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Review

Instrumentals behind embryo and cancer: a platform for prospective future in cancer research

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Abstract: The cancer cells could be celled biomass without normal cellular regulation. They bypass most of the signaling pathways leading to programmed cell division. On the other hand, the embryos are highly regulated, giving rise to the whole organism based on the planned regulation. Understanding the bridge concepts between them might be an interventional art for discovering valuable cancer drugs. The present review highlighted the most similarities between them and recent literary works.

Keywords: human embryo; signal transduction; embryogenesis; anticancer agents; tumor cells

1. Introduction

Anticancer drugs target vital cellular functions such as deoxyribonucleic acid (DNA), topoisomerases, microtubules, histone deacetylases, and other essential protein kinases such as CDK9 in cancer cells also may act similarly on normal cells. When those drugs are extending their inhibitory activity on the normal cells than cancerous cells, they are said to be "side- effects". The side effects may range from simple ones such as neutropenia, anemia, mucositis, and colitis, diarrhoea to the fatal ones viz., mitotic spindle arrest and vital cell signaling processes. Nausea and vomiting are the most common side effects of anticancer drugs. Besides, morning sickness in pregnancy is a common symptom of avoiding any harmful chemical substances to the developing

embryos. These chemicals are commonly called "teratogens", many of the medicinal plants have been known to cause morning sickness in women [1,2]. Teratogens are often found following a rise in the incidence of a certain birth abnormality [3]. A medicine called thalidomide, for example, was used to treat morning sickness in the early 1960s. The mother's and fetal genetic susceptibilities also influence the types and degree of defects generated by a teratogenic substance. Variation in maternal metabolism of medication will dictate which metabolites the fetus is exposed to and for how long [4]. The fetus's genetic vulnerability to a certain teratogenic agent will also influence the eventual result. Histological approaches indicate changes in brain structure sensitivity following the administration of specific teratogenicity chemicals at various stages of embryo development [5]. The period of the nausea of pregnancy coincides with critical periods in embryogenesis, particularly of the development of the central nervous system in the embryo. Thus nausea and vomiting of pregnancy may protect the developing embryo from teratogens found in vegetables and food-associated microorganisms [6]. Ginseng, ginger, and ginkgo Biloba are examples of natural compounds that have been shown to suppress fetal development [7]. At least the embryos have this type of evaluating mechanisms for the omission, but the cancer cells lack. Unfortunately, limited research has been done on the impact of numerous anticancer drugs on embryonic development, where their biological activities may impact [8]. Natural products' anticancer action may prevent embryonic cell growth, and its chemical content varies according to the region, season, bee type, and manufacture technique. As a result, appropriate research should be undertaken to determine the impact of drug administration on embryo development throughout pregnancy. The modern scientific era aims to explore these teratogens as anticancer drugs since; they can differentiate the normal and cancer cells, thus reducing or devoid of fatal side effects.

2. Cancers and embryos – how are they different from each other?

Cancer is one of the most common causes of morbidity and mortality globally; it is the second biggest cause of death, behind cardiovascular disease, and one of the most serious public health issues today [9]. Normal cells acquire DNA mutations over time, losing their capacity to grow and multiply in a controlled way, resulting in unconstrained cell proliferation. Cancer cells can form in almost any tissue, although the breast, ovary, prostate, liver, stomach, pancreas, lung, brain, and bone marrow are the most prevalent sites [10]. On the other hand, embryonic cells have the potential to divide rapidly while still producing stem cells and cells that can develop into specialized cells. Cancer stem cells (CSCs) have the same cellular and molecular pathways as embryonic cells, but they lack the regulatory system needed to avoid excessive multiplication [11]. While the exact origin of CSCs is unknown, evidence shows that they are stem cells that have lost control of their multiplication due to aberrant conditions. CSCs might also result via cell-cell fusion between cancer cells and adult stem cells, gene transfer between somatic and cancers cells, or stem cell mutations, according to some theories [12].

Furthermore, transformation may occur during tissue regeneration due to inflammation, infection, toxin exposure, and metabolic processes, resulting in mutations. The peculiarity of the early embryo and its intrinsic similarity with cancer is just in chaos, and further, human embryonic chromosomes appear to be more unstable than initially believed. In vitro fertilization, embryos had a significant risk of structural defects, according to a study [13]. Furthermore, the remarkable disorder was discovered in the genome of an early mammalian embryo, which is very comparable to cancer.

It is shown by chromosomal instability, abnormal mitoses, heteroploidy, anaphase bridges, structural chromosome aberrations, and loss of heterozygosity in certain single cells, among other things. The hyper-dynamic behaviour of structural chromatin proteins and the diffusion of chromocenters identified in ESC indicate that positional information is being erased [14]. It is a relatively new research topic on the impact of chaotic rules on environmental adaptability. Certain characteristics found during the production of complicated cell division events that occur as a result of evolutionary and adaptive analogies can aid in the development of more effective anticancer medicines and provide a better understanding of the adaptive nature of cancer genome chaos [15].

