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Myeloid-derived suppressor cells coming of age

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Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of 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, on the basis of 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 their biological roles in cancer, infectious diseases, autoimmunity, obesity and pregnancy.

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

Intensive clinical studies identified MDSCs as a valuable predictive marker in cancer, and extensive efforts in MDSC targeting are 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 have been addressed in many reviews in recent years[4,5]), but rather our attempt to address the most controversial issues pertinent to these cells. We discuss new information regarding development, activation status, phenotype and function that allows for better discrimination of MDSCs from other myeloid cells. We also discuss the role of MDSCs in the regulation of different pathologic conditions.

What are these cells?

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

The major populations of bone marrow (BM)-derived myeloid cells are granulocytes (with their most abundant representative, neutrophils) and mononuclear cells (monocytes, terminally differentiated macrophages and dendritic cells (DCs)). Unlike in experiments in vitro, in which both macrophages and DCs can be easily differentiated from monocytes, in tissues under steady-state conditions macrophages 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 macrophages, especially tumor-associated macrophages (TAMs) and a population of inflammatory DCs[7].

Myeloid cells have emerged as a major contributor to protection against pathogens and are an important element of tissue remodeling. Under physiological conditions, the cell-signaling molecule GM-CSF drives myelopoiesis, and G-CSF and M-CSF induce the differentiation of granulocytes and macrophages, respectively[8]. In cancer and other pathological conditions, these factors are overproduced and favor the generation of MDSCs[2,9]. Thus, accumulation of MDSCs takes place alongside the same differentiation pathways as for neutrophils and monocytes.

Classical activation of myeloid cells occurs in response to relatively strong signals from pathogens, primarily in the form of Toll-like receptor (TLR) ligands, various damage-associated molecular patterns, and pathogen-associated molecular pattern molecules[10]. This results in rapid mobilization of monocytes and neutrophils from the BM, a dramatic increase in phagocytosis, respiratory burst, the production of proinflammatory cytokines, and upregulation of major histocompatibility complex (MHC) class II and costimulatory molecules[11,12]. This response is usually of short duration and ends in elimination of the threat. During unresolved inflammation such as in 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, and they often come in the form of growth factors and inflammatory mediators, as described in detail below. Neutrophils and monocytes generated under these conditions have an immature phenotype and morphology; relatively weak phagocytic activity; increased background levels of reactive oxygen species (ROS) and nitric oxide (NO) production; and 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 pathologic activation state 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 metastasis. Cells in this pathologic state of activation can be identified functionally, biochemically and, to some extent, phenotypically, and are now collectively termed MDSCs. The longer the myeloid compartment is exposed to the effects of the factors described above, the more potent the pathologic activation of these MDSCs is in humans and mice. Therefore, at any given moment, there is a heterogeneous population of cells in tissues that includes classically activated neutrophils and monocytes, and pathologically activated

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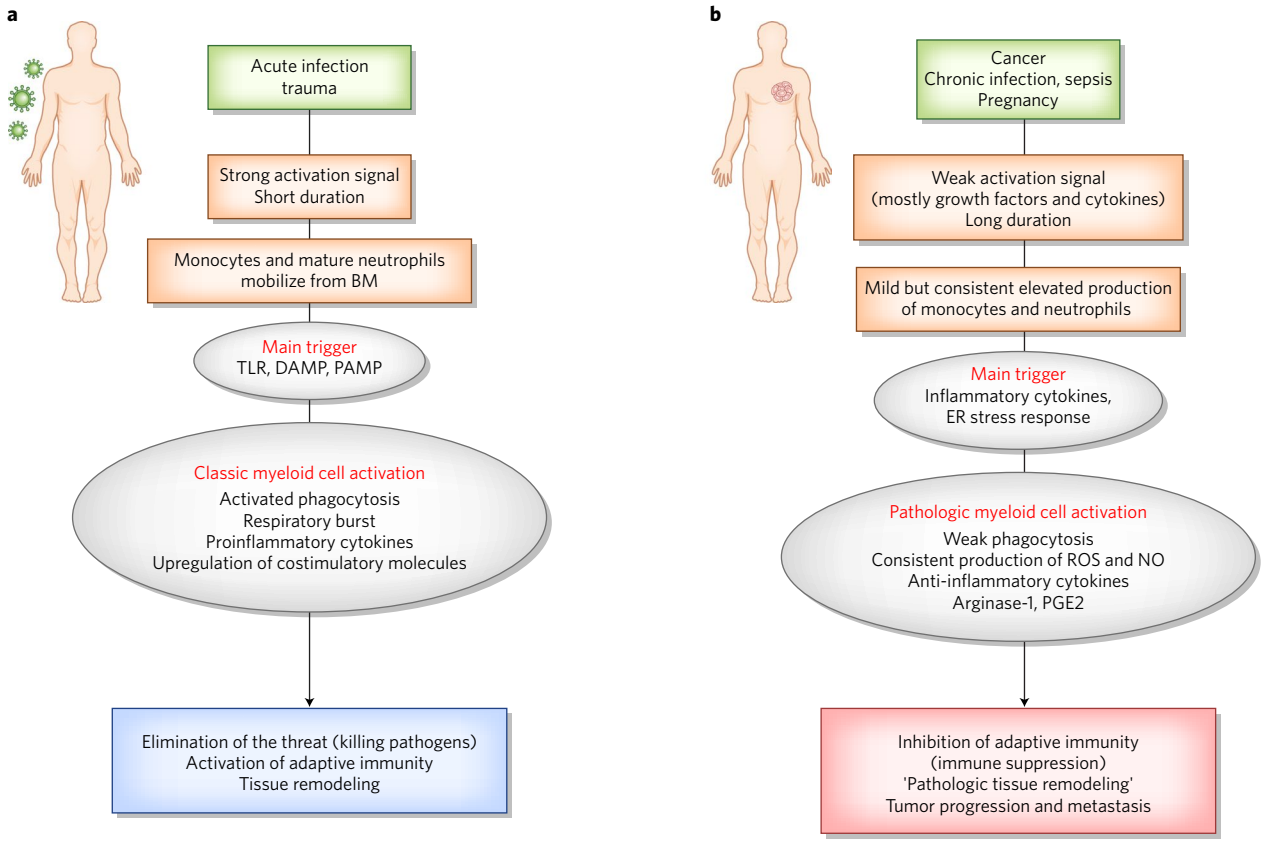

Fig. 1 | Pathologic activation of neutrophils and monocytes. a, In the presence of strong activation signals coming from pathogens in the form of Toll-like receptor (TLR) ligands, damage-associated molecular patterns (DAMPs) and/or pathogen-associated molecular patterns (PAMPs), monocytes and neutrophils are mobilized from the bone marrow (BM). This response results in classic myeloid cell activation. **b**, In the presence of weak activation signals mediated mostly by growth factors and cytokines, myeloid cell populations undergo modest but continuous expansion. Proinflammatory cytokines and ER stress responses contribute to pathologic myeloid cell activation that manifests as weak phagocytic activity, increased production of reactive oxygen species (ROS) and nitric oxide (NO), and expression of arginase-1 (not expressed in human monocytes or M-MDSCs) and prostaglandin E2 (PGE2). This results in immune suppression. Credit: Marina Corral Spence/Springer Nature.

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 MDSCs[5,17,18] that probably represent an intrinsic phase of MDSC development; they could be called MDSC-like cells (Fig. 2). It may be possible for pathologic activation of MDSCs to be transferred via hematopoietic progenitor cells, as a sort of innate immune memory triggered by chronic inflammatory conditions through signals that interfere with transcription factors and epigenetic reprogramming[19]. 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 MDSCs needs to be elucidated.

The accumulation of MDSCs is a complex and gradual phenomenon governed by multiple factors. We previously suggested that accumulation of MDSCs depends on two groups of interconnected signals. The first group of signals is important for the expansion of populations of immature myeloid cells, whereas the second group is responsible for their pathologic activation[20]. The first group of signals is driven by factors produced by tumors or BM stroma in response to chronic infection and inflammation, and includes the following: GM-CSF, G-CSF, M-CSF, S-SCF, VEGF and polyunsaturated fatty acids[21–24]. The transcriptional factors/regulators STAT3, STAT5, IRF8, C/EBP-β and NOTCH have a major role in this process[25]. Other factors involved in this process include adenosine receptor A2b, cytoplasmic receptor NLRP3, retinoblastoma protein 1 (RB1), and alarmins S100A9 and S100A8. Furthermore, a recent study showed that the antiapoptotic molecules c-FLIP and MCL-1 are involved in the development of M-MDSCs and PMN-MDSCs in cancer, respectively[26]. The second group of signals is mediated by inflammatory cytokines and damage-associated molecular patterns, including interferon-γ (IFN-γ), IL-1β, IL-4, IL-6, IL-13, tumor necrosis factor (TNF), and the TLR ligand HMGB1. These factors mainly signal via NF-κB, STAT1 and STAT6[25]. 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-MDSCs[27].

