Applications of Myeloid-Derived Suppressor Cells in Haematology

Subjects: Hematology

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Myeloid-derived suppressor cells (MDSCs) are immature cells of myeloid origin that have gained researchers' attention, as they constitute promising biomarkers and targets for novel therapeutic strategies (i.e., blockage of development, differentiation, depletion, and deactivation) in several conditions, including neoplastic, autoimmune, infective, and inflammatory diseases, as well as pregnancy, obesity, and graft rejection. They are characterised in humans by the typical immunophenotype of $CD11b^{+}CD33^{+}HLA\text{-}DR^{-/low}$ and immune-modulating properties leading to decreased T-cell proliferation, induction of T-regulatory cells (T-regs), hindering of natural killer (NK) cell functionality, and macrophage M2-polarisation. The research in the field is challenging, as there are still difficulties in defining cell-surface markers and gating strategies that uniquely identify the different populations of MDSCs, and the currently available functional assays are highly demanding. There is evidence that MDSCs display altered frequency and/or functionality and could be targeted in immune-mediated and malignant haematologic diseases, although there is a large variability of techniques and results between different laboratories.

Keywords: myeloid-derived suppressor cell (MDSC) ; haematology ; immunology ; cancer

1. Introduction

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of cells, identified by the immunophenotype $CD11b^{+}CD33^{+}HLA\text{-}DR^{-/low}$ in humans and divided into $CD14^{+}$ (monocytic, M-MDSCs), $CD15^{+}$ (granulocytic or polymorphonuclear, G- or PMN-MDSCs), and $CD14^{-}/CD15^{-}$ (early stage, eMDSCs) MDSCs. In mice, they are divided into $Gr1^{+}CD11b^{+}Ly6G^{+}Ly6C^{low}$ (PMN-MDSCs) and $Gr1^{+}CD11b^{+}Ly6G^{-}Ly6C^{hi}$ (M-MDSCs) [1]. They are immature myeloid cells with an activation profile that deviates from the standard pathway of differentiation, mostly during emergency myelopoiesis in chronic inflammation, autoimmune diseases, and tumour progression, and possess immune-modulating properties [2]. They can also play an ambiguous role in the myeloid microenvironment. While their expansion may promote carcinogenesis through angiogenesis, metastasis, and immune-suppression, as well as chronic inflammation in infections, aging, and neurodegenerative diseases, their existence is also essential for the foetal–maternal immune-tolerance in pregnancy, the graft tolerance in allo-transplantation, and the avoidance of autoimmunity [3][4].

MDSCs have gained the attention of researchers and clinicians during recent years; therefore, there is an abundance of ongoing studies concerning their implication in almost every trending research field: in the tumour microenvironment (TME) communicating with various cell types [5]; in cancer cachexia, where their expansion may be a contributing factor [6]; in tumour progression due to their secreting exosomes and micro-RNAs [7]; in autophagy, which regulates their immune-suppression properties [8]; in immunosenescence and aging where their increase is associated with low-grade chronic inflammation and impairment of the clearance of senescent cells [9][10][11][12]; in metabolomics and energy metabolism showing a unique metabolic profile associated with their functionality and maturation [13][14]; in gut microbiome, which may affect the expansion of PMN-MDSCs [15]; in foetal–maternal tolerance and breastfeeding by accumulating in the maternal and foetal organisms and the breast milk [16][17][18]; in infant infections, as they surprisingly present antimicrobial properties and a particular protective role in newborns [19][20]; in sepsis, where they can serve as important biomarkers and therapeutic targets [21]; even in severe COVID-19, where MDSC populations seem to be upregulated and may predict worse outcomes [22]. Additionally, there are preliminary data that MDSCs may affect the sex dimorphism and differences between genders in the survival rates and response to treatments in various conditions, as they may present different levels in male versus female subjects [23].

