ANNUAL REVIEWS

Myeloid-Derived Suppressor Cells: Facilitators of Cancer and Obesity-Induced Cancer

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Abstract

Immature myeloid cells at varied stages of differentiation, known as myeloid-derived suppressor cells (MDSC), are present in virtually all cancer patients. MDSC are profoundly immune-suppressive cells that impair adaptive and innate antitumor immunity and promote tumor progression through nonimmune mechanisms. Their widespread presence combined with their multitude of protumor activities makes MDSC a major obstacle to cancer immunotherapies. MDSC are derived from progenitor cells in the bone marrow and traffic through the blood to infiltrate solid tumors. Their accumulation and suppressive potency are driven by multiple tumor- and host-secreted proinflammatory factors and adrenergic signals that act via diverse but sometimes overlapping transcriptional pathways. MDSC also accumulate in response to the chronic inflammation and lipid deposition characteristic of obesity and contribute to the more rapid progression of cancers in obese individuals. This article summarizes the key aspects of tumor-induced MDSC with a focus on recent progress in the MDSC field.

INTRODUCTION

Checkpoint blockade immunotherapy (CBI) has revolutionized cancer therapy and has demonstrated that a patient's adaptive immune system can eradicate malignant cells provided immune-suppressive mechanisms are neutralized (Park & Youn 2019, Tavazoie et al. 2018). However, CBI is only effective in a subset of cancer patients, and it is clear that there are additional immune-suppressive mechanisms that block T cell–mediated antitumor immunity. Immune-suppressive cells of myeloid origin, known as myeloid-derived suppressor cells (MDSC) (Gabrilovich et al. 2007), have been detected in cancer patients and tumor-bearing mice for over 30 years. However, the significance of MDSC as critical cells that inhibit antitumor immunity, and act via CBI-independent pathways, has only recently been appreciated (Highfill et al. 2014, Tavazoie et al. 2018). MDSC also inhibit antibody-mediated therapies targeting tumor-promoting soluble factors (Horikawa et al. 2020) and promote tumor progression through a variety of nonimmune mechanisms. Because of the universal presence of MDSC in cancer patients and their obstruction of immune and nonimmune therapies, MDSC are a focal point for researchers developing cancer therapeutics.

The chronic, low-grade inflammation of many solid tumors is the dominant driving force for MDSC accumulation (Ostrand-Rosenberg & Sinha 2009), leading investigators in noncancer fields to explore if MDSC are involved in other inflammatory settings. MDSC were found to expand in patients and mice in noncancer pathological settings, such as bacterial and viral infection (O'Connor et al. 2017, Ost et al. 2016) including HIV/AIDS (Gama et al. 2012) and tuberculosis (Magcwebeba et al. 2019); sepsis (Schrijver et al. 2019); and autoimmune diseases including lupus erythematosus (Florez-Pollack et al. 2019), arthritis (Zhang et al. 2015), and inflammatory bowel disease (Kontaki et al. 2017). MDSC also expand in normal physiological settings where immune suppression is important, such as pregnancy, where they facilitate maternal-fetal tolerance (Kostlin et al. 2014, Ostrand-Rosenberg et al. 2017, Pan et al. 2016). The low-grade inflammation associated with ageing is also accompanied by induction of MDSC in mice and probably in humans (Flores et al. 2017, Pawelec et al. 2019, Verschoor et al. 2013). Given their potent immune-suppressive activity, MDSC are being exploited to retain allogeneic grafts (Nakamura & Ushigome 2018). Clearly, MDSC are widespread and are detrimental as well as beneficial. Whether there are differences in the regulation and functions of tumor-induced versus non-tumor-induced MDSC remains to be determined. This article reviews the key aspects of tumor-induced MDSC and focuses on recent progress in the MDSC field.

WHAT ARE MDSC AND HOW ARE THEY IDENTIFIED? DISTINGUISHING MDSC FROM NEUTROPHILS

The term "MDSC" was originally ascribed to human and mouse immature cells of myeloid lineage that have immune-suppressive activity and are elevated in experimental animals and patients with cancer (Gabrilovich et al. 2007). There are two established subpopulations of MDSC, mononuclear MDSC (M-MDSC) and polymorphonuclear or granulocytic MDSC (PMN-MDSC). M-MDSC are mononuclear and morphologically similar to blood monocytes. PMN-MDSC are polymorphonuclear and morphologically similar to neutrophils. In mice, MDSC express the cell surface molecules Gr1 and CD11b. Gr1 consists of the Ly6C and Ly6G markers. Mouse PMN-MDSC are $CD11b^+Ly6G^+$ and M-MDSC are $CD11b^+Ly6C^+Ly6G^{-/low}$ (Movahedi et al. 2008, Youn et al. 2008). Human PMN-MDSC are $CD33^{dim}CD11b^+CD15^+CD14^-HLA\text{-}DR^{-/low}$ and M-MDSC are $CD33^+CD11b^+CD14^+CD15^-HLA\text{-}DR^{-/low}$. CD66b can substitute for CD15. A third subpopulation of human MDSC, termed early-stage MDSC, are $CD33^+CD11b^+$ and lack the myeloid lineage markers CD14, CD15, and CD66b. The absence or very low expression of

HLA-DR in human M-MDSC phenotypically distinguishes them from normal monocytes. Human and mouse MDSC are negative for T cell, B cell, and natural killer (NK) cell lineage markers (Bronte et al. 2016, Cassetta et al. 2019, Lang et al. 2018).

Because PMN-MDSC are polymorphonuclear and share markers with neutrophils, there has been a continuing discussion of whether PMN-MDSC are a unique population or are neutrophils (Fridlender et al. 2009, Sagiv et al. 2015). On standard Ficoll density gradients (1.077 g/L), classical neutrophils band at a high density while PMN-MDSC accumulate with mononuclear cells at a lower density, although some activated neutrophils may also be in the low-density fraction (Dumitru et al. 2012). Using whole-genome analysis and flow cytometry, the lectin-type oxidized low-density lipoprotein receptor 1 (LOX1) was detected in human PMN-MDSC from head and neck cancer patients and not in neutrophils from the same individuals. Thus, LOX1 is a marker that distinguishes human PMN-MDSC from neutrophils (Condamine et al. 2016). Computational analysis of 14,646 single-cell transcriptomes of splenic PMN-MDSC from PyMT (polyoma middle tumor-antigen) mice with spontaneous breast tumors identified Cd84 and junctional adhesion molecule as markers that distinguish mouse PMN-MDSC from neutrophils (Alshetaiwi et al. 2020). This analysis also revealed that PMN-MDSC and neutrophils share characteristics of maturation, but in the presence of tumors, MDSC undergo a deviant maturation pathway and become immune suppressive.

