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Mesenchymal Stem Cells from Different Tissues: Immune Status and Activity

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Abstract

Mesenchymal stem cells (MSCs) have been found in almost all tissues and due to their regenerative properties represent promising tools in cell-based therapy. Role of MSCs in tissue repair is strongly governed by their interplay with immune cells and regulating factors. In addition to the first and most investigated MSCs isolated from bone marrow (BM-MSCs), other tissues were also reported as abundant sources of MSCs, such as peripheral and menstrual blood, fetal and perinatal tissues, adipose and dental tissue. Although BM-MSCs have been shown to be immunosuppressive in both *in vitro* and *in vivo* conditions, multiple evidences indicate that these cells have immunogenic properties, making their immune privileged status at least questionable. Besides their similarity with BM-MSCs, MSCs isolated from alternative sources manifest significant differences in their phenotype, functionality, immune status and activity. Complexity of interactions of BM-MSCs with the immune system is also found for MSCs isolated from other tissues. Due to specific conditions present in different tissues, variability in the immune repertoire of resident MSCs is to be expected and must be taken into consideration during experimental or clinical protocol planning.

Keywords: Mesenchymal stem cells; Immunomodulatory; Bone marrow; Inflammation

Introduction

As tissue-derived stem cells, mesenchymal stem/stromal cells (MSCs) have been found in almost all vascularized tissues where they are engaged in long term maintenance of tissue homeostasis and repair [1]. Until recently, the concept of MSCs as defined by The International Society for Cellular Therapy (ISCT) [2], enabled classification of stem cells derived from various tissues, such as bone marrow, umbilical cord, adipose tissue, skin, dental tissues, peripheral blood, muscle, and amnion etc., based on their immunophenotype and trilineage differentiation potential. Recent analyses pointed out that use of MSCs in preclinical and clinical approaches failed to keep pace with established clinical applications of hematopoietic stem cells (HSCs). This raised concerns about the necessity to further standardize validation assays and compare MSCs obtained in different laboratories [3]. Although MSCs isolated from various tissues meet the same proposed criteria of ISCT (Table 1), it is questionable whether all types of tissue-derived MSCs possess similar paracrine (immunomodulatory, trophic and chemoattractant) activities, which signed them as *Medicinal Signaling Cells* [4]. Finally, the authors of the aforementioned criteria for MSCs characterization have suggested their extension, marking the importance of immune activity and paracrine effects of MSCs [5-7].

Although MSCs have been labeled as immunosuppressive both *in vitro* [8,9] and *in vivo* [10,12], some reports suggest that these cells can possess immunogenic properties as well [13,14]. Due to their importance in tissue repair, process associated with local or systemic inflammatory microenvironment, it is highly important to understand interactions between MSCs and immune system before their potential application in regenerative medicine [15]. MSCs sense stimuli in their microenvironment, which can govern their differentiation fate, as well as their immunomodulatory properties [16]. Moreover, in order to find the most suitable source of MSCs with desired properties, many authors reported immunomodulatory activities of MSCs isolated from various tissues, indicating possible mechanisms of action (Table 2). Also, many studies compared the immunomodulatory capacity of various MSCs (Table 3). As has been observed by Pevsner-Fisher [17], inter-population heterogeneity of MSCs isolated from various donors and tissues, is the main reason for great variability in experimental results. Heterogeneity in observed data might result from different nature of isolated MSCs from various tissues, examined mechanism of activity which could be predetermined for certain type of MSCs, experimental design etc. Because of the high importance of MSCs immune status in their potential clinical application, the inconsistent results require additional extensive review [18]. Here, we aim to give an overview of recent data about

immunomodulatory capacity of MSCs, and justifiably speculate that tissue origin and specific microenvironment adjust the immune status and activity of MSCs *in vitro* and *in vivo*.

