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Review

Phenotypes, accumulation, and functions of myeloid-derived suppressor cells and associated treatment strategies in cancer patients

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ABSTRACT

Myeloid-derived suppressor cells (MDSCs) comprise a group of heterogeneous and immature myeloid-derived cells. MDSCs accumulate in the blood, lymphoid organs, spleens and tumor tissues under different pathogenic conditions such as infection, trauma, hematosepsis, and especially oncogenesis. MDSCs can suppress both adaptive and innate immunities through multiple mechanisms. However, most of our knowledge of MDSCs is based on pre-clinical studies. Clinical observations have shown that the number of MDSCs in the peripheral blood of patients is closely related to tumor stage, tumor burden, remote metastasis and prognosis, though inconsistencies in MDSC phenotypes among cancer patients mean that results have been inconclusive, and subsequent research progress has been slow. This review summarizes recent studies that have investigated MDSCs in cancer patients.

Contents

Abbreviations: MDSC, myeloid-derived suppressor cell; G-MDSC, granulocytic MDSC; M-MDSC, monocytic MDSC; HNSCC, squamous cell carcinomas of the head and neck; PBMC, peripheral blood mononuclear cell; RCC, renal cell cancer; GM-CSF, granulocyte–macrophage colony-stimulating factor; CXCL1, chemokine (C-X-C motif) ligand 1; VEGF, vascular endothelial growth factor; M-CSF, macrophage colony-stimulating factor; IL, interleukin; TGF-β, transforming growth factor beta; HCC, hepatocellular carcinoma; PGE-COX2, prostaglandin E-cyclooxygenase-2; CCR2, chemokine (C-C motif) receptor 2; HBD3, CCR2 ligand human β-defensin 3; MSC, mesenchymal stromal cell; HGF, hepatocyte growth factor; STAT3, signal transducer and activator of transcription 3; PSC, pancreatic stellate cell; HSC, human hepatic stellate cell; Arg1, arginase 1; iNOS, inducible NO synthase; IDO, indoleamine oxidase; ROS, reactive oxygen species; NSCLC, non-small cell lung cancer; NK cell, natural killer cell; CSC, cancer stem cells; CtBP2, C-terminal binding protein-2; DLBCL, diffuse large B-cell lymphoma; IPI, international prognostic index score; GC, gastric cancer; DFI, disease-free interval; $1,25(OH)_2D3$, 1,25-dihydroxyvitamin D3; ATRA, all-trans-retinoic acid; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; SCLC, small cell lung cancer; IES, impact of event scale.

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1. Introduction

Myeloid-derived suppressor cells (MDSCs) comprise a heterogeneous population of cells of myeloid origin composed of myeloid progenitor cells, and immature macrophages, granulocytes and dendritic cells. MDSCs accumulate in the peripheral blood, lymphoid organs, spleens and tumor tissues under pathological conditions such as infection, sepsis, trauma, bone marrow transplantation, some autoimmune diseases, and especially cancer. As many as 20–40% of nucleated splenocytes were shown to be MDSCs in several mouse tumor models, compared with the 2–4% seen in normal mice [1]. The numbers of MDSCs in the peripheral blood in cancer patients are positively correlated with tumor burden, clinical stage [2–4]. The phenotype of MDSCs in mice is $CD11b^{+}Gr1^{+}$, and MDSCs can be classified as either granulocytic MDSCs (G-MDSCs) ($CD11b^{+}Ly6G^{+}Ly6C^{low}$) or monocytic MDSCs (M-MDSCs) ($CD11b^{+}Ly6G^{-}Ly6C^{hi}$). Terminally-differentiated G-MDSCs represent 70–80% of MDSCs and generate reactive oxygen species (ROS). M-MDSCs, which account for 20–30% of MDSCs, retain the ability to differentiate into mature dendritic cells and macrophages, and produce reactive nitrogen species [5]. In addition to their suppressive effects on adaptive immune responses, MDSCs have also been reported to suppress innate immune responses, and have demonstrated non-immunological functions, such as the promotion of tumor angiogenesis and metastasis [1]. Most of our knowledge of MDSCs is based on pre-clinical studies. However, despite the plasticity of MDSCs and variations in their phenotypes among different human malignancies, much progress has recently been made in understanding their role in human cancer. This review summarizes and discusses the phenotypes, accumulation mechanisms and functions of MDSCs, their relationship with clinical outcome, and the potential of targeting these cells for therapeutic benefit in cancer patients. This review not only considers MDSCs in human cancer, but also discusses the different subtypes of MDSCs (Fig. 1).