Therefore, mouse and human PMN-MDSC are phenotypically and transcriptionally distinguishable from neutrophils. Whether one calls PMN-MDSC a derivative of neutrophils or a separate cell population is more of a semantic/nomenclature issue than an identification issue. The two cell types are functionally distinct, and the defining characteristic of MDSC is their immune-suppressive phenotype that is mediated through multiple suppressive mechanisms that are not shared with neutrophils.

MDSC PROMOTE TUMOR PROGRESSION BY TARGETING MULTIPLE IMMUNE CELL POPULATIONS

MDSC are multitalented and use multiple suppressive mechanisms to inhibit adaptive and innate immunity. T cells are a major target for MDSC. Mouse M-MDSC have been considered more immune suppressive than PMN-MDSC on a per-cell basis. However, recent studies with MDSC from head and neck and urothelial cancer patients have indicated that PMN-MDSC have the strongest suppressive activity on a per-cell basis (Lang et al. 2018). Regardless of which population is the most suppressive, most tumor-bearing mice and cancer patients have more PMN-MDSC than M-MDSC. Early studies demonstrated that MDSC mediate some of their suppressive effects via the release of soluble mediators, but that cell contact is required (Sinha et al. 2005), probably due to the short half-life and concentration of the effector molecules. Recent studies have shown that suppressive activity is also mediated by MDSC-derived exosomes (Burke et al. 2014, Chauhan et al. 2017, Geis-Asteggiante et al. 2018).

MDSC prevent T cell activation by limiting the availability of amino acids needed for T cell proliferation and by producing substances that block antigen recognition or inhibit T cell function. MDSC produce arginase 1 (ARG1), which depletes arginine in the local environment, resulting in T cell loss of the T cell receptor (TcR) ζ chain, which is essential for signal transduction and T cell activation (Bronte & Zanovello 2005, Ezernitchi et al. 2006, Raber et al. 2012). Most cells can generate cysteine intracellularly by converting methionine or by importing cystine, which they convert to cysteine. However, T cells lack cystathionase, which converts methionine to cysteine, as well as the transporter for importing cystine, and must therefore obtain cysteine from other cells. MDSC sequestration of cysteine therefore inhibits T cell proliferation (Srivastava et al. 2010).

LOX1: low-density lipoprotein receptor 1 expressed by human PMN-MDSC distinguishes PMN-MDSC from neutrophils

ARG1: MDSC produce arginase 1, which contributes to MDSC-mediated suppression by degrading arginine, which T cells require for activation

MDSC also produce IDO (indoleamine 2,3-dioxygenase), an enzyme that catabolizes tryptophan (Yu et al. 2013).

PMN-MDSC generate reactive oxygen species (ROS) and reactive nitrogen species. Phosphorylation of signal transducer activator of transcription 3 (STAT3) is a hallmark of MDSC and results in the upregulation of p47[phox] and gp[91], two subunits of NADPH oxidase. This upregulation generates ROS, which enable nitric oxide (NO) to react with superoxide to produce peroxynitrite (PNT) (Corzo et al. 2009, Schmielau & Finn 2001). PNT nitrates and thereby alters the TcR and the MHC (major histocompatibility complex) on antigen-presenting cells so that T cells cannot recognize antigens (Lu et al. 2011, Nagaraj et al. 2007). PNT also nitrates chemokines that chemoattract T cells to the tumor, thereby preventing T cell infiltration (Molon et al. 2011). NO, which also destabilizes IL-2 messenger RNA, is generated in MDSC by the inducible nitric oxide synthase (iNOS)-mediated breakdown of ʟ-arginine. ROS and ARG1 are characteristics of human and mouse MDSC, and their intracellular presence serves as MDSC biomarkers (Bronte et al. 2016).

In addition to inactivating tumor-infiltrating T cells, MDSC limit T cell trafficking into lymph nodes where they might be activated. T cell extravasation from the blood and lymphatics into lymph nodes requires T cell expression of L-selectin/CD62L. MDSC express the enzyme ADAM-17, which cleaves L-selectin on T cells, thereby preventing extravasation and limiting T cell entry into lymph nodes (Hanson et al. 2009, Ku et al. 2016).

NK cell–mediated cytotoxicity is also inhibited by mouse and human MDSC (Hoechst et al. 2009, Liu et al. 2007, Suzuki et al. 2005). In mice, tumor-produced IL-1β induces the accumulation of a novel MDSC subset that targets NK cells (Elkabets et al. 2010). In melanoma patients, M-MDSC impair NK cell function following activation by prostaglandin E2 (PGE2), which activates the p38 MAPK/ERK pathway, resulting in the production of immune-suppressive TGFβ (Mao et al. 2014).

MDSC also impair dendritic cells (DC), T helper type 1 (Th1) cells, T regulatory cells (Tregs), B cells, and macrophages. MDSC reduce the antigen-presentation capacity of DC (Hu et al. 2011) and attenuate Th1 development by the production of IL-6 (Tsukamoto et al. 2013). They facilitate the development and increase immune-suppressive Tregs through an ARG1- and CD40-dependent mechanism that requires IL-10 and interferon gamma (IFNγ) (Huang et al. 2006, Pan et al. 2010, Serafini et al. 2008). Treg accumulation is also driven by MDSC in HIV/AIDS patients (Wang et al. 2016). In hepatocellular carcinoma patients, Treg induction is mediated by M-MDSC (Hoechst et al. 2008). In mice with lung tumors, MDSC suppress B cell function and differentiation. Tumor-bearing mice have reduced IL-7 and Stat5 signaling, conditions that are essential for B cell differentiation, resulting in reduced circulating levels of IgG. MDSC depletion restores IL-7 levels, activates Stat5, and induces serum IgG (Wang et al. 2018).