Tissue-origin	Positive markers	Negative markers	Source
Bone marrow	CD90, CD105, CD73, CD44, CD29, HLA I,CD106 b, CD166	CD14, CD11b, CD19, CD31, CD34, CD45, CD133, HLA II, CD144, CD80, CD62L, CXCR4	Kern et al., Barcia et al, Yanez et al
Adipose tissue	CD90, CD105, CD73, CD44, CD29, HLA I,CD106 b, CD166	CD14, Cd11b, CD34, CD45, CD133, HLA II, CD144, CD80, CD62L, CXCR4, CD33, CD235	Kern et al, Yanez et al., Trivanović et al.
Umbilical cord	CD90, CD105, CD73, CD44, CD29, CD106	CD11b, CD14, CD19, CD31, CD34, CD45, HLA II, CD80, CD86	Barcia et al., Zhuang et al., Chen et al., Trivanović et al.
Umbilical cord blood	CD90, CD105, CD73, CD44, CD29, HLA I, CD106 b	CD14, CD34, CD45, CD133, HLA II, CD144, CD38	Kern et al., Jing et al.
Peripheral blood	CD90, CD105, CD73, CD44, CD29, CD166, CD140a	CD11b, CD45, CD34, CD19	Krstić et al., Trivanović et al., Chong et al., Li et al.
Menstrual blood	CD90, CD105, CD73, CD44, HLA I, CD49	CD14, CD34, CD45, CD31, HLA II, EPCAM, CD117, CD271, CD146	Miranda et al.
Dental pulp	CD90, CD105, CD73, CD44	CD11b, CD33, CD34, CD45, CD235a	Nikolić et al., Vasandan et al.
Gingiva	CD90, CD105, CD73, CD44, CD29, CD39, HLA I	CD11b, CD14, CD34, CD45, CD31, HLA II, CD80, CD86	Chen et al., Zhang et al.
Periodontal ligament	CD90, CD105, CD73, CD44, CD29	CD14, CD45, CD34, CD19, CD235, CD11b	Vasandan et al., Okić Djordjević et al.

Table 1: Comparison of immunophenotype of MSCs isolated from various tissues

Tissue-origin	Mechanisms of immunomodulation	Source
Bone marrow	Production of IDO, PDL-1, PGE2, TGF-β, IL-6, IL-10, HLA-G5, HGF. Inhibition of CD4+, CD8+, B cell, NK cell. Induction of Treg, CD14 CD11b+CD33+ (MDSCs), tolerogenic DC	Riberia et al., Yen et al., Cahill et al.
Adipose tissue	Production of IDO, PDL-1, PGE2, TGF-β, IL-6, IL-10, HLA-G5. Inhibition of CD4+, CD8+, B cell, NK cell. Induction of Treg, tolerogenic monocytes, Breg	Riberia et al., Crop et al., Hof Nahor et al., Garimella et al.
Umbilical cord	Production of PDL-1, PGE2, IL-10, HO-1, HLA-G. Inhibition of CD4+, CD8+, B cell, NK cell. Induction of Treg. Inhibition of maturation of DC	Riberia et al., Barcia et al., Castro Manrezza et al., Saiedi et al.
Umbilical cord blood	Production of GRO chemokines, IL-10, TGF-β, HGF. Inhibition of proliferation of lymphocytes. Induction of MDSCs.	Chen et al., Schwaki et al., Chen et al.
Peripheral blood	Production of IL-10, TGF-β. Inhibition of proliferation of lymphocytes. Decresed cytotoxity of NKT and CD8+ cells. Induction of Treg.	Trivanović et al., Ljujić et al.
Menstrual blood	Production of IDO, PDL-1, PGE2 and TGF-β, IL-6, IL-10, inhibiton of generation and maturation of DC	Luz-Craford et al., Bozogmehr et al.
Dental pulp	Production of IDO-1, TGF-β. Expression of Fas ligand. Inhibition of proliferation of lymphocytes. Induction of apoptosis of T cells.	Trivanović et al., Tomic et al., Zhao et al.
Gingiva	Production of IL-10, IDO, iNOS, COX-2. Inhibition of proliferation of lymphocytes. Induction of Treg	Zhang et al., Chen et al.
Periodontal ligament	Production of IL-10, IL-6. Expression of PDL-1. Inhibition of proliferation of lymphocytes. Induction of Treg. Suppression of activation of B cells	Liu et al., Liu et al.

