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REVIEW

Recent advances in myeloid-derived suppressor cell biology

Mahmoud Mohammad Yaseen (✉)[1], Nizar Mohammad Abuharfeil[1], Homa Darmani[2], Ammar Daoud[3]

[1]*Department of Biotechnology and Genetic Engineering;* [2]*Department of Applied Biology, Faculty of Science and Arts;* [3]*Department of Internal Medicine, Faculty of Medicine, Jordan University of Science and Technology, Irbid 22110, Jordan*

Abstract **In recent years, studying the role of myeloid-derived suppressor cells (MDSCs) in many pathological inflammatory conditions has become a very active research area. Although the role of MDSCs in cancer is relatively well established, their role in non-cancerous pathological conditions remains in its infancy resulting in much confusion. Our objectives in this review are to address some recent advances in MDSC research in order to minimize such confusion and to provide an insight into their function in the context of other diseases. The following topics will be specifically focused upon: (1) definition and characterization of MDSCs; (2) whether all MDSC populations consist of immature cells; (3) technical issues in MDSC isolation, estimation and characterization; (4) the origin of MDSCs and their anatomical distribution in health and disease; (5) mediators of MDSC expansion and accumulation; (6) factors that determine the expansion of one MDSC population over the other; (7) the Yin and Yang roles of MDSCs. Moreover, the functions of MDSCs will be addressed throughout the text.**

Keywords non-human primates (rhesus macaques); myeloid-derived pro-inflammatory cells (MDPCs); autoimmune disorders; alloimmune responses; pregnancy; mature MDSCs; multiple sclerosis; Yin-Yang law of MDSCs

Introduction

The identification of myeloid-derived suppressor cells (MDSCs) was first achieved in tumor-bearing mice and shortly after in cancer patients. Since then MDSCs have emerged as important regulators of immunity, and this is reflected in the immense research interest during the past decade, with more than 4000 articles related to MDSCs being published. Indeed, in 2019 alone, more than 650 articles were published, indicating that MDSCs have become an attractive research area. Although, the role of these cells has been extensively studied in cancer, in recent years the involvement of MDSCs in different non-cancer inflammatory conditions has also been highlighted. The latter include but are not limited to infectious diseases, autoimmune disorders, sepsis, stress, trauma, wounds/injuries, aging, and organ/tissue transplantation, as well as pregnancy and lactation [1–8]. Since most of our knowledge about MDSCs has stemmed from cancer studies, it will not be surprising to see a particular emphasis on the results obtained from cancer studies throughout the text.

MDSCs are a heterogenous population of innate immune cells of myeloid origin that are best known for their ability to express extremely potent immunosuppressive activity. Once at the site of inflammation, they participate in inhibition of inflammatory responses via different mechanisms. Indeed, MDSC expansion has been highlighted in many inflammatory pathological conditions (Fig. 1) [1–6]. To some extent, such expansion should be considered as a normal immune response to counteract chronic immune activation which could worsen the clinical status if the inflammatory response is not kept under control. On the other hand, uncontrolled expansion and accumulation of MDSCs, in turn, can also worsen the clinical status, indicating that they could be involved in the pathogenesis of certain pathological conditions. For example, in the setting of cancer (which is a good example of a chronic inflammatory condition), expansion of MDSCs result in suppression of immune responses against tumor cells, particularly those mediated by the T cell immune response. This, in turn, creates a suitable environment that facilitates tumor growth and metastasis, both of which are associated with bad clinical outcomes. Since the mechanisms of immune suppression by MDSCs

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Correspondence: Mahmoud Mohammad Yaseen, mmyasin08@ams.just.edu.jo or mahmoudhiv1@yahoo.com

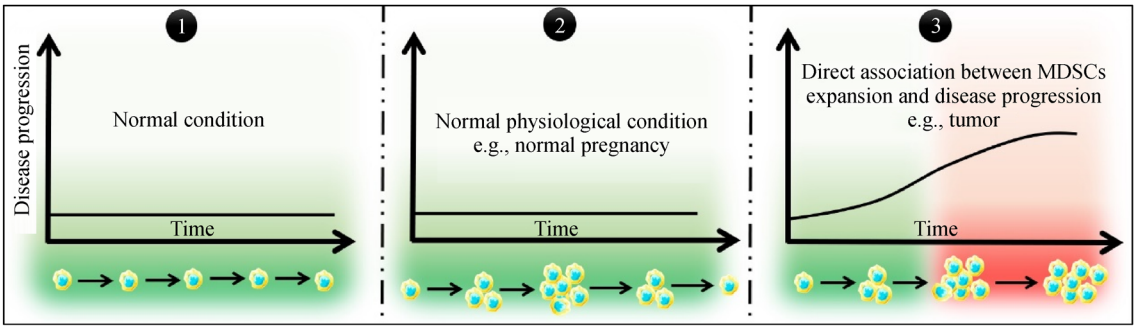

Fig. 1 MDSCs in health and disease. The case number 1 represents healthy subjects without MDSCs expansion. The case number 2 represents a normal physiologic condition, i.e., pregnancy, in which MDSCs expansion occurs during all pregnancy stages and their levels are normalized post-delivery. The case number 3 represents a pathological condition where MDSCs expansion directly correlates with the disease progression.

are out of the scope of this review, we will not discuss them any further.

Recent investigations have also shown that MDSCs could express pro-inflammatory immune responses under certain inflammatory conditions, such as autoimmune disorders [9–11], which in turn could worsen the inflammatory status. This is in contrast to their already established immunosuppressive function by definition. Therefore, we suggest to name these cells as "myeloid-derived pro-inflammatory cells" (MDPCs). Furthermore, MDSCs have always been defined as immature immune suppressor cells of myeloid origin, however, recent findings have indicated that even the immaturity feature of such cells is also debatable. Taken together, these data indicate that the pathological role of MDSCs is more complicated than we envisage, and that the old definition should be reevaluated. Herein, we aim to provide some recent advances in the knowledge about the different biological roles of MDSCs. In particular, we will focus on the properties and origins of MDSCs and their anatomical distribution in health and disease, the technical issues faced in their isolation and characterization, the mediators of MDSC expansion and the factors that determine the expansion of one MDSC population over the other, as well as the Yin and Yang roles of MDSCs.

MDSCs definition and characterization

The term "myeloid-derived suppressor cells" was originally coined in 2007 to differentiate between myeloid and lymphoid immune suppressor cells in cancer patients and to minimize the ambiguity present in the literature about these cells [12]. MDSCs are a morphologically, phenotypically, and functionally heterogeneous population of immature innate immune cells of myeloid origin with potent capabilities to suppress immune responses [13–15]. By definition, MDSCs express common myeloid markers and lack the expression of lymphoid markers. In mice, they express Gr-1 and CD11b (also known as αM-integrin), whereas in humans, they express CD33 and CD11b, and lack expression of maturation markers, such as HLA-DR. MDSCs are subdivided into two main populations according to their morphology and the expression of monocytic (mononuclear monocytic "M-MDSCs") and granulocytic (polymorphonuclear granulocytic "G-MDSCs or PMN-MDSCs") markers. Human M-MDSCs and PMN-MDSCs can be described as $HLA\text{-}DR^{-/low}CD11b^{+}CD33^{+}CD14^{+}CD15^{-}$ and $HLA\text{-}DR^{-}CD11b^{+}CD33^{mid}CD15^{+}CD14^{-}$ bearing cells, respectively, according to the presence of the monocytic marker (CD14) and the granulocytic marker (CD15), as well as the expression level of CD33 marker which is highly expressed on M-MDSCs and intermediately on PMN-MDSCs. Of note, certain markers such as CD66b could also be used to differentiate between human PMN-MDSCs and M-MDSCs. On the other hand, the phenotypes of M-MDSCs and PMN-MDSCs in mice can be described as $CD11b^{+}Ly6C^{high}Ly6G^{-}$ and $CD11b^{+}Ly6C^{low}Ly6G^{+}$, respectively, based on the expression level of Ly6C and Ly6G. Furthermore, a new population of MDSCs with a more immature state has also been proposed recently [14]. These early-stage MDSCs (E-MDSCs) lack the expression of monocytic and granulocytic markers with a $CD33^{+}HLA\text{-}DR^{-}Lin^{-}$ phenotype (Lin includes CD3, CD14, CD15, CD19, and CD56 markers) [14]. It is believed that E-MDSCs could give rise and differentiate to PMN-MDSCs and M-MDSCs [15,16], indicating that such cells could act as precursors for both M-MDSCs and PMN-MDSCs. Highfill *et al.* [17] have also identified a more potent immunosuppressive subset called "MDSC-IL13" in mice. More recently, a new subpopulation of MDSCs was also reported in mice infected with *Staphylococcus aureus* that phenotypically resembles eosinophils, namely

"Eo-MDSCs" [18]. The identification of such new subsets of MDSCs further complicates the picture and opens a new door that could lead to the identification of additional subsets. However, the counterparts of such subsets of MDSCs remains to be determined in humans.

