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The origin of cancer stem cells

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1. ABSTRACT

Cancer stem cells (CSCs), also known as tumor-initiating cells (TICs), are cancer cells that possess capability of proliferation, differentiation, and self-renewal. It is widely believed that CSCs play critical role in the initiation, metastasis, and relapse of cancers, but the origin of CSCs remains unclear. Up to date, several hypotheses have been described, and cell fusion and horizontal gene transfer, which may occur during development and tissue repair process, are considered as important origins of CSCs. In addition, critical gene mutations in stem cells, progenitor cells or even differentiated cells may also contribute to the formation of CSCs, and cell microenvironment is critical to CSC self-renewal and differentiation. The ongoing efforts to identify the CSCs origins may shed more light on understanding of cancer initiation and progression, as well as the development of novel cancer therapies.

2. INTRODUCTION

The concept that cancer arises from cancer stem cells (CSCs) has changed the way how people think about cancer. For decades, cancer initiation and progression is considered as a multistep process, including progressive genetic alterations that drive malignant transformation of normal cells (1, 2). However, current view suggests that most cancers arise from a single clonal cell that is malignantly transformed and shows increasingly aggressive phenotypes. In most cases, CSC may represent the clonally selected cell, giving rise to cancer. As the extension of studies on CSCs, the tumor biology of this specific type of cells is increasingly understood, but their origins remain puzzling. A typical question is whether a cancer always begins from normal stem cells which lose the control of proliferation and differentiation, and the difficulty to experimentally address this question may be derived from

the limited quantity of normal stem cells or progenitor cells in a given tissue.

During the tumorigenesis, pro-oncogenes, tumor suppressor genes and genes involved in DNA repair or mitosis play important roles. Critical mutations, amplifications, deletions of these genes usually lead to deregulation of normal cell biology, initiating malignant transformation(3, 4). This review article introduces recent understanding of CSC origins, including genetic events leading to cell transformation, cell fusion, horizontal gene transfer, and cell microenvironment promoting CSC formation and clonal selection. It is understood that the fusion of stem cells and somatic cells that have gained some mutational hits can lead to genomic instability and initiate CSC transformation (5, 6). During life-long time, the mutation hits may occur and are accumulated in proliferating stem cells, progenitor cells, and even differentiated somatic cells. The hybrid of such somatic and stem cells may provide the cell with self-renewal capability and transformational features. Published data have shown that circulating hematopoietic stem cells can fuse with cells that reside in specific tissues, which provide a possible origin of cancer stem cells (7). Up to date, a series of cell fusion factors have been identified, and some of the factors are related to cancer initiation and progression signalings (8). Genomic instability is another mechanism of CSC formation, and the deficiency of important oncogenes, cancer suppressor genes and cell cycle regulators are important factors for the formation of CSCs. For instance, cell growth checkpoint abnormalities have been suggested to cause chromosomal aberrations and CSC formation (9). The third theory of CSC formation is horizontal gene transfer. The horizontal gene transfer usually happens in prokaryotic cells, but it is reported that in eukaryotic cells, DNA in apoptotic cells may transfer to recipients by this mechanism, leading to nuclear programming and cancer initiation (10). Finally, microenvironment is important for the formation and clonal selection of CSCs. In some cases, such as the context of tissue repair, signals are given to replace dying cells. Cancer can be considered as a wound that never heals. Therefore, if the microenvironment signals are constitutively given, the repair process lasts forever, initiating cancer. In this review article, we will discuss in detail the cancer stem cells in terms of their origins, cell biology, tumorigenicity, and roles in cancer therapy.

3. NORMAL STEM CELLS AND CANCER STEM CELLS

3.1. Normal stem cells

To better understand the biology of CSCs, we should first define normal stem cells (NSCs). Normal stem cells are cells that have ability to self-renew and generate different lineages of specifically differentiated tissue cells (11, 12). The most important features of stem cells are self-renewal and differentiation. In general, a stem cell divides by asymmetric cell division into a new self-renewal stem cell and a transit amplifying cell (progenitor cell). Self-renewal of stem cells allows maintenance of the undifferentiated stem cell pool over lifetime, and this is the most important feature of stem cells distinguished from regular cells (13). In response to local or systematic signals, stem cells are triggered to massive proliferation. Disruption of asymmetric stem cell division will lead to a rapid escalation in stem cell number, which may leads to developing cancer(14, 15). Another characteristic of stem cells is their capability of differentiating into different tissue-specifically specialized cells. For instance, in blood system, stem cells differentiate into transiently amplifying progenitor cells, which are rapidly amplified and produce various lineages of differentiated cells, such as lymphocytes and macrophages (16). The differentiated cells eventually die or are replaced by new cells, but the stem cells keep the same in life-long time. In many tissues or organs, the stem cells are perhaps the most long-live cells and have more pluripotent capability than progenitor cells or specialized cells. Because of this feature, the number of stem cells is strictly regulated.

