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Mesenchymal-myeloid interaction in the regulation of immunity

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ABSTRACT

Several studies have demonstrated how different cell types of mesenchymal and myeloid origin can independently exhibit immunoregulatory activities. In response to inflammatory cues, they transcribe a molecular repertoire that restores the tissue microenvironment to what it was before the injury. There is accumulating evidence that stromal and myeloid-derived cells do not act independently but that the establishment of a cross-talk between them is a fundamental requirement. Stromal cells, prompted by inflammatory molecules, orchestrate and initiate myeloid cell recruitment and their functional reprogramming. Once instructed, myeloid cells effect the anti-inflammatory activity or, if alternatively required, enhance immune responses. The cross-talk plays a fundamental role in tissue homeostasis, not only to regulate inflammation, but also to promote tissue regeneration and cancer progression.

1. Introduction

During the last decade, much attention has been paid to the role of stromal cells in innate immune responses. The initial evidence that they exhibited potent immunosuppressive activities [1] prompted many studies aimed at better characterizing these properties but also at their exploitation in the clinical setting [2]. The data produced have highlighted that stromal cells regulate innate anti-inflammatory responses in tissues and, consequently, in the process of tissue regeneration and in the tumor microenvironment. In particular, most responses revolve around the interaction between stromal cells and myeloid cells. A better understanding of such an interaction is fundamental to dissect the components that regulate the inflammatory niche and harness the molecular pathways for regenerative medicine and cancer immunotherapies.

2. The heterogeneity of stromal cells

The definition of stromal cells remains largely ambiguous as it simply refers to cell populations that do not belong to the tissue parenchymal compartment. Further confusion is generated by the fact that investigators in selected fields also include monocytes/macrophages in this category. For the purpose of this review, we will consider stromal cells only those of mesenchymal origin and that we will list in this section.

Probably the most classical example of stromal cells is fibroblasts. They are generally present as single cells scattered in the interstitial space and embedded in the extracellular matrix. They are generally resting cells with very low metabolic and transcriptomic activity. Despite being known as an entity for far more than a century, their identification relies on the combination of several markers. Fibroblasts express CD73, CD90, CD105 and are negative for the hematopoietic CD45 marker (Table 1). The molecular repertoire includes α-smooth muscle actin (α-SMA), vimentin, fibroblast specific protein (FSP), fibroblast activation protein (FAP). Other molecular markers often identifiable in fibroblasts include thrombospondin-1 (TSP-1), tenascin-*C*, platelet derived growth factor receptor-α and -β (PDGFR-α and PDGFR-β), periostin, osteonectin, paladin, podoplanin and stromelysin [3]. Although it is acknowledged that fibroblasts exhibit functional

Abbreviations: ARG-1, arginase 1; CCL-, CC motif chemokine ligand-; CXCL-, CX-C motif chemokine ligand-; CAF, cancer associated fibroblast; CO, carbon monoxide; CVB3, coxsackievirus B3; COX-2, cyclooxygenase-2; DC, dendritic cell; EAU, experimental autoimmune uveitis; ECM, extracellular matrix; FAP, fibroblast activation protein; FSP, fibroblast specific protein; GRO, growth-regulated oncogene; HO-1, heme oxygenase-1; HLA-G, human leukocyte antigen-G; HIF-1α, hypoxia-inducible factor-1α; IDO, indoleamine 2,3-dioxygenase; NOS, inducible NO synthasei; IFN-γ, interferon-γ; IL-, interleukin-; LIF, leukemia inhibitory factor; LPS, lipopolisaccaride; TOR, mammalian target of rapamycinm; MSC, mesenchymal stem/stromal cell; MAP, mitogen activated protein; MPS, mononuclear phagocytic system; MDSC, myeloid-derived suppressor cell; DAPT, *N*-[[*N*-(3,5-difluorophenacetyl)-L-alanyl]-*S*-phenylglycine t-butyl ester; NK cells, natural killer cells; NG2, neural/glial antigen 2; NO, nitric oxide; PDGFR-α, platelet derived growth factor receptor-α; PDGFR-β, platelet derived growth factor receptor-β; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PGE2, prostaglandin E2; Treg, regulatory T cell; SSEA-4, stage-specific embryonic antigen 4; Stro-1, stromal precursor antigen-1; Th-, T helper-; TSP-1, thrombospondin-1; TLR, toll-like receptor; TKA, total knee arthroplasty; TGF-β, transforming growth factor-β; TME, tumor microenvironment; TNF-α, tumor necrosis factor-α; TSG-6, tumor necrosis factor-inducible gene 6 protein; TAM, tumor-associated macrophage; Tr1, type 1 regulatory T; VTCN1, V-set domain containing T cell activation inhibitor 1; VEGF, vascular endothelial growth factor; vWF, von Willebrand factor; α-SMA, α-smooth muscle actin

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Table 1
The heterogeneity of stromal cells.

Stromal cell type	Main sources of tissues	Marker profiles in human (Positive: +; Negative: −)		Reference
Fibroblasts	Every tissue	+	CD73, CD90, CD105, FSP, FAP, α-SMA, vimentin	[3,5]
		−	CD31, CD34, CD45	
Mesenchymal stem cells	Bone marrow, adipose tissue, fetal and puerperal tissues	+	CD73, CD90, CD105, CD146, PDGFR-β, NG2, Stro-1	[3,7,8,10,11]
		−	CD31, CD34, CD45	
Pericytes	Blood microvessels	+	CD73, CD90, CD105, CD146, PDGFR-β, NG2, Stro-1	[17,18]
		−	CD31, CD34, CD45	
Endothelial cells	Blood and lymphatic vessels	+	CD31, CD34, CD105, vWF	[25]
		−	CD45	
Fibrocytes	Peripheral blood, inflamed tissues, tumors	+	CD34, CD45, Collagen, α-SMA	[36,37,39]

heterogeneity, it was only recently that distinct fibroblast lineages have been correlated with different activities. In the skin, whilst upper dermis fibroblasts regulate hair follicle formation, those in the lower dermis synthesize extracellular matrix (ECM) and give origin to adipocytes [4]. These and other activities require appropriate stimuli to be initiated, with functional flexibility being a typical feature of fibroblasts [5]. In this perspective, it can be proposed that most properties assigned to fibroblasts are the result of an activated phenotype and that other stromal cell categories could be the expression of a different type of activation. This notion would explain the several overlaps shared amongst stromal cells that we will describe in this review.

Mesenchymal stem/stromal cells (MSC) represent a paradigm in this context, whereby a fibroblast-looking cell has been attributed with unique functions following exposure to stimuli of various nature. MSC are typically defined as non-haematopoietic, plastic-adherent and colony forming cells that, under appropriate stimuli, are capable of differentiating into multiple mesenchymal lineages *in vitro* [6]. They have originally been identified in the bone marrow [7], then in adipose tissue [8] and many other tissues and organs, often using criteria largely shared with the definition of fibroblasts [9]. Adipose tissue and fetal tissues are a major source of both fibroblasts and MSCs (Table 1), with the most immature cells exhibiting enhanced survival and stem cell-more like properties compared with those isolated from adult tissues.

A proportion of cultured MSCs, like activated fibroblasts, exhibit progenitor activity because they can differentiate *in vitro* into osteoblasts, adipocytes, and chondroblasts. Amongst the highly heterogeneous population of $CD105^+CD73^+CD90^+$ MSCs, a number of studies have successfully characterized subpopulations with prominent stemness activity in the bone marrow and the specific ability to form components of the haemopoietic stem cell niche (Table 1). These subsets express CD146, PDGFR-β, neural/glial antigen 2 (NG2), CD271 and stage-specific embryonic antigen 4 (SSEA-4) in human [3,10,11], NG2, stem cells antigen-1 (Sca-1), nestin and leptin receptor in mouse [12–14]. CD146 is expressed in MSCs from various sources and, together with PDGFR-β, NG2 and stromal precursor antigen-1 (Stro-1) can also be detected in perivascular stromal cells such as pericytes, thus raising the question of whether and how MSCs are affiliated to pericytes [15].

Pericytes are perivascular stromal cells found in blood capillaries and microvessels and play an essential role in vessel contraction, architecture, angiogenesis, and survival of endothelial cells [16]. Pericytes and MSCs share numerous characteristics. An early study showed that $CD146^+$ bone marrow and dental pulp MSCs localized in blood vessel walls of human bone marrow and dental pulp, expressing markers of pericytes but not endothelial cells [17]. This finding has led speculatations about the ontogenic relationship between MSCs and pericytes. Later, Crisan et al. (2008) demonstrated that long-term cultured pericytes can be identified as perivascular cells with the same signature of MSCs [18]. Sorted pericytes ($CD146^+CD34^-CD45^-CD56^-$) could differentiate into osteogenic, chondrogenic, adipogenic, and myogenic lineages *in vitro* (Table 1). Likewise, $CD34^+CD31^-CD146^-CD45^-$ tunica adventitia cells, which reside in the outermost layer of arteries and veins, natively expressed MSC markers and gave rise in culture to clonogenic multipotent progenitors identical to standard bone marrow-derived MSCs [19]. The ability of pericytes to regulate tissue regeneration has been confirmed in the dental pulp [20]. Despite the large overlapping features, there is sufficient evidence to suggest that not all MSCs are pericytes, either because of differential markers [21], but especially because MSCs do not localize exclusively in the perivascular tissues [14,22].

Endothelial cell is another extensively investigated stromal cell that lines the inner luminal surface of blood and lymphatic vessels [23,24]. The identification of endothelial cells is more accurate and relies on the expression of CD31/PE-CAM1, CD34, CD105/endoglin and von Willebrand factor (vWF) [25] (Table 1). Although their origin differs from other stromal cells [26], a recent study has identified a pathway by which cardiac endothelial cells may differentiate into pericytes and vascular smooth muscle cells [27]. Conversely, MSCs have been described for the ability to differentiate into endothelial cells [28,29]. These pieces of evidence indicate substantial plasticity amongst vascular stromal cells. Yet, whether endothelial cells can directly differentiate into bone, fat and cartilage cells is unclear. In the context of tissue homeostasis, endothelial cells regulate vessel formation, permeability and the blood flow [30,31]. Another important function is their ability to actively regulate T cell migration as well as antigen presentation [32], by which they modulate the activity of antigen-experienced effector T cells, promoting inflammation or tolerance [33,34] or the recruitment of regulatory T cells (Treg) [35].

First characterized by Bucala and colleagues [36], fibrocytes represent a more controversial entity for at least two main reasons. The first is that, despite their fibroblast-like appearance, they are of haemopoietic origin. The second is that they can be found circulating in the blood. Fibrocytes originate from $CD14^+$ bone marrow-derived monocytes in humans [37] and $Gr1^+CD115^+CD11b^+$ in mice [38]. Like the more conventional mesenchymal stromal cells, they produce ECM proteins, exhibit a fibroblast-like morphology, express α-SMA (Table 1) and differentiate into adipocytes, chondrocytes, and osteoblasts [39]. Whether the phenotype represents developmental plasticity or a genuine subset between monocytes and fibroblasts has yet to be elucidated. It has also been suggested that fibrocytes may be a subset of myeloid-derived suppressor cells (MDSC) [40].

3. Stromal cells exhibit potent immunomodulatory activities

Despite the heterogeneity amongst stromal cells, it has been extensively demonstrated that they all have a great degree of similarity in their ability to modulate immune responses and in the underlying mechanisms. Most information regarding the immunobiology of stromal cells was originally generated by studying MSC and subsequently confirmed in other types of stromal cells. MSCs have been shown not only to influence the differentiation and functions of lymphoid effector cells but also recruit and reprogram myeloid cells to become immunosuppressive. We will review the different types of

immunomodulatory mechanisms described in stromal cells, with an emphasis on the interaction with myeloid cells.

3.1. The direct immunomodulatory activity of stromal cells

Several modes of action have been described mediating the immunosuppressive activity of stromal cells. Probably because it is a fundamental physiological activity, none of the candidate molecules taken alone is sufficient to account for the whole immunosuppressive function and there is a remarkable redundancy in the molecular armamentarium. Together with the fact that the large majority of immunosuppressive pathways identified are soluble factors, this explains the potent activity even at low stromal:effector cell ratios.