The characterization of MDSCs in mice is of importance, since they are widely considered as a key preclinical model for studying a diverse range of human diseases and used for testing novel therapeutic strategies including vaccines, before the commencement of the clinical phases. However, it must be remembered that significant differences exist in the immune responses of mice and humans, underscoring the need to study other animal models that are much closer to humans than mice, in particular the non-human primates [19–22]. Until recently, mice were the favorite animal model but recently, Zahorchak *et al*. [23] studied MDSCs in rhesus macaques and found that normal M-MDSCs with similar phenotypes ($CD11b^+HLA\text{-}DR^-Lin^-$ or $CD33^+CD14^+HLA\text{-}DR^-Lin^-$) to those isolated from the peripheral blood of healthy individuals [24,25] can be isolated, albeit at very low levels, from peripheral blood mononuclear cells (PBMCs). The primary objective of their study was to mobilize and isolate M-MDSCs from non-human primate PBMCs for use in adoptive cell therapy in the hope of mediating immune tolerance to allografts (organs/tissue transplantation). Zahorchak *et al*. [23] chose to characterize M-MDSCs but not PMN-MDSCs for two major reasons. Firstly, because M-MDSCs are less susceptible to damage from the freezing-thawing process than PMN-MDSCs (discussed later) and secondly due to the compatibility of M-MDSCs with the study objectives, in that M-MDSCs have a positive role in mediating tolerance against organ/tissue transplantation. In a more recent study, Zahorchak *et al*. [26] generated M-MDSCs from rhesus macaque bone marrow and observed that M-MDSC populations can be further subdivided into three sub-populations based on the differential expression of CD11b, CD14, CD33, and CD34 markers. The phenotypes of these sub-populations were as follows: $HLA\text{-}DR^-Lin^-CD14^+CD33^+CD34^+CD11b^+$, $HLA\text{-}DR^-Lin^-CD14^{-/low}CD33^{high}CD34^+CD11b^{-/low}$, and $HLA\text{-}DR^-Lin^-CD14^{high}CD33^{-/low}CD34^{low}CD11b^{high}$. Notably, $HLA\text{-}DR^-Lin^-CD14^{high}CD33^{-/low}CD34^{low}CD11b^{high}$ expressing cells were the most immunosuppressive of the three groups [26]. In 2017, a study on simian immunodeficiency virus (SIV) infected rhesus macaques was conducted to investigate the role of MDSCs in the pathology of SIV infection [27]. This study identified two main MDSC populations in rhesus macaques, namely PMN-MDSCs and M-MDSCs, in different anatomical tissues including the blood, liver, and bone marrow. M-MDSCs in the bone marrow were also subdivided into $CD14^{high}$ and $CD14^{intermediate}$ subpopulations [27]. The important finding from these studies is that MDSC populations could be further subdivided into subpopulations that vary in phenotypes and suppressive functions even within the same host. In 2018, Lin and colleagues conducted a study with a primary objective of characterizing MDSCs in rhesus macaques [28] and in consistence with previous studies on humans and mice, they identified and characterized two main populations of MDSCs, namely, M-MDSCs and PMN-MDSCs. Three surface markers (CD66abce, CD14, and CD33) were used to differentiate between M-MDSCs and PMN-MDSCs in these non-human primates beside the myeloid and maturation markers, namely CD11 and HLA-DR, respectively. Lin and colleagues have shown that M-MDSCs can be described as $CD11^+HLA\text{-}DR^-CD14^+CD66abce^-$ bearing cells, while PMN-MDSCs can be described as $CD11^+CD33^{mid}HLA\text{-}DR^-CD14^-CD66abce^+$ bearing cells [28]. Initially, as expected, these data confirm that MDSC phenotypes in rhesus macaques are much closer to those of humans than mice, especially since CD66b could also be used to differentiate between PMN-MDSCs and M-MDSCs in humans, as previously mentioned. It goes without saying that non-human primates are much closer to humans in immune responses [19], but we still need additional investigations to establish the role of MDSCs in different pathological conditions in this unique animal model. Subsequent comparisons between the results obtained from non-human primates with those obtained from both mouse models and humans are essential because it can guide us to decisively determine which animal model is better for studying the role of MDSCs in the future.

It is worthy to note that there are many other potential markers that could also be used to characterize human MDSCs. The latter include lectin-type oxidized LDL receptor 1 (LOX-1), CD40, CD66b, CD80 (also known as B7.1), CD115 (macrophage-colony stimulating factor (M-CSF) receptor), CD124 (IL-4 receptor α-chain), S100A9, and SPARC (secreted protein acidic and rich in cysteine also known as osteonectin or as basement-membrane protein 40 (BM-40)) [29–31]. It has been established that these markers are expressed by MDSCs, however, none of them can be harnessed to characterize distinct MDSC populations, with an exception to CD66b, and possibly LOX-1 and SPARC [15,29–31]. Both LOX-1 and CD66b can be used to differentiate between PMN-MDSCs and M-MDSCs. Interestingly, unlike CD66b, LOX-1 could be used as a specific marker of PMN-MDSC populations without the need to use other assays to distinguish them from normal neutrophil populations. This is especially advantageous because $LOX\text{-}1^+$ but not $LOX\text{-}1^-$ neutrophils show immunosuppressive activity which seems to fulfill the need to characterize PMN-MDSC populations directly [15,29]. In addition, studies have shown that using this marker, it was possible to quantify PMN-MDSCs from entire neutrophil populations among cancer patients. Similarly, the recently suggested SPARC could also be considered as a potential marker for direct isolation of

MDSCs, particularly PMN-MDSCs, in both humans and mice as reported by Sangaletti and colleagues [31]. However, although the latter study was able to provide evidence that SPARC$^{-/-}$ MDSCs are not immunosuppressive, the data obtained could not confirm that such a marker is exclusively expressed on PMN-MDSCs since the levels of M-MDSCs were very low in the study and additional work is required to confirm these findings.

Finally, an important issue that needs to be mentioned here is that although different isolated MDSC populations share common markers, characterization of MDSCs from different pathological conditions and/or different anatomical sites could necessitate using additional markers. For example, studies on bone marrow-derived MDSCs have shown that additional markers, such as CD34, could be used to differentiate between blood and bone marrow MDSCs [26]. Indeed, immature myeloid suppressive cells expressing CD34 were also detected in the blood of patients with certain types of cancer [32–35], indicating that CD34$^+$ MDSCs could be considered a distinct population [34], which leave the bone marrow as a result of increased myelopoietic output. One could assume that this subset is a precursor for MDSC populations, however, the co-expression of monocytic (CD14$^+$) or granulocytic (CD15$^-$) markers beside CD34 on MDSCs would prove this assumption to be unfounded, unless the presence of CD34$^+$CD14$^-$CD15$^-$ myeloid suppressor cells coincides with the presence of CD34$^+$CD14$^+$CD15$^-$ or CD34$^+$CD14$^-$CD15$^+$ myeloid suppressor cells. Taken together, it can be observed that the heterogeneity of MDSCs is much more complex than is known at present, necessitating additional investigations to further clarify this heterogeneity.

Do all MDSC populations consist of immature cells?