There are two classes of normal stem cells; one is adult stem cells, and the other is embryonic stem (ES) cells (17). Adult stem cells have the common features of stem cells, but possess narrowed lineage specificity, mainly differentiating into tissue-specialized cell types. The primary roles of adult stem cells in a living organism are to maintain and repair the tissues where they exist. Therefore, the adult stem cells are also termed somatic stem cells (18). The fate of adult stem cells was thought to be limited in the tissue of origin, but new evidence shows that under certain physiological conditions, some tissue adult stem cells may undergo a fate other than that. For example, stem cells from bone marrow can differentiated, other than blood cells, into hepatocytes (19), skeletal muscle (20), cardiomyocytes (21), and neural cells (22). There are two major subpopulations of stem cells in bone marrow; one is hematopoietic stem cells that give rise to red blood cells, platelets, monocytes and lymphocytes, and the other is non-hematopoietic stromal cells (BMSC), which can differentiate into myogenic, osteogenic, chondrogenic and adipogenic lineages (23, 24).

Embryonic stem cells are pluripotent stem cells derived from the inner cell mass of the blastocyst, an early-stage embryo (25-27). Embryonic stem cells are distinguished by two distinctive properties: pluripotency and ability to replicate indefinitely. Embryonic stem cells are pluripotent, with potentials to differentiate into any type of cells in the body. During the embryonic development, embryonic cells can differentiate into all derivatives of the three primary germ layers: ectoderm, endoderm and mesoderm; and it has been shown that embryonic stem cells can differentiate into 220 cell types in the adult body (28, 29). Another characteristic of embryonic stem cells is their capability to proliferate indefinitely under certain conditions (30). Because of their plasticity and unlimited self-renewal, embryonic cells are employed as tools in research and regenerative medicine. The difference between embryonic stem cells and adult stem cells is the pluripotency. Embryonic stem cells are able to generate any type of cells in the body, while adult stem cells are usually limited to the cell types of origin (31, 32).

3.2. Cancer stem cells

Cancer stem cells (CSCs) are cancer cells that have the ability to self-renew and give rise to other type malignant cells (13, 33, 34); they are phenotypically and

Table 1. Biological roles of cell fusions

Function	Biological behavior	References
Fertilization	Fusion of sperm and eggs	(114)
Muscle development	Fusion of mononucleated myoblasts to form multinucleated muscle fibers	(78)
Bone development	Differentiation and fusion of macrophages to form osteoclasts	(115, 116)
Placenta development	Fusion of trophoblasts to form syncytiotrophoblasts to better transport nutrients and hormones across the maternal-fetal barrier	(117-119)
Immune response	Fusion of macrophages to form giant cells	(116)
Tissue repair	Bone marrow cells migrate to damaged muscle, fuse with muscle cells, restore muscle function	(120, 121)

functionally diversified tumor cells. Some controversies about CSCs exist since current studies are not successful in fully exploring their similarities and differences from normal tissue stem cells (35).

One important observation which leads to the hypothesis of CSCs is the heterogeneity of cancer (36). There exist many different types of cells in a tumor, including cancerous and infiltrating normal cells. This fact is contradictory to the hypothesis that a tumor is originated from a single cell clonal selection (37, 38). Another observation helps to build the cancer stem cell theory is that a large number of regular tumor cells are required to form a tumor in immunodeficient animal (39, 40). This does not support the assumption that cancer cells have a great potential to proliferate new cells and can clonally expand to grow tumors even with a small amount of cells. Based on these observations, one possible explanation is that some tumor cells have greater potentials to differentiate into various types of tumor cells and have unlimited proliferation capability. The number of this specific type of cells is not large in a tumor, and therefore, they are called side population.

The first compelling evidence for the existence of cancer stem cells was published in 1997 (41). Transplantation of primary acute myeloid leukemia (AML) cells into NOD/SCID mice led to the finding of SCID leukemia initiation cells (SL-IC), which is capable of initiating and sustaining leukemia growth *in vivo*. Thereafter, a series of transplantation experiments demonstrated that the SL-IC has high self-renewal capacity and is termed AML stem cells, also named leukemia stem cells (LSCs) (41). Further studies have revealed that the CSCs also exist in solid tumors and have strong tumorigenicity. In animal tumor modeling, millions of regular cancer cells are required to generate a tumor, but the cell number required to produce a tumor is largely decreased to hundreds when CSCs are used (42). Additional evidence for the existence of cancer stem cells is stemmed from tumor histological studies. Tumors are characterized with heterogeneity and contain multiple cell types, which is consistent with the features of CSCs that have multi-differentiative potentials, generating multiple cancer cell types.

