Review Article

The impact of tumor microenvironments on stem cells

Lina Wang, Tao Cheng, Guoguang Zheng

State Key Laboratory of Experimental Hematology, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin 300020, China

Corresponding to: Guoguang Zheng, PhD. State Key Laboratory of Experimental Hematology, Institute of Hematology and Blood Diseases Hospital, CAMS & PUMC, 288 Nanjing Rd, Tianjin 300020, China. Email: zhengggtjchn@aliyun.com.

Abstract: Stem cells are defined as cells that possess the ability to both self-renew and differentiate into specialized, mature cell types, and the choice between maintenance and differentiation in stem cells is tightly controlled by both intrinsic and extrinsic mechanisms. The extrinsic regulation of stem cells *in vivo* is largely under the control of the local multi-cellular microenvionment, also known as the "stem cell niche." Furthermore, in tumor-bearing hosts, stem cells might also be affected within their niches by the tumor microenvironment (TME). Although cancer stem cells (CSCs) and tumor-initiating cells have been extensively studied in the context of the TME over the previous decade, the impact of the TME on normal tissue stem and progenitor cells has not been as well investigated. As normal tissue stem or progenitor cells are ultimately responsible for tissue regeneration following targeted anti-cancer therapies in most tissue types, understanding how normal tissue stem or progenitor cells are influenced by TMEs is of great importance. Therefore, this review is focused on the effects of TMEs on normal tissue stem cells.

Keywords: Tumor microenvironment (TME); tissue stem cells; self-renewal; differentiation; signaling pathway; leukemia

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Introduction

Stem cells possess the ability to both self-renew and differentiate, which they use to maintain their overall numbers and to generate new specialized cells. Furthermore, stem cells are generally found within defined microenvironments known as "stem cell niches" (1), which protect stem cells from being depleted and maintain their "stemness" (2). Similarly, the survival of tumor cells—including cancer stem cells (CSCs)—depends on the surrounding tumor microenvironment (TME). The TME consists of many cell types, including cancer cells, immune cells, fibroblasts, and myofibroblasts, as well as the surrounding extracellular matrix and signaling molecules (3). Overall, the TME supports tumor cell growth and invasion, protects tumors from host immunity, fosters therapeutic resistance, and provides niches for dormant tumor cells to thrive. In addition to CSCs, normal tissue stem cells and progenitor cells within the TME during the processes of tumorigenesis and cancer progression may also exist. Therefore, unlike stem cells under normal physiological conditions, the functions and phenotypes of these cells are likely affected by the disease conditions of the TME.

Stem cell-based therapies have been applied in clinical settings with some promising results. For example, autologous bone-marrow transplantations as well as hematopoietic stem cells (HSCs) transplantations have been combined with chemotherapy and radiotherapy to treat both leukemia and solid tumors. Because TMEs can also affect normal tissue stem cells, the state of these cells should also be considered when designing cancer treatments. In other words, the impact of the TME on normal tissue stem cells can be significant and may affect cancer outcome. In this review, we focus on the effects of TMEs on normal tissue stem cells.

Stem cells under physiological conditions and TMEs

Stem cells have the remarkable ability to develop into numerous specific cell types within the body. In many tissues, stem cells serve as an internal system for repairing diseased or injured cells. However, during the course of some diseases, changes in tissue environments can significantly affect the function and fate of stem cells. For example, the TME can exert profound effects on stem cells through intercellular interactions or via specific signaling molecules. These effects are often achieved by activating specific signaling pathways that regulate cell proliferation and/or migration and can lead to relatively stable cellular alterations, including changes in cell-fate determination and differentiation (4).

In the leukemia microenvironment (LME), normal HSCs and leukemia stem cells (LSCs) coexist and compete with one another (5). However, the state of normal tissue stem cells within solid tumors remains contentious, and many researchers currently maintain that all cells that show stem-like properties within solid tumor tissue are CSCs. Moreover, CSCs are generally thought to be derived from the transformation of normal stem cells. Nevertheless, it is likely that stem cells within TMEs differ from normal tissue stem cells under physiological conditions as well as from CSCs. Here, we focus on common changes to adult stem cells in TMEs.

