermentum* CECT5716 [103], to mice with DSS-induced colitis.

On the other hand, altered microRNA biogenesis resulting in decreased miR-150 activity was suggested to intensify intestinal inflammation following ethanol and burn injury [104]. Similarly, another study revealed the down-regulated miR-150 expression in inflamed but not fibrostenotic areas of intestinal mucosa collected from patients with Crohn’s disease [50], which suggested its important anti-inflammatory function in this disorder. Additionally, diminished anti-fibrotic activity of miR-150 may contribute to IBD progression by promoting intestinal fibrosis [105]. miR-150 was also proposed to regulate the impaired fibroblast’s autophagy in IBD [105,106]. Besides, significant decrease in serum miR-150 level was observed in patients with ulcerative colitis that were not sensitive to glucocorticoids, implying its role as a biomarker of treatment resistance [107]. Finally, reduced expression of miR-150 in intestinal mucosa may promote colitis-induced malignant transition [108].

4.2. Organ-specific autoimmune diseases

Multiple sclerosis (MS) is a quite common, chronic autoimmune disease with predominant aberration of CD4+ T-cell functions, Th1, Th17, and Treg lymphocytes especially. However, a

critical role of self-antigen-presenting B cells and monocytes/macrophages in MS pathogenesis has recently emerged [109]. MS is characterized by chronic inflammation that affects the central nervous system and leads to demyelination, which in turn is responsible for degenerative processes. The most common course of MS; i.e. relapsing-remitting MS, is associated with exacerbations of symptoms and remission periods linked to the kinetics of inflammatory responses.

The role of miR-150 in MS is widely studied due to its immune regulatory potential. So far, analysis of its expression in various samples from MS patients has produced inconsistent results (Table 1), likely due to the diversity among clinical stages and treatment protocols between the enrolled individuals [110–113]. On the other hand, two-step assessment of the profile of circulating miRNAs in cell-depleted cerebrospinal fluid in large cohorts of patients with MS and controls uncovered miR-150 as a leading biomarker candidate for MS diagnosis and monitoring. In addition, miR-150 levels correlated with clinical markers of active inflammation and changed under the influence of treatment with natalizumab and fingolimod [114]. Along these lines, the findings of Spanish study suggested that increased miR-150 levels in cerebrospinal fluid may have a biomarker potential also in subjects with lipid-specific oligoclonal IgM bands [115]. Besides, the results from other study conducted in the Netherlands suggested that miR-150 levels in cerebrospinal fluid differ depending on the MS onset [116].

Discrepancy of the results obtained in clinical studies increases the value of examination of the role of miRNAs in a well-established mouse model; i.e. experimental autoimmune encephalomyelitis (EAE). Interestingly, miR-150 knock out mice were shown to develop less severe EAE than wild type mice as indicated by lower clinical scores and reduced demyelination. This suggested that miR-150 may exacerbate the course of EAE [110]. Accordingly, another research demonstrated the increased miR-150 levels in mouse spinal cord at the acute phase of EAE. However, at the chronic phase, level of miR-150 in spinal cord significantly decreased. Similar decrease was observed in mouse bone marrow-derived macrophages following activation with lipopolysaccharide. In addition, expression of miR-150 negatively correlated with expression of PU.1 transcription factor both in spinal cord and in activated macrophages. Further attempts to unravel these findings demonstrated that miR-150 alters macrophage inflammatory activation and shifts their polarization towards anti-inflammatory M2-like phenotype by targeting PU.1 mRNA [117]. Therapeutic modulation of this pathway may thus alleviate the symptoms of EAE.

Recently, some studies assessed the impact of agents considered for MS therapy on miR-150 expression. The randomized, double-blind, placebo-controlled trial involving 50 Iranian MS patients demonstrated that treatment with nanocurcumin elevates the down-regulated expression of miR-150 in peripheral blood mononuclear cells [118]. On the other hand, treatment of EAE mice with a combination of Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) extracted from *Cannabis* was demonstrated to significantly down-regulate miR-150 expression in brain-derived CD4+ T cells [119].

