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Myeloid-derived suppressor cells coming of age

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Abstract

Myeloid-derived suppressor cells (MDSCs) are a population of myeloid cells generated during a large array of pathologic conditions ranging from cancer to obesity. These cells represent a pathologic state of activation of monocytes and relatively immature neutrophils. MDSCs are characterized by a distinct set of genomic and biochemical features, and can, with recent findings, be distinguished by specific surface molecules. The salient feature of these cells is their ability to inhibit T cell function and thus contribute to the pathogenesis of various diseases. In this review, we discuss the origin and nature of these cells, their distinctive features and biological roles in cancer, infectious diseases, autoimmunity, obesity and pregnancy.

The name myeloid-derived suppressor cells (MDSCs) was introduced to scientific literature 10 years ago[1] describing initially a loosely defined group of myeloid cells with potent immune regulatory activity. In recent years, the nature and biological role of MDSC became clearer and MDSC emerged as a universal regulator of immune function in many pathologic conditions. MDSCs consist of two large groups of cells: granulocytic or polymorphonuclear (PMN-MDSC) and monocytic (M-MDSC). PMN-MDSC are phenotypically and morphologically similar to neutrophils, whereas M-MDSC are more similar to monocytes [2]. Studies in humans demonstrated the existence of a third small population of MDSCs that are represented by cells with colony forming activity and other myeloid precursors. These cells are currently termed early-stage MDSC (eMDSC) [3] and have yet to be defined in mice.

Intensive clinical studies identified MDSC as a valuable predictive marker in cancer and extensive efforts in MDSC targeting is ongoing. However, despite such advances, the nature of MDSCs still raises questions and skepticism. This review is not a comprehensive analysis of MDSC phenotype or function (these topics were addressed in many reviews in recent years[4, 5]), but is our attempt to address the most controversial issues pertinent to these cells. We discuss new information regarding the development, activation status, phenotype and function that allow for a better discrimination of MDSCs from other myeloid cells. We also discuss their role in regulation of different pathologic conditions.

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What are these cells?

The main controversial issue associated with MDSCs since initial discovery is their nature. Morphologically and phenotypically MDSCs are similar to neutrophils and monocytes. What is so special about these cells that would justify a separate name? What makes these cells different? Below, we will present our view on why MDSC are indeed a very special group of cells with unique features and biological roles.

The major populations of bone marrow (BM)-derived myeloid cells include granulocytes (with their most abundant representative – neutrophils) and mononuclear cells: monocytes and terminally differentiated macrophages (MΦ) and dendritic cells (DC). In contrast to experiments *in vitro*, where both MΦ and DCs can be easily differentiated from monocytes, in tissues under steady state conditions, MΦ expand largely *in situ* and most DCs differentiate from their specific BM precursors[6]. However, during inflammation and cancer, BM-derived monocytes are the primary precursors of MΦ, especially tumor associated macrophages (TAM) and a population of inflammatory DCs[7].

Myeloid cells have emerged in evolution as one of the major protective mechanisms against pathogens and are an important element of tissue remodeling. Under physiological conditions, GM-CSF drives myelopoiesis and G-CSF and M-CSF induce the differentiation of granulocytes and macrophages, respectively[8]. In cancer and in other pathological conditions, these factors are overproduced and favor the generation of MDSC[2, 9]. Thus, accumulation of MDSC takes place alongside the same differentiation pathways as neutrophils and monocytes.

Classical activation of myeloid cells takes place in response to relatively strong signals coming from pathogens primarily in form of toll-like receptor (TLR) ligands, various damage associated molecular patterns (DAMP) and pathogen-associated molecular pattern (PAMP) molecules[10]. This results in rapid mobilization of monocytes and neutrophils from the BM, a dramatic increase in phagocytosis, respiratory burst, production of pro-inflammatory cytokines, as well as up-regulation of major histocompatibility complex (MHC) class II and co-stimulatory molecules[11, 12]. This response is usually of short duration and ends in elimination of the threat. During unresolved inflammation such as persistent infection, cancer, and other chronic conditions, the nature of signals activating myeloid cells differs[13, 14]. These signals are relatively weak and of a long duration, often in the form of growth factors and inflammatory mediators as described in detail below. Neutrophils and monocytes generated under these conditions display an immature phenotype and morphology, relatively weak phagocytic activity, increased background levels of reactive oxygen species (ROS) and nitric oxide (NO) production, high expression of arginase, PGE2, and a number of anti-inflammatory cytokines[15, 16]. Most of these features are absent in classically activated neutrophils and monocytes. Therefore, this state of activation can be characterized as pathologic (Fig. 1). This state of activation leads not to the elimination of the threat or activation of immunity, but to the inhibition of adaptive immunity (immune suppression) and support of tumor progression and metastases. Cells in this pathologic state of activation can be identified functionally, biochemically, and to some extent, phenotypically, and are now termed MDSC. The longer the myeloid compartment is exposed

to the effects of factors described above, the more potent the pathologic activation of these MDSCs detected in patients and mice. Therefore, at any given moment, there is a heterogeneous population of cells in tissues represented by classically activated neutrophils, monocytes, and pathologically activated MDSCs (Fig. 2). For instance, at early stages of cancer, bona-fide immune suppressive MDSCs are rarely detected. However, there are cells with some biochemical and genomic characteristics of MDSC [17, 18, 19] probably representing an intrinsic part of MDSC development. They could be called MDSC-like cells (MDSC-LC) (Fig. 2). It could be possible that pathologic activation of MDSC can be transferred via hematopoietic progenitor cells, as a sort of innate immune memory triggered by chronic inflammatory conditions through signals interfering with transcription factors and epigenetic reprogramming[20]. Memory or trained immunity can rely on an altered functional state of immune cells that persists for weeks to months after the elimination of the initial stimulus. The true nature of this process in MDSC needs to be elucidated.

