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Review article

Cancer stem cells - normal stem cells "Jedi" that went over to the "dark side"

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Abstract: Evidence has accumulated that cancer develops from a population of quiescent tissue committed/pluripotent stem cells (TCSC/PSC) or cells developmentally closely related to them that are distributed in various organs. To support this notion, stem cells (SC) are long lived cells and thus may become the subject of accumulating mutations that are crucial for initiation/progression of cancer. More important, they may maintain these mutations and pass them to the daughter stem cells. Therefore, mutations that occur in normal SC, accumulate during the life of an organism at the clonal level in the stem cell compartment committed to a given tissue/organ. As a consequence, this may lead to the malignant transformation of SC and tumor initiation. Furthermore, many biological features of normal and cancer SC such as the physiological trafficking of normal and metastasis of cancer stem cells involve similar molecular mechanisms, and we discuss these similarities here. Therefore, looking both at the origin and behavioral aspects we can envision cancer SC being normal SC "Jedi" that went over to the "dark side".

Key words: Cancer stem cells - CXCR4 - SDF-1 - HGF/SF - LIF - Metastasis

Introduction

Evidence supports that many if not all cancers depend on a small population of cancer stem cells for their continuous growth and expansion. The concept of cancer stem cells has been postulated in the past by several investigators [33, 39, 41, 48], and recently experimentally documented for human leukemias [4, 27], brain [43], breast [11], prostate [5, 49] and lung cancers [18]. To support this notion, stem cells (SC) are long lived cells and thus become the subject of accumulating mutations that are crucial for the initiation/progression of cancer. Thus, mutations that occur in normal SC accumulate in the SC compartment and finally may lead to malignant transformation and clonal expansion of SC and tumor initiation [3, 9, 17, 40].

Compelling evidence accumulated that quiescent pluripotent stem cells (PSC) or tissue committed stem cells (TCSC) or cells developmentally closely related to them that are distributed in various organs to maintain physiological cell turnover may be a cellular origin of cancer development. Since cancer SC similarly as normal SC exist in a quiescent state, they may be relatively more resistant to the cytostatics than target dividing cells. Therefore in a growing tumor, cancer SC represent a subpopulation of tumor cells which are capable of re-growing new tumors after unsuccessful treatment and initiate metastases [9]. Therefore, development of effective therapies that will specifically target cancer SC may become a promising therapeutic option to fight cancer. Moreover, several mechanisms that are involved in self renewal and trafficking of normal SC are also involved in expansion and metastasis of cancer SC [25]. This will be discussed in this review.

The concept of cancer stem cells - back to the past

The concept that adult tissues contain embryonic remnants that generally lie dormant and that malignancies originate in this population of very primitive, embryonic like stem cells that were "lost" during developmental organogenesis was postulated almost 150 years ago by Vrichow, Connheim and Durante [17, 40, 48]. The ma-

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lignant transformation of dormant embryonic stem cell-like cells corresponds very well with the development of some rare tumors (*e.g.*, teratomas) that usually are encountered in younger patients [41]. Nowadays, however, it is postulated that normal TCSC/PSC are the equivalent of Virchow's embryonic rests, and that most cancers arise from maturation arrest and proliferation of these normal SC whose major physiological role is supplying cells for a given organ or tissue.

The idea that cancer may originate in the compartment of stem/progenitor cells was recently proven in a model of human leukemias where only a very small population of leukemic cells is able to establish leukemia in immunodeficient mice [4, 27]. Similarly, it was also shown that a small population of CD133 positive cells in growing brain tumors is able to establish tumors in immunodeficient mice [43]. Recently, $CD34^+$ $Sca\text{-}1^+$ $CD45^-$ cells isolated from bronchial epithelium were found to be the origin of lung adenocarcinomas [18] and $Sca\text{-}1^+$ $CD45^-$ cells to be the origin of prostate cancer [5, 49].