Surface protein markers are often used to isolate normal stem cells or CSCs by fluorescent tagged methods (43-46). For instance, the AML stem cells are marked with CD34 protein, but lack CD38 ($CD34^+/CD38^-$). New protein marker recently identified for AML stem cells include IL-$3R^+$, $CD90^-$, $CD71^-$, HLA^-, DR^-, and $CD117^-$ (47). Cell surface protein markers are also identified in CSCs of various solid tumors. For instance, in breast cancer, $CD24^-/low/CD44^+$ cells were reported to have higher tumorigenic potential (48). In addition to CD44, the surface protein CD133 (prominin-1) is identified as a cancer stem cells marker in several types of tumors, such as prostate (49) and head and neck carcinoma (50), but not in breast (48). A general rule to identify a CSC surface protein marker is to sort cancer cells in different populations and then implant various subsets of cells into immunodeficient mice to assess xenograft tumor formation and growth.

4. ORIGINS OF CANCER STEM CELLS

CSC origins remain to be fully understood, but several hypotheses have been described, including cell fusion, horizontal gene transfers, genetic instability, and cell microenvironment influences.

4.1. Cell fusion

Cell-cell fusion is involved in numerous biological processes and plays an important role in fertilization, formation of placenta, bone and muscle tissues, immune response, tissue repair and regeneration (Table 1). Cell fusion has a close relationship with cancer initiation and progression. It has been shown that circulating hematopoietic stem cells can fuse with several types of cells, including hepatocytes, cardiac myocytes, oligodendrocytes and Purkinje cells, and the cell fusion may contribute to cancer development and progression as a consequence of hybridization between leukocytes and somatic cells (51-58). Recent studies found that hybridization of tumor cells with lymphocytes leads to the formation of metastatic cells; and also, the cell fusion may promote the phenotypic and genotypic diversity of tumors, thereby stimulating cancer progression (5, 59-62).

Figure 1 depicts the hypothesis of cell fusion as an origin of cancer stem cells. A fusion of two cells leads to the formation of a multinucleated or mononucleated cell. Multinucleated giant cells (syncytia) are normally formed during the development of the bone, muscle, and placenta (63). The fusion of a stem cell and a differentiated cell forms a heterokaryon. The heterokaryon was first observed in Sendai virus-mediated fusion of murine Erlich ascites cells and human HeLa cells *in vitro* (64). The formed heterokaryons remain stable over time and have the function and characteristic of each fusion partner. Therefore, the fusion cell from a stem cells and a transformed differentiated cell may possess both of their characteristics, and gain self-renewal activity and transformed ability. Another consequence of the cell fusion