This is still a controversial question that needs to be answered. In fact, early studies have shown that MDSCs were immature myeloid cells, however, more recent studies have concluded that the immature myeloid cell profile and the lack of activation markers may not be sufficient features to describe MDSCs. Therefore, it is important to point out that we need to reevaluate the maturation feature of these cells. This is, in particular, because of several reasons. First, some cells of myeloid origin could lose their activation markers in certain conditions, for example, in response to hypoxia, upon exposure to certain cytokines, or signaling with toll-like receptors (TLR) in a repeated manner [36–39]. Second, even the immature property of MDSCs has recently been debated as a result of detection of activation markers on MDSCs. For example, it has been shown that low-density immunosuppressive CD66b$^+$ neutrophils (PMN-MDSCs) present in the circulation of healthy individuals treated with G-CSF for stem cell mobilization, consist of a mixture of mature activated CD10$^+$ and immature CD10$^-$ PMN-MDSCs populations [40]. Of note, activated low-density immunosuppressive CD10$^+$ neutrophils can also be detected in systemic lupus erythematous (SLE) and psoriasis [41]. Interestingly, it has been concluded that CD10$^+$ can be utilized to distinguish between mature and immature neutrophils isolated from low- and normal-density blood fractions of G-CSF-treated volunteers [40]. Furthermore, a recent study on patients with Hodgkin's lymphoma has reported that most of patients' PMN-MDSCs isolated from the low-density fraction were immunosuppressive mature neutrophils in an activated state [42]. More recently, in head and neck cancer patients, a very potent immunosuppressive subset of mature PMN-MDSCs has also been reported [43]. Indeed, these cells possess even more suppressive activities on T cell proliferation than M-MDSCs and E-MDSCs. In another example, CD80 and CD83 expression on M-MDSCs were also reported in melanoma and breast cancer patients [44,45]. Third, many published studies have called immunosuppressive myeloid cells "with almost the same M-MDSCs and PMN-MDSCs features" as inflammatory monocytes and neutrophils, respectively [46,47]. In addition, even normal cells without these features were also called MDSCs based on their phenotypes. Forth, interesting evidence has emerged that both MDSCs populations could represent monocytes and neutrophils, especially because some studies have indicated that monocytes, CD1a$^+$ dendritic cells, and neutrophils can be reprogrammed and give rise into immunosuppressive cell populations [48–52]. Taken together, these data provide strong evidence that the immature state of MDSCs that used to be included in the old definition of such cells should be reevaluated.

Moreover, a question on whether MDSCs really differ from monocytes and neutrophils has been raised. Gabrilovich and others have answered this question and have clearly shown that MDSCs really do differ from normal or tumor activated monocytes/macrophages and neutrophils in various aspects including function, protein and genomic profiles, phenotype, and biochemical features [13,53]. This indicates that for a cell population to be described as MDSCs, the phenotype profile is not sufficient to be used alone in most cases, rather it should be coupled with other MDSC defining-tests, especially those that measure immunosuppressive activity, unless highly specific markers are revealed/used. Gabrilovich [13] has also concluded that monocytes and neutrophils cannot be easily reprogrammed to a suppressive state similar to that of MDSCs *in vitro* by treatment with pro-inflammatory cytokines, or danger-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) molecules. To some extent, this is challenged

from two points of view. First, different studies have shown that the *in vitro* and *ex vivo* expansion of MDSCs can be achieved either by inducing the normal differentiation of the precursors of MDSCs or reprogramming peripheral mature myeloid cells, such as, monocytes and dendritic cells to M-MDSCs or M-MDSCs-like cells [38,52,54–57], or mature neutrophils into PMN-MDSCs [30,49,58]. Second, studies have demonstrated that MDSCs can be differentiated into mature macrophages and DCs *in vitro* [59,60], indicating that MDSCs include precursors of such mature cells. Although this may hold true in that the *in vitro* activated MDSCs could express less immunosuppressive activity than those isolated from inflamed tissues such as tumor sites, it must be remembered, however, that this is similar to what already has been observed for MDSCs *in vivo*, which are distant from the site of inflammation, i.e., tumor microenvironment. In this regard, Haverkamp *et al.* [61] have shown that MDSCs isolated from the liver or spleen are not as immunosuppressive as those in the inflammatory microenvironment, which further challenges the Gabrilovich view. In sum, MDSC populations could comprise a mixture of immature and mature myeloid cells with suppressive capabilities even within a single host. Nonetheless, to remove the confusion in this regard, the previously-mentioned potential markers could be used for this purpose. Further, uncovering new highly-specific markers could simplify the characterization of such cells into distinct functional and phenotypical populations.

Technical issues in MDSC isolation, estimation, and characterization

An important issue to be considered in this context is the "avoidable" technical factors that could accompany and influence the isolation, estimation/quantification, and characterization of MDSCs, especially because MDSCs are very sensitive to some manipulations. For instance, delay in sample processing and freezing of whole blood or PBMC samples have been demonstrated to exert negative effects on viability of MDSCs. Although PMN-MDSCs can tolerate relatively longer storage times than M-MDSCs (24 h vs. less than 4 h, respectively, following blood withdrawal), they are still much more sensitive to the freezing/thawing process than M-MDSCs [27,62,63]. As such, investigators have to avoid, or at least limit, the use of cryopreserved samples, as much as possible, to avoid false results, and if the use of cryopreserved samples cannot be avoided, they should mention this in the discussion of their study.

Another important point is that although polymorphonuclear MDSCs (i.e., PMN-MDSCs) are similar to neutrophils in morphology, investigations have demonstrated that they should be isolated from the low-density gradient fraction of human PBMC samples (mononuclear cell fraction), a procedure that is not carried out for isolation of normal polymorphonuclear immune cells which include both normal and high density neutrophils [29,64,65]. Thus, for enhanced isolation and estimation of PMN-MDSC populations in blood samples in normal and pathological conditions, the high-density gradient fraction (polymorphonuclear "neutrophils" cell fraction) should not be the target. Indeed, the similarities in phenotype between MDSC populations and their cognate normal monocytes and neutrophils can affect the characterization of MDSCs [46,47,53]. To overcome these problems, the use of whole blood, as suggested by Apodaca and colleagues [66], as well as, the identification of highly specific markers that are exclusively expressed on each MDSC population, but not on the normal monocytes and granulocytes (e.g., LOX-1 marker for PMN-MDSCs), can help evade the need for density gradients and lead to a better isolation and characterization of MDSC populations [29]. A similar candidate marker is also needed for definitive identification of M-MDSCs, since the identification of M-MDSCs based on the already available surface phenotyping markers often results in a mixture of monocytes/M-MDSC populations. Until achieving this goal, investigators have to use assays that at least measure the immunosuppressive activity besides the cell surface phenotyping, so that we can differentiate between suppressive myeloid cells (MDSCs), non-suppressive mature granulocytes and agranulocytes, in particular, the M-MDSC population and normal monocytes.

Apodaca *et al.* [66], very recently, have comprehensively assessed the factors that could significantly affect quantification of MDSCs in blood samples at different stages during the process of isolation and characterization of MDSCs including the: (1) target sample (whole blood vs. PBMC samples), (2) collection tube types (K_2EDTA and Na^+ heparin), (3) time elapsed between venipuncture and antibody labeling (i.e., processing the sample as soon as possible after blood collection or after 4, 8, 24 h), and (4) temperature (i.e., room temperature or refrigerator at 4 or 8 °C) at which samples are maintained until antibody labeling before flow cytometry analyses is carried out, as well as, (5) the analytical step of "flow cytometry gating" especially for those using complex panels that require multiple sub-setting steps [66]. Initially, in contrast to the results of Flörcken *et al.* [67] who observed no difference in MDSC numbers after processing whole blood vs. PBMC, Apodaca *et al.* [66] have reported that using whole blood yields more accurate results than using PBMC samples. In the context of collection tubes, they have shown that there was a comparable difference in results (i.e., total MDSCs and M-MDSC levels) obtained using K_2EDTA and Na^+ heparin collection tubes with a positive trend to use K_2EDTA tubes. Consistent with the results of Flörcken *et al.* [67], Apodaca *et al.* [66] have shown that

the time elapsed until the sample processing occurs is also a critical factor that significantly affects the quantification of MDSCs. Indeed, sample processing as soon as possible after blood collection yielded much better results than after storing samples either at room temperature or at 4 or 8 °C for 24 h. Interestingly, processing the samples upon storage at 4 °C after 4 or 8 h, but not after 24 h, was shown to ameliorate the time-dependent effect. Finally, the gating step is also very critical, since small changes in how to define positive and negative populations could significantly impact the results, particularly, for those using complex panels that require multiple sub-setting steps to yield the ultimate results.

