

Chapter 2

Differentiation of Murine Myeloid-Derived Suppressor Cells

David Escors

Abstract Myeloid-derived suppressor cells (MDSCs) are frequently defined as a heterogeneous population of immature cells belonging to the myeloid lineage which possess strong immunosuppressive activities. These cells ultimately derive from myeloid progenitors mainly present in the bone marrow that undergo a dysregulated differentiation pathway, ending up with the systemic mobilization of MDSCs of “monocytic” or “granulocytic” characteristics. Here we will review the current knowledge on MDSC differentiation mostly in murine cancer models, and reflect on whether MDSCs represent a unique, well-defined distinct myeloid lineage or just immature stages of myeloid cells.

Keywords Haematopoiesis • Myeloid lineage • Granulocytes • Monocytes • Dendritic cells • Myeloid-derived suppressor cells • Bone marrow

2.1 Introduction

An extensive review of the specialized literature quickly shows to the non-specialized reader that myeloid-derived suppressor cells (MDSCs) are defined in many ways, depending on the cancer model and the particular standards adopted by each research team. These variable definitions widely used by researchers highlight the ultimate question in MDSC research: Do MDSCs belong to a distinct, genuine myeloid lineage or are they a collection of myeloid cells halted at several differentiation steps of a disturbed myelopoiesis?

MDSCs are most commonly defined as a “heterogenous population of immature cells of myeloid origin with strong suppressive activities”. It is also assumed by

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many researchers that MDSCs arise from two independent myeloid lineages, namely, monocytic and granulocytic lineages. A significant number of researchers define these cells as “dysfunctional inflammatory monocytes” (for monocytic MDSCs) or “dysfunctional neutrophils” (for granulocytic MDSCs). Finally, others have adopted a nomenclature that englobes all possible immunosuppressive cells of myeloid origin without any attempt at their distinction or classification; the “immature suppressive myeloid cells” or “myeloid regulatory cells”.

Nevertheless, the existence and nature of MDSCs cannot be ignored, and the ultimate question on the origin of MDSCs must be consequently addressed. First, it will expand our knowledge on how cancer subverts our immune system to its advantage. Second, from a therapeutic point of view, it is necessary to find out if we are working with a single differentiation pathway, or if immunosuppressive MDSCs arise independently from multiple precursors by redundant differentiation pathways.

In this chapter we will revise the physiological myeloid differentiation pathway, MDSC differentiation, and whether we can consider MDSCs as a genuine myeloid lineage arising from a well-defined differentiation pathway.

2.2 Physiological Myeloid Differentiation

2.2.1 Conventional Myeloid Cell Types and Their Role in Immunity

Myeloid cells play key regulatory and effector roles in both innate and adaptive immunity. Some of the myeloid cell lineages possess very strong antigen-presenting capacities, and they express a wide range of pathogen pattern-recognition receptors on their surface. These receptors, when engaged by their respective ligands, start a process of “maturation” in these cells leading to characteristic phenotypic and functional changes resulting in cytokine secretion, production of a wide range of biologically active molecules and acquisition of strong antigen-presenting capacities. Classically, “mature” myeloid cells englobe four main well-defined classical cell types. Nevertheless, it has to be pointed out that these myeloid cell types usually present a high degree of plasticity. For example, macrophages and DCs can differentiate from monocytes. These cell types will be described briefly as follows.

2.2.1.1 Monocytes

They represent between 2 % and 10 % of haematopoietic-derived cells. Monocytes circulate systemically and play important roles in replenishing tissue-resident macrophages. Although monocytes have been classically considered “only the precursors” of macrophages, this view is certainly highly simplistic. Monocytes quickly respond to infection, and enhance inflammation, tissue repair, and eliminate

pathogens through phagocytosis. These cells have a life span of about 2 days. Currently, murine monocytes are divided in two categories according to their surface phenotype. The Ly6C^{high} monocyte subset (also known as inflammatory monocytes) is mainly involved in inflammation and antimicrobial immune responses, while the Ly6C^{low/neg} subset (also known as “patrolling monocytes”) is rather a tissue-infiltrating monocyte involved in tissue repair. In fact, monocytes are quite capable of microbe phagocytosis and killing through production of reactive oxygen species (ROS) following the respiratory burst. They can also trigger (in some circumstances) T cell responses, and polarize immune responses through cytokine secretion. Phenotypically, both subsets express the myeloid lineage marker CD11b, together with CD115, F4/80^{low}, and MHC II [1, 2]. Importantly, the Ly6C^{high} subset lacks expression of CD62L while the Ly6C^{low} subset expresses this homing surface molecule [3]. Monocytes do not express Ly6G or CD11c.

