

Review Article

Mesenchymal Stem Cells and Myeloid Derived Suppressor Cells: Common Traits in Immune Regulation

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To protect host against immune-mediated damage, immune responses are tightly regulated. The regulation of immune responses is mediated by various populations of mature immune cells, such as T regulatory cells and B regulatory cells, but also by immature cells of different origins. In this review, we discuss regulatory properties and mechanisms whereby two distinct populations of immature cells, mesenchymal stem cells, and myeloid derived suppressor cells mediate immune regulation, focusing on their similarities, discrepancies, and potential clinical applications.

1. Introduction

Immune response protects host against pathogen invasion and cancer. However, if uncontrolled, it may induce severe tissue damage and therefore under steady-state conditions is tightly regulated. Understanding cells and mechanisms that regulate immune response is critical to unravel pathogenesis of many diseases and develop new strategies for immune modulation during cancer, chronic infections, autoimmune disorders, allergies, and following organ transplantation.

Several populations of immune cells have been implicated in the control of immune response including natural and induced CD4⁺ T regulatory cells (Treg), CD8⁺ Treg, Breg, macrophages, and dendritic cells. To control immune response, these cells utilize a set of core suppressive mechanisms, the main of which are the secretion of inhibitory cytokines (e.g., IL-10, TGF- β , and IL-35), the expression of inhibitory receptors (e.g., PD-L1), the inhibition of antigen-presenting cell maturation, and cytolysis [1–4].

Besides mature immunocompetent cells designated to control immune response, other populations may also contribute to immune regulation. In particular, two distinct populations of functionally immature cells, mesenchymal stem cells (MSCs), and a population of immature myeloid cells, myeloid derived suppressor cells (MDSCs), have

been implicated in immune suppression and regulation [5, 6].

MSCs and MDSCs belong to distinct differentiation lineages; however, their immunoregulatory properties have several common traits. Here, we review the underlying mechanisms and regulatory properties of MSCs and MDSCs focusing on their similarities and distinctions.

2. MSCs and MDSCs: General Characteristics

2.1. MSCs. MSCs are multipotent stromal self-renewing cells capable to differentiate into mesenchymal tissues like osteocytes, chondrocytes, and adipocytes [7]. MSCs exhibit paracrine effects and participate in immunomodulation and tissue repair. The cells are found in the bone marrow (BM) and other embryonic and adult tissues such as cord blood, placenta, adipose tissue, and perivascular sources. In the BM, MSCs fulfill a supportive function for hematopoietic cells and participate in the control of their renewal and differentiation [8–10]. Phenotypically, MSCs are characterized by the expression of CD105, CD90, and CD73 and lack of the expression of haemopoietic markers, such as CD45, CD34, CD14, CD11b, CD79 α , CD19, and HLA-DR [11–13].

The immunomodulatory properties of MSCs were first demonstrated by Di Nicola and coauthors, who showed that

BM-MSCs inhibited T cell proliferation in mixed lymphocyte reaction (MLR) [14]. Since then, the ability of MSCs to suppress immune responses has been extensively studied. Currently, it is understood that MSCs possess rather immunoregulatory than immunosuppressive properties: depending on the microenvironment they can inhibit, modulate or even enhance immune function of various immune cells [5, 15]. Proinflammatory conditions induce suppressive properties in MSCs. Due to their immunoregulatory properties and the feasibility of generating the large numbers of autologous MSCs, MSCs are considered as a potentially valuable tool for clinical immunomodulation.

2.2. MDSCs. MDSCs belong to the hematopoietic lineage and represent the heterogeneous population of early myeloid progenitors/precursors of granulocytes, macrophages, and dendritic cells (DCs) able to mediate immune suppression [6]. In steady-state conditions, MDSCs are rare and are primarily found in the BM. During different pathologies accompanied by inflammation, MDSCs accumulate abundantly in the BM, blood, spleen, lungs, and other organs [16–19].

In mice, MDSCs are defined as Gr-1^{+/dim}CD11b⁺ cells. In human, MDSCs are generally identified based on the expression of CD33 and CD11b and lack of the expression of HLA-DR. Two main subsets of MDSCs, monocytic and granulocytic, have been described according to their nuclear morphology and phenotype. In mice, monocytic and granulocytic MDSCs are identified as Ly-6G^{-/low}Ly-6C^{hi}CD11b⁺ (F4/80⁺CD115⁺CD49d⁺) and Ly-6G⁺Ly-6C^{low}CD11b⁺ (F4-80⁻CD115⁻CD49d⁻) cells, respectively. In human, they are CD14⁺HLA-DR⁻ and CD15⁺/CD66b⁺, respectively [6, 19–22].

MDSCs are the main negative regulators of immune response in cancer [6, 23] and are also involved in the immune suppression in many other pathological conditions [19, 24–26]. Similar to MSCs, the suppressive activity of MDSCs is inducible and dramatically increases under proinflammatory conditions [6]. Expressed immunosuppressive properties and abundant accumulation of MDSCs under proinflammatory conditions make them an attractive target for immunomodulation in cancer and other diseases.

3. Molecular Mediators of Immune Suppression

To regulate immune response, MSCs and MDSCs utilize a set of mediators and mechanisms, which they partially share with other immune regulatory cells. In this section, we summarize the main mechanisms whereby MSCs and MDSCs mediate immune regulation focusing on their cellular targets and activation.

3.1. Indoleamine 2,3-dioxygenase (IDO) and Tryptophan Metabolism

3.1.1. Effects. IDO enzymes (expressed as two distinct enzymes, IDO1 and IDO2) catalyze the essential amino acid tryptophan into metabolites, that is, kynurenine, quinolinic

acid, and picolinic acid. Tryptophan consumption increases the level of uncharged tryptophan tRNA in immune cells. This activates general control nonderepressible 2 (GCN2) stress-response kinase, eukaryotic translation initiation factor 2 (eIF2), and GCN2-eIF2-mediated pathway, which leads to the reduction in protein synthesis, retards cellular proliferation, arrests T cells in G0/G1 cell cycle, and increases lymphocyte sensitivity to Fas-mediated apoptosis [27, 28]. The activation of GCN2-mediated pathway also downregulates IL-6 supporting the suppressive status of Tregs and restricting their conversion to Th17-like cells [29]. In a model of Th17-associated experimental autoimmune encephalomyelitis (EAE), halofuginone, a small molecule that induces amino acid starvation, selectively inhibited the differentiation of Th17, verifying a role of amino acid deficiency in the suppression of Th17 [30]. Tryptophan depletion decreases the expression of costimulatory molecules and increases the expression of the inhibitory receptors ILT3 and ILT4 by DCs; DCs differentiated under low-tryptophan conditions become tolerogenic [31] (Figure 1).

