Minireview

Cancer and stem cells

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Impact statement

There have been many breakthroughs at cellular and molecular levels for understanding cancer origin and spreading, leading to a constant renewal of cancer therapeutic approaches. However, cancer remains to be a leading mortality disease worldwide. The emerging of novel treatments for cancers reflects the revolution of our understanding of cancers and their living environment. The interaction between stem cells and cancer cells becomes an emerging attention for an out-of-box thinking for alternative approaches to cancer treatment. This article provides such a clue for a possible novel strategy in cancer therapy through manipulation of (cancer) stem cells.

Abstract

Being the second leading cause of death globally, cancer has been a long-standing and rapidly evolving focus of biomedical research and practice in the world. A tremendous effort has been made to understand the origin of cancer cells, the formation of cancerous tissues, and the mechanism by which they spread and relapse, but the disease still remains mysterious. Here, we made an attempt to scrutinize evidences that indicate the role of stem cells in tumorigenesis and metastasis, and cancer relapse. We also looked into the influence of cancers on stem cells, which in turn represent a major constituent of tumor microenvironment. Based on current understandings of the properties of (cancer) stem cells and their relation to cancers, we can foresee that novel therapeutic approaches would become the next wave of cancer treatment.

Keywords: Cancer, stem cells, cancer stem cells, tumorigenesis, metastasis, tumor microenvironment

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Introduction

Cancer, being considered as "a wound that never heals", is characterized by uncontrolled proliferation of abnormal cells and aberrant recognition of the immune system. According to a report from The World Health Organization, cancer is responsible for an estimated 9.6 million deaths worldwide in 2018 (https://www.who.int/news-room/fact-sheets/detail/cancer). Conventional treatments involving surgery, chemotherapy and radiation therapy, together with newly developed immunotherapy, have been applied to eliminate cancer cells or to inhibit their proliferation. Although the survival time of cancer patients has been prolonged after these treatments, a great proportion of patients experience recurrence and are not able to gain a long-term survival. Thus, it is important to make an exploitive understanding of cancer from initiation to metastasis and relapse.

Over the last few decades, cancer researchers and practitioners have gradually shifted their interests from a focal point of cancer cells to a dual attention to cancer and stem cells. The merging of the two fast evolving fields, the existing cancer field and the emerging stem cells field, would produce unprecedented sparkles in the development of novel therapies for cancers. Stem cells are capable of self-renewal, migration without restriction to tissues, and differentiation into various mature cells. However, with gene mutations or under certain circumstances, these processes can be disrupted, leading to malignant transformation of stem cells. These cells with plasticity then become increasingly aggressive and are highly adaptive to harsh conditions, for example, anticancer treatments. It, however, remains unclear whether stem cells themselves or any other cells that acquire stem cell-like phenotypes become drivers of cancer progression. Here, we present speculations based on currently existing evidences, and provide our perspectives for further scoping the emerging field of stem cells and cancer.

The stem cell origin of cancer

A comprehensive understanding of the origin of cancer cells is critical for designing effective strategies to treat or prevent cancer, as well as for guiding the risk assessment of cancer. Over the past several decades, numerous studies have come to a conclusion that cancer cells are "transformed cells", with a series of genetic and epigenetic mutations that permit them to self-renew, proliferate, and form tumors. The resulting behaviors not only depend on the genotype of the host, but are also affected by many host factors, for example, excessive calorie/nutrient intake, infection, smoking, etc., which may promote tumorigenesis and increase the risk of developing certain types of cancer.[1–3] The defective ability of immune cells in detecting and destroying newly formed cancer cells also plays a critical role in tumor growth and spreading.[4]

For most cancers, the original cells with mutations of transforming potential are unknown. However, there are considerable evidences that suggest cancer may arise from (a) cancer stem cells;[5] (b) bacteria's acquisition and hybridization of host's DNAs;[6] (c) embryonal rest;[7,8] (d) maturation arrest;[9] (e) dedifferentiation of mature cells;[10] (f) mutations of stem cells;[11,12] and (g) transformation of progenitor cells[11] (Figure 1). It has been well accepted that gene mutations play a significant role in carcinogenesis. It was known that carcinogenesis requires more than one critical mutation and the required number of mutations was estimated to be 3–7, in order to overcome DNA repair, apoptosis, and to gain inordinate functions such as indefinite proliferation.[13,14] However, the knowledge of the acquisition patterns of gene mutations in normal cells is limited. In a recent study using whole-genome sequencing, it was found that normal people can carry "driver" mutations during the first decades of life, the burden of which increases with age.[15] There are similarities between stem (stem-like) cells and cancer cells in gene expression and biological characteristics.[11,16–18] However, the transformation of stem cells to cancer cells still requires a few mutations.[19–22] Once stem (stem-like) cells have undergone the mutagenesis process, they may become the origin, or the transmitter, of cancers.[11,12]