2. When to Call a Cell “MDSC”?

The term MDSCs was proposed for the first time in 2007 to substitute the earlier-used term “myeloid suppressor cells” in order to better describe the heterogeneity, origin, biological role, and functionality of these cells [24][25]. According to the last recommendations, for the characterisation of a cell population as MDSCs, the typical immunophenotype, functional characteristics, and/or expression of certain molecules and biochemical markers are needed. More specifically, Bronte et al. suggested that cells demonstrating the typical immunophenotype and molecular and biochemical characteristics, but lacking the immunosuppressive functionality, should rather be characterised as MDSC-like cells (MDSC-LC) [26]. The reason for this recommendation is that MDSCs are found in different stages of differentiation and activation in patients with cancer and inflammation, and probably acquire their suppressive character in later stages of disease [26]. However, the term MDSC-LC is rarely used in the literature, whereas occasionally it is also used to characterise mature cells that acquire immunosuppressive properties typically found in MDSCs. Umemura et al., for example, characterised as MDSC-LC the murine Gr-1^{hi} IL-4Rα^{hi} cells that presented no suppressive properties against CD8^{+} T-cells [13]. On the other hand, Li et al. used the term G-MDSC-LC in order to refer to a population of PMN-MDSCs that can be contaminated with mature neutrophils with suppressive properties [15].

3. Where do MDSCs Originate from?

The theories for the origin of MDSCs are still diverse. The questions to be answered are numerous and concern the site of their generation, the factors needed for their development, their progenitor forms, etc. [27].

There is no doubt that key players for their generation are the colony stimulating factors (CSFs), as indicated by the *ex vivo* expansion of MDSCs from progenitor cells in cultures containing them [28][29][30][31]. Especially, granulocyte-CSF (G-CSF) is thought to drive haematopoiesis to the myeloid lineage in the bone marrow (BM) [32]. The classical theory, called the “two-signal model” and firstly introduced by Gabrilovich et al., suggests the development of the MDSC from the haematopoietic stem cell (HSC) during emergency myelopoiesis in a two-step process. Initially, the HSC, under the exposure to growth factors, mainly CSFs, transforms to an immature myeloid cell (IMC). Finally, under the exposure to pro-inflammatory factors, including signal transducers and activators of transcription (STATs), especially STAT3, S100 calcium-binding protein A8/A9 (S100A8/A9), nuclear factor-kB (NF-kB), retinoic-acid-related orphan receptor C1 (RORC1/RORγ) [33][34], and CCAAT/enhancer-binding protein b (C/EBPb), the IMC pauses its differentiation, becomes activated, and acquires its MDSC character [27][32][33]. When the cell is taken away from the malignant microenvironment, it may be further developed into a more mature form.

Besides the BM, other sites and organs are also responsible for the generation of MDSCs. Even on the site of the tumour or on newly formed pre-metastatic niches, progenitor cells that originated from the BM may transform to IMCs and then activated MDSCs. Spleen, as the major representative of extramedullary haematopoiesis under signals such as lipopolysaccharide (LPS) or interferon-γ (IFN-γ), is one of these sites. MDSCs in the spleen may be either the activated forms of IMCs that initiated from the BM and reached the spleen through the periphery, or *de novo* (in the spleen) generated from remaining progenitor cells from the embryonic life [27][32].

Interestingly, MDSCs in diverse sites differ from each other. MDSCs in the spleen produce higher amounts of reactive oxygen species (ROS) and smaller amounts of nitric oxide (NO) and express less arginase 1 (Arg-1), while MDSCs in the TME show the opposite trend. These differences are attributed, according to Corzo et al., to several factors present in the TME including hypoxia via the hypoxia-inducible factor 1α (HIF-1α) [35]. The relation of MDSCs and TME is bidirectional. On the one hand, tumour cells express and release factors that induce the generation of MDSCs in the BM and their recruitment and accumulation at the tumour site, such as chemokine (C-C motif) ligand 2 (CCL2), CCL5, CXC chemokines, STATs, interleukin 10 (IL-10), transforming growth factor β (TGF-β), and vascular endothelial growth factor (VEGF), while on the other hand MDSCs play a crucial role in the formation of the pre-metastatic niche through secretion of soluble factors and exosomes resulting this way in a positive loop for their development [36][37][38][39][40].

High numbers of MDSCs can also be found in the placenta and the umbilical cord. These two sites have distinct types of MDSCs; the umbilical cord MDSCs display a more immature phenotype indicating their foetal origin, while the placental MDSCs are of maternal origin. Umbilical cord MDSCs, and mainly the PMN-MDSCs, are generated from the abundant progenitor cells of the umbilical cord blood and are normally expanded to sustain the essential foetal–maternal tolerance [18]. According to Zhang et al., the human trophoblast cells can induce the development of a novel CD14^{+}HLA-DR$^{-/low}$ MDSC population from peripheral CD14^{+} myelomonocytic cells [41].

