

Cancer Stem Cell – Essence of Tumorigenesis

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Abstract

Cancer stem cells (CSC) are pool of dedicated undifferentiated cells responsible for maintenance of tumorigenesis. They play a key role by continuing growth and propagation of cancer. These cancer stem cells share many similarities with natural stem cells like self renewal and plasticity of differentiation. Activity of these stem cells is regulated by various paracrine signals. Stem cell activity is dependent on complex interplay between cancer stem cell and its microenvironment called niche. MicroRNAs are newer class of molecules involved in modulating differentiation of stem cells. Cancer stem cells also determine propensity for metastasis of a tumour. They have considerable resistance against conventional chemotherapy or radiation. Therefore pose significant challenge for elimination of tumour. Now days, targeting these stem cells are a new focus of attention in cancer therapeutics.

Keywords: Cancer stem cells; Differentiation; Stem cell markers; Microenvironment; MicroRNAs; Cancer therapy

Introduction

Pathogenesis of cancer has always remained an enigmatic area of cell biology. Numerous efforts have been made to identify the key factors involved in genesis of a tumour mass. Unique properties of tumour cells endow them with the ability to keep on multiplying and evade body defences. Metastasis disseminates these tumour cells from their original locations ramifying the clinical consequences and creating newer challenges for therapeutics.

The bulk of the tumour consists of rapidly proliferating cells as well as post-mitotic differentiated cells. Similar to growth of normal tissues like bone marrow, skin or intestinal epithelium, constant growth of tumour is maintained by limited number of dedicated stem cells. The contribution of differentiated cell lines to the long term sustenance of tumour is negligible [1]. There are enormous advancements occurring globally in research of cancer stem cells. Present article is a brief attempt to recapitulate some of the developments in understanding of this concept.

Concept of Stem Cell

Maximow [2] was one of the earliest workers to introduce concept of stem cell. In his 'Unitarian theory of haematopoiesis' (1906), he proposed that all blood cells originated from common mother cell [3]. Becker et al., Siminovitch et al. [4,5] demonstrated that bone marrow cells are clonal in nature and suggested that all lineages of bone marrow cells are derived from common stem cell. Stem cells thus multiply and undergo differentiation according to the need of the tissue.

Based on their ability of differentiation, stem cells are classified into following types [6-8].

- **Totipotent:** Able to give rise all embryonic and extra-embryonic cell types e.g. fertilised oocyte or zygote
- **Pluripotent:** Give rise to all cells of embryo proper e.g. embryonic stem cells
- **Multipotent:** Give rise to subset of cell lineages e.g. adult somatic/tissue based stem cells

- **Oligopotent:** Give rise to a more restricted subset of cell lineages than multipotent stem cells e.g. mammalian ocular surface
- **Unipotent:** Contribute to only one mature cell type e.g. Type II pneumocyte

A normal stem cell can divide either symmetrically or asymmetrically. When it divides symmetrically it forms two identical daughter cells. They can also divide asymmetrically forming one stem cell and one progenitor cell. Progenitor cell undergoes differentiation to form mature cell line. This asymmetry in division is necessary for healthy growth. If this polarity is lost, stem cells will continue to divide forming a tumour [9]. Stem cells can renew themselves. They are built to last a life time, to be resilient to electromagnetic and chemical insults, to be able to sustain for longer periods of time and colonize to other parts of body [1].

Cancer and stem cells

Pierce, while working on malignant teratocarcinomas found that it contains highly tumorigenic cells that, as a single cell, can differentiate into multiple differential non-tumorigenic cell type [10]. Also in some solid tumours like glioblastoma multiforme and colonic carcinoma, a fraction of cells in the tumour mass are characterized to be responsible for maintenance and propagation of cancer. These have been identified with the term cancer stem cells or stem cell like cancer cells [11,12].

With the help of radiolabeling and autoradiography, several experiments were carried out on mouse squamous cell carcinoma to

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study hierarchy of cells. With the radiolabeling of DNA it was found that early labelling occurred almost exclusively in undifferentiated areas. Later on DNA label appeared in well differentiated areas which were thus shown to derive from undifferentiated cells. These well differentiated cells did not form tumours when transplanted into compatible hosts [13].