Finally, it is of importance to point out to the fact that studies addressing the technical factors in MDSC research are limited, and we, therefore, encourage researchers to conduct more investigations to further clarify and determine such factors that could affect MDSC isolation, quantification, and characterization of both blood and other tissue samples, such as the liver, lymphatic tissues, and/or tumor/inflamed sites. In parallel, as much as possible, we need solutions that prevent, or at least minimize, the occurrence of technical errors in the future.

On the origin of MDSCs and their anatomical distribution in health and disease

By definition — undoubtedly — all MDSC populations are of myeloid origin, and thus we can conclude that the same scenario that governs the differentiation of myeloid cells from myeloid progenitors/precursors during myelopoiesis will govern the differentiation of MDSCs as well. Under normal (steady-state) conditions, myelopoiesis is a highly coordinated and regulated process in which hematopoietic stem cells are transited to myeloid precursors (immature myeloid cells) that rapidly undergo through the differentiation process, in a step-wise manner, into terminally differentiated mature myeloid cells (i.e., granulocytes: neutrophils, eosinophils, and basophils; and agranulocytes: monocytes and dendritic cells) in the bone marrow before being released to the peripheral tissues [68,69]. This process is essential to maintain the physiologic levels of circulating granulocytes and agranulocytes and is under the control of growth factors and cytokines. Only a very small proportion of immature myeloid cells migrate outside the bone marrow to the periphery before being fully differentiated. In normal mice, it has been shown that MDSCs which express Gr-1 and CD11b comprise about 20%–30% of the total cells in the bone marrow [70]. The number of MDSCs in other tissues such as liver, spleen, and lymph nodes of normal mice reaches up to 5%, 4%, and less than 1%, respectively [70–72]. In non-human primates, Zahorchak *et al.* [23] reported that M-MDSCs account for only 2.1% ± 1.7% of normal Rhesus macaque $Lin^{-}HLA\text{-}DR^{-}$ PBMC. Sui *et al.* [27] were the first group that investigated the distribution of MDSCs in many anatomical sites of normal and simian immunodeficiency virus (SIV) infected Rhesus macaques. They observed that normal Rhesus macaques had a very low frequency (less than 0.5%) of MDSCs in PBMC samples (0.09% ± 0.02% and 0.20% ± 0.04% for M-MDSCs and PMN-MDSCs, respectively), and similarly there was also a low frequency (less than 2%) of MDSCs in liver tissues. In contrast, MDSCs accounted for more than 20% of the bone marrow cells (14.5% ± 1.3% and 7.7% ± 0.6% for M-MDSCs and PMN-MDSCs, respectively). In humans, peripheral blood of healthy individuals contains only about 0.5% of immature myeloid cells of the total peripheral blood immune cells [73,74]. Recently, MDSCs were also isolated from breast milk cells of normal breastfeeding mothers of healthy term infants [75]. Interestingly, the levels of PMN-MDSCs in breast milk were about 20-fold higher than that of peripheral blood [75], whereas the breast milk M-MDSCs were much lower in number than that in peripheral blood. Although some studies have isolated MDSCs from bone marrow of healthy individuals, quantification of such cells was out of the scope of these studies [76]. To the best of our knowledge, MDSCs were not quantified in the bone marrow of healthy humans and, if present, the data cannot be generalized because of the small sample size and inconsistency in results [77,78]. Indeed, the main reason behind the absence of such data in healthy subjects is referred to the invasiveness of bone marrow aspiration, making such isolation method clinically undesirable. Similar to the bone marrow, there is a lack of available data about the distribution of MDSCs in the spleen, liver, or lymphatic tissues of healthy humans. Based on these data, we can say that the bone marrow is considered to be the reservoir of MDSCs under normal conditions, at least in animal models, with some conditional exceptions in humans. The latter is seen during a healthy pregnancy (i.e., in mothers and their embryos) and also during lactation in breastfeeding mothers (i.e., in milk) [75], and we could postulate that these examples are the only normal physiologic conditions where MDSCs are expanding and accumulating in maternal and fetal organisms for the purpose of achieving maternal-fetal tolerance (discussed later). In other words, to our knowledge, these are the only normal physiologic conditions where MDSCs are naturally (without human intervention, e.g., using certain drugs) expanded and able to express positive impacts. Although it could be argued that MDSC expansion and accumulation in other physiologic conditions such as aging also occur in both humans and mice, however their accumulation is undesired, especially because it is associated with unwanted consequences [79–81]. In addition, some members of the scientific community are now regarding aging as a disorder (pathological condition) rather than a normal condition [81–83]. Indeed, the quantification and

characterization of MDSCs in the bone marrow and other lymphatic and non-lymphatic tissues of healthy subjects of different ages in both genders and comparing them to nonhealthy conditions may enhance our understanding of their functions in physiologic and pathologic conditions, and thus may enhance treatment interventions of pathologic conditions.

On the other hand, in the setting of pathological conditions, especially those with chronic inflammatory responses such as cancer, chronic infections, and certain autoimmune disorders, MDSCs can be detected at very high levels in the bone marrow and peripheral tissues (e.g., spleen, liver, lymph nodes, and blood circulation), as well as within the inflammation sites, especially as the disease progresses [70–72,84–93] (Fig. 1). For example, in many tumor mice models, a several-fold increase in the number of MDSCs in the spleen was reported [94–96]. Similarly, an up to 10-fold increase in the number of MDSCs in peripheral blood was reported in humans with different cancer types [73,84–86]. In another example, Delano *et al*. [93] reported up to 3-fold and 10 to 20-fold increase in the number of MDSCs in the bone marrow and spleen of late septic mice, respectively. Similarly, Brudecki *et al*. [88] reported that septic mice experience at least a 3-fold increase in the number of MDSCs in the bone marrow (up to 88% in septic and 30% in normal mice). In other words, MDSC expansion is triggered in certain pathological but not in normal conditions, with some exceptions as seen for example in pregnancy (as aforementioned and will be discussed later). This raises a major question "on the origin of such expansion in abnormal conditions" in terms of whether it results from the differentiation of myeloid precursors, or from reprogramming of terminally differentiated granulocytes and agranulocytes, or both. Generally speaking, there is no doubt that there is an increased body demand for myeloid cells in response to the development of certain pathological conditions, e.g., cancer and infections, and/or as a result of their idiopathic depletion in peripheral tissues inducing "emergency myelopoiesis" [69], a process by which hematopoiesis is triggered and directed to the myeloid over lymphoid lineage in the bone marrow to such a degree that meets the increased body demand to myeloid cells in the periphery. This process depends on the microenvironment triggering factors such as hematopoietic growth factors (mainly granulocyte/macrophage-CSF (GM-CSF), granulocyte-CSF (G-CSF), and macrophage-CSF (M-CSF)) in addition to other factors that govern the differentiation line. As a result of this increase in hematopoietic output, higher levels of immature myeloid cells will be found inside and outside the bone marrow, which is logically expected. However, whether the expansion of MDSCs in the setting of pathological conditions occurs exclusively as a result of triggering myelopoiesis in the bone marrow only or not remains a debatable issue. In recent years, increased evidence suggests that MDSC expansion could also be triggered outside the bone marrow in lymphatic tissues in a process called extramedullary myelopoiesis, which mainly occurs in spleen. It could also occur as a result of either activating the differentiation of immature myeloid cells (i.e., MDSC progenitors) present in peripheral tissues into MDSCs, or reprograming of mature myeloid immune cells (i.e., monocytes and neutrophils) to become less mature [97], or they could still mature as they are, but gain immunosuppressive activities. For example, it has been shown that monocytes can be reprogramed to M-MDSCs in sepsis and breast cancer [44]. Interestingly, other studies have also revealed the possibility of M-MDSCs differentiating into PMN-MDSCs [98]. An important point to be mentioned here is that all adult myeloid cells are generated from bone marrow-derived precursors upon differentiation of hematopoietic stem cells, with two exceptions namely tissue macrophages, and resident mast cells [69]. This is consistent with the notion that all MDSCs isolated from different anatomical structures (e.g., bone marrow, spleen, peripheral blood, or tumor tissues) share a similar phenotype, indicating that they could share a common ancestor. Based on these notions, we can say that the anatomical structure/site where MDSC expansion occurs in the setting of pathological conditions is an arguable issue, but the question of whether they have originated in tissues other than the bone marrow should not be an arguable issue anymore. However, in certain circumstances some exceptions are observed, for example, in chronic SIV infection MDSCs expand in peripheral blood while dramatically decrease in the bone marrow [27]. Taken together, recent evidence suggests that MDSC expansion is not exclusive to the expansion of immature myeloid cells in the bone marrow via myelopoiesis. Indeed, MDSC expansion also involves extramedullary myelopoiesis in lymphatic tissues and reprograming of mature myelocytes to become MDSCs or MDSC-like cells in peripheral tissues. In addition, the aforementioned evidence about the notion that MDSC populations comprise a mixture of mature and immature myeloid suppressor cells supports this idea (Fig. 2).