The accumulation of MDSC is a complex and gradual phenomenon governed by multiple factors. We have previously suggested that accumulation of MDSC depends on two groups of interconnected signals. The first group of signals is important for the expansion of immature myeloid cells, whereas the second group is responsible for their pathologic activation[21]. The first group of signals is driven by factors produced by tumors or BM stroma in response to chronic infection and inflammation and includes: GM-CSF, G-CSF, M-CSF, S-SCF, VEGF, and polyunsaturated fatty acids (PUFAs). [22, 23, 24, 25]. The transcriptional factors/regulators STAT3, STAT5, IRF8, C/EBPβ, NOTCH play a major role in this process[26]. Other factors involved in this process include adenosine receptors A2b, NLRP3, retinoblastoma protein 1 (RB1), and alarmins S100A9 and A8. Furthermore, a recent study showed that the antiapoptotic molecules c-FLIP and MCL-1 are involved in the development of M-MDSC and PMN-MDSC in cancer, respectively[27]. The second group of signals is mediated by inflammatory cytokines and DAMP, which include interferon (IFN)-γ, IL-1β, IL-4, IL-6, IL-13, TNF and the, TLR ligand, HMGB1. These factors mainly signal via NF-κB, STAT1, and STAT6 [28]. A recent study provided a direct experimental demonstration of this concept showing that the licensing of monocytes with GM-CSF was required for subsequent IFN-γ-mediated conversion of these cells to immune suppressive M-MDSC [29].

Phenotypic and molecular features of MDSC

Another controversial issue that was apparent from the beginning is how to identify these cells. The field of MDSC research is still immature and it is difficult to distinguish these cells from neutrophils and monocytes. In mice, PMN-MDSC can be defined as CD11b $^{+}$Ly6G^{+}Ly6C^{lo} with high side scatter (SSC)[30]. However, this phenotype is typical for neutrophils but in some experimental models, PMN-MDSC can express markers not normally present on neutrophils like CD115 and CD244[16]. The direct phenotypic distinction between murine PMN-MDSC and tumor associated neutrophils (TANs) is even more difficult. TANs are a heterogeneous population of cells, including neutrophils (N1) with anti-tumor properties and neutrophils (N2) with potent suppressive functions[31]. Based on these functional characteristics, it is likely that N2 neutrophils are in fact PMN-MDSC [32, 33, 34].

However, this question cannot be resolved until specific markers of mouse PMN-MDSC are identified.

M-MDSCs are defined as $CD11b^{+}Ly6G^{-}Ly6C^{hi}$ with low SSC[30]. This is the classic phenotype of inflammatory monocytes present in healthy mice. Other typical markers shared by these cells include CD115, CCR2 and CD49d (VLA4)[35]. However, M-MDSC usually lack surface markers of monocytes like CD11c and MHC class II[23, 36]. Phenotypically, M-MDSC can be readily separated from TAMs[2, 37] since TAMs have high expression of F4/80, low-to-intermediate expression of Ly6C and low or undetectable expression of S100A9 protein (Table 1).

In humans, the equivalent of murine PMN-MDSC and M-MDSC has been found in the low-density Ficoll gradient fraction of peripheral blood mononuclear cell (PBMC). In contrast, neutrophils are isolated from the high-density fraction. PMN-MDSC and neutrophils share similar phenotype $CD11b^{+}CD14^{-}CD15^{+}$ (or $CD66b^{+}$) $CD33^{+}$. However, different density allowed for distinction of these cells (Table 1). In healthy individuals, PMN-MDSC are practically undetectable. Recently identified lectin-type oxidized LDL receptor 1 (LOX-1) allows for better distinction between human neutrophils and PMN-MDSC without use of a gradient[38]. Immune suppressive $LOX\text{-}1^{+}$ cells, with features defining them as PMN-MDSC, represent 4–15% of all neutrophils in blood of cancer patients and up to 40% in tumor tissues. In healthy individuals, these cells represent less than 1% of neutrophils[38].

Monocytes and M-MDSC can be separated based of expression of MHC class II molecules. M-MDSC have a phenotype $CD11b^{+}CD14^{+}CD15^{-}CD33^{+}HLA\text{-}DR^{-/lo}$, whereas monocytes are $HLA\text{-}DR^{+}$[19]. M-MDSC represents a very small fraction of PBMC[39]. eMDSC are defined as Lin^{-} (CD3, CD14, CD15, CD19, CD56) $HLA\text{-}DR^{-}CD33^{+}$ [19, 39].

Thus, in humans, MDSC can be separated from neutrophils and monocytes based on phenotypic markers and density gradient, whereas in mice such distinction is much more challenging. This is probably due to differences between mouse models and human diseases. Most of the cancer models utilize transplantation of tumor cells, which is associated with inflammation and rapid tumor progression. This leads to a dramatic expansion of MDSC that may replace most of the neutrophils and monocytes. This is not the case in human disease[40]. More detailed studies including single cells sequencing may help to address this question.

Human PMN-MDSC have a gene expression profile that distinguishes them from neutrophils in cancer patients, and from healthy donors[38]. They include eukaryotic translation initiation factors 2 and 4 (eIF2 and eIF4) associated with ER stress (discussed below), up-regulation of mTOR signaling, the MAPK pathway, CSF1, and the IFN-γ regulated pathways[38]. It is important to point out that none of these pathways by themselves can define MDSC. cDNA array analyses of sorted mouse PMN-MDSC and neutrophils revealed that PMN-MDSC had a higher expression of genes associated with cell cycle, autophagy, G-protein signaling, and the CREB pathway[16]. Neutrophils, on the other hand, had higher expression of genes associated with NF-κB signaling via CD40, IL-1, IL-6, TLR, and TNF pathways, as well as lymphotoxin-β receptor signaling. Substantial differences

between PMN-MDSC from tumor-bearing and neutrophils from tumor -free mice were identified using whole transcriptomic analysis [41]. Quantitative proteomics of murine MDSC determined that these cells constitute a distinct myeloid population characterized by a "kinase signature" and well-defined interactomes[42, 43]. Thus, it appears that distinct genomic and proteomic signatures of MDSC can be developed based on available information but more formal validation studies are needed to establish their value.

