The disruption of hematopoiesis in tumor progression

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Abstract

Human adult hematopoiesis maintains homeostasis by replacing depleted progeny pools and inducing a primary immune response to infectious diseases and tumors. Recent studies have shown that tumor progression is associated with profound perturbations in hematopoiesis. Scientists have sought to clarify the complex mechanisms underlying the developmental fate of hematopoiesis by assessing hematopoietic stem and progenitor cells in various tumors. Results have shown that tumors disrupt normal hematopoiesis, resulting in extramedullary hematopoiesis and myeloid skewing. The key regulatory roles played by myeloid-derived suppressor cells induce immune suppression. Here, we summarize recent findings and discuss mechanisms underlying the disruption of hematopoiesis in solid tumors.

Keywords: Hematopoiesis, MDSCs, Microenvironment, Tumors

1. INTRODUCTION

Hematopoietic stem cells (HSCs) maintain lifelong hematopoiesis via their ability to self-renew and differentiate into all blood cell lineages in humans.[1] HSCs are an extremely rare population of cells that usually reside in the highly organized bone marrow architecture (also called niche).[2] Any perturbation of the bone marrow niche affects the hematopoiesis process.[3] Under physiological conditions, a small number (1%–5%) of hematopoietic stem and progenitor cells (HSPCs) regularly enter circulation and travel through peripheral blood.[4] HSPCs sense stress signals and are capable of converting environmental cues into versatile cytokine signals to regulate hematopoiesis.[5] Multiple factors, including growth factors, chemokines, and adhesion molecules, can influence HSPC circulation and activity.

Extensive attention has been paid to the emergence and evolution of tumors, yet how the growth of malignant clones affect normal hematopoiesis is poorly understood. However, circulating HSPCs are highly enriched in tumor tissues and correlate with tumor progression.[6] Furthermore, tumor progression is manifested by alterations in intra- and extramedullary hematopoiesis (EMH), which supports a systemic tumor-promoting myeloid response.[7,8] Therefore, understanding the process by which tumors interrupt normal hematopoiesis is an important question that is highly relevant to tumor progression. Cheng et al[9] have reviewed normal hematopoiesis in the context of hematopoietic malignancies. In this review, we outline the impact of solid tumors on hematopoiesis and summarize their underlying mechanism.

2. RESPONSE OF HEMATOPOIESIS TO MALIGNANT MICROENVIRONMENTS

In clinical observations, the progression of different types of solid tumors has resulted in an increased peripheral neutrophil-to-lymphocyte ratio[10,11] and circulating granulocyte–macrophage progenitors (GMPs).[12] HSPCs, which are upstream of these cells, have been increasingly recognized as playing key roles in tumor growth and metastasis progression. It has been well-established that elevated levels of HSPCs correlate with higher tumor stage and decreased progression-free survival.[12,13] Tumors usually accumulate immune-suppressive hematopoietic lineages at primary sites. HSPC production and circulation are elevated in tumor patients and murine models before detectable metastases.[13] The number of circulating HSPCs decrease if tumor-mediated mobilization is inhibited, whereas the pharmacological mobilization of HSPCs increases metastasis.[13] When tumors are removed, the elevated HSPCs return to their normal levels. However, in malignant microenvironments, HSPCs exhibit a myeloid-biased differentiation manner and result in the accumulation of tumor-associated myeloid cells including myeloid-derived suppressor cells (MDSCs), neutrophils, and macrophages.[14–16] Thus, we can conclude that activated hematopoiesis is one of the earliest steps in the metastasis process; HSPCs can be potential clinical indicators of metastatic niche formation.

In addition to the bone marrow, studies have shown that the liver[17] and spleen[18] are also major sites of EMH, serving as distinct niches for generating myeloid HSPCs and MDSCs. The spleen is an important site of tumor-induced EMH, which is a

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supplement to the bone marrow hematopoiesis in tumor-bearing hosts. The spleen actively recruits HSPCs via the CCL2/CCR2 signaling pathway and selectively amplifies a specific HSPC response committed to immunosuppressive myeloid cells.[18] In contrast, the granulocyte–macrophage colony-stimulating factor (GM-CSF) secreted by tumors contributes to increased hematopoiesis in the liver.[17] Hematopoiesis in the liver leads to the expansion of MDSCs in this organ. Selective abrogation of these two processes may be helpful in enhancing the therapeutic efficacy of immune checkpoint blockade.