2.2.1.2 Macrophages

Macrophages comprise a very heterogeneous, highly phagocytic cell population. These cells are further classified into several “subclasses” according to ontology, tissue localization, and specialized functions. Thus, we can have osteoclasts, microglia, Kupffer cells, alveolar macrophages, and ubiquitous tissue-resident macrophages. While it was previously thought that macrophages differentiated from bone marrow-derived monocytes, it has been shown that adult macrophages arise from at least two other different sources, one of these being embryonic progenitors [4, 5], and the other from tissue-resident precursors. Phenotypically, macrophages are similar to other myeloid cells, characterized as CD11b⁺ CD11c^{low/neg}, F4/80^{+/high}, MHC II⁺, and CD68⁺ [6, 7]. Most macrophages also express IL4R α , CD163 and they can also express Ly6C to varying levels. Nevertheless, murine macrophages are Ly6G^{neg/low} and they are most frequently identified by high expression levels of CD11b, F4/80, and CD68 [8].

2.2.1.3 Dendritic Cells (DCs)

Dendritic cells are probably the most immunogenic myeloid cell lineage, and they play a fundamental role in linking innate with adaptive immunity [9–12]. DCs are very efficiently activated through the recognition of pathogen-derived and danger molecules, leading to strong up-regulation of T cell co-stimulatory molecules. Therefore, they are potent activators of naive T cells. DCs are roughly classified in two main groups; conventional (or myeloid) DCs, and plasmacytoid DCs [13]. Here we will focus on conventional DCs. The phenotype of DCs is certainly very plastic, and depends on their anatomical localization and their maturation degree. Nevertheless, they are frequently identified as CD11b⁺, CD11c^{high}, and MHC II⁺ cells. They lack Ly6G and F4/80 expression, and they can express Ly6C at varying

degrees. DC-SIGN and CD123 are also additional good markers frequently used to differentiate DCs from macrophages.

2.2.1.4 Granulocytes

Granulocytes are short-lived, highly cytotoxic myeloid cells with very high phagocytic activities. They are produced from bone marrow precursors at very large numbers, and are subdivided in three classes: neutrophils, basophils, and eosinophils. This classification is based on the staining properties of their numerous cytoplasmic granules. Possibly, the most common markers for their differentiation from other myeloid lineages are CD11b and GR-1^{high}. The GR-1 epitope is present on two surface molecules, Ly6C and Ly6G. Granulocytes express high levels of Ly6G. Apart from these molecules, granulocytes also express CD62L at varying levels. They are also negative for CD11c, a useful marker to discriminate them from DCs. Myeloperoxidase (MPO) is also used as a granulocyte (neutrophil) marker, although this is still controversial as it might also be expressed in monocytes and macrophages [14].