Furthermore, recent evidence accumulated that an α-chemokine receptor CXCR4 that is expressed on embryonic stem cells [25] as well as normal TCSC/PSC for different organs/tissues [1, 2, 14, 19, 37, 38] is also highly expressed on several tumors derived from these cells (Table 1). This implies that the SDF-1-CXCR4 axis may influence the biology of cancer and plays a pivotal role in directing the metastasis of $CXCR4^+$ tumor cells by chemoattracting them to organs that highly express its specific ligand (*e.g.*, lymph nodes, lungs, liver, or bones), α-chemokine stromal derived factor-1 (SDF-1). Supporting this notion, it has been recently reported that several $CXCR4^+$ cancers (*e.g.*, breast, ovarian, prostate cancers, as well as rhabdomyosarcoma, and neuroblastoma) metastasize to the bones and lymph nodes from the bloodstream in an SDF-1-dependent manner [12, 28, 31, 35, 44]. The involvement of SDF-1 seems to be crucial for metastasis of several cancer SC, however, other motomorphogens are involved in this process as well.

Presence of pluripotent/tissue committed stem cells in adult tissues

It is well known that SC are present in all the tissues as a pool of cells that maintains the cell number in various organs. For example, the presence of stem cells is very well demonstrated in certain anatomical areas of skin, intestinal epithelium , liver, lungs, bone marrow, skeletal muscles and brain. These TCSC distributed in various organs are able to differentiate into cells for all of those tissues to which they are committed. However, several intriguing reports postulated that tissues from adult organisms may also contain even more primitive populations of PSC that may differentiate into cells from various germ layers [16, 22, 24].

Table 1. Normal tissue/organ-specific stem cells are origin of cancer stem cells for different tumors

Normal tissue	Corresponding tumor
Hematopoietic stem cells	Leukemias
Neural stem cells	Brain tumors
Bronchial endocrine stem cells	Small cell lung cancer
Mammary gland epithelium stem cells	Breast cancer
Skeletal muscle satellite cells	Rhabdomyosarcoma
Neuroectodermal stem cells	Neuroblastoma
Renal tubular epithelium stem cells	Willms tumor
Retina pigment epithelium stem cells	Retinoblastoma
Liver oval stem cells	Hepatoblastoma
Ovarian epithelium stem cells	Ovarian cancer
Cervical epithelium stem cells	Cervical cancer

Our laboratory focused on the potential presence of these PSC/TCSC in the bone marrow (BM) tissue and we noticed that this organ in addition to hematopoietic stem cells (HSC) also harbors versatile subpopulations of non-hematopoietic PSC/TCSC. These rare cells accumulate in BM during ontogenesis and being a mobile population of cells are released from BM into peripheral blood after tissue injury to regenerate damaged organs [21, 22, 24, 37]. The concept that BM may contain non-hematopoietic PSC/TCSC was surprisingly not taken carefully enough into consideration in several recently reported experiments demonstrating so-called plasticity or trans-dedifferentiation of BM-derived HSC. These studies, without including proper controls to exclude this possibility, often lead to wrong interpretations.

Thus, the presence of TCSC/PSC in BM tissue should be considered before experimental evidence is interpreted simply as trans-dedifferentiation/plasticity of HSC. We postulate that BM-derived stem cells are heterogeneous and that these non-hematopoietic TCSC/PSC are enriched in populations of $CXCR4^+$ $CD34^+$ $AC133^+$ lin^- $CD45^-$ and $CXCR4^+$ $Sca\text{-}1^+$ lin^- $CD45^-$ in humans and mice, respectively, and display several markers of PSC (*e.g.*, are very small ~ 5 μm in diameter, contain open-type chromatin/euchromatin, express early embryonic transcription factors such as Oct-4, Nanog and Rex-1) [21, 22, 24, 37]. It is possible that these BM CD45 (negative) non-hematopoietic SC identified by us can harbor cells described/identified by other investigators as mesenchymal SC (MSC), multipotent adult progenitor cells (MAPC), unrestricted somatic SC (USSC) or MIAMI cells by employing different approaches [23].

