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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