REVIEW

Immunomodulatory properties of dental tissue-derived mesenchymal stem cells: Implication in disease and tissue regeneration

Oleh Andrukhov, Christian Behm, Alice Blufstein, Xiaohui Rausch-Fan

ORCID number: Oleh Andrukhov (0000-0002-0485-2142); Christian Behm (0000-0002-3065-3200); Alice Blufstein (0000-0002-2992-6099); Xiaohui Rausch-Fan (0000-0002-8010-1914).

Oleh Andrukhov, Christian Behm, Alice Blufstein, Xiaohui Rausch-Fan, Division of Conservative Dentistry and Periodontology, University Clinic of Dentistry, Medical University of Vienna, Vienna 1090, Austria

Corresponding author: Oleh Andrukhov, PhD, Associate Professor, Division of Conservative Dentistry and Periodontology, University Clinic of Dentistry, Medical University of Vienna, Sensengasse 2a, Vienna 1090, Austria. oleh.andrukhov@meduniwien.ac.at
Telephone: +43-1-400702620
Fax: +43-1-400702609

Abstract

Mesenchymal stem cells (MSCs) are considered as an attractive tool for tissue regeneration and possess a strong immunomodulatory ability. Dental tissue-derived MSCs can be isolated from different sources, such as the dental pulp, periodontal ligament, deciduous teeth, apical papilla, dental follicles and gingiva. According to numerous *in vitro* studies, the effect of dental MSCs on immune cells might depend on several factors, such as the experimental setting, MSC tissue source and type of immune cell preparation. Most studies have shown that the immunomodulatory activity of dental MSCs is strongly upregulated by activated immune cells. MSCs exert mostly immunosuppressive effects, leading to the dampening of immune cell activation. Thus, the reciprocal interaction between dental MSCs and immune cells represents an elegant mechanism that potentially contributes to tissue homeostasis and inflammatory disease progression. Although the immunomodulatory potential of dental MSCs has been extensively investigated *in vitro*, its role *in vivo* remains obscure. A few studies have reported that the MSCs isolated from inflamed dental tissues have a compromised immunomodulatory ability. Moreover, the expression of some immunomodulatory proteins is enhanced in periodontal disease and even shows some correlation with disease severity. MSC-based immunomodulation may play an essential role in the regeneration of different dental tissues. Therefore, immunomodulation-based strategies may be a very promising tool in regenerative dentistry.

Key words: Mesenchymal stem cells; Dental tissue; Immunomodulation; Peripheral blood mononuclear cells; Oral diseases; Tissue regeneration

Core tip: In the present review, the complex mechanisms of interactions between dental-tissue derived mesenchymal stem cells (MSCs) and immune cells are considered. Potential implication of MSC-mediated immunomodulation into progression of periodontal disease and dental tissue regeneration is discussed.

DENTAL TISSUE-DERIVED MESENCHYMAL STEM CELLS AND THE BASIC MECHANISMS OF MESENCHYMAL STEM CELL-MEDIATED IMMUNOMODULATION

Mesenchymal stem/stromal cells (MSCs) are defined as cells that fulfil the following minimal criteria: First, they adhere to culture plastic under standard cell culture conditions; second, they express the mesenchymal surface markers CD29, CD73, CD90, and CD105 and do not express the haematopoietic surface markers CD11b, CD14, CD34, CD45, and HLA-DR; third, they are able to differentiate into osteoblasts, adipocytes, and chondrocytes under certain conditions *in vitro*[1]. MSC-like cells were found in different postnatal tissues, inclusive of numerous dental tissues such as the dental pulp, human exfoliated deciduous teeth, the periodontal ligament, the apical papilla, the dental follicles and the gingival tissue[2-8]. Most dental tissue-derived MSCs express several neural lineage markers, which may be due to their neural crest origin[9,10].