2.2.2 Physiological Myelopoiesis

Haematopoiesis is a highly regulated process absolutely necessary to keep the homeostasis of the whole body. Thanks to this process, erythrocytes, platelets, and immune cells are continuously produced to meet the demands of the organism. This process entirely relies on a relatively low number of pluripotent haematopoietic stem cells (HSCs, Lin^{neg}, Sca-1⁺, and cKit⁺; also called LSK stage) which are kept most of the time quiescent within a specialized niche within the bone marrow (Fig. 2.1). LSK cells are maintained in the presence of stem cell factor (SCF) and leukemia inhibitory factor (LIF), mainly. The differentiation from HSCs toward myeloid cells is usually thought to be a sequentially-regulated pathway through different intermediate differentiation stages (Fig. 2.1) [15, 16]. Stromal cells and other cell types produce cytokines that mobilize these HSCs to differentiate in all the variety of blood cells. The specific site and cytokine combination will lead to the differentiation of each cell lineage. Within the LSK population, a CD41^{high} subset is committed toward myeloid–erythroid differentiation [17]. These cells then give rise to the common myeloid progenitor mainly by the activities of GM-CSF and SCF (CMP, Lin^{neg} Sca-1^{neg} cKit⁺ CD41^{low/neg} CD64^{low} CD34⁺ CD115^{neg}). Other cytokines also contribute to their differentiation, including IL3, IL6, and Flt3L. CMPs further differentiate into the granulocyte/monocyte progenitor (GMP, Lin^{neg} Sca-1^{neg} cKit⁺ CD64^{high} CD34⁺). GM-CSF, IL3, and macrophage colony-stimulating factor (M-CSF) drive further their differentiation toward monocytes, macrophages, and DCs through a common progenitor termed the “monocyte-macrophage-DC progenitor” or MDP (CD11b^{neg}, Ly6C^{neg}, CD117⁺, CD115⁺ CD135⁺). MDPs give rise

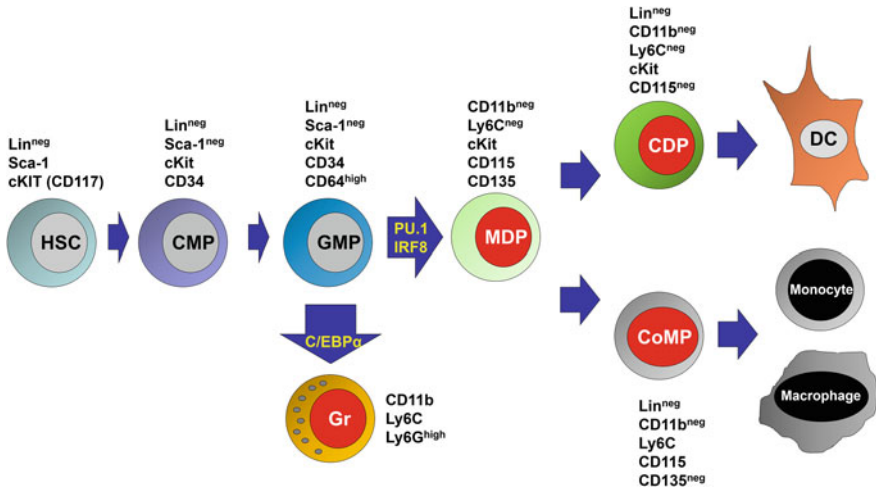


Fig. 2.1 Physiological myelopoiesis. A simplified scheme of myelopoiesis in physiological conditions. Each intermediate precursor is shown with the most characteristic phenotype above. The key transcription factors regulating lineage commitment are shown within the appropriate arrows. *HSC* haematopoietic stem cell; *CMP* common myeloid precursor; *GMP* granulocyte–monocyte precursor; *MDP* monocyte–macrophage–DC precursor; *CoMP* common monocyte–macrophage precursor; *CDP* common DC progenitor; *DC* dendritic cell; *Gr* granulocyte

to at least two distinct committed myeloid precursors, the common DC progenitor (CDP) and the common monocyte progenitor (CoMP, Lin^{neg} , $\text{CD11b}^{\text{neg}}$, Ly6C^+ , CD115^+ , $\text{CD135}^{\text{neg}}$). Importantly, the CDP gives rise to both conventional and plasmacytoid DCs [13, 18], while the CoMP leads to monocyte–macrophage differentiation [2]. Granulocytes are differentiated from the GMP mainly by the activity of granulocyte colony-stimulating factor.

Myelopoiesis can also take place extramedullary, in the spleen where myeloid progenitors are present and can differentiate into several myeloid lineages including monocytes and DCs [2, 19].