However, as far as the M-MDSCs are concerned, the expression of CD14, CD80, and CD83, their mature-like morphology, and the fact that they can differentiate into tumour-associated monocytes (TAMs) and dendritic cells (DCs), raises questions on the theory described above and it is believed by some experts that they are in fact re-programmed mature monocytes, under the signals of hypoxia or damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) [27][42][43]. At this point, it would be useful to note that M-MDSCs differ from TAMs. TAMs are mature macrophages of the TME and are divided in two categories, the M1 that have anti-tumoural activities and the M2 that have pro-tumoural activities. Large numbers of M-MDSCs are correlated with more advanced neoplastic disease, worse outcome and prognosis, and poor response to treatment, while large numbers of M2 predispose for poor outcomes and prognosis in patients with cancer but this cannot be stated for TAMs in general. TAMs share common markers and mechanisms of action with M-MDSCs but also have differences. Both cell populations express Arg-1, inducible nitric oxide synthase (iNOS), programmed death-ligand 1 (PD-L1), CD80, CD86, CD11b, C-C chemokine receptor type 2 (CCR2), and TGF-β, and secrete immune-suppressive cytokines such as IL-10, while TAMs express more intensely CD115 and interferon regulatory factor 8 (IRF8), but not S100A9 [26][34][44][45][46][47].

A lot of debate has also been over the actual presence of PMN-MDSCs. Some researchers still think that these cells are not a distinct type of cell, but rather an activated form of neutrophils with an immunosuppressive character and a de-granulated form and, resultantly, low-density [48], while others that they derive from re-programmed mature neutrophils [49][50]. Moreover, it is mentioned in the literature that M-MDSCs under the appropriate conditions can differentiate into PMN-MDSCs [51]. Similarly as with TAMs and M-MDSCs, it needs to be stressed that PMN-MDSCs are a different cell population from tumour-associated neutrophils (TANs). TANs are thought to exist, also, in two states, i.e., the N1 anti-tumoural and the N2 pro-tumoural subpopulations, but their distinction from PMN-MDSCs is still challenging as they share the same phenotypical markers, and further research is needed to make it possible [26][52].

4. Which Are the Key Points of Studying MDSCs in Haematology?

4.1. Increased MDSCs: Haematologic Malignancies and Myelodysplasia

As researched earlier [53], MDSCs have been studied in many haematologic diseases. In malignancies and dysplasia, MDSCs are generally found at higher levels and related to the abnormal BM niche. More specifically, there are studies on increased PMN-MDSCs, mostly in patients with myeloproliferative neoplasms (MPNs), i.e., chronic myeloid leukaemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). In all MPNs, MDSCs are found to express Arg-1 in higher amounts [54]. Especially in CML, these cells contribute to the immune escape and, according to studies, there is a bidirectional relation with the leukemic cells, as cells from patients can convert monocytes from healthy donors into cells with the MDSC-suppressive character [55]. In rather limited studies, PMN-MDSCs seem to accumulate in acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL) [53][56][57], while M-MDSCs seem to accumulate in chronic lymphocytic leukaemia (CLL) [58][59][60][61][62]. In AML, the mucin 1 (MUC1) oncoprotein is shown to facilitate the proliferation of MDSCs [63], and there seems to be a correlation between increased numbers of this population and extramedullary involvement, plasma D-dimers, higher minimal residual disease (MRD), blast cell frequency, and Wilms 1 (WT-1) gene detection [64]. In myelodysplastic syndromes (MDS), more research is needed, but several studies showed increased MDSC populations, upregulated related pathways and molecules, and a positive correlation with the T-regs population [65][66][67]. Moreover, in MDS, the expression of S100A8/A9 and its interaction with CD33 seems to play an important role in the induction of dysplasia [67]. The MDSC populations were also expanded in a number of studies for multiple myeloma (MM) [53], where MDSCs seem to attenuate the survival of MM cells in several ways, such as via the phosphorylation of 5’ adenosine monophosphate-activated protein kinase (AMPK) [68], with PMN-MDSCs being the main population [69]. Ramachandran et al. showed that both BM PMN-MDSCs and neutrophils from mice with MM attenuated via soluble factors the survival of MM cells treated with chemotherapy [70], while according to Binsfeld et al., PMN-MDSCs present an upregulation in pro-angiogenic factors in the context of MM [71]. Lymphomas, including both Hodgkin lymphomas (HL) and non-Hodgkin lymphomas (NHL), are also correlated with increased numbers of M-MDSCs and PMN-MDSCs [72][73][74][75]. Especially in diffuse large B-cell lymphoma (DLBCL), M-MDSCs showed a positive correlation with T-regs [76].