An embryo could be differentiated from cancer, where it has tight control over its cell growth, differentiation and morphogenesis. If not on self-control, it leads to the formation of simple cell mass, i.e., tumor/cancer. Thus, the embryos are controllable at unique cellular mechanisms on migration, invasion, gene expression, protein profiles, signaling pathways, cell differentiation, immune escape and so on (Figure 1). While these mechanisms are bypassed due to defects in normal genetic makeups, they lead to carcinogenesis. Lobstein et al. [16] first expressed the idea of tumors from the embryonic origin, and Pierce postulated that tumorigenesis was concerned intimately with developmental biology to a large extent. The next progression of molecular biological reports revealed a certain kinship between them. Multiple reports in the literature recently reviewed the cancer progression on the embryonic origin to a different extent. They emphasized the role of common regulators such as Nanog, Oct4, Sox2 and c-Myc in cancers and the embryos [17–21]. Ben-Porath et al. [22] showed that the onset of cancer cell differentiation is preferentially overexpressed of the activation targets such as Nanog, Oct4, Sox2 and c-Myc, similar to developing embryos. These genes are overexpressed in the onset of cancer by carcinogenic differentiation than the differentiated ones such as breast cancers (estrogen receptor (ER)-negative tumors), basal-like subtype, glioblastomas and bladder carcinomas [23,24].

Apart from these genes, different epigenetic mechanisms were proposed to participate in embryo metabolism. Single nucleotide substitutions (SNS) play a significant role in regulating the embryos. The SNS are the sole player for modifying the mutational landscape of the cell's chromosome and strongly determine the fate of the cells adjusting with the environmental stimuli (i.e., *external* or *internal*). The epigenetic cascades specifically determine the changes such as nuclear organization, replication line and chromatin modification. Any violation in their normal regulating mechanisms resulted in a dysregulated proliferation of the cells, including embryo cells (refer [25] for further reading). Recently, intense research on molecular biological pathways reported that the malignancy ensued by the persistency of the problems in the maintenance and renewal of post-embryonic modifications. Since the cancer stem cells are modified normal stem cells, they can control differentiation or replication according to the environmental signals. Thus the cancer cells remain the stem cells that lack control over their proliferating ability rather than the differentiation [26,27]. Thus, Pierce (1983) proposed that these malignant signatures are already encoded within the cell's genome and can produce neoplasms just like their descendant cells. The malignancy occurs when the repressed genes on normal embryonic development tend to be expressed at certain conditions (i.e., *abnormal physiological signalling,* refer, [28] for further reading). Recent studies also showed that *mutational signatures* finely determine the nature of the tumours that are originated in later stages. Several epigenetic factors determine the function of the *transcriptional gatekeepers,* such as the phosphatidylinositol 3-kinase (PI3K) system during the normal physiology of the cells. Recent developments showed that those violated signatures even

persist with the embryos and lead to developing [25] cancers in later stages. These abnormal embryo cells are termed the Polyploidy Giant Cancer Cells (PGCC) and play a prominent role in determining drug resistance and metastasis [29]. Since the cancer cells are a simple mass of clonal cells, few of their proportions represent embryonic tissue status. During gastrulation, the embryonal cells have the capability of migratory behaviours; those undifferentiated cancel stem cells also showed similarity to such kind of mobility. Moreover, their mobility is strongly determines their invasive properties [30,31].