The idiopathic inflammatory myopathies constitute a heterogeneous group of diseases characterized by myositis of autoimmune origin. They comprise dermatomyositis, polymyositis and inclusion body myositis that can occur in juvenile and adult patients. Cytotoxic CD8+ T cell responses dominate the underlying pathomechanism of the latter two disorders, while autoantibody-driven complement activation is observed in dermatomyositis [120]. Rarely, such myopathies may also develop in patients with other autoimmune diseases, SLE especially [121]. So far, a single study examined the expression of immune-related microRNAs in dermatomyositis, and

showed the significantly decreased level of miR-150 both in serum and peripheral blood mononuclear cells (Table 1). Furthermore, among other miRNAs tested, miR-150 was the most significantly down-regulated in serum from dermatomyositis patients with autoantibodies against either antinuclear matrix protein 2 (NXP2) or melanoma differentiation-associated gene 5 (MDA5), when compared to subjects without these autoantibodies. Simultaneously, its serum concentration was significantly higher in patients with either nonspecific interstitial pneumonia or organized pneumonia than in those with usual interstitial pneumonia [122].

Myasthenia gravis is a chronic autoimmune disorder, in which autoantibodies target in most cases the nicotinic acetylcholine receptors. This leads to the weakness and rapid fatigue of the striated muscles. The biomarker role of miR-150 in myasthenia was discovered quite early [123] (Table 1). In addition, this research revealed that thymectomy reduced miR-150 levels in most of the patients, which was associated with significant improvement in clinical condition, while the two patients with increased miR-150 levels that had been preserved after thymectomy failed to achieve remission [123]. The elevation of serum miR-150 level was then validated in a larger cohort of myasthenic patients. However, these subsequent studies also suggested that miR-150 increase is observed in subjects not treated with immunosuppressant drugs, while miR-150 levels in serum of patients undergoing immunosuppressive medication was comparable to that of healthy controls [124]. Similarly, lowering of serum miR-150 was observed in thymectomized individuals 24 months after the surgery [125], in patients with mild disease after 12-week period of supervised aerobic and resistance training [126], as well as in patients with late onset myasthenia gravis after inclusion of immunosuppressive therapy [127]. Thus, serum miR-150 levels were proposed to serve as a biomarker in patients with generalized myasthenia gravis [128,129], with much lower sensitivity in the case of ocular disease [130]. Finally, bioinformatic analysis predicted that miR-150 expression in myasthenic patients could be regulated by various inflammation- or estrogen-activated transcription factors [131]. Other independent pilot studies confirmed the biomarker potential of miR-150, and additionally found the reduction of miR-150 levels in serum-derived EVs after treatment with low doses of rituximab in 12 Chinese patients with acetylcholine receptor antibody-positive refractory myasthenia gravis. Interestingly, miR-150 reduction correlated with decreased numbers of CD19+ B cells [132]. However, further examination of the consequences of miR-150 dysregulation in myasthenia uncovered its increased levels in the hyperplastic thymuses, which correlated with the presence of B cells, and decreased expression in peripheral blood CD4+ T cells [133]. Therefore, it was speculated that miR-150 is one of the leading modulators of altered B- and T-cell reactivity in myasthenia gravis [134].

Type 1 diabetes mellitus (T1D), so-called juvenile diabetes or insulin-dependent diabetes, is a chronic condition that in most cases results from autoimmune damage of islets of Langerhans in pancreas. Pathologic immune response to β cell self-antigens is mostly driven by both CD4+ and CD8+ T cells, but the involvement of autoantibody-secreting B lymphocytes along with innate immune cells has recently been highlighted as well [135]. Spanish study demonstrated the decreased levels of miR-150 in peripheral blood mononuclear cells without any correlation with the autoimmune profile of the patients [136]. However, subsequent Chinese research confirmed the significant decrease of miR-150 level in peripheral blood mononuclear cells of T1D patients, comparing to both type 2 diabetic subjects and healthy controls [137]. These findings suggested both the biomarker potential of miR-150 and its role in regulation of autoimmune response [138] (Table 1). Next studies demonstrated the down-regulated expression of miR-150 in plasma EVs from

T1D patients, especially those with retinopathy [139], whereas in the case of patients suffering from type 2 diabetes complicated with nephropathy, miR-150 was up-regulated in both serum [140] and urine [141] EVs. This suggests an inverse role for miR-150 in type 2 diabetes. Especially that further analysis revealed that reduced miR-150 expression together with increased expression of miR-21 and miR-30b in plasma EVs from T1D patients could be considered a hallmark of diabetic retinopathy [142]. Accordingly, the role of miR-150 seems to negatively correlate with HIF-1α activity, which may be responsible for hypoxia-induced damage of the blood vessels in the diabetic eye [142]. Thus, one can speculate that miR-150 down-regulation likely promotes not only the pathogenesis of T1D but also of its complications.

Table 1. The biomarker potential of miR-150 in autoimmune diseases.