2.2.3 Transcription Factors Driving Myelopoiesis

Transcriptionally, myelopoiesis is also regulated by the coordinated expression of a few key transcription factors that shift the commitment of precursors toward monocyte, macrophage, or granulocyte differentiation. HSCs require the expression of PU.1 and GABP to differentiate toward the myeloid lineages [20]. Runx1 leads to C/EBPα expression [21], and then a regulated interplay of C/EBP-AP1 transcription factors determines monocyte or granulocyte differentiation [22]. At high AP-1:C/EBP ratios, these factors heterodimerize leading to monocytes. However, the formation of C/EBPα homodimers favors granulocyte differentiation. IRF8 expression is also critical for monocyte/DC differentiation, as it blocks C/EBP

activities and inhibits granulocyte (neutrophil) differentiation [23]. Additionally, its inactivation by p38-mediated phosphorylation is enough to inhibit neutrophil development [24]. Monocyte differentiation also seems to be controlled by NFAT through ERK-dependent activities, while granulocyte differentiation was shown to depend on PU.1 and STAT3 through the participation of JAK1 and calmodulin kinase II [25]. It is important to mention that steady-state haematopoiesis can be significantly altered under certain circumstances, resulting in nonsteady-state haematopoiesis. This is the result of circumstances such as infection or cytokine stimulation. In this situation, large numbers of neutrophils are produced through the activities of C/EBP β [26]. Significantly, C/EBP β is also highly induced in cancer-bearing patients [27].

2.3 MDSC Differentiation in Cancer

2.3.1 *Myeloid Cells and Cancer Progression in Murine Models*

Since the early 70s, it was observed that tumor-bearing patients exhibited a systemic increase in myeloid cells, particularly cells resembling neutrophils (neutrophilia) [28]. Tumor infiltration by myeloid cells also correlated with tumor progression, metastasis, and poor prognosis. Although most studies focused on tumor-infiltrating macrophages and DCs, there was a significant population of cells that did not fit within these myeloid populations. These cells were highly suppressive and exhibited a markedly immature phenotype, as they did not express high levels of maturation markers and MHC molecules characteristically found in classical myeloid cells [28, 29]. Removal of tumors reverted to the numbers of circulating myeloid cells and neutrophilia, suggesting that tumors were directly producing factors leading to the expansion of these cells.

2.3.2 *The Definition of Myeloid-Derived Suppressor Cells*

These cancer-related immunosuppressive cells exhibited a variety of phenotypes, and they seemed to correspond to a heterogenous population of cells of myeloid origin. These cells were known by several nomenclatures which included “null cells”, “immature suppressive cells” or they were even confounded with tumor-infiltrating macrophages or tolerogenic DCs. Studies in murine cancer models showed that these cells highly co-expressed CD11b and GR1, and could be further classified into two subtypes according to the expression of Ly6C and Ly6G [30]; monocytic Ly6C^{high}Ly6G^{neg/low} M-MDSCs, and granulocytic Ly6C^{low}Ly6G^{high} G-MDSCs. As monocytic and granulocytic MDSCs exhibited mono- or polymorphonuclei, respectively, many researchers concluded that these cell subsets were

either dysfunctional inflammatory monocytes or tumor-associated neutrophils [31, 32]. Nevertheless, although their phenotypes might resemble those of monocytes and neutrophils, their functional differences suggested that these cells could either represent alternative functional states of these myeloid cells, or arise independently from monocytes and neutrophils through a perturbed myelopoiesis [30, 33]. Thus, M-MDSCs and G-MDSCs were considered at first dysfunctional immature myeloid cells that arose independently from each other.

Consequently, to avoid misunderstandings, the term “myeloid-derived suppressor cell” was coined by a group of researchers that pioneered research in MDSCs [34]. Although there is still some controversy on terminology, the MDSC term is proving useful from a practical point of view until the MDSC ontology is unambiguously unmasked.

2.3.3 Perturbed Myelopoiesis Behind MDSC Differentiation

Whether MDSCs are considered a “dysfunctional state” of monocytes/neutrophils, or myeloid lineages that arise independently, it is evident that perturbed myelopoiesis caused by cancer is behind MDSC differentiation and expansion. Growing tumors secrete a wide range of cytokines and metabolites that distribute systemically through circulation, also reaching the bone marrow. Some of these secreted factors have been identified in vitro in cultures of a wide range of cancer cell lines. Not surprisingly, they comprise of a collection of molecules that drive myeloid differentiation and include cytokines such as GM-CSF, G-CSF, M-CSF, IL6, IL13, IL4, and SCF [27, 30, 35, 36]. Other molecules have also been shown to contribute to MDSC differentiation and acquisition of immunosuppressive functions, such as prostaglandin E₂, TGF-β, and vasoactive intestinal peptide [37–40]. Recently, it was shown that IL18 increases the differentiation of M-MDSCs from CD11b^{neg} precursors [41]. Thus, the significant increase in levels of these circulating molecules and tumor-derived exosomes perturbs myelopoiesis leading to the mobilization of MDSCs [42] (Fig. 2.2).