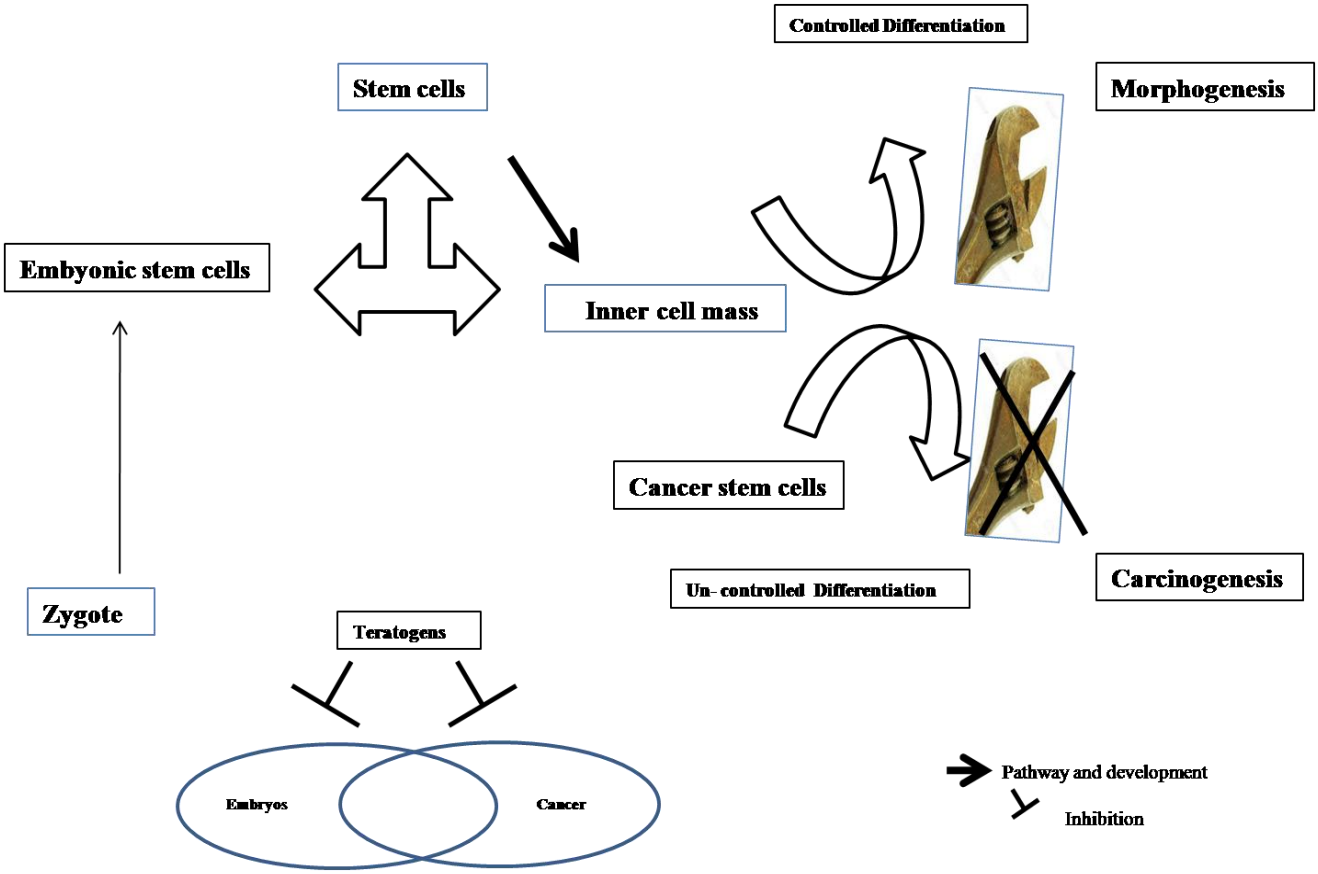

Figure 1. Cancers and embryos: how are they different from each other? The cancer cells are characteristically behaving like the developing embryos but differing in uncontrolled signalling mechanisms.

3. Invasiveness of cancer and embryonic cells

The implantation of the zygote is the foremost important step in embryogenesis. Murray et al. [32] have reviewed the implantation mechanism and suggested that the cancer cells use the same machinery for tumor implantation as the embryos do. After their implantation, the embryo cells activate repressing pathways (*viz.,* ATM- p53, ATM – ChK1) against the maternal immune system. Likewise, the cancers also use such pathways and share similarities with normal trophoblasts. The trophoblasts are used to invade the endometrium, uterus attachment, *neo*angiogenesis at the sites, and repress the maternal immune functions. Recently, Costanzo et al. [33] reviewed the behaviour of cancer cells that mimic the embryo's migrating pattern and exclusively discussed the factors and

environmental conditions behind it. During embryonal development's early stages, the urge to replicate results in replication stress (RS) and chromosomal instability. These revoke many mutations, and the embryos seem to persist with that defect due to several physiological adaptations. The cancer cells particularly vary with the embryos at this stage, in which they selectively activate the cell proliferation based on those persisted mutations [34].

The cancer cells mimic the striking behaviour of invasive placental cells [35]. In particular, both use trophinin, a kind of protein that aids in cell adherence. Fukuda et al. [36] suggested that trophinin-expressing cancers use the bystin and tastin, the sister proteins of trophinin, which are potentially involved in human embryo implantation. Their work also revealed that the cancer cells secrete a cell adhesion protein, trophinin, as in embryos then implant themselves aggressively against the cell matrix. They also added that 20%-40% of all epithelial cancers in humans had expressed the human chorionic gonadotrophin (hCG), a marker for trophoblast, similar to other studies [37,38]. Harada et al. [39] report that trophinin is expressed in 64% of colon cancer patients and is closely associated with colon carcinogenesis due to the HMGB1/RAGE mechanism. High mobility group box 1 (HMGB1) is a DNA binding protein predominately expressed for cytokine production and cell death on inflammatory diseases [40]. RAGE is a pattern recognizing molecule likewise the TLR proteins and linked with the different pathology such as diabetes, cancer and Alzheimer's disease [41]. Cui et al. [42] reported that HMGB1 expression decreased with the zygote to blastocyst stage and was stable in mouse embryos. The unregulated and overexpressed HMGB1 may hasten the unrestricted replicative, antiapoptosis and neoangiogenic potential in cancers [36,37]. HMGB1 can associate with other molecules, including TLR ligands and cytokines, and activate cells through multiple surface receptors' differential engagement, including TLR2, TLR4, and RAGE. RAGE is a multiligand receptor that binds structurally diverse molecules, including not only HMGB1 but also S100 family members and amyloid-beta [45]. Integrins are cell cementing materials, but they can alter cellular behaviour by modulating non-receptor tyrosine kinases such as focal adhesion kinase (FAK) and c-Src [46]. They facilitate the formation of the FAK–Src complex and pave the road to phosphorylation of wide adaptor proteins such as p130Cas and paxillin. This activation promotes cell motility, cell cycle progression, survival, etc. The integrin αvβ3 is fundamentally involved in the maturation of blood vessels during embryonic neovascularization (vasculogenesis) [47]. LM609, an antagonist of integrin αvβ3, disturbed the normal angiogenesis development in zebra fishes and led to vessel patterns with defected lumen. αvβ3 is highly expressed only on endothelial cell activation, newborn vessel formation, and in most cancer types and used targeted anti-angiogenic therapy [48].