4.2. Decreased MDSCs: Immune-Mediated Cytopenias

A decreased number of MDSCs is related with fewer conditions, such as immune-cytopenias. In on-going study in the Haemopoiesis Research Laboratory at the University of Crete, it has been found this to be true for patients with chronic idiopathic neutropenia (CIN) (also known as idiopathic neutropenia of undetermined significance, ICUS-N) [77], which correlates with the immune dysregulation accompanying the disease [78]. The decreased numbers of MDSCs are likely in part responsible for the chronic inflammation in these patients. Although, as pointed out by Bizymi et al., the frequency of

MDSCs in immune thrombocytopenia (ITP) is still controversial [53], their contribution in the pathophysiology of the disease is undoubted [79]. In the small numbers of studies, MDSCs seem to decrease and have reduced immunosuppressive properties, such as downregulation of Arg-1, with disease activity [80]. However, Shao et al. showed that newly diagnosed patients present higher numbers compared to healthy controls [81][82], although those expanded cells in the start of the pathology may not have immunosuppressive properties as Weng et al. hypothesised [83].

4.3. MDSCs versus Mesenchymal Stem Cells (MSCs)

Both MDSCs and MSCs are immature cell populations with immunomodulatory properties (through common and different mechanisms) and are activated by the same factors, although they originate from distinct differentiation lines. They block the maturation of DCs and macrophages, antigen presentation, T-cell proliferation, Th1 responses, and NK cell action via common molecules, such as IDO, prostaglandin E2 (PGE2), IL-10, and TGF-β. However, they possess many differences as well. Only MDSCs produce Arg-1 and ROS, while the production of galectins and HLA-G is a unique feature of MSCs. MDSCs seem to be more sensitive to type 2 cytokines. MSCs foster the development and survival of neutrophils, in contrast to MDSCs that seem to react negatively to the neutrophilic differentiation. However, there is still limited data on the actual effect of MDSCs on neutrophils and more study is needed [84]. More detailed analysis of the interactions of MDSCs and MSCs in myeloid malignancies is provided by Kapor et al., in the context of the Special Issue of the Journal of Clinical Medicine "Myeloid-Derived Suppressor Cells (MDSCs) in Haematology" [85].

4.4. Umbilical Cord Blood Subsets

Since allografts transplanted in haematologic patients can be from cord blood stem cells, the nature of MDSCs in cord blood is of great importance. MDSCs are supposed to play an important role for the foetal–maternal tolerance and decreased numbers of them are associated with miscarriage [86][87]. In agreement to this hypothesis, several studies proved the suppressive function of increased cord blood PMN-MDSCs. The number of M-MDSCs was unchanged [88][89][90]. Kostlin et al. also found PMN-MDSCs accumulated in the healthy placenta and polarised T-cells to Th2 responses [17]. Moreover, a recent study conducted by Schwarz et al. showed increased levels of PMN-MDSCs in the cord blood of preterm infants. The increase was sustained in the peripheral blood during the neonatal period [91]. Zoso et al. and Mazza et al., as aforementioned, expanded ex vivo the distinct novel subpopulation of MDSCs that originated from umbilical cord blood precursors, named f-MDSCs. The researchers propose this novel subset as a tool for treatment of allograft rejection and in vitro generation of T-regs [29][92]. A detailed research of the literature is provided by Bizymi et al. in the context of the Special Issue of the Journal of Clinical Medicine "Myeloid-Derived Suppressor Cells (MDSCs) in Haematology" [93].

5. What Are the Potential Clinical Applications of MDSCs in Haematology?

5.1. MDSCs as Biomarkers

MDSCs are found to be increased in a number of studies in patients suffering from MDS, MPN, MM, lymphomas, and leukaemia. This increase is associated in most cases with poor outcome, relapsed and refractory disease, and higher risk of therapy failure. Thus, the levels of MDSCs may work as biomarkers of diagnosis, disease activity, response to treatment, or disease progression, and there are a number of studies in this direction in the literature [53].

