Macrophages in leukemia microenvironment

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Abstract

Macrophages, the important component of tissue microenvironment, play important roles in both physiological and pathological processes, including tumor and leukemia. Tumor-associated macrophages are involved in tumor proliferation, angiogenesis, invasion, metastasis, and chemotherapy resistance. In leukemia, macrophages are educated by leukemia microenvironment to obtain specific activated phenotype and participate in leukemia progression. Recent studies have shown that accumulation of macrophages in leukemia patients or mouse model is correlated with poor prognosis. Hence, increasing attentions have been paid to study the characteristics of them and to develop novel therapeutic strategies targeting macrophages against leukemia. In this article, we summarize recent development of macrophages in leukemia microenvironment.

Keywords: Heterogeneity, Leukemia microenvironment, Leukemia-associated macrophages (LAMs), Macrophages, Targeting therapy

1. INTRODUCTION

Macrophages are a population of immune cells with a high degree of phenotypic and functional heterogeneity.[1] Besides their roles in homeostasis, tissue repair, and development, roles of macrophages in tumor and leukemia become the focus.[2] In solid tumor tissues, there are various immune cells and stroma cells in addition to tumor cells, such as macrophages, neutrophils, mast cells, fat cells, and fibroblasts.[3] Tumor-associated macrophages (TAMs) promote tumor progression, and their accumulation in the tumors correlates with poor prognosis in many cancer types.[4] In hematological malignancies, such as lymphoma, myeloma, and leukemia, macrophages infiltrate into disease microenvironment, obtain specific activation phenotypes, and participate in disease progression.[5] Compared with solid tumors, leukemia has different clinical features. During leukemogenesis, leukemia cells outcompete their normal counterparts (hematopoietic stem cells [HSCs]) in bone marrow (BM), which is the major site for hematopoiesis.[6–8] Macrophages, as an important component in BM microenvironment, have remarkable plasticity. Their functional phenotype is controlled by microenvironmental signals. Macrophages in leukemia microenvironment are called leukemia-associated macrophages (LAMs). They are involved in disease progression.

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2. HETEROGENEITY OF MACROPHAGES

Under physiological conditions, macrophages are heterogeneous in several aspects, that is, tissue-specific phenotypes/functions, developmental origins, and polarization by different stimuli.[9] It is well-established that tissue-specific microenvironments give rise to the heterogeneity of tissue macrophages. The phenotypic markers and transcription regulators of tissue-resident macrophages in different macroenvironments are summarized in Table 1.

Recent evidence reveals that macrophages in adult have different developmental origins. In general, adult tissue-resident macrophages have three origins, that is, yolk sac, fetal liver, and circulating monocytes. The origin of tissue macrophages varies among tissues. Tissue-resident macrophages in brain, known as microglia, may arise only from yolk sac macrophages. Langerhans, alveolar macrophages, and Kupffer cells originate from both yolk sac and fetal liver monocytes. In heart-, pancreas-, and gut tissue-resident macrophages of fetal origin will gradually be replaced by BM- and monocyte-derived macrophages.[10] Although they have almost identical phenotype and function in the same microenvironment, macrophages from different origins may have different developmental imprints. For example, Siglec-F and CCR2 can be used to identify alveolar macrophages with embryonic and monocytic origins since embryonic origin macrophages are Siglec-F^{hi} and monocytic origin ones are CCR2^{hi}.[10]

Macrophages have remarkable plasticity that allows them to respond efficiently to numerous environmental signals. They are heterogeneous in activation phenotype. The classically activated macrophages (M1) and alternatively activated macrophages (M2) are well-accepted phenotypes of macrophage activation. M1 macrophages are polarized by LPS and IFN-γ. They express high level of iNOS and secrete proinflammatory cytokines and express inflammatory chemokines such as CXCL9 and CXCL10. M2 macrophages are polarized by IL-4 and IL-6. They express high level of Arg1 and secrete TGF-β, IL-10, arginase, and metalloprotease to participate in immunosuppression.[11] However, macrophage phenotypes may be more appropriately

Table 1

Phenotypic markers and transcriptional regulators of tissue macrophages.