Similar to integrins, fibronectin binds to collagen, fibrin, and heparan sulfate proteoglycans (e.g. syndecans), leading to neoangiogenesis in the developing embryos [49]. George et al. [50], generated fibronectin deficient, reported that the embryo implantation was normal in homozygous and heterozygous embryos; but, the mutant allele causes early embryonic mortality in homozygous. They also added that several defects occurred in the absence of fibronectin, such as shortened anterior-posterior axes, deformed neural tubes and severe defects in mesodermally derived tissues, deformed heart, embryonic vessels, extraembryonic vasculature and amnion. Thus they proved that the absence of fibronectin directed to deficits in mesodermal migration, adhesion, proliferation or differentiation. Snow et al. [51] showed defects in mussel development in zebrafish embryos on fibronectin absent. The cancer cells differ from normal embryonic cells on the dependence of the fibronectin requirement. The cancer angiogenesis will not depend on endothelial fibronectin since; it is produced by almost all of the cells in the tumor and is also abundant in plasma. Its absence showed

no differences in vascular density or the deposition of basement membrane laminins, ColIV, Nid1, Nid2, or the TGFβ binding matrix proteins, fibrillin-1 and -2 [52]. However, the cancer cells use another protein called cancer procoagulant [53].

Cancer procoagulant is another hypothesized protein in malignant cells and the undifferentiated tissues of the human placenta, not in any normal cells. These proteins initiate neoangiogenesis in embryos and increase thrombosis in cancer patients [54], and the defects in embryonic angiogenic would lead to carcinogenesis. In addition, such complex mechanisms differentiate the cancer stem cells from the embryos. The previous studies revealed that the division rate in cancer stem cells is slower than the normal somatic stem cell [55]. Embryonic liver fodrin (ELF) is a protein that organizes the TGF-beta pathway in embryos. Baek et al. [56] reported that Embryonic liver fodrin (ELF) deficiency initiate tumor angiogenesis in livers by deregulating the normal hepatocyte proliferation. A better understanding of the maternal mechanisms to control this invasive behaviour may provide novel insights into the behaviour of metastatic cancer cells and lead to better methods to control their growth and spread within host tissues and concluded that ELF would be a potential target for TGF-beta pathway tumor suppression of HCC cells [57]. A better understanding of the similarity of cancer and embryonic cells would be very useful in dissecting future cancer-targeted drugs. Thus major adaptations in differentiating pathways bifurcate the embryo and cancer cells, particularly cancer stem cells and attract intense scientific research for discovering novel cancer drugs [58–60].

4. Cancer cells and embryos: similarity in cell microenvironment

Self-renewal and division is the main concept in developmental biology. The stem cells and cancer cells are typically express the same gene signatures at certain stages, particularly the early at carcinogenesis (Figure 2). The cancer cell microenvironment is similar to embryos, and both of them are profoundly influenced by the same gene signatures [61]. Thus the cancers and embryonic stem cells can undergo rapid clonal proliferation but vary with the execution of molecular signalling [62–64]. Out of nine main signalling pathways, seven (JAK/STAT, NOTCH, MAP-Kinase/ERK, PI3K/AKT, NFkB, Wnt and the TGFβ pathways) are similarly involved in embryonic development and cancer [65]. Surprisingly, the embryonic microenvironment suppresses several tumor growths, and the embryonic cell extracts showed inhibition of cancer cells [66]. Induced Pluripotent Stem Cells (iPSCs), Adult Stem Cells (ASCs) and Cancer Stem Cells (CSCs) have overlaps in many pathways due to the similar gene expression pattern and epigenetic status [67]. The p53 has an important role in stem cell maintenance, self-renewal and differentiation capacity. The mutated p53 gene led to the generation of CSCs from SCs capable of forming aggressive tumors in mice fibroblasts. Many studies have identified Nanog as a gene expressed in the CSCs population of different tumors [68].

Moreover, Nanog is essential for breast, prostate, and colon cancer initiation. Oct 4- Nanog complex regulates the CSCs population, enhanced sphere formation, drug resistance, EMT, and the ability to initiate tumors in several cancer types. The p53 negatively regulates Nanog, Oct4 expression and Focal adhesion kinase (FAK), suggesting that it had an important mechanism that reconciled the CSCs generation. Resveratrol, an antitumor phytochemical, activated the p53 by reducing the Nanog level. Moreover, FAK inhibits p53 transcriptional activation and stability in addition to activating NANOG through phosphorylation. Thus, these findings suggest the

p53-Nanog-FAK axis as a potential target for CSC therapy. In addition, the β3 - Adrenoceptor (β3-Ar) is involved in different carcinogenesis processes by using the hypoxia growth factor. On regulating the glucose metabolism, β3- Ar also mimics the intratumor ischemic environment and determines the stem- cell-like properties and cancer cell dedifferentiation. The studies showed that the β3- Ar regulates differentiation, immune tolerance and chemoresistance of embryos and cancer cells [69].