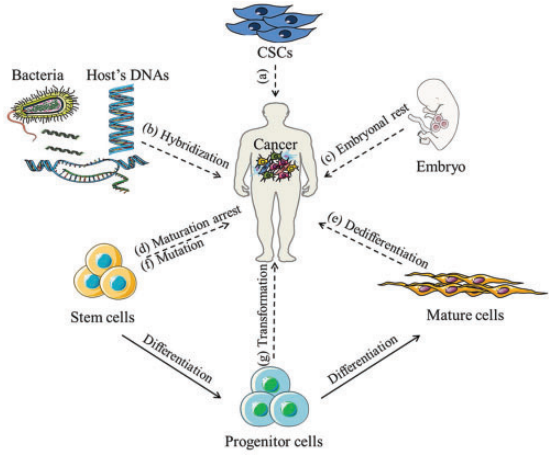

Figure 1. Possible cell origins of cancer. (a) In a clonal evolution concept, stepwise acquisition of mutations may transform cells to be CSCs, which have tumor initiating potential; (b) The intracellular bacteria may take up the host's DNAs and then develop into cancer cells by hybridizing the acquired DNAs with their own ones and expressing the hybrid genomes; (c) Cancer in adults may develop from embryonal rudiments that are produced in excess and that remain in the tissues of the fully mature organs; (d) Cancer may arise in a cell that has the potential to divide and not be lost during normal tissue turnover; (e) Factors such as chemicals or viruses may induce dedifferentiation of mature adult cells to cause cancer; (f) Stem cells with gene mutations may acquire malignant phenotype and lead to cancer; (g) Progenitor cells may undergo transformation and become cancer cells. (A color version of this figure is available in the online journal.)

Stem cell mutations

Stem cells, generally defined as clonogenic cells that are capable of both self-renewal and multi-lineage differentiation, are units of biological organization responsible for the development and regeneration of tissues and organ systems.[23] Since cancer is a disease of unregulated self-renewal, the similarities in the mechanism that regulate self-renewal of cancer cells to that of stem cells were noticed. Signal transduction pathways of Wnt, Shh, and Notch, contributing to the self-renewal of stem cells or progenitors, are also functional in a number of human tumors.[11] Moreover, a stem-cell like gene expression signature was found in various human tumor types, including breast cancer, glioblastomas, and bladder carcinomas.[18]

There are evidences that implicate tissue-specific stem cells are the cells of origin for many types of cancer.[11] One example is that a subset of cells with a $CD34^+$ and $CD38^-$ phenotype that are similar to normal hematopoietic stem cells (HSCs) were found to be capable of initiating human acute myeloid leukemia (AML), suggesting normal HSCs are the target of leukemic transformation.[24] Moreover, other studies have provided evidences that stem cells are a common target of pre-leukemic events or leukemic transformation because some mutations in leukemic cells were found in normal HSCs.[25–27]

The idea of stem cell origin of cancer is also supported by studies on gene manipulation in stem cells. It was shown that loss of tumor suppressor gene *Apc* in $Lgr5^+$ intestinal stem cells (ISCs) resulted in a progressive growth of neoplasia.[19] However, the growth of microadenomas occurring in short-lived transit-amplifying cells was rapidly stalled when *Apc* was deleted in these cells.[19] This study thus suggests that stem-cell-specific loss of *Apc* results in a progressively growing neoplasia. Similar results were observed in $Lrig1^+$ colonic stem cells, in which the loss of *Apc* led to intestinal adenomas.[20]

A number of studies demonstrated that post-natal stem cells can be transformed to malignant cells under standard culture conditions without any genetic manipulation. For instance, human mesenchymal stem cells (MSCs) proceeded to a malignant transformation state after a long-term in vitro culture, resulting in tumor formation in vivo.[21,22,28,29] The accumulation of chromosomal abnormalities, amplified c-Myc expression, elevated telomerase activity, and *p53* mutation are proposed to be responsible for the spontaneous malignant transformation.[21,22] Therefore, these studies suggest that stem cells with accumulation of mutations may become the origin of carcinogenesis.

