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Myeloid Derived Suppressor Cells and Their Role in Diseases

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Abstract:

Myeloid derived suppressor cells (MDSCs) are a heterogeneous population of myeloid progenitors that can play a major role in tumour development and chronic inflammation. The importance of the suppressive function of MDSCs was first suggested by studies involving cancer patients and cancer-bearing mice. In addition, recent studies have demonstrated that MDSCs can also be involved in many other pathological conditions. MDSCs have unique ways of abrogating an immune response in addition to those utilised by other immune-suppressive cell types, for example via the induction of arginase-1 and consequent upregulation in reactive oxygen species (ROS) production. Due to their heterogeneity, they further can express a variety of lineage markers, which overlap with other myeloid cell types such as Gr1, CD11b, MHCII^{lo}, Ly6C and Ly6G, making it difficult to identify them by surface phenotype alone. The disparity between mouse and human MDSCs further complicates the identification of these elusive cell populations. In this review, we will summarise the recent updates on the methods for eliciting and studying different MDSC subsets, including newly proposed surface phenotypes, as well as insights into how their function is being characterised in both mice and humans. In addition, exciting new discoveries suggesting their involvement across a number of different pathological settings, such as sepsis, autoimmunity and *Leishmaniasis*, will be discussed.

Keywords:
Myeloid derived suppressor cells (MDSCs); arginase-1; inducible nitric oxide synthase (iNOS); reactive oxygen species (ROS); chronic inflammation; dendritic cells (DCs); granulocytes; monocytes; immune response; suppression; tumour development;

List of abbreviations:
Myeloid derived suppressor cells, MDSCs; dendritic cells, DCs; inducible nitric oxide synthase, iNOS; reactive oxygen species, ROS; major histocompatibility complex class II, MHCII; monocytic MDSCs, Mo-MDSCs; granulocytic MDSCs, G-MDSCs; transforming growth factor-β, TGF-β; interferon-γ, IFN-γ; granulocyte/ macrophage colony stimulating factor, GM-CSF; vascular endothelial growth factor, VEGF; prostaglandin E_2, PGE_2; natural killer, NK; regulatory T-cells, T-regs; hematopoietic stem cells, HSCs; nitric oxide, NO; janus-kinase, JAK; signal transducer and activator of transcription, STAT; antigen-presenting cells, APCs; hepatitis C virus, HCV; hemagglutinin, HA; S100 calcium binding protein A8 and 9, S100A8 and S100A9; inflammatory bowel diseases, IBD

1. INTRODUCTION

Myeloid derived suppressor cells (MDSCs) are a heterogeneous population of early myeloid progenitors, which includes immature granulocytes, macrophages, and dendritic cells (DCs) [1-3]. MDSCs are often generated and expanded and acquire their suppressive abilities during pathological conditions such as traumatic injuries, tumour development and pathogenic infections [4-8].

MDSCs can play a major role in tumour development and chronic inflammation due to their potent regulatory roles in immune responses [9-11]. For example, upon activation by tumour-derived mediators or host-induced cytokines, these cells express immunosuppressive factors such as arginase-1, inducible nitric oxide synthase (iNOS) or reactive oxygen species (ROS), which can initiate programmed cell death and apoptosis in T cells and other effector cells [12, 13]. In this review, we will summarise the recent updates on diverse phenotypes and functions of MDSCs, as well as new insights recently gained into their involvement in different pathological settings.

2. ORIGIN AND SUBSETS OF MDSCs

At normal steady-state conditions, MDSCs are commonly found in naïve mouse bone marrow (20-30%), and are scarce in the spleen (2-4%), blood (2-4%), pancreas (1-2%), liver (2-5%) and lymph nodes (<1%) [14, 15]. As a heterogeneous population of cells, MDSCs can often express a variety of markers, which overlap with other myeloid lineage cells such as dendritic cells (DCs), granulocytes and monocytes (Figure 1) [1-3]. Although MDSCs are not a defined subset of cells, in mice they are characterised by the co-expression of myeloid lineage differentiation antigen Gr-1, myeloid cell marker, CD11b and low levels of major histocompatibility complex class II (MHCII), which are expressed on antigen-presenting cells to present antigens and activate the adaptive immunity [16] (Table 1).