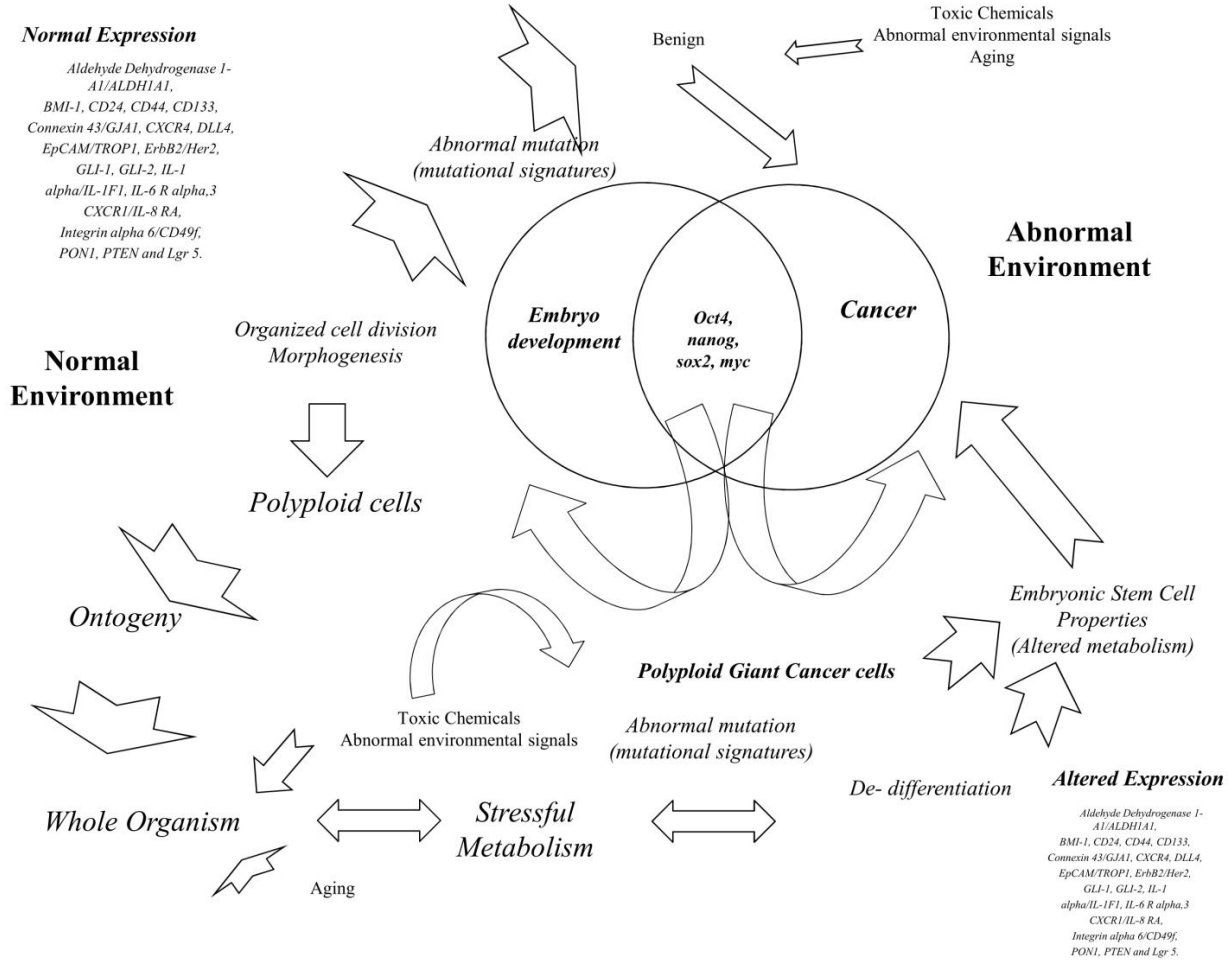

Figure 2. Cancer and embryos have similar gene expression signatures at certain pathways. These similarities help to discover novel therapeutic drugs (Refer to the text for details).

In contrast to embryonic stem cells, in which OCT4 and SOX2 are tightly regulated and physically interact to regulate a wide spectrum of target genes, de novo SOX2 expression alone in pancreatic cancer cells is sufficient to promote self-renewal, dedifferentiation and imparting stemness characteristics via impacting specific cell cycle regulatory genes and epithelial-mesenchymal transition driver genes [29,70–72].

5. Similar invasive behaviour between cancer cells and embryos

Preeclampsia is a pregnancy complication characterized by high blood pressure. Preeclampsia commonly develops after 20 weeks of pregnancy in women who previously had normal blood pressure. Women who suffer from preeclampsia (low oestrogen and high progesterone levels) had a lower risk of breast cancer. The novel chemical factors discovered subsequently as preceding and accompanying preeclampsia and referred to by writers may be beneficial in treating cancer [73] and higher circulating soluble FMS-like tyrosine kinase-1 (sflt-1, also referred to as svegfr-1). These similarities made the scientific community investigate new possibilities for cancer therapies. Innes and Byers [73] claimed that preeclampsia might decrease the cancer risk from their epidemiological study among the affected women. Their classic study explained that the synergistic effects of hormones might be a major reason for the reduced risk.

Similarly, Mahendra et al. [74] showed that the stable expression of the sflt-1 in the human ovarian cancer cell line, SKOV3, inhibited the cancer growth and stated to be a feasible way for anticancer therapy. Bellamy et al. [75] found no association of preeclampsia with the cancer risk, but the patients were more vulnerable to vascular diseases. Wu et al. [76] also showed that preeclampsia increased the risk of vascular diseases rather than cancer . Meanwhile, Fong et al. [77] reported the dual role of salt-1 on cancer as an angiogenic enhancer and as an inhibitor in embryos. Shibuya [78] also reported that the binding ability of sflt-1 to the VEGF was the major reason for its dual role by analyzing the deficient sflt-1 that lost the tyrosine kinase activity in mice. The stronger binding resulted in the excessive production of endothelial cells leading to preeclampsia. The weaker binding resulted in enhanced cancer growth. Their studies revealed that sflt-1 could be an alternative drug target for antiangiogenesis in cancer.