A tumour consists of heterogeneous population of cells differing by their states of differentiation. Outside of tumour mass contains fully differentiated cells [14]. The region closer to the centre contains progenitor cells capable of undergoing limited number of cell divisions to form several daughter cells [15]. At the centre lie cancer stem cells which are distinct from other cells and bear the capacity of self renewal. In self renewing mitosis, one or both of the daughter cells retain the identity of the stem cell. The other one can become a progenitor cell which has capacity of limited number of cell divisions and gives rise to pool of fully differentiated tumour cells.

After advent of this concept, new enthusiasm aroused in array of workers to characterise markers of these stem cells. Most studies on cancer stem cells take help of xenograft assays. A marker combination is found to be expressed heterogeneously in the tumour. The cells are sorted on the basis of this and then transplanted into immunodeficient mice by limiting dilution and tumour growth is scored week or months later [1].

In a study of breast tumour, it was found to be comprised of heterogeneous populations of breast cancer cells. In a xenograft assay, as few as hundred CD44⁺CD24^{-low} cells were tumorigenic whereas tens of thousands of cells with alternate phenotypes were not. No clear morphological distinction was observed between tumorigenic and non-tumorigenic breast cancer cells and two fractions showed equal cell cycle kinetics [16]. Subsequently similar stem cell markers were found in brain [17] and colonic cancers [18].

Table 1 lists some of the stem cell markers found in various cancers [19].

Xenograft assays provide cross section of state of cancer cells at the time when these cells were harvested. Answer remained elusive whether

Marker	Expression in healthy tissue	Marks cancer stem cells in
CD19	Broadly on B lymphocytes	B cell malignancies
CD20	Broadly on B lymphocytes	Melanoma
CD24	Broadly on B cells; neuroblasts	Pancreas/lung cancer negative on breast cancer
CD34	Hematopoietic and endothelial progenitors	Hematopoietic malignancies
CD38	Multiple stages of B and T cells	Negative on AML
CD44	Broadly on many tissues	Breast/liver/head and neck/pancreas cancer
CD90	T cells neurons	Liver cancer
CD133	Proliferative cells in multiple organs	Brain/colorectal/lung/liver cancer
EpCAM/ESA	Panepithelial marker	Colorectal cancer , pancreatic cancer
ABC5	Keratinocyte progenitors	Melanoma

ABC5: ATP-Binding Cassette transporter B5; EpCAM: Epithelial Cell Adhesion Molecule; ESA: Epithelial-Specific Antigen

Table 1: Surface markers used for the identification of CSCs.

population remains stable into the tumour or fluctuates between cancer stem cell and non cancer stem cell states. To throw light on this aspect Shackleton et al. [20] in a study of melanoma showed that original ratio of CD 133⁻ and CD 133⁺ cells in parent tumour was re-established in the xenograft. Rosech et al. studied differential expression of H3K4 demethylase JARID1B in melanoma cells culture. He observed that JARID1B expression fluctuates between JARID1B⁺ and JARID1B⁻ even when starting from a single cell. So he concluded that tumour maintenance may be viewed as a dynamic process mediated by temporarily distinct subpopulations of cancer cells [21].

Regulation of stem cell activity

Cancer has long been seen as a disease that arises from mutations that impair the capacity of any cell within the organism to respond to signal that regulate proliferation. Cancer stem cells are a small subset of cancer cells that constitute a pool of self sustaining cells with exclusive ability to maintain the tumour [22]. Currently there are two hypothetical explanations for existence of CSC that they may arise from normal stem cells by mutation of genes that render stem cell cancerous or they may come from differentiated tumour cells that experience further genetic alterations and therefore become de-differentiated and acquire cancer stem cell like feature [7].

Polarity of cell division is regulated by many genes. This occurs in highly specific niches, specific to each tissue e.g. close apposition of osteoblasts in bone marrow, at the base of crypts in the colon. Here various paracrine signals like sonic hedgehog or Notch ligands or upregulation of β -catenin and telomerase help to maintain stem cell features of unlimited self renewal while preventing differentiation or cell death [23]. This occurs in part through upregulation of transcriptional repressor Bmi-1 and inhibition of p16^{Ink4a} and p53 pathways.