Table 2: Immunomodulatory activities of MSCs isolated from various tissues

Immunomodulatory Properties of Bone Marrow Mesenchymal Stem Cells

Most of MSC paradigms are derived from investigation of bone marrow MSCs (BM-MSCs), first defined by Friedenstein in 1970's [19-21]. In the literature, BM-MSCs are frequently labeled as the "holy grail" cells, with desired properties: hematopoiesis support [22,23], multipotent differentiation capacity, self-renewal ability [2], and immunoregulatory potential [24]. However, it is well known that MSCs isolated from bone marrow represent a heterogenic population. Similar to HSCs, a theoretical model has provided the concept of mesenchymal cell hierarchy where MSCs lie at the top, progressing through stages of differentiation in an orderly manner to give mature cells of bone, fat, muscle and cartilage [25]. Therefore, intra-population heterogeneity of MSCs is a consequence of MSCs phenotype plasticity on the single-cell level [26] where bulk MSCs population consists of a small subpopulation of multipotent stem cells and subpopulation of bi- and uni-potent progenitors [17,27,28].

BM-MSCs occupy distinct niches in bone marrow: endosteal, stromal and perivascular niche. Because *in vitro* cultured pericytes share the phenotype and differentiation capacity with BM-MSCs, there are many studies which aim to elucidate relationship between them. Major question is whether BM-MSCs and pericytes are same cells which adjust their properties in response to microenvironment stimuli [16,29]. Although the origin of MSCs remains elusive, pericytes have recently emerged as likely candidates for an *in vivo* native counterpart of the *ex vivo* expanded MSCs [30]. However, since MSCs were also found in non-pericyte

regions, their origin still remains questionable [31]. In general, MSCs are present in all vascularized organs and tissues, while their current status regarding origin, properties and function *in vitro* and *in vivo* is not well defined and is still unclear due to obvious difference between native and culture-expanded MSCs [32].

MSCs	Immunomodulatory activity	Stronger effects/similarity	Source
BM, AT, UCB	Reduced expression of inflammatory cytokines: IL-1α, IL-6, IL-8	UCB	Jin et al.
BM, AT	Production of IDO-1, PGE2 and TGF-β	AT	Li et al.
BM, AT, UC, CH	Inhibition of IFN-γ production by lymphocytes	CH	Yang et al.
BM, SHEDs	Induction of Treg and inhibition of Th17 cells	SHEDs	Yamaza et al.
BM, AT, UCB, UC	Inhibition of proliferation of lymphocytes. Expression of HGF, IL-10, TGF-β, COX-2	Similar effects	Yoo et al.
UC, AT,PB, DP	Inhibition of proliferation of lymphocytes. Expression of TGF-β1, COX-2	Similar effects. Variability in gene expression	Trivanović et al.
BM, G	Inhibition of proliferation of lymphocytes.	Similar effects	Zhang et al.
BM, AT	Inhibition of proliferation of lymphocytes.	Similar effects	Yanez et al.
BM, UC, UCB	Inhibition of proliferation of lymphocytes. Induction of CD4+CD25+CTLA-4+	BM, UC	Castro-Manrreza et al.
BM, AT, UC	Inhibition of T cell, B cell and NK cell-mediated immune response	BM, AT regarding inhibitory effects on B cells	Ribeiro et al.
BM, Men	Inhibition of T cell response. Production of IDO, PDL-1, PGE2,TGF-β	BM	Luz-Craford et al.
BM, DP, PDL	Inhibition of proliferation of lymphocytes. Expression of TGF-β, HGF, IDO-1	Similar effects. Variability in gene expression	Wada et al.

BM: Bone marrow; AT: Adipose tissue; UCB: Umbilical cord blood; UC: Umbilical cord; CH: Chorion; SHEDs: Exfoliated deciduous teeth; PB: Peripheral blood; DP: Dental pulp; G: Gingiva; Men: Menstrual blood; PDL: Periodontal ligament

Table 3: Results of studies which investigated immunomodulatory capacity of various MSCs

Although heterogeneity of bulk MSCs in the context of their multipotent differentiation capacity has been described, other functional properties, such as immunodulatory properties remain to be further investigated. However, it is rational to assume that tissue microenvironment which shapes their multipotency, also manages their immune status and activity, thus giving more complexity to experimental and clinical approach, in autologous as well as in allogeneic settings [29].

Immunosuppressive properties of BM-MSCs

Many preclinical models have demonstrated that BM-MSCs can migrate to sites of inflammation and have immunomodulatory effects through direct cellular contact with immune cells or through the production of immunosuppressive soluble factors [33]. Therefore, there are number of clinical studies that use BM-MSCs to treat immune-mediated diseases, such as: Graft versus Host Disease (GVHD) [34], aplastic anemia [35], Crohn's disease [36], multiple sclerosis [37], and ischemic heart failure [38].