Stem cells as origin of tumors - many roads lead to the appearance of cancer stem cells

Figure 1 shows different scenarios how cancer SC can originate in the tissues. The first possibility is the development of cancer SC from a mutated clone of the

tissue/organ specific SC. Accordingly, cancer can develop both in the compartment of the most primitive normal SC (NSC) or derive from a population of more differentiated transient amplifying/progenitor cells. The second possibility is that tumor development originates from BM-derived TCSC/PSC chemoattracted to damaged organs initially in an attempt "to regenerate damaged tissues". As mentioned above, BM contains a mobile pool of TCSC/PSC [37] and these cells may home to damaged tissues as a result for example of chronic inflammation. If these cells incorporate at the "wrong time" to the "wrong place", they may instead of regenerating the damaged organ, contribute to the origin of a cancer SC. This possibility had been recently demonstrated for gastric cancer [34] and intestinal andenocarcinomas (Dr. Ed Scott, personal communication). This scenario makes a strong link between chronic inflammation/tissue injury/irradiation and development of some tumors. On the other hand it is well known that BM is a source of circulating TCSC for endothelium that plays a crucial role in subsequent tumor vascularization [36]. Next, some cancers such as teratocarcinomas or some of the pediatric sarcomas (*e.g.*, nephroblastoma) may also develop from very early embryonic stem cell-like cells (ESC) that are "aberrantly" left in the tissues during ontogenesis [41]. Finally, the possibility also exists that more differentiated cells if affected by mutations that render them immortal may dedifferentiate/become in certain situations cancer SC. This scenario may be more common in some patients who have a family history of cancer and who carry predisposing inborn mutations and chromosomal abnormalities.

Similarities between normal and cancer stem cells

Table 2 summarizes the similarities between normal and cancer SC. Firstly, both normal and cancer stem cells possess high/unlimited self-renewal capability rendering them practically immortal. While normal stem cells differentiate properly into mature cells, this process is severely perturbed in malignant cancer SC. Secondly, similar genes are involved in regulating the self-renewal of these cells for example Jagged-Notch or Wnt-Frizzled pathways [17]. Both types of SC also highly express telomerase and ABC transporter proteins on their surface [9]. This latter fact is responsible for their relative resistance to chemotherapeutics. Due to the high ABC activity they weakly accumulate Ho3342 and are present in the so called side population of cells stained with this fluorochrome. Third, since both normal and cancer SC may secret some growth factors/cytokines [29], several steps of the growth of normal and cancer stem cells may be regulated by autocrine mechanisms. For example, several factors secreted by these cells may stimulate angiogenesis. Finally, normal and cancer SC respond to similar motomorphogens (Fig. 2) such as SDF-1, hepatocyte growth factor/scatter factor (HGF/SF), leukemia inhibitory factor (LIF) or vascular growth factor (VEGF) explaining why these factors may regulate the trafficking of normal SC during development/regeneration and at the same time may promote metastasis of corresponding cancer SC (Table 1). Finally as already mentioned, normal and cancer SC share several markers characteristic for the SC compartment such as: CXCR4, antigens CD133, CD34, Sca-1 (mouse), LIF-R and c-met receptor. Thus, similar markers may be employed to sort SC from the normal and malignant transformed tissues.

Pivotal role of the SDF-1-CXCR4 axis in accumulation of CXCR4+ stem/progenitors in bone marrow