Tumor-associated macrophages (TAMs) are another myeloid population that promotes tumor progression. Within hypoxic regions of solid tumors, M-MDSC rapidly become TAMs (Corzo et al. 2010). MDSC also engage in cross talk with macrophages to enhance TAM protumor activity. Tumoricidal M1-like macrophages produce IL-12, which is downregulated by MDSC-produced IL-10. MDSC decrease macrophage expression of MHC class II, which is needed for macrophage antigen presentation, thus converting macrophages to protumor M2-like TAMs. This process also reduces NK cell function since NK cells require IL-12 for maturation. Macrophages, in turn, upregulate MDSC production of IL-10, thereby amplifying the effect of MDSC on macrophages. MDSC-macrophage cross talk is accentuated by IL-1β and signaling through MDSC-expressed Toll-like receptor 4 (TLR4) (Beury et al. 2014, Bunt et al. 2009, Parker et al. 2014, Sinha et al. 2007a) (see the sidebar titled Do MDSC Contribute to Malignant Transformation?).

DO MDSC CONTRIBUTE TO MALIGNANT TRANSFORMATION?

Chronic inflammation is associated with increased cancer risk and tumor initiation and has led to the hypothesis that inflammation-induced MDSC accumulate in premalignant states and may facilitate malignancy by inhibiting immune surveillance (Ostrand-Rosenberg & Sinha 2009). Patients with inflammatory conditions that predispose to cancer have elevated levels of MDSC, and vaccine studies support the concept that MDSC in patients with a history of advanced precancerous colonic adenomas inhibit activation of the immune system. Topical application of a carcinogen causing benign epithelial papillomas in mice drives the accumulation of PMN-MDSC in the skin. CCL4 produced by MDSC recruits CD4^{+} T cells, producing IL-17. Depletion of CD4^{+} T cells or inhibition of CCL4 or IL-17 reduced papilloma formation, indicating that the MDSC acted not via immune suppression, but indirectly by chemoattracting CD4^{+} T cells (Kimura et al. 2013, Ma et al. 2019, Ortiz et al. 2015). These studies are consistent with MDSC facilitating malignant transformation, but additional studies are needed to confirm the mode of action of MDSC.

MDSC TARGET NONIMMUNE PATHWAYS

In vivo studies demonstrate that tumor-induced MDSC also facilitate tumor progression via non-immunological mechanisms. In tumor-bearing mice and triple-negative breast cancer patients MDSC promote angiogenesis and metastasis by releasing matrix metalloproteinase 9 (Mmp9). Mmp9 causes the release of vascular endothelial growth factor (VEGF), which promotes neo-angiogenesis. Mmp9 also degrades the extracellular matrix, thereby facilitating invasion of normal tissue (Shojaei et al. 2009, Yang et al. 2004). In breast cancer patients MDSC-produced MMP9 is triggered by upregulation of ΔNP63 in tumor cells, which drives the production of CXCL2 and CCL22 (Kumar et al. 2018). MDSC also facilitate metastasis by inducing the epithelial-mesenchymal transition when they are chemoattracted to primary tumors by the proinflammatory chemokine CXCL5 (Toh et al. 2011). MDSC promote tumor growth by protecting tumor cells from senescence by secreting the IL-1 receptor antagonist, which blocks the production of prosenescence factors (Di Mitri et al. 2014). Ovarian cancer patients' MDSC activate microRNA (miRNA) 101 in the cancer cells. Activation of miRNA 101 blocks expression of the corepressor gene *C-terminal-binding protein 2*, resulting in upregulation of cancer stem cell genes and increased metastatic potential (Cui et al. 2013).

MDSC-MEDIATED SUPPRESSIVE MECHANISMS VARY DEPENDING ON TYPE OF TUMOR, MDSC DIFFERENTIATION STATE, AND STAGE OF DISEASE

The multitude of mechanisms used by MDSC suggests that MDSC may inhibit most, if not all, of the pathways used by the immune system to combat tumor growth. However, not all mechanisms are used by all MDSC, and various factors are likely to determine which suppressive mechanism(s) is (are) utilized. MDSC are a heterogeneous population of myeloid cells in different stages of differentiation, and different mechanisms may be used depending on the differentiation state of the cells. The microenvironment of different tumors varies depending on the cytokines, chemokines, and bioactive lipids produced by the tumor and host cells that are present in the tumor microenvironment (TME), and these factors may determine which mechanisms are active. As tumors progress, the TME changes, and it is likely that MDSC evolve with different stages of disease.

TME: the tumor microenvironment includes tumor cells, host cells, and their products (chemokines, cytokines, DAMPs, alarmins) deposited at the tumor site

ABNORMAL MYELOPOIESIS LEADS TO THE ACCUMULATION OF MDSC

In healthy individuals, hematopoietic stem cells (HSC) in the bone marrow differentiate into common myeloid progenitor cells (CMPs), which give rise to the granulocyte/monocyte lineage. Factors present in the TME perturb myelopoiesis, resulting in the generation of MDSC. These factors are predominantly proinflammatory mediators produced by tumor cells and by immune and nonimmune host cells within the TME. Proinflammatory mediators may act at the very early stages of myelopoiesis, as well as on myeloid cells that are further advanced in their differentiation pathway.

During normal myelopoiesis, CMPs differentiate into granulocytes (neutrophils, basophils, and eosinophils), DC, and macrophages. In contrast, under stress conditions and in response to tumor-produced factors, MDSC accumulate during so-called emergency myelopoiesis. Emergency myelopoiesis traps MDSC in immature stages and provides them with abnormal immune-suppressive activity.

At least two transcription factors contribute to abnormal early myelopoiesis. Interferon regulatory factor 8 (IRF8) is critical for the development of monocytes from CMPs. The absence of Irf8 signaling in mice results in excessive PMN-MDSC (Stewart et al. 2009, Waight et al. 2013) and overexpression of Irf8 reduces MDSC levels. Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF), which are important inducers of mouse and human PMN-MDSC, act by downregulating IRF8 (Netherby & Abrams 2017, Netherby et al. 2017, Papaspyridonos et al. 2015). The Notch family of receptors regulates interactions between HSC and bone marrow stroma and is critical for the differentiation of DC and macrophages. Inactivation of Notch via the upregulation of casein kinase 2 (CK2) prevents Notch from binding to the transcriptional repressor CSL and results in abnormal myelopoiesis and increased levels of MDSC (Cheng et al. 2014).