The first class of molecules consists of those involved in metabolic reprogramming. Probably the most extensively studied is indoleamine 2,3-dioxygenase (IDO), an intracellular cytosolic enzyme that catalyzes the catabolism of essential amino acid tryptophan into kynurenine [41]. The depletion of tryptophan and accumulation of tryptophan suppress T cell activation and proliferation [41]. IDO has been one of the first candidate to be identified in stromal cell mediated immunosuppression, both in human MSCs [42–46] and fibroblasts [47]. IDO expression in stromal cells is not constitutive but is dependent on the exposure to interferon-γ (IFN-γ), usually derived from activated monocytes or T cells [43,44,47]. The inhibition of IDO partially restores the proliferation and function of T and natural killer (NK) cells stimulated in the presence of MSCs [48]. Despite its importance in human MSCs, murine MSCs do not produce IDO [49] but rather use an alternative mechanism involving inducible NO synthase (iNOS) and its product nitric oxide (NO) [50]. In rat, another metabolism-based mechanism has been identified, which relies on heme oxygenase-1 (HO-1) [51]. HO-1 is a stress-responsive enzyme that transforms heme into Fe^{2+}, biliverdin and carbon monoxide (CO). CO is believed to mediate the immunosuppressive activity *via* the mitogen activated protein (MAP) kinase pathway [52]. By producing HO-1, MSCs also recruit and differentiate induced regulatory T cells like interleukin-(IL-)10^+ type 1 regulatory T (Tr1) cells and transforming growth factor-β (TGF-β)$^+$ T helper 3 (Th3) cells [53].

Another metabolic pathway elicited by stromal cells leads to the production of prostaglandin E2 (PGE2), one of the most abundant metabolites of arachidonic acid generated through an enzymatic cascade controlled by cyclo-oxgenase-2 (COX-2) [54]. PGE2 regulates both innate and adaptive immune responses, preventing excess inflammation. Multiple studies have shown that MSCs and fibroblasts suppress T cell proliferation through PGE2 since COX-2 inhibitors restore T-cell proliferative activity [55]. Multiple downstream effects are induced by PGE2, which include the suppression of lymphocyte growth factors (IL-2 or IL-15) and the differentiation of antigen presenting cells and effector T cells [54].

Cytokines are another class of molecules that feature highly in the stromal cell repertoire. TGF-β is a potent immunoregulatory cytokine that has an essential role in the induction of immune tolerance and resolution of inflammation [56]. TGF-β is constitutively secreted by MSCs [57] and has been identified as a key molecular mechanism either by inhibiting T cell proliferation in a contact dependent fashion [58] or by recruiting monocytes [59]. Mechanistically, one of the main target of TGF-β is IL-2 [60] that is inactivated either by impairing its transcription or *via* the activation of Smad3 [61]. In a ragweed induced asthma model, the beneficial effect of MSCs on lymphoid and eosinophil infiltration was abrogated by treatment with anti-TGF-β but not anti-IL-10. In this study, the production of TGF-β in MSCs was not constitutive but resulted from IL-4 and IL-13 activating the STAT6 pathway [62].

It has been claimed that IL-10 is produced by human MSCs [63] and pericytes [64], but the data are controversial, possibly depending on which type of experimental inflammatory conditions MSC are exposed to [65]. The role of IL-10 in the immunosuppressive activity could be indirect and result from MSCs instructing T cells and monocytes/macrophages to produce it. Whatever the source, MSCs up-regulate IL-10 receptor (CD210) on T cells, thus forming a positive feedback loop to promote T cell to produce more IL-10 [63].

Amongst other soluble factors identified as contributing to the immunosuppressive activity, there is human leukocyte antigen-G5 (HLA-G5), the soluble isoform of HLA-G [66]. Human MSCs also secrete galectin-1 [67,68], -3 [69] and -9 [70] that regulate both innate and adaptive immunity in acute and chronic inflammation. Remarkably, galectin-9 impairs immunoglobulin secretion by activated B cells [70]. Finally, human MSCs have also been shown to secret leukemia inhibitory factor (LIF) [71], a glycoprotein involved in preventing fetus rejection during pregnancy and in the induction of transplantation tolerance.

Although largely effected by soluble molecules, the immunomodulatory activity of stromal cells can be mediated by cell contact interactions with immune cells through programmed death-ligand 1 (PD-L1/B7-H1/CD274), the ligand of immune-inhibitory receptor programmed cell death protein 1 (PD-1/CD279) [72]. Different types of stromal cells such as MSCs [46,73], pericytes [64] and endothelial cells [74] engaged in inhibiting both the proliferation and effector functions of activated T cells with studies conducted both in humans and mice. Antagonizing these pathways with antibodies or siRNA successfully reduced – albeit not completely – the immunosuppressive effects. PD-L1 expression is enhanced in MSCs and endothelial cells by IFN-γ [46,73], whilst tumor necrosis factor-α (TNF-α) augments its expression in endothelial cells [74].

The membrane-bound HLA-G1 has also been shown to contribute to MSCs immunosuppression by interfering with cell-cycle regulation, reducing IFN-γ and increasing IL-10 secretion of activated T cells [75]. Human bone marrow-derived MSCs also express a v-set domain containing T cell activation inhibitor 1 (VTCN1/B7H4) [76], a ligand of the B7 family that binds to an unknown receptor to induce inhibitory signals in activated T cells [77]. Furthermore, notch receptor ligand Jagged-1 is also expressed on human bone marrow MSCs. Blocking Jagged-1 or the corresponding notch signalling abrogates the anti-proliferative effect of MSCs on $CD4^+$ T cells [78]. Other studies have reported cell contact mediated interactions involved in the suppression of T-cell proliferation by fibroblast [79,80] and pericytes [81] although the molecular targets were not identified.

3.2. The indirect immunomodulatory activity of stromal cells and the mediation of myeloid cells

From the mechanisms of immunosuppression listed in the previous section, it is quite apparent that stromal cells cannot simply exert a direct inhibitory activity on the ultimate effectors of inflammation but the several molecules they produce have also an impact on the recruitment and instruction of other immunoregulatory cells, which can in turn exert further immunosuppression and sustain the activity in a longer term. This concept can explain the paradox observed in the clinical use of stromal cells, whereby the therapeutic benefit extends largely beyond the persistence of stromal cells in the recipients.

Originating from the hematopoietic stem cells, the mononuclear phagocytic system (MPS) comprises monocytes, macrophages, and dendritic cells, which are the myeloid cells critical for regulating inflammation and immune responses. Early *in vitro* studies had already indicated an important role of the MPS as at least supplementary, if not indispensable, for the delivery of MSC immunosuppressive activity [82]. Further data has supported the crucial role of such an interaction, which can be demonstrated on virtually any type of MPS cells (Fig. 1).

3.2.1. Stromal cells recruit monocytes to tissues

In peripheral blood, monocyte is the most abundant MPS contributing for around 10% of circulating leukocytes [83]. Monocytes express chemokine receptors and adhesion receptors that regulate their

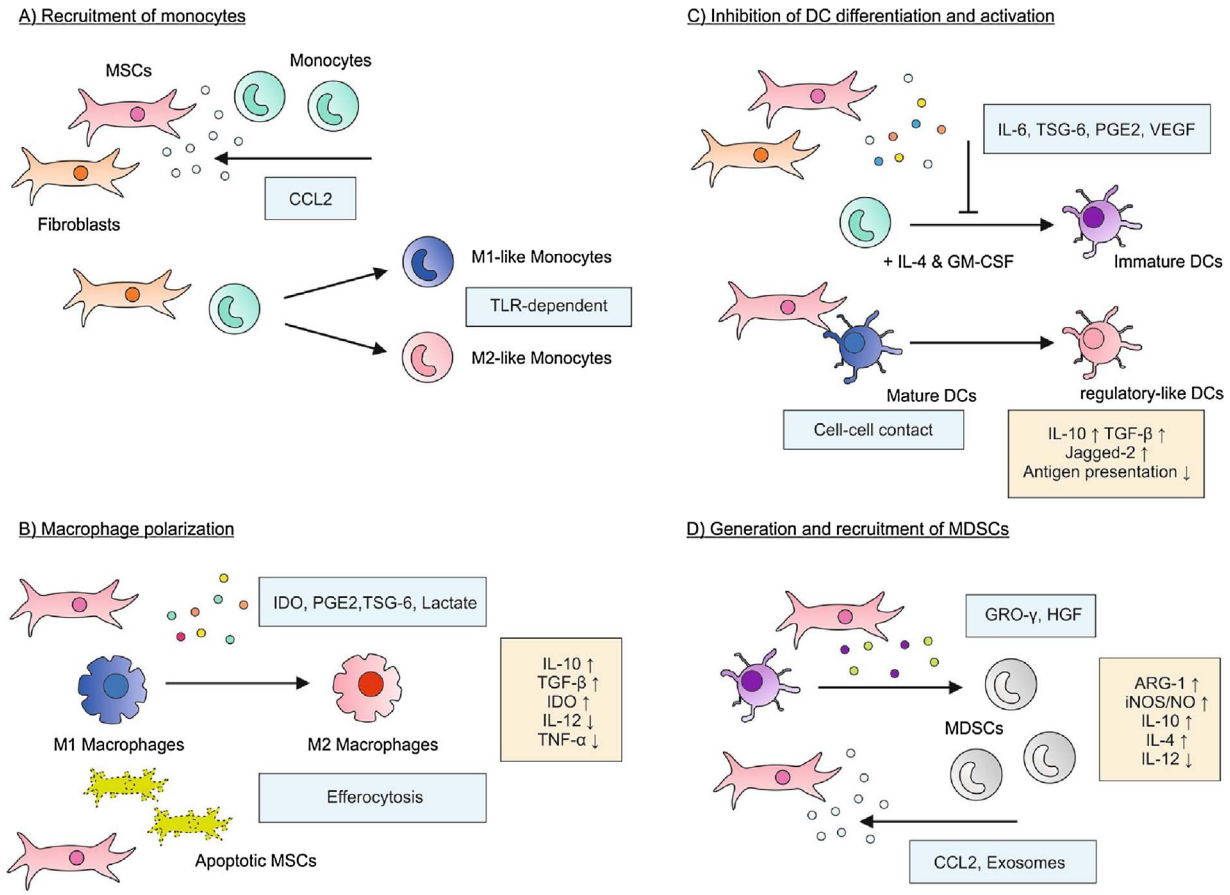

Fig. 1. Stromal cells educate myeloid cells to immunomodulate. Myeloid-derived cells are essential target of stromal cells to deliver immune regulation. **A**. Monocytes are recruited to the site of inflammation *via* the secretion of different chemokines and, depending on the inflammatory stimulus, they acquire an M1 or M2-like profile. **B**. MSCs drive macrophage polarization through the production of IDO, COX-2/PGE2, TSG-6 and lactate. Alternatively, apoptotic MSCs can polarize macrophage to produce IDO-1 after efferocytosis. **C**. Fibroblasts and MSCs inhibit DC differentiation *via* IL-6, VEGF, TSG-6 and COX-2/PGE2 and prevent DC priming activity. Furthermore, MSCs skew mature DCs into regulatory-like DCs (IL-10 and TGF-β). **D**. MSCs can also differentiate MDSCs through the secretion of GRO-γ and HGF and recruit MDSCs through exosomes and CCL2. MSC-primed MDSCs up-regulate ARG-1, iNOS/NO, IL-4 and IL-10.

migration from blood to tissues during inflammation or infection [84]. They can differentiate into macrophages or dendritic cells depending on the inflammatory milieu [85].

A seminal study demonstrated that stromal cells recruit monocytes *in vivo* to the site of inflammation. In a murine model of toll-like receptor-induced inflammation, it was shown that bone marrow-derived MSCs and their progeny including CXC chemokine ligand (CXCL)12-abundant reticular (CAR) cells upregulate the monocyte chemotactic protein 1/C-C motif chemokine ligand 2 (MCP1/CCL2) in response to lipopolysaccharides (LPS) or bacterial infection and, as a consequence, induce the mobilization of monocytes from the bone marrow to the bloodstream [86]. In total knee arthroplasty (TKA), a human model of surgery-induced fibrosis, it was observed that several months after the procedure, the fibrotic joint exists in a state of unresolved chronic inflammation. Fibroblasts isolated from the post-TKA fibrotic infrapatellar fat pad express the interleukin-1 receptor and, upon exposure to interleukin-1α (IL-1α), polarize to a highly inflammatory state that enables them to stimulate the recruitment of monocytes [87].