The BM tissue itself develops relatively late during ontogenesis at a time when fetal marrow replaces fetal liver as the hematopoietic organ. This developmental process establishes hematopoiesis in the human BM by the end of the second trimester of gestation. At this time fibroblasts and osteoblasts in early bones begin to express/secrete SDF-1 that chemoattracts $CXCR4^+$ HSC from the fetal liver into BM [32, 45]. The important message from developmental studies is that $CXCR4^+$ HSC from the fetal liver colonize the BM microenvironment (to which they are chemoattracted by an SDF-1 gradient) as the first wave of $CXCR4^+$ stem cells. Our recent data suggest that during ontogenesis, in addition to HSC, other TCSC (*e.g.*, for muscles, neurons, liver, heart, endocrine pancreas and kidney tubular epithelium) and perhaps even more primitive PSC (precursors for various TCSC) accumulate gradually in the BM environment in a SDF-1-dependent manner, where they find an environment conducive to their survival [21-24, 37]. Thus, BM can be envisioned not only as the "home" of HSC but also as the "home" of a small population of versatile $CXCR4^+$ TCSC that may serve in adult life as a reserve/mobile pool of stem cells for tissue/organ regeneration [6, 19, 20, 24, 37].

To investigate this idea further we hypothesized that $CXCR4^+$ stem/progenitor cells residing in BM can be recovered, like $CXCR4^+$ HSC, from a suspension of BM mononuclear cells (BMMNC) using chemotactic isolation to an SDF-1 gradient [37]. To confirm that cells isolated by a chemotactic SDF-1 gradient are enriched in TCSC, real-time RT-PCR, immunohistochemical staining and the appropriate *in vitro* culture assays were used to identify the isolated population of cells. We found that cells isolated in this way are enriched in mRNA for markers for early skeletal muscle (Myf-5, MyoD, myogenin), heart muscle (Nkx2.5/Csx, GATA-4, MEF-2C), neural (Nestin, GFAP), liver (CK19, α-

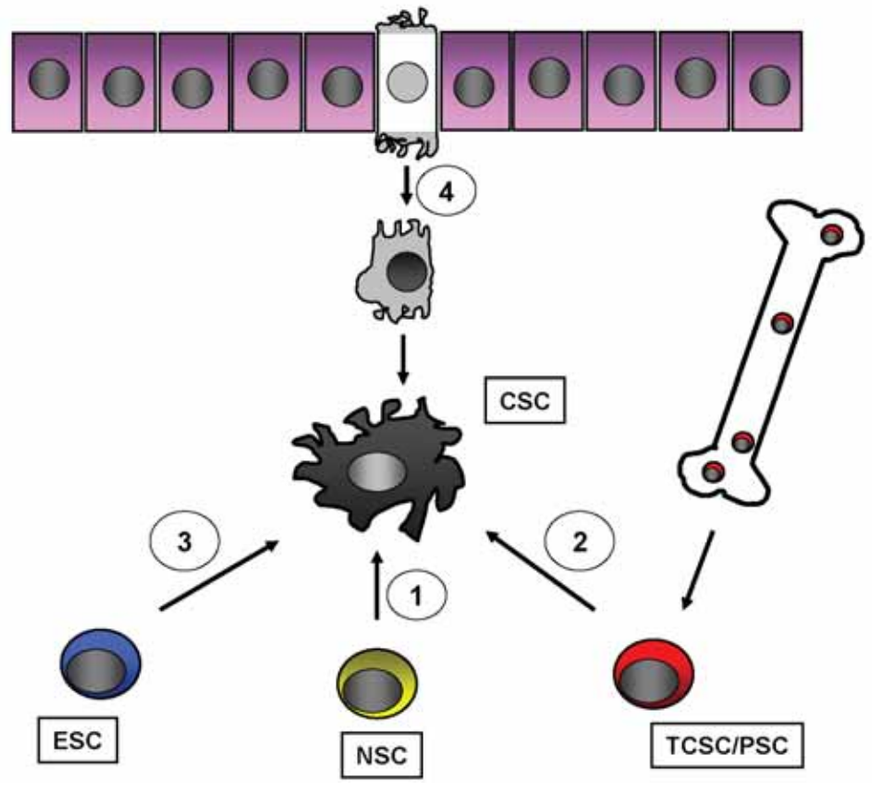

Fig. 1. Different scenarios how cancer SC may originate in the tissues. Scenario 1: cancer SC (CSC) may develop from a transformed local pool of tissue stem cells (NSC) or more differentiated transient amplifying progenitor cells. Scenario 2: circulating BM-derived TCSC/PSC if incorporated at the wrong time to the wrong place (e.g, chronic inflammation, tissue damaged/irritation) may mutate to cancer SC. Scenario 3: cancer SC may originate from embryonic stem cell-like cells aberrantly deposited during ontogenesis (Virchow's hypothesis) (ESC). Scenario 4: effective mutations that will render more differentiated cells immortal may lead to the development of cancer SC. This scenario is possible more frequently in patients with a family history of cancer.