Mediators of MDSC expansion and accumulation

One important issue to be addressed also in this regard is to understand the factors and mechanisms that mediate the expansion and accumulation of MDSCs. MDSCs expansion is a multifactorial process which heavily depends on the pathological condition. Condamine and Gabrilovich [99–101] have generalized a model describing this process by proposing a two-signal model that only works in the setting of chronic (with persistent "prolonged duration of" inflammatory signals of weaker strength) but not in the

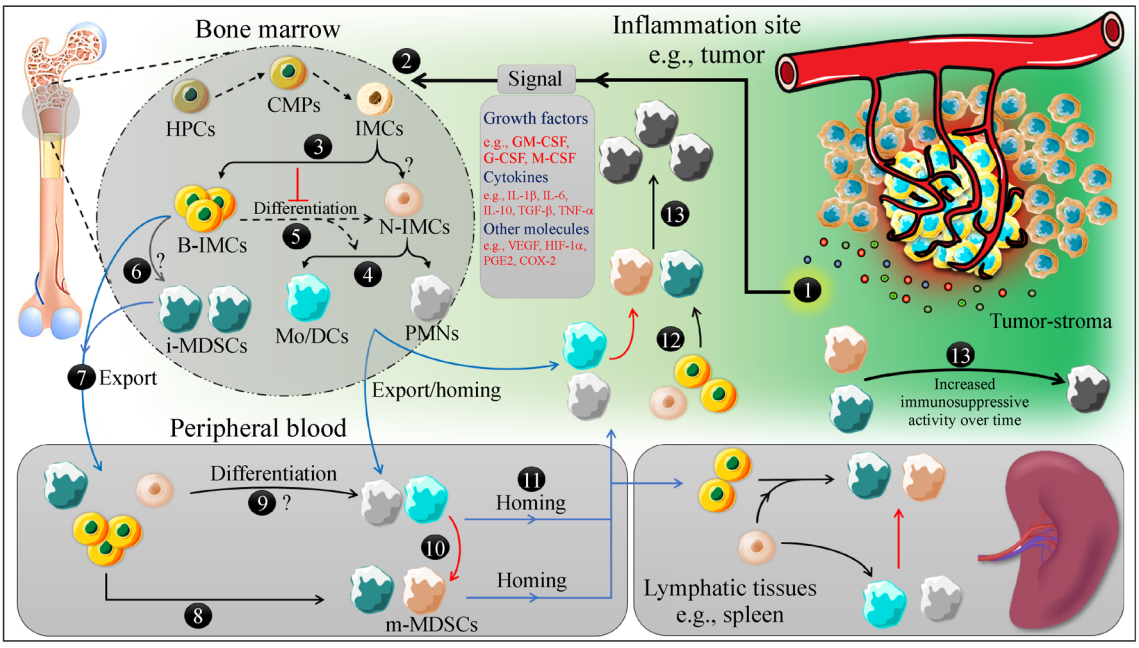

Fig. 2 Expansion of MDSCs during inflammation (e.g., cancer). (1) Produced molecules by tumor/stroma cells initiates (2) a signal that trigger emergency myelopoiesis in which hematopoietic progenitor cells (HPCs) transit to common myeloid progenitors (CMPs). These CMPs continue the differentiation process to immature myeloid cells (IMCs). (3) Some of them will be able to continue the differentiation process normally (the so-called normal-IMC (N-IMC)) to generated mature monocytes/dendritic cells (Mo/DCs) and polymorphonuclear neutrophils (PMNs) in the bone marrow. (4) Then these cells can be released to periphery (blood circulation and tissues). (5) The other portion of IMCs cannot continue their normal differentiation to Mo/DCs or PMNs, since their differentiation is blocked at this immature stage (the so-called blocked-IMC (B-IMC)) in response to tumor/inflammation signal. (6) These cells could acquire immunosuppressive activity signal so that we called them immature-myeloid derived suppressor cells (immature-MDSCs (i-MDSCs)). (7) As the hematopoietic output is increased, releasing (exporting) both the B-IMCs and N-IMCs to peripheral tissues is normally expected. Once outside the bone marrow, (8) blood B-IMCs could acquire suppressive activity and become i-MDSCs or are recruited to the inflammation sites and/or lymphatic tissues (11). On the other hand, (9) N-IMC could be differentiated to mature cells or recruited to the lymphatic tissues and inflammation sites (11). Furthermore, (10) peripheral blood PMNs and Mo/DCs could be reprogrammed to either i-MDSCs or gain immunosuppressive activity while remain in their mature state, so that we call them mature-MDSCs (m-MDSCs). Alternatively, PMNs and Mo/DCs are recruited to the site of inflammation where they could be reprogrammed to i-MDSCs or m-MDSCs. (12) A similar scenario occurs for B-IMC and N-IMC upon recruitment to lymphatic tissues. Importantly, at the inflammation site, (13) the recruited MDSCs (i-MDSCs and m-MDSCs) to the inflammation site (e.g., tumor) become more suppressive over time as they exposed to tumor-stroma cells and their byproducts. Red arrows, reprogramming; blue arrows, export/homing.

acute (with temporary "short duration of" inflammatory signals of stronger strength) inflammatory conditions. In this model, they have shown that for MDSCs to accumulate, a combination of two partially overlapping groups of regulatory factors called first and second signals should be simultaneously activated. The first signal induces the differentiation of myelocytes while retaining the differentiation process at the immature stage. The second signal potentiates the activation of immunosuppressive activity of such cells. At the molecular level, there are several transcription factors and signaling pathways. These include signal transducer and activator of transcription (STAT3), interferon related factor-8 (IRF-8), CCAAT/enhancer binding protein-β (C/EBPβ), cyclic adenosine 3′,5′-monophosphate/mitogen-activated protein kinase (cAMP/MAPK), and retinoblastoma protein 1 (RB1) which includes p105, p107, and p130. The latter are not transcription factors, instead they interact with certain transcription factors such as the E2-factor and cause repression. Immature myeloid cells, therefore, upon activation with different cytokines and/or interaction with specific ligands or other molecules (e.g., growth factors (GM-CSF, G-CSF, M-CSF), IL-6, Notch ligands, and adenosine), differentiate from their progenitors/precursors. On the other hand, MDSCs during this process gain their suppressive activity upon interaction with different cytokines such as IFN-γ, IL-1β, IL-6, IL-4/IL-13, tumor-necrosis factor (TNF-α) or other molecules such as TLRs, and prostaglandin E2 (PGE2) that activate specific cellular signaling pathway(s) (e.g., STAT1, STAT3, STAT6, cyclooxygenase (COX), and NF-κB) depending on their interaction with the corresponding receptor(s) on the

surface of these cells (reviewed in References [100,102]).

The model presented by Condamine and Gabrilovich in 2011, describes the processes that govern MDSC expansion and accumulation [99]. However, recent advances show that this model is still a premature model and can only describe the process partially. This is especially because the expansion and accumulation of MDSCs according to this model does not occur in acute inflammatory settings, as mentioned previously. This contradicts the results of recent investigations which show that MDSC expansion occurs in response to acute/temporary inflammatory signal(s), as seen in response to acute-phase protein "C-reactive protein" and upon vaccination, as well as, in response to tolerogenic treatment for organ/tissue transplantation [28,74,103]. Furthermore, recent advances that are mentioned earlier in the text regarding the maturation state of MDSCs (i.e., the presence of mature MDSCs) debate the first signal of this model in that the differentiation of myeloid cells is induced while their differentiation is blocked at the immature status. Indeed, this does not mean that we exclude this mechanistic way by which MDSCs are generated. Instead we believe it is, at least in part, one of the mechanistic ways involved in MDSC generation (Fig. 2).