However, under other conditions, stromal cells do not promote inflammatory monocytes. In a murine model of wound healing, the MSC secretome was shown to chemoattract monocytes, keratinocytes and endothelial cells *in vitro*, whilst recruiting macrophages and endothelial progenitor cells at the site of the injury *in vivo* [88] that expedited tissue repair. These data were confirmed in at least two recent studies. In coxsackievirus B3 (CVB3)-induced myocarditis, the intravenous injection of human MSCs successfully mitigated the severity of myocarditis by the recruitment of anti-inflammatory monocytes ($Ly6C^{low}$) and the reduced homing of pro-inflammatory monocytes ($Ly6C^{high}$ and $Ly6C^{intermediate}$) to the heart [89]. A previous study showed that these findings should be considered in the context of the underlying inflammatory environment. According to the type of inflammatory stimulus, cardiac fibroblasts treated with LPS or TGF-β1 upregulate intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion protein 1 (VCAM-1) in monocytes and their CCL2-dependent migration to fibroblasts. However, whilst LPS-treated fibroblasts induced the secretion of pro-inflammatory cytokines (M1 polarization), TGF-β1 stimulated fibroblasts skewed monocyte differentiation towards an M2 anti-inflammatory profile [90].

3.2.2. Stromal cells induce the differentiation and functional skew of monocytes/macrophages

Macrophages are professional phagocytic cells displaying remarkable plasticity in response to the environmental stimuli. Unlike monocytes, macrophages reside in different tissues *in vivo* and they are specialized in different functions according to the anatomical location, maintaining homeostasis [91]. Macrophages derive from fetal hematopoietic stem cells and in adult life they retain the capacity to recover from insults without the contribution of monocytes [92]. Functionally, they are classified into two main categories according to whether they display a pro-inflammatory profile (classically activated macrophages or M1) or an anti-inflammatory phenotype (alternatively activated macrophages or M2) [93]. Macrophage polarization can be induced by several cytokines or inflammatory cues, many of which can be produced by stromal cells, thus making these cells potent modulators of

monocyte-macrophage activity.

It has been demonstrated that MSCs can directly drive the differentiation of macrophages. Bone marrow-derived MSCs have the ability to selectively induce the rapid differentiation of $CD11b^+$ myeloid cells from bone marrow myeloid progenitors. Such an activity largely depends on the expression of nitric oxide synthase-2 by stromal cells. The majority of the myeloid population driven by MSC express F4/80 and other macrophage-associated markers. The administration of *ex-vivo* mesenchymal stromal cell-educated $CD11b^+$ cells accelerates hematopoietic reconstitution in bone marrow transplant recipients [94]. These findings highlight the importance of the interaction between MSCs and bone marrow macrophages in the hematopoietic stem cell niche, which contributes to the retention of hematopoietic stem cells in the bone marrow [95] and prevent their exhaustion [96]. Furthermore, one should consider osteoclasts are in fact a tissue specific version of macrophages and their interplay with osteoblasts, the ultimate progeny of MSCs in the bone marrow, is a fundamental process in bone remodeling [97].

Early studies indicated that co-culture of human MSCs with isolated monocytes upregulated the M2 surface marker CD206 (C-Type Mannose Receptor 1) and IL-10 secretion while pro-inflammatory cytokines such as IL-12 and TNF-α were reduced [98]. The phagocytic efficiency against *Escherichia coli* was also improved after the co-culture with MSCs, further supporting an M2-like differentiation [98]. IDO-1 and COX-2/PGE2 have been identified amongst the factors contributing to polarization, with MSC-induced IL-10 secretion being specifically dependent on IDO-1 [42]. In the same study, the depletion of $CD14^+$ monocytes abrogated MSC immunosuppression, although it did not necessarily clarify whether monocytes were required for the induction of immunosuppression or for its effector phase, or both. Further studies have demonstrated the key role of monocytes in delivering MSC immunosuppressive functions. The addition of MSC to monocytes cultured with IL-4 and granulocyte-monocyte colony-stimulating factor significantly reduces the generation of $CD14^-CD1a^+$ and resulted in the generation of $CD14^+CD1a^-$ cells with compromised antigen-priming activity. The neutralization of IL-6 also inhibited IL-10 production in monocytes, which was largely responsible for their impaired function [99]. An alternative and more novel strategy has been described by which umbilical cord-derived MSCs can re-programme monocytes, subject to dendritic cell differentiation, into M2-like cells through a lactate-mediated metabolic reprogramming. Pre-treatment of MSCs with lactate dehydrogenase inhibitors restored the normal differentiation and prevented the downstream polarization of naïve $CD4^+$ T-cells into Th2 cells [100].

More recently, a relatively unusual form of alternatively activated macrophage has been identified as a result of exposing monocytes to MSCs in the presence of macrophage colony-stimulating factor. By a PGE2-dependent mechanism, MSCs induced M2-like macrophages characterized by high expression of scavenger receptors, increased phagocytic capacity, and high production of IL-10 and TGF-β ($CD206^+$ IL-10^{high} TGF-β^{high}). Apart from suppressing T cells, these monocyte-derived macrophages also impaired NK cell activation and IFN-γ production, thus affecting both innate and adaptive immune response. Neutralization of IL-10 and TGF-β could completely restore the NK activation [101].

The *in vivo* data have provided further support to the notion that stromal cells can re-programme monocytes/macrophages. A seminal study in murine sepsis observed that the administration of murine bone marrow MSCs produced beneficial effects that were crucially dependent on recipient IL-10-producing macrophages, because their depletion or IL-10 neutralization largely abrogated the anti-inflammatory activity of MSCs [102]. The data demonstrated that, in the MSC-macrophage co-culture system, Toll-like receptor (TLR)-4 and TNF receptor-1α stimulation up-regulated COX-2 and PGE2 production in MSC, which was necessary to induce IL-10. Another study conducted in a *Tripanosoma cruzi* model confirmed these findings and the role of COX-2/PGE2. Furthermore, it showed that MSC stimulated the recruitment of anti-inflammatory $IL\text{-}10^+/IL\text{-}12^-$ macrophages and turned macrophages into cells highly susceptible to infection with *Trypanosoma cruzi* [103].

Macrophage education by MSCs *in vivo* also involves tumor necrosis factor-inducible gene 6 protein (TSG-6). The intravenous injection of human MSCs reduced murine zymosan-induced peritonitis through TSG-6 that ultimately impaired TNF-α production, after binding to CD44 [104]. Similar observations were reported in corneal allo-transplantation and experimental autoimmune uveitis (EAU) murine models, whereby a population of myeloid cells expressing MHC class II, B220, CD11b and high levels of IL-10, F4/80 and Ly6C, accumulated in the lungs, peripheral blood, spleen, and draining cervical lymph nodes after MSC infusion. MSC-primed $B220^+$ $CD11b^+$ cells suppressed proliferation of $CD4^+$ murine T cells activated by anti-CD3/28 antibodies. More importantly, the adoptive transfer of these primed macrophages could also provide tolerance in a secondary recipient mouse, prolong their graft acceptance and slow down the development of EAU. Microarray analysis and qPCR validation identified TSG-6 in MSCs was the most up-regulated during the co-culture with murine macrophages [105].

Most recently, an entirely novel mechanism involving MSC-macrophage interaction has been identified in a mouse model of graft-*versus*-host disease. When MSCs were infused in recipients harboring activated NK or cytotoxic T cells, they rapidly underwent caspase-dependent apoptosis, which is essential to initiate immunosuppression. *Ex vivo*-generated apoptotic MSCs are phagocytosed by the $CD11b^+$ and $CD11c^+$ phagocytes, which are then induced to upregulate and produce IDO-1. The depletion of $CD11b^+$ and $CD11c^+$ cells or the inhibition of IDO-1 activity in MSC recipients impaired the immunosuppressive activity of infused MSCs [106]. Accordingly, MSCs infused into asthmatic mice were previously found to be phagocytosed by $F4/80^+CD11c^+$ macrophages in the lungs, which were induced to express high mRNA levels of IL-10 and TGF-β [107]. Collectively, these findings indicate that efferocytosis of apoptotic MSCs is a further mechanism to polarize macrophages and strengthen the pivotal role of macrophages in the delivery of MSC immunosuppression.

3.2.3. Stromal cells inhibit dendritic cell differentiation and activation

Dendritic cells (DCs) are professional antigen presenting cells that potently stimulate antigen-specific $CD4^+$ and $CD8^+$ T cells [108]. It has been widely documented that stromal cells prevent the differentiation of DCs. The earliest findings were reported using both human [109,110] and murine [111] MSCs. By inhibiting cyclin D2 and entry into cell cycle, MSCs inhibit monocyte differentiation into DCs and their ability to prime T cells. IL-6 has been identified as the main effector of DC impairment by murine MSCs and fibroblasts [112]. However, IL-6 neutralization did not seem to restore the expression of co-stimulatory molecules. More recently, RNA silencing of TSG-6 in MSCs restored DC maturation, thus suggesting a role for this molecule and the existence of some redundancy in the molecular repertoire mediating such MSC function [113]. The findings in human MSCs partly differ, because the inhibition of PGE2 synthesis but not of IL-6 was demonstrated to antagonize the activity [114]. However, IL-6, together with vascular endothelial growth factor (VEGF) may play a role in the prevention of DC differentiation by human fibroblasts [115]. In contrast, other studies suggest that human dermal fibroblasts may promote rather than inhibit DC maturation although partly interfering with their activation [116].

Beyond soluble factors, cell–cell contact interactions may be responsible for MSC-induced DC impairment. Murine MSCs skew mature DCs into a regulatory-like DCs that express low levels of IL-12, high levels of IL-10 and TGF-β and exert Jagged-2 dependent immunosuppression [117,118].

The impairment of DCs by MSCs was also documented in an adoptive transfer model *in vivo*. Murine MSCs impair TLR-4 induced activation of DCs resulting in the down-regulation of molecules involved in migration to lymph nodes and antigen presentation. In fact, the intravenous administration of MSCs decreased the number of C-C

chemokine receptor type 7 and CD49dβ1 expressing DCs in the draining lymph nodes and impaired local antigen priming. In this study, it was shown that MSC blocks, almost instantaneously, the migration of DCs to the draining lymph nodes [119].

3.2.4. Stromal cells generate myeloid-derived suppressor cells (MDSC)

MDSCs are a distinct population of myeloid cells that have been classified into two categories, according to their affiliation to monocytes or neutrophils [120]. These two types of MDSCs have different physiological distribution, immunosuppressive mechanisms and chemotactic responses towards the chemokines. There is evidence that stromal cells can also hijack MDSCs to deliver their immunosuppressive activities. One of the earliest reports in the human system, described that monocyte-derived DCs can be driven toward a MDSC-like phenotype by the growth-regulated oncogene (GRO) chemokines produced by human MSCs. GRO-γ-treated MDSCs exhibited a tolerogenic phenotype, characterized by an increase in the secretion of IL-10 and IL-4 and a reduction in the production of IL-12 and IFN-γ [121]. The same results were observed in a similar setting whereby human MSCs could expand $CD14^-$ $CD11b^+$ $CD33^+$ human MDSCs expressing arginase-1 (ARG-1) and iNOS. In this case, the expansion was dependent on hepatocyte growth factor (HGF) [122].

The ability of MSCs to expand MDSCs was also documented *in vivo*. In a mouse model of EAU amenable to MSC treatment a study reported that, following MSC infusion, there was an increase in MHC class II^{low} $Ly6G^-$ $Ly6C^{high}$ $CD11b^+$ MDSCs in draining lymph nodes that was necessary to induce the suppression of $CD4^+$ cell proliferation and Th1/Th17 differentiation. The recruitment of MDSCs at the site of inflammation was CCL2-dependent [123]. Further support to the ability of MSCs to expand MDSCs comes from studies in multiple myeloma in which bone marrow-derived MSCs, obtained from patients but not from normal donors, were found able to programme MDSCs to become immunosuppressive despite similar ability in expanding the number of cells [124]. A potential mechanism of MDSC education consists in the production of exosomes by MSCs, which directly induce the survival of MDSCs through activating STAT3 and STAT1 pathways and increasing the anti-apoptotic proteins Bcl-xL and Mcl-1 [125].