After establishing their immunomodulatory potential *in vitro*, BM-MSCs have been introduced into the clinical settings [39], in which these cells show their therapeutic effects in treatment of acute grade IV GvHD after bone marrow transplantation. It is important to mention the lack of optimization protocols considering BM-MSCs and their products including isolation, expansion and functionality, and especially for retention of their immunomodulatory potential [40,41], since these efforts are crucial for safe and efficient cell-based therapy.

Recently, many cellular and molecular mechanisms involved in the interaction between BM-MSCs and various participants in the inflammation process have been highlighted. Depending on their type and intensity, inflammatory stimuli affect MSCs in a way to modulate their ability to suppress the immune response in some cases or to enhance it in others [42].

BM-MSCs express low levels of human leukocyte antigen (HLA) major histocompatibility complex (MHC) class I antigens, do not express co-stimulatory molecules (B7-1 and -2, CD40, or CD40L), and can be induced to express MHC class II antigens and Fas ligand. However, low expression of MHCII and co-stimulatory molecules indicates that direct cell contact is not the main mechanism of BM-MSCs immunomodulatory activity [40,43]. These features have often been used to explain their "immune privileged" status in allogeneic hosts. Furthermore, BM-MSCs have been shown to inhibit dendritic cell maturation [44], B cell [45] and T cell proliferation [46] and differentiation [47], impair natural killer cell activity [48], as well as support the generation of suppressive immune cells such as: regulatory T cells (Tregs) [43,49], myeloid derived suppressor cells (MDSCs) and tolerogenic dendritic cells (tDCs) [50].

Combination of many soluble factors are meritorious for immunosuppressive activity of BM-MSCs, such as: indoleamine 2,3-dioxygenase (IDO), inducible nitric oxide synthase (iNOS), cyclooxygenases (COX), metabolite prostaglandin E2 (PGE2), tumor necrosis factor α-induced protein 6 (TSG6), transforming growth factor β (TGF-β), soluble form of HLA-G5 [35,44]. Production of these factors is increased by inflammatory microenvironment stimuli, such as immune cells presence, inflammatory cytokines or activation of Toll-like receptors (TLRs) [40,51].

Immunogenic properties of BM-MSCs

Despite large number of data about immunosuppressive activity of BM-MSCs, there are few studies describing their immunogenic nature [52-54]. Since immunogenicity is of major concern in transplantation, clinical safety and efficacy of BM-MSCs application is therefore questioned. As described above, even though BM-MSCs have expressed low levels of MHC I molecules and lack MHC II antigens, in presence of inflammatory conditions and cytokines (interferon (IFN)-γ, tumor necrosis factor (TNF)-α) in culture, expression of these MHC molecules increases [40,51,55,56]. Strong influence of microenvironment on the immune status of MSCs has been observed in an experiment using diabetic rats where allogeneic MSCs have been transplanted into tail vein or pancreas. During the later phase of transplantation, BM-MSCs which have been transplanted into pancreas develop an immunogenic phenotype, while BM-MSCs which have been transplanted into tail vein stay immunosuppressive [53]. These findings provide evidence that different microenvironment, even in one recipient, can condition opposite immune properties of BM-MSCs. Moreover, similar to all nucleated cells, BM-MSCs express MHC I molecule, and can induce allogeneic immune cell responses, as it has been demonstrated by the lysis of BM-MSCs by HLA class I mismatched memory $CD8^+$ T cells [57]. Also, BM-MSCs are also susceptible to be lysed by autologous IL-2-activated NK cells, via expression of MHC I molecule [58]. These findings suggest that despite their immunoregulatory properties, *in vitro* cultured BM-MSCs can be recognized as immunogenic by the immune system. Also, presence of inflammatory factors can induce expression of MHC class II in BM-MSCs, where these cells present exogenous antigens to T cells, similar as dendritic cells or macrophages [40,56]. In addition, it has been observed that BM-MSCs stimulate proliferation and differentiation of naïve and memory B cells into immunoglobulin secreting plasma cells [59,60].