HSCs in the LME

HSCs are primarily found in the bone marrow (BM), and they give rise to all blood cell types. They are also found in umbilical cord blood and, to a small degree, in peripheral blood. The surface markers Lin^- $CD34^+$ $CD38^-$ are commonly used to define and isolate HSCs in humans, and the Lin^- c-Kit^+ Sca-1^+ (LKS) marker set is used to isolate HSCs in mice (6,7). It was reported that mouse LKS cell populations were (0.0165±0.0035)% positive for B6 and (0.0276±0.0035)% positive for Trp53 (6). Furthermore, HSCs can be subdivided into long-term HSCs (LT-HSCs) ($CD34^-$ LKS, $CD34^-$ LKS^+), short-term HSCs ($CD34^+$ LKS, $CD34^-$ LKS^+) and multipotent progenitors (MPPs) (8,9). In recent years, the signaling lymphocyte activation molecule (SLAM) markers (Lin^- $CD41^-$ $CD48^-$ $CD150^+$) have been utilized to enrich HSCs from fetal mouse liver tissue as well as from bone morrow (6,10,11). Under physiological conditions, HSCs can expand to generate daughter HSCs as well as differentiate into mature blood cells. Therefore, a small number of HSCs can reconstitute the hematopoietic system, which is why HSC transplantation is a widely used clinical therapy for patients with leukemia and other types of cancer.

In the LME, the over-proliferation of leukemic cells disrupts the normal stem cell niche, interfering with the proper interactions between HSCs and factors within the niche. Because HSC maintenance and function are strictly regulated by the HSC niche, altering this cellular environment, e.g., during the inception and development of leukemia, can profoundly affect HSC fates.

Factors from the LME can affect the migration, mobilization and localization of stem cells. Zhang *et al*. used a transgenic BCR-ABL model to study leukemia-induced alterations to the BM microenvironment and to determine the effects of these changes on the growth and localization of LT-HSCs in mice with normal and chronic myeloid leukemia (CML). They found reduced numbers of LT-HSCs in the BM and increased numbers of spleen LT-HSCs in BCR-ABL mice, and they demonstrated that these changes were related to the decreased expression of CXCL12 in CML BM cells, resulting from increased G-CSF production by leukemia cells. This study suggests that changes in LT-HSC growth and trafficking are linked to altered cytokine expression in the HSC niche (12). It was also reported that malignant cells could metastasize to specific stromal cell-derived factor 1 (SDF-1)-positive vascular niches within the BM that overlapped with perivascular HPC niches in a SCID mouse xenograft model of Nalm-6 pre-B acute lymphoblastic leukemia (ALL) (13). Furthermore, it was observed that normal HSCs/HPCs could be forced out of their bone marrow niches by stem cell factor (SCF) secreted by leukemic cells in a Nalm6 B-ALL model. In this scenario, the therapeutic inhibition of the interaction between HPCs and tumor niches using neutralizing SCF antibodies helped maintain normal HPC function in the presence of malignant tumors (14).

A recent report showed that BM failure in AML is not due to the depletion of HSC numbers or to changes in HSC location but instead occurs because HSCs from leukemic BM fail to produce sufficient progenitors as a result of a differentiation block at the HSC-progenitor transition (15). In a previous study by our group, we showed that in Notch1-induced T-ALL leukemia, normal hematopoiesis in a leukemic microenvironment decreases over time. Although normal HSCs in a leukemia host could be maintained in a relatively quiescent state with preserved

self-renewal potential, HPCs eventually became exhausted after undergoing accelerated proliferation (16). Furthermore, we found that SCF expression in the peripheral blood and BM was increased in this model and that this upregulation was primarily due to non-leukemic cells in response to the leukemia environment (17).