In contrast to these studies, a survey disclosed that preeclampsia might increase the risk of cancer based on environmental and genetic factors [79]. A similar study in Jerusalem revealed that the protective effect of preeclampsia on cancer is not universal, and it was based on environmental factors [80]. These studies indicated that though hormonal imbalance plays a vital role in cancer prevalence in preeclampsia patients, the in-depth molecular analysis may open new doors for effective anticancer therapy. The cell adhesion molecules, including the integrins, extracellular matrix and matrix metalloproteinases, are mainly involved in the regulation of implantation and angiogenesis. Thus the proper regulation is important for metazoan development and tissue homeostasis. The integrins are negatively regulated by tumour suppressor PTEN, a protein with homology to protein tyrosine phosphatases and tensin at development and carcinogenesis on pathogenic conditions. Pten inactivation resulted in early embryonic lethality. Mutated Pten ES cells formed aberrant embryoid bodies. They displayed an impaired endodermal, ectodermal and mesodermal derivatives differentiation and its inactivation enhanced the ability of ES cells to generate tumours in nude and syngeneic. Yoshitomi et al. [81] reported that the JunB is responsible for forming a vascular network in embryos . Besides the PTEN playing a role as a signalling barrier on metastatic prostate cancer, it is based on the epigenetic or genetically expressions. Thus the mechanism behind the maternal control for invasiveness in an embryo could be used to discover newer efficient drugs for cancers that spawn in host tissues.

6. Defects in embryos during their regulated divisions and polyploid giant cancer cells

The cell division in embryos is tightly regulated by the maternal and subsequent environmental factors, even though there are occasionally loosened nucleated cells. Those cells contain more than a

set of homologous chromosomes and are collectively called Polyploidy cells [82]. Those cells result from two significant defectives, either endoreplication, endomitosis, or both [83]. During endoreplication, the chromosomes replicate each other but fail to divide; on endomitosis, there is a failure for cytokinesis. Both types strongly influence the cell physiology from severity to malignant level [84]. Other defects such as microcells, failed mitosis and aneuploidy are also found frequently in developing human embryos [75,76]. Double spindle formation on blastomeres is another major reason for such defects in the embryos and results in erroneous cell divisions [87,88]. Several studies showed that those cells play as the origination aberrant mutational signatures for producing the cancer phenomenon in later stages [29,89–93].

Polyploidy is a normal phenomenon in cancerous growth, and it has been reported in several cancer types [12,89–93]. The endomitosis produces Polyploid Giant Cancer Cells (PGCC) in cancers, and nearly 37% of all human tumors exhibited PGCCs [94]. The frequency of PGCCs was also increased with benign, tumor, cancer and metastasis stages [95]. Several studies showed that PGCCs inhibit cancer growth [96] and bring senescence [97–99] among the cancer cell. In contrast, recent studies showed that PGCCs aided in bypassing the senescence-induced replication blockade and led to tumor progression [100,101]. Thura et al. [102] also showed that relapsed tumors were enriched with PGCCs and seemed to be a reason for chemoresistance. The PGCCs play an important role in the chemoresistance of ovarian cancer cell lines Hey and SKOV3 cells and PGCC-derived daughter cells on paclitaxel treatment [103,104]. Further, their study also showed that the daughter cells developed proportionally higher resistance and PGCCs than the normal cells.

Phosphatases of Regenerating Liver (PRLs) are an oncogene that regulates many of the essential cells signaling pathways for implementing cancer growth and metastasis [105]. Its isoform, PRL3, overexpressed in more than 80% of cancers and strongly positively attributed to initiating the PGCCs. These PRL^+ PGCCs co-expressed with embryonal stem cell markers (SOX2 and OCT4) showed due to incomplete cytokinesis and DNA damage. This co-expression inhibit the pro-apoptotic ataxia–telangiectasia mutated (ATM) DNA damage-signaling pathway and increased the tumor relapse [102]. In another study, Niu et al. [104] showed that Interleukine-6 (IL-6) induced the PGCCs by activating the conversion of Cancer Associated Fibroblast (CAF) from normal fibroblasts in cancer stroma and participated in cancer progression in a patient-derived xenograft high-grade serous ovarian carcinoma model. They showed that the IL-6 induced the embryonic stemness properties and increased the collagen synthesis, VEGF expression through regulating the CAF population. They also showed the IL-6 blockade reversed the inhibition of PGCCs and CAFs.

Shankaranarayanan et al. [106] showed that PGCCs produced resistant daughter cells after the cytotoxicity treatment with doxorubicin (DOX). They showed that the bovine lactoferrin conjugated with DOX increased the mortality rate in ADR1000-DU145 cells. After the treatment, the remaining cells developed into PGCCs and produce drug resistant daughter cells against DOX. They also found the higher elevation of drug resistance gene expression is upto 32 fold. Dedifferentiation in PGCCs mimics the embryonal cell divisions (blastomere into morula stage) in several cancers [93] (for further reading, refer [29,103,107–109]). Several studies showed that PGCCs induce cell budding [110–112], and Niu et al. [107] showed that the budding results from senescence escape. Further they showed that PGCCs also expressed the embryonic stem cell markers, such as OCT4, NANOG, SOX2 and SSEA1. SSEA1 is a stage-specific embryonic antigen-1 (SSEA-1) that differentiates the embryonic stem cells and initiates stem cells. This antigenic maker expression lead to aggressiveness in thyroid tumors [113]. The above studies indicated that the targeting of PGCCs

has the potential use of immunomodulatory medicines in combination. PGCCs could form any of the three germ layers, and spheroids derived from them could be an initiator for several cancer types including carcinomas, and further details are reviewed in the literature extensively [109,113–117].