Tryptophan metabolites are directly toxic to CD8⁺ and CD4⁺ Th1 cells, whereas Th2 cells are more resistant to their toxicity. Therefore, IDO releases Th2 from Th1-mediated suppression and skews T helper response towards Th2 type [27, 32, 33]. Kynurenines are also natural ligands for the aryl hydrocarbon receptor (AhR); their interaction with AhR promotes the differentiation of CD4⁺Foxp3⁺ Treg cells, interferes with the generation of Th17, and decreases the immunogenicity of DCs [34].

3.1.2. IDO Expression by MSCs and MDSCs. In the immune system, IDO are expressed primarily by professional antigen-presenting cells [28]. Both MSCs and MDSCs express IDO and utilize IDO mediated mechanisms for immune suppression [35–37].

3.1.3. Regulation of IDO Expression. The IDO gene is inducible in the presence of IFN- γ and regulated by upstream IFN- γ -responsive elements that bind activated STAT1, interferon regulatory factor-1 (IRF-1), and NF- κ B [27, 35, 38, 39]. IRF-8 contributes to IFN- γ -induced IDO expression by enhancing the expression of IDO and decreasing DAPI2 which basally opposes IDO expression [40]. It was suggested that MSCs utilize IDO mediated mechanism in the presence of IFN- γ but not in basal state [41]. IDO expression is also increased by PGE2 [42], thus relating the two mechanisms of immune control utilized by MSCs and MDSCs.

3.2. Cyclooxygenase-2 and Prostaglandin E2

3.2.1. Effects. PGE2 synthesizes from the arachidonic acid after the latter releases from membrane phospholipids and is metabolized by either the constitutive cyclooxygenase-1 (COX-1) or the inducible cyclooxygenase-2 (COX-2) [43]. PGE2 mediates pain, edema, and fever, the main features of inflammation. At the same time, it exerts anti-inflammatory effects. The interaction of PGE2 with EP2 and EP4 receptors expressed by immune cells leads to increase in cyclic AMP, activates protein kinase A and

Inducers	Mediators	Downstream mechanisms	Effects on DC and Mphs	Effects on T cell generation and function					Produced by
				Proliferation	Th1	Th17	Th2	Treg	
IFN- γ [27, 38–41] PGE2 [42], TNF- α [42]	IDO	TRP consumption \rightarrow GCN2 \rightarrow eIF2 [27, 28, 31] TRP metabolites \rightarrow toxicity, AhR [27, 28, 34]	\downarrow costimulation [31] \uparrow ILT3, ILT4 [31] \uparrow tolerogenic DCs [31, 34]	\downarrow [27, 28, 135] (G0/G1 arrest)	\downarrow [27] (toxicity)	\downarrow [29, 30] (\downarrow IL-6)	\uparrow [32, 33] (release from Th1 control)	\uparrow [31, 34] (AhR, tolerogenic DCs)	MSCs MDSCs
IFN- γ , TNF- α , T cells [41, 59]	COX-2/PGE2	Cyclic AMP, Ca ²⁺ mobilization [43, 44]	\downarrow maturation [44, 166] \uparrow M2 [47] \uparrow maturation [44]	\downarrow [44, 134] \uparrow [44]	\downarrow [44–46] \uparrow [44] (at low doses)	\uparrow [43, 44, 48, 49] \downarrow [50]	\uparrow [44, 45]	\uparrow [51]	MSCs MDSCs
IFN- γ , TNF- α [35, 59, 91] IL-13 [92]	TGF- β	SMAD \rightarrow histone acetyltransferase/deacetylase [85]	\downarrow costimulation \downarrow MHC II [85]	\downarrow [85]	\downarrow [87]	\uparrow (in the presence of IL-6, IL-1 β , IL-23) [88]	\downarrow [86]	\uparrow [5, 15, 88]	MSCs MDSCs
TLR4, TLR9 [94, 100] PGE2 [101]	IL-10	JAK1/TYK2/STAT3/SOCS3 [98]	\downarrow costimulation [93] \downarrow MHC II [93] \uparrow M2 [97]	\downarrow [93, 94]	\downarrow [93, 94]	\downarrow [95]	\downarrow [94, 214]	\uparrow [95, 96]	MSCs MDSCs
IFN- γ [105]	HGF	ERK1/2 [104]	\downarrow costimulation \uparrow M2, IL-10 [102, 104]	\downarrow [14]	\downarrow [102]	\downarrow [102, 103]	\uparrow [102, 103]	\uparrow [102]	MSCs MDSCs
IFN- γ [79], IL-17 [80]	NO (iNOS)	\downarrow [69, 70] Jak3/STAT5/ERK/AKT	\downarrow MHC II [6, 71]	\downarrow [69, 70]	\downarrow [72, 73] (mice, human)		\downarrow [73] (human)		MSCs MDSCs
IL-4, IL-13, TLR [64], PGE2 [81, 205]	ARG-1	L-arginine depletion, \downarrow TCR- ζ [6, 61]	\downarrow [230]	\downarrow [6, 60, 61]	\downarrow [62]	\downarrow [63]	\uparrow [64, 65] \downarrow [66]	\uparrow [63, 67, 68]	MDSCs
IL-10 [108], IFN- γ TNF- α [114]	HLA-G5	ILT2, ILT4, KIR2DL4 [107–109]	\downarrow [107–109]	\downarrow [113, 114]	\downarrow [111] \uparrow [115] (at low doses)	\downarrow [111]	\downarrow [111] \uparrow [115] (at low doses)	\uparrow [112]	MSCs
IFN- γ , TNF- α , IL-1 [105]	Galectins	Apoptosis [121]	\downarrow [120]	\downarrow [122]	\downarrow [121]	\downarrow [121]	No effect [121]	\uparrow [122, 124]	MSCs

\uparrow : enhances function and/or generation; \downarrow : inhibits function and/or generation.