Gr-1 is expressed on mature granulocytes in bone marrow and peripheral tissues and also transiently on monocytes during their differentiation in the bone marrow. Furthermore, it is an epitope expressed on Ly6C (monocytic/macrophage marker) and Ly6G (granulocytic/neutrophil marker). Studies have shown that MDSCs can be further divided into two different subsets based on the expression of Ly6C and Ly6G molecules [17]. Cells that have a monocytic MDSC phenotype express CD11b, high levels of Ly6C but no Ly6G. They are less granular (low side-scatter when assessed by flow cytometry) and express higher levels of monocytic markers such as F4/80, ICAM-1, and CCR2 when compared to the granulocytic subset of MDSCs [1, 18, 19]. Monocytic MDSCs (Mo-MDSCs), characterised as $CD11b^{+}Ly6C^{hi}Ly6G^{-}$ cells express arginase-1 and exert their suppression on antigen-specific $CD8^{+}$ T-cell activation via a NOS-mediated mechanism [19]. Granulocytic MDSCs (G-MDSCs) are described as $CD11b^{+}Ly6C^{lo/int}Ly6G^{hi}$ and are more granular (high side-scatter when assessed by flow cytometry) when compared to Mo-MDSCs [19]. These cells also express high levels of arginase-1, but unlike Mo-MDSCs, they mediate suppression of $CD8^{+}$ T-cell activation and proliferation via a ROS-mediated mechanism [17]. Although both subsets of MDSCs initiate suppression of $CD8^{+}$ T-cell activity via different mechanisms, both populations generally express CD115 (M-CSF receptor), CD16/32 (Fc receptor), CD124 (IL-4 receptor) and low levels of CD80 [20-22]. However, these molecules appear not to be involved in the immunosuppressive roles of MDSCs [17].