7. Similarity in metabolism

The recent scientific insights showed a peculiar difference in Embryonic Stem Cells (ESCs) and Cancer Stem Cells (CSCs) on utilizing the intra and intercellular signals for changing their metabolic dependency. ESCs are mainly depend on glycolysis for differentiation; the cancer cells use glycolytic pathways, oxidative phosphorylation centralized on the mitochondrial pathways [118]. The aerobic glycolysis is a key metabolic pathway in the cancer cells, and the active embryo cells also use the same to produce the energy currencies for cell divisions [119]. The glycolysis produces the lactates and free acids (H+) as by-products; cancer cells acidy the neighbouring environment, thus breaking down the extracellular matrix breakdown, disrupting gap junctions, and ultimately promoting invasion and metastasis. Similarly, after forming blastocyst, a crucial step in embryogenesis, the embryos use the same mechanism to de-cement the cell-matrix materials for implantation. The role of glycolysis in embryos and cancer cells has been reviewed in the literature in detail [116]. Oct4, Myc, KRAS, HIF, TFAM, SLC2A1, STAT3 and p53 genes are important genes that regulate the cell progression of many cancers and normal embryonic development. The oct4 expression is mainly altered by the GLUT1 and GLUT3 during differentiation in hESCs based on the environmental oxygen condition [120].

In addition, Myc is one of the transcription factors (including Oct3/4, Sox2, and Klf4, under ES cell culture conditions) that collectively can reprogram the adult cells reverse to a pluripotent stem cell. C- Myc is regulated by normal circuits such as the growth factor in embryos to render proliferation and appropriate point at cell cycle for tissue repairing. C- Myc restrain the cell signalling mechanism while controlled by the short circuits (genetic alterations). Myc could directly bind to the promoters of 30% of existing genes, but the transcription factors perform the up-regulation or down-regulation in Myc activation. In embryos, Myc combined with the transcription factor, E2F1 and hypoxia-inducible factor (HIF-1) to activate the genes involved in nucleotide and glucose metabolism. The transcription factors determine the c-Myc role in controlling embryos and cancer for biosynthesis and cell growth [121]. Varlakhanova et al. [122] also studied the role of cMyc in self-renewal in pluripotent of the embryonic stem cells. They reported that the embryonic cells are strongly c-Myc dependent for stemness maintenance, and the inhibition or any deregulation could lead to cancer formation. Their self-renewing capacity has been regularised by VEGF receptor-2 (VEGFR-2)/STAT3-mediated pathway.

The placenta and cancer both develop in environments with graded oxygen availability. Hypoxia-inducible factor (HIF) is highly regulated by the expression ratio of oxygen-sensitive enzymes in cells. Gabryelska et al. [123] reviewed and suggested that HIF regulation is a common mechanism to achieve the epithelial-mesenchymal transition, migration and proliferation in embryonic cells in neuron crust formation. The cells need adequate oxygen and a highly sensitive stage of normal embryonic development. Similarly, after a detailed analysis, they concluded that the same mechanism is utilized in cancer stem cells but without proper signalling compared to the embryos. In addition, recently, Yu et al. [124] had reviewed the HIF's role in cancer and embryos. The oxygen gradient makes a switch in the progression of cancer or embryos. At the same time, the

chaotic regulation or gradient leads to carcinogenesis besides the other epigenetic deregulations. Mitochondrial transcription factor A (TFAM or mtTFA) is essential to maintain the mitochondrial genome copy number. Since embryonic development is highly dependent on the energy currency, ATP, the TFAM is also a highly important mediator of embryonic development.

On the other hand, TFAM is highly upregulated in glioma non-small cell lung cancer (NSCLC)[125]. TFAM mediated embryos' energy utilization via the ROS-mediated JNK/p38MAPK signalling pathway as the cancer cells produce more reactive oxygen species (ROS) and disturb the normal JNK/p38MAPK signalling resulting in cancer progression due to excessive energy production. Their study also revealed that TFAM knockdown in NSCLC cells could lead to elevated p53 expression due to the phosphorylation on serine residue. In this light, the antagonist for embryos (*viz., teratogens*) may constitute a novel therapeutic strategy for combating the spread of cancer.

8. Oncofetal proteins and teratogens

The oncofetal antigens are typically expressed in embryogenesis and at certain pathogenic conditions, especially on cancer types. These are used for diagnosis and cancer treatments. α-fetoprotein, carcinoembryonic antigen, trophoblast glycoprotein precursor, IMP3, the receptor tyrosine kinase-like orphan receptors (ROR) and immature laminin receptor protein are some of the oncofetal proteins which are promising cancer drug targets against several cancer types. The receptor tyrosine kinase-like orphan receptors (ROR) family proteins are oncofetal proteins expressed on embryos rather than the normal adult cells. Receptor tyrosine kinase-like orphan receptor (ROR) proteins are involved in skeletal and neuronal development, cell movement and cell polarity in embryos. Worthwhile, they act as the antagonist of the Wnt target by sequestering Wnt ligands. ROR1 was found to be selectively expressed in different tumors than the adult tissues and could be a unique drug target [126]. The ROR proteins consist of ROR1 and ROR2. RORs are highly expressed in blood and solid malignancies. α-fetoprotein (AFP) is an important embryonic protein that binds to the estradiol receptor to establish male characters in the specific tissues on development.

Meanwhile, it is a prominent cancer biomarker in hepatocellular carcinoma; studies related to other cancer types are scarcely found. Vujanovic et al. [128] showed that cord blood-derived AFP regulated the natural killer cells (NK) by inducing pro-inflammatory markers such as IL2, IL1β, IL6, and TNF secretion and CD69 upregulation against the hepatocellular carcinoma [127]. The tumour cells also produced the AFP (AFP), which degraded and minimized the NK cells' viability and population. The mechanism underlined this specificity had not been elucidated.