The main effects, inhibition (pink), stimulation (green), and both inhibition and stimulation, have been described (checked). Not enough data or no effect (white).

AhR: aryl hydrocarbon receptor; DC: dendritic cells; eIF2: eukaryotic translation initiation factor 2; GCN2: general control nonderepressible 2 stress-response kinase; JAK1, Janus kinase 1; Mphs, macrophages; SOCS3: suppressors of cytokine signaling 3; STAT3: Signal transducer and activator of transcription 3; TRP: tryptophan.

FIGURE 1: Main mediators utilized by MSCs and MDSCs to suppress T cell responses and their effects.

phosphatidylinositol-3 kinase dependent signaling pathways, and inhibits Ca²⁺ mobilization. Cyclic AMP interferes with IL-2-mediated pathways, inhibits the expression of proinflammatory cytokines and chemokines (i.e., IL-12p70, TNF- α , CCL3, and CCL4), and induces the expression of IL-10, IL-4, and IL-5 [43, 44]. This suppresses cell proliferation, induces alternative macrophages (M2), stimulates Th2, and weakens Th1 responses [44–47]. Besides inducing immunosuppression, PGE2 may play proinflammatory role in T cell function. In some studies, exogenous PGE2 enhanced DC maturation and T cell proliferation (reviewed in [44]). The above-mentioned inhibition of IL-12p70 induced by PGE2 is due to the inhibition of IL-12p35 chain. IL-12p40 chain is not affected by PGE2. IL-12p40 and p19 form IL-23, the cytokine involved in the generation of Th17. PGE2 increases the expression of p19 resulting in the increased production of IL-23 and Th17 polarization [43, 48]. In a model of EAE, EP4 antagonist decreased the accumulation of Th17 and Th1 cells and suppressed disease progression [49]. However, in some other studies, PGE2 inhibited Th17 differentiation [50]. Recent advances suggest that effects of PGE2 on Th17 and even Th1 depend on its concentration in such a way that micromolar concentrations suppress the responses while nanomolar concentrations promote the responses [44].

PGE2 enhances the differentiation of Foxp3⁺ Treg cells [51], elevates TGF- β secretion by monocytes, and induces the generation of MDSCs and their accumulation in tumor environment. The inhibition of COX-2 suppresses these processes [52–54].

3.2.2. Regulation of COX-2/PGE2 and Their Expression by MSCs and MDSCs. Both MSCs and MDSCs express COX-2 [41] and can produce PGE2 [41, 54–58]. PGE2 production increases in inflammatory conditions, that is, in the presence of IFN- γ and TNF- α and after cell coculture with peripheral blood cells [41, 59].

3.3. Arginase-1, Inducible Nitric Oxide Synthase, and Arginine Metabolism

3.3.1. Effects. Arginase-1 (ARG1) hydrolyses L-arginine to ornithine and urea reducing local arginine concentration. The latter activates GCN2, which inhibits cell cycling [60]. ARG1 downregulates the ζ -chain of the T cell receptor (TCR) complex, disturbing the process of T cell activation [6, 61]. There is only limited data on the subset-specific effects of ARG1. The studies have reported the inhibition of IFN- γ [62] and Th17 [63], and both the stimulation [64, 65] and the suppression [66] of Th2 responses by ARG1 produced by various cells. Tregs are expanded by ARG1; the inhibitor of ARG1 N-hydroxy-L-arginine (NOHA) abrogates this effect [67, 68].

Besides ARG1, L-arginine is metabolized by inducible nitric oxide (NO) synthase (iNOS) that generates NO. NO suppresses T cell function through the inhibition of JAK3, STAT5, ERK, and AKT involved in IL-2 signaling and the control of T cell proliferation [69, 70]. NO also inhibits the expression of MHC class II and induces T cell apoptosis [6, 71]. In murine T cells, NO was shown to suppress

the secretion of Th1 cytokines [72]; in human T cells, it suppressed the secretion of both Th1 and Th2 cytokines [73].

3.3.2. ARG1 and iNOS Expression by MSCs and MDSCs. In the immune system, ARG1 and iNOS are generally expressed by polymorphonuclear cells (PMN) and monocyte/macrophages [74]; T helper cells are also able to produce NO [72]. In M1 and M2 macrophages, ARG1 and iNOS are expressed reciprocally: ARG1 is expressed by M2, whereas iNOS by M1 subset [75]. MDSCs express both ARG1 and iNOS [6, 70]; however, the levels of their expression in monocytic and granulocytic populations may differ so that ARG1 is expressed predominantly by granulocytic MDSCs [76] and iNOS by monocytic MDSCs [6]. MSCs express iNOS and can produce NO [77], but there is no evidence for their expression of ARG1. In spite of this, MSCs can contribute to the depletion of L-arginine by promoting the generation of MDSCs [78].

3.3.3. The Regulation of ARG1 and iNOS. Generally, ARG1 and iNOS undergo reciprocal induction: ARG1 is induced by Th2 cytokines, whereas iNOS by Th1 cytokines [79]. Recently, IL-17 was shown to contribute to iNOS expression by enhancing its mRNA stability [80]. PGE2 stimulates ARG1 [81].

3.4. Reactive Oxygen Species and Peroxynitrite

3.4.1. Effects. Reactive oxygen species (ROS) are generated by NADPH oxidase which produces superoxide anion (O_2^-). Superoxide anion reacts with NO to form peroxynitrite. Peroxynitrate oxidates membrane molecules and nitrates amino acids. Nitration of TCRs alters antigen-recognition and inhibits the responses of $CD4^+$ and $CD8^+$ cells [82]. Nitration of the chemokine CCL2 was shown to block T cell migration to the inflammatory site [83].