Factors that determine the expansion of one MDSCs population over the other

The simultaneous expansion of both MDSC populations can be observed in different pathological conditions, however, the expansion of one population over the other is also observed. For instance, several studies have shown that PMN-MDSCs represent the predominant immunosuppressive population with about 80% or even more of the total MDSC populations present in blood and at the tumor site(s) of most forms of cancer [13,43,100,104]. Activation of MDSCs through certain transcription factors and signaling pathways was shown to direct/shift the cell differentiation toward either M-MDSCs or PMN-MDSCs. For example, inhibition of STAT3 in tumor cells has been shown to decrease PMN-MDSC differentiation, while retaining the levels of M-MDSCs unchanged or sometimes increased [105,106]. In another example, studies on mice with fibrosarcoma have shown that C/EBPβ deficiency can affect the differentiation of M-MDSCs [107]. It is worthy to note that C/EBPβ, which belongs to the basic-region-leucine zipper transcriptional factor family, is also an essential regulator of the immunosuppressive activity of MDSCs, since it regulates the expression of inducible nitric oxide synthase (NOS2) and arginase (ARG1) [108]. RB1, which is a member of retinoblastoma protein (RB), was shown to play a critical role in the differentiation of MDSCs in both humans and mice [109], where the skewed differentiation of M-MDSCs, unlike PMN-MDSCs, is favored in the presence of high levels of RB1 [110]. Still, a decreased level of PMN-MDSCs at the tumor sites of mice with Lewis lung carcinoma as a result of decreased adenosine receptors, i.e., A2b, was also observed [111]. Downregulation of IRF8 is particularly associated with PMN-MDSC expansion [112–115]. Deletion of nuclear factor I-A (NFIA), an integral transcriptional component of myeloid differentiation in myeloid cells, blocks the expansion of MDSCs during sepsis [116]. Recently, NFIA was also revealed to be associated with the immunosuppression function of PMN-MDSCs [117]. Inhibition of NFIA is known to guide the differentiation toward granulopoiesis [118], yet whether it participates in PMN-MDSC accumulation over M-MDSCs remains to be determined. Likewise, the long noncoding RNA plasmacytoma variant translocation 1 (lncRNA Pvt1) has also been demonstrated to be involved in regulating PMN-MDSC immunosuppressive function. Although, the level of expression of IncRNA Pvt1 is thought to be directly associated with PMN-MDSC expansion in tumor tissues [119], additional investigations are needed to determine whether it is involved in PMN-MDSCs expansion or not. Hypoxia-inducible factor-1 α (HIF-1α), which is a subunit of a heterodimeric transcription factor HIF-1 consisting of both HIF-1α and HIF-1β, was responsible for the elevation of this long noncoding RNA under hypoxic condition, indicating that HIF-1 could have an indirect role in mediation of PMN-MDSCs expansion.

Taken together, these data show that transcription factors are extremely important in expansion of one MDSC population over the other. However, it is essential to point out that signaling pathways and activation of transcription factors are determined as a consequence of MDSC interaction with molecules and/or cells within the inflammatory microenvironment, which, in turn, determines the differentiation fate of such cells. Therefore, the microenvironment could be considered the real driving force behind this process. However, additional investigations are needed to further clarify the factors involved in expansion of one subset over the other.

The Yin and Yang roles of MDSCs

The role of MDSCs in cancer and infection

As discussed earlier, most of our knowledge about MDSCs comes from cancer studies, yet surprisingly, until now there is no single indication that could show any beneficial role of the expansion of such cells in the setting of cancer [120]. Rather, it is generally agreed that such expansion is directly associated with the disease progression and tumor burden in cancer patients and animal models bearing different types of tumors. In recent years, MDSCs have become an attractive research area in which different

pathological and non-pathological conditions have been included. In the setting of non-cancer studies, expansion of MDSCs was also observed in different microbial infections including: parasitic infections with *Trypanosoma cruzi*, *Toxoplasma gondii*, and *Leishmania major*; bacterial infections with *Listeria monocytogenes* and *Porphyromonas gingivalis*; and fungal infection with *Candida albicans* [46,87,121–127]. Furthermore, studies on mice and humans have shown MDSC expansion during different viral infections such as influenza virus, hepatitis C virus (HCV) and human immunodeficiency virus (HIV) [91,92,128,129]. Unfortunately, as expected, the expansion of MDSCs during these pathological conditions was not associated with any beneficial effects in the terms of controlling disease progression, rather, it was associated with disease progression, supporting the notion that MDSCs are bad, i.e., MDSCs have a "Yin" role in such conditions.

The role of MDSCs in autoimmune and alloimmune responses

On the other hand, immune activation downregulation is very important for both the autoimmune disorders and alloimmune responses to allografts (graft-rejection). Perhaps, this could shed light on the possibility that MDSCs might have a good "Yang" role in these conditions, since they are potent immunosuppressive cells. On this basis, the role of MDSCs in alloimmune responses and autoimmune disorders such as inflammatory bowel disease (IBD), type 1 diabetes (T1D), multiple sclerosis (MS), rheumatoid arthritis (RA), autoimmune hepatitis (AH), alopecia areata (AA), and systemic lupus erythematosus (SLE) has started to be investigated in recent years [130–132]. Generally speaking, autoimmune disorders are associated with a remarkable increase in the activity of immune (inflammatory) responses against certain self-antigens. Therefore, downregulating these responses is indeed a rational way to restore immune-tolerance to self-antigens and to contain inflammation, both of which would result in reversing the pathological immune activation to a normal or semi-normal state, or at least maintaining the inflammatory process under control [133–140]. Similarly, alloimmune responses are inflammatory responses triggered in the recipient patient to foreign (non-self-antigens) grafts (organ/tissue) that consequently result in graft-rejection. Therefore, downregulating immune responses is essential for the success of organ/tissue transplantation (preventing allograft rejection) [141,142].

Some reports indicate that MDSCs could also have a "Yang" role based on initial results obtained from *in vitro* and *in vivo* (animal models) studies on both autoimmune disorders, as well as, immune responses to allografts. In the context of organ/tissue transplantation, to date, the role of MDSCs in prevention of allografts rejection have been reported to be generally consistent, in that they have a good "Yang" role. Taking into account that MDSCs are recruited to the allografts upon adoptive transfer or upon their expansion as a result of the immunosuppressant treatments (tolerogenic treatments) given before the transplantation, suggests that such cells could be considered as a potential therapeutic approach for downregulating immune activation and mediating graft-host tolerance upon transplantation (for more details see References [7,132,143–148]). Of note, these cells are not naturally (i.e., without human intervention) expanded upon organ/tissue transplantation [7,147,148], and thus cannot be described as good cells by themselves, simply because mediating tolerance to a foreign transplant (non-self-organ/tissue) is considered to be an abnormal condition if human intervention was not involved. Furthermore, adoptively transferred MDSCs that fail to be recruited to the site of the allograft fail to protect these allografts from the host immune responses [132].

On the other hand, as indicated earlier, the role of MDSCs in autoimmune disorders could be beneficial. In theory, this is true, but it could be argued that if the regulatory immune cells including MDSCs are naturally expanded and accumulated in autoimmune disorders, they may be without any beneficial outcomes [9–11]. If this is the case, there are two plausible possibilities to explain such events: first, these expanded MDSCs are functionally defective, i.e., they have no or at least have suboptimal immunosuppressive capabilities which could be due to intrinsic or extrinsic defects. This is important especially because the loss of MDSC suppressive function makes them unable to fulfill their anticipated jobs (i.e., immune suppression) [149]. Second, they could be functionally intact, i.e., they are immunosuppressive, but they cannot be recruited to the site of inflammation upon expansion in blood circulation. The latter, could be due to the downregulation of expression of chemoattractant chemokines in the inflammatory microenvironments or downregulation of the expression of certain chemokine ligands on MDSC surfaces that subvert their homing. This explains the extreme importance of the presence of chemotactic markers on MDSCs for the success of adoptively transferred MDSCs to downregulate inflammatory responses against allografts. Indeed, $CCR2^{-/-}$ MDSCs failed to protect allografts from the recipient immune responses because they failed to be recruited to the site of inflammation (allograft) [132]. Furthermore, if the disease progression (inflammation markers) in an autoimmune disorder directly correlates with the expansion and accumulation of MDSCs, then we could postulate that these cells could behave like pro-inflammatory cells rather than anti-inflammatory cells and that's why we proposed to call them MDPCs as mentioned earlier (Fig. 3). Surprisingly, this is exactly what has been recently documented by many studies [9–11]. Thus, if MDSCs are not "naturally" expanded in autoimmune conditions, then mediating their

expansion *in vivo* using certain drugs and/or cytokines/growth factors, or alternatively, adoptive MDSC transfer upon activation and expansion *in vitro* will be a rational therapeutic approach in this case (Fig. 3).