Phenotypic and molecular features of MDSCs

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-MDSCs can be defined as $CD11b^{+}Ly6G^{+}Ly6C^{lo}$ cells with high side scatter[28]. This phenotype is typical for neutrophils, but in some experimental models PMN-MDSCs can also express markers not normally present on neutrophils, such as CD115 and CD244[16]. Direct phenotypic distinction between mouse PMN-MDSCs and tumor-associated neutrophils (TANs) is even more difficult. TANs are a heterogeneous population of cells that includes neutrophils with antitumor properties and neutrophils with potent suppressive functions[29]. On the basis of

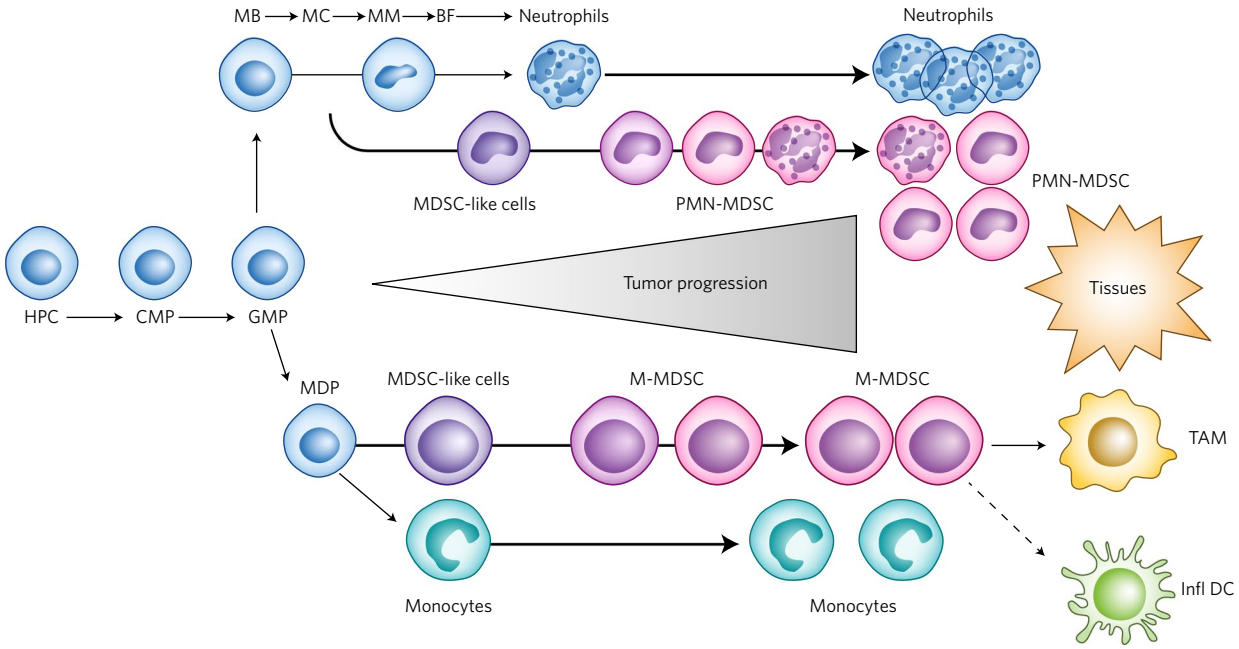

Fig. 2 | MDSC differentiation and accumulation. Neutrophils and monocytes are differentiated in bone marrow from hematopoietic progenitor cells (HPCs) via common myeloid progenitors (CMPs) and granulocyte-macrophage progenitors (GMPs). Neutrophil differentiation progresses through several progenitor and precursor stages. Among these are myeloblasts (MBs), myelocytes (MCs), metamyelocytes (MMs) and band forms (BFs). Monocytes originate from monocyte/macrophage and dendritic cell precursors (MDPs). Under pathologic conditions, populations of immature myeloid cells are expanded and converted to immunosuppressive MDSCs. In early stages, cells with some biochemical features of MDSCs do not have suppressive activity and can be called MDSC-like cells. In people with cancer, at any given moment neutrophils, monocytes and pathologically activated MDSCs coexist, and more MDSCs accumulate during tumor progression. In tumors, M-MDSCs rapidly differentiate in tumor-associated macrophages (TAMs) and inflammatory dendritic cells (infl DCs). Credit: Marina Corral Spence/Springer Nature.

these functional characteristics, it is likely that the second group of 'neutrophils' are in fact PMN-MDSCs[30–32]. However, this question cannot be resolved until specific markers of mouse PMN-MDSCs are identified.

M-MDSCs are defined as $CD11b^+Ly6G^-Ly6C^{hi}$ cells with low side scatter[28]. 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)[33]. However, M-MDSCs usually lack surface markers of monocytes such as CD11c and MHC class II[22,34]. Phenotypically, M-MDSCs can be readily separated from TAMs[2,35], as 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 mouse PMN-MDSCs and M-MDSCs has been found in the low-density Ficoll-gradient fraction of peripheral blood mononuclear cells. In contrast, neutrophils are isolated from the high-density fraction. PMN-MDSCs and neutrophils share a similar phenotype: $CD11b^+CD14^-CD15^+$(or $CD66b^+$)$CD33^+$. However, different densities allow for the distinction of these cells (Table 1). In healthy individuals, PMN-MDSCs are practically undetectable. Recently identified lectin-type oxidized LDL receptor 1 (LOX-1) allows for better distinction between human neutrophils and PMN-MDSCs without the use of a gradient[36]. Immune-suppressive $LOX\text{-}1^+$ cells, with features that define them as PMN-MDSCs, represent 4–15% of all neutrophils in the blood of cancer patients and up to 40% of neutrophils in tumor tissues. In healthy individuals, these cells represent <1% of neutrophils[36].

Monocytes and M-MDSCs can be separated on the basis of expression of MHC class II molecules. M-MDSCs have the phenotype $CD11b^+CD14^+CD15^-CD33^+HLA\text{-}DR^{-/lo}$, whereas monocytes are $HLA\text{-}DR^{+5}$. M-MDSCs represent a very small fraction of peripheral blood mononuclear cells[37]. Early-stage MDSCs are defined as $Lin^-HLA\text{-}DR^-CD33^+$, where Lin comprises CD3, CD14, CD15, CD19 and CD56[5,37].

Thus, in humans, MDSCs can be separated from neutrophils and monocytes on the basis of 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 mouse cancer models involve the transplantation of tumor cells, which is associated with inflammation and rapid tumor progression. This leads to a dramatic expansion of MDSC populations that may replace most of the neutrophils and monocytes. This is not the case in human disease[38]. More detailed studies including single-cell sequencing may help to address this question.

Human PMN-MDSCs have a gene expression profile that distinguishes them from neutrophils in people with cancer, as well as those from healthy donors[36]. This includes eukaryotic translation-initiation factors 2 and 4 (eIF2 and eIF4), associated with endoplasmic reticulum (ER) stress (discussed below), and upregulation of mTOR signaling, the MAPK pathway, CSF1 and the IFN-γ-regulated pathways[36]. It is important to point out that none of these pathways by themselves can define MDSCs. cDNA array analyses of sorted mouse PMN-MDSCs and neutrophils showed that PMN-MDSCs have higher expression of genes associated with cell cycle, autophagy, G protein signaling and the CREB pathway[16]. Neutrophils, in contrast, have 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-MDSCs from tumor-bearing mice and neutrophils from tumor-free mice have been identified via whole transcriptomic analysis[39]. Quantitative proteomics of mouse MDSCs determined that these cells constitute a distinct myeloid population characterized by a 'kinase signature' and well-defined interactomes[40,41]. Thus, it seems that distinct genomic and proteomic signatures of MDSCs

Table 1 | Phenotypical, molecular and functional properties of neutrophils, monocytes and MDSCs

Human

	Neutrophils	PMN-MDSCs	Monocytes	M-MDSCs	e-MDSCs	TAMs
Surface phenotype	$CD11b^+CD14^-$ $CD15^+CD66b^+LOX\text{-}1^-$	$CD11b^+CD14^-$ $CD15^+CD66b^+LOX\text{-}1^+$	$CD14^+CD15^-$ $HLA\text{-}DR^+$	$CD14^+CD15^-$ $HLA\text{-}DR^{-/lo}$	$CD3^-CD14^-CD15^-CD19^-$ $CD56^-HLA\text{-}DR^-CD33^+$	$CD206^+CD163^+C$ $D204^+CD45^+$
Density	High	Low	Low	Low	Low	Not applicable
Immune suppression	-	+	-	++	++	+++
ROS	+	+++	-/+	-/+	++	++
NO	-	+	+	+++	++	+++
ARG1	+	++	-	-	-/?	-
PGE2	-	++	-	+	N/A	-
S100A8/A9	+	++	-/+	+	N/A	-
ER stress	-/+	++	-/+	++	N/A	N/A
STAT3	-/+	++	-/+	++	N/A	N/A

Mouse

	Neutrophils	PMN-MDSCs	Monocytes	M-MDSCs	TAMs
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	-	+	+	++	++
ARG1	-	++	+	++	++
PGE2	-	++	-	+	N/A
S100A8/A9	+	++	-/+	+	-
ER stress	-/+	++	-/+	++	N/A
STAT3	-/+	++	-/+	++	-/+
IRF8	+	-/+	+	N/A	++
C/EBP-β	-/+	++	-/+	+	N/A
RB1	+	-/+	+	-/+	N/A

Comparisons between cells are shown separately for each factor. Therefore, different factors should not be compared with each other. e-MDSCs, early-stage MDSCs; N/A, not available.

could be developed on the basis of the available information, but more formal validation studies are needed to establish their value.

In addition to gene and protein expression profiles, MDSCs are distinguished from neutrophils and monocytes by the activity and expression of specific molecules. Upregulation of STAT3 is a hallmark of MDSCs, as this transcription factor is directly implicated in the accumulation of MDSCs in humans and mice[35,42–44]. Interestingly, although STAT3 activity is critical for the expansion of MDSC populations in BM and spleen, inside tumors MDSCs seem to downregulate STAT3 activity via a mechanism that involves the hypoxia-inducible activation of CD45 phosphatase[45]. This promotes rapid differentiation of M-MDSCs to TAMs. Downregulation of IRF8, a member of the interferon-related factor (IRF) family, is closely associated with the expansion of PMN-MDSC populations in mice[28–30]. A very recent study showed that the growth of 4T1 mammary adenocarcinoma is associated with the selective population expansion of $IRF8^{lo}$ granulocyte progenitors. These progenitors have an increased ability to form PMN-MDSCs[46]. Upregulation of C/EBP-β, a member of a family of basic-region leucine zipper transcription factors, is also associated with the expansion of MDSC populations[47]. C/EBP-β regulates the expression of arginase (ARG1) and inducible nitric oxide synthase (iNOS), which are required for the suppressive functions of MDSCs[48]. RB1 (p105) is a member of the RB family, as are RB2 (p130) and p107, which repress the transcription factor E2F and block cell proliferation. Low expression of RB1 in M-MDSCs is associated with these cells' ability to differentiate to PMN-MDSCs, whereas $RB1^{hi}$ M-MDSCs give rise to macrophages and DCs[49]. The accumulation of $RB1^{lo}$ PMN-MDSCs has also been described in the PyMT transgenic model of breast cancer[50].

Immune-suppressive activity of MDSCs

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 MDSCs that allows them 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 after several days of culture on plastic. This approach is used to generate MDSCs in vitro. However, although these in vitro–derived cells share suppressive activity and some suppressive mechanisms (such as those related to NO) with M-MDSCs, at this moment it is not clear whether these cells have similar biochemical and genomic profiles. MDSCs generated from hematopoietic progenitors also have the same issue[51,52]. The generation of suppressive neutrophils in vitro is a more difficult task, probably because of their nature as terminally differentiated cells and their very short survival in culture. However, neutrophils isolated from the blood of healthy donors acquire potent suppressive activity after treatment with ER-stress inducers[36].