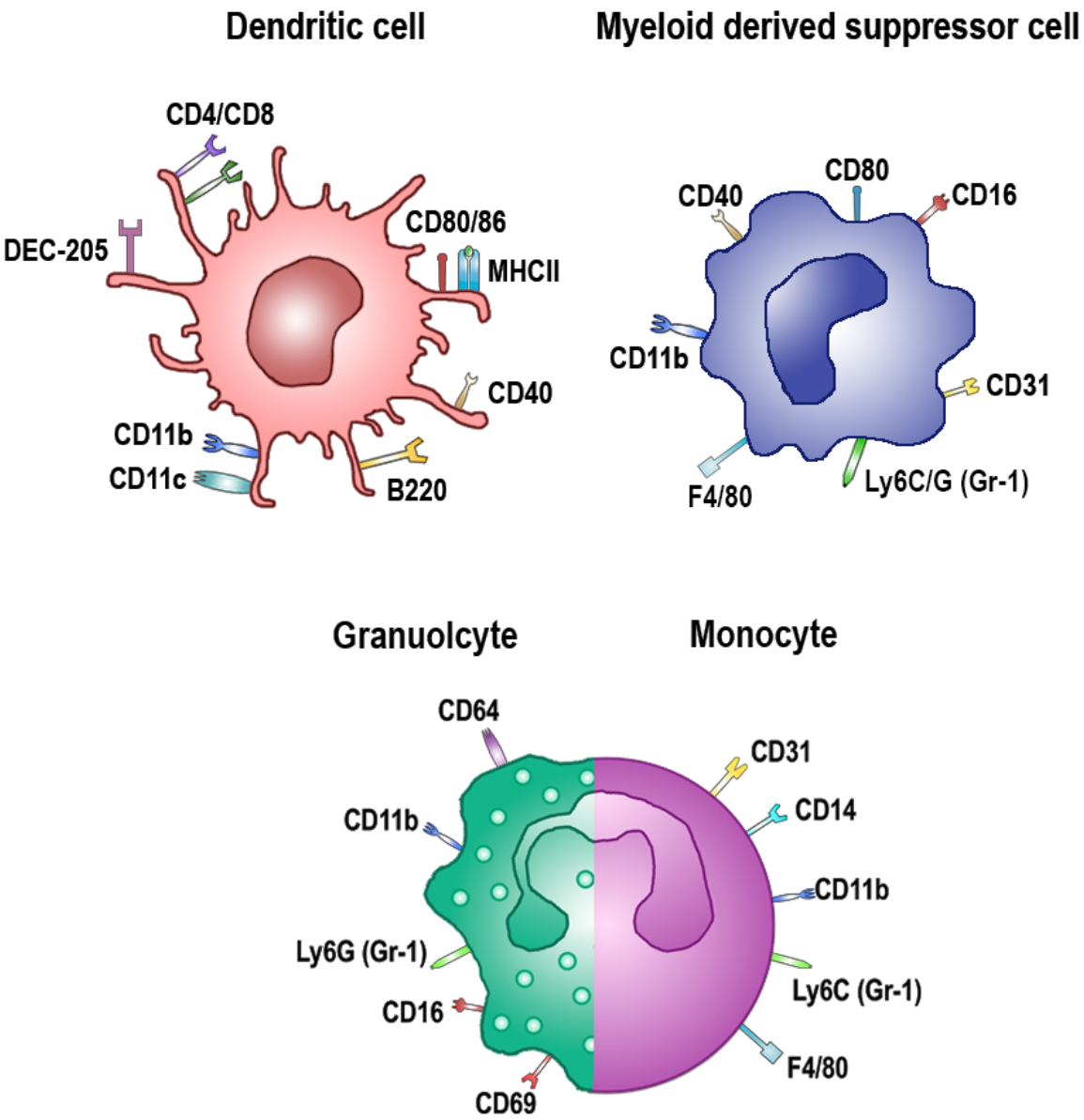

Fig. (1). Comparison of marker expression on dendritic cells and MDSCs

		Phenotype		Functional Markers		Functional Proteins	
Mouse	Mo-MDSCs	$CD11b^{+}$ $CD16^{+}$ $CD31^{+}$ $CD115^{+/-}$ $CD120b^{lo}$ $CD124^{+/-}$	SSC^{lo} $CD49d^{hi}$ $F4/80^{+}$ $Ly6C^{+}$ $Ly6G^{-}$	$CD40^{+}$ $CD80^{+}$ $MHCII^{-/lo}$		$S100A8^{+}$ $S100A9^{+}$ Arginase-1 IL-10	iNOS
	G-MDSCs		SSC^{hi} $CD49d^{lo}$ $F4/80^{-}$ $Ly6C^{lo/int}$ $Ly6G^{+}$		$CCR2^{+}$ $ICAM\text{-}1^{+}$		ROS
Human	Mo-MDSCs	$CD11b^{+}$ $CD66^{hi}$ $CD124^{+}$ $CD125^{+}$ $VEGFR^{+}$	SSC^{lo} $CD14^{+}$ $CD15^{-}$ $CD33^{hi}$	$CD40^{-}$ $CD80^{-}$ $CD83^{-}$ $HLA\ DR^{-/lo}$		$S100A9^{+}$ Arginase-1	iNOS Il-10 IL-13 TGFβ
	G-MDSCs		SSC^{hi} $CD14^{-}$ $CD15^{+}$ $CD33^{int}$				ROS

Table 1. Phenotypic and functional markers of murine and human MDSCs.