Similar to MSCs from other tissues, dental MSCs possess a strong immuno-modulatory ability[11-13]. Potential mechanisms of the immunomodulatory effects of MSCs include the expression of enzymes, the production of soluble factors, and cell-to-cell contact, and these mechanisms are reviewed in detail elsewhere[14-16]. MSC-mediated immunosuppression in humans is largely mediated by indoleamine-2,3-dioxygenase-1 (IDO-1), which catalyses the catabolism of L-tryptophan into L-kynurenine. As a result, depletion of tryptophan leads to the suppression of different immune cells[17]. Further important soluble factors involved in the MSC-dependent immunomodulation are prostaglandin E2 (PGE-2), tumor necrosis factor α-stimulated gene 6 (TSG-6), hepatocyte growth factor (HGF), transforming growth factor (TGF)-β, interleukin (IL)-10, galectins, and human leukocyte antigen (HLA)-G5[18]. PGE-2, a metabolic product of the arachidonic acid cascade, is produced by cyclooxygenase 2 (COX-2) and influences both the innate and adaptive immune systems[19]. MSCs continuously produce the potent immunomodulatory cytokines TGF-β and its production can be enhanced by other immunomodulatory cytokines, such as IL-4 and IL-13[20]. The anti-inflammatory cytokine IL-10 can be produced either by MSCs themselves or MSC-regulated immune cells[21]. Additionally, direct cell-to-cell contact accounts for at least some of the immunosuppressive effects of MSCs, and these effects are mediated mainly through programmed cell death ligand 1 (PD-L1), PD-L2 and membrane-bound HLA-G1[22].

IMMUNOMODULATORY EFFECTS OF DIFFERENT DENTAL TISSUE-DERIVED MSCS

Dental tissue-derived MSCs, similar to MSCs from other tissues, modulate the activity of different immune cell subsets. Our knowledge in this field arises mainly from *in vitro* cell culture studies. Usually, these studies have used different co-culture models of MSCs with various subsets of immune cells and can be relatively easily controlled. Some studies have used a so-called direct co-culture model, in which the immune cells are added directly to tissue culture plastic-adherent dental MSCs. Other studies have used an indirect co-culture model in which the immune cells and MSCs are separated by a liquid-permeable membrane. In most studies, dental MSCs have been co-cultured with peripheral blood mononuclear cells (PBMCs), followed by the analysis of specific markers and/or functional characteristics of different immune cell

subsets. These experimental approaches have some advantages and limitations. PBMCs are a heterogeneous population of different immune cells, with a composition of 70%-90% lymphocytes (T cells, B cells, and NK cells), 10%-20% monocytes, and 1%-2% dendritic cells[23]. These co-culture models are relatively easily controlled and are convenient for studying the mechanisms of MSCs' immunomodulatory effects. However, such co-culture models hardly mimic any known *in vivo* interaction. Furthermore, this approach does not allow for the evaluation of the direct effects of MSCs on different subpopulations of PBMCs. In some studies, the co-culture of dental MSCs with isolated immune cell subsets has been performed. In most co-culture experiments, immune cells have been activated with different stimuli, such as concanavalin A (Con A), phytohemagglutinin (PHA), anti-CD3/CD28 antibodies, lipopolysaccharide, etc. These stimuli are crucial for activating immune cell proliferation and/or differentiation and, as we discuss in chapter 3, for stimulating the immunomodulatory ability of dental MSCs. However, the activation of PBMCs with most of these stimuli is rather artificial and hardly representable for the situation *in vivo*.

Dental pulp stem cells

In 2002, the first characterized dental-derived mesenchymal stem cells were isolated from the dental pulp by Gronthos *et al*[4]. These cells were located in the perivascular region and fulfilled all minimal criteria for mesenchymal stem cells[4,24]. Several studies have investigated the interaction of dental pulp stem cells (DPSCs)with various components of both the innate and adaptive immune systems like T cells, natural killer cells, and macrophages, as well as the complement system. A pioneering study by Wada *et al*[25] showed that DPSCs suppress the proliferation of allogeneic PHA-activated PBMCs in a cell-to-cell contact-independent manner. The same study showed that the conditioned medium from interferon (IFN)-γ pre-treated DPSCs inhibits PBMC proliferation[25]. Another study investigated the effect of DPSCs on PHA-activated CD4+ T cells. This study showed that IFN-γ-primed DPSCs inhibit T cell proliferation, reduce IL-17 production and stimulate regulatory T cell (T_{reg}) differentiation[26]. A recent study demonstrated that DPSCs inhibit PHA-induced PBMC proliferation but have no effect on T_{reg} differentiation[27]. The same study also showed that DPSCs in co-culture with anti-CD3/CD28 antibody-activated PBMCs inhibit CD8+ T cell proliferation and B cell immunoglobulin production[27]. The inhibitory effects of DPSCs on T cells and B cells are enhanced by IFN-γ and mediated by TGF-β[27]. One study reported that DPSCs also induce T cell apoptosis, which is supposed to have an anti-inflammatory effect *in vivo*[28]. DPSCs in co-culture with PHA-activated CD3+ T cells inhibit T cell proliferation, induce T cell apoptosis and stimulate T_{reg} formation[29]. A recently published study showed that osteogenic-differentiated DPSCs also inhibit the proliferation of PHA-activated PBMCs[30]. DPSCs isolated from healthy and inflamed pulp tissue suppress LPS-triggered TNF-α secretion by macrophages *via* an IDO-dependent mechanism but have no effect on IL-1β production[31]. DPSCs also influence macrophage polarisation *in vivo*. In particular, transplanting DPSCs into the unilateral hindlimb skeletal muscle triggers macrophage M2 polarization and suppresses sciatic nerve inflammation[32]. DPSCs can sometimes be susceptible to NK cell-mediated cytotoxicity[33]. The resistance of DPSCs to NK cell-mediated lysis is substantially increased after DPSC differentiation, the overexpression of hypoxia-inducible factor 1 or monocyte co-culture[34,35]. Furthermore, DPSCs activate the complement system. In particular, lipoteichoic acid-treated dental pulp progenitor cells express almost all factors necessary for complement system activation[36]. Furthermore, the complement system seems to influence DPSC proliferation and mobilization by activating the C3a and C5a complement system receptors, which are expressed by DPSCs[37,38].