3. MDSCs: DERIVED FROM BIASED HEMATOPOIESIS AND CONTRIBUTE TO IMMUNOSUPPRESSION

HSPCs cultured in tumor-conditioned media demonstrate a signature of proliferation and differentiate into MDSCs. MDSCs are a heterogeneous population of immature myeloid cells and myeloid progenitors that negatively regulate immune responses, facilitating tumor metastasis and angiogenesis.[6,19] In humans, MDSCs express granulocytic markers ($CD33^+CD11b^+HLA\text{-}DR^-CD15^+$) or monocytic markers ($CD14^+HLA\text{-}DR^{low/-}$).[20,21] However, these cells are short lived and must be continuously replenished by continuous HSPC differentiation.

MDSC blockade of antitumor immunity is an accepted key mechanism by which tumors evade the immune system. MDSCs interact with multiple immune cells and regulatory cells.[22] These cells can block nature killer cell cytotoxicity,[23] modulate macrophages to become an immunosuppressive M2 phenotype,[24] and induce the production of regulatory T cells.[25] MDSCs suppress the T-cell response in two main different manners: an antigen-specific and nonspecific manner associated with the production of nitric oxide and cytokines[26] and induction of antigen-specific T-cell tolerance related to the production of reactive oxygen species.[27,28] This leads to T-cell dysfunction and immunosuppression. In addition, MDSCs in the liver interact with Kupffer cells and increase their expression of programmed death-1, a negative costimulatory molecule. In this manner, defining the nature and characteristics of mobilized HSPCs and MDSCs emerging in tumors is crucial for understanding tumor immunosuppression and direct therapies based on reestablishing the balance of altered hematopoiesis.

4. UNDERLYING MECHANISMS OF ALTERED HEMATOPOIESIS IN CANCER

It has been reported that various inflammatory cytokines and microbial products affect the direction of HSPC differentiation.[29–31] Although the precise underlying mechanisms are not yet clear, the accumulation of MDSCs is generally thought to be elicited by tumor-derived factors.[28,32] In tumors, such as liver, colorectal, and lung cancers, hematopoietic cytokines (GM-CSF, G-CSF, IL-6, and IL-1) are produced and carried throughout the circulation to mediate effects.[33,34] For instance, the growth factor GM-CSF, which is produced by malignant and stromal cells, induces the rapid generation of MDSCs from precursors present