Disease	Observed changes in miR-150 expression	Patient's cohort	Reference
SLE	Decrease in plasma	50 Chinese*	[58]
		29 Danish*	[59]
		13 Taiwanese*	[61]
	Decrease in serum EVs	5 Chinese*	[62]
	Increase in plasma	30 Chinese*	[64]
Lupus nephritis	Decrease in plasma	26 Iranian*	[60]
	Increase in urinary EVs	45 Spanish*	[66]
CLE	Decrease in serum	42 Mexican*	[63]
Sjögren's syndrome	Decrease in peripheral blood mononuclear cells	8 Hungarian*	[69]
SSc	Increase in plasma	120 Danish*	[59]
	Increase in peripheral blood mononuclear cells	50 Iranian*	[77]
	Decrease in serum	40 Japanese*	[49]
RA	Increase in peripheral blood mononuclear cells	6 Japanese*	[85]
		50 Iranian*	[86]
	Increase in serum	90 Iranian*	[87]
Spondyloarthritis	Decrease in plasma	15 American*	[92]
		53 Spanish*	[93]
Psoriasis	Increase in serum	39 Italian*	[97]
MS	Decrease in peripheral blood mononuclear cells	19 Italian*	[112]
	Decrease in isolated T cells	10 Swedes*	[113]
Dermatomyositis	Decrease in serum	49 Chinese*	[122]
	Decrease in peripheral blood mononuclear cells	49 Chinese*	[122]
Myasthenia gravis	Increase in serum	4 Swedes*	[123]
		71 Swedes*	[124]
T1D	Decrease in peripheral blood mononuclear cells	20 Spanish*	[136]
		78 Chinese*#	[137]

*versus healthy control; #versus patients with type 2 diabetes.

Along these lines, miR-150 derived by small EVs isolated from the culture of human umbilical cord blood mononuclear cells was found crucial in wound healing in mice with streptozotocin-induced T1D. By targeting MYB gene, miR-150 was suggested to increase

keratinocyte proliferation and fibroblast migration to promote re-epithelization and neovascularization processes [143]. Furthermore, recent experimental investigation in non-obese mice with streptozotocin-induced T1D revealed that activation of nuclear factor-kappa B (NF-κB) elevates the expression of miR-150, which then suppresses p53-up-regulated modulator of apoptosis (PUMA) to inhibit the T1D-associated inflammation and β-cell apoptosis [144]. In contrast, however, other studies demonstrated the elevated levels of miR-150 in both plasma and islet xenografts of humanized mice prior to the development of hyperglycemia and graft rejection, which implied the possible involvement of miR-150 in early β-cell loss [145]. Thus, these contradictory findings indicate the need for further research to validate the role of miR-150 in pathologic autoimmune responses underlying T1D.

So far, several studies have also investigated the involvement of miR-150 in other autoimmune disorders that are less common in humans. Accordingly, Japanese research demonstrated that miR-150 was the most commonly up-regulated miRNA in serum from patients with autoimmune pancreatitis, when compared to healthy controls and patients with other pancreatic diseases [146]. Furthermore, a study conducted in Poland demonstrated significantly increased miR-150 expression in liver tissues collected from patients undergoing transplantation due to primary biliary cholangitis. Additionally, in this study miR-150 levels in serum were found higher in the case of anti-mitochondrial antibody (AMA)-negative patients, when compared to AMA-positive patients and healthy controls. This suggests the inhibitory activity of this miRNA against AMA-secreting B cells [147]. In contrast, Chinese study showed the significant decrease in miR-150 expression in peripheral blood B lymphocytes from patients suffering from autoimmune hemolytic anemia/Evans syndrome in active hemolysis phase, when compared to healthy controls and subjects with remission. Moreover, miR-150 levels negatively correlated with c-Myb expression, suggesting the therapeutic potential of overexpressed miR-150 in suppression of the autoimmune B-cell responses in autoimmune cytopenia [148]. In addition, the reduced expression of miR-150 was found in untreated patients with a rare autoinflammatory disorder called tumor necrosis factor-receptor associated periodic syndrome (TRAPS), and this reduction was reversed by treatment with anakinra [149].

5. Postulated molecular effects of miR-150 targeting

Findings discussed above imply the crucial role of miR-150 in modulating T cell [43] and B cell activities [69] in autoimmunity. In addition, miR-150 influences the functions of innate immune cells, including macrophages [39,150,151], NK cells and NKT cells [43]. Finally, this miRNA appears to contribute to both the induction of immune tolerance to self-antigens and suppression of allergies and autoimmunity by Treg and Ts lymphocytes [40,98]. However, the exact molecular mechanisms underlying miR-150-induced effects remain to be elucidated.

c-Myb is a first discovered transcription factor targeted by miR-150 [7,8]. An inhibition of B cell development along with a reduction in B1 cell numbers is observed as a result of c-Myb down-regulation. Thus, this mechanism may at least partly underlie the suppressive effect of miR-150 in B-cell-dependent autoimmune and allergic responses [148]. Furthermore, targeting of this and other transcription factors made miR-150 an important regulator of hematopoiesis, thereby being able to orchestrate the differentiation of immune cells, including T lymphocytes and NKT cells [9]. On the other hand, miR-150-mediated c-Myb targeting in other cell types may induce

opposite effect; i.e. may exacerbate the course of autoimmune disease, as suggested above in the case of IBD [100].