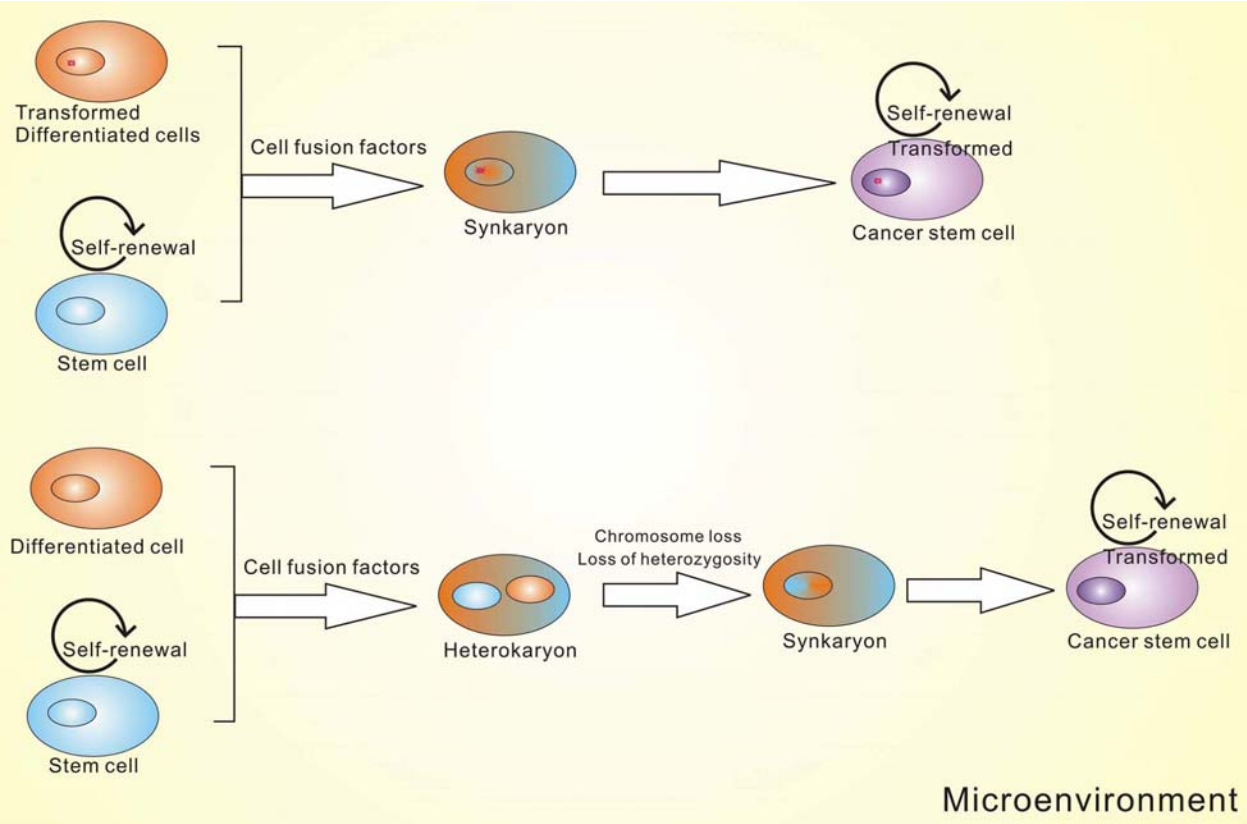

Figure 1. Cell fusion as an origin of cancer stem cells. In the presence of cell fusion factors, a normal stem cell may fuse with a transformed cell to form a mononucleated cell (synkaryon) or a multinucleated cell (heterokaryon). The heterokaryon is considered as an intermediate of the synkaryon with chromosome loss. The hybrid fusion cell possesses self-renewal activity and transformed capability, and thus are cancer stem cells.

is to form a synkaryon, a single nucleated cell, with the heterokaryon as an intermediate step (63). Therefore, the synkaryon is generally featured by chromosome loss. A classic example of synkaryon formation is the fusion between murine myeloma cells and B-cells from an immunized mouse, which forms hybridomas (54). The chromosomal loss during a fusion process between stem cells and transformed cells may lead to the formation of cancer stem cells. Thereby, increased cell-cell fusion rates may be closely related to cancer initiation. It is believed that many tumor cells are fusogenic, and the hybrid cells produced by fusion between tumor and normal somatic cells are often more malignant than the parental tumor cells (5, 6, 65). For instance, human stem cells from a grafted kidney cancer migrate to the skin and fuse to adopt a keratinocyte phenotype and undertake transformation (65).

Due to the striking similarities between CSCs and normal stem cells, it is perceived to presume the normal stem cells as targets for malignant transformation. A possible tumor initiating model may be the fusion of stem cells with cells that have obtained a set of genetic alterations relative to cancer development. Such fused cells may have the features of large chromosomal aberrations and aneuploidy, or harbor unique cell-survival programs from normal stem cells, driving tumor initiation (66). This feature of cancer stem cells explains the tumor chromosomal derangements (Figure 2) that may happen at early stages of cancer development. In another word, a trans-differentiation of a normal cell into a cancer cell may occur, due to cell fusion, at the early cancer development stages or during progressive tumor growth, leading to cellular aneuploidy and heterogeneity of cancers. Further study efforts are required to clarify the extent of normal stem cell contribution to CSC formation and cancer initiation and progression. Of note, cell fusion may also happen between different tumor cells or between tumor cells and normal somatic cells. Although probably rare, it may be important for tumor progression (67).

Several cell type-specific or species-specific cell fusogenic factors have been identified, which helps to understand the mechanism of the cell fusion. In mammalian cells, fusogenic proteins identified include CD44, CD47 and the macrophage fusion receptor PTPNS1 (68). Cell fusion occurs in various organisms, from yeasts to mammalian cells, and for study convenience, *C. elegans* have been used to study its role in organ development and identify fusion mechanism and fusogenic factors (69). Tysnes's group has recognized several cell fusion regulators in C. elegans and putative human homologs. For instance, HOXA5 (homeobox A5) in humans is the