M-MDSCs are more suppressive than PMN-MDSCs on a per-cell basis[22,34]. PMN-MDSCs and M-MDSCs use different mechanisms to suppress immune responses, and some of the mediators of

suppression can be used to distinguish MDSCs from neutrophils and monocytes. The most prominent factors implicated in MDSC suppressive activity include ARG1, NO, upregulation of ROS, and the production of prostaglandin E2 (PGE2)[53–55]. Changes in oxidative phosphorylation and glycolysis in tumors have also been associated with the function of MDSCs. In mice, glycolysis increases concurrently with increased ARG1 activity in MDSCs. Interestingly, AMP-activated protein kinase is also activated and normally drives metabolism toward oxidative phosphorylation[56]. A very recent study showed that tumor-infiltrating MDSCs preferentially use fatty acid-β oxidation (FAO) as a primary source of energy. Tumor-infiltrating MDSCs show increased mitochondrial mass, expression of key FAO-associated genes, and an increased oxygen-consumption rate[57]. Inhibition of FAO affects the suppressive functions of MDSCs and enhances the efficacy of cancer immune therapy.

The stress response of ER has emerged in recent years as an important mechanism regulating the pathologic activation of MDSCs, and thus is critical for the functions of these cells. The ER stress response is an evolutionarily 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 CHOP is a critical mediator of the PERK pathway, whereas spliced X-box binding protein-1 (sXBP1) is a mediator of the IRE1 pathway[58,59]. In tumor DCs, ER stress leads to increased lipid peroxidation and is directly implicated in defective function in these cells[60]. MDSCs from tumor-bearing mice and from humans with cancer demonstrate a much greater ER stress response than neutrophils and monocytes from tumor-free hosts[61]. Upregulation of the PERK and IRE1 pathways has been observed. The level of ER stress response at the tumor site is substantially higher than that in peripheral lymphoid organs in mice[61]. The direct cause of ER stress induction in MDSCs is not clear. However, the functional consequences have been identified. Experimental induction of ER stress enhances the immunosuppressive capacity of tumor-infiltrating MDSCs by increasing expression of *Arg1*, *Nos2* and *Nox2* (*Cybb*)[62]. Tumor MDSCs from CHOP-deficient mice show low expression of phosphorylated STAT3 and decreased production of IL-6 and ARG1, which are directly involved in immune suppression. CHOP-deficient MDSCs isolated from tumor-bearing mice have reduced immunosuppressive activity[63]. Increased amounts of sXBP1 were observed in human LOX-1$^+$ PMN-MDSCs as compared with the levels in LOX-1$^-$ neutrophils[36]. Moreover, the induction of ER stress in neutrophils isolated from healthy donors converts the neutrophils to potent suppressive cells[36]. ER stress also controls MDSC survival in tumors and favors apoptosis through TNF-related apoptosis-induced ligand receptor 2 and caspase-8 activation[61]. In fact, targeting of the proapoptotic molecule TRAIL-R2 results in the elimination of different populations of MDSCs without effects on mature myeloid or lymphoid cells in people with cancer[64]. 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[65]. Consistent with these observations, the absence of CHOP was shown to delay apoptosis and prolong survival of MDSCs in cancer[63]. Other mechanisms of MDSC-mediated immune suppression include upregulation of regulatory T cells and immune suppressive cytokines; these are reviewed in detail elsewhere[2]. Together, these unique features of MDSCs allow for the identification of these cells and provide 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 MDSCs are immature cells. A large number of studies in mice and humans have demonstrated that most PMN-MDSCs have a morphology similar to that of immature granulocytes, and in some in vitro studies PMN-MDSCs were able to acquire characteristics of mature neutrophils after short-term culture[16]. However, a recent study showed that granulocytic MDSC populations in people with Hodgkin's lymphoma were composed mostly of mature low-density suppressive neutrophils in an activated state[66]. Another recent study confirmed that activated mature neutrophils expressing CD10, isolated from human subjects with systemic lupus erythematosus and cancer and from G-CSF treated donors, also have suppressive properties[67]. Although more studies are needed to clarify this issue, it is likely that pathologic activation of PMN-MDSCs would include mature cells.

In tumor tissues, M-MDSCs rapidly differentiate into TAMs and inflammatory DCs[27,61]. 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[68,69]. Some studies have shown that inflammatory DCs can promote antitumor T cell responses[70,71]. However, it also has been shown that they can contribute to immune suppression in tumor-bearing hosts[72].

Do MDSCs have similar roles in different pathologic conditions?

Cancer was historically the first condition in which MDSCs were described. Below we discuss the data that directly implicate MDSCs in clinical outcome and response to therapy. In recent years, a large body of evidence demonstrated the role of MDSCs in the regulation of immune responses and the pathogenesis of many pathologic conditions. The question is whether these MDSCs have similar origins and functions. No direct side-by-side comparisons have been carried out so far. However, analysis of available data (below) may clarify this question.

Cancer

The role of MDSCs in mouse tumor models is well established[15]. In most studies reported so far, PMN-MDSC populations expanded much more than M-MDSC populations. In recent years, the clinical role of MDSCs has emerged. Initial studies monitored MDSCs in people with cancer, analyzing the total MDSC population (PMN-MDSCs and M-MDSCs together). Results showed positive correlation of MDSC numbers in peripheral blood with cancer stage and tumor burden in colorectal carcinomas and in breast, bladder, thyroid and non-small-cell lung cancer (NSCLC)[73–79]. In melanoma and breast cancer, both PMN-MDSC and M-MDSC numbers correlate with stage and metastasis[80]. In a meta-analysis, elevated numbers of MDSCs in the circulation were found to be an independent indicator of poor outcomes in subjects with solid tumors[81]. Accumulation of M-MDSCs in peripheral blood was associated with shorter progression-free interval and/or overall survival in subjects with NSCLC or with colorectal, bladder, thyroid, uterine or cervical cancer[77–79,82–84]. In melanoma and hepatocellular carcinoma, higher numbers of both PMN-MDSCs and M-MDSCs are correlated with poorer outcomes compared with those for subjects with low numbers of these cells[80,85]. In non-solid tumors, M-MDSC numbers correlate with reduced survival in subjects with multiple myeloma, Hodgkin's or non-Hodgkin's lymphoma, and diffuse large B cell lymphoma[66,86,87]. Notably, most studies have considered only circulating MDSCs, 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[88]. TANs can also contribute to tumor progression, upregulating tumor-proliferation pathways, promoting angiogenesis, and supporting tumor extravasation by disrupting the extracellular matrix (reviewed elsewhere[89]). Until recently, histological studies presented technical challenges, as multiple markers were required to identify MDSCs. The introduction

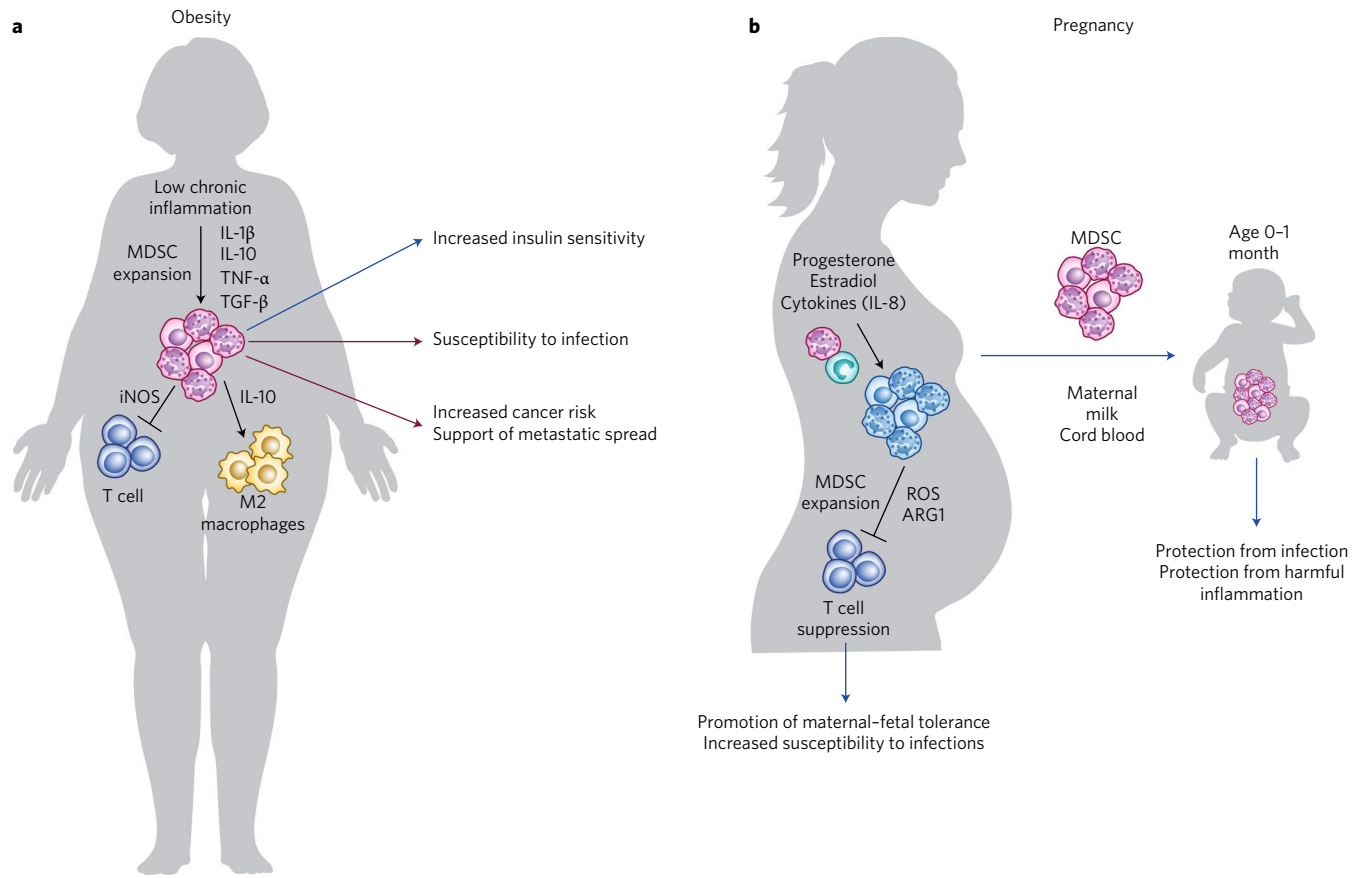

Fig. 3 | The role of MDSCs in obesity and pregnancy. a, MDSC populations are expanded in obese subjects because of chronic inflammation and contribute to increased insulin sensitivity. MDSCs in obese subjects directly inhibit T cells via NO secretion and induce macrophage differentiation to the M2 phenotype via IL-10 secretion, thus leading to increased susceptibility to infection. Moreover, increased numbers of MDSCs increase cancer risk and favor metastatic spread of early-stage cancers. **b**, MDSC populations are expanded during pregnancy, and are crucial for successful pregnancy. In pregnant women, MDSCs suppress T cells via ROS and ARG1, thus sustaining maternal–fetal tolerance. Moreover, MDSC populations also are expanded in cord blood and in neonates, and protect newborns from infections and harmful inflammation. Credit: Marina Corral Spence/Springer Nature.

of multiplex immunohistochemistry and new markers of MDSCs (such as LOX-1) should help address this problem.