THE TRANSCRIPTION FACTORS STAT3 AND NF-κB ARE MAJOR REGULATORY FACTORS FOR MDSC ACCUMULATION AND FUNCTION

Studies using an inhibitor of STAT3 have demonstrated that STAT3 enhances MDSC accumulation through several pathways (Nefedova et al. 2005a). It upregulates p47^{phox} and gp^{91}, which increases NO and PNT (Corzo et al. 2009), and upregulates the proliferation gene *CCND1* and the antiapoptotic genes *BCL2L1* and *MYC* (Nefedova et al. 2005b, Xin et al. 2009). The enhanced suppressive potency of MDSC within hypoxic regions of the TME is most likely the result of STAT3 activation since MDSC within hypoxic regions have activated hypoxia-inducible factor 1α, which activates STAT3 (Corzo et al. 2010, Doedens et al. 2010). G-CSF (Kowanetz et al. 2010, Okazaki et al. 2006, Shojaei et al. 2009, Waight et al. 2011) and GM-CSF (Bronte et al. 1999, Dolcetti et al. 2010), cytokines produced by many mouse and human tumors, activate MDSC via STAT3.

GM-CSF also drives MDSC through a pathway involving adenosine monophosphate–activated protein kinase (AMPK). AMPK regulates cellular homeostasis and can have pro- and antitumor activities depending on where and when it is activated (Salminen et al. 2019). GM-CSF activates the *PRKAA1* gene in M-MDSC of tumor-bearing mice and ovarian cancer patients via a STAT5-dependent mechanism. Deletion of *Prkaa1* in mouse M-MDSC prevented differentiation into TAMs and favored development of antitumor immunity (Trillo-Tinoco et al. 2019).

IL-1β and IL-6 are proinflammatory cytokines that are produced by many mouse and human cancers and activate MDSC through STAT3 (Arman & Auron 2003, Bunt et al. 2006, Nakajima

et al. 1996, Song et al. 2005). Provision of IL-6 restores MDSC accumulation and suppressive potency to IL-1R-knockout mice, suggesting that IL-6 acts downstream of IL-1β (Bunt et al. 2007).

The alarmin S100A8/A9 complex is highly proinflammatory and ubiquitously present in the TME. In S100a9-knockout mice, tumors increase S100a8/a9 heterodimers in serum, resulting in MDSC accumulation (Cheng et al. 2008, Sinha et al. 2008). S100A8/A9 mediates its effect by binding to carboxylated N-glycans on the receptor for advanced glycation end products (RAGE) and to TLR4 on MDSC, and it activates MDSC through NF-κB and STAT3. S100A8 and S100A9 also chemoattract MDSC into solid tumors. MDSC produce S100A8/A9 and maintain themselves through an autocrine feedback mechanism. Tumor necrosis factor alpha (TNFα), another proinflammatory cytokine, also upregulates S100A8/A9 to drive MDSC (Sade-Feldman et al. 2013). Given the prevalence of S100A8/A9 in MDSC, S100A9 has been proposed as a biomarker for human MDSC (Wagner et al. 2019).

The proinflammatory damage-associated molecular pattern (DAMP) molecule high-mobility group box protein 1 (HMGB1) is commonly found in the TME and activates MDSC through NF-κB. Similar to S100A8/A9, RAGE (Kokkola et al. 2005) and TLR4 (Park et al. 2004) are cellular receptors for HMGB1. MDSC development from bone marrow progenitors and increased MDSC suppressive potency are regulated by HMGB1. HMGB1 also enhances cross talk between MDSC and macrophages by increasing MDSC production of IL-10 and driving MDSC-mediated downregulation of naïve T cell L-selectin. (Parker et al. 2014). Additionally, HMGB1 sustains MDSC survival by inducing MDSC autophagy (Parker et al. 2016).

THE ENDOPLASMIC RETICULUM STRESS PATHWAY IS A MAJOR DRIVER OF MDSC

The endoplasmic reticulum (ER) stress response pathway is activated by conditions in the TME, including low nutrient levels, inflammation, and hypoxia. CCAAT/enhancer-binding protein beta (C/EBPβ) is a key transcription factor in the pathway. In vitro studies generating MDSC from bone marrow progenitor cells using G-CSF or GM-CSF plus IL-6 and in vivo studies using C/EBPβ-knockout mice demonstrated that C/EBPβ is essential for the differentiation of M-MDSC (Marigo et al. 2010).

C/EBP homologous protein (CHOP) is upregulated during ER stress, and it turns on proapoptotic genes and turns off antiapoptotic genes. CHOP activity requires dimerization with the LIP isoform of C/EBPβ (Chiribau et al. 2010). CHOP is elevated in human and mouse MDSC and CHOP activation contributes to the short half-life of MDSC (Condamine et al. 2014).

ER stress also increases mouse MDSC-suppressive potency by upregulating iNOS and Arg1 and increases tumor-infiltrating MDSC (Lee et al. 2014). This latter effect may be responsible for the homeostatic regulation of MDSC, in which a decrease in MDSC in the periphery leads to increased production of MDSC in the bone marrow (Beury et al. 2016). MDSC deficient for CHOP are less suppressive, can prime T cells, and induce antitumor immunity. CHOP is induced in MDSC in response to tumor-generated ROS and PNT and results in MDSC production of IL-6 via STAT3 activation (Thevenot et al. 2014).

The *general control nonderepressible 2* (*GCN2*) gene is also in the ER stress pathway. In autoimmunity GCN2 promotes an immune-suppressive IL-10$^+$TGFβ$^+$ phenotype. CyTOF (cytometry time-of-flight) and single-cell RNA analyses of mouse MDSC revealed that GCN2 enhances translation of CREB-2/ATF4, a transcription factor essential for the development of MDSC (Halaby et al. 2019). Since CHOP is partially regulated by GCN2, it is likely that the impact of GCN2 on MDSC is via CHOP.