In addition to gene and protein expression profiles, MDSC are distinguished from neutrophils and monocytes by the activity and the expression of specific molecules. Up-regulation of STAT3 is a hallmark of MDSC as this transcriptional factor is directly implicated in the accumulation of MDSC in human and mice[37, 44, 45, 46]. Interestingly, although STAT3 activity is critical for MDSC expansion in bone marrow and spleen, inside the tumor, MDSC seem to down-regulate STAT3 activity by a mechanism involving the hypoxia-inducible activation of CD45 phosphatase[47]. This promotes rapid differentiation of M-MDSC to TAMs. Down-regulation of IRF8, a member of the interferon related factor (IRF) family is closely associated with PMN-MDSC expansion in mice[30, 31, 32]. A very recent study showed that growth of 4T1mammary adenocarcinoma was associated with a selective expansion of $IRF8^{lo}$ granulocyte progenitors. These progenitors had an increased ability to form PMN-MDSC[48]. Up-regulation of C/EBPβ, a member of a family of basic-region-leucine zipper transcriptional factors, is also associated with MDSC expansion [49]. C/EBPβ regulates the expression of arginase (ARG1) and inducible nitric oxide synthase (NOS2), which are required for the suppressive functions of MDSC[50]. RB1 (p105) is a member of RB family, that also includes RB2 (130) and p107, which repress E2F and block cell proliferation. Low expression of RB1 in M-MDSC was associated with these cells ability to differentiate to PMN-MDSC, whereas $RB1^{hi}$ M-MDSC give rise to MΦ and DCs[51]. The accumulation of $RB1^{lo}$ PMN-MDSC has also been described in the PyMT transgenic model of breast cancer[52].

Immune suppressive activity of MDSC

Another controversial issue in MDSC biology is whether the functional activity of these cells is uniquely associated with a specific set of biochemical events. Immune suppression is the main feature of MDSC that allows MDSC to be distinguished from monocytes and neutrophils in peripheral blood in humans and in spleens of mice. Splenic monocytes in mice and monocytes isolated from peripheral blood of humans can acquire immune suppressive features upon culture for several days on plastic. This approach is used for generation of MDSC *in vitro*. However, although suppressive activity of these in vitro-derived cells and some suppressive mechanisms (like NO) are shared with M-MDSC, at this moment, it is not clear whether these cells have similar biochemical and genomic profiles. MDSC generated from hematopoietic progenitors also have the same issue[53, 54]. Generation of suppressive neutrophils *in vitro* is a more difficult task probably due to their nature as terminally differentiated cells and their very short survival in culture. However, neutrophils isolated from healthy donor's blood acquire potent suppressive activity upon treatment with ER stress inducers[38].

M-MDSC are more suppressive than PMN-MDSC when assessed on a per cell basis [23, 36]. PMN-MDSC and M-MDSC use different mechanisms to suppress immune responses and some of the mediators of suppression can be used to distinguish MDSC from neutrophils and monocytes. The most prominent factors implicated in MDSC suppressive activity includes arginase, NO, up-regulation of ROS and the production of prostaglandin E2 (PGE2)[55, 56, 57]. Changes in oxidative phosphorylation and glycolysis in tumors has also been associated with the function of MDSC. In mice, glycolysis is increased concurrently with increased ARG1 activity in MDSC. Interestingly, AMP-activated protein kinase (AMPK) is also activated and normally drives metabolism towards oxidative phosphorylation[58]. A very recent study showed that tumor-infiltrating MDSC preferentially use fatty acid β oxidation (FAO) as a primary source of energy. Tumor-infiltrating MDSC show increased mitochondrial mass, key FAO-associated genes, and oxygen consumption rate[59]. The inhibition of FAO affects the suppressive functions of MDSC and enhances the efficacy of cancer immune therapy.

Endoplasmic reticulum (ER) stress response has emerged in recent years as an important mechanism regulating pathologic activation of MDSC and thus critical for their functions. The ER stress response is an evolutionary conserved mechanism used by cells for protection from dysregulated proliferation, oxidative stress, nutrient deprivation, hypoxia and acidic extracellular pH. Three major sensors of ER stress are currently described: protein kinase RNA-like ER kinase (PERK), inositol-requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6). The transcription factor CCAAT-enhancer-binding protein homologous protein (CHOP) is a critical mediator of the PERK pathway, whereas spliced X-box binding protein-1 (sXBP1) is a mediator of the IRE1 pathway[60, 61]. In tumor DCs, ER stress leads to increased lipid peroxidation and was directly implicated in their defective function [62]. MDSC from tumor-bearing mice and cancer patients demonstrate a much higher ER stress response than neutrophils and monocytes from tumor-free hosts[63]. Up-regulation of PERK and IRE1 pathways was observed. The level of ER stress response at the tumor site was substantially higher than in peripheral lymphoid organs in mice [63]. The direct cause of ER stress induction in MDSC is not clear. However, the functional consequences have been identified. Experimental induction of ER stress enhanced the immunosuppressive capacity of tumor-infiltrating MDSC by increasing expression of *ARG1*, *NOS2*, and *NOX2*[64]. Tumor MDSC from mice deficient for CHOP showed low expression of pSTAT3, decreased production of IL-6 and ARG1, which are directly involved in immune suppression. CHOP-deficient MDSC isolated from tumor-bearing mice had reduced immunosuppressive activity[65]. Increased sXBP1 was observed in human LOX-1^{+} PMN-MDSC as compared to LOX-1^{-} neutrophils[38]. Moreover, the induction of ER stress in neutrophils isolated from healthy donors converts them to potent suppressive cells[38]. ER stress also controls MDSC survival in tumors and favors apoptosis through tumor necrosis factor (TNF)-related apoptosis-induced ligand receptor 2 (DR5) and caspase-8 activation[63]. In fact, targeting TRAIL-R2 results in elimination of different populations of MDSC without affecting mature myeloid or lymphoid cells in cancer patients[66]. Another study showed that trabectedin, an approved chemotherapeutic agent, induces apoptosis of monocytes and macrophages by activating the extrinsic apoptotic pathway downstream of TRAIL receptors[67]. Consistent with these observations, the absence of CHOP was shown to delay apoptosis and prolonged

survival of MDSC in cancer[65]. Other mechanisms of MDSC-mediated immune suppression include up-regulation of regulatory T cells and immune suppressive cytokines. They are reviewed in detail elsewhere[2]. Altogether, these unique features of MDSC allow for identification of these cells and provide an insight into their biological activity.

