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Targeting of Myeloid Derived Suppressor Cells Using Anti-inflammatory and Pro-inflammatory Agents

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Abstract

Myeloid-derived suppressor cells (MDSC) have been considered to be key mediators of immuno-suppression in cancer. The numbers of MDSCs increased in the blood and in the tumor microenvironment during inflammation. Due to the strong correlation between inflammation and cancer that results in tumor progression through MDSCs-associated immune-suppression, it is posited that modulating MDSCs using anti-inflammatory drugs will enhance the activity of immunotherapy and antitumor immunity. This review will discuss strategies using both pro-inflammatory and anti-inflammatory agents that modulate MDCSs, with a particular focus on potential advantages and disadvantage of some strategies. The use of anti-inflammatory agents that suppress MDSCs activation with pro-inflammatory agents that enhance immune responses may provide a logical reason for using new combination therapy in cancer.

Keywords

MDSC, Anti- inflammatory, Pro- inflammatory, Cancer

Introduction

It is identified that there are various immunosuppressive cells in the tumor microenvironment including regulatory T cells (Tregs) [1-3], N2 neutrophils [4], regulatory dendritic cells (DCs) [5], Tie2-expressing monocytes [6], and myeloid-derived suppressor cells (MDSCs) [7,8]. Among of those, MDSC, a heterogeneous population of immature myeloid cells containing precursors of granulocytes, macrophages, and immature DCs, has recently made a lot of attention because of their key roles in creating inflammatory tumor microenvironment.

Association of inflammation with tumor progression through accumulation of MDSC has been resulted in inhibition of anti-tumor immunity and facilitating tumor growth [9,10]. MDSCs are expanded in bone marrow and recruited into the blood, lymph nodes, and tumor microenvironment of experimental animals or patients with cancer to inhibit both adaptive and innate immunity [9,11-14]. In individuals with established cancer, MDSCs were introduced as a key factor in preventing the efficacy of immunotherapies [10,15].

So far, several approaches have been suggested to modulate MDSCs via different mechanisms including: inhibition of tumor-derived factors, suppression of generation and/or expansion of MDSCs from hematopoietic progenitors, differentiation of MDSCs into mature cells, blockade of MDSC trafficking, and abrogating immune suppressive activities of MDSCs [16-19]. Despite using several clinical trials in patients with different tumor types, however, the overall results of these trials are disappointing [20,21]. To overcome immunosuppression in the tumor microenvironment and to achieve better efficiency of cancer immunotherapy, new promising agents that modulate MDSCs numbers or functions parallel with increasing immune responses are needed.

Characteristic of MDSCs

MDSCs are immature myeloid cells that under chronic inflammatory conditions like tumor microenvironment acquire strong immunosuppressive functions that allow them to inhibit efficiently T-cell mediated anti-tumor reactivity by various mechanisms [22-25]. MDSCs express Gr1 and CD11b surface markers in mice, whereas there is no human analog of Gr1. Mouse MDSCs consist of two major subsets: $CD11b^{+}Ly6G^{+}Ly6C^{low}$ (granulocytic) and $CD11b^{+}Ly6G^{+/-}Ly6C^{high}$ cells (monocytic) which showed difference in their immunosuppressive mechanisms [12,26]. Counterparts of mouse MDSCs in human, distinguished as $CD11b^{+}CD15^{+}$ for granulocytic and $CD11b^{+}$ $CD14^{+}$ for monocytic cells in a $Lin^{-}HLA\text{-}DR^{-}CD33^{+}$ cells [14,18].