Progenitor cell transformation

Progenitor cells are also susceptible to transformation. Expression of *Wnt-1* protooncogene in mammary glands of transgenic mice resulted in an expansion of a population of epithelial cells expressing progenitor cell markers (keratin 6 and Sca-1).[30] The expression of these markers was also observed in the subsequent tumors, which contained luminal epithelial and myoepithelial tumor cells that shared a secondary mutation, loss of *Pten*, implying that they arose from a common progenitor cell.[30] In another study, a new prognostic subtype of hepatocellular carcinoma (HCC) that shares the patterns of gene expression with that of fetal hepatoblasts was identified, suggesting that HCC of this subtype may arise from hepatic progenitor cells.[31] There was a study showing that a transgenic mouse model of myeloid leukemia was generated by targeting the expression of transgenes specifically to myeloid progenitors using an *hMRP-8* promoter,[32] although it was shown that additional mutations like *Fas*-deficient were needed to make these mice develop acute malignancies.[33]

The transformation of progenitor cells may be another origin of carcinogenesis, but it is possible that the mutations are accumulated in stem cells while the effects are expressed in progenitor cells. It was shown that primary bone marrow–derived mesenchymal progenitor cells were successfully transformed by EWS-FLI-1 fusion protein (an aberrant transcriptional activator that is believed to contribute to Ewing's sarcoma) and generated tumors that displayed hallmarks of Ewing's sarcoma.[34] The progenitor cell origin of cancers still needs more but rather difficult proofs because there is a confounding fact that the surface antigens used to identify progenitor cells are often shared by stem cells. In addition, experimental conditions may easily affect the exchange between stem cells and their relevant progenitor cells.

Cancer stem cells

CSCs, postulated as a subpopulation of cancer cells with greatly-enhanced tumor-initiating potential relative to other cancer cells within a tumor, display the self-renewal potential and the ability to spawn non-CSC progeny. This concept helps explain the histological heterogeneity of the original tumor. Similar to normal stem cells, a small number of CSCs can give rise to a tumor consisting of rapidly proliferating cells as well as differentiated cells.[35,36]

The first evidence for CSCs was documented in 1937 that a single cell from leukemic mice could initiate a new tumor in a recipient mouse.[37] Subsequent studies demonstrated that the frequency of CSCs in various tumor types was extremely low, for example, the frequency of CSCs in human melanoma was <1 per million cells.[38] However, by using different CSCs identification markers, the number escalates, even increasing to more than 10^5 folds over the original counts.[39] Regardless, the observation that just a few cancer cells are capable of tumorigenesis which led to the conceptualization of CSCs.

By realizing that gene mutations in cells (stem cells, progenitor cells, or differentiated cells) result in tumorigenesis, Fearon and Vogelstein developed a clonal evolution concept to explain the progression of tumors towards a more malignant behavior; they proposed that stepwise acquisition of mutations is needed to transform cells to be aggressive, i.e., tumor cells can become CSCs with a sufficient accumulation of mutations.[40]

It is affirmative that these CSCs are tumorigenic, however, the precise identification of CSCs within tumor cell populations is still blurry because almost all the studies are based on the differential expression of surface markers without a deep understanding of the characteristics of CSCs. Gene mapping together with linage tracing will need to be performed, in order to unmask the veil of CSCs and tumor evolution.

Cancer metastasis and stem cells

Metastasis is responsible for as much as 90% of cancer-associated mortality.[36] Understanding the cellular origin of metastasis is important for preventing this process in early diagnosed cancer patients. However, due to the technical difficulties in capturing the process under naturally metastatic conditions, it remains the most enigmatic aspect of cancer pathogenesis.

Based on current understandings, metastatic cascade comprises two major events: (a) physical translocation of a cancer cell from the primary tumor to the microenvironment of a distant tissue and (b) colonization.[36] In order to detach from the primary tumor, invade the distant organs and proliferate to form metastases, some cells acquire aggressive phenotypes with greatly enhanced migration and proliferation abilities. Although it is widely accepted that the emerging of these cells results from a sequence of genetic and epigenetic alterations, the origin where the metastatic cells arise from is largely unknown. Currently, there are a number of perspectives that suggest metastases arising from: (a) circulating tumor cells (CTCs),[41] (b) CSCs,[5] (c) epithelial to mesenchymal transition (EMT),[42] and (d) myeloid/macrophage lineage[43] (Figure 2). Recent studies have reported a detection of a population of MSCs that was recruited from nearby or distant tissues to tumor, promoting tumor growth and increasing metastatic potential.[44] Given that MSCs are well known for their abilities of proliferation, migration and differentiation, it can be speculated that MSCs could become CTCs or CSCs, leading to cancer "metastasis".

The relationship between CTCs and CSCs remains unexplored. CTCs have a diameter of approximately 20–30 μm, which is far too large to be allowed passing through the capillaries (6–7 μm), indicating that most metastases may not result from CTCs, although it is not exclusive that exceptionally small or physically plastic CTCs may exist.[36,45] It is now suggested that within the population of CTCs, there exist CSCs or stem-like cells, which may be the actual cells that form metastases.[45] For example, a study has identified glioblastoma-derived CTC as CSC-like cells,[46] while another study identified the existence of patient-derived colorectal CTCs that bear all the functional attributes of CSCs.[47] These results suggested that CTCs with CSCs characteristics were responsible for metastasis.