Periodontal ligament stem cells

A heterogeneous population of periodontal ligament stem cells (PDLSCs) was isolated for the first time from the periodontal ligament, a highly specialized connective tissue located between the alveolar bone and cementum, and characterized by Seo *et al*[6] in 2004. To date, these cells have been shown to exhibit immunomodulatory effects *in vitro* and/or *in vivo* on T cells, B cells, dendritic cells, macrophages and poly-morphonuclear neutrophils (PMNs). Wada *et al*[25] showed that human PDLSCs, similar to DPSCs, suppress PBMC proliferation by a paracrine mechanism and this ability is enhanced by pre-treatment with IFN-γ. A later study reported that IFN-γ-primed PDLSCs in co-culture with PHA-stimulated PBMCs inhibit T cell proliferation, stimulate T_{reg} differentiation and decrease IL-17 production by T cells[39]. The same study showed that human PDLSCs isolated from inflamed tissue suppress Th1 differentiation and IFN-γ secretion by T cells, which are effects that have not been observed with human PDLSCs isolated from healthy tissue[39]. Human PDLSCs inhibit

proliferation and IFN-γ production by Con A-stimulated PBMCs *via* both indirect soluble mediators and direct cell-to-cell contact[40]. Human PDLSCs inhibit proliferation and IL-2 and IFN-γ production in PHA-stimulated PBMCs[41]. A further study investigated the effect of human PDLSCs on the proliferation of CD3+ T cells primed by monocyte-derived dendritic cells[42]. This study showed that the STRO1+ CD146+ subpopulation of human PDLSCs inhibits T cell proliferation by suppressing the expression of the non-classical major histocompatibility complex-like glycoprotein CD1b on dendritic cells[42]. One study showed that human PDLSCs negatively regulate the proliferation, differentiation and chemotaxis of differently stimulated B cells *in vitro*, mainly through cell-to-cell contact mechanisms mediated by PD-L1, and inhibit B cell apoptosis *via* an IL-6-dependent mechanism[43]. Furthermore, the transplantation of allogenic human PDLSCs suppresses humoral immunity in a minipig periodontitis model[43]. The effect of human PDLSCs on macrophages is controversial in the literature. One study reported that medium from PDLSCs suppresses TNF-α expression in the murine monocyte/macrophage RAW 264.7 cell line[44]. In contrast, another study did not find any effect of conditioned medium from PDLSCs on the polarisation of the human monocyte/macrophage THP-1 cell line[45]. Moreover, the same study showed that extracellular vesicles from LPS-pre-treated PDLSCs promote macrophage polarization towards an inflammatory M1 phenotype[45]. A study on periodontal ligament cells (PDLs), which share many features with PDLSCs[46], demonstrated that these cells downregulate TNF-α production by THP-1 macrophages in the presence of *Porphyromonas gingivalis* (*P. gingivalis*) through cell-to-cell contact and the secretion of IL-6 and IL-10[47]. The same study showed that periodontal ligament fibroblasts increase the phagocytosis of *P. gingivalis* by macrophages[47]. There is some evidence that human PDLSCs modulate the function of PMNs. One study showed that human PDLSCs reduce apoptosis and enhance the antimicrobial activity of human PMNs *via* both cell-cell interactions and paracrine mechanisms[48]. Another study found that human PDLSCs reduce PMN apoptosis *via* an IL-6-dependent mechanism[49]. A very recent study demonstrated that reactive oxygen species produced by neutrophil-differentiated leukemic HL-60 cells are inhibited by conditioned medium from resting PDLSCs but stimulated by that from *P. gingivalis*-treated PDLSCs[50]. In addition to the effect on different immune cell subsets, human PDLSCs can also influence their tissue recruitment. A very recent study reported that LPS-stimulated PDLSCs reduce CD29 expression in PBMCs and inhibit the transendothelial migration of PBMCs *in vitro*[51].