4. The tumor microenvironment: a paradigm for the interaction between stromal and myeloid cells

Tumorigenesis and cancer progression are not isolated, tumor-centered programs but are heavily dependent on the support of the tumor microenvironment (TME). The TME mainly consists of mesenchymal and myeloid cells that, alone or in combination, are responsible for driving resistance to conventional therapies and suppressing anti-tumor immune responses. The phenotype and function of these cells in the tumor recapitulate the characteristics of their immunosuppressive mode described in the previous sections.

The contribution of stromal cells to the recruitment and education of tumor-associated macrophages (TAM) is well documented. In prostate carcinoma, the conditioned medium obtained from cancer associated fibroblasts (CAF), exhibited high chemotactic activity towards monocytes, largely mediated by CXCL12 and induced the differentiation of monocytes into immunosuppressive TAMs [126]. Further studies have confirmed that the CAFs can differentiate normal monocytes to become M2-like macrophages through ROS production [127] or the secretion of glycoprotein chitinase 3-like 1 (Chi3-L1) [128]. Silencing Chi3L1 in fibroblasts attenuates tumor growth and macrophage recruitment, thus restoring infiltration of $CD8^+$ and $CD4^+$ T cells within the tumor. TGF-β has been consistently identified as inducer of an M2 phenotype, reinforced by other polarizing cytokines, such as IL-4, IL-6 and CXCL8. In pancreatic cancer, M2 polarization can be also mediated by ROS induced by CAF-secreting M-CSF [127].

An interesting angle comes from the metabolic properties of stromal cells. It has been proposed that cancer cells could induce aerobic glycolysis in stromal fibroblasts, which would then secrete lactate and pyruvate [129]. Apart from supporting cancer cell growth, lactate has been shown to induce the expression of VEGF and M2-like polarization of TAMs [130].

There is ample evidence that cancer associated fibroblasts and MSCs express chemokines like CCL2, CCL5, CXCL8 and CXCL12 involved in facilitating cancer progression [131–133] and enhancing the migration of MDSCs to the tumor site [134,135]. Furthermore, MSCs have been shown to produce IL-6, which is a crucial differentiating factor for MDSC differentiation from bone marrow precursors [136]. Similar properties have been described in tumor-associated pericytes for their ability to facilitate tumor growth and spreading by inducing MDSC infiltration [137]. Recently, it has been suggested that MDSCs provide a major source of TAMs under hypoxic conditions or exposure to hypoxia-inducible factor-1α (HIF-1α) [138], LIF and IL-6 [139].

Strikingly, the interaction between CAFs and MDSCs or TAMs are also reciprocal. In a triple-negative breast cancer model, human monocytes were injected into breast cancer murine model and became MDSC-like ($S100A9^+$) in the proximity of the tumor site [140]. These $S100A9^+$ cells up-regulated CXCL16 in CAFs and consequently increased monocyte infiltration, thus forming a positive feedback loop to establish an immunosuppressive TME. Furthermore, TAM appeared to induce the upregulation of α-SMA in normal fibroblasts, suggesting they can enhance CAF production [126].

5. Conclusions and future perspectives

The cross-talk between stromal cells and the different types of myeloid cells plays a crucial role in normal and pathological tissue homeostasis. Despite the yet unresolved heterogeneity, all stromal cells respond in a very similar way to inflammation. Depending on the inflammatory cues to which they are exposed, stromal cells can resource to a large and often redundant repertoire of molecules that initiate and regulate both the magnitude and duration of inflammation. The impact of stromal-myeloid cell interaction on the TME is recapitulated by the information obtained from studies on their immunobiology.

Interestingly, the nature of the immunosuppressive mechanisms is not necessarily and exclusively immunological and has implications on tissue stem cell renewal and differentiation and on tissue repair. For example, there is accumulating evidence that IDO, either directly produced by stromal cells but especially induced in myeloid cells, play a central role in immunosuppression. However, IDO-mediated tryptophan starvation also inhibits the immunoregulatory kinase mammalian target of rapamycin (mTOR) [141] which was recently demonstrated to regulate stem cell maintenance [142]. Furthermore, the glycolytic pathway, activated in stromal cells in hypoxic niche [143], can promote the reprogramming of tissue macrophages that expedite tissue regeneration [144].

Therefore, elucidating the different pathways by which stromal cells orchestrate myeloid differentiation and functions will have profound repercussions on how to modulate therapeutically tissue regeneration in inflammation and malignancy.

Conflict of interest

The authors do not have any competing interest to disclose.

References

[1] M. Krampera, S. Glennie, J. Dyson, D. Scott, R. Laylor, E. Simpson, F. Dazzi, Bone marrow mesenchymal stem cells inhibit the response of naive and memory antigen-specific T cells to their cognate peptide, Stem Cells 101 (2003) 3722–3729, http://dx.doi.org/10.1182/blood-2002-07-2104 Supported.

[2] H. Roelofs, F. Frassoni, K. Le Blanc, L. Ball, F. Locatelli, I. Lewis, E. Lanino, B. Sundberg, M.E. Bernardo, M. Remberger, G. Dini, R.M. Egeler, A. Bacigalupo, W. Fibbe, O. Ringdén, D.C. of the E.G. for B. and M. Transplantation, S. Matteo, K. Le Blanc, F. Frassoni, L. Ball, F. Locatelli, H. Roelofs, I. Lewis, E. Lanino,