Most studies support the idea that tumor-induced changes to the TME confer a selective growth advantage to tumor cells over normal tissue stem cells. However, studies from Castor A *et al*. showed that of the effects of the TME on normal HSCs varied in different leukemia models. For example, a committed B-cell progenitor phenotype was observed in leukemia-initiating stem cells in both P190 and P210 BCR-ABL1 ALL and in ETV6-RUNX1 ALL. Furthermore, the size of the normal HSC compartment in ETV6-RUNX1 and P190 BCR-ABL1 ALL is unaffected by the expansion of leukemic stem-cell populations, whereas HSC numbers decline in P210 BCR-ABL1 ALL. Studies suggest that P210 BCR-ABL1 ALL arises predominantly from multipotent HSCs and that P190 BCR-ABL1 ALL arises from B cell-committed progenitor cells (18). Therefore, the origins of cancer cells can impact the fate of the corresponding normal stem cells. However, the actual effects of a specific TME on normal tissue stem cells are dependent on multiple factors.

Mesenchymal stem cells (MSCs) in the TME

MSCs are multipotent stromal cells that can differentiate into a variety of cell types, including osteoblasts, chondrocytes, and adipocytes (19). Under physiological conditions, MSCs are a significant portion of the adult stem-cell population, and they exist in a variety of tissues, including bone marrow, adipose tissue, muscle, fetal liver, umbilical cord, and peripheral blood (20). In particular, these cells are positive for stem-cell surface molecules, such as CD90, CD105, CD166, CD44, and CD29, and negative for most hematopoietic and endothelial cell markers, such as CD45, CD34, CD11a, CD235a, HLA-DR, and CD144. In addition, MSCs can be readily isolated from almost any tissue and efficiently expanded *in vitro*, making MSCs a popular research model, especially as they relate to cancer.

MSCs have attracted a great deal of attention due to their multiple sites of origin, their capacity for multilineage differentiation, and their support of hematopoiesis and immunoregulation. MSCs are also closely linked to tumorigenesis and tumor development. The role of MSCs in tumor biology has been extensively covered by several earlier reviews (20-22). Most importantly, MSCs can be recruited to tumors, where they can promote tumor growth, angiogenesis, and metastasis, suppress the immune response, and inhibit the apoptosis of tumor cells (20). However, the specific effects of the TME on MSCs remain largely unknown.

As important components of the TME, MSCs are complexly associated with this microenvironment. It has been reported that MSCs home in on and engraft at injury sites under numerous pathological conditions, including tumor sites (20). MSC migration to tumors may be due to the overexpression of chemokines/cytokines by the TME, which can be sensed by MSC receptors. These signaling molecules include monocyte chemotactic protein-1 (MCP-1/CCL2), epidermal growth factor (EGF), vascular endothelial growth factor-A (VEGF-A), RANTES (CCL5), and CXCL8, as well as receptors, such as CCR1 and CCR5 (20,21). However, the role of MSCs in cancer progression is complex, and there exist bidirectional effects between MSCs and tumor cells. Here, we focus mainly on the effects of the TME on MSCs.

Blau *et al*. studied whether bone marrow derived MSCs (BMSCs) from patients with hematological disorders had cytogenetic abnormalities using molecular cytogenetic analyses. Their results showed that BMSCs from AML patients showed chromosomal abnormalities. Furthermore, they found that cytogenetic markers in BMSCs could differ from markers in hematopoietic cells within the same individual. The fact that MSCs often showed chromosomal aberrations suggested that they might be affected by the leukemia environment (23). Another study showed that CML-derived $Flk1^{+}CD31^{-}CD34^{-}$ MSCs had a normal morphology, phenotype, and karyotype but displayed deficiencies in immunoregulatory function (24). Studies by Li *et al*. demonstrated that the osteogenic potential of MSCs from myeloma patients was impaired, supporting the hypothesis that decreased bone formation contributes to this bone disease. This decreased osteogenic potential was partly due to the suppression of TAZ (transcriptional coactivator with PDZ-binding motif) expression by TNF-α. Furthermore, this phenomenon suggests that both soluble factors and the cell contact-mediated myeloma microenvironment might contribute to the inhibition of MSC function (25). It was reported that MSCs within the colorectal cancer stroma showed similarities to carcinoma-associated fibroblasts (CAFs), and the researchers hypothesized that MSCs within the cancer

stroma could differentiate into CAFs. CAFs and MSCs both play key roles in tumor progression, and they can provide a supportive environment to cancer cells by secreting key inflammatory factors (26). The bidirectional relationship between TMEs and MSCs appears to be quite complex, and more effort should be expended to clarify the biology of MSCs within the TME.