Moreover, it has been shown that administration of MSCs elicits innate immune attack [61] and allograft rejection in kidney transplantation [62], warning about the possibility of indirect or semi-direct allo-recognition of MSCs [33]. Taken together, these data indicate that BM-MSCs can function as immune cells. Despite inability of allogeneic BM-MSCs to be immunogenic as unmatched fibroblasts or HSCs [40,63], their immune privileged status is not uncontested anymore and it has to be reassessed, especially in the context of transplantation immunology and regenerative medicine.

Transient immunomodulatory properties of BM-MSCs: MSC1 and MSC2 phenotype

The observed changes of the immune profile of BM-MSCs, ranging from immunosuppressive to immunogenic draw attention to existence of transient immune status of these cells. Waterman *et al*. has explained the paradigm of pro-inflammatory MSC1 and anti-inflammatory MSC2 phenotype, similar to that in M1 and M2 macrophages. This study has showed that different TLR 2, 3 or 4 ligands shape different profiles of BM-MSCs by stimulating expression and production of immunosuppressive (IL-10) or immunogenic molecules (IL-6) [51]. As previous evidence has demonstrated that MSCs immune profile can change depending on the transplantation site and microenvironment stimuli [52,53], it is justifiable to assume the immune status of MSCs as transient [55,56,59,64]. In this context, it is important to acknowledge the physiological nature of MSCs whose fate is determined by their physiological setting. Considering their inherent ability to differentiate, special notice must be given to indications that MSCs immune status could be related to their differentiation state. For instance, it has been shown that osteogenic differentiation can inhibit expression of MHC II molecules in BM-MSCs, which was previously stimulated with IFN-γ [65,66]. Contrary, while BM-MSCs show immunosuppressive properties *in vitro*, their chondrogenic differentiation has been shown to cause immunogenicity *in vivo* by stimulating proliferation of T cells [67]. In general, priming of MSCs with IFN-γ is an efficient approach for stimulation of MSCs to produce immunosuppressive molecules. However, it was observed that although *in vitro* expanded IFN-γ-primed MSCs were immunosuppressive, their administration *in vivo* led to the loss of their immunosuppressive properties and finally immune rejection [64]. Taken together, it is important to consider multiple factors present during *ex vivo* cultivation and *in vitro* manipulation of BM-MSCs prior to their *in vivo* application, such as nutrients in media, oxygen level, growth factors or serum quality, which could interweave with the immune status of MSCs [68]. Moreover, it is possible that MSCs balance between immunosuppressive and immunogenic profile through active interplay with immune cells and regulatory factors present in native or allogeneic microenvironment. This ability of MSCs to adjust their immune profile is related to the plasticity of their immune status [69].

Immunomodulatory Properties of MSCs in Peripheral Blood

Existence of circulating MSCs has been reported when donor MSCs have been found to be engrafted in bone marrow after allogeneic transplantation of mobilized peripheral blood (PB) stem cells [70]. Previously, Wexler *et al*. provided data about low frequency of isolated PB-MSCs in comparison to bone marrow and umbilical cord blood [71]. The presence of a small number of MSCs has been detected in mobilized PB of healthy patients as well as those with malignancies [71,72]. Moreover, PB-MSCs have been isolated from non-mobilized peripheral blood of healthy donors and have met the criteria of ISCT [73,74]. It has been demonstrated that PB-MSCs can be mobilized to PB using granulocyte colony-stimulating factor (G-CSF), although this approach is not specific for MSCs mobilization, but for HSCs/progenitor cells or blasts [72]. It has been shown that PB-MSCs have immunosuppressing role *in vivo* by increasing the level of Th2 and decreasing the level of Th1 cytokines, while stimulating generation of $CD4^+FoxP3^+$ T cells and producing IL-10. Thus, by impairing immune response, PB-MSCs have also been shown to promote breast tumor growth [75]. Furthermore, it has been demonstrated that osteogenic differentiation of PB-MSCs plays a crucial role in bone tissue healing [76]. While presence of circulating MSCs is to be expected in the peripheral blood of a patient, when they migrate toward sites of

inflammation or injury, their presence in peripheral blood of healthy donors opens a question about their origin. However, these findings suggest that peripheral blood could be a promising source of MSCs, while their immune status and activity need to be further elucidated.