B. Sundberg, S. Matteo, Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study, Lancet 371 (2008) 1579–1586, http://dx.doi.org/10.1016/S0140-6736(08)60690-X.
[3] L. Raffaghello, F. Dazzi, Classification and biology of tumour associated stromal cells, Immunol. Lett. 1 (2015) 1–8, http://dx.doi.org/10.1016/j.imlet.2015.06.016.
[4] R.R. Driskell, B.M. Lichtenberger, E. Hoste, K. Kretzschmar, B.D. Simons, M. Charalambous, S.R. Ferron, Y. Herault, G. Pavlovic, A.C. Ferguson-Smith, F.M. Watt, Distinct fibroblast lineages determine dermal architecture in skin development and repair, Nature 504 (2013) 277–281, http://dx.doi.org/10.1038/nature12783.
[5] R. Kalluri, The biology and function of fibroblasts in cancer, Nat. Rev. Cancer 16 (2016) 582–598, http://dx.doi.org/10.1038/nrc.2016.73.
[6] M.F. Pittenger, A.M. Mackay, S.C. Beck, R.K. Jaiswal, R. Douglas, J.D. Mosca, M.A. Moorman, D.W. Simonetti, S. Craig, D.R. Marshak, Multilineage potential of adult human mesenchymal stem cells, Science 284 (1999) 143–147 http://www.ncbi.nlm.nih.gov/pubmed/10102814 . (Accessed 18 July 2014).
[7] A.J. Friedenstein, U.F. Deriglasova, N.N. Kulagina, A.F. Panasuk, S.F. Rudakowa, E.A. Luriá, I.A. Ruadkow, Precursors for fibroblasts in different populations of hematopoietic cells as detected by the in vitro colony assay method, Exp. Hematol. 2 (1974) 83–92 http://www.ncbi.nlm.nih.gov/pubmed/4455512 . (Accessed 12 December 2017).
[8] P.A. Zuk, M. Zhu, P. Ashjian, D.A. De Ugarte, J.I. Huang, H. Mizuno, Z.C. Alfonso, J.K. Fraser, P. Benhaim, M.H. Hedrick, Human adipose tissue is a source of multipotent stem cells, Mol. Biol. Cell 13 (2002) 4279–4295, http://dx.doi.org/10.1091/mbc.E02-02-0105.
[9] S. Jones, N. Horwood, A. Cope, F. Dazzi, The antiproliferative effect of mesenchymal stem cells is a fundamental property shared by all stromal cells, J. Immunol. 179 (2007) 2824–2831, http://dx.doi.org/10.4049/jimmunol.179.5.2824.
[10] I.R. Murray, C.C. West, W.R. Hardy, A.W. James, T.S. Park, A. Nguyen, T. Tawonsawatruk, L. Lazzari, C. Soo, B. Péault, Natural history of mesenchymal stem cells, from vessel walls to culture vessels, Cell. Mol. Life Sci. 71 (2014) 1353–1374, http://dx.doi.org/10.1007/s00018-013-1462-6.
[11] F.-J. Lv, R.S. Tuan, K.M.C. Cheung, V.Y.L. Leung, Concise review the surface markers and identity of human mesenchymal stem cells, Stem Cells 32 (2014) 1408–1419, http://dx.doi.org/10.1002/stem.1681.
[12] S. Morikawa, Y. Mabuchi, Y. Kubota, Y. Nagai, K. Niibe, E. Hiratsu, S. Suzuki, C. Miyauchi-Hara, N. Nagoshi, T. Sunabori, S. Shimmura, A. Miyawaki, T. Nakagawa, T. Suda, H. Okano, Y. Matsuzaki, Prospective identification, isolation, and systemic transplantation of multipotent mesenchymal stem cells in murine bone marrow, J. Exp. Med. 206 (2009) 2483–2496, http://dx.doi.org/10.1084/jem.20091046.
[13] B.O. Zhou, R. Yue, M.M. Murphy, J.G. Peyer, S.J. Morrison, Leptin-receptor-expressing mesenchymal stromal cells represent the main source of bone formed by adult bone marrow, Cell Stem Cell 15 (2014) 154–168, http://dx.doi.org/10.1016/j.stem.2014.06.008.
[14] S. Méndez-Ferrer, T.V. Michurina, F. Ferraro, A.R. Mazloom, B.D. MacArthur, S.A. Lira, D.T. Scadden, A. Mag'Ayan, G.N. Enikolopov, P.S. Frenette, Mesenchymal and haematopoietic stem cells form a unique bone marrow niche, Nature 466 (2010) 829–834, http://dx.doi.org/10.1038/nature09262.
[15] L.E.B. de Souza, T.M. Malta, S. Kashima Haddad, D.T. Covas, Mesenchymal stem cells and pericytes: to what extent are they related? Stem Cells Dev. 25 (2016) 1843–1852, http://dx.doi.org/10.1089/scd.2016.0109.
[16] G. Bergers, The role of pericytes in blood-vessel formation and maintenance, Neuro Oncol. 7 (2005) 452–464, http://dx.doi.org/10.1215/S1152851705000232.
[17] S. Shi, S. Gronthos, Perivascular niche of postnatal mesenchymal stem cells in human bone marrow and dental pulp, J. Bone Miner. Res. 18 (2003) 696–704, http://dx.doi.org/10.1359/jbmr.2003.18.4.696.
[18] M. Crisan, S. Yap, L. Casteilla, C.-W. Chen, M. Corselli, T.S. Park, G. Andriolo, B. Sun, B. Zheng, L. Zhang, C. Norotte, P.-N. Teng, J. Traas, R. Schugar, B.M. Deasy, S. Badylak, H.-J. Buhring, J.-P. Giacobino, L. Lazzari, J. Huard, B. Péault, A perivascular origin for mesenchymal stem cells in multiple human organs, Cell Stem Cell 3 (2008) 301–313, http://dx.doi.org/10.1016/j.stem.2008.07.003.
[19] M. Corselli, C.-W. Chen, B. Sun, S. Yap, J.P. Rubin, B. Péault, The tunica adventitia of human arteries and veins as a source of mesenchymal stem cells, Stem Cells Dev. 21 (2012) 1299–1308, http://dx.doi.org/10.1089/scd.2011.0200.
[20] Y.W.Y. Pang, J. Feng, F. Daltoe, R. Fatscher, E. Gentleman, M.M. Gentleman, P.T. Sharpe, Perivascular stem cells at the tip of mouse incisors regulate tissue regeneration, J. Bone Miner. Res. 31 (2016) 514–523, http://dx.doi.org/10.1002/jbmr.2717.
[21] A. Kumar, S.S. D'Souza, O.V. Moskvin, H. Toh, B. Wang, J. Zhang, S. Swanson, L.W. Guo, J.A. Thomson, I.I. Slukvin, Specification and diversification of pericytes and smooth muscle cells from mesenchymoangioblasts, Cell Rep. 19 (2017) 1902–1916, http://dx.doi.org/10.1016/j.celrep.2017.05.019.
[22] D.L. Worthley, M. Churchill, J.T. Compton, Y. Tailor, M. Rao, Y. Si, D. Levin, M.G. Schwartz, A. Uygur, Y. Hayakawa, S. Gross, B.W. Renz, W. Setlik, A.N. Martinez, X. Chen, S. Nizami, H.G. Lee, H.P. Kang, J.M. Caldwell, S. Asfaha, C.B. Westphalen, T. Graham, G. Jin, K. Nagar, H. Wang, M.A. Kheirbek, A. Kolhe, J. Carpenter, M. Glaire, A. Nair, S. Renders, N. Manieri, S. Muthupalani, J.G. Fox, M. Reichert, A.S. Giraud, R.F. Schwabe, J.P. Pradere, K. Walton, A. Prakash, D. Gumucio, A.K. Rustgi, T.S. Stappenbeck, R.A. Friedman, M.D. Gershon, P. Sims, T. Grikscheit, F.Y. Lee, G. Karsenty, S. Mukherjee, T.C. Wang, Gremlin 1 identifies a skeletal stem cell with bone, cartilage, and reticular stromal potential, Cell 160 (2015) 269–284, http://dx.doi.org/10.1016/j.cell.2014.11.042.
[23] E.A. Jaffe, L.W. Hoyer, R.L. Nachman, Synthesis of antihemophilic factor antigen by cultured human endothelial cells, J. Clin. Invest. 52 (1973) 2757–2764, http://dx.doi.org/10.1172/JCI107471.
[24] M.A. Gimbrone, R.S. Cotran, J. Folkman, Human vascular endothelial cells in culture. Growth and DNA synthesis, J. Cell Biol. 60 (1974) 673–684 http://www.ncbi.nlm.nih.gov/pubmed/4363161 . (Accessed 12 December 2017).
[25] J. Rakocevic, D. Orlic, O. Mitrovic-Ajtic, M. Tomasevic, M. Dobric, N. Zlatic, D. Milasinovic, G. Stankovic, M. Ostojić, M. Labudovic-Borovic, Endothelial cell markers from clinician's perspective, Exp. Mol. Pathol. 102 (2017) 303–313, http://dx.doi.org/10.1016/j.yexmp.2017.02.005.
[26] A.P.D.F. Murray, The development in vitro of the blood of the early chick embryo, Proc. R. Soc. B: Biol. Sci. 111 (2011) 497–521, http://dx.doi.org/10.2307/81556.
[27] Q. Chen, H. Zhang, Y. Liu, S. Adams, H. Eilken, M. Stehling, M. Corada, E. Dejana, B. Zhou, R.H. Adams, Endothelial cells are progenitors of cardiac pericytes and vascular smooth muscle cells, Nat. Commun. 7 (2016) 1–13, http://dx.doi.org/10.1038/ncomms12422.
[28] G.V. Silva, S. Litovsky, J.A.R. Assad, A.L.S. Sousa, B.J. Martin, D. Vela, S.C. Coulter, J. Lin, J. Ober, W.K. Vaughn, R.V.C. Branco, E.M. Oliveira, R. He, Y.J. Geng, J.T. Willerson, E.C. Perin, Mesenchymal stem cells differentiate into an endothelial phenotype, enhance vascular density, and improve heart function in a canine chronic ischemia model, Circulation 111 (2005) 150–156, http://dx.doi.org/10.1161/01.CIR.0000151812.86142.45.
[29] M.-Y. Chen, P.-C. Lie, Z.-L. Li, X. Wei, Endothelial differentiation of Wharton's jelly–derived mesenchymal stem cells in comparison with bone marrow–derived mesenchymal stem cells, Exp. Hematol. 37 (2009) 629–640, http://dx.doi.org/10.1016/j.exphem.2009.02.003.
[30] W.C. Aird, Phenotypic heterogeneity of the endothelium: I. Structure, function, and mechanisms, Circ. Res. 100 (2007) 158–173, http://dx.doi.org/10.1161/01.RES.0000255691.76142.4a.
[31] W.C. Aird, Phenotypic heterogeneity of the endothelium: II. Representative vascular beds, Circ. Res. 100 (2007) 174–190, http://dx.doi.org/10.1161/01.RES.0000255690.03436.ae.
[32] C.V. Carman, R. Martinelli, T lymphocyte-endothelial interactions: emerging understanding of trafficking and antigen-specific immunity, Front. Immunol. 6 (2015), http://dx.doi.org/10.3389/fimmu.2015.00603.
[33] L.V. Riella, T. Watanabe, P.T. Sage, J. Yang, M. Yeung, J. Azzi, V. Vanguri, A. Chandraker, A.H. Sharpe, M.H. Sayegh, N. Najafian, Essential role of PDL1 expression on nonhematopoietic donor cells in acquired tolerance to vascularized cardiac allografts, Am. J. Transplant. 11 (2011) 832–840, http://dx.doi.org/10.1111/j.1600-6143.2011.03451.x.
[34] N. Grabie, I. Gotsman, R. DaCosta, H. Pang, G. Stavrakis, M.J. Butte, M.E. Keir, G.J. Freeman, A.H. Sharpe, A.H. Lichtman, Endothelial programmed death-1 ligand 1 (PD-L1) regulates CD8+ T-cell-mediated injury in the heart, Circulation 116 (2007) 2062–2071, http://dx.doi.org/10.1161/CIRCULATIONAHA.107.709360.
[35] H. Fu, M. Kishore, B. Gittens, G. Wang, D. Coe, I. Komarowska, E. Infante, A.J. Ridley, D. Cooper, M. Perretti, F.M. Marelli-Berg, Self-recognition of the endothelium enables regulatory T-cell trafficking and defines the kinetics of immune regulation, Nat. Commun. 5 (2014) 1–14, http://dx.doi.org/10.1038/ncomms4436.
[36] R. Bucala, L.A. Spiegel, J. Chesney, M. Hogan, A. Cerami, Circulating fibrocytes define a new leukocyte subpopulation that mediates tissue repair, Mol. Med. (Cambridge, Mass.) 1 (1994) 71–81 http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=8790603&retmode=ref&cmd=prlinks%5Cnpapers2://publication/uuid/0795ED84-A885-440D-973E-317834B0B326.
[37] S.J. Curnow, M. Fairclough, C. Schmutz, S. Kissane, A.K.O. Denniston, K. Nash, C.D. Buckley, J.M. Lord, M. Salmon, Distinct types of fibrocyte can differentiate from mononuclear cells in the presence and absence of serum, PLoS One 5 (2010), http://dx.doi.org/10.1371/journal.pone.0009730.
[38] M. Niedermeier, B. Reich, M.R. Gomez, A. Denzel, K. Schmidbauer, N. Gobel, Y. Talke, F. Schweda, M. Mack, CD4+ T cells control the differentiation of Gr1+ monocytes into fibrocytes, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 17892–17897, http://dx.doi.org/10.1073/pnas.0906070106.
[39] Y.H. Choi, M.D. Burdick, R.M. Strieter, Human circulating fibrocytes have the capacity to differentiate osteoblasts and chondrocytes, Int. J. Biochem. Cell Biol. 42 (2010) 662–671, http://dx.doi.org/10.1016/j.biocel.2009.12.011.
[40] H. Zhang, I. Maric, M.J. DiPrima, J. Khan, R.J. Orentas, R.N. Kaplan, C.L. Mackall, Fibrocytes represent a novel MDSC subset circulating in patients with metastatic cancer, Blood 122 (2013) 1105–1113, http://dx.doi.org/10.1182/blood-2012-08-449413.
[41] D.H. Munn, A.L. Mellor, 2 Indoleamine, 3 dioxygenase and metabolic control of immune responses, Trends Immunol. 34 (2013) 137–143, http://dx.doi.org/10.1016/j.it.2012.10.001.
[42] M. François, R. Romieu-Mourez, M. Li, J. Galipeau, Human MSC suppression correlates with cytokine induction of indoleamine 2, 3-dioxygenase and bystander M2 macrophage differentiation, Mol. Ther. 20 (2012) 187–195, http://dx.doi.org/10.1038/mt.2011.189.
[43] M. Krampera, L. Cosmi, R. Angeli, A. Pasini, F. Liotta, A. Andreini, V. Santarlasci, B. Mazzinghi, G. Pizzolo, F. Vinante, P. Romagnani, E. Maggi, S. Romagnani, F. Annunziato, Role for interferon-γ in the immunomodulatory activity of human bone marrow mesenchymal stem cells, Stem Cells 24 (2006) 386–398, http://dx.doi.org/10.1634/stemcells.2005-0008.
[44] J.M. Ryan, F. Barry, J.M. Murphy, B.P. Mahon, Interferon-γ does not break, but promotes the immunosuppressive capacity of adult human mesenchymal stem cells, Clin. Exp. Immunol. 149 (2007) 353–363, http://dx.doi.org/10.1111/j.

