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Mini-review

Expansion and functions of myeloid-derived suppressor cells in the tumor microenvironment

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ABSTRACT

Myeloid derived suppressor cells (MDSCs) are a group of immature myeloid cells accumulated in most cancer patients and mouse tumor models. MDSCs suppress host immune response and concurrently promote tumor angiogenesis, thereby promote tumor growth and progression. In this review, we discuss recent progresses in expansion and activity of tumor MDSCs, and describe new findings about immunosuppressive function of different subtypes of MDSCs in cancer. We also discussed tumor angiogenic activities and pro-tumor invasion/metastatic roles of MDSCs in tumor progression.

Introduction

MDSCs are heterogeneous population of myeloid lineage cells including myeloid progenitors and immature myeloid cells (IMCs). MDSCs are highly increased in humans and mouse models with various pathological disorders. They exert potent immune-suppressive functions and are important negative regulators of immune responses in chronic inflammation and cancer [1–3]. In various cancer patients, MDSCs might be used as a prognostic marker and potential therapeutic targets toward elimination of their immunosuppressive activity and enhancement of anti-tumor immune responses [4–7].

MDSCs are defined as Gr-1 + CD11b+ cells in mice. They are further divided into two subsets using antibodies that distinguish between Ly-6C and Ly-6G: co-expression of CD11b with Ly-6G+/Ly-6C^{high} as monocytic lineage cells (M-MDSCs) whereas CD11b with Ly-6G+/Ly-6C^{low} as granulocytic lineage cells (PMN-MDSCs). Both subsets are elevated in tumor-bearing mice, although the higher increase is primarily observed in PMN-MDSCs [8]. In humans, three subgroups of MDSCs have been reported on the basis of their ability to mediate immune suppression using a variety of different markers such as CD11b, CD14 and CD33. Human PMN-MDSCs are CD14-CD11b + CD33 + CD15+, and human M-MDSCs are CD14 + HLA-DR$^{-/low}$ cells. The third sub group of human MDSCs is Lin-HLA-DR-CD33+ cells [9]. Human MDSCs are enumerated primarily in peripheral blood from cancer patients and characterized by immature myeloid cell surface markers. On the other hand, the markers for murine MDSC are CD11b and Gr-1. Murine MDSCs have been studied in the context of peripheral circulation, spleen and bone marrow from tumor mouse models [10].

Expansion and activation of MDSCs in tumor bearing hosts

MDSCs are highly elevated in cancer patients as well as tumor bearing animal models. They possess strong immune suppressive activities. What regulates MDSC expansion and activation in tumor conditions is an important question that has been investigated extensively in the past. Studies have shown that many secreted factors, such as growth factors and microbial products, are released in the tumor microenvironments. These factors activate the expansion or production of MDSCs [11]. Among them, granulocyte-macrophage colony stimulating factor (GM-CSF), G-CSF, IL-6, prostaglandin-E2 (PGE2), cyclooxygenase 2 (Cox2) and VEGF seem to play a major role [12–17]. Accordingly, clinical studies demonstrate that the numbers of CD45 + lin–HLA-DR– human MDSCs decrease with a treatment of bevacizumab, a monoclonal antibody directed against VEGF-A, on patients with lung, breast and colorectal cancers [18]. Cytokines inducing MDSCs acted on a common molecular pathway and the immune-regulatory activity of both tumor-induced and BM-derived MDSCs is shown entirely dependent on the C/EBPβ transcription factor [10].