However, a growing body of research demonstrates the involvement of miR-150 in regulation of various intracellular signaling cascades both in physiological and pathological conditions. Some of them seem to contribute to regulation of allergic and autoimmune responses as well (Figure 3).

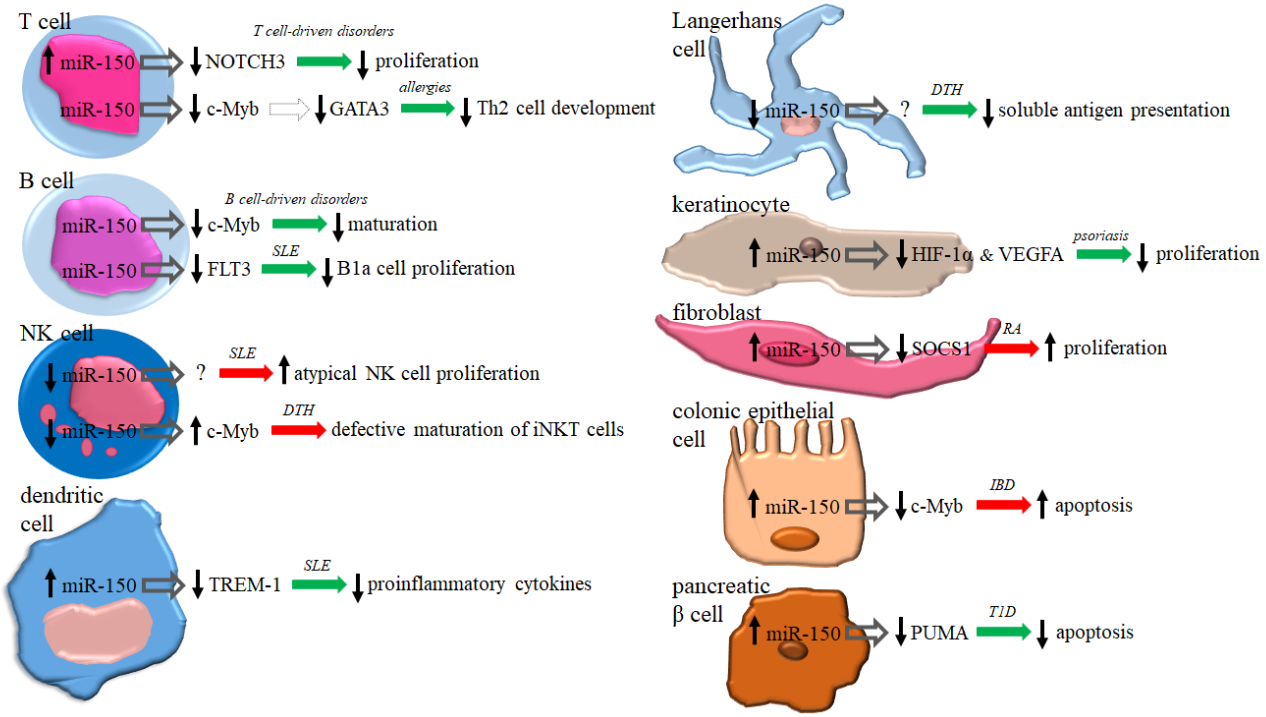

Figure 3. miR-150-induced effects at the cellular and molecular level. Depending both on the cell population and the targeted molecule, miR-150 may induce different, beneficial (green arrows) or deleterious (red arrows) effects in particular allergic or autoimmune disorders. Up and down arrows indicate the expression of miR-150 that was experimentally forced/induced or depleted/antagonized, respectively. Dotted-line arrow points out that miR-150 modulates Th2 cell differentiation indirectly, as described in the main text.