1365-2249.2007.03422.x.
[45] R. Meisel, A. Zibert, M. Laryea, U. Göbel, W. Däubener, D. Dilloo, Human bone marrow stromal cells inhibit allogeneic T-cell responses by indoleamine 2, 3-dioxygenase-mediated tryptophan degradation, Blood 103 (2004) 4619–4621, http://dx.doi.org/10.1182/blood-2003-11-3909.
[46] S. Tipnis, C. Viswanathan, A.S. Majumdar, Immunosuppressive properties of human umbilical cord-derived mesenchymal stem cells: role of B7-H1 and IDO, Immunol. Cell Biol. 88 (2010) 795–806, http://dx.doi.org/10.1038/icb.2010.47.
[47] M.A. Haniffa, X.-N. Wang, U. Holtick, M. Rae, J.D. Isaacs, A.M. Dickinson, C.M.U. Hilkens, M.P. Collin, Adult human fibroblasts are potent immunoregulatory cells and functionally equivalent to mesenchymal stem cells, J. Immunol. 179 (2007) 1595–1604, http://dx.doi.org/10.4049/jimmunol.179.3.1595.
[48] G.M. Spaggiari, A. Capobianco, H. Abdelrazik, F. Becchetti, M.C. Mingari, L. Moretta, Mesenchymal stem cells inhibit natural killer cell proliferation, cytotoxicity, and cytokine production: role of indoleamine 2, 3-dioxygenase and prostaglandin E2, Blood 111 (2008) 1327–1333, http://dx.doi.org/10.1182/blood-2007-02-074997.
[49] G. Ren, J. Su, L. Zhang, X. Zhao, W. Ling, A. L'huillie, J. Zhang, Y. Lu, A.I. Roberts, W. Ji, H. Zhang, A.B. Rabson, Y. Shi, Species variation in the mechanisms of mesenchymal stem cell-mediated immunosuppression, Stem Cells 27 (2009) 1954–1962, http://dx.doi.org/10.1002/stem.118.
[50] K. Sato, K. Ozaki, I. Oh, A. Meguro, K. Hatanaka, T. Nagai, K. Muroi, K. Ozawa, Nitric oxide plays a critical role in suppression of T-cell proliferation by mesenchymal stem cells, Blood 109 (2007) 228–234, http://dx.doi.org/10.1182/blood-2006-02-002246.
[51] P. Blancou, V. Tardif, T. Simon, S. Rémy, L. Carreño, A. Kalergis, I. Anegon, Immunoregulatory properties of heme oxygenase -1, Methods Mol. Biol. (2010) 247–268, http://dx.doi.org/10.1007/978-1-60761-869-0_18.
[52] N. Haven, C.V. Affairs, W. Haven, N. Haven, A. Ochsner, M. Foundation, N. Orleans, B. Israel, D. Medical, A.M.K. Choi, L.E. Otterbein, F.H. Bach, J. Alam, M. Soares, H. Tao Lu, M. Wysk, R.J. Davis, R.A. Flavell, Carbon monoxide has anti-inflammatory effects involving the mitogen-activated protein kinase pathway, Nat. Med. 6 (2000) 422–428, http://dx.doi.org/10.1038/74680.
[53] D. Mougiakakos, R. Jitschin, C.C. Johansson, R. Okita, R. Kiessling, K. Le Blanc, The impact of inflammatory licensing on heme oxygenase-1–mediated induction of regulatory T cells by human mesenchymal stem cells, Blood 117 (2011) 4826–4835, http://dx.doi.org/10.1182/blood-2010-12-324038.
[54] P. Kalinski, Regulation of immune responses by prostaglandin E2, J. Immunol. 188 (2012) 21–28, http://dx.doi.org/10.4049/jimmunol.1101029.
[55] S. Aggarwal, M.F. Pittenger, Human mesenchymal stem cells modulate allogeneic immune cell responses, Blood 105 (2005) 1815–1822, http://dx.doi.org/10.1182/blood-2004-04-1559.
[56] M.O. Li, Y.Y. Wan, S. Sanjabi, A.-K.L. Robertson, R.A. Flavell, Transforming growth factor-B regulation of immune responses, Annu. Rev. Immunol. 24 (2006) 99–146, http://dx.doi.org/10.1146/annurev.immunol.24.021605.090737.
[57] M. Di Nicola, C. Carlo-Stella, M. Magni, M. Milanesi, P.D. Longoni, P. Matteucci, S. Grisanti, A.M. Gianni, Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli, Blood 99 (2002) 3838–3843, http://dx.doi.org/10.1182/blood.V99.10.3838.
[58] A. Nasef, A. Chapel, C. Mazurier, S. Bouchet, M. Lopez, N. Mathieu, L. Sensebé, Y. Zhang, N.-C. Gorin, D. Thierry, L. Fouillard, Identification of IL-10 and TGF-beta transcripts involved in the inhibition of T-lymphocyte proliferation during cell contact with human mesenchymal stem cells, Gene Expr. 13 (2007) 217–226.
[59] M.E. Groh, B. Maitra, E. Szekely, O.N. Koç, Human mesenchymal stem cells require monocyte-mediated activation to suppress alloreactive T cells, Exp. Hematol. 33 (2005) 928–934, http://dx.doi.org/10.1016/j.exphem.2005.05.002.
[60] T. Brabletz, I. Pfeuffer, E. Schorr, F. Siebelt, T. Wirth, E. Serfling, Transforming growth factor β and cyclosporin A inhibit the inducible activity of the interleukin-2 gene in T cells through a noncanonical octamer-binding site, Mol. Cell. Biol. 13 (1993) 1155–1162, http://dx.doi.org/10.1128/MCB.13.2.1155 Updated.
[61] S.C. McKarns, R.H. Schwartz, N.E. Kaminski, Smad3 is essential for TGF-beta 1 to suppress IL-2 production and TCR-induced proliferation, but not IL-2-induced proliferation, J. Immunol. 172 (2004) 4275–4284, http://dx.doi.org/10.4049/jimmunol.172.7.4275.
[62] K. Nemeth, A. Keane-Myers, J.M. Brown, D.D. Metcalfe, J.D. Gorham, J.D. Gorham, V.G. Bundoc, V.G. Bundoc, M.G. Hodges, I. Jelinek, S. Madala, S. Karpati, E. Mezey, Bone marrow stromal cells use TGF-beta to suppress allergic responses in a mouse model of ragweed-induced asthma, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 5652–5657, http://dx.doi.org/10.1073/pnas.0910720107.
[63] M. Najar, G. Raicevic, H. Fayyad-Kazan, C. De Bruyn, D. Bron, M. Toungouz, L. Lagneaux, Bone marrow mesenchymal stromal cells induce proliferative, cytokinic and molecular changes during the T cell response: the importance of the IL-10/CD210 axis, Stem Cell Rev. Rep. 11 (2015) 442–452, http://dx.doi.org/10.1007/s12015-014-9567-3.
[64] Z. Tu, Y. Li, D.S. Smith, N. Sheibani, S. Huang, T. Kern, F. Lin, Retinal pericytes inhibit activated T cell proliferation, Investig. Ophthalmol. Vis. Sci. 52 (2011) 9005–9010, http://dx.doi.org/10.1167/iovs.11-8008.
[65] E. Ivanova-Todorova, I. Bochev, R. Dimitrov, K. Belemezova, M. Mourdjeva, S. Kyurkchiev, P. Kinov, I. Altankova, D. Kyurkchiev, Conditioned medium from adipose tissue-derived mesenchymal stem cells induces CD4 + FOXP3+ cells and increases IL-10 secretion, J. Biomed. Biotechnol. 2012 (2012), http://dx.doi.org/10.1155/2012/295167.
[66] Z. Selmani, A. Naji, I. Zidi, B. Favier, E. Gaiffe, L. Obert, C. Borg, P. Saas, P. Tiberghien, N. Rouas-Freiss, E.D. Carosella, F. Deschaseaux, Human leukocyte antigen-G5 secretion by human mesenchymal stem cells is required to suppress T lymphocyte and natural killer function and to induce CD4 + CD25 high FOXP3 + regulatory T cells, Stem Cells 26 (2008) 212–222, http://dx.doi.org/10.1634/stemcells.2007-0554.
[67] F. Gieseke, J. Böhringer, R. Bussolari, M. Dominici, R. Handgretinger, I. Müller, Human multipotent mesenchymal stromal cells use galectin-1 to inhibit immune effector cells, Blood 116 (2010) 3770–3779, http://dx.doi.org/10.1182/blood-2010-02-270777.
[68] Y. Lepelletier, S. Lecourt, A. Renand, B. Arnulf, V. Vanneaux, J.-P. Fermand, P. Menasché, T. Domet, J.-P. Marolleau, O. Hermine, J. Larghero, Galectin-1 and semaphorin-3A are two soluble factors conferring T-cell immunosuppression to bone marrow mesenchymal stem cell, Stem Cells Dev. 19 (2010) 1075–1079, http://dx.doi.org/10.1089/scd.2009.0212.
[69] M. Sioud, A. Mobergslien, A. Boudabous, Y. Fløisand, Evidence for the involvement of galectin-3 in mesenchymal stem cell suppression of allogeneic T-cell proliferation, Scand. J. Immunol. 71 (2010) 267–274, http://dx.doi.org/10.1111/j.1365-3083.2010.02378.x.
[70] C. Ungerer, P. Quade-Lyssy, H.H. Radeke, R. Henschler, C. Königs, U. Köhl, E. Seifried, J. Schüttrumpf, Galectin-9 is a suppressor of T and B cells and predicts the immune modulatory potential of mesenchymal stromal cell preparations, Stem Cells Dev. 23 (2014) 755–766, http://dx.doi.org/10.1089/scd.2013.0335.
[71] A. Nasef, C. Mazurier, S. Bouchet, S. François, A. Chapel, D. Thierry, N.-C. Gorin, L. Fouillard, Leukemia inhibitory factor: role in human mesenchymal stem cells mediated immunosuppression, Cell. Immunol. 253 (2008) 16–22, http://dx.doi.org/10.1016/j.cellimm.2008.06.002.
[72] S.J. Turley, V. Cremasco, J.L. Astarita, Immunological hallmarks of stromal cells in the tumour microenvironment, Nat. Rev. Immunol. 15 (2015) 669–682, http://dx.doi.org/10.1038/nri3902.
[73] H. Sheng, Y. Wang, Y. Jin, Q. Zhang, Y. Zhang, L. Wang, B. Shen, S. Yin, W. Liu, L. Cui, N. Li, A critical role of IFNγ in priming MSC-mediated suppression of T cell proliferation through up-regulation of B7-H1, Cell Res. 18 (2008) 846–857, http://dx.doi.org/10.1038/cr.2008.80.
[74] N. Rodig, T. Ryan, J.A. Allen, H. Pang, N. Grabie, T. Chernova, E.A. Greenfield, S.C. Liang, A.H. Sharpe, A.H. Lichtman, G.J. Freeman, Endothelial expression of PD-L1 and PD-L2 down-regulates CD8+ T cell activation and cytolysis, Eur. J. Immunol. 33 (2003) 3117–3126, http://dx.doi.org/10.1002/eji.200324270.
[75] M. Giuliani, M. Fleury, A. Vernochet, F. Ketroussi, D. Clay, B. Azzarone, J.J. Lataillade, A. Durrbach, Long-lasting inhibitory effects of fetal liver mesenchymal stem cells on T-lymphocyte proliferation, PLoS One 6 (2011), http://dx.doi.org/10.1371/journal.pone.0019988.
[76] Q. Xue, X.-Y. Luan, Y.-Z. Gu, H.-Y. Wu, G.-B. Zhang, G.-H. Yu, H.-T. Zhu, M. Wang, W. Dong, Y.-J. Geng, X.-G. Zhang, The negative co-signaling molecule B7-H4 is expressed by human bone marrow–derived mesenchymal stem cells and mediates its T-cell modulatory activity, Stem Cells Dev. 19 (2010) 27–38, http://dx.doi.org/10.1089/scd.2009.0076.
[77] G.L. Sica, I.H. Choi, G. Zhu, K. Tamada, S.D. Wang, H. Tamura, A.I. Chapoval, D.B. Flies, J. Bajorath, L. Chen, B7-H4, a molecule of the B7 family, negatively regulates T cell immunity, Immunity 18 (2003) 849–861, http://dx.doi.org/10.1016/S1074-7613(03)00152-3.
[78] F. Liotta, R. Angeli, L. Cosmi, L. Filì, C. Manuelli, F. Frosali, B. Mazzinghi, L. Maggi, A. Pasini, V. Lisi, V. Santarlasci, L. Consoloni, M.L. Angelotti, P. Romagnani, P. Parronchi, M. Krampera, E. Maggi, S. Romagnani, F. Annunziato, Toll-like receptors 3 and 4 are expressed by human bone marrow-derived mesenchymal stem cells and can inhibit their T-cell modulatory activity by impairing notch signaling, Stem Cells 26 (2008) 279–289, http://dx.doi.org/10.1634/stemcells.2007-0454.
[79] R.A. Denu, S. Nemcek, D.D. Bloom, A.D. Goodrich, J. Kim, D.F. Mosher, P. Hematti, Fibroblasts and mesenchymal stromal/stem cells are phenotypically indistinguishable, Acta Haematol. 136 (2016) 85–97, http://dx.doi.org/10.1159/000445096.
[80] Y. Shimabukuro, S. Murakami, H. Okada, Interferon-gamma-dependent immunosuppressive effects of human gingival fibroblasts, Immunology 76 (1992) 344–347 http://www.ncbi.nlm.nih.gov/pubmed/1634256 . (Accessed 18 December 2017).
[81] C.L. Maier, J.S. Pober, Human placental pericytes poorly stimulate and actively regulate allogeneic CD4 T cell responses, Arterioscler. Thromb. Vasc. Biol. 31 (2011) 183–189, http://dx.doi.org/10.1161/ATVBAHA.110.217117.
[82] M.E. Groh, B. Maitra, E. Szekely, O.N. Koç, Human mesenchymal stem cells require monocyte-mediated activation to suppress alloreactive T cells, Exp. Hematol. 33 (2005) 928–934, http://dx.doi.org/10.1016/j.exphem.2005.05.002.
[83] T.P. Mikołajczyk, J.E. Skrzeczyńska-Moncznik, M.A. Zarebski, E.A. Marewicz, A.M. Wiśniewska, M. Dzieba, J.W. Dobrucki, J.R. Pryjma, Interaction of human peripheral blood monocytes with apoptotic polymorphonuclear cells, Immunology 128 (2009) 103–113, http://dx.doi.org/10.1111/j.1365-2567.2009.03087.x.
[84] F.K. Swirski, M. Nahrendorf, M. Etzrodt, M. Wildgruber, V. Cortez-Retamozo, P. Panizzi, J.-L. Figueiredo, R.H. Kohler, A. Chudnovskiy, P. Waterman, E. Aikawa, T.R. Mempel, P. Libby, R. Weissleder, M.J. Pittet, Identification of splenic reservoir monocytes and their deployment to inflammatory sites, Science (80-.) 325 (2009) 612–616, http://dx.doi.org/10.1126/science.1175202.
[85] N.V. Serbina, T. Jia, T.M. Hohl, E.G. Pamer, Monocyte-mediated defense against microbial pathogens, Annu. Rev. Immunol. 26 (2008) 421–452, http://dx.doi.org/10.1146/annurev.immunol.26.021607.090326.
[86] C. Shi, T. Jia, S. Mendez-Ferrer, T.M. Hohl, N.V. Serbina, L. Lipuma, I. Leiner, M.O. Li, P.S. Frenette, E.G. Pamer, Bone marrow mesenchymal stem and progenitor cells induce monocyte emigration in response to circulating toll-like receptor ligands, Immunity 34 (2011) 590–601, http://dx.doi.org/10.1016/j.immuni.2011.02.016.