Immunomodulatory Properties of MSCs in Menstrual Blood

Regeneration of human endometrium is dependent on resident epithelial and stromal stem/progenitor cells. One of the layers of endometrium, signed as *functionalis* layer, is shed during menstruation and is a major part of the menstrual fluid. First evidence about stem cells in endometrium has been obtained in 2004 by Chan *et al*. [77], while MSCs were first isolated from endometrium 2007 by Meng *et al*. [78]. Menstrual blood could be available, abundant, low cost and free of ethical concerns source of MSCs (MenSCs) [79,80]. Besides their supportive role in the expansion of hematopoietic stem cells [81], it has been demonstrated that MenSCs possess lower immunosuppressive properties when compared to BM-MSCs, because they produce lower levels of IDO, PDL-1, PGE2 and TGF-β1 [82]. However, it has been observed that MenSCs impair maturation of DC, an effect where IL-6 and IL-10 has been proposed to be involved [83]. Although MenSCs represent promising MSCs type, their immune properties and mechanisms involved in the regulation of their immunomodulatory activity have to be investigated in detail.

Immunomodulatory Properties of MSCs in Fetal and Perinatal Tissues

MSCs can be isolated from extra-embryonic tissues without ethical concerns, because these tissues are normally discarded after birth [84]. Fetal tissues are considered to be abundant source of MSCs and progenitor cells, obtained after normal pregnancy and also spontaneous abortion or stillbirth [85]. Today, MSCs has been isolated from many fetal and perinatal tissues: amniotic fluid (AF-MSCs) [86], human amnion membrane (HAM-MSCs) [87], chorion membrane (CM-MSCs), decidua (D-MSCs) [88], placenta (P-MSCs) [89], cord blood (CB-MSCs) [90], whole umbilical cord (UC-MSCs) [91] and Wharton's Jelly (WJ-MSCs) [73,92]. In the literature, there are many claims about the immune privileged status of MSCs derived from fetal tissues which can be transplanted into the host without immune rejection [84]. In order to establish tolerogenic fetal immune system, fetal $CD4^+$ T cells are forced to differentiate to Treg toward antigens expressed by chimeric maternal cells to promote self-tolerance in fetal tissue. Fetal cells express HLA-G for immune tolerance during pregnancy and this suggests low immunogenicity and tolerogenic state of fetal stem cells. This ability of fetal cells to provide self-tolerance is also known as layered immune system, which in adult tissue becomes more defensive [85,93].

Similar as BM-MSCs, WJ-MSCs express MHC class I (HLA-ABC) at low levels but do not express class MHC class II (HLA-DR) and co-stimulatory antigens such as CD80, CD86, CD40 and CD40L implicated in activation of both T and B cell response. Therefore, WJ-MSCs are considered for both autologous and allogeneic use [94]. Contrary to BM-MSCs, treatment with IFN-γ did not induce expression of HLA-DR in WJ-MSCs, suggesting their less immunogenic nature than BM-MSCs [95]. Moreover, it has been shown that WJ-MSCs produce larger amounts of IL-10, TGF-β, heme oxygenase-1 (HO-1) and HLA-E, HLA-G and HLA-F than BM-MSCs [84,96,97]. However, it has been shown that exposure to IFN-γ induce immunogenicity of transplanted WJ-MSCs, thus opening a question whether it is possible to maintain the immunosuppressive profile of WJ-MSCs upon transplantation [98].

Efficiency of WJ-MSCs and UCB-MSCs as immunosuppressive cells which inhibit proliferation of T cells has been demonstrated [99,100], suggesting them as alternative to BM-MSCs. In another study, it has been observed that BM-MSCs and P-MSCs have stronger immunosuppressive capacity than WJ-MSCs, due to generation of $CD4^+CD25^+FoxP3^+$ T cells [101,102]. It was also found that human P-MSCs can expand $CD14\text{-}CD11b^+CD33^+$ human MDSCs which suppress allogeneic lymphocyte proliferation and increase the number of Treg cells [103]. In addition, UCB-MSCs produce soluble factors, such as GRO chemokine's, which promote generation of MDSCs from monocyte-derived dendritic cells [50]. Interestingly, it was reported that UC-MSCs express glycocalyx matrix which contains TSG6 when they were exposed to inflammatory conditions. These UC-MSCs stimulated generation of Treg and inhibited polarization of macrophages toward pro-inflammatory M1 phenotype [104].