Along these lines, it was shown that miR-150 targets the 3′UTR of CD25 mRNA in cytotoxic CD8+ T cells [152]. This effect is supposed to regulate IL-2 signaling in a manner that promotes effector CD8+ T lymphocytes to differentiate into memory cells [153]. Thus, one can speculate that miR-150 favors the formation of immunological memory for example in cytotoxic T cell-dependent delayed-type hypersensitivities, such as Stevens-Johnson syndrome, and autoimmune disorders, including some myopathies. Furthermore, this miRNA plays a role in enhancing the activation of effector Th lymphocytes by dendritic cells by regulating early growth response 2 (EGR2) expression in the latter cells, as shown in chronic rhinosinusitis [154].

In contrast, EV-enclosed miR-150 mediates immune regulatory activity of Treg and Ts lymphocytes, as discussed above [40,98], emerging the therapeutic potential of miR-150 contained in

EVs [155]. Treg and Ts cell-derived EVs were shown to suppress effector Th1 cell functions in contact and autoimmune hypersensitivities in miR-150-dependent manner [36,38,40,98]. This effect could be achieved by miR-150 through down-regulating the v-akt murine thymoma viral oncogene homolog 3 (AKT3)/B-cell lymphoma 2 interacting mediator of cell death (BIM) signaling [156], and CD28-dependent co-stimulatory pathway [157] in CD4+ T cells. Furthermore, Treg and Ts cell-derived EV-contained miR-150 was shown to induce the tolerogenic activity of dendritic cells [158] and antigen-primed macrophages [38,39], respectively. In addition, miR-150 was proposed to regulate the immune suppressive activity of myeloid-derived suppressor cells (MDSCs) induced by ligation of aryl hydrocarbon receptor (AhR) [159]. Interestingly, AhR is involved in maintenance of intestinal homeostasis, and its malfunctioning was linked to experimental and human intestinal bowel disease [159]. These observations bring another evidence for the important role of miR-150 in IBD.

It is worth noting that together with miR-99a, miR-150 promotes the differentiation of Treg lymphocytes by repressing mTOR-dependent signaling [160]. Moreover, miR-150 expression was found to increase in B lymphocytes upon B-cell receptor (BCR) stimulation, which was shown to induce their apoptosis during antigen-driven selection process [161]. On the other hand, high-level expression of miR-150 was found to inhibit BCR signaling potential in malignant B cells [162]. Since miR-150 plays an important role in malignant hematopoiesis [9], lessons learned from these observations [162–164] may also have a great importance in attempts to induce antigen-specific immune tolerance and to control allergic and autoimmune responses.

Besides, the number of B1a cells is increased in patients with SLE, and these cells seem to be involved in pathogenic autoimmune responses, while miR-150 could likely inhibit their proliferation. Accordingly, it was demonstrated that the expression of a histone H2A deubiquitinase; i.e. Myb Like, SWIRM And MPN Domains 1 (MYSM1) recruits c-Myc to activate the transcription of miR-150, which then inhibits the FMS-like tyrosine kinase 3 (FLT3). This in turn inhibits the proliferation of B1a cells [165]. Conversely, miR-150 can inhibit cell apoptosis by targeting NF-κB1 pathway, as shown in the case of human umbilical vein endothelial cells [166].

Finally, miR-150 expression appears to be induced by glucocorticoid therapy [167], which suggests its possible involvement in beneficial immunosuppressive effect of this treatment in patients with allergies and autoimmune disorders. However, glucocorticoid treatment suppresses the reactivity of immune cells not selectively. Thus at present, searching for new strategies to induce antigen-specific immune tolerance is a crucial approach for therapy of allergies and autoimmune diseases. In this regard, miR-150 appears to be an interesting candidate for genetic-based strategies. Especially that, as shown by our data, it could be transferred by EVs equipped with antigen-specific antibody light chains, which ensures the specificity of miR-150 targeting and activity against APCs [26,36–40,42]. In turn, the latter cells release miR-150-carrying EVs expressing MHC class II molecules to suppress allergen- and self-reactive effector T lymphocytes [168].

6. Conclusions

Ability to therapeutically induce durable antigen-specific immune tolerance would be a crucial step forward in treatment of allergic and autoimmune diseases. miR-150 is well known to regulate immune responses, thus is considered an interesting and efficient modulator of immune cell functions at genetic level (Figure 3). However, miR-150 activities seem to vary depending on both

the target cells and the immune mechanisms that underlie the pathogenesis of a particular allergic or autoimmune disease. Accordingly, in some instances miR-150 overactivation seems to contribute to the development of autoimmunity, while in other circumstances it induces the opposite effect, i.e. it appears to inhibit the activity of self-reactive immune cells (Figure 2). Thus, detailed investigation of the role of miR-150 in each immune-related disorder is essential for further approaches of its use in personalized therapies (Figure 1).

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Conflict of interest

The author declares no conflict of interest.

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