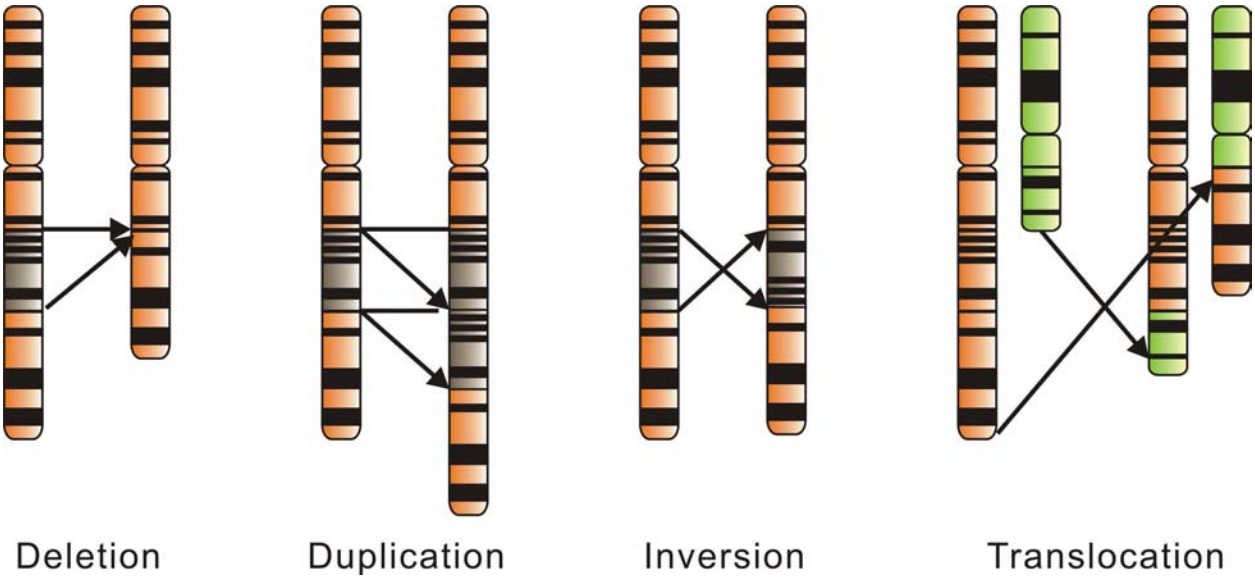

Figure 2. Chromosomal aberrations in cancer stem cells. Chromosome abnormalities that are often involved in cancer initiation and progression include deletion, duplication, inversion, and translocation. Deletion indicates the loss of a chromosomal fragment, which results in gene loss or deficiency. Duplication is a chromosomal aberration resulted from abnormal chromosome crossovers, in which a segment of chromosome has been copied twice. Duplication may create fusion proteins or amplification of oncogenes. Inversion denotes that a segment of chromosome is reversed end by end. All these three chromosomal abnormalities are derived from homologous chromosomes. Another chromosomal aberration is called translocation that occurs between non-homologue chromosomes, resulting in exchange of two chromosome segments. Of note, these chromosomal derangements may produce loss of heterozygosity, leading to cell susceptibility to carcinogens.

homolog of lin-39 in *C. elegans*, and lin-39 is a fusogenic factor (70-72). Interestingly, cross-regulatory interactions are evident between various homeobox genes and the Wnt, Hedgehog and Notch signaling pathways, all of which are crucial pathways regulating cancer development (73-76). Therefore, the cell fusion process may contribute to the formation of CSCs and cancer initiation.

In addition to fusogenic factors, some cytokines and chemokines are also implicated in the cell fusion process, facilitating cell fusion or increasing cell fusion frequencies. Interleukin-4 (IL-4) is a good example that promotes myoblast fusion with myotubes through its receptor-mediated mechanism (77, 78). Gliomas express high levels of the IL-4 receptor, which may raise IL-4-mediated cell-cell fusion.

4.2. Horizontal gene transfer

Horizontal gene transfer serves as another mechanism in the origin of CSCs (79, 80). The horizontal gene transfer often occurs in bacteria and fungi, which helps the organisms to establish various adaptations, such as resistance to antibiotics(81-83). A horizontal gene-transfer process includes three steps: delivery of the donor DNA to recipient cells, insertion of the acquired sequences into the recipient's genome; and finally, expression of the incorporated genes in a manner beneficial for the recipient (84, 85). The first two steps may occur through the mechanisms, such as transformation, transduction or conjugation (83). In eukaryotic cells, horizontal gene transfer refers to DNA transfer from apoptotic cells to recipient cells by phagocytosis or endocytosis (Figure 3). Mutations in somatic cells may trigger apoptosis and DNA fragmentation. The later may be taken up by other somatic cells by phagocytosis or endocytosis, leading to nuclear reprogramming and new aggressive cell formation (86). Fragmented DNA could also be taken up by other tumor cells (87). Experimental studies have shown the transfer in co-cultivation of Epstein–Barr virus (EBV) from the integrated cells into the nucleus of the phagocytosing cell, in which EBV-encoded genes are expressed at both mRNA and protein levels (86); and apoptotic bodies from tumor cells can induce p53-deficient fibroblasts to form colonies *in vitro* and tumors *in vivo* (80). It is currently understood that whole chromosomes or fragments could be transferred via the phagocytosis to recipient tumor cells (79, 80). This extensive phagocytic capacities of tumor cells indicate the genetic material transfer may play a critical role in tumor initiation and progression (88). Tunneling nanotubes (TNTs) is a structure of complex networks between cells, aiding in the selective transfer of membrane vesicles and organelles between cells (89). This finding supports the concept that cell-to-cell communication and molecule transfer, including genetic materials, may occur actively.