Recent studies demonstrated the value of MDSCs in predicting the response to various cancer therapies. The frequency of M-MDSCs is negatively correlated with the response to chemotherapy in breast, cervical, prostate and colorectal cancer[76,82,84,90]; squamous cell carcinoma; multiple myeloma; and Hodgkin's lymphoma[91–93]. Similarly, PMN-MDSC numbers are negatively correlated with chemotherapy response in colorectal cancer[82]. High M-MDSC numbers are a predictor of radiotherapy failure in hepatocellular carcinoma[75,94]. High numbers of circulating MDSCs have been associated with vaccine failure in subjects with melanoma, NSCLC and colon adenocarcinoma[95,96]. The percentage of circulating M-MDSCs and PMN-MDSCs is negatively correlated with objective clinical response to ipilimumab (anti-CTLA-4) in patients with unresectable melanoma[97–99]. Moreover, in melanoma patients, M-MDSC frequency predicted the failure of second-line immunotherapy with anti-PD1 (nivolumab) after failure of first-line ipilimumab treatment[100]. Recent studies in mouse tumor models showed that inhibition of MDSCs during immunotherapy increases therapeutic effect[101–106].

Infectious diseases

Many studies have shown that bacteria (both Gram-positive and Gram-negative) can induce or modulate MDSCs both in vitro and in vivo (reviewed elsewhere[107]). In some studies, subpopulations of MDSCs were not 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 populations expand and suppress T cells[108], thereby contributing to the aggravation of infection[109]. *Mycobacterium tuberculosis* induces the expansion of PMN-MDSC and M-MDSC suppressive activity in mice[110]. Humans with sepsis show increased numbers of MDSCs; PMN-MDSC populations are expanded mainly in cases of sepsis caused by Gram-positive pathogens, whereas M-MDSC populations expand in response to Gram-positive or Gram-negative pathogens[111]. Sepsis-associated MDSCs have upregulated ARG1 expression and are associated with adverse outcome[112]. However, the expansion of MDSC populations after bacterial infection does not always translate to worse outcomes. In *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* infection, expanded MDSC populations are associated with host protection and better outcomes[113]. It seems that in early stages of sepsis (and probably in other infections as well) the accumulation of neutrophils and monocytes with potent antipathogen activity protects the host. MDSCs are probably either not present or present at very low frequency. However, if infection is not resolved, the frequency of MDSCs 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 have been observed to regulate the immune system and directly induce MDSC accumulation. In those studies, MDSCs were monitored as $Gr1^+CD11b^+$ cells, without further

distinction between PMN-MDSCs and M-MDSCs. *Albicans fumigatus* and *Candida albicans* induced MDSCs through recognition of the receptor Dectin-1. Interestingly, MDSCs were protective against *C. albicans* infection, but not *A. fumigatus* infection[114]. In a follow-up study, the same group demonstrated that MDSC induction and suppressive activity on T cells during *Candida* infection depend on the *Candida* species[115]. MDSC populations were observed to expand in mouse and rat models of *Pneumocystis* pneumonia infection, in which MDSCs exert their function through ARG1 and iNOS and contribute to increased severity of infection[116].

M-MDSC populations are expanded in people with chronic hepatitis C virus (HCV) infection. This cell accumulation correlates with disease progression and response to antiviral therapy[117]. Different studies report ROS production[118] or ARG1[117] as the main mechanism for MDSC-mediated T cell suppression. HCV-induced MDSCs can directly inhibit NK cell activities via ARG1-independent mechanisms[119,120]. In vitro studies show that HCV directly induces M-MDSCs through TLR2–STAT3 signaling. These MDSCs stimulate the accumulation of regulatory T cells (T_{reg} cells) and inhibit the proliferation of $CD4^+$ T cells[121].

M-MDSC populations are also expanded in HIV-1-infected individuals, and suppress T cell function via ARG1[122,123]. Similarly to HCV, HIV directly induces the expansion of M-MDSC populations[124] that promote the differentiation of T_{reg} cells[125]. PMN-MDSCs may induce T cell anergy by suppressing CD3-ζ expression and inhibiting $CD8^+$ T cells through PD-L1–PD1 interaction[123,126]. PMN-MDSC accumulation in people with primary HIV-1 infection may be regulated by TRAIL and GM-CSF, and positively correlates with disease progression[126,127]. Thus, the accumulation, functional activity and major biochemical features of MDSCs in infectious disease closely resemble those of cancer-associated MDSCs.

Autoimmune disorders

In cancer and infectious disease MDSC activity is deleterious for patients, but the role of MDSCs in autoimmune disease is more complex. It has been shown that MDSC populations are expanded in murine models of and humans with autoimmune diseases[128]. Nevertheless, the role of MDSCs in this process is not established, and contrasting studies show positive and negative roles for MDSCs in the regulation of disease progression. Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder with high cellular infiltration of organs. In mouse models, MDSCs suppressed $CD4^+$ T cell proliferation via ARG1, and MDSC populations expanded in peripheral blood and kidney during disease progression[129]. The ability of MDSCs to expand regulatory B cell populations has also been demonstrated[130]. However, in lupus-prone mice MDSC function was found to be impaired, which suggests that SLE development is associated with a defect in MDSCs[131]. A recent study demonstrated that populations of both M-MDSCs and PMN-MDSCs are expanded in the peripheral blood of people with SLE, and their frequency positively correlates with serum ARG1 concentration, IL-17-producing helper T cell (T_H17 cell) responses and lupus severity[132].

Rheumatoid arthritis (RA) is a chronic inflammatory disease that leads to inflammation of multiple joints and can progress to cartilage destruction and bone erosion. Initial studies in a mouse collagen-induced arthritis (CIA) model showed that suppressive MDSCs accumulate in the spleen, and adoptive transfer of MDSCs reduces the severity of RA by blocking the $CD4^+$ T cell proinflammatory immune response[133]. In that study, MDSCs lost suppressive activity during arthritis development, and thus were not able to control the disease[133]. M-MDSCs isolated from BM of CIA mice were also able to inhibit B cell proliferation and function, thereby improving CIA outcome[134]. In support of a beneficial role of MDSCs in RA models, synovial fluid of individuals with RA was found to contain PMN-MDSCs that were able to suppress T cell activity in vitro[135], similar to what was previously shown in mice[136]. Moreover, the number of circulating MDSCs in people with RA negatively correlates with the number of T_H17 cells and with plasma arginin concentrations[137]. Recently, it has been reported that MDSCs could have the opposite role and promote RA onset in mice by sustaining T_H17 cell differentiation. MDSC infiltration in arthritic joints positively correlates with high disease activity, but MDSC frequency in peripheral blood negatively correlates with T_H17 cell numbers[134]. Overall, RA studies consistently report beneficial effects of adoptive transfer of MDSCs for inhibiting RA progression in mouse models, consistent with the suppressive activity of these cells, but MDSC recruitment shows inconsistent effects with regard to the expansion of T_H17 cell and T_{reg} cell populations and to RA onset. This inconsistency could be due to the heterogeneity of the myeloid cell population discussed above, with variable frequencies of MDSCs present among the total population of myeloid cells. Several studies have also associated MDSCs with inflammatory bowel disease. MDSCs reduce the severity of experimentally induced colitis in mice[138]. In a study involving people with inflammatory bowel disease, populations of cells with the M-MDSC phenotype were expanded. However, these cells did not suppress T cell function[139].

Thus, the importance of MDSCs in autoimmune diseases is evident. However, compared with what is observed in cancer and infectious diseases, the expansion of MDSC populations in autoimmune disease states is less prominent; this results in greater heterogeneity of the myeloid population and variable frequency of MDSCs among myeloid cells, which may in turn lead to contradictory results. This heterogeneity is apparently due to the different severities of autoimmune diseases and specifics of the microenvironment.

Obesity and pregnancy

Obesity is associated with chronic inflammation and with increased risk of breast, prostate and colorectal cancer, as well as cardiovascular and metabolic disorders and type 2 diabetes mellitus[140,141]. The metabolic changes in the microenvironment associated with obesity and the associated chronic inflammation led to the hypothesis that MDSCs could have a role in maintaining immune homeostasis in obese subjects. In a mouse model of diabetes, MDSCs were able to downregulate immune responses and prevent diabetes onset[142]. Tissue-infiltrating MDSCs are crucial in controlling obesity-associated inflammation and increasing insulin sensitivity. MDSCs suppress $CD8^+$ T cells by iNOS and IFN-γ-dependent mechanisms. MDSCs also induce M2 macrophage polarization, probably through IL-10[143]. Obese subjects are often susceptible to infections and respond poorly to vaccines. This observation could be explained by the expansion of MDSC populations and consequent suppression of T and B cell functions, as demonstrated in obese mice[144]. 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[145]. Recent work showed that obesity causes the expansion of neutrophil populations in mouse lungs, thus enhancing breast cancer metastasis through IL-5 and GM-CSF activity[146] (Fig. 3a).

Insulin resistance promotes the development of metabolic syndrome, characterized by elevated levels of 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 previously[147]). 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 previously[148]). 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[149,150]. The obesity microenvironment can also induce the differentiation of M2 macrophages to M1 macrophages that then recruit T cells[151] and induce monocyte migration via CCL2[152]. In vitro, macrophages

from obese subjects or exposed to conditions that mimic the obesity microenvironment show increases in migration and in upregulation of TAM markers[153]. In the same study, it was also demonstrated that obesity promotes macrophage infiltration in the prostate tumor microenvironment and induces TAM polarization through the COX2–PGE2 pathway[153].