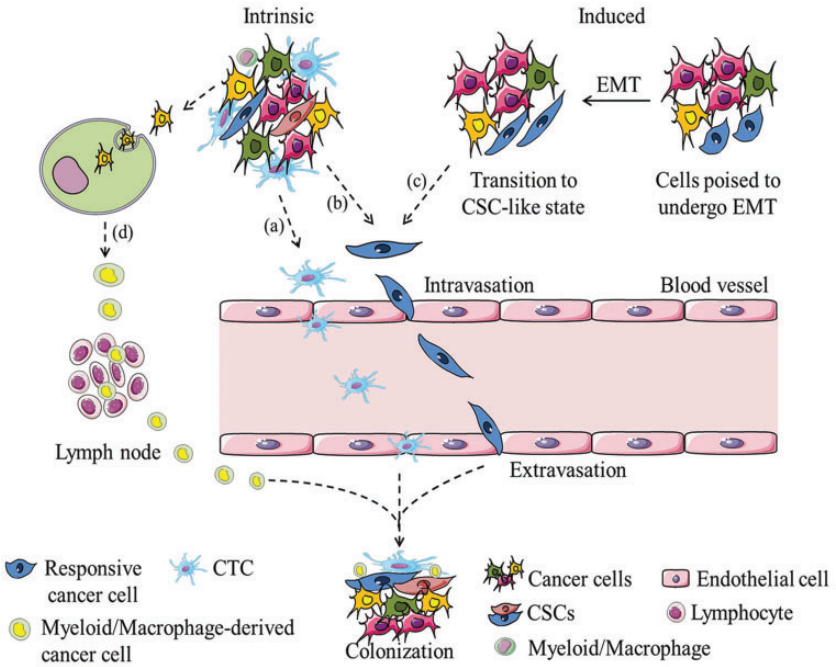

Figure 2. Possible ways of cancer metastasis. (a) Primary tumor cells may translocate from the primary tumor to a distant organ and colonize within that organ; (b) CSCs within the population of CTCs may be the actual cells that form metastases; (c) Cells within TME may become induced CSCs as a consequence of EMT and lead to cancer metastasis; (d) Metastatic cancer cells may arise from cells of myeloid origin or from hybrid cells following fusion between macrophages and non-metastatic cancer cells, which travel to the lymph nodes and form matastases. (A color version of this figure is available in the online journal.)

However, the identities of CSCs in CTCs are indistinct, because different types of cancers vary their expression of surface markers under different experimental conditions.[45] With the consideration of tumor-initiating potential of CSCs, it is possible that some subsets of CSCs, either intrinsic or induced, are able to migrate from the primary tumor to distant organs and form metastases.

The idea of EMT contributing to metastasis comes from the finding that many cancers arise in epithelial tissues.[43] The transformation of a cancer cell from an epithelial cell phenotype to a mesenchymal cell type enables the cell to invade and migrate.[48] However, this idea was challenged by a study using breast cancer CTCs, showing that CTCs expressing epithelial markers contributed to their metastatic potential and correlated with poor clinical outcomes.[49] There are many studies demonstrating that EMT can induce non-CSCs to enter a CSC-like state. In particular, CSC-like cells derived from the EMT induction in human mammary epithelial cells (HMECs) expressed stem cell markers, formed mammospheres, and differentiated to multiple linages.[50–52] When the induction of EMT was performed after activation of HER2/neu oncogene and infection with a vector expressing tamoxifen-activated form of either Snail (Snail-ER) or Twist (Twist-ER), the tumorigenicity of the CSC-like cells was greatly enhanced.[50] Knockdown of CD44 (a most commonly used CSC marker in hepatocellular carcinoma) inhibited the invasion and metastasis of hepatocellular carcinoma both in vitro and in vivo by reversing EMT.[53]

Based on the similarities between macrophages and metastatic cancer cells, it was proposed that metastatic cancers were also arisen from cells of the myeloid lineage. As reviewed before, the similarities not only refer to their ability of intravasation, migration, survival in hypoxic and necrotic environments, and extravasation, but also include their behaviors of phagocytosis, fusogenicity, and expression of some myeloid antigens, for example, CD26, C3bi and CD11b.[54] Because macrophages are derived from circulating monocytes that originate from HSCs[55,56] and abnormalities of HSCs themselves lead to cancers of the hematopoietic system,[57,58] it is reasonable to assume that HSCs may directly or indirectly account for metastasis in some extent.

MSCs, like HSCs and their descendants, can also circulate in the blood. In response to tissue injury, MSCs are mobilized from their niches, access to the blood circulation system, and migrate to the damaged tissue to participate in tissue repair.[59] It is well accepted that tumor shares many common features with the injured tissue, and thus has long been considered as a "wound" that never heals. In cancer, the recruited MSCs would constitute tumor stroma and secrete factors that facilitate tumor growth.[44] On the other hand, MSCs present in tumor microenvironment (TME) can be transdifferentiated to myeloid-derived suppressor cells (MDSC) or M2-type microphages under the influence of cytokines or chemokines.[60–62] The phenotype and function of MSCs are tightly regulated by its surrounding microenvironment. Based on the proliferation, migration, and differentiation properties of MSCs and their potential interaction with molecules released from cancer cells, it is speculated that MSCs in the TME would make a contribution to cancer metastasis.