4.3. Genomic instability

Genetic instability and alterations are fundamental basis of cell transformation and cancer initiation. Genomic alterations may occur at the chromosome level, so called aneuploidy, which includes chromosomal gain, loss or derangement (66). Genetic alterations may also happen at the molecular level, such as

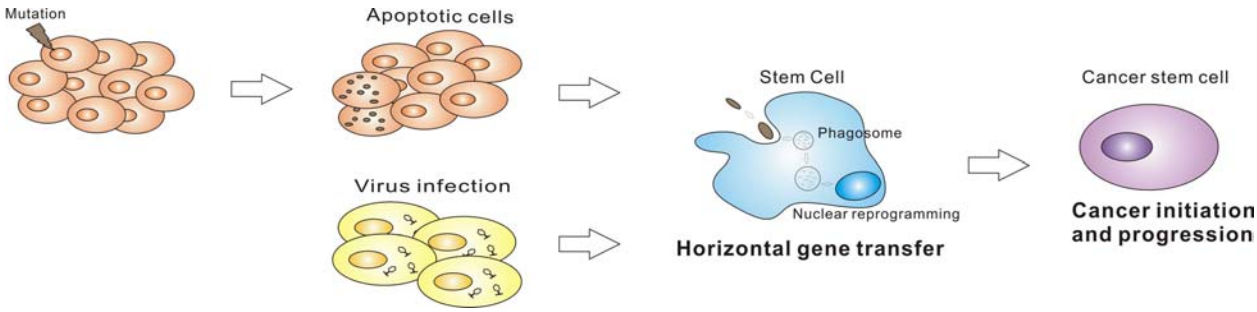

Figure 3. Horizontal gene transfer. Somatic cells may undergo programmed cell death (apoptosis) in response to genetic or other stress. Normal stem/progenitor cells may take up the fragment of DNA from apoptotic cells via phagocytosis or endocytosis, leading to genetic material reprogramming and cancer stem cell formation. This process is termed horizontal oncogene transfer. During lytic viral infection, the viral oncogenes can also been taken up by stem cells through this mechanism.

point mutations in tumor suppressors or proto-oncogenes (90). Chromosomal instability leads to an imbalance in chromosome number and loss of heterozygosity (LOH). The LOH of important tumor suppressors may enhance the susceptibility of cells to carcinogens or mutagens, accelerating tumorigenesis (91, 92).

In reality, most mutations are eliminated from the pool of replicating cells by cell defense system, such as apoptosis, but some mutations may be accumulated at a somewhat low frequency. However, the low frequencies may be accelerated by carcinogens or due to the alterations of the cell defense system. In some cases, mutation rates are not changed, but certain epigenetic events make the cells divide more frequently than usual, which leads to an accumulation of genetic mutations. For instance, selective advantages in the tumor microenvironment as aberrant humeral, cell-substratum and cell–cell interactions allow clonal expansion (93), and mutations that occur in stem cells would have cumulating advantages due to their relative long-live terms. As for aneuploidy, it is controversial that aneuploidy occurs as a cause or effect of cancer development. The evidence that supports aneuploidy as a cause of cancer initiation includes the aneuploidy and carcinogenic transformation of normal cells induced by chemical carcinogens (94, 95).

It is accepted that gene mutations and chromosome derangements in stem cells, progenitor cells, and even differentiated cells may give rise to CSCs and tumor initiation, but the extent in cancer development to which genetic and epigenetic factors contribute remains to be defined. The chromosomal derangements and mutations may be both critical during the initial stages of tumorigenesis, but in view of the rare rates of tumorigenic transformation of normal cells, some unidentified factors may also be involved in tumor initiation.

4.4. Microenvironment

Mutations and chromosome derangement in stem cells, progenitors or differentiated cells may trigger CSC formation, but microenvironment of cells is also critical for their selective clonal expansion. Numerous factors in the host microenvironment regulate stem cell differentiation and transformation, and trigger the initial steps of tumorigenesis. Recent studies have shown that the narrowed lineage specificity of tissue-specific stem cells is regulated by the microenvironment, and under specific conditions, such as an injury or infection, the microenvironmental cells may provide specific signals that counteract the restrictions (96, 97).