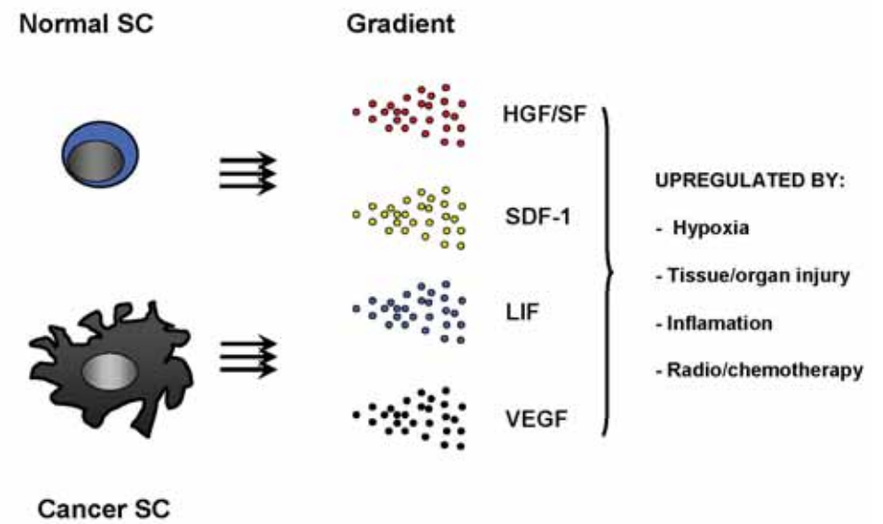

Fig. 2. Similar factors regulate trafficking of normal SC for regeneration and metastasis of cancer SC. Evidence accumulated that SDF-1-CXCR4, HGF/SF-c-met, LIF-LIF-R and VEGF-VEGF-R axes are involved in trafficking of normal and cancer SC. While CXCR4, c-met and LIF-R receptors are expressed on normal and cancer SC, their corresponding ligands are upregulated in a HIF-1α dependent manner in various tissues/organs damaged by hypoxia, inflammation, injury, and radio-chemotherapy.

fetoprotein) and endocrine pancreas (Nkx6.1, Pdx1, Ptf1) [21-24, 27, 37]. Furthermore, using immunohistochemical staining we also detected in these cells the presence of various proteins characteristic of TCSC such as Myf-5, nestin, Nkx2.5/Csx and GATA-4. More importantly, the tissue/organ commitment and stem/progenitor nature of BM-derived $CXCR4^+$ TCSC was demonstrated in *in vitro* cultures - where these cells were found to be able to differentiate into cardiomyocytes [21], grow neurospheres [24] and formed endothelial colonies [42]. Interestingly, $CXCR4^+$ BMMNC also highly expressed mRNA for transcription factors of pluripotent stem cells (PSC) such as mRNA for Oct-4, Nanog and Rex-1, which suggested that (1) some PSC

Table 2. Properties of normal and cancer stem cells

Immortality - ability for self-renewal
Differentiation ability (normal SC but very rare cancer SC)
Long telomers, high activity of telomerase
High expression of ABC transporters (efflux pump) - relative resistance to cytostatics
Secretion of several growth factors, cytokines - predisposition to autocrine growth
Secretion of chemoattracants for endothelial progenitors - stimulation of angiogenesis
Motility-migration (normal SC), metastasis (cancer SC)
Expression of similar surface receptors (*e.g*, CXCR4, Sca-1 antigen, CD133, c-met, c-kit, LIF-R)

could possibly be present among cells enriched for TCSC or (2) TCSC may express some markers typical of PSC [21, 22, 24]. We envision that TCSC accumulate during ontogenesis in BM as a reserve pool of stem cells for regeneration [37]. These cells, however, if chemoattarcted into the wrong places at the wrong time may in certain circumstances contribute to cancer development [15, 25].