Tissues	Macrophages	Phenotypic markers[48–50]	Transcriptional regulators[51]
Brain	Microglia	F4/80^{+}, CD11b^{+}, CD45^{lo}[52]	Sall1, Sall3, Meis3
Lung	Alveolar Mϕ	F4/80^{lo}, CD11b^{lo}, CD11c^{hi}, CD68^{+}, Siglec F^{+}, MARCO^{+}, CD206^{+}, Dectin-1^{+}[53]	Pparg
Liver	Kupffer cell	F4/80^{hi}, CD11b^{lo}, CD169^{+}, CD68^{+}, Galectin-3^{+}[54]	Id3, Id1, Nr1h3, Spic
Kidney	Resident kidney Mϕ	/	Irf9, Nfat
Skin	Langerhans cells	F4/80^{+}, CD11b^{+}, CD11c^{+}, Langerin^{+}[55,56]	Ahr, Runx3
Bone marrow	Bone marrow Mϕ	CD169^{+}, F4/80^{+}, ER-HR3^{+}[57]	/

described as a continuum of functional states. M1 and M2 macrophages represent only the two extremes of macrophage activation phenotypes.[12] Nowadays, M2 macrophages refer to all non-M1 macrophages and are further divided into M2a to M2d subtypes. TAMs are regarded as an M2-like phenotype, M2d.[13] M1- and M2-associated genes have been suggested. Though no gene expression is unique for either M1 or M2 macrophages, high-level expression of some genes is commonly observed in M1 or M2 macrophages. For example, iNOS and Arg1 are frequently used as markers for M1 and M2 macrophages, respectively. In general, M1 macrophages have antitumor effects, whereas M2 macrophages have protumor effects. A color wheel hypothesis has also been proposed based on three fundamental populations of macrophages that include classically activated macrophages, wound-healing macrophages, and regulatory macrophages.[14]

Under pathological conditions, such as tumor and leukemia microenvironments, macrophages retain their plasticity and respond to disease microenvironmental signals.[1] Macrophages recruited into tumor microenvironment are educated to an M2-like phenotype.[15] TAMs, as an important component of the tumor microenvironment, involve in the tumor-related immunosuppression.[16] M2-like TAMs promote tumor growth, invasion, and metastasis by secreting growth factors, cytokines such as angiogenesis factors, and various proteases.[17] LAMs express both M1- and M2-associated genes. Similar to TAMs, LAMs consist of M1- and M2-like subpopulations based on CD206 expression.[18] Macrophages in chronic lymphocytic leukemia (CLL) are known as "nanny-like cells" (NLCs), which exhibit similar phenotype with TAMs in B-cell lymphoma.[19]

3. CHARACTERISTICS OF LAMS IN LEUKEMIA MICROENVIRONMENT

In hematological malignancies, TAMs in lymphoma and myeloma are widely studied and in many cases TAM counts in tissue sections correlate with poor prognosis.[20,21] In recent years, studies on phenotype and function of macrophages in leukemia microenvironment reveal their characteristics.

From different leukemia models, increase of LAMs in hematopoietic microenvironment is observed during the development of leukemia, especially early and middle stages of leukemia. In nonirradiated Notch1-induced mouse T-cell acute lymphoblastic leukemia (T-ALL) and MLL-AF9-induced mouse acute myeloid leukemia (AML) models, macrophages infiltrated into BM and spleen increase during early stage of leukemia progression and decrease thereafter.[18,22] In another report, in which macrophages in AML are also defined as AML-associated macrophages (AAMs), increase of macrophages in BM is detected in AML patients. This phenomenon is also observed in NUP98-HOXD13 mouse AML model.[23] These observations suggest that noninfectious inflammation occur in the development of leukemia and macrophages play pathological roles in the progression of leukemia.

Although LAMs are generally considered as M2-like macrophages, the activation phenotype of LAMs is heterogeneous. In Notch1-induced T-ALL and MLL-AF9-induced AML, LAMs from different organs express both M1 and M2 macrophage activation-associated molecules.[18,22] AAMs in leukemia burden mice express higher levels of Arg1 and lower levels of IL-6 and Nos2, exhibiting M2 like phenotype.[23] LAMs in T-ALL model consist of CD206^{+} and CD206^{-} subpopulations, especially at early stage of leukemia. Two subpopulations express both M1- and M2-associated genes. But CD206^{+} LAMs expressed higher levels of both M1- and M2-associated genes than CD206^{-} LAMs.[18] Similar results are also observed in AML model, and gene expression profiles of LAMs from BM and spleen in T-ALL and AML mice show that they have distinct gene expression signature.[22] During the development of CLL, leukemia cells secrete chemokines to induce peripheral monocytes migration to them. And infiltrative monocytes differentiate into NLCs with M2 phenotype, which express high level of CD14, CD68, CD163, and CD206.[24]