Some of these factors activate STAT transcription factors (STAT3, STAT5, STAT6) in MDSCs, which function as important signal transducers in the expansion and activation of MDSCs [19]. The development of MDSCs is also regulated by interferon regulatory factor 8 (IRF-8). MDSC-inducing factors such as G-CSF and GM-CSF downregulate IRF-8 via STAT3- and STAT5-dependent pathways. The levels of IRF-8 in MDSCs in cancer patients decline with increasing MDSC frequency, implicating IRF-8 as a negative regulator in human MDSC biology [19]. Our studies also support the importance of STAT3 in MDSC expansion. We show that myeloid specific

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expression of either apoptosis inhibitor 6 (Api6) or metalloprotease-12 (MMP12) activates STAT3 in these cells and consequently leads to systemic expansion of MDSCs. Inhibition of STAT3 *in vitro* abolishes the proliferation and suppressive activity of MDSCs [20,21]. Moreover, factors that promote myeloid-lineage cell differentiation reduce MDSC population expansion [22]. A growing number of studies have demonstrated a strong correlation between the levels of MDSCs in blood of cancer patients and tumor stage and metastatic status [23–25].

Regulatory functions of MDSCs in the tumor microenvironment

The pro tumor functions of MDSCs are at least two folds: (1) immune suppression through inhibition of functional T cells and NK cells as well as induction of Treg expansion; (2) promoting tumor angiogenesis and tumor invasion/metastasis via production of angiogenic factors and proteases in tumor tissues.

Immune suppressive activities of MDSCs

As reflected in its name, a major function of MDSC is potent immune suppressive activity via targeting other immune cells, such as T cells in tumor conditions [26–30]. MDSCs also suppress proliferation and cytokine secretion in both T lymphocytes and Natural Killer (NK) cells, as well as induction of apoptosis in T cell subsets [31]. Many factors have been implicated in MDSC-mediated immune suppression, including inducible nitric oxide synthase (iNOS), arginase-1 (Arg1), Cox-2, PGE2 and TGF-β [32–35]. MDSCs deliver the suppressive functions through a combination of multiple molecules.

In general, PMN-MDSCs are more prevalent in the tumor microenvironment, however, M-MDSCs have much stronger immune suppressive activity [9]. The suppressive function of M-MDSCs is associated with the metabolism of L-arginine. Both Arg1 and iNOS use L-arginine as a common substrate to produce urea or NO that blocks T cell proliferation, differentiation and cytokine production [33]. In addition to direct signaling effects through NO, iNOS can also decreases the available levels of its substrate L-arginine, a process that can be further accelerated by the metabolic activities of Arg-1. Up-regulation of Arg1 activity leads to a depletion of L-arginine from the pathological microenvironment, which leads to a reduction of TCR expression and T cell proliferation [36]. This metabolic targeting is not unique to L-arginine, and studies have identified additional metabolic targets utilized in MDSC-mediated immune suppression, such as cystine and cysteine [37]. Moreover, M-MDSCs are also capable of differentiating into tumor associated macrophages (TAMs), which promote T cell apoptosis and lead to immune suppression [9]. Both M-MDSCs and TAMs suppress CD8+ T cell functions in a non-specific manner at the tumor site. M-MDSCs produce high levels of Arg1 and NO, whereas TAMs up-regulate the expression of either Arg1 or iNOS, but not of both proteins, dependent on the tumor microenvironment [38]. TAMs also inhibit T cell function by secreting cytokines such as IL-1β and TGF-β [39] (Fig. 1).

PMN-MDSCs utilize various mechanisms to subdue the host immune response. They produce TGF-β, a potent immune suppressor [34,40]. PMN-MDSCs also have the ability to suppress immune responses in an antigen-specific manner. They can take up, process and present antigens to antigen-specific T cells [1]. Or through cell–cell contact, PMN-MDSCs induce nitration of T-cell receptors (TCR), which makes T cells unresponsive to antigen stimulation [11]. ROS is another major factor responsible for PMN-MDSCs mediated immune suppression. Inhibition of ROS production using an upstream inhibitor abolished PMN-MDSC mediated suppression *in vitro* [41]. The combination of ROS and NO suppresses CD8+ T cell responses by producing peroxynitrite, which resulted in nitration of