Maternal–fetal tolerance is critically important for normal pregnancy. Pregnancy failure (e.g., miscarriage, implantation failure, preterm birth, preeclampsia) is associated with dysregulation of the immune system (reviewed elsewhere[154]). Early observations in mice showed that MDSCs accumulate in mouse placenta[155] and that their numbers decrease toward the time of delivery. Subsequently, expansion of MDSC populations was observed in peripheral blood and the uterus of pregnant mice, in association with anti-inflammatory functions[156]. MDSC recruitment is driven by CXCR2[157], and progesterone supports MDSC differentiation and activation via STAT3 signaling[158]. MDSCs suppress T cells via either ARG1[159] or ROS production[158] or by preventing T cell activation by downmodulating L-selectin expression on naive T cells[160].

MDSC populations are expanded in the peripheral blood[161] and decidua[162] during pregnancy in healthy women, and rapidly decrease to normal levels after birth[163]. Reduced numbers of MDSCs in peripheral blood, endometrium and placenta are associated with early miscarriage[164], and low levels of arginine and reduced iNOS expression in placental tissues are found in women with preeclampsia[165,166]. A study demonstrated that MDSC populations are expanded during the first trimester and decrease toward the third trimester[164]. Conversely, a different study showed that MDSC populations are equally expanded during the entire gestation period[163]. In that study, the main population of MDSCs observed to be expanded in peripheral blood was PMN-MDSCs, expressing ARG1 and iNOS and producing high levels of ROS[163].

During pregnancy, estradiol expands M-MDSC populations in the circulation via STAT3 activation that suppresses T cells in an ROS-dependent fashion[158]. Conversely, in placental tissue, M-MDSC populations were observed to be expanded by CCL2 and to overexpress IDO1, ARG1 and COX2[166]. PMN-MDSCs in the placenta can also interact with other immune-system cell populations, directly expanding T_{reg} cell populations via the TGF-β–β-catenin pathway[159] (Fig. 3b).

The expansion of MDSC populations is rapidly canceled in postpartum women, but MDSC populations are expanded in neonates during the first month of life. In neonates, the expanded MDSC populations consist mainly of PMN-MDSCs that suppress T cells in a contact-dependent manner and reduce IFN-γ production. Numbers of PMN-MDSCs decrease rapidly in the first 6 weeks of life and reach adult levels by the time the infant is 6 months of age[167]. In the same studies, PMN-MDSC populations were expanded in the cord blood (CB), where the cells' frequency correlated with the proliferative capacity of T cells after stimulation in vitro. Expansion of M-MDSC and PMN-MDSC populations in CB modulated the adaptive immune response[168]. PMN-MDSCs from CB directly inhibited type 1 helper T cell responses and induced type 2 helper T cell responses and T_{reg} cells. In this setting PMN-MDSCs mediated suppression via the expression of ARG1 and iNOS, the production of ROS, and the degradation of tryptophan by IDO expression[169]. PMN-MDSCs in neonates show reduced apoptosis and immunosuppressive activity after infection with *Escherichia coli*[170]. A recent study showed that M-MDSC populations are expanded in neonates and respond to microbial stimulation[171]. Mouse studies by the same group showed that S100A8/A9 prevents the expansion of these cell populations and prevents death from septic shock[171]. Studies in humans showed that S100A9 secretion protects neonates from sepsis by regulating MyD88-dependent gene programs[172]. Thus, MDSCs in pregnancy mainly follow the pattern observed in cancer and are apparently one of the important regulators of fetal–maternal tolerance. Because of limited information, at this time the biological role of MDSCs in newborns is not clear. It is possible that MDSCs have evolved as a protective mechanism to limit inflammation associated with bacterial colonization of the gut.

Conclusions

MDSCs 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 MDSCs 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, MDSCs are not present in steady-state conditions. This provides a unique opportunity to target these cells without possible side effects. Understanding the molecular mechanisms that regulate the accumulation and function of these cells will allow for more precise targeted therapy. The clinical significance of MDSCs in cancer and in some infectious diseases is now established. The next step is to determine whether targeting MDSCs can provide tangible clinical benefits. Work conducted over the next several years will provide an answer to this question.

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References

1. Gabrilovich, D. I. et al. The terminology issue for myeloid-derived suppressor cells. *Cancer Res.* **67**, 425 (2007).
2. Gabrilovich, D. I., Ostrand-Rosenberg, S. & Bronte, V. Coordinated regulation of myeloid cells by tumours. *Nat. Rev. Immunol.* **12**, 253–268 (2012).
3. Dumitru, C. A., Moses, K., Trellakis, S., Lang, S. & Brandau, S. Neutrophils and granulocytic myeloid-derived suppressor cells: immunophenotyping, cell biology and clinical relevance in human oncology. *Cancer Immunol. Immunother.* **61**, 1155–1167 (2012).
4. Solito, S. et al. Myeloid-derived suppressor cell heterogeneity in human cancers. *Ann. NY Acad. Sci.* **1319**, 47–65 (2014).
5. Bronte, V. et al. Recommendations for myeloid-derived suppressor cell nomenclature and characterization standards. *Nat. Commun.* **7**, 12150 (2016).
6. Geissmann, F. et al. Development of monocytes, macrophages, and dendritic cells. *Science* **327**, 656–661 (2010).
7. Veglia, F. & Gabrilovich, D. I. Dendritic cells in cancer: the role revisited. *Curr. Opin. Immunol.* **45**, 43–51 (2017).
8. Barreda, D. R., Hanington, P. C. & Belosevic, M. Regulation of myeloid development and function by colony stimulating factors. *Dev. Comp. Immunol.* **28**, 509–554 (2004).
9. Marvel, D. & Gabrilovich, D. I. Myeloid-derived suppressor cells in the tumor microenvironment: expect the unexpected. *J. Clin. Invest.* **125**, 3356–3364 (2015).
10. Newton, K. & Dixit, V. M. Signaling in innate immunity and inflammation. *Cold Spring Harb. Perspect. Biol.* **4**, a006049 (2012).
11. Kruger, P. et al. Neutrophils: between host defence, immune modulation, and tissue injury. *PLoS Pathog.* **11**, e1004651 (2015).
12. Shi, C. & Pamer, E. G. Monocyte recruitment during infection and inflammation. *Nat. Rev. Immunol.* **11**, 762–774 (2011).
13. Colotta, F., Allavena, P., Sica, A., Garlanda, C. & Mantovani, A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis* **30**, 1073–1081 (2009).
14. Landskron, G., de la Fuente, M., Thuwajit, P., Thuwajit, C. & Hermoso, M. A. Chronic inflammation and cytokines in the tumor microenvironment. *J. Immunol. Res.* **2014**, 149185 (2014).
15. Umansky, V., Blattner, C., Gebhardt, C. & Utikal, J. The role of myeloid-derived suppressor cells (MDSC) in cancer progression. *Vaccines (Basel)* **4**, E36 (2016).
16. Youn, J. I., Collazo, M., Shalova, I. N., Biswas, S. K. & Gabrilovich, D. I. Characterization of the nature of granulocytic myeloid-derived suppressor cells in tumor-bearing mice. *J. Leukoc. Biol.* **91**, 167–181 (2012).
17. Viale, A. et al. Oncogene ablation-resistant pancreatic cancer cells depend on mitochondrial function. *Nature* **514**, 628–632 (2014).
18. Ortiz, M. L., Lu, L., Ramachandran, I. & Gabrilovich, D. I. Myeloid-derived suppressor cells in the development of lung cancer. *Cancer Immunol. Res.* **2**, 50–58 (2014).