[87] H.L. Paish, N.S. Kalson, G.R. Smith, A. Del Carpio Pons, T.E. Baldock, N. Smith, K. Swist-Szulik, D.J. Weir, M. Bardgett, D.J. Deehan, D.A. Mann, L.A. Borthwick, Fibroblasts promote inflammation and pain via IL-1α induction of the monocyte chemoattractant chemokine (C-C motif) ligand 2, Am. J. Pathol. (2017) 1–20, http://dx.doi.org/10.1016/j.ajpath.2017.11.007.
[88] L. Chen, E.E. Tredget, P.Y.G. Wu, Y. Wu, Paracrine factors of mesenchymal stem cells recruit macrophages and endothelial lineage cells and enhance wound healing, PLoS One 3 (2008) e1886, http://dx.doi.org/10.1371/journal.pone.0001886.
[89] K. Miteva, K. Pappritz, M. El-Shafeey, F. Dong, J. Ringe, C. Tschöpe, S. Van Linthout, Mesenchymal stromal cells modulate monocytes trafficking in coxsackievirus B3-induced myocarditis, Stem Cells Transl. Med. 6 (2017) 1249–1261, http://dx.doi.org/10.1002/sctm.16-0353.
[90] C. Humeres, R. Vivar, P. Boza, C. Muñoz, S. Bolivar, R. Anfossi, J.M. Osorio, F. Olivares-Silva, L. García, G. Díaz-Araya, Cardiac fibroblast cytokine profiles induced by proinflammatory or profibrotic stimuli promote monocyte recruitment and modulate macrophage M1/M2 balance in vitro, J. Mol. Cell. Cardiol. 101 (2016) 69–80, http://dx.doi.org/10.1016/j.yjmcc.2016.10.014.
[91] D.M. Mosser, J.P. Edwards, Exploring the full spectrum of macrophage activation, Nat. Rev. Immunol. 8 (2008) 958–969, http://dx.doi.org/10.1038/nri2448.
[92] D. Hashimoto, A. Chow, C. Noizat, P. Teo, M.B. Beasley, M. Leboeuf, C.D. Becker, P. See, J. Price, D. Lucas, M. Greter, A. Mortha, S.W. Boyer, E.C. Forsberg, M. Tanaka, N. van Rooijen, A. García-Sastre, E.R. Stanley, F. Ginhoux, P.S. Frenette, M. Merad, Tissue-resident macrophages self-maintain locally throughout adult life with minimal contribution from circulating monocytes, Immunity 38 (2013) 792–804, http://dx.doi.org/10.1016/j.immuni.2013.04.004.
[93] F.O. Martinez, S. Gordon, The M1 and M2 paradigm of macrophage activation: time for reassessment, F1000Prime Rep. (2014) 1–13, http://dx.doi.org/10.12703/P6-13.
[94] C. Trento, I. Marigo, A. Pievani, A. Galleu, L. Dolcetti, C.-Y. Wang, M. Serafini, V. Bronte, F. Dazzi, Bone marrow mesenchymal stromal cells induce nitric oxide synthase-dependent differentiation of CD11b+ cells that expedite hematopoietic recovery, Haematologica 102 (2017), http://dx.doi.org/10.3324/haematol.2016.155390.
[95] A. Chow, D. Lucas, A. Hidalgo, S. Méndez-Ferrer, D. Hashimoto, C. Scheiermann, M. Battista, M. Leboeuf, C. Prophete, N. van Rooijen, M. Tanaka, M. Merad, P.S. Frenette, Bone marrow CD169 + macrophages promote the retention of hematopoietic stem and progenitor cells in the mesenchymal stem cell niche, J. Exp. Med. 208 (2011) 261–271, http://dx.doi.org/10.1084/jem.20101688.
[96] A. Ludin, T. Itkin, S. Gur-Cohen, A. Mildner, E. Shezen, K. Golan, O. Kollet, A. Kalinkovich, Z. Porat, G. D'Uva, A. Schajnovitz, E. Voronov, D.A. Brenner, R.N. Apte, S. Jung, T. Lapidot, Monocytes-macrophages that express α-smooth muscle actin preserve primitive hematopoietic cells in the bone marrow, Nat. Immunol. 13 (2012) 1072–1082, http://dx.doi.org/10.1038/ni.2408.
[97] S. Lymperi, N. Horwood, S. Marley, M.Y. Gordon, A.P. Cope, F. Dazzi, Strontium can increase some osteoblasts without increasing hematopoietic stem cells, Blood 111 (2008) 1173–1181, http://dx.doi.org/10.1182/blood-2007-03-082800.
[98] J. Kim, P. Hematti, Mesenchymal stem cell-educated macrophages: a novel type of alternatively activated macrophages, Exp. Hematol. 37 (2009) 1445–1453, http://dx.doi.org/10.1016/j.exphem.2009.09.004.
[99] S.M. Melief, S.B. Geutskens, W.E. Fibbe, H. Roelofs, Multipotent stromal cells skew monocytes towards an anti-inflammatory interleukin-10-producing phenotype by production of interleukin-6, Haematologica 98 (2013) 888–895, http://dx.doi.org/10.3324/haematol.2012.078055.
[100] S. Selleri, P. Bifsha, S. Civini, C. Pacelli, M.M. Dieng, W. Lemieux, P. Jin, R. Bazin, N. Patey, F.M. Marincola, F. Moldovan, C. Zaouter, L.-E. Trudeau, B. Benabdhalla, I. Louis, C. Beauséjour, D. Stroncek, F. Le Deist, E. Haddad, Human mesenchymal stromal cell-secreted lactate induces M2-macrophage differentiation by metabolic reprogramming, Oncotarget 7 (2016) 30193–30210, http://dx.doi.org/10.18632/oncotarget.8623.
[101] L. Chiossone, R. Conte, G.M. Spaggiari, M. Serra, C. Romei, F. Bellora, F. Becchetti, A. Andaloro, L. Moretta, C. Bottino, Mesenchymal stromal cells induce peculiar alternatively activated macrophages capable of dampening both innate and adaptive immune responses, Stem Cells 34 (2016) 1909–1921, http://dx.doi.org/10.1002/stem.2369.
[102] K. Németh, A. Leelahavanichkul, P.S.T. Yuen, B. Mayer, A. Parmelee, K. Doi, P.G. Robey, K. Leelahavanichkul, B.H. Koller, J.M. Brown, X. Hu, I. Jelinek, R.A. Star, E. Mezey, Bone marrow stromal cells attenuate sepsis via prostaglandin E(2)-dependent reprogramming of host macrophages to increase their interleukin-10 production, Nat. Med. 15 (2009) 42–49, http://dx.doi.org/10.1038/nm.1905.
[103] J. Maggini, G. Mirkin, I. Bognanni, J. Holmberg, I.M. Piazzón, I. Nepomnaschy, H. Costa, C. Cañones, S. Raiden, M. Vermeulen, J.R. Geffner, Mouse bone marrow-derived mesenchymal stromal cells turn activated macrophages into a regulatory-like profile, PLoS One 5 (2010), http://dx.doi.org/10.1371/journal.pone.0009252.
[104] H. Choi, R.H. Lee, N. Bazhanov, J.Y. Oh, D.J. Prockop, Anti-inflammatory protein TSG-6 secreted by activated MSCs attenuates zymosan-induced mouse peritonitis by decreasing TLR2/NF-κB signaling in resident macrophages, Blood 118 (2011) 330–338, http://dx.doi.org/10.1182/blood-2010-12-327353.
[105] J.H. Ko, H.J. Lee, H.J. Jeong, M.K. Kim, W.R. Wee, S. Yoon, H. Choi, D.J. Prockop, J.Y. Oh, Mesenchymal stem/stromal cells precondition lung monocytes/macrophages to produce tolerance against allo- and autoimmunity in the eye, Proc. Natl. Acad. Sci. U. S. A. 113 (2016) 158–163, http://dx.doi.org/10.1073/pnas.1522905113.
[106] A. Galleu, Y. Riffo-Vasquez, C. Trento, C. Lomas, L. Dolcetti, T.S. Cheung, M. von Bonin, L. Barbieri, K. Halai, S. Ward, L. Weng, R. Chakraverty, G. Lombardi, F.M. Watt, K. Orchard, D.I. Marks, J. Apperley, M. Bornhauser, H. Walczak, C. Bennett, F. Dazzi, Apoptosis in mesenchymal stromal cells induces in vivo recipient-mediated immunomodulation, Sci. Transl. Med. 9 (2017) 1–12, http://dx.doi.org/10.1126/scitranslmed.aam7828.
[107] F. Braza, S. Dirou, V. Forest, V. Sauzeau, D. Hassoun, J. Chesné, M.-A. Cheminant-Muller, C. Sagan, A. Magnan, P. Lemarchand, Mesenchymal stem cells induce suppressive macrophages through phagocytosis in a mouse model of asthma, Stem Cells 34 (2016) 1836–1845, http://dx.doi.org/10.1002/stem.2344.
[108] I. Mellman, R.M. Steinman, Dendritic cells: specialized and regulated antigen processing machines, Cell 106 (2001) 255–258, http://dx.doi.org/10.1016/S0092-8674(01)00449-4.
[109] X. Jiang, Y. Zhang, B. Liu, Human mesenchymal stem cells inhibit differentiation and function of monocyte-derived dendritic cells, Blood 105 (2005) 4120–4126, http://dx.doi.org/10.1182/blood-2004-02-0586 Supported.
[110] A.J. Nauta, A.B. Kruisselbrink, E. Lurvink, R. Willemze, W.E. Fibbe, Mesenchymal stem cells inhibit generation and function of both CD34+-derived and monocyte-derived dendritic cells, J. Immunol. 177 (2006) 2080–2087, http://dx.doi.org/10.4049/jimmunol.177.4.2080.
[111] R. Ramasamy, H. Fazekasova, E.W.-F. Lam, I. Soeiro, G. Lombardi, F. Dazzi, Mesenchymal stem cells inhibit dendritic cell differentiation and function by preventing entry into the cell cycle, Transplantation 83 (2007) 71–76, http://dx.doi.org/10.1097/01.tp.0000244572.24780.54.
[112] F. Djouad, L.-M. Charbonnier, C. Bouffi, P. Louis-Plence, C. Bony, F. Apparailly, C. Cantos, C. Jorgensen, D. Noël, Mesenchymal stem cells inhibit the differentiation of dendritic cells through an interleukin-6-dependent mechanism, Stem Cells 25 (2007) 2025–2032, http://dx.doi.org/10.1634/stemcells.2006-0548.
[113] Y. Liu, Z. Yin, R. Zhang, K. Yan, L. Chen, F. Chen, W. Huang, B. Lv, C. Sun, X. Jiang, MSCs inhibit bone marrow-derived DC maturation and function through the release of TSG-6, Biochem. Biophys. Res. Commun. 450 (2014) 1409–1415, http://dx.doi.org/10.1016/j.bbrc.2014.07.001.
[114] G.M. Spaggiari, H. Abdelrazik, F. Becchetti, L. Moretta, MSCs inhibit monocyte-derived DC maturation and function by selectively interfering with the generation of immature DCs: central role of MSC-derived prostaglandin E2, Blood 113 (2009) 6576–6583, http://dx.doi.org/10.1182/blood-2009-02-203943.
[115] S. Séguier, E. Tartour, C. Guérin, L. Couty, M. Lemitre, L. Lallement, M. Folliguet, S. El Naderi, M. Terme, C. Badoual, A. Lafont, B. Coulomb, Inhibition of the differentiation of monocyte-derived dendritic cells by human gingival fibroblasts, PLoS One 8 (2013) 2–9, http://dx.doi.org/10.1371/journal.pone.0070937.
[116] A. Saalbach, C. Klein, J. Sleeman, U. Sack, F. Kauer, C. Gebhardt, M. Averbeck, U. Anderegg, J.C. Simon, Dermal fibroblasts induce maturation of dendritic cells, J. Immunol. 178 (2007) 4966–4974, http://dx.doi.org/10.4049/jimmunol.178.8.4966.
[117] B. Zhang, R. Liu, D. Shi, X. Liu, Mesenchymal stem cells induce mature dendritic cells into a novel Jagged-2–dependent regulatory dendritic cell population, Hematop. Stem Cells 113 (2009) 46–57, http://dx.doi.org/10.1182/blood-2008-04-154138.
[118] E.F. Cahill, L.M. Tobin, F. Carty, B.P. Mahon, K. English, Jagged-1 is required for the expansion of CD4+ CD25+ FoxP3+ regulatory T cells and tolerogenic dendritic cells by murine mesenchymal stromal cells, Stem Cell Res. Ther. 6 (2015) 19, http://dx.doi.org/10.1186/s13287-015-0021-5.
[119] S. Chiesa, S. Morbelli, S. Morando, M. Massollo, C. Marini, A. Bertoni, F. Frassoni, S.T. Bartolome, G. Sambuceti, E. Traggiai, A. Uccelli, Mesenchymal stem cells impair in vivo T-cell priming by dendritic cells, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 17384–17389, http://dx.doi.org/10.1073/pnas.1103650108.
[120] V. Kumar, S. Patel, E. Tcyganov, D.I. Gabrilovich, The nature of myeloid-derived suppressor cells in the tumor microenvironment, Trends Immunol. 37 (2016) 208–220, http://dx.doi.org/10.1016/j.it.2016.01.004.
[121] H.-W. Chen, H.-Y. Chen, L.-T. Wang, F.-H. Wang, L.-W. Fang, H.-Y. Lai, H.-H. Chen, J. Lu, M.-S. Hung, Y. Cheng, M.-Y. Chen, S.-J. Liu, P. Chong, O.K.-S. Lee, S.-C. Hsu, Mesenchymal stem cells tune the development of monocyte-derived dendritic cells toward a myeloid-derived suppressive phenotype through growth-regulated oncogene chemokines, J. Immunol. 190 (2013) 5065–5077, http://dx.doi.org/10.4049/jimmunol.1202775.
[122] B.L. Yen, M.L. Yen, P.J. Hsu, K.J. Liu, C.J. Wang, C.H. Bai, H.K. Sytwu, Multipotent human mesenchymal stromal cells mediate expansion of myeloid-derived suppressor cells via hepatocyte growth factor/c-Met and STAT3, Stem Cell Rep. 1 (2013) 139–151, http://dx.doi.org/10.1016/j.stemcr.2013.06.006.
[123] H.J. Lee, J.H. Ko, H.J. Jeong, A.Y. Ko, M.K. Kim, W.R. Wee, S. Yoon, J.Y. Oh, Mesenchymal stem/stromal cells protect against autoimmunity via CCL2-dependent recruitment of myeloid-derived suppressor cells, J. Immunol. 194 (2015) 3634–3645, http://dx.doi.org/10.4049/jimmunol.1402139.
[124] C. Giallongo, D. Tibullo, N.L. Parrinello, P. La Cava, M. Di Rosa, V. Bramanti, C. Di Raimondo, C. Conticello, A. Chiarenza, G.A. Palumbo, R. Avola, A. Romano, F. Di Raimondo, Granulocyte-like myeloid derived suppressor cells (G-MDSC) are increased in multiple myeloma and are driven by dysfunctional mesenchymal stem cells (MSC), Oncotarget 7 (2016) 85764–85775, http://dx.doi.org/10.18632/oncotarget.7969.
[125] J. Wang, K. De Veirman, N. De Beule, K. Maes, E. De Bruyne, E. Van Valckenborgh, K. Vanderkerken, E. Menu, The bone marrow microenvironment enhances multiple myeloma progression by exosome-mediated activation of myeloid-derived suppressor cells, Oncotarget 6 (2015) 43992–44004, http://dx.doi.org/10.18632/oncotarget.6083.
[126] G. Comito, E. Giannoni, C.P. Segura, G. Baroni, M. Lanciotti, S. Serni, P. Chiarugi, Cancer-associated fibroblasts and M2-polarized macrophages synergize during prostate carcinoma progression, Oncogene 33 (2013) 2423–2431, http://dx.doi.org/10.1038/onc.2013.191.