The retinoic acid–related orphan receptor (RORC1/RORγ) also regulates emergency myelopoiesis. It activates C/EBPβ and IRF8 while suppressing the negative signals SOCS3 and BCL3, resulting in increased MDSC (Strauss et al. 2015). Emergency myelopoiesis also involves apolipoprotein E (ApoE), a secreted protein involved in lipometabolism. Activation of ApoE by binding of the transcription factor LXRβ to its target LXR response element increases MDSC accumulation and suppressive activity (Tavazoie et al. 2018).

The role of G-CSF and GM-CSF as MDSC inducers led to studies of how these cytokines are produced by tumor cells. Studies in triple-negative breast cancer revealed that the TME drives aerobic glycolysis in tumor cells, upregulating AMPK and activating the liver-enriched activator protein (LAP) isoform of C/EBPβ, resulting in production of G-CSF and GM-CSF (Li et al. 2018). Therefore, the ER stress pathway not only activates MDSC internally, but is also active in tumor cells to generate cytokines that drive MDSC.

MDSC ARE ACTIVATED VIA β2-ADRENERGIC RECEPTORS

Early animal studies indicated that traumatic stress induces MDSC (Makarenkova et al. 2006), and recent studies provide a mechanistic understanding of this phenomenon. Nerve fibers in the vicinity of tumors can release neurotransmitters such as norepinephrine that act locally and systemically by binding to cell surface β2-adrenergic receptors (β2-AR). Most immune cells, including MDSC, express these receptors. When mice are housed at a subthermoneutral temperature ($\sim$22°C), but not at a thermoneutral temperature ($\sim$30°C), their sympathetic nervous system is activated to maintain their body temperature. Under subthermoneutral conditions, tumors progress more rapidly and MDSC accumulate faster and to higher levels (Bucsek et al. 2017, Kokolus et al. 2013). Studies using temperature regulation and β2-AR-deficient mice demonstrated that β2-AR activation during chronic stress increases MDSC accumulation and suppressive potency via phosphorylation of Stat3. Experiments with human peripheral blood mononuclear cells confirmed that β2-AR agonists stimulate the generation of MDSC (Mohammadpour et al. 2019).

Figure 1a summarizes the cytokines, DAMPs, alarmins, and adrenergic signals in the TME that drive MDSC accumulation and activation. **Figure 1b** summarizes the signal transduction pathways used by these molecules.

STROMAL CELLS IN THE TME INCREASE MDSC ACCUMULATION AND SUPPRESSIVE POTENCY

The TME includes host cells that facilitate MDSC development. Cancer-associated fibroblasts (CAFs) in the TME of lung squamous cell carcinomas secrete CCL2 and chemoattract CCR2^{+} monocytes. Within the TME, CAFs convert monocytes into M-MDSC (Xiang et al. 2020). Mast cells are early entrants into the TME, where they facilitate angiogenesis and promote metastasis by remodeling the extracellular matrix (Maltby et al. 2009). In mice, M-MDSC-suppressive activity is enhanced through an IFNγ and NO-dependent mechanism involving CD40-CD40L mast cell–MDSC cross talk (Danelli et al. 2015). MDSC, in turn, enhance IgE-mediated mast cell responses (Morales et al. 2014). Macrophages also undergo cell contact–dependent cross talk with MDSC to increase MDSC production of IL-10 through a TLR4-mediated mechanism (Beury et al. 2014, Bunt et al. 2009, Parker et al. 2014, Sinha et al. 2007a).

OBESITY INCREASES TUMOR PROGRESSION BY INDUCING MDSC

Obesity is a risk factor for the onset and progression of many cancers, and epidemiological studies indicate that in the United States approximately 20% and 14% of cancer deaths in women and
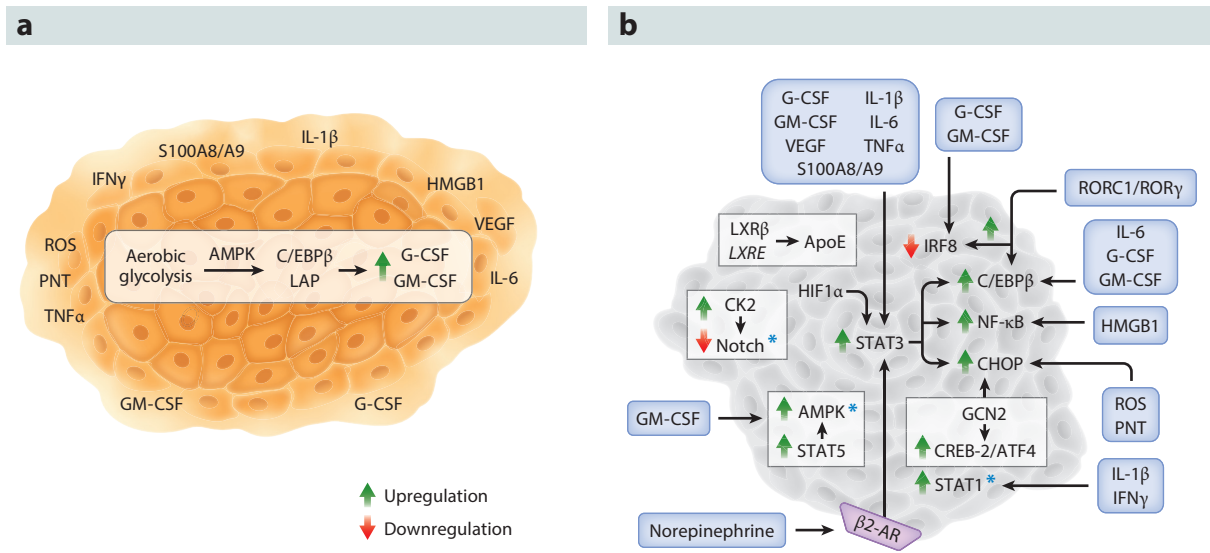
Figure 1

