Cellular Immunology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Cellular Immunology

journal homepage: www.elsevier.com/locate/ycimm

Research paper

Tissue regeneration: The crosstalk between mesenchymal stem cells and immune response

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ARTICLE INFO

Keywords:
Mesenchymal stem cells
Immune responses

ABSTRACT

Mesenchymal stem cells (MSCs) exist in almost all tissues with the capability to differentiate into several different cell types and hold great promise in tissue repairs in a cell replacement manner. The study of the bi-directional regulation between MSCs and immune response has ushered an age of rethinking of tissue regeneration in the process of stem cell-based tissue repairs. By sensing damaged signals, both endogenous and exogenous MSCs migrate to the damaged site where they involve in the reconstitution of the immune microenvironment and empower tissue stem/progenitor cells and other resident cells, whereby facilitate tissue repairs. This MSC-based therapeutic manner is conferred as cell empowerment. In this process, MSCs have been found to exert extensive immunosuppression on both innate and adaptive immune response, while such regulation needs to be licensed by inflammation. More importantly, the immunoregulation of MSCs is highly plastic, especially in the context of pathological microenvironment. Understanding the immunoregulatory properties of MSCs is necessary for appropriate application of MSCs. Here we review the current studies on the crosstalk of MSCs and immune response in disease pathogenesis and therapy.

1. Introduction

While embryonic stem cells initiate the ontogenetic development, stem cells are critical in maintaining the cellularity of tissue homeostasis by their series of activities, including renewal, activation, expansion, and differentiation. According to their differentiation potential, stem cells are conceived to do regeneration in a cell replacement manner which has been widely studied in both preclinical and clinical studies [1–3]. Indeed, administration of *in vitro* expanded stem cells can accomplish tissue repairs by replacing damaged cells in inflammatory diseases or tissue injuries, such as experimental autoimmune encephalomyelitis [2]. A series of studies have demonstrated that conditioned medium from neural progenitor cells (NPCs) or mesenchymal stem cells (MSCs) ameliorated the functional deficits in experimental allergic encephalitis (EAE) by either downregulating pathogenic function of T cells or stimulating the neural development, suggesting the paracrine effect in stem cell-based tissue regeneration [4–6]. More deep investigations on MSCs disclosed that the tissue reparative function of MSCs in various inflammatory diseases is relying on their regulation of inflammation and their production of multiple growth factors [7,8]. Thus, through the concerted actions, MSCs localized in the damaged tissue calmed down the inflammation and promotes tissue stem/progenitor cells and other resident cells to regenerate the normal functional cells and tissue microenvironment. A cell empowerment manner is conferred on MSCs-based therapy.

Many studies have exploited the potential application of MSCs in autoimmune diseases, myocardial infarction, spinal cord injury, bone injury, type 1 diabetes, Alzheimer's diseases [9,10]. Tissue regeneration by MSCs is considered to be closely related to inflammation nearby. Not only the plenty of growth factors production by MSCs is enhanced by inflammation, but also the immunosuppression of MSCs is licensed by inflammatory cytokines, such as those in the inflammatory microenvironment [11]. More importantly, in the progression of inflammatory diseases, the amounts and kinds of inflammatory cytokines change dynamically, resulting in immunosuppression or immune enhancement by MSCs. Such plasticity of MSC immunoregulation influences the application of MSCs in both preclinical and clinical studies [8]. Here, we review recent advancement and development about comprehending the immunomodulation of MSCs and discus their effects on the immune-related diseases.

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https://doi.org/10.1016/j.cellimm.2017.11.010
Received 4 February 2017; Received in revised form 18 November 2017; Accepted 18 November 2017

2. Mesenchymal stem cells (MSCs)

MSCs are fibroblast-like cells with self-renewal and multiple differentiation potentials [12]. They can differentiate into some types of cells of mesodermal lineage such as adipocytes Osteoblasts chondroblasts and skeletal myocytes [13]. MSCs can also trans-differentiate into both ectodermal and endodermal cells such as hepatocytes neuron cells and epithelial cells [13]. MSCs were firstly identified in bone marrow (BM) and it has been further found that these cells can be easily isolated from a variety of organs and tissues which include adipose tissue (AT) umbilical cord blood (UCB) skin placenta Tendon muscle dental pulp and several fetal tissues [14].