All subtypes of MDSCs seem to have increased numbers in HL, as well as in NHL and MM. However, the studies concerning MDSCs in NHL and MM are diverse and still share contrary results. Interestingly, in all studies, the patients with higher numbers of these populations also have poorer markers of survival and worse disease progression [74]. For example, Wang et al. described in their original study that elevated levels of circulating M-MDSCs are correlated to tumour progression and poorer overall survival in patients with DLBCL [94]. Additionally, Wu et al. described the prognostic value of M-MDSCs in DLBCL [95]. A special mention of MDSCs and lymphoid malignancies is provided in the context of the Special Issue of the Journal of Clinical Medicine "Myeloid-Derived Suppressor Cells (MDSCs) in Haematology" as Papafragkos et al. have published their detailed research concerning this subject [96].

In the study of Kittang et al., MDSCs seemed to be higher in high-risk patients compared to lower risk, indicating that these cells may serve as biomarkers of severity in myelodysplasia in the future [65]. In the novel study by Geskin et al. including patients with mycosis fungoides (MF) and Sézary syndrome (SzS), MDSC activity, as evaluated by the ROS production, increased with the activity of the disease, i.e., it was higher in patients with >IB MF than in IA stage, although the numbers of MDSCs did not differ among the study groups [97]. However, more research on the field is needed in order to establish whether MDSCs are related to severity in T-cell malignancies.

Despite the small number of studies and the contradictory results in ITP as explained above, all studies agree that an increase in MDSCs is a common finding in remission, indicating that MDSCs can be a biomarker of disease activity and therapeutic response [80][81][82].

5.2. MDSCs as Therapeutic Targets

MDSCs are promising therapeutic targets. Up to now, the strategies have been focusing on depletion, deactivation, differentiation, or blockage of their development. The targeting of MDSCs functions synergistically with immunotherapy, leading to better results for the patient. Older as well as novel agents (all-trans retinoic acid (ATRA), IL-4, celecoxib, gemcitabine, etc.) seem to affect the number or properties of these cells, as they act on pathways essential to them as well [98][99][100][101][102][103][104][105]. Olivares-Hernández et al. researched in the context of the Special Issue of the Journal of Clinical Medicine "Myeloid-Derived Suppressor Cells (MDSCs) in Haematology" the current literature on an interesting subject, i.e., how targeting MDSCs in haematologic malignancies can facilitate the therapy with immune checkpoint inhibitors (ICIs), as resistance to ICIs could be secondary to MDSCs [106].

Treatment with high-dose dexamethasone (DXM) restored the levels of MDSCs in patients with ITP in a dose-dependent manner [80][81][82][107]. In the experiments of Hou et al., MDSCs from ITP patients treated with DXM improved their capacity to suppress T-cells and upregulated the expression of Ets1. The researchers transferred MDSCs to a mouse model of ITP and observed an increase in the platelet counts and Ets1 expression [79][107]. Similarly, intravenous immunoglobulin (IVIG) treatment improved the numbers of MDSCs in spleen cells of ITP patients and trauma patients [80][108].

Eksioglou et al. targeted MDSCs in low-risk MDS patients with an antibody against CD33. Blocking CD33 led to direct cell toxicity and cell death, as well as disruption of the downstream signalling and the interaction with S100A8/A9 [109]. In the aforementioned study of Geskin et al., the researchers claimed that the treatment with IFN-a2b used in patients with MF owes in part its effect to preventing the immunosuppressive properties of MDSCs, as the treated individuals, although not changing their cell population numbers, presented decreased serum arginase levels and MDSC ROS production [97].

5.3. Graft-versus-Host Disease

An important step that historically boosted the research on MDSCs was their involvement in allogeneic haematopoietic stem cell transplantation (AHSCT), a crucial subject in haematology. It seems that they can enhance the amelioration of the graft-versus-host disease (GvHD), the state where the transplanted cells reject and attack the host. The observation that has led to this hypothesis was that the mobilisation of stem cells with G-CSF was correlated with an increase in MDSCs as well. Since then, several targeting strategies have been suggested and are under investigation, in order to eliminate the risk of GvHD in patients treated with AHSCT [110][111][112][113]. A paper by Demosthenous et al. was published in the context of the Special Issue of the Journal of Clinical Medicine "Myeloid-Derived Suppressor Cells (MDSCs) in Haematology" dedicated to MDSCs in GvHD [114].

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