Cytokines, DAMPs, alarmins, and adrenergic signals in the TME drive the accumulation and activation of MDSC through multiple signal transduction pathways. (*a*) Within the TME, tumor cells undergo aerobic glycolysis, which activates C/EBPβ (LAP subunit) in the ER stress pathway and stimulates the production of GM-CSF and G-CSF. GM-CSF and G-CSF, along with other cytokines (IL-1β, IL-6, TNFα, and VEGF), DAMPs (HMGB1), alarmins (S100A8/A9), and reactive oxygen and nitrogen species (ROS, PNT) generated by tumor and host cells, are released into the TME. (*b*) These inducers act via separate and overlapping signal transduction pathways. G-CSF, GM-CSF, IL-1β, TNFα, and VEGF access MDSC through their cognate plasma membrane receptors. The alarmin S100A8/A9 and DAMP HMGB1 bind to plasma membrane RAGE or TLR4. Stress-induced norepinephrine binds to the β2-AR. Downregulation of the transcription factors Notch and IRF8 at early stages of myelopoiesis skews differentiation away from normal myelopoiesis and toward emergency myelopoiesis and MDSC development. The asterisks indicate pathway components that apply to M-MDSC only. Abbreviations: DAMP, damage-associated molecular pattern; ER, endoplasmic reticulum; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; MDSC, myeloid-derived suppressor cells; M-MDSC, mononuclear MDSC; TME, tumor microenvironment.

men, respectively, are due to obesity (Calle & Kaaks 2004, De Pergola & Silvestris 2013, Deng et al. 2016, Donohoe et al. 2016). The worldwide increasing rates of obesity make it essential to understand how obesity facilitates cancer.

Obesity is accompanied by dysregulated metabolism and chronic low-grade inflammation of white adipose tissue. The inflammation is induced by adipose-associated macrophages that are polarized toward a proinflammatory M1-like phenotype and produce multiple tumor-promoting cytokines including TNFα, IL-6, and IL-1β. Polarization is driven by the exacerbated uptake of saturated fatty acids and by DAMPs that are produced by stressed cells and dying adipocytes (Font-Burgada et al. 2016). The association between obesity and cancer risk and progression is attributed to the local and systemic inflammation that accompanies obesity (Deng et al. 2016; Donohoe et al. 2016; Fujita et al. 2019; Iyengar et al. 2015; Kolb et al. 2016, 2019).

Given that chronic inflammation induces MDSC, and that MDSC promote tumor onset and progression, it has been proposed that obesity also drives malignancy by inducing MDSC (Clements et al. 2018, Okwan-Duodu et al. 2013). This concept is supported by observations in obese mice and men. M-MDSC are significantly elevated in the blood of obese Chinese men compared to lean controls (Bao et al. 2015). Resting T cells of obese men express less TcRζ chain and elevated S100A9 in plasma, hallmarks of MDSC activity. Tumor-bearing BALB/c mice fed a high-fat diet (HFD) develop diet-induced obesity (DIO) and have reduced splenic and

intratumoral Gr1$^+$CD11b$^+$ cells compared to mice fed a low-fat diet (LFD) (Hale et al. 2015). The DIO mice contain elevated levels of the MDSC chemoattractant Ccl2, and tumors grow more rapidly. HFD/DIO C57BL/6 mice without tumors also have elevated levels of splenic Gr1$^+$CD11b$^+$ cells compared to C57BL/6 mice fed an LFD (Turbitt et al. 2019). This correlation between obesity and increased Gr1$^+$CD11b$^+$ cells suggests that enhanced production of DAMPs and chemokines is responsible for obesity-driven MDSC accumulation. Obesity-driven Gr1$^+$CD11b$^+$ cells are immune-suppressive MDSC because DIO mice with elevated splenic and liver MDSC have a less robust response to a hepatitis B antigen (HBsAg) vaccine compared to mice on a normal diet. Gr1$^+$CD11b$^+$ cells from the livers or spleen of the DIO mice are potent immune suppressors of HBsAg-specific T cells, whereas Gr1$^-$CD11b$^+$ cells are not suppressive (Chen et al. 2015).

Direct evidence attributing increased tumor progression in obese individuals to MDSC comes from a study using mice carrying the BALB/c 4T1 mammary carcinoma. Excess MDSC accumulated in the blood and tumors of HFD and LFD mice; however, MDSC accumulated to much higher levels in HFD mice. Obese HFD mice had more rapidly growing primary tumors and a shorter survival time than LFD mice. HFD-induced MDSC were responsible for the rapid tumor growth because depletion of MDSC reverted primary tumor growth rate and survival time to that of LFD mice. In vivo depletion of CD4$^+$ and CD8$^+$ T cells in HFD mice increased tumor growth and reduced survival time, and antigen-specific T cells adoptively transferred into HFD tumor-bearing mice were less activated than T cells transferred into LFD mice. Depletion of MDSC in HFD tumor-bearing mice restored T cell activation. Consistent with the concept that inflammation drives MDSC suppressive potency, HFD tumor-infiltrating MDSC were more suppressive and expressed more PD-L1 on a per-cell basis than tumor-infiltrating LFD MDSC. The adipokine leptin, which is produced by adipose tissue, is overexpressed in obesity, and regulates appetite satiety, stimulates MDSC accumulation. Leptin has been implicated in the inhibition of T cell proliferation, inhibition of NK cell function, and induction of Tregs—activities that are also mediated by MDSC. Therefore, it is likely that leptin mediates these latter activities via the induction of MDSC (Clements et al. 2018).

MDSC PROTECT AGAINST SOME OF THE METABOLIC DYSFUNCTION ASSOCIATED WITH OBESITY

MDSC are detrimental in the setting of cancer; however, in cancer-free obese individuals, MDSC are beneficial. Type 2 diabetes, which frequently occurs in obese individuals, is characterized by the inability to clear glucose from the blood (elevated fasting glucose levels, insulin tolerance). HFD C57BL/6 and BALB/c mice have elevated fasting glucose and high levels of insulin tolerance relative to LFD mice. Depletion of MDSC in HFD mice further increases fasting glucose and insulin tolerance, indicating that HFD MDSC protect against some of the metabolic dysfunction caused by excessive nutrient uptake (Clements et al. 2018, Xia et al. 2011). This yin/yang protective/detrimental relationship of MDSC in obesity and cancer may provide an evolutionary explanation for how and why MDSC have evolved.