[127] A. Zhang, Y. Qian, Z. Ye, H. Chen, H. Xie, L. Zhou, Y. Shen, S. Zheng, Cancer-associated fibroblasts promote M2 polarization of macrophages in pancreatic ductal adenocarcinoma, Cancer Med. 6 (2017) 463–470, http://dx.doi.org/10.1002/cam4.993.

[128] N. Cohen, O. Shani, Y. Raz, Y. Sharon, D. Hoffman, L. Abramovitz, N. Erez, Fibroblasts drive an immunosuppressive and growth-promoting microenvironment in breast cancer via secretion of Chitinase 3-like 1, Oncogene 36 (2017) 4457–4468, http://dx.doi.org/10.1038/onc.2017.65.

[129] S. Pavlides, D. Whitaker-Menezes, R. Castello-Cros, N. Flomenberg, A.K. Witkiewicz, P.G. Frank, M.C. Casimiro, C. Wang, P. Fortina, S. Addya, R.G. Pestell, U.E. Martinez-Outschoorn, F. Sotgia, M.P. Lisanti, The reverse Warburg effect: aerobic glycolysis in cancer associated fibroblasts and the tumor stroma, ABBV Cell Cycle 8 (2009) 3984–4001, http://dx.doi.org/10.4161/cc.8.23.10238.

[130] O.R. Colegio, N.Q. Chu, A.L. Szabo, T. Chu, A.M. Rhebergen, V. Jairam, N. Cyrus, C.E. Brokowski, S.C. Eisenbarth, G.M. Phillips, G.W. Cline, A.J. Phillips, R. Medzhitov, Functional polarization of tumour-associated macrophages by tumour-derived lactic acid, Nature 513 (2014) 559–563, http://dx.doi.org/10.1038/nature13490.

[131] G. Di Pompo, S. Lemma, L. Canti, N. Rucci, M. Ponzetti, C. Errani, D.M. Donati, S. Russell, R. Gillies, T. Chano, N. Baldini, S. Avnet, Intratumoral acidosis fosters cancer-induced bone pain through the activation of the mesenchymal tumor-associated stroma in bone metastasis from breast carcinoma, Oncotarget 8 (2017) 54478–54496, http://dx.doi.org/10.18632/oncotarget.17091.

[132] W. Zhong, Y. Tong, Y. Li, J. Yuan, S. Hu, T. Hu, G. Song, Mesenchymal stem cells in inflammatory microenvironment potently promote metastatic growth of cholangiocarcinoma via activating Akt/NF-(B signaling by paracrine CCL5, Oncotarget 8 (2017) 73693–73704, http://dx.doi.org/10.18632/oncotarget.17793.

[133] X. Yang, Y. Lin, Y. Shi, B. Li, W. Liu, W. Yin, Y. Dang, Y. Chu, J. Fan, R. He, FAP Promotes immunosuppression by cancer-associated fibroblasts in the tumor microenvironment via STAT3-CCL2 signaling, Cancer Res. 76 (2016) 4124–4135, http://dx.doi.org/10.1158/0008-5472.CAN-15-2973.

[134] A.L. Chang, J. Miska, D.A. Wainwright, M. Dey, C.V. Rivetta, D. Yu, D. Kanojia, K.C. Pituch, J. Qiao, P. Pytel, Y. Han, M. Wu, L. Zhang, C.M. Horbinski, A.U. Ahmed, M.S. Lesniak, CCL2 produced by the glioma microenvironment is essential for the recruitment of regulatory t cells and myeloid-derived suppressor cells, Cancer Res. 76 (2016) 5671–5682, http://dx.doi.org/10.1158/0008-5472.CAN-16-0144.

[135] N. Obermajer, R. Muthuswamy, K. Odunsi, R.P. Edwards, P. Kalinski, PGE 2-induced CXCL 12 production and CXCR4 expression controls the accumulation of human MDSCs in ovarian cancer environment, Cancer Res. 71 (2011) 7463–7470, http://dx.doi.org/10.1158/0008-5472.CAN-11-2449.

[136] I. Marigo, E. Bosio, S. Solito, C. Mesa, A. Fernandez, L. Dolcetti, S. Ugel, N. Sonda, S. Bicciato, E. Falisi, F. Calabrese, G. Basso, P. Zanovello, E. Cozzi, S. Mandruzzato, V. Bronte, Tumor-induced tolerance and immune suppression depend on the C/EBPbeta transcription factor, Immunity 32 (2010) 790–802, http://dx.doi.org/10.1016/j.immuni.2010.05.010.

[137] W. Zhao, L. Zhang, Y. Xu, Z. Zhang, G. Ren, K. Tang, P. Kuang, B. Zhao, Z. Yin, X. Wang, Hepatic stellate cells promote tumor progression by enhancement of immunosuppressive cells in an orthotopic liver tumor mouse model, Lab. Investig. 94 (2014) 182–191, http://dx.doi.org/10.1038/labinvest.2013.139.

[138] C.A. Corzo, T. Condamine, L. Lu, M.J. Cotter, J.-I. Youn, P. Cheng, H.-I. Cho, E. Celis, D.G. Quiceno, T. Padhya, T.V. McCaffrey, J.C. McCaffrey, D.I. Gabrilovich, HIF-1α regulates function and differentiation of myeloid-derived suppressor cells in the tumor microenvironment, J. Exp. Med. 207 (2010) 2439–2453, http://dx.doi.org/10.1084/jem.20100587.

[139] D. Duluc, Y. Delneste, F. Tan, M. Moles, L. Grimaud, J. Lenoir, L. Preisser, I. Anegon, L. Catala, N. Ifrah, P. Descamps, E. Gamelin, H. Gascan, M. Hebbar, Tumor-associated leukemia inhibitory factor and IL-6 skew monocyte differentiation into tumor-associated-macrophage-like cells, Blood 110 (2007) 4319–4331, http://dx.doi.org/10.1182/blood-2007-02-072587.

[140] R. Allaoui, C. Bergenfelz, S. Mohlin, C. Hagerling, K. Salari, Z. Werb, R.L. Anderson, S.P. Ethier, K. Jirström, S. Påhlman, D. Bexell, B. Tahin, M.E. Johansson, C. Larsson, K. Leandersson, Cancer-associated fibroblast-secreted CXCL16 attracts monocytes to promote stroma activation in triple-negative breast cancers, Nat. Commun. 7 (2016), http://dx.doi.org/10.1038/ncomms13050.

[141] R. Metz, S. Rust, J.B. DuHadaway, M.R. Mautino, D.H. Munn, N.N. Vahanian, C.J. Link, G.C. Prendergast, IDO inhibits a tryptophan sufficiency signal that stimulates mTOR: a novel IDO effector pathway targeted by D-1-methyl-tryptophan, Oncoimmunology 1 (2012) 1460–1468, http://dx.doi.org/10.4161/onci.21716.

[142] S. Haller, S. Kapuria, R.R. Riley, M.N. O'Leary, K.H. Schreiber, J.K. Andersen, S. Melov, J. Que, T.A. Rando, J. Rock, B.K. Kennedy, J.T. Rodgers, H. Jasper, mTORC1 activation during repeated regeneration impairs somatic stem cell maintenance, Cell Stem Cell 21 (2017) 806–818.e5, http://dx.doi.org/10.1016/j.stem.2017.11.008.

[143] K. Ito, T. Suda, Metabolic requirements for the maintenance of self-renewing stem cells, Nat. Rev. Mol. Cell Biol. 15 (2014) 243–256, http://dx.doi.org/10.1038/nrm3772.

[144] B. Kelly, L.A.J. O'Neill, Metabolic reprogramming in macrophages and dendritic cells in innate immunity, Cell Res. 25 (2015) 771–784, http://dx.doi.org/10.1038/cr.2015.68.