MSCs in tumor microenvironment

The TME

The TME is composed of a heterogeneous population of cells, including tumor cells and nearby endogenous stromal cells recruited by the tumor.[44] Tumor-associated stromal cells can be arisen from at least six distinct cellular origins: fibroblasts,[63] pericytes,[64] bone marrow-derived MSCs,[64] adipocytes,[65] macrophages,[66] and immune cells.[67] There is no consensus on the role of these cells in supporting tumor growth, as some contradictory results have been reported that MSCs either support or suppress tumor growth.[68] However, these different observations and interpretations may result from varying experimental conditions and tumors used in different studies.

In fact, detailed *in vivo* analysis of the cellular composition of TME is difficult, especially at early stages of metastasis, as it is constrained by the difficulty of spatially discriminating the metastatic-niche cells within the bulk tissue. To resolve this issue, a mCherry niche-labeling system was invented, in which metastatic cancer cells release a cell-penetrating fluorescent protein that can be taken up by neighboring cells.[69] By using this method, the presence of parenchymal cells within the TME was identified. These cells exhibit stem-like cells features, multi-lineage differentiation potential, and self-renewal activity.[69] In consistence with previous studies,[41,70] these results suggest that stem cells or stem-like cells may play a critical role in tumor growth and progression.

MSC transformation by tumor-derived factors

MSCs have been reported to undergo transformation by different tumor-derived factors and contribute to tumor progression by either becoming tumor-associated stromal cells or acquiring pro-metastatic phenotypes.[64,71–76] As displayed in Table 1, both bone marrow- and adipose tissue-derived MSCs have been observed to display transformation induced by tumor-derived factors to myofibroblasts or tumor-associated fibroblasts (TAFs), as revealed by the expression of specific cell markers. The conversion of MSCs to these phenotypes is mostly accomplished by transferring these cells with tumor-secreted factors or tumor-derived exosomes (Figure 3). A study demonstrated that bone marrow progenitor cells can be educated by melanoma exosomes towards a pro-vasculogenic phenotype through MET.[71] To further explore the origin of TAFs and vascular stromal elements in the TME, a study used a series of multi-colored bone marrow and adipose tissue transplantations prior to tumor establishment to quantitate the contributions of these populations to TAFs and vascular stromal elements. The results demonstrated that the majority of fibroblast specific protein (FSP) positive and fibroblast activation protein (FAP) positive TAFs were originated from BMSC (bone marrow-derived MSCs), whereas most vascular and fibrovascular stroma (pericytes, α-SMA$^+$ myofibroblasts, and endothelial cells) were originated from neighboring adipose tissue.[44]

Interestingly, there are some studies demonstrating that cancer cells could malignantly transform MSCs in the

Table 1. Studies reporting the transformation of MSCs by tumor-derived factors.

Author	Cell type	Tumor model	Resulting cell type	Tumor-derived factors	Proposed mechanism
Spaeth *et al.*[64]	Human BMSCs	Tumor-conditioned medium (Skov-3 ovarian carcinoma cell line)	TAFs	Unknown	Induced expression of IL-6, VEGF, HGF and TGF-β in BMSCs
Peinado *et al.*[71]	Mouse bone marrow progenitor cells	B16-F10, SK-Mel-28 and B16-F1 melanoma	c-Kit$^+$ Tie2$^+$ Met$^+$ pro-vasculogenic phenotype	Tumor-derived exosomes	Upregulated Met
Jeon *et al.*[72]	Human ADSCs	Unknown	α-SMA$^+$ myofibroblasts	Tumor-derived LPA	Activation of TGF-β1-Smad signaling pathway
Cho *et al.*[73]	Human ADSCs	MCF-7 and MDA-MB231 breast adenocarcinoma cell lines	α-SMA$^+$ myofibroblasts	Tumor-derived exosomes	Activation of TGF-β receptor and SMAD2 signaling pathway
Paggetti *et al.*[74]	Human BMSCs	Primary chronic lymphocytic leukemia cells and MEC-1 cell line	TAFs	Tumor-derived exosomes	Transfer of exosomal protein and microRNA
Mishra *et al.*[75]	Human BMSCs	Tumor-conditioned medium (MDA-MB231, PANC-1 and U87 cell lines)	α-SMA$^+$ FSP$^+$ myofibroblasts	Unknown	Upregulation of TAF-associated genes
Emura M *et al.*[76]	Human BMSCs	HCT 15 and HT 29 colon carcinoma cell lines	CD34$^+$ α-SMA$^+$ Calponin$^+$ myofibroblasts	TGFβ1	Unknown
Zhao *et al.*[77]	Mouse BMSCs	Human glioma stem-like cells	Malignantly transformed BMSCs	Unknown	Activation of TERT expression
Cui *et al.*[78]	Rat BMSCs	Rat glioma C6 cells	Malignantly transformed BMSCs	Unknown	Activation of IL22RA1/STAT3 signaling pathway
Fu *et al.*[79]	Human BMSCs	Human leukemia cells line K562	Malignantly transformed BMSCs	BCR-ABL1-positive microvesicles	The enhanced secretion of TGF-β1