Gingival mesenchymal stem cells

The gingiva is a specialized oral tissue attached to the alveolar bone that is considered as a mucosal barrier and is of essential importance for oral mucosal immunity. Currently, gingival mesenchymal stem cells (GMSCs) are assumed to be the best stem cell source for cell-based therapies and regenerative dentistry[52]. The isolation and characterization of GMSCs and their immunomodulatory properties were first described by Zhang *et al*[2] in 2009. In this study, GMSCs were shown to suppress PHA-induced PBMC proliferation[2]. Human GMSCs inhibit proliferation and Th1/Th2/Th17 differentiation in mouse CD4+ T cells[53]. Furthermore, GMSCs promote the polarization of PBMC-derived macrophages towards the M2 phenotype[54]. Similarly, a recent study using THP-1 macrophages showed that human GMSCs suppress the activation of M1 macrophages and promote their polarization into the M2 phenotype[55]. GMSCs have also been shown to inhibit the maturation and differentiation of monocyte-derived dendritic cells through a PGE-2-dependent mechanism[56]. The same study also showed that GMSCs suppress the release of inflammatory cytokines by the human mast cell line HMC-1 through a PGE-2-dependent mechanism but have no effect on the proliferation of HMC-1 cells[56]. There are also some studies showing that gingival fibroblasts (GFs), which are isolated from the gingival tissue and share many characteristics with GMSCs, possess an immunomodulatory ability[57]. In particular, human GFs suppress the Con A-induced proliferation of PBMCs, and this effect is quantitatively similar to that of DPSCs on PDLSCs[25]. Both primary human GFs and the HGF-1 cell line suppress LPS-induced TNF-α production by THP-1 macrophages[47].

Stem cells of human exfoliated deciduous teeth

In 2003, mesenchymal stem cells were first isolated from human exfoliated deciduous teeth by Miura *et al*[5] and termed stem cells of human exfoliated deciduous teeth (SHEDs). In particular, these cells were obtained from the pulp of deciduous teeth and show a higher proliferation rate, faster cell-proliferation doubling time and higher osteoinductive capacity than DPSCs isolated from permanent teeth[5]. A study using anti-CD3/CD28 antibody-activated PBMCs and naïve CD4+ T cells showed that SHEDs inhibit Th17 differentiation, and the effect of SHEDs was stronger than that of

bone marrow MSCs[58]. Furthermore, the differentiation, maturation, and T cell-activation ability of monocyte-derived DCs have been shown to be influenced by SHED[59]. Particularly, DCs exhibit decreased production of the inflammatory cytokines IL-2, TNF-α, and IFN-γ and increased production of anti-inflammatory IL-10 protein after the exposure to SHEDs. Further, DCs have been observed to exhibit enhanced ability of T_{reg} cells induction under the influence of SHEDs[59]. Recently, polarization of mouse bone marrow-derived macrophages toward M2 phenotype has been shown to be promoted by human SHEDs[60].

Dental follicle stem cells and stem cells from apical papilla

MSCs from dental follicles [dental follicle stem cells (DFSCs)] were first isolated from the ectomesenchymal tissue surrounding the developing tooth germ and characterized in 2005[8]. MSCs from human root apical papilla tissue [stem cells from apical papilla, (SCAP)] obtained from the exterior of the root foramen area were first isolated and characterized in 2006[7]. Only a few studies have addressed the immunomodulatory ability of these dental MSCs. After priming with toll-like receptor (TLR)-3 or TLR-4 agonists, DFSCs inhibit the PHA-stimulated proliferation of PBMCs, and this inhibition is mediated by IDO and TGF-β[61]. Human DFSCs infected with the periodontal pathogen *Prevotella intermedia* or *Tannerella forsythia* reduce neutrophil chemotaxis, phagocytic activity and NET formation[62]. SCAP in co-culture with PHA-stimulated porcine PBMCs inhibit the proliferation of CD3+ T cells[63].