3.4.2. ROS Production by MSCs and MDSCs. NADPH oxidase is generally expressed by leukocytes. In MDSCs, it is expressed predominantly by the granulocytic population [6]. MSCs do not generate ROS, but they are responsive to them: ROS promote MSCs' aging. In physiological levels, ROS improve MSCs' proliferation and differentiation [84].

3.5. Cytokines and Growth Factors. The main immunoregulatory cytokines produced by MSCs and MDSCs are TGF- β and IL-10.

3.5.1. TGF- β . TGF- β binds to the heterodimeric TGF- β receptor and initiates SMAD-dependent and SMAD-independent signal transduction pathways. SMAD-dependent pathway induces the recruitment of histone acetyltransferase and deacetylase to the promoters of target genes [85]. This leads to the blockade of IL-2 production, downregulates cell cycle promoting factors, upregulates cyclin-dependent kinase inhibitors, and inhibits the expression of MHC class II and costimulatory molecules in DCs and effector molecules (i.e., IFN- γ and perforin) in T cells. Consequently, the proliferation, helper, and cytotoxic

activity of T and NK cells are suppressed. TGF- β inhibits the differentiation of both Th1 and Th2 cells [86, 87]. In contrast, it promotes the generation of Treg and Breg cells. TGF- β is a key regulator of Foxp3 expression [5, 15, 88]. In the presence of IL-6, IL-1 β or IL-23 TGF- β promotes the generation of Th17 [88]. Recently, TGF- β was shown to inhibit the expression of iNOS in MSCs reversing their suppressive effect on T cell proliferation and manifesting immunostimulatory effect [89].

MSCs constitutively secrete TGF- β [90] and upregulate its production in the inflammatory environment, that is, in the presence of IFN- γ and TNF- α [35, 59, 91]. In MDSCs, the expression of TGF- β was induced by IL-13 [92].

3.5.2. IL-10. IL-10 is produced by various immune cells, including DCs, macrophages, Th1, Th2, Th17, Treg, $CD8^+$ T cells, and B lymphocytes, and also by MSCs and MDSCs. IL-10 directly acts on antigen-presenting cells (APC), decreasing their maturation, and the expression of MHC and costimulatory molecules [93]. IL-10 inhibits the production of proinflammatory cytokines and chemokines (i.e., IL-1 α , IL-1 β , IL-6, IL-12, TNF- α , CCL2, and CCL5, IL-8) and hampers DC migration to lymph nodes and the generation of effector T cells. Direct effects of IL-10 on T lymphocytes include the inhibition of proliferation, IL-2, IFN- γ , TNF- α , IL-4, and IL-5 production and memory formation [93, 94]. IL-10 also inhibits the differentiation of Th17 [95] but enhances the differentiation of IL-10 producing Treg cells and M2 macrophages [96, 97]. The anti-inflammatory effects of IL-10 are mediated through the phosphorylation of JAK1, TYK2, the activation of STAT3, and the induction of SOCS3, which negatively regulates various cytokine genes [98]. Apart from the immunosuppressive activity, IL-10 may display immunostimulatory properties: it inhibited or stimulated $CD8^+$ T cells depending on the type of pathogen and cell microenvironment [99]. Induction of IL-10 goes on as a result of toll-like receptors (TLR4 and others) activation [100]. PGE2 is a potent inducer of IL-10 [101].

3.5.3. Hepatocyte Growth Factor (HGF). HGF is primarily produced by MSCs. HGF displays pleiotropic immunosuppressive activity. It stimulates IL-10 production by monocytes, downregulates costimulatory molecules on DCs, inhibits Th1, and induces IL-10 producing Treg cells [102–105]. HGF produced by MSCs expanded human MDSCs [78]. One study reported the production of HGF by tumor-infiltrating MDSCs [106], which highlights the similarities between the two populations.

MSCs and MDSCs produce a number of other cytokines that contribute to cell biological activity, for example, IL-6, IL-8, and GM-CSF.

3.6. Other Mechanisms

3.6.1. HLA-G. HLA-G are nonclassical class I tolerogenic molecules expressed as four membrane-bound (HLA-G1 and HLA-G4) and three secreted (HLA-5 and HLA-G7) isoforms. In the immune system, HLA-G are largely expressed by DCs and macrophages. HLA-G act through the inhibitory

Cells	DCs and Mphs	T cell generation and function					B cells		PMN	NK cells	
		Proliferation & viability	Th1	Th17	Th2	Treg	B cells/plasma cells	Breg			
MSCs	↓ DC maturation, ↑ tolerogenic DCs [91, 163–177] ↑ M2 [178–186]	↓ [14, 131–137]	↓ [55, 136, 138, 139] ↑ (in Th2-conditions) [144]	↓ [50, 140–142] ↑ [145]	↓ (in Th2 conditions) [144]	↑ [55]	↑ [90, 91, 112]	↓ [131, 189–191, 193] ↑ [192, 193]	↑ [190, 194, 195]	↑ [207–211]	↓ [36, 112, 201]
MDSCs	↓ DC maturation [187, 188] ↑ M2 [153, 156]	↓ [19, 26, 146–152]	↓ [18, 19]	↑ [157] ↓ [158]	↑ [154–156], ↓ [231]	↑ [67, 159–162]	↓ [197–200]			↓ [212, 213]	↓ [203–206]

↑: enhances function and/or generation; ↓: inhibits function and/or generation.

The main effects, inhibition (pink), stimulation (green), and both inhibition and stimulation, have been described (checked). Not enough data (white).

DC: dendritic cells; Mphs: macrophages; PMN: polymorphonuclear cells.

FIGURE 2: Cellular targets and modulatory effects of MSCs and MDSCs.

receptors ILT2 and ILT4 expressed by myeloid DCs, CD4⁺ and CD8⁺ T cells, B cells, monocytes/macrophages, and NK cells [107–109]. HLA-G inhibit alloproliferative T cell response, Th1 cell migration, Th1, and Th17 cytokine production, induce Treg cells, and suppress the cytotoxic function of NK cells [110–114]. This general pattern has been reported by several groups. However, the effect of HLA-G may depend on their concentration: in the study by Kapasi and coauthors, high doses of HLA-G promoted Tregs, whereas low doses fostered the development of Th1 cells [115].