Unlike murine MDSCs, human MDSCs are often identified as lineage^{-} CD11b^{+} HLA DR$^{-/lo}$ [23, 24]. Several recent studies have shown that subsequent characterisation of human MDSC subsets can be done with the expression of CD14 and CD15 molecules [25-28]. Identification of a CD11b^{+} CD14^{-} CD15^{+} population with granulocyte morphology in renal cell carcinoma patients has been described as the human equivalent to G-MDSCs in mice [29] (Table 1). These cells have been shown to be a subpopulation of activated granulocytic cells expressing high levels of CD66b and VEGFR1. They have low to no expression of classic activation markers such as CD80, CD83, CD86 and MHCII, but are capable to secrete high levels of arginase-1, which can be released through degranulation of intracellular granules upon activation [29, 30]. Depletion of CD11b^{+} cells and not CD14^{+} cells has shown to re-establish T-cell proliferation, cytokine secretion and expression of CD3ζ chain, suggesting that G-MDSCs are the main source of arginase-1 secretion in these patients [29]. Human Mo-MDSCs on the other hand can be identified as CD11b^{+} CD14^{+} HDR$^{-/lo}$ in melanoma patients [27, 31]. These cells promote immunosuppression by spontaneously expressing transforming growth factor-ß (TGF-ß) [31]. Depletion of CD14^{+} cells restores T-cell proliferation and interferon-γ (IFN-γ) secretion. Although it is generally agreed that murine MDSCs are identified as CD11b^{+} Gr-1^{+} cells, and various studies have attempted to investigate human MDSCs with various combinations of lineage markers [32-36], until a definitive marker is found, the phenotypic definition of MDSCs will remain ambiguous.

3. GENERATION AND ACTIVATION OF MURINE MDSCs

Murine MDSCs can be generated in *in vitro* cultures from bone marrow cells using granulocyte/macrophage colony stimulating factor (GM-CSF). Depending on the concentration of GM-CSF, MDSCs can be generated between 3-10 days [3]. Higher concentration of GM-CSF leads to a more rapid development of MDSCs within the culture, but will also generate neutrophils. In contrast, at lower concentrations of GM-CSF in culture MDSCs can be generated within 8-10 days. However, DCs are generated simultaneously in those cultures [37]. GM-CSF can be secreted at a high concentration by T-cells, DCs and natural killer (NK) cells in the presence of an immune response [38-40] leading to an accumulation of MDSCs within the site of inflammation.

In addition to GM-CSF, several soluble factors such as granulocyte colony-stimulating factor (G-CSF) [41], macrophage colony-stimulating factor (M-CSF) [42], stem cell factor [43] and vascular endothelial growth factor (VEGF) [44] can directly induce the expansion of MDSCs.

VEGF is secreted by macrophages [45], DCs [46], T-cells [47] and renal tubular epithelial cells [48] and is often found after injury or in tumour-related diseases. It is also an important factor for differentiation of haematopoietic progenitor cells [49, 50]. VEGF suppresses DC generation and activation in favour of increased production of immature myeloid progenitor cells [49, 50]. Furthermore, recent studies have shown that inhibiting VEGF interaction with its receptors can prevent infiltration of MDSCs and regulatory T-cells (T-regs) while simultaneously increasing DC differentiation [51].

G-CSF often plays a vital role in neutrophil generation and mobilisation in inflammatory conditions [41]. However G-CSF have also been shown to induce G-MDSC proliferation and accumulation in the presence of tumour [52-54]. M-CSF and stem cell factor are generally found secreted in tumour microenvironment. M-CSF were found to be secreted in conjunction with IL-6 by in human renal cell carcinoma cell line, which have prevented DC generation from hematopoietic stem cells (HSCs) and triggered their commitment to monocytic cells [42]. Stem cell factor have been shown to be secreted by murine and human tumour cell lines, and tumour-

bearing mice, and blockade of stem cell factor function have greatly reduced MDSC expansion and enhanced tumour regression [43].

PGE_2 is also often associated with inflammatory responses and tumour-related diseases [32, 51, 55]. Tumour cells were found to express PGE_2, which can directly interact with HSCs through PGE_2 receptors to induce proliferation into MDSCs, thus promoting tumour survival [32, 51, 55]. PGE_2 can also induce indirect MDSC proliferation and accumulation by inducing secretion of factors such as VEGF, cyclooxygenase 2 (COX2) and IL-6 [32].