LIPIDS DRIVE THE ACCUMULATION OF MDSC

DC of cancer patients and tumor-bearing mice internalize excessive amounts of triglycerides, resulting in diminished antigen presentation ability and impaired antitumor immunity (Herber et al. 2010). Lipid uptake also plays a critical role in the regulation of MDSC. The addition of polyunsaturated fatty acids (PUFAs) to mouse bone marrow cells cultured under conditions favoring the differentiation of MDSC, or the inclusion of PUFAs in mouse diets, increases the quantity

and suppressive potency of PMN-MDSC. PUFAs mediate their effect by upregulating STAT3, which in turn drives S100A8/A9 and activates MDSC (Yan et al. 2013). Monophosphoryl lipid A (MLA), a derivative of the TLR4 agonist lipopolysaccharide, also induces MDSC (Chen et al. 2013). Five days after inoculation with MLA, mice have fewer DC and more Gr1$^+$CD11b$^+$ cells in their spleen, consistent with the concept that MDSC differentiate at the expense of DC. The Gr1$^+$CD11b$^+$ cells prevent the expansion of antigen-specific CD4$^+$ T cells, confirming their identity as MDSC.

Studies conducted in multiple mouse tumor models and confirmed in cancer patients have demonstrated that MDSC in the TME undergo metabolic reprogramming to become dependent on the uptake of lipids and fatty acid oxidation (FAO). Reprogramming involves an increase in mitochondria and the biosynthesis of enzymes essential for FAO, as well as an enhanced oxidation rate (Hossain et al. 2015). Increased lipid uptake is stimulated by G-CSF and GM-CSF, which increase MDSC expression of lipid transporters. The intracellular lipids amplify oxidative metabolism and increase MDSC immune-suppressive activity. Oxidative metabolism in MDSC can be reversed by deleting the fatty acid translocase CD36, resulting in delayed tumor growth and enhanced tumor-reactive T cells (Al-Khami et al. 2017a,b).

LIPIDS REGULATE MDSC FUNCTION

The bioactive lipid PGE2 is produced by many tumor cells and is a potent immune suppressant and promoter of tumor growth. PGE2 is also a driver of MDSC accumulation and suppression (Mao et al. 2013, 2014; Rodriguez et al. 2005; Sinha et al. 2007b). Arachidonic acid, the precursor for PGE2, is taken up by cells through the long chain fatty acid transport protein 2 (FATP2). FATP2 is upregulated in tumor-infiltrating mouse PMN-MDSC and in blood PMN-MDSC of cancer patients, resulting in amplified levels of intracellular arachidonic acid and production of PGE2. GM-CSF induces FATP2 overexpression by signaling through STAT5. Tumor-bearing mice depleted for Fatp2 or treated with the selective Fatp2 inhibitor ipofermata have delayed tumor progression and reduced PMN-MDSC, demonstrating that FATP2 contributes to the lipid-driven protumor effects of MDSC. Although lipid levels are similarly elevated in M-MDSC in mice and cancer patients, FATP2 does not drive M-MDSC suppressive potency (Veglia et al. 2019). **Figure 2** summarizes how obesity and lipid metabolism regulate MDSC accumulation and activation.

THERAPEUTIC TARGETING OF MDSC IS ESSENTIAL FOR OPTIMIZING CANCER IMMUNOTHERAPY

Given the profound immune-suppressive potency and virtually universal presence of MDSC in cancer patients, it has become apparent that elimination or inactivation of MDSC will significantly facilitate T cell–based immunotherapies and natural antitumor immunity. Potential methodologies and drugs have been proposed and tested in animal models, particularly in mouse tumor models. Some of the drugs have also been used in clinical trials, either as stand-alone therapies or in combination with immunotherapy or non-immune-based established cancer therapies, including chemotherapy and radiotherapy. Several studies have demonstrated that combining MDSC inhibition with CBI yields significantly better control of tumor growth compared to monotherapy (Christmas et al. 2018, Clavijo et al. 2019, Kim et al. 2014, Loeuillard et al. 2020, Orillion et al. 2017). For example, in a clinical trial of advanced melanoma patients treated with all-*trans* retinoic acid, an inhibitor of MDSC, in combination with the CTLA-4 monoclonal antibody ipilimumab, patients had significantly reduced levels of PD-L1, IL-10, and IDO-expressing MDSC (NCT02403778) (Tobin et al. 2018). Likewise, the treatment of patients with
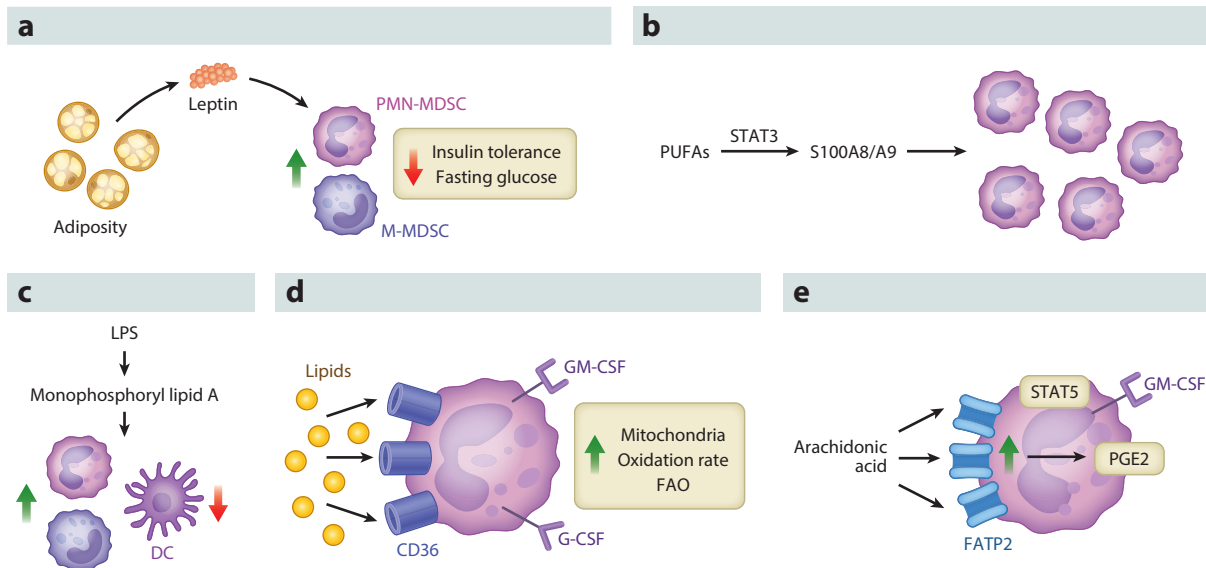
Figure 2