The Yin-Yang law of MDSCs

One important note that we should be aware of, is that there is a critical difference between pathologically-activated/expanded and normally-activated/expanded MDSCs. As such, we can employ this information, in theory, to solve the perplexing results addressing the "Yin and Yang roles" of such cells. Although the expansion of MDSCs in an inflammatory condition is considered a normal immune response to contain that inflammation, still the outcome of such expansion will determine whether it is beneficial (Yang) or not (Yin). According to our understanding of the recent advances in MDSC research and upon extrapolating the results, we can say that the natural expansion of MDSCs under abnormal pathological conditions is always "Bad." This is due to the fact that they contribute to the pathogenesis of the pathological condition one way or another, or at least, there is no association with better clinical outcomes when such cells were identified and quantified (as seen in cancer, infections, stress, sepsis, etc.). On the contrary, the natural expansion of such cells under normal physiologic conditions is "Good." For example, the number of PMN-MDSCs was shown to be drastically expanded in healthy pregnant women during all pregnancy stages when compared to non-pregnant women as reported by Köstlin and coworkers [150]. Furthermore, the number of M-MDSCs was shown to be expanded in the first trimester when compared to the third trimester indicating that M-MDSCs in particular could play an important role in the implantation process [151]. This is also supported by the notion that a reduction of such cells in the peripheral blood and endometrium is observed in early miscarriage outcomes [151]. The failure of *in vitro*-fertilization (IVF) was also shown to be, at least in part, as a result of a reduction in the number of PMN-MDSCs in the patients [152]. Indeed, such immunosuppression activity is essential to protect the fetus from the maternal immune responses and to achieve mother-fetal tolerance [2,3]. Nonetheless, one could argue against this by taking into account the results of Zhang *et al.* [153] who showed that elevated numbers of PMN-MDSCs is observed in patients with endometriosis which is an inflammatory condition that affects women in the reproductive age and often leads to infertility. Importantly, Zhang *et al.* [153] have also demonstrated that a marked reduction in endometrial lesions can be achieved by depleting PMN-MDSCs in mice. At first glance, there seems to be a

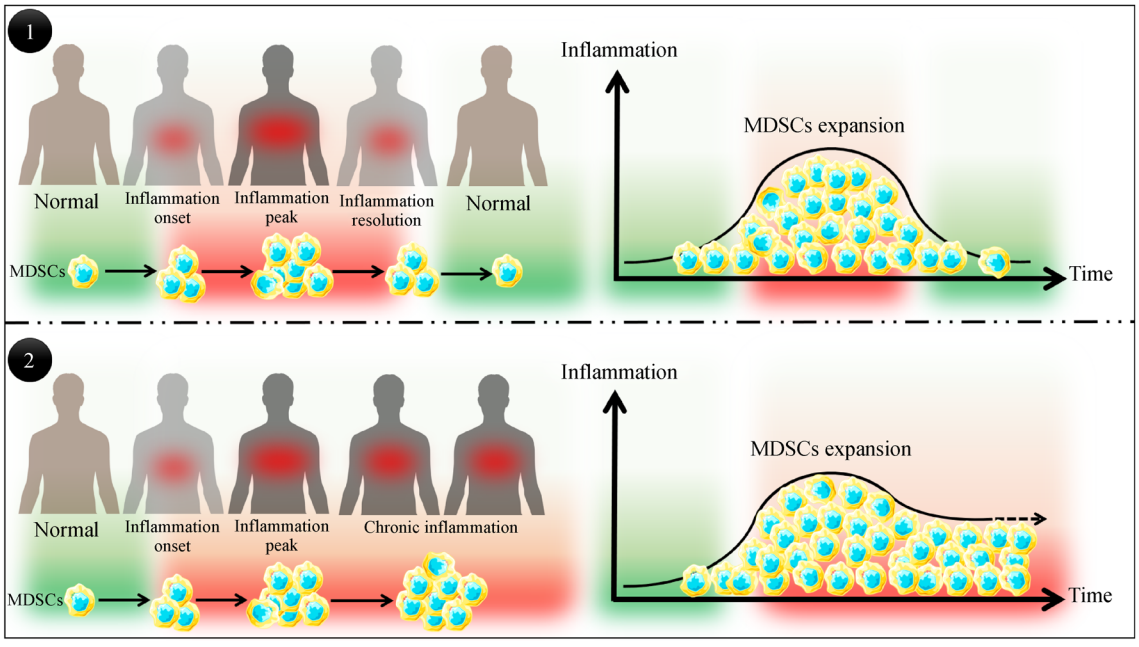

Fig. 3 Yin and Yang faces of MDSCs. Natural (without human intervention) MDSCs expansion is considered to be beneficial (Yang face) only if it blunted the inflammation process that in turn consequently results in better clinical outcomes (disease resolution) and their levels returned to the normal level before the inflammation onset started, as seen in the case 1. Otherwise, if the natural expansion of MDSCs is not associated with inflammation resolution, rather, the inflammation continues, then these cells are considered to be directly associated with the disease progression, or could be considered to be pro-inflammatory cells, indicating that they have a Yin face, as seen in the case 2.

contradiction in their results as illustrated by Budhwar and colleagues [120], yet, we would say this is not a plausible argument if the following notes are taken into consideration: (1) the elevated count of PMN-MDSCs is normally reported in healthy pregnant women but not in healthy non-pregnant women, (2) unlike pregnancy, which is a normal physiologic condition that is associated with different normal changes that can only be observed in pregnant females, endometriosis is a pathological condition where an elevation in the number of PMN-MDSCs in non-pregnant women is observed. In other words, reduction of PMN-MDSCs in pregnant women is an abnormal condition, as it is the case with PMN-MDSC elevation in endometriosis in non-pregnant women. From this point of view, one could suggest mediating the expansion of PMN-MDSCs as a therapeutic strategy for pregnant women with reduced PMN-MDSC numbers. Similarly, targeting PMN-MDSCs for depletion could be suggested to be a therapeutic strategy for endometriosis. Hence, when talking about MDSCs, investigators have to separate the pathological from the non-pathological conditions. More importantly, they have to consider this issue when addressing therapeutic strategies, i.e., harnessing such cells to control certain inflammatory conditions by inducing their expansion *in vivo* therapeutically (using certain drugs or molecules) or via adoptive transfer of *in vitro* activated and expanded MDSCs. As such, MDSCs could have a "Yang" role only if human intervention is included into the equation.