Due to lack of specific markers, a panel of surface markers are used to define MSCs. MSCs are generally, but not homogeneously, expressing CD29, CD44, CD54, CD73, CD90, CD105, CD166 and Stro-1, however, lacking expression of major histocompatibility complex (MHC) class II surface molecules, CD31 and hematopoietic-specific antigens (CD34, CD45, CD14 or CD11b, CD79 or CD19, and HLA-DR) [15]. Recently, some markers, including nestin, leptin receptor, Gli1 and FAP, are used to delineate the characteristic and function of certain MSCs subpopulation *in vivo* [16–19]. Similar to exogenously administrated MSCs, these endogenous subtypes of MSCs were observed to migrate to the damaged tissues [16]. After arriving at the injured sites, MSCs proceed to prepare the immunomicroenvironment and empower the resident cells, whereby facilitate tissue repairs [7].

3. Immunomodulatory properties of MSCs

The most attractive property of MSCs in tissue repairs is their immunosuppression on innate and adaptive immune responses. In 1998, MSCs were firstly reported to suppress T cell proliferation *in vitro* [20]. Henceforth, further studies demonstrated that MSCs can modulate the activation and function of various innate and adaptive immune cells, such as macrophages, dendritic cells, NK cells, neutrophils, T cells, B cells [21,22]. Interestingly, the immunosuppressive function of MSCs, which is induced by inflammatory cytokines, such as IFNγ and TNFα or IL-1, is not inherent [23]. Under the stimulation by combined cytokines, MSCs produce various immunosuppressive molecules, such as nitric oxide (NO), prostaglandin E2 (PGE2), indoleamine 2,3-dioxygenase (IDO), transforming growth factor beta (TGF-β), and interleukin-6 (IL-6), PD-L1, hemoxygenase-1 (HO-1), leukocyte inhibitory factor (LIF), HLAG5 and chemokines. All these factors can exert the immunoregulation of MSCs [24–27]. (Table 1)

4. MSCs and adaptive immune responses

The major cell populations in adaptive immune systems are effector T cells, regulatory T cells (Tregs), and B cells. Many studies have shown that MSCs are able to suppress T cell proliferation, inhibit the differentiation of T cells into Th1, Th17, enhance the generation of Tregs as well as dampen the activation and function of B cells [8,41]. Extensive investigations have found that a number of immunoregulatory factors, such as IDO, PGE, IL-10, TGF-β, NO, HLA-G5, PD-L1, PD-L2, and TNF-α–induced gene/protein 6 (TSG-6), are important in MSCs-mediated regulation on T cells [42–46]. In additions, other paracrine factors, like stem cell–derived extracellular vesicles, have been reported to involve in the immunosuppressive activity of MSCs [47]. Although soluble factors are critical in mediating the immunosuppression of MSCs, a plenty of studies have demonstrated that a clear role for cell-cell contact in MSC-based immunosuppression on T cells. For instance, ICAM-1 was found to be indispensable for the inhibitory effects[48]. In additions, the PD-1/PD-L1 interaction was found to be involved in this process, since PD-L1 knockdown impaired the immunosuppressive capability of MSCs[49]. Meanwhile, other indirect regulation has also been noted. Among the complexity, MSC-mediated regulation on T cells lies on their capability to promote the production of IL-10 or TGF-β by macrophages, and to induce tolerogenic dendritic cells. These cells in turn suppress T cell proliferation induce T cell apoptosis, as well as Tregs induction[50]. Nevertheless, the detailed molecular mechanism underlying the immunoregulatory effects of MSCs need further exploration.