In addition to these growth factors, MDSCs can also be exposed to factors such as IFN-γ to induce activation. IFN-γ is secreted by a number of different immune cells to influence T-cell and MDSC functions [12, 13]. When exposed to IFN-γ, MDSCs express arginase-I and iNOS, which in turn prevent T-cell activation and promote T-cell apoptosis [12, 13]. Several studies have also shown that other cytokines such as IL-1ß, IL-4, IL-6, IL-10 and TGF-ß can also play a role in promoting MDSC generation and may enhance their suppressive function [20, 56, 57].

4. MECHANISMS OF MDSC-MEDIATED IMMUNE SUPPRESSION

MDSC-induced suppression requires cell-to-cell contact due to interaction of cell surface markers and secretion of transitory mediators [30, 58, 59]. The main suppressive activity of MDSCs is associated with secretion of arginase-I, iNOS and ROS [12, 60] (Figure 2). iNOS breaks down L-arginine into nitric oxide (NO) while arginase-I breaks down L-arginine into urea and L-ornithine. Depleting L-arginine prevents CD3 generation on T-cells [61]. NO inhibits effector T-cell activation through Janus-Kinase (JAK) 3 and signal transducer and activator of transcription (STAT) 5 pathways and also abrogates MHCII molecule expression on antigen presenting cells (APCs) [60, 62]. MDSCs can also induce effector T-cell apoptosis [12, 13, 60, 62].

ROS expression plays an important role in MDSC-mediated suppression. Its production by MDSCs can be induced in response to T-cell interaction or by exposure to cytokines such as TGF-ß IL-6, IL-10 and GM-CSF [57]. Hydrogen peroxide, a common form of ROS, prevents cytokine secretion by T-cells and induces T-cell apoptosis [63]. Earlier studies have also shown that IFN-γ produced by immune cells at the site of injury can induce ROS and NO production in MDSCs [64].

Peroxynitrite is produced by a reaction of NO with hydrogen peroxide and is one of the most damaging oxidants in the body [65]. Secretion of peroxynitrite has been observed at sites of inflammation and where MDSCs and immune cells accumulate [66]. Different types of cancers have also been shown to induce high levels of peroxynitrite in their microenvironment, which renders T-cells unresponsive to antigen-specific stimulation [67, 68].

Recent findings have shown that MDSCs also secrete S100 calcium binding protein A8 and A9 (S100A8 and S100A9) [36]. Expression of these functional proteins is often associated with inflammatory conditions such as rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, cystic fibrosis and psoriasis [69-73]. However, STAT3-dependent upregulation of S100A9 can be initiated by tumour-derived factors, preventing DC differentiation while promoting MDSC accumulation [74]. S100A8 and S100A9 secreted within a tumour microenvironment can promote MDSC migration to tumour sites by inducing an autocrine pathway through activation of carboxylated N-glycan receptors on these cells [75].

Furthermore, MDSCs can induce T-reg expansion in the presence of IFN-γ and IL-10, disrupt innate immunity by interacting with macrophages, NK cells and NK T-cells, thus enhance tumour progression [76].