Following are some of the important signals involved in maintaining stem cell proliferation in cancer:

- **Oct-4:** It is normally expressed only in the inner cell mass of the embryo. It is essential in maintaining totipotency. Its loss of expression is associated with differentiation of cells. It is a marker of embryonal cell carcinomas. Treatment with retinoids decreases its expression and brings out differentiation of cells [24].
- **Notch:** It is normally expressed in vasculature. Notch signalling activates endothelial cells and promotes angiogenesis [25].
- **Wnt/Catenin:** It affects orientation of chromosomes during mitotic divisions. In general it activates proliferation and inhibits apoptosis [24].
- **BMP:** These are members of TGF- β superfamily. These may function as oncogenes and tumour suppressors depending on relative dosage and disease stage [26].
- **Sonic hedgehog signalling pathway:** major regulator of many fundamental processes including stem cell maintenance, cell differentiation, tissue polarity and cell proliferation [27].

Role of microenvironment

Normal stem cells reside in a distinct environment called stem cell niche. Tumorigenicity not only involves biology of tumour cells but also complex interplay between tumour cells and non-malignant cells that make up tumour environment [28].

In adult mammalian brain, neural stem cells are found in hippocampus and subventricular zone close to blood vessels. During early brain development ventricular neuroectoderm secretes high levels of vascular endothelial growth factor (VEGF) which attracts and stimulates vessel growth in this region of brain [29]. Thus neural stem cells and endothelial cells remain in close proximity. These endothelial cells maintain neural stem cell renewal via Notch signalling and simultaneously inhibit stem cell differentiation [30].

Glioblastoma multiforme is an aggressive primary brain tumour. Calbrese et al. [27] showed existence of close relationship between brain cancer stem cells and blood vessels, vascular endothelial cells were also able to maintain patient derived brain tumour cells in a stemlike state and promote their tumorigenicity when co-injected in immunocompromised mice [28]. Furthermore, inhibition of angiogenesis and depletion of blood vessels by VEGF neutralising antibody bevacizumab reduced the cancer stem cell pool and subsequently inhibited tumour growth [28].

Another example of impact of stem cell niche is seen in intestine. Stem cells reside in bottom region of the crypt within the niche composed of mesenchymal cells of myofibroblast lineage. Myofibroblasts lining the crypt produce wnt ligands together with BMP antagonist gremlin $\frac{1}{2}$ which are involved in maintaining stem cell pool [31].

Mutations in APC gene, an inhibitor of wnt signalling are early events in the transition of healthy colon mucosa towards colonic carcinoma. High wnt activity levels mark the cancer stem cell population in the colon and are orchestrated by myofibroblasts residing in tumour microenvironment [32]. Also hepatocyte growth factor (HGF) produced by myofibroblasts is capable of enhancing wnt signalling activity in colon cancer stem cell suggesting a strong link between microenvironment and stem cell features in colorectal cancer as well [33]. Vermeulen et al. [31] also observed that HGF producing myofibroblasts were able to de-differentiate non tumorigenic tumour cells into more immature cells showing stem cell phenotype by reactivating wnt pathway [34].

Cancer stem cells and microRNAs (miRNAs)

Differentiation is an important paradigm in the lifespan of a stem cell. Recently a class of molecules has been discovered which plays a key role in regulation of this process- MicroRNAs (miRNAs) [35].

These are 21-23 nucleotides long molecules which bind to non coding region within target messenger RNA (mRNA). MiRNAs regulate self renewal, differentiation and division of cells via post-transcriptional gene silencing [36]. Majority of human miRNAs are expressed from introns [37]. MiRNAs regulate gene expression by promoting degradation or inhibition of translation of specific mRNA transcripts.

MiRNAs have been shown to act as both tumour suppressors and oncogenes [38]. A recent study has shown that global inhibition of mRNA processing increased tumorigenicity and transformation [39].

One example of MiRNA involved in cancer pathogenesis is family miRNA-34 (miR-34). It consists of miR-34a, b and c. These have been shown to be regulated by tumour suppressor gene p53. miR 34 inhibits a group of m-RNAs which support tumour formation by inhibiting apoptosis, promoting cell cycle progression past G1 check point, preventing cellular aging and promoting migration [40]. Mir-

34a gene is commonly lost in many human tumour types including neuroblastoma [41] and pancreatic tumours [42]. Similarly aberrant mir-34c expression has been observed in a subset of non small cell lung cancers [36]. Mir-34 family also targets Notch, HMGA-2, E2F3, CDK-4, CDK-6, cyclin E₂ and BCL2 gene products which are involved in self renewal and survival of cancer stem cells because of their effect on cell cycle control, apoptosis and DNA repair [40,43,44]. In non tumorigenic cells also regulatory miRNA levels are generally lower in cells that are less differentiated i.e. stem cells. Like these cells, cancer stem cells also contain low miRNA levels but it is still unknown if this is a cause or effect of differentiation. Aberrant miRNA expression levels, both upregulation of some miRNAs and down regulation or absence of others have been found in cancer stem cells [45].