Table 1
Summarization on the key factors meditating the immunoregulation of MSCs.

Key Factors	Roles in MSC-mediated immunoregulation
HLA-G	Inhibits PBMC response [28]
LIF	Inhibits T-cell proliferation [29]
TSG6	Regulates macrophages [30]; inhibits inflammation [31]
HO-1	Inhibits T-cell response [32]; induces IL-10 and TGF-β Tregs[33]
IL-6	Inhibit the differentiation of dendritic cells [34]; inhibit T-cell proliferation [35]
TGF-β	Induces Tregs [36]; inhibits NK cell activation and function [37]
PGE2	Induces Foxp3 Tregs [38]; inhibits NK cell function [37]; induces type II macrophages [39]; inhibit DC maturation [40]

Abbreviations: IL-6, Interleukin 6; DC, dendritic cells; NK cells, natural killer cells; Tregs, regulatory T cells; HLA-G, human leukocyte antigen G; HO-1, heme oxygenase-1; LIF, leukemia inhibitory factor; MSCs, mesenchymal stem cells; PGE2, prostaglandin E2; PBMC, peripheral blood mononuclear cells; TSG6, TNF-α stimulated gene 6.

5. MSCs and effector T cells

It has been demonstrated that MSCs can inhibit T cell proliferation induced by mitogens or anti-CD3 and anti-CD28 antibodies *in vitro*. In the presence of MSCs, T cells are arrested in the G0/G1phase with decreased levels of cycling D2 [51,52]. Also, it has been reported that MSCs are able to suppress the production of proinflammatory cytokines such as TNF-α, IFN-γ, and IL-17 by Th1 and Th17 cells, whereas they can enhance the production of anti-inflammatory cytokines, such as IL-4 by Th2 cells [53–55]. These results demonstrate that MSCs can polarize a Th1/Th17 type response to a Th2 type response. MSCs also dampen the proliferation and cytotoxic function of cytotoxic T lymphocytes (CTL) [56]. Of note, MSCs are “licensed” to implement their immunosuppression under the stimulation of IFN-γ and TNF-α/IL-1 [23,57]. And, IFN-γ is indispensable within this process. Blocking IFN-γ or its receptor IFN-γR, as well as using MSCs deficient in IFN-γR1 through experiments, the immunosuppression role of MSCs on T cells repressed dramatically [58]. Under stimulation with combined IFN-γ and TNF-α, or IL-1, MSCs could express large amounts of immunoregulatory molecules, such as IDO and iNOS, as well as chemokines that mediate T cell chemotaxis to the proximity of MSCs. Therefore, MSCs can deploy the immunosuppression on recruited T cells by producing nitric oxide (in murine MSCs) or IDO catabolites (in human MSCs) which suppress T cells in short distance [59,60]. Indeed, blockade of iNOS in murine MSCs by L-NMMA or IDO in human MSCs by using 1-MT can diminish the immunosuppression of MSCs on T cells [61]. Other factors, such as TGF-β, TSG-6, PGE2, produced by MSCs have been related to the immunosuppressive function of MSCs [62]. Thus, the broad diversification of immunosuppressive factors might result from the difference of tissue types and species, from which MSCs were isolated.

Of note, MSCs do the sharp immunosuppression on Th1/Th17 cells, while do the promotion on Th2 cell activity. Studies found that human MSCs inhibit Th1 cytokine production in a PGE2-dependent manner. For Th17 cells, MSCs suppress them differentiation through upregulation of PD-1 expression, IL-10 secretion, and PGE2 production [63,64]. Also, a CCL2-dependent manner was demonstrated to be crucial in MSC-mediated inhibition on Th17 cells [65]. Not only do the regulation on Th1/Th17 cell subtype, human MSCs were shown to promote IL-4 production by Th2 cells [66]. Such polarization on Th2 cells can help MSCs to restrain the aberrant immune responses and promote the endogenous tissue repair [67].