How important is the immature state for MDSC biology?

One of the controversial questions of MDSC biology is whether all MDSC are immature cells. Large number of studies in mice and humans demonstrated that most of PMN-MDSC have a morphology similar to immature granulocytes and in some in vitro studies PMN-MDSCs are able to acquire characteristic of mature neutrophils upon short term culture[16]. However, a recent report showed that granulocytic MDSC in patients with Hodgkin's lymphoma were mostly composed of mature low-density suppressive neutrophils in an activated state[68]. Another recent study confirms that activated mature neutrophils expressing CD10, isolated from G-CSF–treated donors, systemic lupus erythematous and cancer patients, also have suppressive properties[69]. Although more studies are needed to clarify this issue, it is likely that pathologic activation of PMN-MDSC would include mature cells.

In tumor tissues, M-MDSC rapidly differentiate into TAMs and inflammatory DCs[29, 63]. These terminally differentiated myeloid cells can persist in tissues for a long time. TAMs have a long-established role as inhibitors of immune responses and promoters of tumor progression[70, 71]. Some studies have shown that inflammatory DCs can promote anti-tumor T cell responses[72, 73]. However, it has been also shown that they can contribute to immune suppression in tumor-bearing hosts[74].

Do MDSC have similar role in different pathologic conditions?

Cancer was historically the first condition where MDSCs were described. We will discuss below the data directly implicating MDSC in clinical outcome and response to therapy. In recent years, a large body of evidence demonstrated the role of MDSC in regulation of immune responses and pathogenesis of many pathologic conditions. The question is whether these MDSC have similar origin and function. No direct side-by-side comparison have been performed so far. However, analysis of available data (below) may clarify this question.

Cancer

MDSC role in mouse tumor models is well established[15]. In most of the studies PMN-MDSC cells expanded the most. In recent years, the clinical role of MDSC has emerged. Initial studies monitored MDSC in cancer patients, analyzing total MDSC population (PMN-and M-MDSC together). Results showed a positive correlation of MDSC numbers in peripheral blood with cancer stage and tumor burden in colorectal carcinomas, breast, bladder thyroid and NSCLC[75, 76, 77, 78, 79, 80, 81]. In melanoma and breast cancer, both PMN- and M-MDSC numbers correlate with stage and metastasis[82]. In a meta-analysis, elevated numbers of MDSC in the circulation was found to be an independent indicator of poor outcomes in patients with solid tumors[83]. Accumulation of M-MDSC in peripheral blood was associated with shorter progression-free interval (PFI) and/or overall survival

(OS) in NSCLC, colorectal, bladder, thyroid and uterine cervical cancer[81, 84, 79, 85, 80, 86]. In melanoma and hepatocellular carcinoma, both PMN- and M-MDSC correlated with poorer outcomes[82, 87]. In non-solid tumors, M-MDSC numbers correlated with reduced survival in multiple myeloma, Hodgkin and non-Hodgkin lymphoma and diffuse large B cell lymphoma[88, 89, 68]. Notably, most of the studies consider only circulating MDSC, but some attention should also be paid to tumor infiltrating cells. In one report, neutrophil ($CD66b^+$) infiltration in colorectal cancer tissue was associated with good prognosis[90]. TANs can also contribute to tumor progression, upregulating tumor proliferation pathways, promoting angiogenesis and supporting tumor extravasation by disrupting the extracellular matrix (reviewed in [91]). Until recently, histological studies presented technical challenges since multiple markers were required to identify MDSC. Introduction of multiplex immunohistochemistry and new markers of MDSC (like LOX-1) should help address this problem.

Recent studies demonstrated the value of MDSC in predicting the response to various cancer therapies. The frequency of M-MDSC numbers negatively correlated with the response to chemotherapy in breast, cervical, prostate and colorectal cancer [78, 86, 92, 84] squamous cell carcinoma, multiple myeloma and Hodgkin lymphoma[93, 94, 95] ; similarly, PMN-MDSC numbers negatively correlated with chemotherapy response in colorectal cancer [84]. M-MDSC numbers were a predictor of radiotherapy failure in hepatocellular carcinoma[77, 96]. High numbers of circulating MDSC have been associated with vaccine failure in melanoma, NSCLC and colon adenocarcinoma[97, 98]. The percentage of circulating M-MDSC and PMN-MDSC negatively correlated with objective clinical response to Ipilimumab (CTLA-4 antibody) in patients with unresectable melanoma [99, 100, 101]. Moreover, in melanoma, M-MDSC frequency could predict the failure of the second line immunotherapy using anti-PD1 antibody (Nivolumab) after failure of first line Ipilimumab treatment[102]. Recent studies in mouse tumor models showed that MDSC inhibition during immunotherapy increases its therapeutic effect[103, 104, 105, 106, 107, 108].

Infectious diseases

Many studies have shown that bacteria (both Gram-positive and Gram-negative) can induce or modulate MDSC in vitro and in vivo (reviewed in[109]). In some studies, subpopulation of MDSC have not been analyzed in detail, thus we refer to those studies with the broader definition of “MDSC”.