2.3.4 Do MDSCs Belong to a Specific Myeloid Lineage? Relationship Between M-MDSCs and G-MDSCs

So far, there has been a wide assumption within the scientific community that M-MDSCs and G-MDSCs are largely unrelated. Possibly, their resemblance to inflammatory monocytes and neutrophils, respectively, provides weight to this assumption. However, a direct ontological relationship between monocytes with M-MDSCs or neutrophils with G-MDSCs has not been shown yet. In fact, morphologically and phenotypically, M-MDSCs do resemble monocytes. M-MDSCs are mononuclear cells which express CD11b, Ly6C^{high}, Ly6G^{low}, CD62L, CD115,

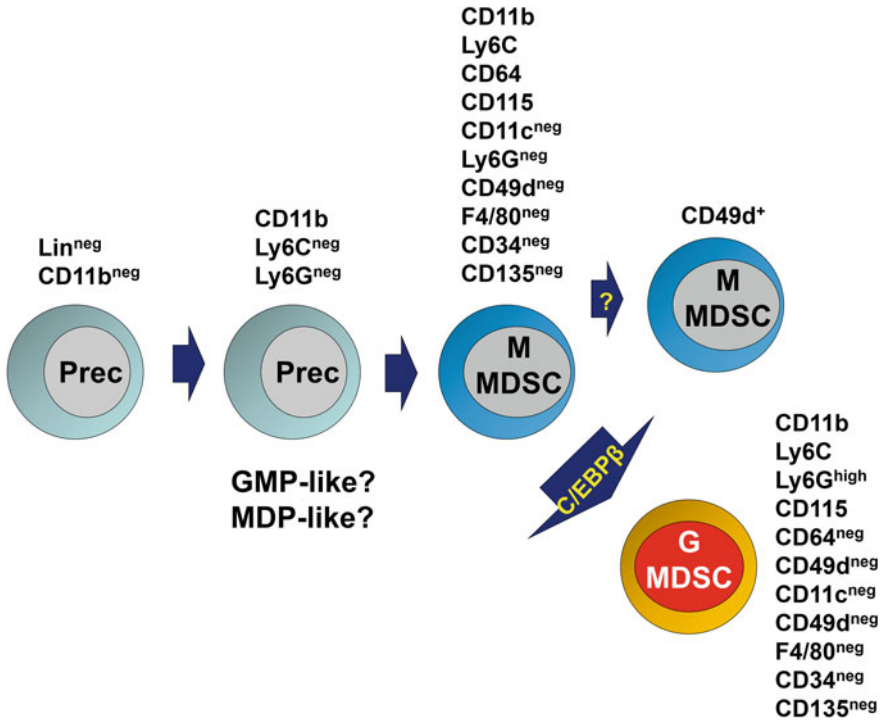


Fig. 2.2 Putative MDSC differentiation pathway. A simplified scheme of MDSC differentiation from putative precursors (Prec) is shown in the figure. So far, the specific nature and phenotype of these precursors are unknown, but they are likely to differ from those involved in physiological myelopoiesis. In this scheme, monocytic MDSCs (M-MDSCs) are precursors of granulocytic MDSCs (G-MDSC). The known phenotype of each MDSC subset is indicated in the figure. The participation in MDSC differentiation of the transcription factor C/EBP β is indicated, although it is likely that this transcription factor is acting at the level of precursors