α-SMA: α-smooth muscle actin; ADSCs: adipose tissue-derived mesenchymal stem cells; BMSCs: bone marrow-derived mesenchymal stem cells; FSP: fibroblast specific protein; HGF: hepatocyte growth factor; IL-6: interleukin- 6; LPA: lysophosphatidic acid; Met: the receptor tyrosine kinase Met; SMAD2: mothers against DPP homolog 2; TAFs: tumor-associated fibroblasts; TGF-β: transforming growth factor-β; VEGF: vascular endothelial growth factor; TERT: telomerase reverse transcriptase; IL22RA1/STAT3: interleukin 22 (IL22)/IL22 receptor subunit α 1/signal transducer and activator of transcription 3; BCR-ABL1: breakpoint cluster region-Abelson leukemia gene human homolog 1.

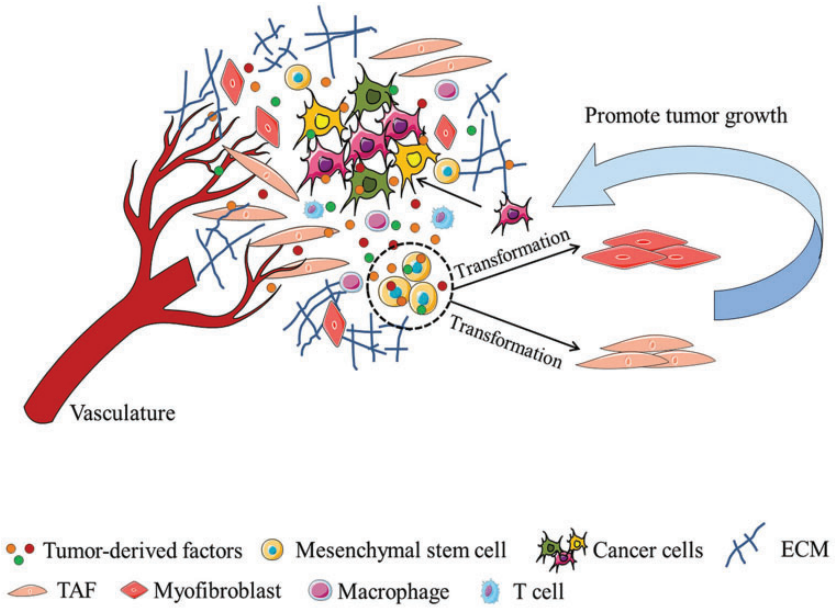

Figure 3. TME and MSCs transformation by different tumor-derived factors. TME is composed of a heterogeneous population of cells, including tumor cells and nearby endogenous stromal cells recruited by the tumor. MSCs within TME could be transformed into myofibroblasts or TAFs, which in turn promote tumor growth. (A color version of this figure is available in the online journal.)

TME.[77] For example, when normal BMSCs were indirectly co-cultured with C6 glioma cells or glioma stem-like cells, they exhibited an increasing growth and proliferation, as well as tumorigenicity in athymic nude mice.[77,78] Similar results were also found in BMSCs co-cultured with microvesicles released from human leukemia cell line K562 (K562-MVs).[79]

It is likely that the different results reported reflect variations in tumor types and differential experimental conditions. Regardless, there is sufficient evidence that suggests alternative approaches should be considered for interrupting the involvement of stem cells in tumor progression in the development of novel therapies for cancers.

Cancer therapy

As summarized in Figure 4, different strategies are developed to treat cancer. Importantly, based on the growing understandings of stem cells in cancer biology, strategies involving bone marrow transplantation, CSC-targeted therapies, and stem cell-based cancer therapies are emerging opportunities for better treatment of different cancers.