2. Phenotypes of MDSCs in cancer patients

The presence of MDSCs in cancer patients was first demonstrated almost two decades ago [6]; however, despite criteria for identifying MDSCs in humans are still lacking. Studies in humans are complicated by the phenotypic diversity of MDSCs, leading to controversial results. Initial studies detected an increase in the number of myeloid origin cells in the peripheral blood of patients with squamous cell carcinomas of the head and neck (HNSCC), compared with the numbers in healthy people. These cells were immature and expressed CD34, and could suppress T cell function [6–11]. Subsequent studies used different combinations of antigens including CD33, CD11b, HLA-DR, Lin, CD14 and CD15 and so on to identify human MDSCs. MDSCs in cancer patients are usually positive for CD33 and CD11b and negative for HLA-DR and Lin. As in mice, MDSCs in humans can also be divided into two groups: G-MDSCs and M-MDSCs. Human G-MDSCs generally express CD15, while M-MDSCs express CD14. The phenotypes identified in recent

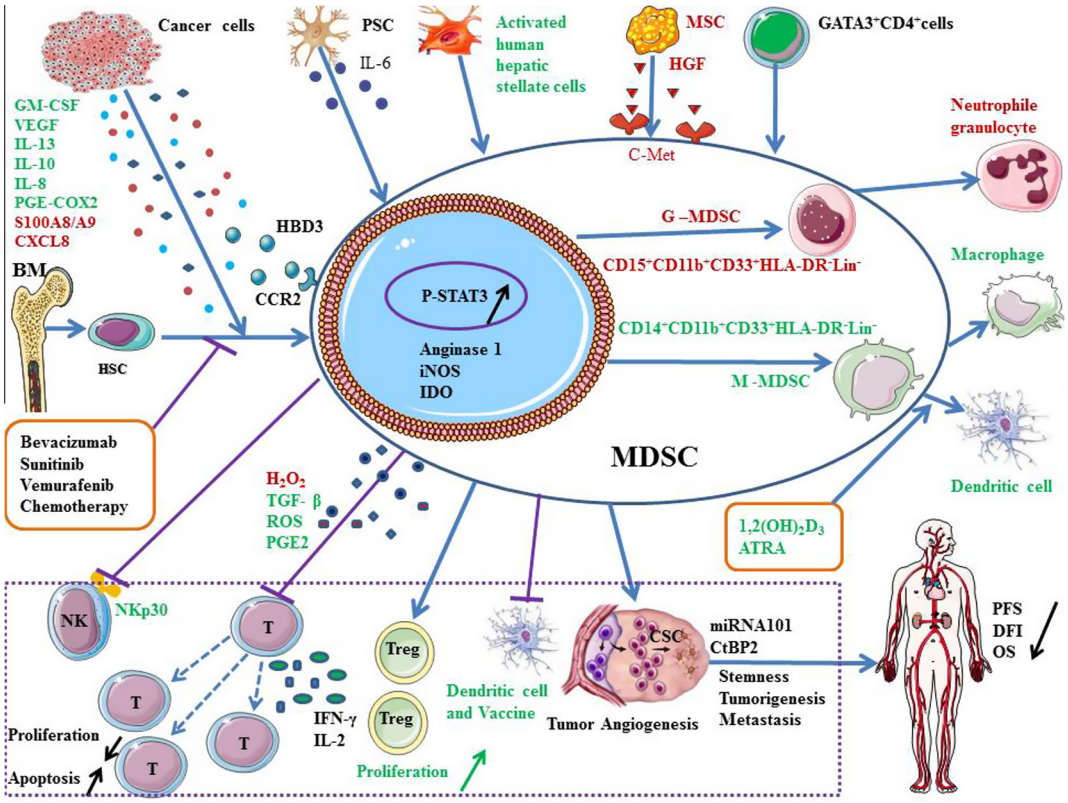

Fig. 1. Phenotypes, accumulation mechanisms, and functions of MDSCs and potential treatment strategies in cancer patients. To distinguish among MDSC subsets, we have indicated the characteristics associated with G-MDSCs, M-MDSCs, and both or unclassified MDSCs by red, green and black words, respectively. Abbreviations: GM-CSF, granulocyte–macrophage colony-stimulating factor; VEGF, vascular endothelial growth factor; IL-13, interleukin-13; IL-10, interleukin-10; IL-8, interleukin-8; PGE-COX2, prostaglandin E-cyclooxygenase-2; BM, bone marrow; HSC, hematopoietic stem cell; CCR2, chemokine (C-C motif) receptor 2; HBD3, CCR2 ligand human β-defensin 3; PSC, pancreatic stellate cell; IL-6, interleukin 6; MSC, mesenchymal stromal cell; HGF, hepatocyte growth factor; p-STAT3, phosphorylated signal transducer and activator of transcription 3; iNOS, inducible NO synthase; IDO, indoleamine oxidase; MDSC, myeloid-derived suppressor cell; M-MDSC, monocytic myeloid-derived suppressor cell; G-MDSC, granulocytic myeloid-derived suppressor cell; TGF-β, transforming growth factor beta; ROS, reactive oxygen species; PGE2, prostaglandin E2; 1,25$(OH)_2$D3, 1,25-dihydroxyvitamin D3; ATRA, all-trans-retinoic acid; NK cell, natural killer cell; IFN-γ, interferon-γ; IL-2, interleukin 2; CSC, cancer stem cells; CtBP2, C-terminal binding protein-2; PFS, progress-free survival; DFI, disease-free interval; OS, overall survival.