Similarly, several investigators hypothesized recently that in addition to BM also other adult tissues (*e.g.*, skin, skeletal muscles and lungs) may also contain a population of very immature stem cells (PSC?) that are able to differentiate into cells from different germ layers [16, 46, 47]. Thus, all of these cells potentially, can give rise to cancer and be equivalent to the developmental embryonic remnants postulated by Virchow 150 years ago [48].

Developmental motomorphogens as pivotal pro-metastatic factors - damaged organ/tissues chemoattract both normal and cancer stem cells

As mentioned above, evidence accumulated that in addition to SDF-1 also several other mottomorphogens such as HGF/SF, LIF or VEGF are important chemoattractants/pro-metastatic factors for tumor cells (Fig. 2). To support this notion both normal and cancer SC express on their surface corresponding receptors such as CXCR4, c-met and LIF-R. Interestingly, promoters of the genes that encode all of these factors and receptors contain binding sites for hypoxia inducible factor 1α (HIF-1α).

The HIF-1α dependent regulation of CXCR4-SDF-1, c-met-HGF/SF and LIFR-LIF axes has several important consequences. Since tissue damage results in reduced oxygen supply and hypoxia, these conditions such as chronic inflammation or tissue/organ injuries create an environment that chemoattracts circulating TCSC/PSC for regeneration/organ repair [2, 7, 34, 37]. However , similar conditions may chemoattract metastasizing cancer SC. This explains an obvious link between inflammation and cancer development and cancer spread. On the other hand, since radio-chemotherapy also upregulates the expression of SDF-1, HGF/SF and LIF in tissues, one of the unwanted side-effects of radio-chemotherapy is generation of a prometastatic environment for cancer SC in various organs. This promotes the spread of cancer cells that survived radio-chemotherapy to the organs that highly express these motomorphogens.

Future investigations

It is straightforward that by studying the biology of normal SC we learn more about the biology of cancer SC. Since cancer SC are responsible for tumor regrowth after radiochemotherapy and tumor metastasis, there is a need to develop efficient strategies to target these cells.

The SDF-1-CXCR4, HGF/SF-c-met and LIF-R-LIF axes have emerged as important regulators of trafficking of normal and malignant SC, which means that they are potential targets for various therapeutic interventions. Small-molecular inhibitors of CXCR4 such as T140 and AMD 3100, modified recombinant SDF-1 or HGF/SF, blocking antibodies against CXCR4 or LIF-R are examples of such potential promising compounds [10, 13]. RNA-mediated interference (RNAi) could also have potential as downregulators of the expression of CXCR4, c-met and LIF-R in target cells [8]. Similarly, downregulation of HIF-1α by an siRNA strategy may lead to downregulation of the expression of SDF-1, HGF/SF and LIF in various tissues, and as a consequence inhibit spreading of $CXCR4^+$, $c\text{-}met^+$ and $LIF\text{-}R^+$ tumor cells [26, 30]. Recently, a small molecular inhibitor of transcriptional co-activation of HIF-1α, called chetomin, has been identified. Interestingly, systemic administration of chetomin inhibited hypoxia inducible transcription within tumors and inhibited tumor growth in mice [30].

In conclusion, there is no doubt that new, more efficient, powerful compounds free from side-effects will emerge soon, with the ability to control the metastatic behavior of SC. New drugs will also be developed to target specifically the population of cancer SC. These new strategies will give new therapeutic possibilities to effectively fight these "rebelled warriors" of the "dark side".

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