In physiological state, macrophages showed tissue-specific gene expression profiles determined by gene-enhancer landscapes shaped by microenvironments.[25] LAMs present organ-specific activation as well. Peritoneal tissue-derived LAMs simultaneously expressed high-level iNOS and Arg1, which was not commonly observed in macrophages from other tissues and origins. A study comparing the activation phenotype of LAMs from BM, spleen, and peritoneal tissue in T-ALL model demonstrates that considerable phenotypic diversities are detected among those LAMs, although they all express lower level of CSF-1, TGF-β1, and VEGFα than TAMs.[26] A study comparing the activation phenotype of LAMs from BM and spleen in T-ALL and AML models reveals that LAMs in spleen have more M2 characteristics, whereas LAMs in BM have more M1 characteristics. IRF7 promoted M1 characteristics through activation of SAPK/JNK pathway in macrophages.[22] LAMs in liver exhibited a more M1-like phenotype distinct from LAMs in BM or spleen. They express higher level of CCL5, iNOS, IL12β, TNFα, MCSF, MMP9, TGFβ, and VEGFα, while lower level of IL1-β, CD206, and IL 10 than that in BM and spleen LAMs.[27] Furthermore, LAM subpopulations in different organs show considerable diversity. For instance, the expression of IL-1β, iNOS, IL-6, Arg1, and IL-10 from CD206^{+} LAMs in spleen is higher than that in BM.[18] The phenotypic characteristics of macrophages in different types of leukemia are summarized in Table 2.

Table 2

Phenotypic characteristics of macrophages in different types of leukemia.

Leukemia type	Genetic alteration	Tissue	Phenotypic characteristics
AML	MLL-AF9	BM	BM LAMs have more M1 characteristics, with higher levels of iNOS, TNFα[22]
		Spleen	SP LAMs have more M2 characteristics, with higher levels of Arg1, CCL17, CSf1, and[22]
AML	MLL-AF9/AML- ETO9a	BM/spleen	Expressing higher levels of Arg1 and lower levels of IL-6 and iNOS, exhibiting M2-like phenotype[23]
T-ALL	Notch1$^+$	Peritoneal	Expressing high-level iNOS and Arg1[26]
		Liver	Exhibiting a more M1-like phenotype, expressing higher levels of CCL5, iNOS, IL12β, TNFα, MCSF, MMP9, TGFβ, and VEGFα, while lower level of IL1-β, CD206, and IL 10[27]
		BM	Expressing higher level of CCL17[18]
		Spleen	Expressing higher levels of IL-1β, iNOS, IL-6, Arg1, and IL-10 from CD206$^+$ LAMs in spleen[18]
CLL		Blood/spleen	Expressing high level of CD14, CD68, CD163, and CD206[24]

4. ROLES OF MACROPHAGES IN LEUKEMIA MICROENVIRONMENT

It is well known that TAMs infiltrate into tumors and promote tumor progression through affecting proliferation of tumor cells, angiogenesis, immunosuppression, and so on. Accumulation of TAMs is correlated with worse prognosis in many cancers, including lymphoma and myeloma.[20,28–31] Similar to TAMs, LAMs are an adverse factor in leukemia development. Patients with higher level of CD163 expression have a shorter survival than those with lower level of CD163.[22] In T-ALL and AML mouse models, LAMs promote the proliferation of leukemia cells.[18,22] The leukemia microenvironment polarizes AAMs to M2 phenotype through regulating Gfi1, which supports the growth of AML cells.[23] CD14$^+$ blood cells from healthy donors differentiate into NLCs when cocultured with CLL B cells and protect CLL cells from apoptosis.[24] CLL cells secrete IL-4,[31] IL-13,[32] IL-10 [33], and other cytokines and promote NLCs/TAMs polarization to M2 phenotype, while M2-like NLCs/TAMs inhibits T cell infiltration and mediates local immunosuppression. NLCs/TAMs also promote the survival of CLL cells by secreting IGF1, IL-8, CCL2, and CXCL12.[34] In the Eu-TCL1 transgenic CLL model, macrophages support the growth of CLL cells in mice,[35] protumorigenic and immunosuppressive properties of macrophages can be modulated through the PI3K/mTOR signaling pathway.[36]