In *Staphylococcus aureus* infection models, M-MDSC and PMN-MDSC numbers expand and suppress T cells[110], contributing to the aggravation of infection[111]. *Mycobacterium tuberculosis* induced expansion of PMN-and M-MDSC suppressive activity in mice[112]. Patients with sepsis exhibited expansion of MDSC numbers. PMN-MDSC were expanded mainly in sepsis caused by gram-positive pathogens, while M-MDSC expanded in response to gram-positive or gram-negative pathogens[113]. Sepsis-associated MDSC have upregulated ARG1 expression and are associated with adverse outcome[114]. MDSC expansion after bacterial infection does not always translate to worse outcome. In *Pseudomonas.aeruginosa* and *Klebsiella pneumoniae*, MDSC expansion is associated with host protection and better outcome[115]. It appears that in early stages of sepsis (as probably in other infectious as well)

accumulation of neutrophils and monocytes with potent anti-pathogen activity protect the host. MDSC are probably either not present or present at very low frequency. However, if infection is not resolved, the frequency of MDSC increases gradually and these cells exert an immune suppressive effect on adaptive immunity, which is very similar to the situation observed in cancer

Human pathogenic fungi could regulate the immune system and directly induce MDSC accumulation. In these studies, MDSC were monitored as $Gr1^+CD11b^+$ cells without further distinction between PMN- and M-MDSC. *Albicans fumigatus* and *Candida albicans* induced MDSC through the recognition of the receptor Dectin-1. Interestingly, MDSC were protective against *C.albicans* infections, but not *A.fumigatus* infection[116]. In a follow up study, the same group demonstrated that MDSC induction and suppressive activity on T cells were dependent on the *Candida* species[117]. MDSC expanded in mouse and rat models of *P. pneumonia* infection where MDSC exert their function through ARG1 and NOS2, and contribute to a more severe infection[118].

M-MDSC are expanded in patients with chronic hepatitis C virus (HCV) infection. This accumulation correlated with the disease progression and response to antiviral therapy[119]. Different studies report ROS production[120] or ARG1[119] as the main mechanisms for MDSC mediated T cell suppression. HCV-induced MDSC could directly inhibit NK cell activities via ARG1-independent mechanisms[121, 122]. In vitro studies show that HCV directly induces M-MDSC through TLR2-STAT3 signaling. These MDSC stimulate T_{reg} cell accumulation and inhibit $CD4^+$ T cell proliferation[123].

M-MDSC are also expanded in HIV-1-infected individuals and suppress T cell function via ARG1[124, 125]. Similarly to HCV, HIV directly induced expantion of M-MDSC[126] that promoted differentiation of T_{regs} cell[127]. PMN-MDSC may induce T-cell anergy by suppressing CD3ζ expression and inhibiting $CD8^+$ T cells through PD-L1-PD1 interaction[125, 128]. PMN-MDSC accumulation in patients with primary HIV-1 infection may be regulated by TRAIL and GM-CSF levels and positively correlates with disease progression[128, 129]. Thus, in infectious diseases, accumulation of MDSC, their functional activity, as well as major biochemical features closely resemble cancer-associated MDSC.

Autoimmune disorders

If in cancer and infectious disease MDSC activity is deleterious for patients, the role of MDSC in autoimmune disease is more complex. It has been shown that MDSC are expanded in murine models and patients with autoimmune diseases[130]. Nevertheless, MDSC role in this process is not established, with contrasting studies showing positive and negative roles for MDSC in regulation of disease progression. Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder, with high cellular infiltration of organs. In mouse models, MDSC suppressed $CD4^+$ T cell proliferation via ARG1 and were expanded in peripheral blood and kidney during disease progression[131]. The ability of MDSC to expand regulatory B cells has also been demonstrated[132]. However, in lupus-prone mice MDSC function was found to be impaired suggesting that SLE development is associated with a defect in MDSC[133]. A recent study demonstrated that M-MDSC and PMN-MDSC are both expanded

in peripheral blood of SLE patients and their frequency positively correlates with serum ARG1 concentration, T_H17 cell responses and lupus severity[134].

Rheumatoid arthritis (RA) is a chronic inflammatory disease that leads to inflammation of multiple joints, progressing to cartilage destruction and bone erosion. Initial studies in a mouse collagen induced arthritis (CIA) model showed that suppressive MDSC accumulate in the spleen and adoptive transfer of MDSC reduced the severity of RA by blocking the $CD4^+$ T cell pro-inflammatory immune response[135]. MDSC lost suppressive activity during arthritis development, thus failing to control the disease[135]. M-MDSC isolated from BM of CIA mice were also able to inhibit B cell proliferation and function, improving CIA outcome[136]. In support of a beneficial role of MDSC in RA models, synovial fluid of RA patients contained PMN-MDSC, that were able to suppress T cell activity in vitro[137], similarly to what was previously shown in mice[138]. Moreover, circulating MDSC in patients with RA negatively correlates with T_H17 cells and plasma arginin concentrations[139]. Recently, it has been reported that MDSC could have the opposite role by promoting RA onset in mice by sustaining T_H17 cell differentiation. MDSC infiltration in arthritic joints positively correlated with high disease activity, but MDSC frequency in peripheral blood negatively correlated with T_H17 cell numbers[136]. Overall, RA studies consistently report beneficial effects of MDSC adoptive transfer for inhibiting RA progression in mouse models consistent with the suppressive activity of these cells, but MDSC recruitment shows inconsistency with T_H17 and T_{reg} cell expansion and RA onset. This inconsistency could be due to the heterogeneity of the myeloid cell population discussed above, with variable frequencies of MDSC present in the total population of myeloid cells. Several studies have also associated MDSC with inflammatory bowel disease (IBD). MDSC reduced severity of experimentally-induced colitis in mice[140]. In IBD patients, M-MDSC were expanded and their frequency was associated with disease activity[141].

Thus, the importance of MDSC in autoimmune diseases is evident. However, in contrast to cancer and infectious diseases, the expansion of MDSC is less prominent, which results in a larger heterogeneity of the myeloid population and variable frequency of MDSC among myeloid cells, which may result in contradictory results. This heterogeneity is apparently due to the different severity of autoimmune diseases and specifics of the microenvironment.