Other types of tissue stem cells in solid tumor TMEs

Although studies have found that adult stem cells exist within most tissues, our knowledge of the biology of normal tissue stem cells in the context of solid tumors remains limited. In the human liver, normal hepatic stem cells are generally quiescent, existing mostly in the G0 phase. It is only following severe liver damage and the loss of large numbers of hepatocytes or when proliferation is suppressed by exposure to hepatotoxins or carcinogens that hepatic stem cells become activated and increase in numbers within the portal tracts around the liver nodules (27). A growing body of evidence suggests that hepatic progenitor cells are associated with the development of liver carcinoma in animal models and in humans. For example, a considerable proportion of hepatic cellular cancers express one or more hepatic progenitor cell markers, such as AFP, albumin, CK7, and CK19, which are not present in normal mature hepatocytes (28). Furthermore, the presence of hepatic progenitor cells may be associated with hepatocarcinogenesis, and the transformation of p53-null hepatic progenitor cells can give rise to hepatocellular carcinoma (29).

The impact of altered microenvironments on normal stem cells

Self-renewal and differentiation, which are normally kept in balance by a variety of intrinsic and extrinsic factors, are crucial to proper stem cell function. In particular, stem cell niches maintain this balance by activating specific signaling pathways to modulate gene expression within stem cells. In tumors, the TME can have a great impact on stem cells. In this section, we discuss the effects of the TME on self-renewal, differentiation, signaling and gene expression in stem cells.

Self-renewal and differentiation

In normal stem cell niches, the signaling pathways that regulate self-renewal and differentiation are tightly regulated. During tumorigenesis, the stem cell niche is transformed into a TME, leading to the misregulation of stem cell growth. Whether stem cells maintain their self-renewal and differentiation potentials under pathological conditions remains a fundamental question.

Cell cycle regulators have been demonstrated to be intrinsically involved in the alterations to HSCs in leukemia models. For example, $p18^{-/-}$ HSCs maintain their capacity to self-renew at a level comparable to unmanipulated wild-type HSCs following multiple serial transfers in both competitive and noncompetitive repopulation models (30). However, $CD34^{-}$LKS cells derived from the bone marrow of $p18^{-/-}$ leukemic mice showed decreased responsiveness to cytokine stimulation (e.g., SCF, thrombopoietin, Flt3-L, and IL-3) and failed to form multilineage colonies. Furthermore, it was found that p18-null HSCs from leukemic mice were not only unable to transfer the leukemic phenotype but were also unable to carry out their normal hematopoietic functions. Thereby contrasting the overwhelming effect of p18-null HSCs against the exhausting effect of the irradiated hosts in which leukemia had not developed (31).

In Notch1-induced T-ALL leukemia and MLL-AF9-induced mouse myeloid leukemia models, the progressive suppression of HSCs and HPCs was observed in the leukemic microenvironment (the manuscript describing the MLL-AF9 model is in preparation). However, normal HSCs from a leukemic host could be maintained in a relatively quiescent state, and they retained their capacity for self-renewal and differentiation. Furthermore, when HSCs from a T-ALL leukemic environment were collected and seeded into a non-leukemic recipients, the self-renewal and differentiation potential of the HSCs could be fully recovered, indeed with higher levels of reconstitution compared with cells isolated from control mice (16). Similar results were observed in an MLL-AF9-induced mouse myeloid leukemia model. In a transgenic BCR-ABL CML mouse model, normal LT-HSC numbers were reduced in the BM of CML mice, and there was a concomitant increase in the number of MPPs, suggesting enhanced LT-HSC differentiation and increased MPP proliferation and expansion. The abnormal differentiation and growth of $BCR\text{-}ABL^{+}$ LT-HSCs suggests that these cells were affected by the LME (12). In multiple myeloma patients, the overexpression of DKK1 by myeloma cells blocked the differentiation of osteoblasts and promoted early proliferation, resulting in reduced viability for the MSCs. As the disease progressed, the balance between osteoblast and

osteoclast differentiation was disrupted, leading to a decrease in bone formation and an increase in bone lesions (32).