and CD64a/b [43, 44]. The surface marker CD115 (M-CSF receptor) is expressed early in haematopoiesis at least from the MDP progenitor stage, and this includes all the monocytic progeny. CD64a/b is constitutively expressed by monocytes, macrophages, and DCs [45]. CD49d which is expressed in a highly suppressive M-MDSC subset is also expressed by monocytes, macrophages, and DCs. Therefore, M-MDSCs are apparently “monocytes”, or at least of monocytic origin. In physiological haematopoiesis, granulocytes arise from a GMP stage, expressing their “hallmark” surface marker GR1. The GR1 epitope is present on two surface molecules, Ly6C and Ly6G. Similarly to inflammatory neutrophils, G-MDSCs are Ly6G^{high} cells. Several studies claim that circulating M-MDSCs can infiltrate tumors, and then under the influence of tumor-derived factors, they differentiate toward tumor-associated macrophages, DCs, and neutrophils-G-MDSCs [46, 47]. Some authors consider G-MDSCs as tumor-infiltrating neutrophils [48]. In fact, transcriptomic analyses between neutrophils and G-MDSCs showed that they are

similar cells, although there were significant differences in the expression of key functional enzymes such as lysosomal proteins, arginase, myeloperoxidase, and production of reactive oxygen species [49]. A second transcriptomic study between naïve neutrophils, splenic G-MDSCs, and tumor-infiltrating neutrophils showed that the mRNA profiles of the three cell populations were significantly different, but MDSCs were more similar to naïve neutrophils [50]. Even so, considering all the available experimental evidence it seems that G-MDSCs are not truly *bona fide* neutrophils [33]. In agreement with the inhibitory role of IRF8 on neutrophil development, IRF8 expression also suppresses MDSC differentiation [51]. However, there is a fundamental difference; as described above, for physiological neutrophil differentiation the expression of C/EBP- α is required [24]. In contrast, the C/EBP- β isoform, which is associated to nonsteady-state haematopoiesis [26] is responsible for driving MDSC differentiation [27].

According to physiological haematopoiesis, monocytes and granulocytes share a common progenitor early in the granulocyte–monocyte progenitor stage. Following this “commitment model”, it seems unlikely that inflammatory monocytes in steady-state conditions may differentiate into neutrophils. Their differentiation is antagonistic and controlled by IRF8 expression. However, there is some evidence of transdifferentiation from inflammatory neutrophils into monocyte/macrophages under inflammatory conditions through the activity of p38 [52].

Surprisingly, purified M-MDSCs quickly differentiate towards G-MDSCs in vitro, ascertained by strong Ly6G up-regulation [44]. Moreover, the same phenomenon was observed in vivo, where M-MDSCs differentiated towards G-MDSCs after infiltrating tumors [53]. Therefore, these results strongly suggest that M-MDSCs and G-MDSCs are directly related rather than being independent myeloid lineages arising from unrelated pathways within the bone marrow. Thus, as the MDSC precursor cell possesses monocytic markers but acquires granulocytic markers toward terminal differentiation, it is highly likely that MDSC subsets directly derive from GMPs.

2.4 Summary and Conclusions

Growing tumors strongly alter physiological myelopoiesis leading to the differentiation and expansion of MDSCs. These cells clearly belong to the myeloid lineage, although their discrimination from “physiological” myeloid cell types is rather challenging. Nevertheless, cancer is a rather unusual pathology, and it is highly likely that the same standards for classifying myeloid cells in physiological conditions do not apply in pathological situations. Classically, MDSCs have been classified into two subsets according to their phenotype; monocytic and granulocytic MDSCs, phenotypically resembling inflammatory monocytes and neutrophils, respectively. As differentiation of granulocytic and monocytic lineages in physiological conditions seems to be antagonistic and dependent on the expression levels of IRF8, it has been assumed that M-MDSC and G-MDSC differentiation pathways

are rather independent from each other. However, there is compelling evidence that MDSCs derive from a CD11b⁺ Ly6C^{neg} Ly6G^{neg} precursor leading to M-MDSCs. Then, these M-MDSCs within the tumor environment further differentiate to G-MDSCs which possess a relatively short life. Therefore, rather than a “heterogeneous population of immature myeloid precursors”, MDSCs should be considered as an alternative “myeloid lineage” that appears in pathological conditions. This MDSC “cell type” is expanded at large levels and it is systemically present at different differentiation degrees, being the G-MDSC the terminal differentiation stage.

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