Human MSCs express and secrete HLA-G5. The secretion of HLA-G5 by MSCs is stimulated by IL-10, IFN- γ , and TNF- α [112–114]. Myeloid APCs were shown to express HLA-G in pathological context (e.g., in cancer and viral infections); it was suggested that HLA-G-expressing myeloid APCs may be viewed as suppressor cells [108]. Yet, the role for HLA-G in the regulatory functions of MDSCs remains to be evaluated.

3.6.2. CD39 and CD73. MSCs express ectonucleotidase CD73 that catabolizes AMP to adenosine. AMP is generated from ATP under the action of ectonucleoside CD39 that is expressed at low levels by MSCs and at high levels by activated T cells. Extracellular ATP exhibits proinflammatory effects; adenosine triggers inhibitory pathways mediated by cAMP and protein kinase A. Thus, the concerted action of CD39 and CD73 cleaves ATP to adenosine resulting in the immune suppression [116, 117]. Our search for data on the expression of CD39 and/or CD73 by MDSCs resulted in two original studies. One study reported the expression of CD73 by granulocytic MDSCs and the involvement of the nucleotidase activity in MDSCs-mediated suppression [118]. In another study, the anticancerogenic drug α -difluoromethylornithine hampered MDSC suppressive activity, in particular, by inhibiting the CD39/CD73-mediated pathway [119].

3.6.3. Galectins. Galectins (Gal), soluble glycan-binding proteins, bind to cell surface glycoproteins. MSCs express Gal-1 and Gal-9. Gal-1 inhibits tissue emigration of immunogenic DCs [120] and selectively binds to Th1 and Th17 cells inducing their apoptosis but does not affect Th2 cells [121, 122]. Gal-1 upregulates the expression of AhR in T cells and the production of IL-10 by Th1 and Th17 cells [122]. Gal-9 mediates antiproliferative effects on T and B cells. In B lymphocytes, it also reduces immunoglobulin release. Gal-9 is upregulated

by IFN- γ [123]. We found no reports on the usage of galectins by MDSCs in the available literature. However, galectins were shown to participate in the induction and the accumulation of MDSCs at tumor site [124].

3.6.4. CCL2. The chemokine CCL2 interacts with CCR2 receptor expressed by myeloid cells and NK cells, activated Th1 and Th17 cells, and recruits them to the site of inflammation. MSCs produce CCL2 and express metalloproteinase that truncates CCL2, generating CCR2 antagonist that suppresses the migration of inflammatory cells. This mechanism seems to be critical for MSC-mediated suppression during autoimmune disorders. Defects in CCL2 processing have been associated with the pathogenesis of SLE [125]. In EAE, adoptively transferred wild-type MSCs induced immune suppression, whereas CCL2^{-/-} MSCs did not [126]. We found no reports on the usage of CCL2-mediated mechanism by MDSCs. However, MDSCs express CCR2 and readily respond to CCL2 by accumulating at the corresponding inflammatory sites [127].

3.6.5. B7-H1. MSCs and MDSCs express negative costimulatory molecules, in particular, B7-H1. B7-H1 interacts with PD-1 [128]. The expression of B7-H1 by MSCs was induced by IFN- γ [129], whereas on MDSCs it could be induced by IL-13 [37]. Whether these differences are due to different experimental settings or are characteristic for MSCs and MDSCs remains to be clarified.

4. Cellular Targets

This section reviews immunomodulatory effects of MSCs and MDSCs on different immune cells (Figure 2).

4.1. T Lymphocytes. Effector T lymphocytes generate after naïve T cells recognize antigen, activate, proliferate, and differentiate into effector subsets. MSCs and MDSCs interfere with T cells at different stages of their differentiation and function.

4.1.1. MSCs. MSCs hamper antigenic presentation by DCs and thus interfere with the antigenic stimulation of T cells, both *in vitro* and *in vivo* (see below). Activation of T cells,

measured by the expression of CD69 and CD25, was inhibited by MSCs in some [130] but not in all [131, 132] studies. MSCs readily suppress T cell proliferation induced by mitogens, anti-CD3/CD28 stimulation, or transplantation antigens in MLR [14, 131–133]. The inhibitory effect is due to cell arrest in G0/G1 phase of cell cycle [131] and can be mediated by iNOS, PGE2 [134], IDO [135], TGF- β [14, 130], IL-10 [136], or PD-1 [134, 137]. The role for these molecular mediators in the suppression of T cell proliferation varies in different experimental settings. For example, the inhibition depended on IDO in some studies [135] but was IDO-independent in others [134, 137].

Functional activity of various T helper subsets is differentially affected by MSCs. Th1 and the production of IFN- γ are inhibited by MSCs through the production of PGE2 [55], IL-10 [136], IDO [138], cell contacts, and other mechanisms [139]. MSCs also suppress the generation of Th17, the expression of ROR γ c in differentiating cells, and the production of IL-17 and IL-22 by Th17. The effects are mediated by PGE2 [50, 140, 141], IDO [50], and IL-10 [142].

MSCs do not suppress Th2 proliferation [138], stimulate the production of IL-4, and may switch from Th1 to Th2 response augmenting the production of IL-4, IL-10, and IL-13, supposedly through the PGE2-dependent mechanism [55].

MSCs promote the generation of Treg and enhance their activity and IL-10 production. The effect is mediated by TGF- β [90], by HLA-G5 [112], and indirectly through the generation of tolerogenic DCs (reviewed in detail in [91]).

This pattern is characteristic for MSCs derived from various sources and examined at different experimental settings. However, several exemptions have been reported. MSCs promoted the survival of quiescent T cells [143]. In Th2-predominating conditions, MSCs inhibited IL-4 and IL-5 and increased the production of IFN- γ and IL-2 [144]. BM-MSCs derived from rheumatoid arthritis and osteoarthritis patients induced the activation and the expansion of Th17 [145]. Dysfunction of MSCs has been associated with several autoimmune disorders [125, 145].