Obesity and pregnancy

Obesity is associated with chronic inflammation and linked to increased risk of breast, prostate, and colorectal cancer, as well as cardiovascular metabolic disorders and type 2 diabetes mellitus[142143]. The metabolic changes in the microenvironment associated with obesity and the associated chronic inflammation led to the hypothesis that MDSC could play a role in maintaining immune homeostasis in obese subjects. In a diabetes mouse model, MDSC were able to down-regulate immune responses and prevent diabetes onset[144]. Tissue-infiltrating MDSC were crucial in controlling obesity-associated inflammation and increasing insulin sensitivity. MDSC suppressed $CD8^+$ T cells by NOS2 and IFN-γ-dependent mechanisms. MDSC also induced M2 MΦ polarization, probably through IL-10[145]. Obese subjects are often susceptible to infections and poorly respond to vaccines. This observation could be explained by MDSC expansion and consequent suppression of T

and B cell functions as was demonstrated in obese mice[146]. There are few human studies in the field, but it was reported that M-MDSC numbers were increased in the peripheral blood of obese subjects[147]. Recent work showed that obesity caused expansion of neutrophils in mouse lungs, enhancing breast cancer metastasis through IL-5 and GM-CSF[148] (Fig. 3a).

Insulin resistance promotes metabolic syndrome development, characterized by elevated serum inflammatory cytokines and high macrophage infiltration in adipose tissue. Macrophages accumulate in adipose tissue as obesity progresses and in late obesity M2 macrophages are induced in parallel with MDSC infiltration of adipose tissue (reviewed in [149]). Insulin resistance could be the result of adaptation to bacterial infection in order to provide glucose to M1 macrophages, which rely on glycolysis. M2 macrophages, instead, rely on oxidative phosphorylation (reviewed in [150]). Increased concentrations of IGF-1 and estrogens associated with insulin resistance and obesity can directly polarize myeloid cells in adipose tissues to the M2 phenotype [151, 152]. The obesity microenvironment can also induce differentiation of M2 macrophages to M1 macrophages, that then recruit T cells[153] and induce monocytes migration via CCL2[154]. In vitro, macrophages coming from obese subjects or exposed to conditions mimicking the obese microenvironment showed increases in migration and upregulation of markers of TAM. In the same study, it was also demonstrated that obesity promoted macrophages infiltration in the prostate tumor microenvironment, and induced TAM polarization through the COX2-PGE2 pathway[155].

Maternal-fetal tolerance is critically important for normal pregnancy. Pregnancy failure (miscarriage, implantation failure, preterm birth, preeclampsia) is associated with dysregulation of the immune system (reviewed in[156]). Early observations in mice showed that MDSC accumulate in mouse placenta[157] and their level decreased towards the time of delivery. Subsequently, MDSC expansion has been observed in peripheral blood and the uterus of pregnant mice, in association with anti-inflammatory functions[158]. MDSC recruitment was driven by CXCR2[159], and progesterone supported MDSC differentiation and activation via STAT3 signaling[160]. MDSC suppressed T cells either via ARG1[161] or ROS production[160] or by preventing T cell activation by down modulating L-selectin expression on naïve T cells[162].

During human pregnancy, MDSC are expanded in peripheral blood[163] and decidua[164] of healthy pregnant women and rapidly drop to normal levels after birth[165]. Reduction of MDSC in peripheral blood, endometrium and placenta is associated with early miscarriage[166,] and low level of arginine and reduced NOS2 expression in placental tissues are found in women with preeclampsia[167,168]. A study demonstrated that MDSC are expanded during the first trimester, with a decrease towards the third[166]. Conversely, another study observed that MDSC are equally expanded during the entire gestation period. In this study, the main population of MDSC expanded in peripheral blood was PMN-MDSC, expressing ARG1 and NOS2 and producing high ROS levels[165].

During pregnancy, estradiol expand M-MDSC in the circulation via STAT3 activation that suppressed T cells in a ROS-dependent fashion[160]. Conversely, in placental tissue, M-MDSC were expanded by CCL2 and overexpressed IDO1, ARG1 and COX2[168]. PMN-MDSC in

the placenta could also interact with other immune system cell populations, directly expanding T_{regs} cells via the TGFβ-β-catenin pathway[161] (Fig. 3b).

MDSC expansion is rapidly canceled in post-partum women, but MDSC are found expanded in neonates during the first month of life. In neonates, the expanded MDSC are mainly PMN-MDSC that suppress T cells in a contact-depended manner and reduce IFN-γ production. PMN-MDSC decrease rapidly in the first 6 week of life and reach adult levels by 6 months of age[169]. In the same studies, PMN-MDSC were found expanded in the cord blood (CB), where their frequency correlated with the proliferative capacity of T cells upon stimulation *in vitro*. M-MDSC and PMN-MDSC expansion in CB modulated the adaptive immune response[170]. PMN-MDSC from CB directly inhibited T_H1 cell responses and induced T_H2 responses and T_{reg} cells. In this setting PMN-MDSC mediates suppression via expression of ARG1 and NOS2, production of ROS, and degradation of tryptophan by IDO expression[171]. Neonatal PMN-MDSC show reduced apoptosis and immunosuppressive activity upon infection with *Escherichia Coli*[172]. A recent study shows that M-MDSC were expanded in neonates and respond to microbial stimulation[173]. Mouse studies from the same group showed that S100A8/A9 prevented expansion of these cells and prevented death from septic shock[173]. Studies in humans showed that S100A9 secretion protected neonates from sepsis by regulating MyD88-dependend gene programs[174]. Thus, MDSC in pregnancy mainly follows the pattern observed in cancer and is apparently one of the important regulators of fetal-maternal tolerance. Because of limited information, at this time the biological role of MDSC in newborns is not clear. It is possible that MDSC has evolved as a protective mechanism limiting inflammation associated with bacterial colonization of the gut.