A gold study in neuroscience demonstrates the important effect of microenvironment in differentiation pluripotency of tissue-specific stem cells. By labeling with green fluorescent protein (GFP) the neural stem cells isolated from the central nervous system in mice, researchers found that when cultured with myoblasts, the labeled stem cells differentiated into GFP-labeled muscle cells (98-100). This data indicates the tissue specific stem cells have lineage plasticity controlled by tissue specific microenvironment. Differentiated cells also have potential to de-differentiate into cancer stem cells under certain microenvironment. For instance, the combination of EGFR pathway activation and suppression of p16 and p19 provokes a high-grade glioma phenotype of both neural stem cells and differentiated astrocytes (101).

Inflammatory microenvironment has strong stimulatory activity to tumor initiation, through the production of inflammatory cytokines/chemokines and DNA-damaging components (96) (Figure 4). In mice, it has been shown that Helicobacter felis infection in the stomach induces bone marrow stem cell influx for the repair of the gastric epithelia lining. Due to the lineage difference, this process may be deregulated, leading to stomach cancer (41). Inflammatory cytokines such as IL-6 may participate in cancer stem cell formation and regulation of their dynamic equilibrium with non-stem cancer cell (102). In regular conditions, cancer stem cells can rapidly convert to non-stem cancer cells, but the conversion of non-stem cancer cells to cancer stem cells is less efficient. The IL-6 secreted by cancer stem cells can facilitate the dedifferentiation of non-stem cancer cells into cancer stem cells. It has been suggested that the inflammatory cytokines and other factors, such as IL-6 and NF-kappa B, contribute to the maintenance of the proportion of cancer stem cells and non-stem cancer cells in a given cell line (103). Factually, infiltration of immune cells (e.g. macrophagy and lymphocytes), growth factors, proteases, cell free