4.1.2. MDSCs. In general, there are less data on the regulatory properties of MDSCs compared to MSCs. MDSCs inhibit the proliferation, IL-2, and IFN- γ production by T cells stimulated *in vitro* with anti-CD3/CD28, specific antigens, or in MLR [146–151]. The suppression is mediated through the production IL-10 [150], NO, and peroxynitrite [19, 26, 148, 151], and ARG1 [151, 152] and indirectly through the formation of M2 [153].

Data on the effects of MDSCs on Th2 and Th17 cells are limited. Several studies have reported that endogenous or adoptively transferred MDSCs increase Th2 response and inhibit graft-versus-host disease (GVHD) [154–156]. Both, promotion and suppression of Th17 by MDSCs have been shown [157, 158].

MDSCs promote *de novo* development of Foxp3+ Tregs *in vivo*. Different studies have associated this effect with the production of ARG-1 [67], IDO [159], IL-10 [160], CD40, and direct MDSC-Treg contacts [161, 162].

Comparison of the effects, which MSCs and MDSCs exert on T cells, shows similarities in (i) the inhibition of T

cell proliferation and Th1 responses and (ii) the stimulation of Treg cells (Figure 2). This pattern corresponds to the mode of action of molecular mediators produced by MSCs and MDSCs (Figure 1). Th17 are generally suppressed by MSCs, although there are exemptions. Data on MDSCs-Th17 interactions are limited and contradictory. In line with this, different molecular mediators, utilized by MSCs and MDSCs, affect Th17 in different ways, suggesting that the final effect may depend on the combination of mediators that the cells produce in a given experimental setting. The same is likely true for Th2 cells.

As discussed above, most of the mediators produced by MSCs and MDSCs are induced by proinflammatory type 1 cytokines (e.g., IFN- γ). This suggests that the cells play immunoregulatory role and control Th1 responses through the negative feedback loop. On the other hand, several mediators (i.e., ARG-1, TGF- β , and HLA-G5) can be induced by type 2 and regulatory cytokines (i.e., IL-13, IL-4, IL-10, and TGF- β). Whether in these “type 2 conditions” MSCs and MDSCs inhibit Th1 and support Th2 responses in a positive feedback manner, or switch their activity towards the suppression of Th2 (as it was demonstrated by Cho and coauthors [144]), is not completely clear. Further complication comes from the observations that the same mediator may play stimulatory or suppressive role depending on its concentration [44, 115] and that mediators produced by MSCs/MDSCs influence each other (see Figure 1). Evidently, studies are needed to create a quantitative model of cellular and molecular interactions that determine the final immunoregulatory properties of MSCs and MDSCs.

4.2. DCs and Macrophages

4.2.1. MSCs. MSCs suppress monocyte differentiation into DCs, decrease the expression of MHC class II, CD80, CD86, CD83, and CD40 by DCs, lower DC capacity for endocytosis, suppress the production of IL-12 and TNF- α by DC type 1, and stimulate the production of IL-10 by DC type 2. Overall, MSCs inhibit antigen presentation and T cell stimulation and promote the generation of tolerogenic DCs [163–170]. These effects have been attributed to the production of PGE2 [166], IL-6 [164, 167], IL-10 [168, 171], HGF [104, 165, 172], and TNF-stimulated gene 6 protein (TSG-6) [169]. Many of these factors operate by activating JAK/STAT pathway and suppressing the activation of mitogen-activated protein kinases (MAPKs) and NF- κ B signaling pathways within DCs responding to TLR4 stimulation [168, 169, 173, 174]. Direct MSCs-DC contacts inhibit DC maturation and induce their tolerization by activating the Notch pathway [175] and altering actin cytoskeleton in the DCs [176]. *In vivo* administration of MSCs decreased DC migration to the draining lymph node and hampered local CD4 T cell priming. The effect was attributed to the inhibition of MyD88 and the impairment of MAPKs and NF- κ B signaling pathways within DCs after TLR4 stimulation [177].

Two main and opposite types of macrophages have been defined, classically activated inflammatory (M1) and alternatively activated anti-inflammatory (M2) [178]. MSCs inhibit M1 and stimulate the generation of M2 macrophages:

coculture of MSCs with BM-derived macrophages decreased the expression of iNOS, TNF- α , IL-6, IL-12, and CCL2 (i.e., the markers of M1) and upregulated the expression of IL-10, ARG-1, CD206, and STAT3 (i.e., the markers of M2) [179, 180]. Similar effects were observed *in vivo* [181]. The underlying factors were PGE2 [181], TSG-6 [182], IDO [183], IL-6 [184], and direct cell contacts.

The activation of M2 likely plays a role in the therapeutic effects of MSCs. In experimental settings, systemically infused gingival MSCs homed to the wound site, promoted host macrophage differentiation into M2, and enhanced wound repair [184]. In the models of acute lung injury, MSCs shifted macrophage phenotype from M1 to M2 attenuating lung tissue inflammation [185, 186]. In one study, the effect was partially due to insulin-like growth factor I (IGF-I) secreted by MSCs [186].

4.2.2. MDSCs. MDSCs are cells that in the presence of appropriate cytokines differentiate into mature DCs and macrophages [6]. However, in pathology this differentiation is inhibited and MDSCs accumulate to affect different branches of immune response. Information on MDSCs-DCs and MDSCs-macrophages interactions is limited. In most studies, the effects were similar to those mediated by MSCs; that is, MDSCs inhibited DC maturation and polarized macrophages towards M2 phenotype, largely through the production of IL-10. In a clinical vaccine study, MDSCs copurified with monocytes suppressed DC maturation, antigen uptake, migration, and Th1 induction in a dose-dependent manner [187]. MDSCs isolated from hepatocellular carcinoma mice decreased the production of IL-12 by DCs [188].

When cocultured with macrophages, MDSCs reduced macrophage expression of MHC class II [17]. MDSCs from mice with spontaneous metastatic 4T1 mouse mammary carcinoma skewed macrophages towards the generation of M2 through IL-10 and cell contact dependent mechanisms [153]. In patients with esophageal cancer, increased ratio of MDSCs and augmented plasma levels of ARG1 were associated with high tissue expression of CD163, decreased IL-12 and IFN- γ , and increased GATA3, IL-4, IL-13, and IL-6 expressions (evidences of M2 polarization) [156].