Conclusions

MDSC are now recognized as one of the major negative regulators of immune responses in many pathologic conditions. The challenge is to identify specific markers of these cells that allow for easy phenotypical distinction of MDSC from neutrophils and monocytes in mice and to expand the already existing panel of markers in humans. This would allow for better understanding of the biology of these cells. It appears that in contrast to T_{reg} cells or checkpoint molecules, MDSC are not present in steady state condition. This opens a unique opportunity to target these cells without possible side effects. Understanding the molecular mechanisms regulating the accumulation and function of these cells allow for more precise targeted therapy. The clinical significance of MDSC in cancer and in some infectious diseases is now established. The next step is to determine whether targeting MDSC may provide tangible clinical benefits. The next several years will provide an answer to this question.

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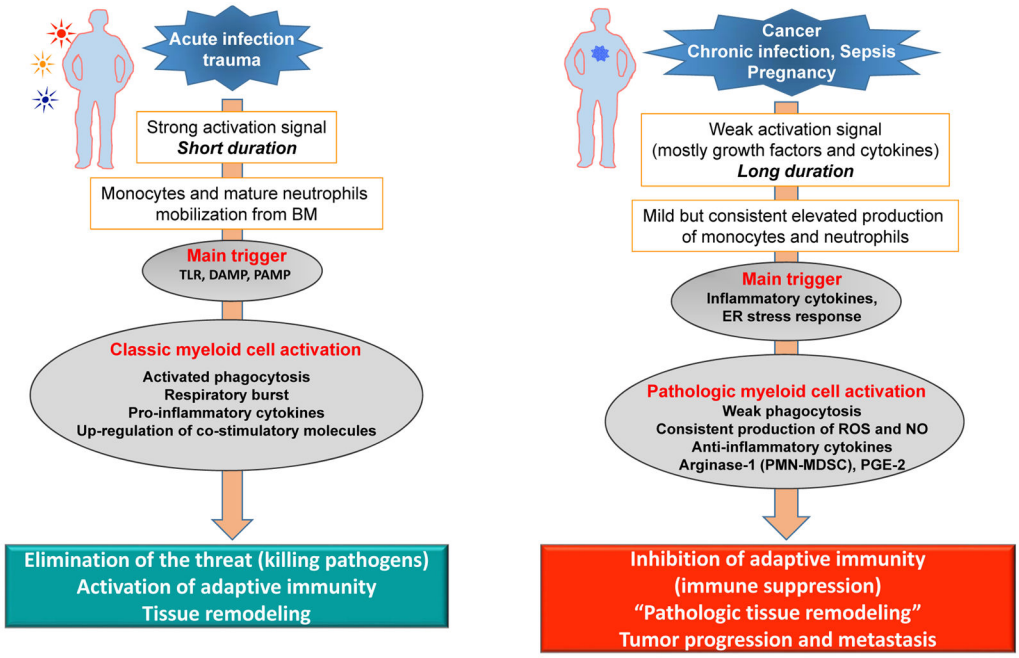

Figure 1.

Pathologic activation of neutrophils and monocytes. (**a)** In the presence of strong activation signals coming from pathogens in the form of toll-like receptors ligands (TLRL), damage associated molecular pattern (DAMP), pathogen-associated molecular patterns (PAMP) molecules monocytes and neutrophils are mobilized from the BM. This response results in classic myeloid cell activation. (**b**) In the presence of weak activation signal mediated mostly by growth factors and cytokines, myeloid cells undergo modest but continuous expansion. Pro-inflammatory cytokines and ER stress responses contribute to pathologic myeloid cells activation that manifests in weak phagocytic activity, increased production of reactive oxygen species (ROS), nitric oxide (NO), arginase 1 (not expressed in human monocytes and M-MDSC) and prostaglandin-E2 (PGE2). This results in immune suppression.

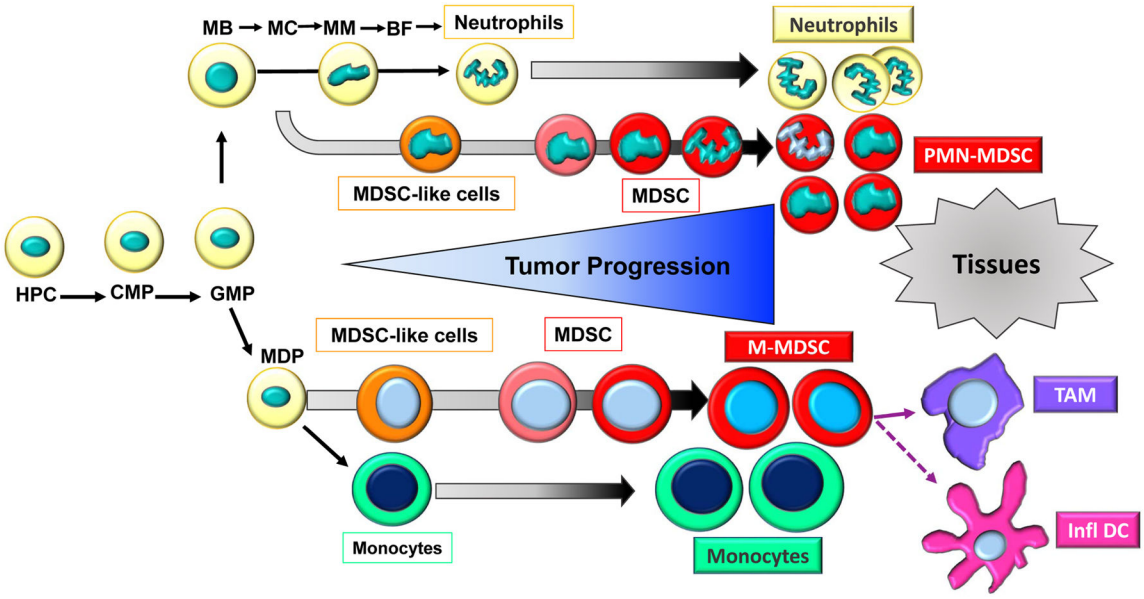

Figure 2.