Taken together, fetal tissues represent a promising source of MSCs with immunomodulatory potential, although all cellular and molecular mechanisms involved need to be further investigated.

Immunomodulatory Properties of MSCs in Adipose Tissue

Adipose tissue is a well-known abundant source of MSCs, which have firstly been isolated by Zuk *et al*. from aspirated fat [105]. Beside abundance, a lack of ethical concerns makes these MSCs promising cells for cell-based therapy. Adipose tissue MSCs (AT-MSCs) persist in stromal-vascular fraction (SVF) together with pericytes, endothelial cells, preadipocytes, hematopoietic cells and immune cells such as macrophages, NK and T cells. Besides their role in tissue homeostasis maintenance, AT-MSCs have an important role in the vascularization of adipose tissue. Also, similar to BM-MSCs, AT-MSCs are known to support hematopoiesis, specifically stimulating generation of macrophages [106]. Distinctive to circulating macrophages, population of CD34 expressing, fibroblast-like macrophages with multipotency similar to AT-MSCs have been identified in human white adipose tissue [107]. These macrophages have M1 anti-inflammatory phenotype [108]. Some reports described adipose tissue as a resident tissue for hematopoietic stem/progenitor cells committed to mast cells [109] and hemangioblasts [110]. Functional properties of AT-MSCs are especially interesting in development of obesity, which involves change of cytokine milleu in adipose tissue. It has been reported that phenotype of AT-MSCs can be altered due to obesity or weight loss-related inflammation [111].

The inhibitory effect of AT-MSCs on T cell proliferation has been demonstrated [9,111], and some reports have found that AT-MSCs have stronger immunosuppressive effects than BM-MSCs [112]. However, Crop *et al*. has observed that, in the presence of lymphocytes, AT-MSCs highly express IL-6, IL-8, TNF-α, as well as immunosuppressive factor IDO-1, while they also stimulate proliferation of T cells and percentage of $CD4^+CD25^+FoxP3^+$ cells within [113]. This discrepancy points out how different approaches used in experimental settings can give different results. Interestingly, it has been found that AT-MSCs actually inhibit activation of T cells and stimulate FoxP3 mRNA expression in activated T cells [8].

Some differences exist between bone marrow- and adipose tissue-derived MSCs for several secreted proteins, such as cytokines (IFN-γ), growth factors (e.g. fibroblast growth factor (FGF), hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF-1)), and chemokines (stem cell factor-1 (SCF-1)), where it has been demonstrated that AT-MSCs have more potent immunomodulatory effects than BM-MSCs through higher production of IDO-1 and PGE2 molecules [114]. Also, in co-culture with AT-MSCs, decreased production of proinflammatory cytokines, such as IFN-γ, IL-2 and IL-17, and increased secretion of anti-inflammatory cytokines, such as TGF-β, IL-4, IL-10 and IL-13, by stimulated splenocytes have been observed. These immunosuppressive effects of AT-MSCs have crucial effects on maintenance of functionality of pancreatic islets in induced diabetic mice model [115]. Additionally, the immunosuppressive role of AT-MSCs in rheumatoid arthritis, autoimmune disease accompanied by chronic inflammation, has been demonstrated, where AT-MSCs suppress T cell proliferation and increase generation of regulatory subsets of T and B cells [116]. Moreover, it has been shown that AT-MSCs decrease the expression level of CD8 on $CD8^+$ cells, and this effect requires direct cell contact of $CD14^+$ monocytes with $CD8^+$ cells. Finally, AT-MSCs induce the suppressive phenotype of $CD8^+$ cells and tolerogenic phenotype of $CD14^+$ monocytes, by decreasing expression of CD80 and CD86 co-stimulatory molecules and, on the other hand, increasing the inhibitory receptors immunoglobulin-like transcripts (ILT)-3 and -4 [117].

As has been previously described for BM-MSCs, osteogenic differentiation can maintain hypoimmunogenic profile of AT-MSCs, even though they have been primed with IFN-γ and TNF-α [118].

Interesting results have been published after investigating AT-MSCs obtained from fat of obesity patients. Results have showed that AT-MSCs obtained from obesity and non-obesity donors possess similar phenotype, although AT-MSC derived from obesity patients have higher gene expression of inflammatory molecules such as IL-8, IL-1β, CCL2 [119,120]. How obesity patient-derived AT-MSCs affect immune response remains to be elucidated.