19. Netea, M. G. et al. Trained immunity: a program of innate immune memory in health and disease. *Science* **352**, aaf1098 (2016).
20. Condamine, T. & Gabrilovich, D. I. Molecular mechanisms regulating myeloid-derived suppressor cell differentiation and function. *Trends Immunol.* **32**, 19–25 (2011).
21. Bronte, V. et al. Unopposed production of granulocyte-macrophage colony-stimulating factor by tumors inhibits $CD8^+$ T cell responses by dysregulating antigen-presenting cell maturation. *J. Immunol.* **162**, 5728–5737 (1999).
22. Dolcetti, L. et al. Hierarchy of immunosuppressive strength among myeloid-derived suppressor cell subsets is determined by GM-CSF. *Eur. J. Immunol.* **40**, 22–35 (2010).
23. Umansky, V. & Sevko, A. Tumor microenvironment and myeloid-derived suppressor cells. *Cancer Microenviron.* **6**, 169–177 (2013).
24. Yan, D. et al. Polyunsaturated fatty acids promote the expansion of myeloid-derived suppressor cells by activating the JAK/STAT3 pathway. *Eur. J. Immunol.* **43**, 2943–2955 (2013).
25. Condamine, T., Mastio, J. & Gabrilovich, D. I. Transcriptional regulation of myeloid-derived suppressor cells. *J. Leukoc. Biol.* **98**, 913–922 (2015).
26. Haverkamp, J. M. et al. Myeloid-derived suppressor activity is mediated by monocytic lineages maintained by continuous inhibition of extrinsic and intrinsic death pathways. *Immunity* **41**, 947–959 (2014).
27. Ribechini, E. et al. Novel GM-CSF signals via IFN-γR/IRF-1 and AKT/mTOR license monocytes for suppressor function. *Blood Advances* **1**, 947–960 (2017).
This study demonstrates an actual example of the two-phase process in the generation of MDSCs.
28. Damuzzo, V. et al. Complexity and challenges in defining myeloid-derived suppressor cells. *Cytometry B Clin. Cytom.* **88**, 77–91 (2015).
This paper provides a detailed description of phenotypic characterization of MDSCs.
29. Fridlender, Z. G. et al. Polarization of tumor-associated neutrophil phenotype by TGF-β: "N1" versus "N2" TAN. *Cancer Cell* **16**, 183–194 (2009).
30. Cimen Bozkus, C., Elzey, B. D., Crist, S. A., Ellies, L. G. & Ratliff, T. L. Expression of cationic amino acid transporter 2 is required for myeloid-derived suppressor cell-mediated control of T cell immunity. *J. Immunol.* **195**, 5237–5250 (2015).
31. Mairhofer, D. G. et al. Impaired gp100-Specific $CD8^+$ T-cell responses in the presence of myeloid-derived suppressor cells in a spontaneous mouse melanoma model. *J. Invest. Dermatol.* **135**, 2785–2793 (2015).
32. Raber, P. L. et al. Subpopulations of myeloid-derived suppressor cells impair T cell responses through independent nitric oxide-related pathways. *Int. J. Cancer* **134**, 2853–2864 (2014).
33. Haile, L. A., Gamrekelashvili, J., Manns, M. P., Korangy, F. & Greten, T. F. CD49d is a new marker for distinct myeloid-derived suppressor cell subpopulations in mice. *J. Immunol.* **185**, 203–210 (2010).
34. Movahedi, K. et al. Identification of discrete tumor-induced myeloid-derived suppressor cell subpopulations with distinct T cell-suppressive activity. *Blood* **111**, 4233–4244 (2008).
35. Gabrilovich, D. I. & Nagaraj, S. Myeloid-derived suppressor cells as regulators of the immune system. *Nat. Rev. Immunol.* **9**, 162–174 (2009).
36. Condamine, T. et al. Lectin-type oxidized LDL receptor-1 distinguishes population of human polymorphonuclear myeloid-derived suppressor cells in cancer patients. *Sci. Immunol.* **1**, aaf8943 (2016).
This paper describes the identification of a specific marker of human PMN-MDSCs and the possibility of converting neutrophils to PMN-MDSCs by inducing ER stress.
37. Mandruzzato, S. et al. Toward harmonized phenotyping of human myeloid-derived suppressor cells by flow cytometry: results from an interim study. *Cancer Immunol. Immunother.* **65**, 161–169 (2016).
38. Eruslanov, E. B., Singhal, S. & Albelda, S. M. Mouse versus human neutrophils in cancer: a major knowledge gap. *Trends Cancer* **3**, 149–160 (2017).
39. Fridlender, Z. G. et al. Transcriptomic analysis comparing tumor-associated neutrophils with granulocytic myeloid-derived suppressor cells and normal neutrophils. *PLoS One* **7**, e31524 (2012).
40. Gato, M. et al. Drafting the proteome landscape of myeloid-derived suppressor cells. *Proteomics* **16**, 367–378 (2016).
41. Gato-Cañas, M. et al. A core of kinase-regulated interactomes defines the neoplastic MDSC lineage. *Oncotarget* **6**, 27160–27175 (2015).
42. Nefedova, Y. et al. Hyperactivation of STAT3 is involved in abnormal differentiation of dendritic cells in cancer. *J. Immunol.* **172**, 464–474 (2004).
43. Rébé, C., Végran, F., Berger, H. & Ghiringhelli, F. STAT3 activation: a key factor in tumor immunoescape. *JAK-STAT* **2**, e23010 (2013).
44. Marigo, I. et al. Tumor-induced tolerance and immune suppression depend on the C/EBPβ transcription factor. *Immunity* **32**, 790–802 (2010).
45. Kumar, V. et al. CD45 phosphatase inhibits STAT3 transcription factor activity in myeloid cells and promotes tumor-associated macrophage differentiation. *Immunity* **44**, 303–315 (2016).
46. Netherby, C. S. et al. The granulocyte progenitor stage is a key target of IRF8-mediated regulation of myeloid-derived suppressor cell production. *J. Immunol.* **198**, 4129–4139 (2017).
47. Ramji, D. P. & Foka, P. CCAAT/enhancer-binding proteins: structure, function and regulation. *Biochem. J.* **365**, 561–575 (2002).
48. Abbasi, K. et al. Concomitant carotid endarterectomy and coronary artery bypass grafting versus staged carotid stenting followed by coronary artery bypass grafting. *J. Cardiovasc. Surg. (Torino)* **49**, 285–288 (2008).
49. Youn, J. I. et al. Epigenetic silencing of retinoblastoma gene regulates pathologic differentiation of myeloid cells in cancer. *Nat. Immunol.* **14**, 211–220 (2013).
50. Casbon, A. J. et al. Invasive breast cancer reprograms early myeloid differentiation in the bone marrow to generate immunosuppressive neutrophils. *Proc. Natl. Acad. Sci. USA* **112**, E566–E575 (2015).
51. Dufait, I. et al. Ex vivo generation of myeloid-derived suppressor cells that model the tumor immunosuppressive environment in colorectal cancer. *Oncotarget* **6**, 12369–12382 (2015).
52. Casacuberta-Serra, S. et al. Myeloid-derived suppressor cells can be efficiently generated from human hematopoietic progenitors and peripheral blood monocytes. *Immunol. Cell Biol.* **95**, 538–548 (2017).
53. Rodriguez, P. C. et al. Arginase I in myeloid suppressor cells is induced by COX-2 in lung carcinoma. *J. Exp. Med.* **202**, 931–939 (2005).
54. Donkor, M. K. et al. Mammary tumor heterogeneity in the expansion of myeloid-derived suppressor cells. *Int. Immunopharmacol.* **9**, 937–948 (2009).
55. Mao, Y. et al. Melanoma-educated $CD14^+$ cells acquire a myeloid-derived suppressor cell phenotype through COX-2-dependent mechanisms. *Cancer Res.* **73**, 3877–3887 (2013).
56. Hammami, I. et al. Immunosuppressive activity enhances central carbon metabolism and bioenergetics in myeloid-derived suppressor cells in vitro models. *BMC Cell Biol.* **13**, 18 (2012).
57. Hossain, F. et al. Inhibition of fatty acid oxidation modulates immunosuppressive functions of myeloid-derived suppressor cells and enhances cancer therapies. *Cancer Immunol. Res.* **3**, 1236–1247 (2015).
This paper shows the involvement of lipid metabolism in the functionality of MDSCs in cancer.
58. Todd, D. J., Lee, A. H. & Glimcher, L. H. The endoplasmic reticulum stress response in immunity and autoimmunity. *Nat. Rev. Immunol.* **8**, 663–674 (2008).
59. Grootjans, J., Kaser, A., Kaufman, R. J. & Blumberg, R. S. The unfolded protein response in immunity and inflammation. *Nat. Rev. Immunol.* **16**, 469–484 (2016).
60. Cubillos-Ruiz, J. R. et al. ER stress sensor XBP1 controls anti-tumor immunity by disrupting dendritic cell homeostasis. *Cell* **161**, 1527–1538 (2015).
61. Condamine, T. et al. ER stress regulates myeloid-derived suppressor cell fate through TRAIL-R-mediated apoptosis. *J. Clin. Invest.* **124**, 2626–2639 (2014).
Together with ref. 63, this study demonstrates the role of ER stress in MDSC function.
62. Lee, B. R. et al. Elevated endoplasmic reticulum stress reinforced immunosuppression in the tumor microenvironment via myeloid-derived suppressor cells. *Oncotarget* **5**, 12331–12345 (2014).
63. Thevenot, P. T. et al. The stress-response sensor chop regulates the function and accumulation of myeloid-derived suppressor cells in tumors. *Immunity* **41**, 389–401 (2014).
Together with ref. 61, this study demonstrates the role of ER stress in MDSC function.
64. Dominguez, G. A. et al. Selective targeting of myeloid-derived suppressor cells in cancer patients using DS-8273a, an agonistic TRAIL-R2 antibody. *Clin. Cancer Res.* **23**, 2942–2950 (2017).
65. Germano, G. et al. Role of macrophage targeting in the antitumor activity of trabectedin. *Cancer Cell* **23**, 249–262 (2013).
66. Marini, O. et al. Identification of granulocytic myeloid-derived suppressor cells (G-MDSCs) in the peripheral blood of Hodgkin and non-Hodgkin lymphoma patients. *Oncotarget* **7**, 27676–27688 (2016).
This paper reports that mature and activated neutrophils isolated from cancer patients have suppressive functions.
67. Marini, O. et al. Mature $CD10^+$ and immature $CD10^-$ neutrophils present in G-CSF-treated donors display opposite effects on T cells. *Blood* **129**, 1343–1356 (2017).
68. Noy, R. & Pollard, J. W. Tumor-associated macrophages: from mechanisms to therapy. *Immunity* **41**, 49–61 (2014).
69. Liu, Y. & Cao, X. The origin and function of tumor-associated macrophages. *Cell. Mol. Immunol.* **12**, 1–4 (2015).