Signal transduction

Although abnormal signal transduction within pathological environments is clearly with a hallmark of tumorigenesis, changes to cellular environments during tumorigenesis and tumor development can also affect the signal transduction pathways of normal stem cells via numerous feedback mechanisms. Changes in the capacity of stem cells within the TME are likely due to altered signal transduction.

A number of different signaling pathways, including Wnt, Notch, and Hedgehog, have been suggested to play critical roles in the maintenance, function, and malignant transformation of stem cells. The Wnt signaling pathway is a critical regulator of many stem-cell properties, and aberrant regulation of the Wnt pathway can lead to neoplastic proliferation. In the AML model, translocation products activate the Wnt signaling pathway in hematopoietic cells, which in turn lead to the enhanced proliferation and survival of murine hematopoietic progenitor cells. Conversely, the opposite phenotype is observed when Wnt signaling is inhibited (33). In multiple myeloma patients, the Wnt signaling antagonist DKK1 was found to be elevated in myeloma cells and peripheral blood, which blocked the differentiation of MSCs into osteoblasts and was correlated with presence of focal bone lesions (32). The Hedgehog signaling pathway has also been implicated in the self-renewal of stem cells. During normal mammary development, Hedgehog and the downstream transcription factor Bmi-1 play important roles in regulating stem cell self-renewal, and this signaling pathway is tightly regulated by factors present in the stem cell niche. Furthermore, the deregulation of these processes during carcinogenesis can result in stem cell expansion, a key event in carcinogenesis (34). Indeed, the misregulation of signaling transduction may be the primary explanation for the abnormal biological behaviors displayed by stem cells in TMEs.

Gene expression changes

Although many studies have reported that the properties of normal tissue stem cells can be affected by changes to their environments, the molecular mechanisms of how normal stem cells are affected by TMEs are of particular interest. In addition, for each type of cancer, it is important to determine the precise genes that are involved in the stem-cell changes.

In Notch1-induced T-ALL leukemia and MLL-AF9-induced mouse myeloid leukemia models, global gene-expression profiling was carried out on normal HSCs in leukemic *vs*. normal environments (the manuscript describing the MLL-AF9 results is in preparation). In the two different leukemia models, a few genes were found with altered expression. In the T-ALL leukemia model, Tian *et al*. found that 169 genes (127 up-regulated and 42 down-regulated) were differentially expressed between HSCs from leukemic mice compared with control mice on day 10 post-transplantation (17). In the MLL-AF9 model, 351 differentially expressed genes were found. Interestingly, some of the differentially regulated genes were not shared between the two models, although the majority of the differentially expressed genes were the same. For example, Hes1 was up-regulated in HSCs in leukemic environments using both leukemia models. In addition, the overexpression of Hes1 in normal hematopoietic stem and progenitor cells (HSPCs) in T-ALL leukemia mice could partially rescue the number and function of normal HSPCs through the p21 signaling pathway. Moreover, Hes1 was differentially expressed in HSCs and HPCs in the T-ALL leukemia environment, which suggests that that this molecular mechanism governs the responses of HSCs and HPCs to leukemic conditions (16,17).

Conclusions and perspectives

Taken together, the above findings indicate that both tumor cells and normal cells contribute to TMEs, which are mostly to the benefit of malignant cells and to the detriment of normal cells. Moreover, the TME can exert profound effects on the localization, stability, self-renewal, and differentiation of stem cells by disrupting signal transduction pathways and gene-expression profiles in these cell types.

Stem cell research is fundamental to translational regenerative medicine, and the use of stem cells to treat pathological conditions is attracting ever more attention (35). Understanding the changes caused by the TME would facilitate the use of normal stem cells for regenerative purposes and the identification of new targets for anticancer therapies. In addition, greater attention should be paid to the crosstalk between various components of the TME and tissue stem cells, which should yield a greater understanding of the effects of the TME on stem cells in the context of specific tumors. Such studies will likely improve future

therapeutics for treating tumors.

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Footnote

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