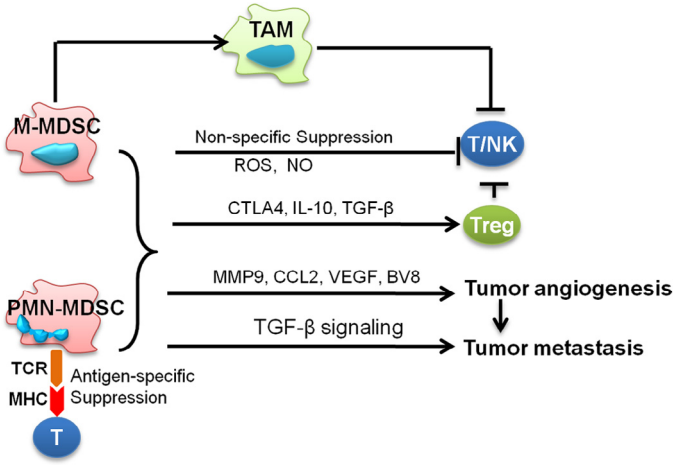

Fig. 1. The regulation mechanisms of MDSCs in the tumor microenvironment. PMN-MDSCs can take up, process and present antigens to antigen-specific T cells. Through cell–cell contact, PMN-MDSCs induce nitration of the T-cell receptors (TCR) on the surface of T cells. T cells become unresponsive to antigen specific stimulation. M-MDSCs are differentiated into tumor associated macrophages (TAM) that inhibit T and NK cell immune responses. Both PMN-MDSCs and M-MDSCs produce reactive oxygen species (ROS) and nitric oxide (NO) which inhibit T and NK cells in a non-specific manner. MDSCs induce Treg expansion via secretion of IL-10 and TGF-β. In some cancer models, the induction of Treg by MDSCs is associated with the expression of cytotoxic lymphocyte antigen 4 (CTLA4). Tregs inhibit T and NK cells. MDSCs contribute to tumor angiogenesis by production of factors such as MMP9, CCL2, VEGF and BV8. TGF-β signaling in MDSCs plays an important role in tumor metastasis.

TCR and inhibition of TCR signaling [42]. PMN-MDSCs also down-regulate the ζ chain of TCR to suppress T cell function [43].

Moreover, MDSCs induce Tregs expansion to promote tumor progression through different mechanisms in various tumor models. In an ovarian cancer model, the induction of Tregs by MDSCs is associated with the expression of cytotoxic lymphocyte 4 antigen (CTLA4), while MDSCs induce Treg expansion via secretion of IL-10/TGF-β in colon tumor models [44]. Studies also find that expression of the immune stimulatory receptor CD40 on MDSCs is required for MDSCs to suppress T-cell and induce Treg accumulation in tumor models [9,45]. MDSC can directly impact on the prevalence of Tregs through IFNγ dependent production of IL-10 or iNOS [46]. Thus, MDSCs participate in both the control of T cell responses and the induction of Tregs capable of potentiating long-term immune suppression.

Tumor angiogenic and pro-tumor invasion/metastatic activities of MDSCs

In addition to suppressing host immune functions within the tumor microenvironment, MDSCs also promote invasion and metastasis of tumor cells. In tumor-bearing hosts, MDSCs are increased in lymph organs or in other organs, including lungs and livers, where MDSCs could facilitate tumor metastasis to these organ sites [10,47]. Preclinical evidence has shown that hypoxic breast cancer cells produce carbonic anhydrase IX (CAIX) and G-CSF to drive mobilization of PMN-MDSCs to the breast cancer lung metastatic niches [48].

It was found that the TGF-β signaling pathway is associated with tumor cell motility, invasion and metastasis [49]. MDSCs produce large numbers of MMPs and TGF-β1, which has a profound impact on tumor progression and metastasis through modulation of tumor vascularization and tumor cell invasion. TGF-β signaling in MDSCs of tumor-bearing hosts is fundamentally important for tumor metastasis. In a breast cancer mouse model, treatment with TGF-β

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