Immunosuppressive mechanisms of MDSCs

It is identified that both G-MDSC and M-MDSC can inhibit T cells through different mechanisms [15,24]. A significant portion of MDSCs abilities to suppress T cells in mouse and human models is through i) generation of Peroxynitrite by arginase (Arg) and inducible nitric oxide synthetase (iNOS) [27,28]. Whereas the generation of NO and secretion of ARG-1 is mainly used by M-MDSC, G-MDSC produced ROS mediated through the increased activity of NADPH oxidase (NOX) 2. ii) Down-regulation of TCR cell surface expression by decreasing CD3 ζ-chain biosynthesis [29]; iii) Interfere with T-cell trafficking through expression of the metalloproteinase domain (ADAM) 17, which decreases CD62 ligand expression [30]. iv) Activation and expansion of Treg cells [31]; v) Induction of anergy in NK cells through membrane bound TGF-β, STAT5 activity, or via the NKp30 receptor [7,32]. Also MDSCs can suppress NK cell cytotoxicity by inhibiting NKG2D and interferon-γ (IFN-γ) production in models of glioma [33]. Collectively, MDSCs can use diverse mechanisms to affect immune and non-immune cells

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and create an environment that suppressing anti-tumor immune responses.

Inflammation, tumor and MDSC

Contribution of chronic inflammation to tumor progression suggested by Rudolf Virchow [15,34,35]. During two last decades, accumulating evidence has indicated that chronic inflammation promotes tumor onset and development through different mechanisms such as the production of reactive oxygen species (ROS), production of vascular endothelial growth factor (VEGF) and production of matrix metalloproteases (MMP) s, which facilitate invasion and metastasis [34]. Additionally, different studies have shown that pro-inflammatory cytokines IL-1β [36], IL-6 [17], GM-CSF, and G-CSF, which are found in the microenvironment of many tumors, significantly increase MDSC accumulation and suppress T cell activation and function [11,37,38]. Furthermore, IL-1β induced inflammation, which aids MDSC and macrophage cross-talk, resulting in increasing MDSC mediated of immune suppression [11,39].

Because of the connection between inflammation and cancer, blocking inflammatory mediators regulating inflammation are expected to be effective in reducing tumor incidence and delaying tumor growth [7,19,40]. Different strategies target MDSCs directly by changing their expansion, recruitment, phenotype and/or immunosuppressive activity [13]. i) Non-steroidal anti-inflammatory drugs (NSAIDs), Cyclooxygenase-2 (COX-2) inhibitors target the COX-2 enzyme and suppress activation of MDSCs through CCL2, CXCL12, or PGE2 inhibition and increase cytotoxic T lymphocytes (CTLs) [41,42]. ii) Peroxisome proliferator-activated receptor-γ (PPARγ) is an anti-inflammatory molecule expressed in the myeloid-lineage [43]. Dominant-negative PPARγ expression in myeloid cells reduces expansion of the $CD11b^{+}Ly6G^{+}$ population [44]. iii) Phosphodiesterase-5 (PDE-5) inhibitors including: sildenafil, tadalafil, and vardenafil are used for treatment of nonmalignant diseases. These drugs increase infiltration of activated CTLs into tumor and tumor-induced T cell through down-regulation of Arg_1, iNOS, and IL-4α expression in MDSCs [40]. VI) Bardoxolone methyl, also known as CDDO-Me or RTA 402, is a synthetic triterpenoid, which has anticancer and cancer-preventive activities. It has been shown to be a potent activator of the transcription factor NFR2, which up-regulates several antioxidant genes resulted in abrogation of immunosuppressive activities of MDSCs and restored immune responses in both preclinical murine model and patients with renal cell carcinoma [45,46]. V) Silibinin, a natural flavonoid from the seeds of milk thistle, has been used as an anti-inflammatory agent to reduce the toxicity of cancer chemotherapy [47]. Our findings in an advanced tumor model of breast (4T1) showed that the decrease in tumor growth and MDSC accumulation in the blood of silibinin-treated tumor-bearing animals is not primarily due to a direct anti-tumor effect on 4T1 cells or suppression of MDSC development in bone marrow, but rather represents an indirect effect of silibinin on T-cells in the tumor microenvironment. Also silibinin treatment resulted in immune polarization to a M1 phenotype in the tumor microenvironment. Our data also indicate that silibinin decreases MDSC in a chemokine (CCR2) dependent manner that provide a mechanism for the decreased accumulation of MDSC in the tumor and a decrease in tumor-associated immunosuppression [48].