In tumor environment, MDSCs can directly differentiate into suppressive tumor-associated macrophages (TAM) [6]. Of note, suppressive macrophages were shown to stimulate MDSCs for the production of IL-10 [17]. Thus, MDSCs may form a positive feedback loop with TAM.

4.3. B Cells

4.3.1. MSCs. Data on MSCs-B lymphocyte interactions is not uniform. In some studies, MSCs inhibited proliferation, plasma-cell differentiation, IgM, IgG, and IgA production by B cells stimulated *in vitro* with CpG, recombinant CD40L, anti-Ig antibodies or IL-2, IL-4, and IL-10 cytokines. MSCs also suppressed B cell expression of CXCR4, CXCR5, and CCR7 and reduced B cell chemotaxis [131, 189–191].

In other studies, MSCs did not affect B cell proliferation [138] or even augmented it. In the study by Traggi and coauthors, MSCs enhanced the proliferation of purified B

cells obtained from healthy donors or pediatric systemic lupus erythematosus (SLE) patients and their differentiation into plasma cells [192]. One possible explanation for these discrepancies comes from the study by Rasmusson and coauthors. The study suggests that MSCs' activity depends on the level of basal B cell response: MSCs reduced high-level IgG response and enhanced low-level production of IgG induced by LPS, cytomegalovirus, or varicella zoster virus, that is, played a homeostatic role [193].

Breg cells are induced by MSCs. The induction has been registered both *in vitro* and *in vivo* and resulted in the amelioration of GVHD [190, 194, 195].

Mechanisms underlying MSCs-B-cell interactions are complex and not fully understood. Different authors reported the involvement of IDO [195], MSC-T-cell contacts [190, 191], IL-10, soluble factor other than IDO, TGF- β or IL-10 [196], Galectin-9 [123], and CCL2 [125]. In SLE patients, BM-MSCs had reduced production of CCL2, which was associated with their defective capacity to suppress B cells. These findings suggest a potential role for MSCs in disease pathogenesis and demonstrate that MSCs generated in healthy and pathological conditions can exhibit different properties, uncovering another potential cause for conflicting data on MSCs-B cell interactions.

4.3.2. MDSCs. Data on MDSCs-B lymphocytes interactions are highly limited and only start to accumulate. Most of existing data report inhibitory effect of MDSCs on B lymphocytes. Following murine retroviral LP-BM5 infection, MDSCs expanded and suppressed *ex vivo* B cell responses, partially through iNOS/NO- and VISTA-mediated mechanisms [197, 198]. MDSCs generated in the presence of adipocyte-conditioned medium inhibited B lymphopoiesis largely through IL-1 [199]. MDSCs from mice with collagen-induced arthritis inhibited autologous B cell proliferation and antibody production in NO, PGE2, and cell-cell contact dependent manner [200]. Administration of monocytic MDSCs reduced autoantibody production and rescued CCR2^{-/-} mice from the exacerbated collagen-induced arthritis [125, 200].

4.4. NK Cells

4.4.1. MSCs. MSCs inhibit NK cell proliferation, expression of activating receptors, and decrease NK cytotoxicity and IFN- γ production [36]. In different settings, the effects were mediated by IDO, PGE2, TGF- β , HLA-5, and cell contacts [36, 112, 201]. Following their coculture with MSCs, NK upregulate the expression of CD73 that has anti-inflammatory effect [202].

4.4.2. MDSCs. NK cultured with MDSCs produce less IFN- γ . The suppression has been attributed to the production of ARG1 [203], COX2/PGE2 [204], cell-cell contacts involving NK cell activation receptor NKG2D, and membrane-bound TGF β [205]. The role for MDSCs in the inhibition of NK *in vivo* was demonstrated in the study by Zhu and coauthors, who described the generation of granulocytic MDSCs following the administration of adenoviral vectors in mice;

depletion of MDSCs enhanced NK responses and accelerated virus clearance [206].

4.5. Neutrophils. Neutrophils are nonproliferating short-living cells that rapidly migrate to the site of infection/inflammation and eliminate pathogens or cellular debris.

4.5.1. MSCs. MSCs generally exhibit proneutrophilic action supporting neutrophil survival and inhibiting their apoptosis. The proneutrophilic effect was demonstrated for MSCs derived from various sources (i.e., BM, glandular, and adipose tissue) and was largely mediated by IL-6 [207]. It has been suggested that the proneutrophilic effect of MSCs plays a role in supporting this short-living population in the BM. MSCs activated by LPS stimulate the expression of CD11b by neutrophils [208] and are able to recruit neutrophils in IL-8 and MIF-dependent manner [209]. Data on the influence of MSCs on antibacterial properties of neutrophils are not uniform. In some studies, BM-MSCs dampened neutrophil respiratory burst [207], while in others enhanced it [208]. The stimulatory effect depended on IL-6, IFN- β , and GM-CSF [208]. Hall and coauthors have demonstrated that MSCs may affect neutrophil function *in vivo*: the administration of BM-MSCs to septic mice stimulated bacteria clearance; neutrophil depletion abrogated the effect [210]. In one study, proneutrophilic effect of MSCs was mediated through the induction of Th17 [211].

4.5.2. MDSCs. The influence of MDSCs on neutrophils remains underinvestigated. Existing data are largely limited by the observation that the accumulation of MDSCs is accompanied by gradual disappearance of mature neutrophils [19]. These opposing relationships between MDSCs and neutrophils may be due to the incomplete differentiation of immature myeloid cells in inflammatory conditions leading to the accumulation of MDSCs and simultaneously to the reduction of mature neutrophils. Another suggested mechanism is efferocytosis of apoptotic neutrophils by MDSCs, which has been described in mice infected with *Klebsiella pneumoniae* or challenged with LPS [212, 213]. Thus, differentially from MSCs, MDSCs and neutrophils seem to be mutually exclusive. However, this speculation needs further investigation.