CSCs in cancer therapy

A major challenge in cancer therapy is the recurrence and progression of the disease, which may attribute to the development of resistance to chemotherapy in a small subpopulation of CSCs. There are evidences that indicate that CSCs develop some mechanisms protecting themselves from toxins and genotoxic stress, including increased expression of drug transporters,[12,80] heightened DNA damage repair capacity,[12,81] maintenance of a low reactive oxygen species (ROS) environment,[82] and recruitment of a protective niche.[12,83] Therefore, current therapeutic strategies directed at CSCs often involve targeting various CSCs signaling pathways that are required for the maintenance of stem cells. For example, vismodegib, a hedgehog pathway inhibitor was approved by the US Food and Drug Administration to target CSCs in basal-cell carcinoma.[84,85] Inhibition of other pathways, such as Notch and Wnt signaling pathways, which are involved in oncogenesis and tumor development, also results in a profound elimination of residual CSCs.[86–91] In addition to these studies, emerging therapeutics targeting CSCs and their surrounding microenvironment have been reported.[92] However, many putative agents to eliminate CSCs have failed to demonstrate the efficacy in clinical trials.[12,93]

It is important to realize that the heterogeneity nature of CSCs and non-specific therapeutic agents make a predictable failure of the agents in eradicating CSCs[93] (Figure 5). Since CSCs own plasticity and can shift between quiescent and proliferative state, it is not surprising that the responses of different populations of CSCs to therapeutic agents can differ and their phenotypes can constantly change in response to anticancer treatment, which ultimately results in cancer relapse. The similarities between CSCs and normal stem cells also hinder the application of many therapeutic agents with less targetability due to potentially severe side effects and toxicity. Hence, a comprehensive understanding of the role of CSCs in cancer relapse would be greatly beneficial to better treatment of cancers.

Stem cells in cancer therapy

The ability of stem cells in promoting tissue regeneration enables their potential to become therapeutic agents. For cancer treatment, bone marrow transplants containing HSCs have been successfully used for more than 60 years to treat patients with hematological cancers.[94] However, the application of HSCs has not been extended to the treatment of other types of cancers. A study has shown that HSCs

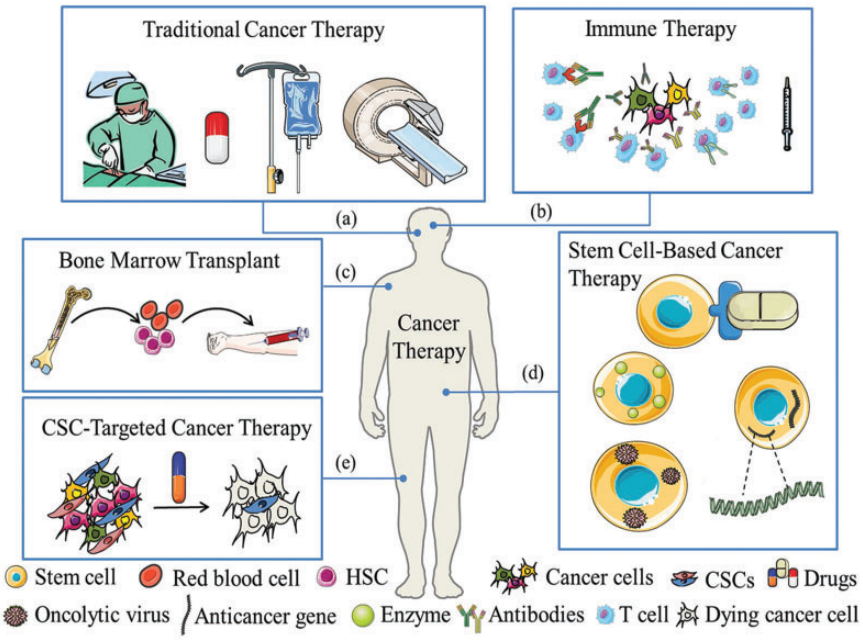

Figure 4. Therapeutic strategies in cancer therapy. (a) Traditional cancer therapies including surgery, chemotherapy, and radiation therapy are commonly used in clinic to treat cancer; (b) With recognition of the immune system in protecting the body from threats such as cancer cells, immune therapy strategies are developed to be a potent type of cancer therapy; (c) Bone marrow transplantation is successfully used to treat patients with hematological cancers; (d) Stem cells are integrated with anticancer drugs/enzymes/genes/oncolytic virus for their targeted delivery to tumors and metastases; (e) Therapeutic strategies directed at CSCs may avoid recurrence of the disease and may lead to better treatments for cancer patients. (A color version of this figure is available in the online journal.)