In contrast to anti-inflammatory mediators, there are a few reports for effects of pro-inflammatory mediators on MDSCs. For example: i) S100A8/A9 proteins induce MDSCs accumulation, therefore, and *in vivo* blocking of S100A8/A9 binding, reduces, but does not eliminate MDSC accumulation in tumor-bearing mice [38]. ii) Tumor necrosis factor-α (TNF-α) blocks myeloid cell differentiation and augment the suppressive activity of MDSCs in chronic inflammatory settings. Administration of a TNF-α antagonist (etanercept) reduces MDSCs' suppressive activity and promotes their maturation into dendritic cells and macrophages [19,49]. While heightened levels of pro-inflammatory mediators or adoptive transfer of inflammatory cells increases tumor development [50], we have shown that iii) Poly (I: C), a pro-inflammatory agent decreased MDSCs in both blood and tumor, directly acting on MDSCs. Poly (I: C) stimulated MDSC exhibited a "matured" phenotype, based on increased CD80, CD86, and MHC II expression when compared to un-stimulated MDSC obtained from murine spleens. Poly (I: C) in the setting of breast cancer affects MDSC generation, differentiation and also targets cancer cells, consequently leading to reduction of MDSC numbers and lower MDSC suppressive function, and improving tumor-specific T-cell functions [51].

Combination therapy and adverse effects of known approaches

Current studies are focused on combination of MDSCs-based approaches with different forms of immunotherapy targeting the function and/or numbers of MDSCs as follows: i) Gemcitabine has been shown to reduce splenic MDSC levels in tumor bearing mice and combining gemcitabine with IFN-beta markedly enhanced anti-tumor efficacy in a HER-2/neu tumor model [52]. ii) sunitinib therapy in combination with low-dose radiotherapy modestly improved survival in a mouse model of glioma [53]. Of note, combined therapy with high dose radiation, resulted in fatal toxicities and limiting the feasibility of this combination [21,53]. iii) Combining the TroVAax (MVA-5T4) vaccine with sunitinib, IL-2, or IFN-α in RCC patients (phase III trial), did not enhance survival relative to sunitinib alone (or IL-2 or IFN-α alone) [54]. Some treatments that target MDSCs showed pleiotropic effects on other immune system components. Chemotherapeutic drugs that are commonly used to treat cancer not only affect the tumor but also the immune system, having a crucial impact on antitumor responses [55,56]. 5-fluorouracil (5-FU) is one of chemotherapy approaches, which selectively eliminated MDSC at low doses also showed strong negative effects on the immune system making immunotherapy ineffective [57]. Another study showed that treatment with CPT11 or the 5FU + CPT11 combination accumulates MDSCs and produce elevated levels of NO and ROS that resulted in DNA damage during colorectal cancer [58,59]. Also, using anti-Gr-1 mAb for depletion of MDSCs in mice [60,61] has been showed adverse effect on memory $CD8^{+}$ T cells, γδT cells and mice plasmacytoid dendritic cells expressing GR-1 [62-65]. Altogether, above reported toxic effects of these approaches must be considered in the future design of new combination therapies.

Summary

Taken together, it is mandatory to have novel strategies that target MDSCs and boost immune responses to achieve better efficiency of cancer immunotherapy. Given the critical role of MDSCs in suppressing T-cell activation and proliferation and regulation of cell mediated anti-tumor immunity, it is time to investigate the influence of drugs with both anti- and pro-inflammatory effects on MDSCs in the tumor microenvironment. The concept of modulation of MDSCSs through combining of anti-inflammatory and pro-inflammatory drugs may lead to the development of a potent anticancer therapy.

Conflict of Interest

Authors declare that they have no conflict of interest.

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