4.6. Interactions between MSCs and MDSCs. Only few studies directly addressed the interplay between MSCs and MDSCs. In the study by Yen and coauthors, human MSCs expanded CD14⁻CD11b⁺CD33⁺ MDSCs that expressed ARG1 and NO, suppressed lymphocyte proliferation, and promoted Treg generation. The effect was mediated through the secretion of HGF and the induction of STAT3 [78]. In another study, growth-regulated oncogene GRO- γ secreted by MSCs suppressed the generation of monocyte-derived DCs and stimulated the formation of MDSCs. The latter secreted IL-10 and IL-4 and expressed ARG1 and iNOS [214]. Galectins, known to be produced by MSCs, were reported to participate in the expansion of MDSCs at tumor sites [124]. MDSCs produce ROS. In physiological levels, ROS support MSCs' proliferation and differentiation, and, in higher amount, ROS

promote MSCs' aging [84]. Other mediators produced by MSCs and MDSCs (e.g., PGE2) can activate both populations of cells in a positive feedback manner.

5. Concluding Remarks

In this review, we have compared mechanisms and modes of immunoregulatory action of two immature cell populations: MSCs and MDSCs. The populations belong to two distinct differentiation lineages, but both are able to regulate immune response. MSCs and MDSCs share many immunomodulatory mechanisms and exert similar effects. In particular, they inhibit DC and macrophage maturation, antigen presentation, and suppress T cell proliferation, Th1 responses and NK activity. Both populations promote the generation of tolerogenic DCs, M2 macrophages, and regulatory T cells. Proinflammatory conditions activate suppressor capacities of both MSCs and MDSCs. This likeness is largely due to the usage of similar set of mediators, for example, IDO, PGE2, IL-10, and TGF- β (Figure 1).

In spite of these similarities, comparative analysis reveals the discrepancies between the two populations. First, some mediators are produced by one but not by another subset. In particular, ARG1 and ROS seem to be restricted to MDSCs; the production of galectins and HLA-G has been attributed to MSCs but not to MDSCs. Second, MSCs and MDSCs are generally activated by proinflammatory type 1 cytokines. However, in some conditions, they can be stimulated by type 2 cytokines, and MDSCs seem to be more prone to this type of stimulation. Indeed, ARG1, which is expressed in MDSCs but not in MSCs, can be induced by IL-4, IL-13, and TGF- β . In MSCs, the expression of B7-H1 and the production of TGF- β were induced by IFN- γ , whereas in MDSCs by IL-10 and IL-13 [37, 129]. Third, MSCs exert proneutrophilic effects, supporting neutrophil survival and function [207–210]. MDSCs, in contrast, seem to oppose neutrophilic inflammation [19, 212, 213]. Fourth, MSCs expand MDSCs. Whether and how MDSCs affect MSCs is largely unknown. Fifth, MSCs are generally considered as immunoregulatory cells that can inhibit or enhance immune function depending on cell microenvironment [5, 15]. MDSCs are currently regarded as immunosuppressive cells. Whether MDSCs may be considered as immunoregulatory cells that act by supporting immune homeostasis is not yet clear.

Several other questions remain unanswered and need further investigation.

In particular, the pattern of the interplay between MSCs/MDSCs and Th2, Th17, and B lymphocytes is not fully clear. Both stimulation and inhibition of these responses by MSCs and MDSCs have been documented [55, 144, 154–156, 189–193, 231], and exact factors that determine the ultimate result are yet to be determined. One group of factors is represented by TLR ligands. The contribution of different TLR-mediated pathways to pro- or anti-inflammatory functions of MSCs/MDSCs is one of the recently emerged areas of research [213, 215].

In proinflammatory conditions, MSCs and MDSCs are activated to inhibit type 1 response, that is, act in a negative feedback manner. Whether in “type 2 conditions” the cells

inhibit Th1 or Th2 responses, that is, participate in positive or negative feedback loop, remains unclear.

As noted above, MSCs and MDSCs share a set of core regulatory mediators and mechanisms. However, they differentially affect some immune cells. Molecular mechanisms underlying these discrepancies remain unknown.

MSCs and MDSC can simultaneously produce a wide range of immunoregulatory factors that have similar but not identical activity (Figure 1). Furthermore, the subsets of the produced factors and the amounts secreted may vary in different conditions. Overall, this creates the possibility for MSCs/MDSCs to fine-tune different branches of the immune response and simultaneously makes their final effect difficult to predict. Quantitative models of cellular and molecular interactions that determine the final immunoregulatory properties of MSCs and MDSCs would help to predict their effects in various microenvironments, both *in vitro* and *in vivo*.

Speaking about possible clinical applications, MSCs are widely considered for the purposes of clinical immunomodulation due to their homeostatic properties and the feasibility of generating the large numbers of autologous cells. MSCs have been suggested as a mean to treat severe life-threatening forms of autoimmune and autoinflammatory diseases (e.g., SLE, systemic sclerosis, and inflammatory bowel disease [216–219]), prevent and treat steroid-refractory graft-versus-host disease [220], improve the outcome after organ transplantation [221], and stimulate tissue repair, regeneration, and wound healing [222–227]. Detailed analysis of MSC therapeutic potential, risks, and limitations of their application is beyond the focus of the current review. In contrast to MSCs, MDSCs are usually regarded as the target for immunomodulation, particularly, in cancer where they accumulate abundantly and contribute to pathology [228, 229]. However, in autoimmune pathology, MDSC dysfunction may be a factor driving disease progression and can be limited by the administration of exogenous MDSCs [24]. Thus, the question whether MDSCs can be used for therapeutic immunomodulation in some pathological conditions remains to be explored. It is important to note that MDSCs can be grown *in vitro* and they are more differentiated compared to MSCs; thus, they have a lower risk of cell transformation.

In conclusion, this review does not imply to describe all effects and mechanisms mediated by MSCs/MDSCs, as they are multiple and vary in different conditions. Rather, it is an attempt to compare the main patterns of MSCs/MDSCs' activities in a way to detect cell similarities and discrepancies and identify new directions for their investigation.

Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

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