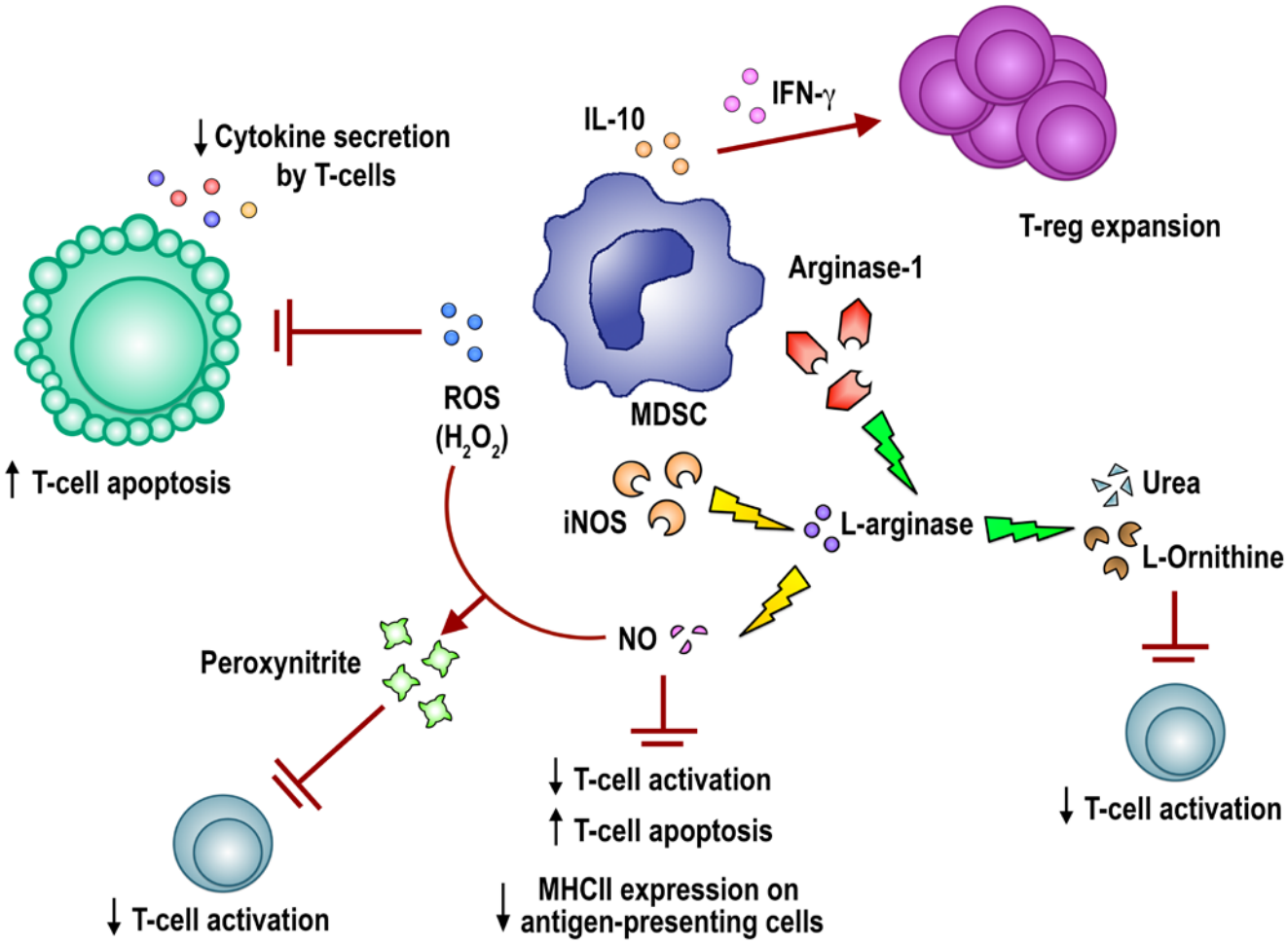

Figure 2. Different mechanisms employed by MDSCs to mediate immunosuppression.

5. MDSCs IN DISEASES

The importance of the suppressive roles of MDSCs was initially characterised in studies involving cancer patients and cancer-bearing mice [66, 77]. However, recent studies have shown that MDSCs are also involved in other pathological settings.

5.1 MDSCs in cancer

Most patients with advanced cancer are immunosuppressed, and the cause of immunosuppression can be instigated by a variety of immune cells such as tumour-associated macrophages, suppressive type II NK T-cells, T-regs and MDSCs, which in turn can promote tumour survival and expansion [11]. Although a variety of immunosuppressive cell types can be present in a tumour microenvironment, it was noted that MDSCs are consistently found in most cancer patients [78]. In fact, MDSCs were increased up to tenfold in the blood of cancer patients when compared to healthy individuals [78]. Similarly, in murine tumour models, 20-40% of nucleated splenocytes (in contrast to 2-4% in healthy mice) and 30–70% of tumour-infiltrating leukocytes were found to be MDSCs [79-81]. Accumulation and activation of MDSCs has been further associated with immunosuppression by abrogating effector T-cell response and mediating T-reg responses [21]. Collectively, these findings suggest that the suppressive effects of MDSCs play a major role in tumour survival by assisting tumour to escape immunosurveillance and recruiting other regulatory cells such as T-regs. While studies have shown that cancer progression can be retarded or reversed with the removal of MDSCs [82, 83], more studies are needed in procuring an effective way of mitigating their suppressive effects in cancer.