Obesity and lipid metabolism regulate MDSC accumulation and activation. (*a*) Excess adipose tissue associated with obesity upregulates leptin, which drives the accumulation of PMN-MDSC and M-MDSC. MDSC increase cancer progression but protect against some metabolic dysfunction by reducing insulin tolerance and fasting glucose levels. (*b*) PUFAs increase the production of S100A8/A9 alarmins via activation of STAT3, which increases the quantity of PMN-MDSC. (*c*) Monophosphoryl lipid A, a derivative of LPS, decreases the levels of DC and increases the accumulation of MDSC. (*d*) GM-CSF and G-CSF in the TME heighten lipid uptake by increasing expression of the fatty acid translocase CD36, resulting in enhanced FAO within MDSC. (*e*) GM-CSF in the TME activates STAT5 to increase expression of the FATP2 transporter, enabling MDSC to take up more arachidonic acid, which is converted intracellularly to immunosuppressive PGE2. Abbreviations: DC, dendritic cells; FAO, fatty acid oxidation; LPS, lipopolysaccharides; MDSC, myeloid-derived suppressor cells; M-MDSC, mononuclear MDSC; PMN, polymorphonuclear; PUFAs, polyunsaturated fatty acids; TME, tumor microenvironment.

acute myeloid leukemia with histamine dihydrochloride, a NOX2 inhibitor, in combination with low-dose IL-2 significantly reduced M-MDSC levels and contributed to a favorable clinical outcome (NCT01347996) (Grauers Wiktorin et al. 2019). These studies suggest that combination therapies aimed at activating antitumor immunity in combination with eliminating MDSC are likely to be more efficacious than current checkpoint blockade immunotherapies alone.

Drugs targeting MDSC can be divided into five mechanistic categories: (*a*) deplete/kill MDSC, (*b*) reduce MDSC function, (*c*) drive MDSC differentiation to nonsuppressive cells, (*d*) inhibit the development/differentiation of MDSC, and (*e*) block the recruitment of MDSC to the tumor site. Some drugs act by multiple mechanisms and therefore are in more than one category. **Supplemental Table 1** lists some of the drugs that have been identified to have an impact on MDSC induction, quantity, recruitment, or function. A more comprehensive listing of drugs can be found in recent reviews (Anani & Shurin 2017, Di Mitri et al. 2015, Draghiciu et al. 2015, Fleming et al. 2018, Law et al. 2020, Parker et al. 2015, Umansky et al. 2017).

Some of the drugs that target MDSC are FDA (US Food and Drug Administration) approved for other purposes. However, there are no FDA-approved drugs specific for MDSC. At present there are no markers or signal transduction pathways unique to MDSC, so many of the drugs that have shown efficacy against MDSC also have effects on other cells. The lack of specific markers or signal transduction pathways specific for MDSC makes it challenging to develop therapies that will specifically target MDSC and not impact other cells. Likewise, the heterogeneous nature

of MDSC, their induction by a variety of mechanisms, and the multitude of mechanisms they use to promote tumor progression make it difficult to identify specific targetable molecules or pathways. Given this variability, it is likely that a one-size-fits-all strategy for eliminating MDSC-mediated immune suppression will not be possible. Therapeutic strategies will have to be tailored for patients based on the type of MDSC and the conditions of the tumor microenvironment that drive the induction and retention of the MDSC.

CONCLUSIONS

MDSC are a profoundly immune-suppressive population of myeloid cells that are present in most cancer patients. Their mechanisms of suppression are independent of the mechanisms used by the PD-1 and CTLA-4 pathways to regulate T cell activation, anergy, and apoptosis. Indeed, elevated levels of circulating and tumor-infiltrating MDSC are negative prognostic biomarkers for the success of CBI, demonstrating the significance of MDSC as major obstacles to immunotherapy (Peranzoni et al. 2020). Therefore, it is imperative to understand the conditions and mechanisms that induce, activate, and sustain MDSC, and to develop therapies that eliminate or inactivate these cells.

The induction and function of MDSC is a complex process that involves multiple cytokines, DAMPs, alarmins, bioactive lipids, and receptors. Many of these are involved in overlapping signal transduction pathways. However, there is also redundancy, with different inducers acting via independent pathways. MDSC biology is further complicated in that MDSC vary in stage of differentiation depending on the specific tumor type, stage of disease, and locale. Numerous drugs have been developed that target MDSC. Some drugs have efficacy in a given setting; however, none is broadly effective, and there are no FDA-approved drugs that specifically target MDSC. The lack of general efficacy is most likely due to MDSC heterogeneity, the different induction mechanisms active in different individuals, and the homeostatic regulation that increases MDSC production in the bone marrow when peripheral MDSC are depleted. Therapies that inhibit the induction of MDSC, rather than eliminate peripheral MDSC, and that are tailored to the induction mechanisms active in a given individual are needed to facilitate antitumor immunity.

SUMMARY POINTS

1. Myeloid-derived suppressor cells (MDSC) are profoundly immune-suppressive cells that are present in virtually all cancer patients and prevent patients' immune systems from eliminating malignant cells.

2. MDSC are induced and their immune-suppressive activities are driven by a diverse multitude of proinflammatory factors present in the tumor microenvironment.

3. STAT3, NF-κB, and the endoplasmic reticulum stress and β-adrenergic pathways are major components and pathways through which MDSC are induced and activated.

4. The chronic, low-grade inflammation associated with obesity drives the accumulation and increases the suppressive potency of MDSC, which drive more rapid cancer progression in obese individuals.

5. Proinflammatory mediators increase expression of lipid transporters in MDSC, thereby increasing lipid uptake by MDSC and driving MDSC accumulation and suppressive potency.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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GM-CSF increases PMN-MDSC FATP2, which increases MDSC production of prostaglandin E2 and MDSC suppressive potency.

Inhibition of interferon regulatory factor 8 in common myeloid progenitor cells switches myelopoiesis to MDSC generation.

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