Immunomodulatory Properties of MSCs in Dental Tissues

Infection and inflammation have significant effects on the regenerative processes in dental tissues [121]. According to their localization in tooth, dental tissue stem cells, termed as MSCs have been classified as: dental pulp stem cells (DP-MSCs) firstly isolated by Gronthos *et al*. [122], stem cells from human exfoliated deciduous teeth (SHEDs) [123], periodontal ligament stem cells (PDLSCs) [124,125] stem cells from apical papilla (SCAPs) [126], dental follicle progenitor cells (DFPCs) [127], tooth germ progenitor cells (TGPCs) [128], alveolar bone MSCs (AB-MSCs) [129] and gingival MSCs (GMSCs) [130]. Their application in dental regenerative medicine is dependent of their origin and localization in the tooth, which shape their phenotype and functionality [131-133].

The oral cavity is enriched by commensal bacteria that live in a mutually beneficial state with the host. In dental tissues, stem cells are homed toward infections, inflammation or tissue damage sites, where they come in contact with various bacteria. In inflammatory microenvironment, immune cells such as macrophages and neutrophils are attracted into dental tissue and periapical lesions. Today it is known that stem cells of dental tissue are actively engaged in the control of infections, through direct or indirect effects on host immune response [132,134]. Therefore, together with regenerative properties, immunomodulatory activity of dental tissue stem cells has strong impact on the maintenance of healthy dental tissue in physiological conditions as well as in diseases such as periodontitis [121,135].

Human DP-MSCs express Fas ligand and are able to provoke apoptosis of T cells and this activity was followed by decreased number of Th17 cells and increased number of Treg cells. It has been shown that these effects are mediated by expression of TGF-β, HGF and IDO-1 in DP-MSCs [9,130,133,135]. Also, it has been demonstrated that SHEDs effectively inhibit proliferation of already activated T cells by inducing their apoptosis and moreover inducing generation of Treg, in similar manner as BM-MSCs, yet with a stronger effect [136]. Furthermore, it has been observed that SHEDs induce an immune regulatory phenotype in monocyte-derived DCs cells [137]. PDL-MSC have also been shown to possess immunosuppressive capacity [138], inhibiting proliferation of peripheral blood mononuclear cells, by producing TGF-β, HFG, IDO-1 and PGE2 molecules [135]. However, it has been demonstrated that PDL-MSCs isolated from inflamed periodontal ligament inhibit proliferation of T cells significantly less than PDL-MSCs isolated from healthy donors. These effects are accompanied by lower generation of Treg and higher differentiation of Th17 cells, induced by PDL-MSCs [139].

Also, an inhibitory role of PDL-MSCs on B cell activation has been reported, where it has been observed that these MSCs regulate innate immune response through the expression of program cell death-1 (PDL-1) [140]. Similarly, G-MSCs show immunosuppressive effects through inhibition of T cell proliferation, mediated by IDO, IL-10, and cyclooxygenase-2 (COX-2) [135]. DFPCs also inhibit proliferation of peripheral blood mononuclear cells, due to increased expression of TGF-β, mediated by activation of inhibitory molecules TLR3 and TLR4 [141]. There are some indications in immunomodulatory activity of SCAPs [142], but mechanisms of their immunosuppressive properties are not clarified yet.

G-MSCs inhibit proliferation of T-cell proliferation via expression of IDO, IL-10, COX-2, and iNOS, while increasing generation of Treg cells [143,144] and polarizing macrophages toward anti-inflammatory M2 phenotype [145]. There is no data about the immunomodulatory activity of AB-MSCs and TGPCs. Also, at this moment there is no evidence about immunogenicity of MSCs derived from dental tissues.

Conclusion

As regenerative medicine requires alternative sources of MSCs, various tissues are being investigated with the aim to substitute bone marrow as the firstly proposed source of MSCs. However, although immune status and activity of MSCs isolated from some tissues such as adipose and fetal tissues are being intensively investigated, there are many obstacles for their potential clinical application. MSCs must be examined in the context of their native tissue microenvironment which shapes their immune activity in accordance with maintenance of tissue homeostasis. Therefore, tissue resident MSCs might possess specific native immune profiles, which are further on reflected during their *in vitro* or *ex vivo* expansion, and therefore must be considered before potential use in clinical settings.

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