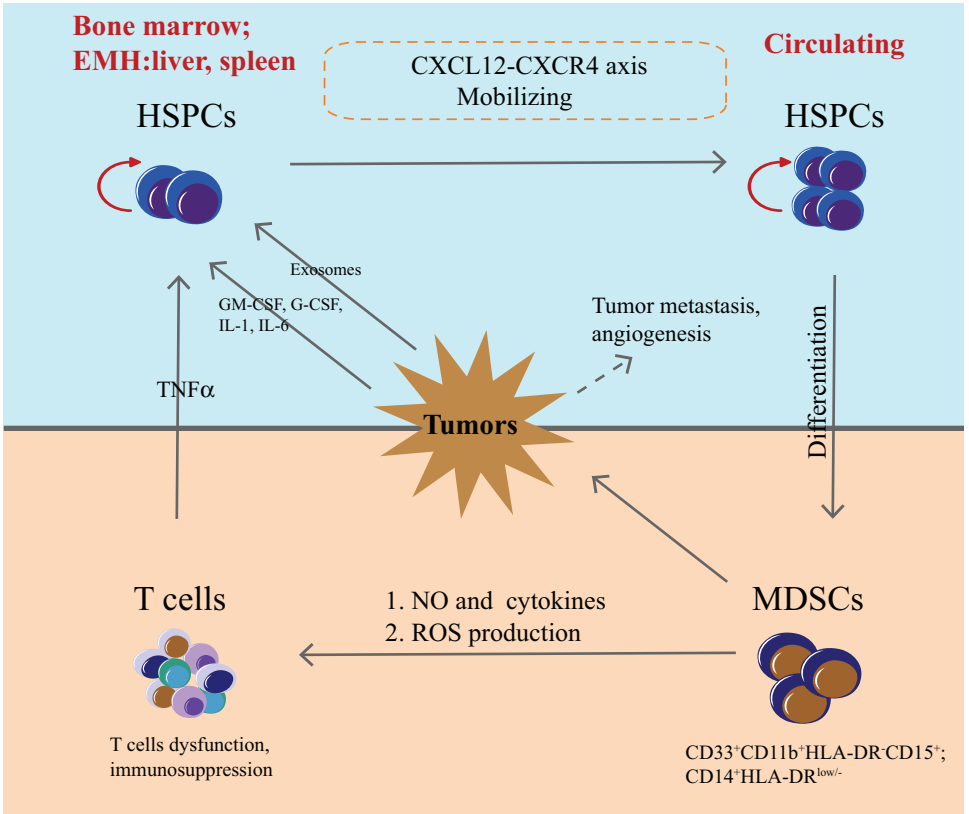

Figure 1. Mechanism for the disrupted hematopoiesis in tumors. Tumor cells secrete soluble factors or exosomes to stimulate HSPC mobilization and alter normal hematopoiesis. HSPCs then have increased circulation and proliferate in EMH sites. Altered hematopoiesis leads to the accumulation of MDSCs. MDSCs induce T-cell dysfunction and immunosuppression. T cells further contribute to HSPC proliferation. In this manner, tumors favor their growth and metastasis. EMH = extramedullary hematopoiesis; HSPCs = hematopoietic stem and progenitor cells; MDSCs = myeloid-derived suppressor cells.

in the bone marrow.[28,35] Furthermore, the CXCL12–CXCR4 axis[36,37] is important in the bone marrow retention and homing of HSPCs.[38] G-CSF is known to antagonize this interaction by mobilizing HSPCs to circulate or prevent their homing back to the bone marrow.[39,40] These findings are consistent with the clinical studies showing that the G-CSF serum concentration is usually elevated in patients with tumors, and in some cases, the levels are associated with poor prognoses.[41,42]

However, a majority of tumor cells do not produce growth factors and how they regulate hematopoiesis remains unknown.[43] Recently, researchers have found that the activated adaptive immune system regulates hematopoiesis in different tumor models.[44] It has been reported that T cells control hematopoiesis through various mechanisms. T cells can secrete Tumor necrosis factorα to induce emergency hematopoiesis by increasing the cell cycle activity of HSCs and myeloid progenitors. In the steady state, effector $CD4^+$ T cells secrete IL-6, IL-3, and GM-CSF to regulate myelopoiesis and ensure terminal differentiation.[45] However, in the presence of inflammation or in tumor environments, $CD8^+$ T cells increase Interferonγ secretion and have effects on HSCs through the STAT5 pathway, eventually impairing their self-renewal.[46] Furthermore, the hematopoietic cytokines (IL-6, IL-17, and colony-stimulating factors) produced by activated T cells also induce myeloid differentiation.

Interestingly, some research groups have found that tumor cells can release high quantities of exosomes acting upon HSPCs to promote tumor growth and metastatic progression.[47] Lung tumor-derived exosomes mediate the production of inflammatory cytokines, including IL-6, IL-8, and monocyte chemotactic protein 1.[48] It would be interesting to dissect the role of tumor-derived exosomes from the impact on hematopoiesis. Therefore, blocking or neutralizing these mechanisms may be promising for better understanding the underlying biology and possibly therapeutic targeting.

5. CONCLUDING REMARKS: CHALLENGES AND THERAPEUTIC OPPORTUNITIES

Tumors remodel the microenvironment to be beneficial for their own survival but induce disruption of normal hematopoiesis. Determining how tumors influence hematopoiesis could facilitate eliminating tumor-associated hematopoiesis dysfunction and thus immune suppression. The interconnections between tumors, MDSCs, and immune cells make it necessary to analyze the dynamic changes of HSPCs.

Although knowledge of the microenvironment contribution to tumor progression is still limited, some issues have been confirmed. First, the cytokine storm brought about by tumor cells must be responsible for the biased hematopoiesis; second, MDSCs play a leading role in tumor immunosuppression, and T cells secrete cytokines to regulate hematopoiesis. Thus, there are the emerging questions of whether blocking these cytokines or their pathways or eliminating MDSCs can improve hematopoiesis and the reconstitution of immunity, which requires further investigation. Moreover, advances in our fundamental understanding of the molecular bases will lead to the identification of new therapeutic paradigms for restoring the balance of hematopoiesis and immune function to improve the clinical outcome of tumors (Fig. 1).

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