From this point of view, the "Yang" role of MDSCs is indeed conditional, meaning that we consider it only if these cells meet the criteria to be employed as a therapeutic tool to contain inflammation in a specific pathological condition, such as autoimmune disorders and organ/tissue transplantation allografts. In other words, mediating their expansion therapeutically or adoptive transfer of MDSCs to certain inflammatory conditions in humans is considered to be a rational therapeutic strategy only when: (1) these cells are not already expanded in the recipient patients, or at least are not expanded at the site of inflammation, (2) the immunosuppressive effects mediated by MDSCs *in vitro* and/or *in vivo* (i.e., animal models) should be associated with remarkable beneficial outcomes, otherwise such adoptive transfer will be meaningless [154]. Therefore, It is suggested that translating the results obtained from the *in vitro* and preclinical studies that showed a beneficial role of MDSCs in a given pathological condition to the clinical phase, while there is no data about the exact role and the anatomical distribution of such cells in that pathological condition in humans should be scientifically unaccepted. In other words, in the absence of enough information about a specific inflammatory pathological condition in humans we cannot provide a scientific interpretation that represents or at least resembles the human case upon taking results from studies on animal models of that pathological condition. For instance, there is no data that either confirms or denies the presence of MDSCs in the tissues of multiple sclerosis patients [155,156]. In this case, a scientific interpretation that represents or at least resembles the human case cannot be made in studying the role of MDSCs in animal models of multiple sclerosis, namely the experimental autoimmune encephalomyelitis (EAE) [157–159]. Moreover, there are contradictions in results between studies on EAE mice. Some investigators agree that MDSCs are good while others disagree, in fact, this further supports our view that we cannot provide definitive conclusions without data from previous human studies. For example, Yi and colleagues [159] were the first group to study multiple sclerosis in EAE mice. They reported that MDSC expansion exacerbated EAE disease in mice. In other words, that MDSC expansion is associated with unwanted outcomes manifested by increased inflammatory responses which was concomitant with increased T helper 17 (Th17) differentiation. These results were consistent with other studies on other autoimmune disorders such as autoimmune arthritis and systemic lupus erythematosus [9–11], in that MDSCs could behave like pro-inflammatory cells in these conditions. On the other hand, other groups have shown that MDSCs could have a good role in controlling EAE disease progression [154,157,158]. Therefore, from the available data we cannot conclude that MDSCs have a Yang role in this pathological condition, but still we cannot exclude this possibility. It is important to note that, unlike studies that indicated that MDSC expansion exacerbates EAE disease progression when the elevation of MDSCs occurred naturally during the disease course [159], we find that the elevation of MDSCs in studies that indicated that these cells could be involved in EAE disease controlling was not naturally occurring, rather it was as a consequence to the given tolerogenic treatments or upon adoptive MDSCs transfer [73,154,157]. Indeed, Elliott and colleagues wanted to uncover the mechanism by which cannabinoids attenuate neuroinflammation in patients with multiple sclerosis upon using marijuana cannabinoids. They treated EAE mice with cannabinoids and reported that the subsequent elevation of MDSCs was the reason for the attenuation of EAE in cannabinoid treated mice [157]. It must be remembered; however, this does not necessarily mean that the same mechanism of action (scenario) would occur in humans, necessitating the performance of studies on humans. Another important note to be considered in this context is that the function of *in vitro* expanded MDSCs differs from those isolated from abnormal donors (pathological conditions). So, even if there is enough information about the role and the distribution of MDSCs in a specific inflammatory condition, the *in vitro* and the preclinical studies do not necessarily represent exactly the clinical status. Therefore, investigating the role and the distribution of MDSCs in autoimmune disorders in humans is urgently

needed, and the final verdict in this case can be made only after studying the role of MDSCs in humans suffering from autoimmune disorders such as multiple sclerosis.

A critical difference between pathologically and normally activated/expanded MDSCs is that, in contrast to pathological conditions in normal conditions (such as pregnancy) these cells are activated and expanded, relatively, for a short period of time. Once the desired outcome is achieved, protecting the fetus from maternal immune response in the case of pregnancy, their counts are normalized (Fig. 1).

Finally, it is important to remember that the role of MDSC is not yet investigated in many inflammatory conditions, and if so, there is no enough evidence to declare whether they have a Yin or Yang role in such conditions, e.g., the role of MDSC in wound healing [1], thus additional investigations are required to delineate their role in such conditions.

Conclusions

Indeed, MDSCs are more complex than initially thought. Although commonly defined as immature potent immunosuppressor cell populations of myeloid origin, it is now evident that MDSCs comprise of both mature and immature cells, indicating that MDSCs should not be defined as immature cells. Moreover, recent advances in MDSC biology indicate that characterization of these cells using the surface phenotype alone is not possible, due to the similarities between M-MDSCs and PMN-MDSCs with their cognate cells, namely monocytes and neutrophils, respectively. For example, in mice, MDSC populations cannot be differentiated from normal monocytes and neutrophils based on their surface phenotypes only, indicating the need for other assays that, at least, measure their suppressive capabilities. A similar case is also observed in humans. The discovery of highly specific markers exclusively expressed on MDSCs populations can help avoid this problem. Fortunately, recent investigations show that the recently discovered markers LOX-1 and SPARC could be used to define PMN-MDSCs populations directly without a need to use other assays that measure their suppressive activities, as they are expressed by the immunosuppressive cells only. The discovery of such highly specific markers for M-MDSCs is also important for better MDSC characterization. To this end, we encourage investigators to uncover such markers.

Of note, when studying MDSCs, the technical issues that could influence the result should also be taken into consideration. These include the type of sample (whole blood vs. PBMC), type of collection tubes, time of sample processing (as soon as possible vs. delayed), storage temperature (room temperature vs. refrigeration or freezing), and flow cytometry gating. If these issues are not addressed the results will be affected and this could widen the contradictions present in the literature. Furthermore, additional studies are also required to investigate such factors in other types of samples, such as the bone marrow, liver, spleen, tumors, etc. in order to fill the gap of knowledge in this regard.

In the context of the origin of MDSC expansion, recent advances suggest that MDSCs may be expanded as a result of emergency myelopoiesis in the bone marrow, extramedullary myelopoiesis mainly in spleen, and reprograming of mature cells in the periphery. These events may occur simultaneously. However, more investigations are needed to further clarify this issue.

The anatomical distribution of MDSCs is also another important matter for better understanding their role in pathophysiology. Although their anatomical distribution is well established in mice, and to some extent in non-human primates, it is not established in humans, particularly in health. This could stand as a barrier to our understanding of their role in human pathophysiology, and limit the understanding and interpretation of results when examining the role of MDSCs in animal models of human disease. The latter is due to the lack of reference information to date in humans and we, therefore, encourage investigators in MDSCs research to open this door as soon as possible.

With respect to the mediators of MDSC expansion we addressed the model presented by Condamine and Gabrilovich. This model describes the processes that govern MDSC expansion and accumulation. However, recent advances show that this model is still a premature model and can only describe the process partially. Thus, additional investigations are required to establish a model that precisely describes the process of MDSC expansion and compensate the limitations of "Condamine and Gabrilovich" model.

In the context of the factors that mediated the expansion of one MDSC population over the other, we have shown that transcription factors are extremely important in expansion of one MDSC population over the other. However, it is essential to point out that signaling pathways and activation of transcription factors is determined as a consequence of MDSC interaction with molecules and/or cells within the inflammatory microenvironment, which, in turn, determines the differentiation fate of such cells. Therefore, the microenvironment could be considered the real driving force behind this process. However, additional investigations are needed to further clarify the factors involved in expansion of one subset over the other.

In the Yin and Yang section we tried to remove the ambiguity surrounding the MDSC Yin and Yang concepts. To this end, we showed that the expansion of MDSCs in pathological conditions including cancer, infection, aging and autoimmune disorders has a negative impact, and this is true when such expansion occurs naturally without

external intervention and such expansion is associated with bad outcomes. On the other hand, we showed that MDSCs could have a Yang role under certain conditions such as pregnancy, and this is the only normal condition to our knowledge where MDSCs are expanded without negative effects. Finally, we showed that MDSCs could be harnessed as a therapeutic strategy to control certain inflammatory conditions where MDSCs are not naturally expanded. As such we wrote the law of Yin-Yang law of MDSCs.

Of note, it is essential to realize that mice are widely used as animal models for studying many human diseases and for testing new treatments and vaccines. However, there are great differences between humans and mice, particularly in the immune system. In fact, this explains why contradicting results are observed upon translating the promising results obtained from mouse studies on a pathological condition to the clinical phase on humans [19]. Non-human primates are much closer to humans in many aspects including the immune system [19–22], yet they are only recently being included in MDSC research. We therefore strongly encourage scientists in this field to include such animal models in the near future.

Finally, in the context of MDSC functions, in addition to their immunosuppressive activity, recent advances have also shown that MDSCs have pro-inflammatory activity in certain pathological conditions (such as autoimmune disorders), suggesting that the previous definition should be reevaluated. Herein, we sub-grouped these cells into immunosuppressive MDSCs and pro-inflammatory MDPCs according to the observed immune responses once expanded in a pathological condition.

Compliance with ethics guidelines

Mahmoud Mohammad Yaseen, Nizar Mohammad Abuharfeil, Homa Darmani, and Ammar Daoud declare that this review manuscript was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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