70. Ma, Y. et al. Anticancer chemotherapy-induced intratumoral recruitment and differentiation of antigen-presenting cells. *Immunity* **38**, 729–741 (2013).
71. Marigo, I. et al. T cell cancer therapy requires CD40-CD40L activation of tumor necrosis factor and inducible nitric-oxide-synthase-producing dendritic cells. *Cancer Cell* **30**, 651 (2016).
72. Tesone, A. J. et al. Satb1 overexpression drives tumor-promoting activities in cancer-associated dendritic cells. *Cell Rep.* **14**, 1774–1786 (2016).
73. Sun, H. L. et al. Increased frequency and clinical significance of myeloid-derived suppressor cells in human colorectal carcinoma. *World J. Gastroenterol.* **18**, 3303–3309 (2012).
74. Zhang, B. et al. Circulating and tumor-infiltrating myeloid-derived suppressor cells in patients with colorectal carcinoma. *PLoS One* **8**, e57114 (2013).
75. Arihara, F. et al. Increase in $CD14^+HLA\text{-}DR^{-/low}$ myeloid-derived suppressor cells in hepatocellular carcinoma patients and its impact on prognosis. *Cancer Immunol. Immunother.* **62**, 1421–1430 (2013).
76. Diaz-Montero, C. M. et al. Increased circulating myeloid-derived suppressor cells correlate with clinical cancer stage, metastatic tumor burden, and doxorubicin-cyclophosphamide chemotherapy. *Cancer Immunol. Immunother.* **58**, 49–59 (2009).
77. Yang, G. et al. Accumulation of myeloid-derived suppressor cells (MDSCs) induced by low levels of IL-6 correlates with poor prognosis in bladder cancer. *Oncotarget* **8**, 38378–38388 (2017).
78. Angell, T. E. et al. Circulating myeloid-derived suppressor cells predict differentiated thyroid cancer diagnosis and extent. *Thyroid* **26**, 381–389 (2016).
79. Huang, A. et al. Increased $CD14^+HLA\text{-}DR^{-/low}$ myeloid-derived suppressor cells correlate with extrathoracic metastasis and poor response to chemotherapy in non-small cell lung cancer patients. *Cancer Immunol. Immunother.* **62**, 1439–1451 (2013).
80. Jordan, K. R. et al. Myeloid-derived suppressor cells are associated with disease progression and decreased overall survival in advanced-stage melanoma patients. *Cancer Immunol. Immunother.* **62**, 1711–1722 (2013).
81. Zhang, S. et al. The role of myeloid-derived suppressor cells in patients with solid tumors: a meta-analysis. *PLoS One* **11**, e0164514 (2016).
A meta-analysis of the association between MDSC accumulation and clinical outcome in people with cancer.
82. Tada, K. et al. Pretreatment immune status correlates with progression-free survival in chemotherapy-treated metastatic colorectal cancer patients. *Cancer Immunol. Res.* **4**, 592–599 (2016).
83. Zhang, H. et al. CXCL2/MIF-CXCR2 signaling promotes the recruitment of myeloid-derived suppressor cells and is correlated with prognosis in bladder cancer. *Oncogene* **36**, 2095–2104 (2017).
84. Kawano, M. et al. The significance of G-CSF expression and myeloid-derived suppressor cells in the chemoresistance of uterine cervical cancer. *Sci. Rep.* **5**, 18217 (2015).
85. Li, X. et al. Neutrophil count is associated with myeloid derived suppressor cell level and presents prognostic value of for hepatocellular carcinoma patients. *Oncotarget* **8**, 24380–24388 (2017).
86. Wang, Z. et al. Tumor-induced $CD14^+HLA\text{-}DR^{-/low}$ myeloid-derived suppressor cells correlate with tumor progression and outcome of therapy in multiple myeloma patients. *Cancer Immunol. Immunother.* **64**, 389–399 (2015).
87. Wu, C. et al. Prognostic significance of peripheral monocytic myeloid-derived suppressor cells and monocytes in patients newly diagnosed with diffuse large B-cell lymphoma. *Int. J. Clin. Exp. Med.* **8**, 15173–15181 (2015).
88. Galdiero, M. R. et al. Occurrence and significance of tumor-associated neutrophils in patients with colorectal cancer. *Int. J. Cancer* **139**, 446–456 (2016).
89. Hurt, B., Schulick, R., Edil, B., El Kasmi, K. C. & Barnett, C. Jr. Cancer-promoting mechanisms of tumor-associated neutrophils. *Am. J. Surg.* **214**, 938–944 (2017).
90. Wang, J. & Yang, J. Identification of $CD4^+CD25^+CD127^-$ regulatory T cells and $CD14{+}HLA\text{-}DR^{-/low}$ myeloid-derived suppressor cells and their roles in the prognosis of breast cancer. *Biomed. Rep.* **5**, 208–212 (2016).
91. Chen, M. F. et al. IL-6-stimulated $CD11b^+CD14^+HLA\text{-}DR^-$ myeloid-derived suppressor cells, are associated with progression and poor prognosis in squamous cell carcinoma of the esophagus. *Oncotarget* **5**, 8716–8728 (2014).
92. Lee, S. E. et al. Circulating immune cell phenotype can predict the outcome of lenalidomide plus low-dose dexamethasone treatment in patients with refractory/relapsed multiple myeloma. *Cancer Immunol. Immunother.* **65**, 983–994 (2016).
93. Romano, A. et al. Circulating myeloid-derived suppressor cells correlate with clinical outcome in Hodgkin lymphoma patients treated up-front with a risk-adapted strategy. *Br. J. Haematol.* **168**, 689–700 (2015).
94. Wang, D., An, G., Xie, S., Yao, Y. & Feng, G. The clinical and prognostic significance of $CD14^+HLA\text{-}DR^{-/low}$ myeloid-derived suppressor cells in hepatocellular carcinoma patients receiving radiotherapy. *Tumour Biol.* **37**, 10427–10433 (2016).
95. Butterfield, L. H. et al. Immune correlates of GM-CSF and melanoma peptide vaccination in a randomized trial for the adjuvant therapy of resected high-risk melanoma (E4697). *Clin. Cancer Res.* **23**, 5034–5043 (2017).
96. Kimura, T. et al. MUC1 vaccine for individuals with advanced adenoma of the colon: a cancer immunoprevention feasibility study. *Cancer Prev. Res. (Phila.)* **6**, 18–26 (2013).
97. de Coaña, Y. P. et al. Ipilimumab treatment decreases monocytic MDSCs and increases CD8 effector memory T cells in long-term survivors with advanced melanoma. *Oncotarget* **8**, 21539–21553 (2017).
98. Sade-Feldman, M. et al. Clinical significance of circulating $CD33^+CD11b^+HLA\text{-}DR^-$ myeloid cells in patients with stage IV melanoma treated with ipilimumab. *Clin. Cancer Res.* **22**, 5661–5672 (2016).
99. Martens, A. et al. Baseline peripheral blood biomarkers associated with clinical outcome of advanced melanoma patients treated with ipilimumab. *Clin. Cancer Res.* **22**, 2908–2918 (2016).
100. Weber, J. et al. Phase I/II study of metastatic melanoma patients treated with nivolumab who had progressed after ipilimumab. *Cancer Immunol. Res.* **4**, 345–353 (2016).
This paper describes the association of high numbers of MDSCs with response and survival after treatment with PD-1 antibody in patients in which disease had progressed with anti-CTLA4 therapy.
101. Iida, Y. et al. Contrasting effects of cyclophosphamide on anti-CTL-associated protein 4 blockade therapy in two mouse tumor models. *Cancer Sci.* **108**, 1974–1984 (2017).
102. Highfill, S. L. et al. Disruption of CXCR2-mediated MDSC tumor trafficking enhances anti-PD1 efficacy. *Sci. Transl. Med.* **6**, 237ra67 (2014).
A demonstration of the therapeutic effect of blocking MDSC trafficking.
103. Du Four, S. et al. Combined VEGFR and CTLA-4 blockade increases the antigen-presenting function of intratumoral DCs and reduces the suppressive capacity of intratumoral MDSCs. *Am. J. Cancer Res.* **6**, 2514–2531 (2016).
104. Davis, R. J. et al. Anti-PD-L1 efficacy can be enhanced by inhibition of myeloid-derived suppressor cells with a selective inhibitor of PI3Kδ/γ. *Cancer Res.* **77**, 2607–2619 (2017).
This paper describes the therapeutic effect in mice after downregulation of MDSCs with PI3K inhibitor.
105. Lu, X. et al. Effective combinatorial immunotherapy for castration-resistant prostate cancer. *Nature* **543**, 728–732 (2017).
This study demonstrates the important role of MDSCs in a prostate cancer model, as well as the potential therapeutic benefit of targeting these cells.
106. Kamran, N. et al. Immunosuppressive myeloid cells' blockade in the glioma microenvironment enhances the efficacy of immune-stimulatory gene therapy. *Mol. Ther.* **25**, 232–248 (2017).
107. Ost, M. et al. Myeloid-derived suppressor cells in bacterial infections. *Front. Cell. Infect. Microbiol.* **6**, 37 (2016).
108. Tebartz, C. et al. A major role for myeloid-derived suppressor cells and a minor role for regulatory T cells in immunosuppression during *Staphylococcus aureus* infection. *J. Immunol.* **194**, 1100–1111 (2015).
109. Heim, C. E. et al. Myeloid-derived suppressor cells contribute to *Staphylococcus aureus* orthopedic biofilm infection. *J. Immunol.* **192**, 3778–3792 (2014).
110. Dietlin, T. A. et al. Mycobacteria-induced $Gr\text{-}1^+$ subsets from distinct myeloid lineages have opposite effects on T cell expansion. *J. Leukoc. Biol.* **81**, 1205–1212 (2007).
111. Janols, H. et al. A high frequency of MDSCs in sepsis patients, with the granulocytic subtype dominating in Gram-positive cases. *J. Leukoc. Biol.* **96**, 685–693 (2014).
112. Uhel, F. et al. Early expansion of circulating granulocytic myeloid-derived suppressor cells predicts development of nosocomial infections in patients with sepsis. *Am. J. Respir. Crit. Care Med.* **196**, 315–327 (2017).
113. Poe, S. L. et al. STAT1-regulated lung MDSC-like cells produce IL-10 and efferocytose apoptotic neutrophils with relevance in resolution of bacterial pneumonia. *Mucosal Immunol.* **6**, 189–199 (2013).
114. Rieber, N. et al. Pathogenic fungi regulate immunity by inducing neutrophilic myeloid-derived suppressor cells. *Cell Host Microbe* **17**, 507–514 (2015).
115. Singh, A. et al. Differential regulation of myeloid-derived suppressor cells by *Candida* species. *Front. Microbiol.* **7**, 1624 (2016).
116. Zhang, C. et al. Accumulation of myeloid-derived suppressor cells in the lungs during *Pneumocystis* pneumonia. *Infect. Immun.* **80**, 3634–3641 (2012).
117. Cai, W. et al. Clinical significance and functional studies of myeloid-derived suppressor cells in chronic hepatitis C patients. *J. Clin. Immunol.* **33**, 798–808 (2013).
118. Tacke, R. S. et al. Myeloid suppressor cells induced by hepatitis C virus suppress T-cell responses through the production of reactive oxygen species. *Hepatology* **55**, 343–353 (2012).