Stem cells and metastasis

Cancer stem cells have also been postulated to play important role in metastasis. On account of inherent plasticity, epithelial tumour stem cells can undergo epithelial mesenchymal transition (EMT). These transformed cells lose cell-cell adhesion properties along with polarity and acquire a more mesenchymal like phenotype including motility, invasiveness and increased resistance to apoptosis. EMT endows disseminated tumour cells with self renewal capacity like cancer stem cells. Mani et al. [32] found that EMT in human mammary epithelial cells was associated with the expression of CSC marker, increased self renewal capacity and enhanced tumour formation [33]. Hypoxia promotes EMT as well as self renewal capability and stem cell phenotype in non stem cell population [34].

Cancer stem cells have been observed to determine propensity for metastasis. In the invasive front of the pancreatic tumours, a distinct subpopulation of CD133⁺ and CXCR4⁺ cancer stem cells was identified that determines metastatic phenotype of individual tumour [46].

In recent paper published by Malachi et al. [46] in 2012, the role of CSC in metastasis was demonstrated in breast cancer cells. The CD 24⁺, CD 90⁺ CSC were separated from CD24, CD90 depleted non stem cells. On introduction into the mouse by tail vein injection, only CSCs were found to be able to produce pulmonary metastasis. Moreover, CD90⁺ CD24⁺ cells isolated subsequently from pulmonary metastases are again the only tumour cell population that efficiently initiates secondary metastases [47].

It is known that metastasis selectively occurs in certain organs like lungs, liver, brain and bones. The local environment of these organs seems to be more receptive to disseminated tumour cells. Conditioning of the microenvironment is essential to promote conducive growth of metastatic tumour. Malachi et al. [46] also demonstrated the role of Periostin, normally produced by the fibroblasts in the stem cell niche. The infiltrating tumour cells need to induce periostin expression to induce colonisation. Here it underlines important role of stem cell niche in harbouring metastasis [47].

Cancer stem cells and therapeutics

Today's cancer treatment aimed at decreasing tumour size is unlikely to result in long term remission unless cancer stem cells are also targeted. They are characterized by their resistance to antineoplastic drugs and ability to regenerate tumorigenic cells after surgery, chemotherapy or radiation [36]. Many protective mechanisms have been suggested in cancer stem cell to evade from chemical and

radiation insults. For example ABC drug pumps, high expression of anti-apoptotic proteins and resistance to DNA damage [1].

Cancer stem cell hypothesis explains why a person with cancer can not be called cured even if he or her initial response to chemotherapy or radiation is robust. Local recurrence is so common of occurrence in case of solid tumours.

Several examples have been found in which cancer stem cells show their resistance to the conventional treatment strategies. For example CD 133⁺ expressing glioma cells were better tolerant to radiation than their negative counterparts [48]. CD44⁺CD24^{low} breast cancer stem cells appeared intrinsically resistant to conventional chemotherapy and ionising radiation [49].

However, on the contrary undifferentiated cells in testicular germ cell tumours were found to be more sensitive to radiation or cisplatin therapy as compared to their differentiated progeny [50]. Recent clinical study by Chiu et al. [50] identified leukemia initiating stem cells in T-lineage acute lymphoblastic leukemia (T-ALL) persist following dexamethasone therapy [51].

Taking these aspects into consideration, targeting stem cells is new focus of attention in cancer therapeutics. Several newer avenues of treatment are being evaluated for this purpose. Therapeutic RNA interference with synthetic small interfering RNAs (SiRNA) and vector based short hairpin RNAs (shRNA) have demonstrated effectiveness in vivo [52]. Stem cell mediated antibody therapy targeting CSC foci in the tumour is one of the emerging hopes in cancer therapeutics [41].

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