MDSC differentiation and accumulation. Neutrophils and monocytes are differentiated in bone marrow from hematopoietic progenitor cells (HPC) via common myeloid progenitors (CMP) and granulocyte-macrophage progenitors (GMP). Neutrophils differentiation progress through several progenitor and precursors stages. Among them are myeloblasts (MB), myelocytes (MC), metamyelocyte (MM), band forms (BF). Monocytes originate from monocyte/macrophages and dendritic cell (MDP) precursors. Under pathologic conditions, immature myeloid cells are expanded and converted to immunosuppressive MDSC. In early stages cells with some biochemical features of MDSC do not have suppressive activity and can be called MDSC-like cells. In cancer patients, in any given moment neutrophils and monocytes and pathologically activated MDSC co-exist, with accumulation of more MDSC during tumor progression. In tumors, M-MDSC rapidly differentiate in tumor associated macrophages (TAM) and inflammatory dendritic cells (infl DC).

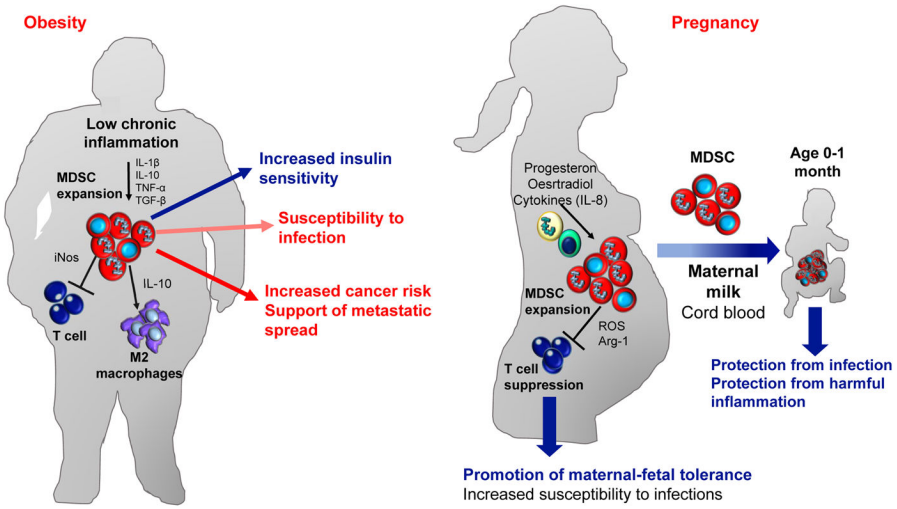

Figure 3.

MDSC role in obesity and pregnancy. **(a)** MDSC are expanded in obese subjects due to chronic inflammation and contribute to increase insulin sensitivity. MDSC in obese subjects directly inhibit T cells via NO secretion and induce macrophage differentiation to the M2 phenotype via IL-10 secretion, leading to increased susceptibility to infections. Moreover, increased MDSC increases cancer risk and favors metastatic spread of early stage cancers. (**b**) During pregnancy MDSC are expanded and are crucial for successful pregnancy. In pregnant women MDSC suppress T cells via ROS and Arg-1 thus sustaining maternal-fetal tolerance. Moreover, MDSC are expanded also in cord blood (CB) and neonates protecting newborns from infections and harmful inflammation.

Table 1

Phenotypical, molecular and functional properties of neutrophils, monocytes and MDSC

Human						
	Neutrophils	**PMN-MDSC**	**Monocytes**	**M-MDSC**	**e-MDSC**	**TAM**
Surface Phenotype	$CD11b^{+}CD14^{-}CD15^{+}CD66b^{+}$ LOX-1^{-}	$CD11b^{+}CD14^{-}CD15^{+}CD66b^{+}$ LOX-1^{+}	$CD14^{+}CD15^{-}$ HLA-DR^{+}	$CD14^{+}CD15^{-}$ HLA-$DR^{-/lo}$	$CD3^{-}CD14^{-}CD15^{-}CD19^{-}CD56^{-}$HLA-$DR^{-}CD33^{+}$	$CD206^{+}CD163^{+}CD204^{+}CD45^{+}$
Density	High	Low	Low	Low	Low	Not applicable
Immune suppression	−	+	−	++	++	+++
ROS	+	+++	−/+	−/+	++	++
NO	−	+	+	+++	++	+++
Arginase-1	+	++	−	−	−?	−
PGE-2	−	++	−	+	N/A	−
S100A8/A9	+	++	−/+	+	N/A	−
ER Stress	−/+	++	−/+	++	N/A	N/A
STAT3	−/+	++	−/+	++	N/A	N/A
Mouse						
	Neutrophils	**PMN-MDSC**	**Monocytes**	**M-MDSC**	**TAM**	
Minimal surface phenotype	$CD11b^{+}Ly6G^{hi}Ly6C^{lo}$		$CD11b^{+}Ly6G^{-}Ly6C^{hi}$		$CD11b^{+}F4/80^{hi}Ly6C^{lo}Ly6G^{-}CD115^{hi}$	
Immune Suppression	−	+	−	++	+++	
ROS	−/+	++	−/+	−/+	++	
NO	−	+	+	++	++	
Arginase-1	−	++	+	++	++	
PGE-2	−	++	−	+	N/A	
S100A8/A9	+	++	−/+	+	−	
ER Stress	−/+	++	−/+	++	N/A	
STAT3	−/+	++	−/+	++	−/+	
IRF8	+	−/+	+	N/A	++	
C/EBPβ	−/+	++	−/+	+	N/A	
RB1	+	−/+	+	−/+	N/A	

N/A=not available

Comparisons are shown between cells for each factor separately. Therefore, different factors should not be compared with each other.