5.2 MDSCs in other pathological conditions

Although most knowledge on MDSCs and their role in the immune system has been gained from studies in cancer, recent findings suggest that these cells are also involved in pathogenic infections [10], sepsis [7], autoimmune diseases [9] and transplantation [84]. For example, the inflammatory heart infiltrate from mice infected with *Trypanosoma cruzi* consisted mainly of $CD11b^+$ $Ly6G^-$ $Ly6C^+$ MDSCs [85]. These cells exhibited a monocytic phenotype and expressed arginase-1 and iNOS, both of which can suppress T-cell proliferation and prevented clearance of the parasite. In another study, looking at *Leishmania major* infection, NO expressing $CD11b^+$ $Gr\text{-}1^+$ ($Ly6C^{hi}$) MDSCs circulated within the blood and infiltrated skin lesions [10]. These cells could suppress effector T-cell proliferation through NO expression. However, upon treatment with IFN-γ and IL-4, they could eliminate the parasites in a NO-dependent manner. A similar expansion of MDSCs was also seen in Hepatitis C virus (HCV) infections in humans, where T-cell proliferation was suppressed through a ROS-mediated mechanism [86].

During polymicrobial sepsis, $CD11b^+$ $Gr\text{-}1^+$ MDSCs increased dramatically in the spleen, lymph nodes and bone marrow and remained elevated for an extended period of time [7]. These cells supressed IFN-γ secretion by CD8 T-cells, skewing the immune response from a Th1 to a Th2 profile.

Immunosuppression is often depicted as the bane of the immune system. However, it can be beneficial in the context of autoimmune diseases and in transplantation settings. In autoimmune diseases such as the inflammatory bowel disease (IBD) mouse model, a substantial population of $CD11b^+$ $Gr\text{-}1^+$ MDSCs was detected in the spleen and the intestine upon adoptive transfer of haemagglutinin (HA)-specific $CD8^+$ T cells. These MDSCs released NO-synthase-2 and arginase-1 to prevent T-cell proliferation and induced T-cell apoptosis [9]. MDSCs also prevent the onset of autoimmune diabetes by inducing antigen-specific T-reg

expansion and suppressing effector T-cell proliferation through an MHCII-dependent processes in diabetic mouse models [87]. Similarly, in transplantation settings, investigators have made use of the suppressive effects of MDSCs. In a recent study by Chou and colleagues, MDSCs mixed with islet allografts were transplanted into diabetic mice [88]. This effectively protected the islet, by preventing a CD8 T-cell response and inducing expansion of T-regs within the graft. This effect was also seen in other cases, where MDSCs were used to prolong graft survival by inducing allograft tolerance [84, 89, 90]. Collating these recent findings, it is clear that the immune regulatory properties of MDSCs are playing an important role in many pathological conditions, albeit their properties are detrimental in cancer and pathogenic infections. This evidence also suggests that not only is it important to remove MDSCs in diseases such as cancer and pathological infections, it is also crucial to learn how to generate these cells so that their properties can be exploited for future treatments for autoimmune diseases and transplantation settings.

6. CONCLUSION

Recent studies have been able to distinguish inflammatory neutrophils, monocytes and DCs from immunosuppressive MDSCs, a heterogeneous population of myeloid cells with distinctly different function. The increased interest in the elusive MDSCs over the recent years has shed new light on how immunity is regulated in different pathological conditions, particularly in animal models. More in-depth research is required to clearly define MDSCs in humans. Also, little is known about the molecular mechanisms which trigger the generation and expansion of these cells from the progenitor cell populations. Deeper understanding of these cells and their function within the immune system is likely to open opportunities for new therapeutic interventions in cancer and autoimmune diseases.

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