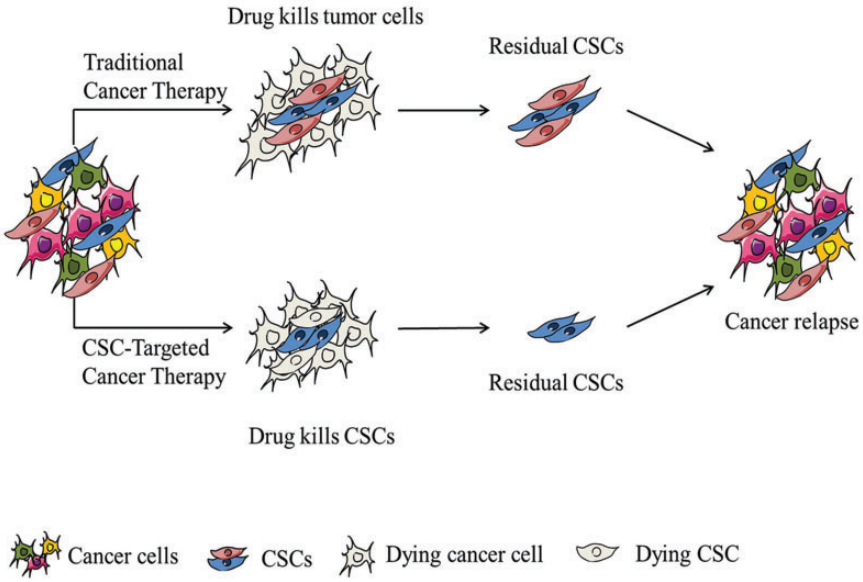

Figure 5. Possible mechanisms of cancer relapse. Due to the heterogeneity nature of CSCs, the therapeutic agents are not particularly specific, leading to the failure of the agents in eradicating CSCs. The residual CSCs are responsible for the recurrence of cancer. (A color version of this figure is available in the online journal.)

mobilization from peripheral blood progenitors antagonized chemotherapy-induced myelotoxicity and thereby allowed dose escalation by a factor of 1.5 to about 20 in the treatment of breast cancer.[95] However, a subsequent study showed that high-dose chemotherapy with autologous HSCs supplement was not superior to dose-dense and dose-escalated therapy.[96]

Since CSCs play important roles in tumor development, relapse, and metastasis, newly developed agents targeting CSCs surface markers bring to a great promise for cancer therapy. For instance, US-FDA approved gemtuzumab ozogamicin (GO, also known as CMA-676) for the treatment of adults with newly diagnosed CD33 (a myeloid differentiation antigen found on blasts in acute myeloid leukemia and leukemic stem cells)-positive acute myeloid leukemia. The indication of gemtuzumab ozogamicin for newly-diagnosed CD33-positive acute myeloid leukemia was extended to include pediatric patients. In a randomized

clinical trial-AAML0531 (NCT00372593), the combination of gemtuzumab ozogamicin with chemotherapy, relative to chemotherapy alone, reached a 20% increase for the percentage of patients free of induction failure, relapse, or death at five years. Other strategies targeting CSCs involve disrupting the microenvironment that enriches CSCs, suppressing signaling pathways or inhibiting CSCs metabolism, were carefully reviewed previously.[92]

Besides targeting CSCs, normal stem cells have been used as "drug deliverers" to treat cancer. Given that MSCs are of inherent tumor-tropic properties, the integration of anticancer genes/drugs with stem cells has been tested for targeted delivery of these genes/drugs to tumors and their metastases.[97,98] Several studies have shown that by using click chemistry to tether chemotherapeutic agents or immune checkpoint inhibitors to stem cells, tumor growth can be inhibited.[99–101] Other studies showed that stem cells can be loaded with prodrug-activating enzymes (cytosine deaminase, carboxylesterase, thymidine kinase), interleukins (IL-2, IL-4, IL-12, IL-23), interferon-beta, apoptosis-promoting genes (tumor necrosis factor-related apoptosis-inducing ligand), oncolytic viruses, or metalloproteinases (PEX).[98,102] These anticancer agent-preloaded stem cells have elicited a significant antitumor response in animal models of various cancers.[98,102] These studies highlight the therapeutic potential of engineered stem cells; however, their clinical application has yet to be explored.

Perspectives

This minireview focuses on how stem cells or cancer stem cells play their role in cancer initiation, metastasis, and therapeutic resistance. This is an emerging field of cancer research, and there are many more questions than few clear answers, but experimental studies continue to shed light on promising new hope in future cancer treatment. It is ultimately important for both clinical and experimental studies to develop alternative approaches applicable to clinical application.

Systemic therapies have displayed an inability to cure metastatic tumors, and had cytotoxic effects on normal functional cells. Patients often suffer from severe side effects and usually die of progressive organ failure. Many efforts have been made to develop new approaches for therapeutic intervention, although the rate of failure remains high. The cells responsible for cancer relapse can protect themselves from toxins and constantly change their phenotypes in order to survive in harsh conditions. This evolving understanding help develop stem cells or cancer stem cells therapy for cancers. Given the possible role of stem cells in promoting cancer, it is likely that restoring the natural microenvironment for stem cells would be a critical factor to treat or prevent cancers.

AUTHORS' CONTRIBUTIONS

WY, JLW, and LLJ drafted the manuscript and figures. YJK edited, revised, and approved the final version of this manuscript.

DECLARATION OF CONFLICTING INTERESTS

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