119. Goh, C. C. et al. Hepatitis C virus-induced myeloid-derived suppressor cells suppress NK cell IFN-γ production by altering cellular metabolism via arginase-1. *J. Immunol.* **196**, 2283–2292 (2016).
120. Goh, Y. S. et al. Bactericidal immunity to *Salmonella* in Africans and mechanisms causing its failure in HIV infection. *PLoS Negl. Trop. Dis.* **10**, e0004604 (2016).
121. Zhai, N. et al. Hepatitis C virus induces MDSCs-like monocytes through TLR2/PI3K/AKT/STAT3 signaling. *PLoS One* **12**, e0170516 (2017).
122. Qin, A. et al. Expansion of monocytic myeloid-derived suppressor cells dampens T cell function in HIV-1-seropositive individuals. *J. Virol.* **87**, 1477–1490 (2013).
123. Tumino, N. et al. In HIV-positive patients, myeloid-derived suppressor cells induce T-cell anergy by suppressing CD3ζ expression through ELF-1 inhibition. *AIDS* **29**, 2397–2407 (2015).
124. Garg, A. & Spector, S. A. HIV type 1 gp120-induced expansion of myeloid derived suppressor cells is dependent on interleukin 6 and suppresses immunity. *J. Infect. Dis.* **209**, 441–451 (2014).
125. Wang, L. et al. Expansion of myeloid-derived suppressor cells promotes differentiation of regulatory T cells in HIV-1^{+} individuals. *AIDS* **30**, 1521–1531 (2016).
126. Zhang, Z. N. et al. Myeloid-derived suppressor cells associated with disease progression in primary HIV infection: PD-L1 blockade attenuates inhibition. *J. Acquir. Immune Defic. Syndr.* **76**, 200–208 (2017).
127. Tumino, N. et al. Granulocytic myeloid-derived suppressor cells increased in early phases of primary HIV infection depending on TRAIL plasma level. *J. Acquir. Immune Defic. Syndr.* **74**, 575–582 (2017).
128. Nicholson, L. B., Raveney, B. J. & Munder, M. Monocyte dependent regulation of autoimmune inflammation. *Curr. Mol. Med.* **9**, 23–29 (2009).
129. Iwata, Y. et al. Involvement of CD11b^{+} GR-1^{low} cells in autoimmune disorder in MRL-*Fas*^{lpr} mouse. *Clin. Exp. Nephrol.* **14**, 411–417 (2010).
130. Park, M. J. et al. Myeloid-derived suppressor cells induce the expansion of regulatory B cells and ameliorate autoimmunity in the sanroque mouse model of systemic lupus erythematosus. *Arthritis Rheumatol.* **68**, 2717–2727 (2016).
131. Vlachou, K. et al. Elimination of granulocytic myeloid-derived suppressor cells in lupus-prone mice linked to reactive oxygen species-dependent extracellular trap formation. *Arthritis Rheumatol.* **68**, 449–461 (2016).
132. Wu, H. et al. Arginase-1-dependent promotion of TH17 differentiation and disease progression by MDSCs in systemic lupus erythematosus. *Sci. Transl. Med.* **8**, 331ra340 (2016).
133. Zhang, H. et al. Myeloid-derived suppressor cells are proinflammatory and regulate collagen-induced arthritis through manipulating Th17 cell differentiation. *Clin. Immunol.* **157**, 175–186 (2015).
134. Guo, C. et al. Myeloid-derived suppressor cells have a proinflammatory role in the pathogenesis of autoimmune arthritis. *Ann. Rheum. Dis.* **75**, 278–285 (2016).
135. Kurkó, J. et al. Identification of myeloid-derived suppressor cells in the synovial fluid of patients with rheumatoid arthritis: a pilot study. *BMC Musculoskelet. Disord.* **15**, 281 (2014).
136. Egelston, C. et al. Suppression of dendritic cell maturation and T cell proliferation by synovial fluid myeloid cells from mice with autoimmune arthritis. *Arthritis Rheum.* **64**, 3179–3188 (2012).
137. Jiao, Z. et al. Increased circulating myeloid-derived suppressor cells correlated negatively with Th17 cells in patients with rheumatoid arthritis. *Scand. J. Rheumatol.* **42**, 85–90 (2013).
138. Guan, Q. et al. The role and potential therapeutic application of myeloid-derived suppressor cells in TNBS-induced colitis. *J. Leukoc. Biol.* **94**, 803–811 (2013).
139. Kontaki, E. et al. Aberrant function of myeloid-derived suppressor cells (MDSCs) in experimental colitis and in inflammatory bowel disease (IBD) immune responses. *Autoimmunity* **50**, 170–181 (2017).
140. Rader, D. J. Effect of insulin resistance, dyslipidemia, and intra-abdominal adiposity on the development of cardiovascular disease and diabetes mellitus. *Am. J. Med.* **120**, S12–S18 (2007).
141. Renehan, A. G., Roberts, D. L. & Dive, C. Obesity and cancer: pathophysiological and biological mechanisms. *Arch. Physiol. Biochem.* **114**, 71–83 (2008).
142. Yin, B. et al. Myeloid-derived suppressor cells prevent type 1 diabetes in murine models. *J. Immunol.* **185**, 5828–5834 (2010).
143. Xia, S. et al. Gr-1^{+} CD11b^{+} myeloid-derived suppressor cells suppress inflammation and promote insulin sensitivity in obesity. *J. Biol. Chem.* **286**, 23591–23599 (2011).
144. Chen, S. et al. Diminished immune response to vaccinations in obesity: role of myeloid-derived suppressor and other myeloid cells. *Obes. Res. Clin. Pract.* **9**, 35–44 (2015).
145. Bao, Y., Mo, J., Ruan, L. & Li, G. Increased monocytic CD14^{+}HLADR$^{low/-}$ myeloid-derived suppressor cells in obesity. *Mol. Med. Rep.* **11**, 2322–2328 (2015).
146. Quail, D. F. et al. Obesity alters the lung myeloid cell landscape to enhance breast cancer metastasis through IL5 and GM-CSF. *Nat. Cell Biol.* **19**, 974–987 (2017).
147. Okwan-Duodu, D., Umpierrez, G. E., Brawley, O. W. & Diaz, R. Obesity-driven inflammation and cancer risk: role of myeloid derived suppressor cells and alternately activated macrophages. *Am. J. Cancer Res.* **3**, 21–33 (2013).
148. Thomas, D. & Apovian, C. Macrophage functions in lean and obese adipose tissue. *Metabolism* **72**, 120–143 (2017).
149. Lu, H. et al. Macrophages recruited via CCR2 produce insulin-like growth factor-1 to repair acute skeletal muscle injury. *FASEB J.* **25**, 358–369 (2011).
150. Satoh, T. et al. The Jmjd3-Irf4 axis regulates M2 macrophage polarization and host responses against helminth infection. *Nat. Immunol.* **11**, 936–944 (2010).
151. Boutens, L. & Stienstra, R. Adipose tissue macrophages: going off track during obesity. *Diabetologia* **59**, 879–894 (2016).
152. Pirvulescu, M. M. et al. Subendothelial resistin enhances monocyte transmigration in a co-culture of human endothelial and smooth muscle cells by mechanisms involving fractalkine, MCP-1 and activation of TLR4 and Gi/o proteins signaling. *Int. J. Biochem. Cell Biol.* **50**, 29–37 (2014).
153. Galván, G. C. et al. Effects of obesity on the regulation of macrophage population in the prostate tumor microenvironment. *Nutr. Cancer* **69**, 996–1002 (2017).
154. Ghaebi, M. et al. Immune regulatory network in successful pregnancy and reproductive failures. *Biomed. Pharmacother.* **88**, 61–73 (2017).
155. Fainaru, O., Hantisteanu, S. & Hallak, M. Immature myeloid cells accumulate in mouse placenta and promote angiogenesis. *Am. J. Obstet. Gynecol.* **204**, 544.e518–544.e23 (2011).
156. Pan, T. et al. Myeloid-derived suppressor cells are essential for maintaining feto-maternal immunotolerance via STAT3 signaling in mice. *J. Leukoc. Biol.* **100**, 499–511 (2016).
Together with ref. 160, this study demonstrates the role of MDSCs in the maintenance of feto-maternal tolerance.
157. Kang, X. et al. CXCR2-mediated granulocytic myeloid-derived suppressor cells' functional characterization and their role in maternal fetal interface. *DNA Cell Biol.* **35**, 358–365 (2016).
158. Pan, T. et al. 17β-Oestradiol enhances the expansion and activation of myeloid-derived suppressor cells via signal transducer and activator of transcription (STAT)-3 signalling in human pregnancy. *Clin. Exp. Immunol.* **185**, 86–97 (2016).
159. Kang, X. et al. Granulocytic myeloid-derived suppressor cells maintain feto-maternal tolerance by inducing Foxp3 expression in CD4^{+}CD25^{-} T cells by activation of the TGF-β/β-catenin pathway. *Mol. Hum. Reprod.* **22**, 499–511 (2016).
160. Ostrand-Rosenberg, S. et al. Frontline science: myeloid-derived suppressor cells (MDSCs) facilitate maternal-fetal tolerance in mice. *J. Leukoc. Biol.* **101**, 1091–1101 (2017).
Together with ref. 156, this study demonstrates the role of MDSCs in the maintenance of feto-maternal tolerance.
161. Gantt, S., Gervassi, A., Jaspan, H. & Horton, H. The role of myeloid-derived suppressor cells in immune ontogeny. *Front. Immunol.* **5**, 387 (2014).
162. Bartmann, C. et al. CD33^{+}/HLA-DR^{neg} and CD33^{+}/HLA-DR$^{+/-}$ cells: rare populations in the human decidua with characteristics of MDSC. *Am. J. Reprod. Immunol.* **75**, 539–556 (2016).
163. Köstlin, N. et al. Granulocytic myeloid derived suppressor cells expand in human pregnancy and modulate T-cell responses. *Eur. J. Immunol.* **44**, 2582–2591 (2014).
164. Nair, R. R., Sinha, P., Khanna, A. & Singh, K. Reduced myeloid-derived suppressor cells in the blood and endometrium is associated with early miscarriage. *Am. J. Reprod. Immunol.* **73**, 479–486 (2015).
165. Kim, Y. J. et al. Reduced L-arginine level and decreased placental eNOS activity in preeclampsia. *Placenta* **27**, 438–444 (2006).
166. Zhang, Y. et al. Human trophoblast cells induced MDSCs from peripheral blood CD14^{+} myelomonocytic cells via elevated levels of CCL2. *Cell. Mol. Immunol.* **13**, 615–627 (2016).
167. Gervassi, A. et al. Myeloid derived suppressor cells are present at high frequency in neonates and suppress in vitro T cell responses. *PLoS One* **9**, e107816 (2014).
168. Rieber, N. et al. Neutrophilic myeloid-derived suppressor cells in cord blood modulate innate and adaptive immune responses. *Clin. Exp. Immunol.* **174**, 45–52 (2013).
169. Köstlin, N. et al. Granulocytic myeloid-derived suppressor cells from human cord blood modulate T-helper cell response towards an anti-inflammatory phenotype. *Immunology* **152**, 89–101 (2017).
170. Leiber, A. et al. Neonatal myeloid derived suppressor cells show reduced apoptosis and immunosuppressive activity upon infection with *Escherichia coli*. *Eur. J. Immunol.* **47**, 1009–1021 (2017).

171. Heinemann, A. S. et al. In neonates S100A8/S100A9 alarmins prevent the expansion of a specific inflammatory monocyte population promoting septic shock. *FASEB J.* **31**, 1153–1164 (2017).
172. Ulas, T. et al. S100-alarmin-induced innate immune programming protects newborn infants from sepsis. *Nat. Immunol.* **18**, 622–632 (2017).

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Competing interests

The authors declare no competing financial interests.

Additional information