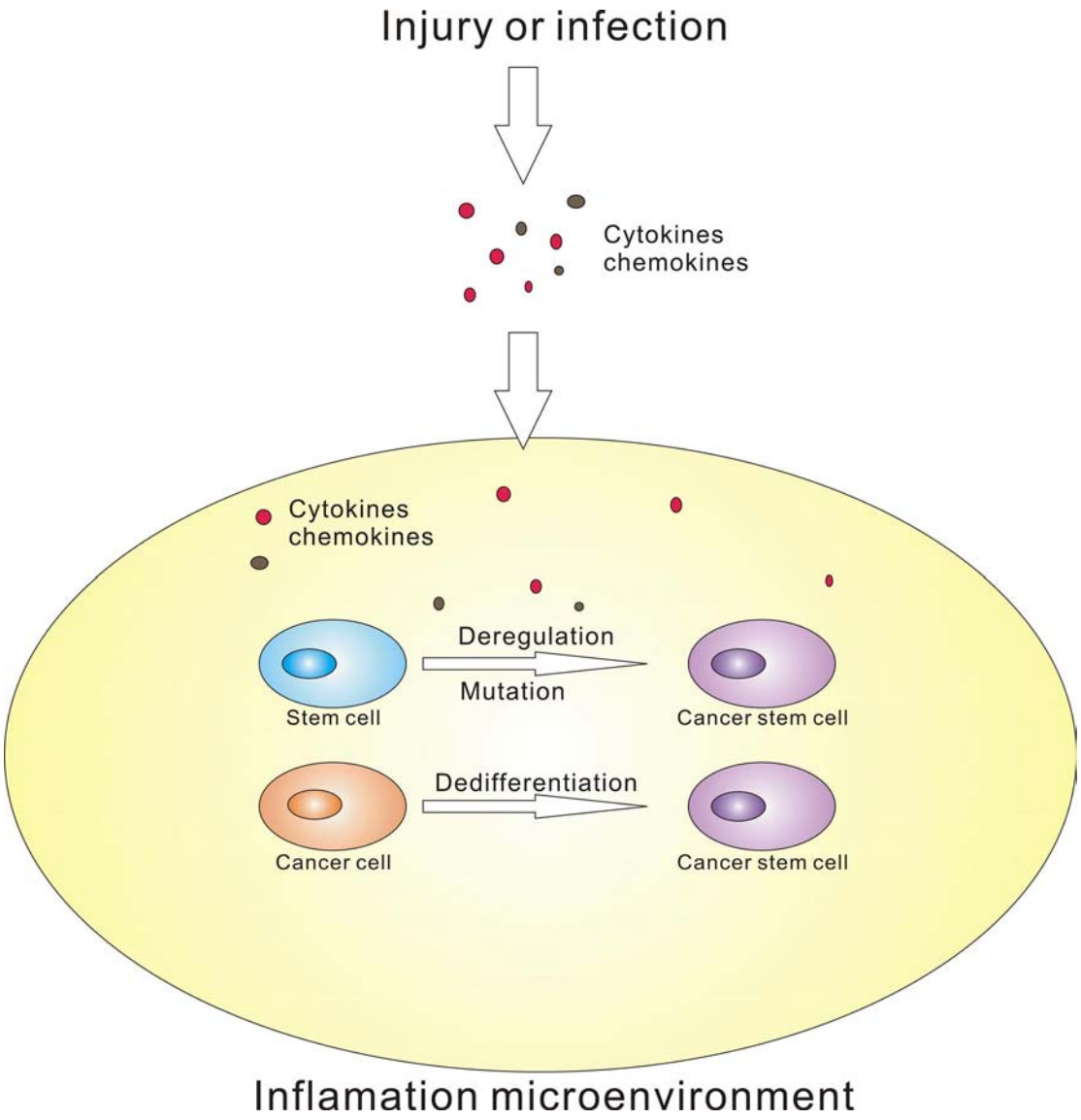

Figure 4. Inflammatory microenvironment triggers the formation and clonal selection of cancer stem cells. Injury or infections may induce inflammation responses. Stem cells that reside in the specific tissue may proliferate and repair the tissue injury, but inflammatory cytokines and microenvironment may deregulate the normal stem cells into cancer stem cells. Inflammatory environment may also dedifferentiate cancer cells into cancer stem cells.

signaling molecules and other components of the microenvironment are all stimulators of stem cell differentiation, or on the opposite, of cell fusion, DNA mutations and chromosome deregulations, triggering CSC formation and tumor initiation. Therefore, better understanding of the roles and effects of tumor initiating microenvironment would be helpful for researchers to develop more effective cancer intervention strategies.

5. CONCLUSIONS

Cancer stem cells may originate from tissue-specific stem cells, bone marrow stem cells, or even differentiated somatic cells that undergo a dedifferentiation process. Although more efforts are needed for a comprehensive understanding of the mechanism of action, the cancer stem cell transition of these cells is a complicated process and may include a set of molecular and cellular events, such as cell fusion, horizontal gene transfer, DNA mutation and aneuploidy, and/or microenvironmental factors. Accumulated mutations in proto-oncogenes and suppressors, chromosome gain/loss and rearrangement in stem cells may give rise to cancer stem cells; the cell fusion between stem cells and cancer cells allows the fused cell to harbor both self-renewal activity and transformation ability; and apoptosis triggered by cell fusion and genetic damage/alterations may stimulate horizontal gene transfer. Microenvironment may play a crucial role in all of these processes and selective clonal expansion of the formed cancer stem cells. A better

understanding of the roles and action mechanisms of the host microenvironment in regulating proliferation, self-renewal and differentiation of normal and malignant stem cells may shed light on the knowledge of cancer initiation and progression. It is currently clear that a successful tumor therapy relies on the ablation of cancer stem cells and the prevention of new cancer stem cell formation, and therefore novel agents are developed for cancer treatment that target CSC signaling pathways Notch (MK-0752, R4733, and TR-4) (104-106), PI3K (CAL-101 and XL-147) (107), AKT (perifosine and Archexin) (108), and Hedgehog (BMS-863923 and IPI-926)(109). Differentiation therapy is also applied into cancer treatment. This concept is to induce CSC differentiation into normal adult cells. It was reported that teratocarcinomas CSCs can be induced to differentiate into normal adult tissue in the embryonic development environment, and all-*trans*-retinoic acid (ATRA) is under clinical tests for differentiation induction through a nuclear receptor RAR-mediated pathway (110-112). Interestingly, salinomycin, a potassium ionophore, showed capability of selectively killing breast cancer stem cells and inducing epithelia differentiation of mammary tumor cells, shedding light on tumor elimination (113). Taken together, genetic alterations in signaling pathways and differentiation status in tumors both should be considered for efficacy of cancer therapies. As an increasing understanding of CSC origins and tumor biology, more curative cancer therapeutic modes will be expectable.

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Abbreviations: AML, acute myeloid leukemia; CSC, cancer stem cell; ES, embryonic cells; IL-4, interleukin-4; LOH, loss of heterozygosity; NSC, normal stem cells; TIC, tumor-initiating cells; and TNT, tunneling nanotube

Key Words: Cancer stem cells, Embryonic Stem Cells, Adult Stem Cell, Cancer Stem Cell Origin, Cell Fusion, Horizontal Gene Transfer, Genomic Instability, And Microenvironment, Review

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