5. LAMS AND TAMS

In leukemia and tumor microenvironments, proliferation of malignant cells largely depends on local malignant niches. LAMs and TAMs in respective niche exhibit similar but different phenotypic and functional characteristics. Several similarities are found between LAMs and TAMs. First, increase of LAMs and TAMs are commonly detected in malignant microenvironments when compared with their normal counterparts.[18,23,37,38] Second, LAM and TAM populations are heterogeneous and can be subdivided into different subpopulations. TAMs in tumor microenvironment consist of M1-like TAMs and M2-like TAMs. The phenotype of TAMs varies in different areas of tumor tissues. In a breast cancer model, TAMs localized in normoxic sites express M1 markers and antiangiogenic chemokines, whereas TAMs in hypoxic sites express M2 markers and have proangiogenic effects.[39] M2 like TAMs have the effects of immunosuppression, angiogenesis, and promoting the metastasis.[40–42] In leukemia microenvironment, LAMs consist of CD206$^+$ and CD206$^-$ subpopulations. Both CD206$^+$ and CD206$^-$ LAMs have proleukemia effects.[18] Third, LAMs and TAMs have tissue-specific phenotypes. TAMs in metastatic tumor exhibit more M2 phenotype than primary lesion.[43] As already discussed, LAMs from BM, spleen, liver, and abdominal cavity have different phenotypic characteristics.[18,22,26,27]

The functional characteristics of LAMs and TAMs also have differences. Although both LAMs and TAMs promote malignant progression, the main mechanisms may be different. As angiogenesis is much more important in solid tumors, high-level expression of pro-angiogenetic factors, such as VEGFα, are frequently detected in TAMs, whereas it is not detected in LAMs in several tissues from different leukemia models.[18,22,26,27] TAMs also promote tumor progression through immunosuppression and promoting invasion and metastasis of tumor cells. In CLL microenvironment, M2-like NLCs/TAMs play important roles in immunosuppression through secreting inflammatory suppressing cytokines, such as IL-4, IL-10, and IL-13.[31–33] It is still unclear whether immunosuppression effects play important roles in other types of leukemia. Furthermore, the role of LAMs in invasion and metastasis of leukemia cells has not been established. In the CLL and AML model, LAMs promote proliferation or inhibit apoptosis of leukemia cells directly in AML microenvironment.[18,23,34,35]

6. TARGETING MACROPHAGE FOR LEUKEMIA THERAPY AND FUTURE EXPECTATION

Macrophage infiltration has been shown to be an independent poor prognostic factor in several cancer types as well as in leukemia.[44] Hence, more attention has been paid to develop immunotherapies targeting TAMs and LAMs. TAMs-targeted therapies have been extensively studied in solid tumors. Intervention strategies include depleting TAMs, blocking their protumor signaling, and restoring their immune-stimulatory properties.[41] With deep understanding of macrophage in hematological malignancies, strategies for targeting macrophages have been suggested and explored for therapy applications. In CLL mouse model, depletion of CLL-associated patrolling monocytes and macrophages using liposomal clodronate results in delay of disease development and repairs immune dysfunction.[45] Targeting macrophages by either CSF1R signaling blockade or liposomal clodronate-mediated depletion has marked inhibitory effects on established leukemia.[35] Interaction between SIRPα on macrophages and CD47 on AML cells is critical for leukemic engraftment and evasion of immune surveillance. Disruption of SIRPα-CD47 interaction by SIRPα-Fc fusion protein impairs AML engraftment and does not adversely affect normal hematopoiesis.[46] Similar to CAR-T cell therapies, modified macrophages have been reported by introducing engineered chimeric antigen receptors for phagocy-

tosis (CAR-Ps): Megf10 in macrophages. CAR-Ps result in specific engulfment of antigen-coated particles and human cancer cells.[47] Macrophages-targeted therapies are promising strategies against leukemia and they may be practicable therapy options in clinical applications.

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