Carcinoembryonic antigens are produced during embryo development and cease at birth. They are found lower in healthy individuals, but an elevated ratio is strongly correlated with cancer and smoking conditions [129]. Recently, its correlation with the different cancer types has been in the limelight [130]. IMP3 (insulin-like growth factor-2 mRNA binding protein 3) is an important oncofetal protein and is frequently detected in cancer patients at different levels in their serum. Samanta et al. [131] reported the role of IMP3 on self-renewal and tumor initiation, properties in breast cancer stem cells (BCSCs) . IMP3 bonds to the SNAI2 (SLUG) transcriptional stage and via its 5′ UTR. SLUG targeted the regulation of SOX2 for reviewing its stem cell properties. Thus IMP3 indirectly contributed to the initiation and progression of BCCSCs. In addition, IMP3 also regulates the ATP-binding cassette (ABC) transporters and breast cancer resistance protein (BCRP/ABCG2) with TGFβ pathway triple-negative breast cancers and HCC. Thus, targeting the

IMP3 could be the most feasible route for cancer suppression and inhibition of drug resistance [132].

9. Teratogenic compounds as anticancer drugs

Inhibiting the Hedgehog signalling pathway (Hh) involved in intercellular communication with cyclopamine has enhanced the survival rate in a genetically engineered mouse model of pancreatic cancer and abrogated the systemic metastases arising from these orthotopic xenografts. This study also provides more evidence that Hh signalling is a valid target for developing novel therapeutics for pancreatic cancer and would be worth evaluating in a clinical setting. Teratogenic alkaloids are found in many plants, including Conium maculatum L., Nicotiana glauca, Nicotiana tabaccum, and Lupinus spp. Fetal musculoskeletal defects produced by alkaloids from these plants include arthrogryposis, scoliosis, torticollis, kyphosis, lordosis, cleft palate, etc. Neferine, a group of bisbenzylisoquinoline alkaloids, from Nelumbo nucifera (Lotus) embryo induced apoptosis between human osteosarcoma cells, but not in non-neoplastic human sarcoma cells. Neferine induced G1 arrest was based on p21(WAF1/CIP1)-dependent and without any role for p53 or RB (retinoblastoma-associated protein). Neferine increased the p21 level in cancer cells dependent on the p38 proteins. The up-regulation of p21 by reference was due to an increase in the half-life of p21 protein. Reveratrol has been found to enhance caspase 3, 8, 9 and cleave the PARP in HeLa cell lines [133]. Besides that, curcumin showed malformed tails (bent or hook-like), curved body, pericardial sac oedema, retarded growth due to delayed yolk sac absorption and shorter body length. The LD50 values of curcumin (24-h incubation) were estimated at 7.5 microM and 5 microM for embryos and larvae, respectively [134]. Curcumin teratogenicity depended on the dose and administration time in the mice embryos. Curcumin exhibited adverse effects at the post- implanted blastocyst and early egg cylinder stages and led to the retarded growth during the gestation period.

Nevertheless, the apoptosis-inducing activity of fucoxanthin was more than fucoxanthin at non-toxic concentrations towards normal cells. Though the underlying mechanism is unclear, the specificity of the seaweed extracts to cancer cells has been cited in several reports as discussed above. Many seaweed compounds are efficient or show enhanced activity when administered with known chemotherapeutic agents such as cisplatin, 5-fluorouracil (5-FU). The tumour inhibition rate increased significantly when tumour-bearing animals were treated simultaneously with sulfated polysaccharides from Champia feldmannii and the chemotherapeutic agent, 5-FU. Fucoidan from Fucus evanescens is reported to induce etoposide, a DNA topoisomerase II inhibitor in HL-MT-4 cells. This is a very interesting finding since one way to improve the efficacy of anticancer therapy is to develop optimal combination regimens of chemotherapeutic drugs, as the objective is to increase efficacy while reducing side effects. Drug-induced over-expression of the multi-drug efflux pump P-glycoprotein (P-GP) could be one of the leading causes of chemotherapy failure in clinical oncology. Because P-GP can remove many unrelated chemotherapeutic agents from the target cells, including agents to which the tumor had not previously exposed, these cells are multi-drug resistant (MDR) mutants. In addition, non-toxic extract of L. translucida can inhibit the MES-SA/Dx5 cell proliferation when administered with doxorubicin, which revealed that the activity was due to the possible presence of P-gp inhibitors or other agents (e.g. pro-apoptotic factors) in the extract.

10. Conclusion and future directions

We attempted to summarize the similar properties of cancer and embryos and explore the possible therapeutic potentials. Frequently, the cancer cells recapitulate the embryonic pathways by different means and activate the normal gene repressors in unique ways. Meanwhile, as complex signaling systems, this field calls for many level analyses in different directions. Overall, these findings might pave the way for a new field of cancer research that draws parallels between cancer rates and embryo development techniques. There has been an enormous understanding and growth of literature that scientifically explores the similarities between embryos and cancer for two decades. Carcinogenesis and embryogenesis are relatively similar in certain aspects in their initial stages. The genes responsible for onset and maintenance for stem cell-like properties are more or less similarly expressed. These striking phenomena are hallmarks of identifying the embryos as model systems for cancer drug discovery.

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Conflict of interest

The authors declare no conflicts of interest.

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