RECIPROCAL REGULATION OF MSC IMMUNOMODULATORY PROPERTIES BY THE IMMUNE SYSTEM

The immunomodulatory properties of dental MSCs are determined by the surrounding microenvironment and are usually low in quiescent MSCs. The activation of MSCs with inflammatory cytokines such as IFN-γ, TNF-α and IL-1β, which are produced in high amounts by activated immune cells, drastically enhances their immunomodulatory potential[64]. Thus, MSCs and activated immune cells reciprocally regulate each other. Moreover, MSCs might adopt either an immuno-suppressive or immunostimulatory phenotype depending on the level of inflammation[65]. Similar to that of MSCs from other sources, the immunomodulatory activity of dental MSCs largely depends on activation by inflammatory cytokines, which are usually produced by immune cells. A pioneering study by Wada *et al*[25] showed that the proliferation of Con A-stimulated PBMCs is inhibited by direct co-culture with PDLSCs, DPSCs and GFs but not by conditioned medium collected from resting dental MSCs. This finding suggests that the activation of the immuno-suppressive abilities of different dental tissue-derived MSCs requires several factors produced by activated PBMCs. A recent study of human DPSCs showed that their ability to inhibit PBMC proliferation and B cell immunoglobulin production was significantly enhanced by IFN-γ and inhibited by anti-IFN-γ antibodies[27]. In a recent study, GFs were co-cultured with PBMCs without any activating stimuli. Under these conditions, the GFs induced the survival and selective proliferation of different lymphocytes but had no immunosuppressive effects[66]. These facts suggest that activated immune cells play a crucial role in inducing the immunomodulatory potential of dental MSCs and suggest tight reciprocal regulation between these cell types.

Activated immune cells induce the upregulation of the expression of various immunomodulatory proteins in dental MSCs. Thus, the expression of IDO, TGF-β1 and HGF in PDLSCs, DPSCs, and GFs is upregulated upon co-culture with Con A-activated PBMCs[25]. Another study found that the expression of IDO, COX-2, TSG-6, and IL-10 in human PDLSCs is upregulated after co-culture with Con A-activated PBMCs[40]. Conditioned medium from PBMCs stimulated with various stimuli, such as phorbol methyl acetate/ionomycin, LPS, Con A, and anti-CD3/CD28 antibodies, upregulates IDO and COX-2 expression in human PDLSCs[67]. The expression of HGF, HLA-G5, IL-6 and TGF-β is upregulated in human DPSCs after co-culture with PHA-activated CD3+ T cells[29]. A recent study showed that the production of PGE-2, TGF-β and IL-10 by human DPSCs is enhanced by PHA-activated PBMCs[30]. The expression of PD-L1 and PD-L2 in human PDLSCs is upregulated after co-culture with activated B cells[43]. COX-2 expression and PGE-2 production by GMSCs are upregulated by activated mast cells through a TNF-α-dependent mechanism[56].

The expression of various immunomodulatory factors in dental MSCs is also upregulated by different inflammatory cytokines. The expression of IDO is drastically upregulated by IFN-γ in human PDLSCs, DPSCs, and GMSCs/GFs[25,68-71]. In GFs, the

gene expression levels of IDO induced by IFN-γ are significantly higher than those of IL-1β and TNF-α; moreover, only IFN-γ is able to enhance the enzymatic activity of IDO[71]. The expression of HLA-G in human PDLSCs is enhanced by IL-12 mediated by autocrine IFN-γ signalling[72]. Another study showed an upregulation of HLA-G5 expression in human PDLSCs induced by IFN-γ[67]. The surface expression of PD-L1 in human PDLSCs is upregulated by different inflammatory cytokines, including TNF-α, IL-1β, and IFN-γ, but the effect of TNF-α is significantly greater than that of other cytokines[73]. Moreover, the effect of TNF-α on PD-L1 expression is further enhanced by the simultaneous application of other cytokines[73]. IL-1β and IFN-γ but not IL-17A enhance the gene expression of PD-L1 in periodontal ligament cells (PDLs)[74]. Interestingly, the expression of other immunomodulatory factors, such as HGF and TGF-β, in human PDLSCs, DPSCs, and GFs is not affected by IFN-γ[25,67]. One study found that the expression of TGF-β in human PDLs is upregulated only by the simultaneous application of IL-1β, IL-17A, and IFN-γ but not by separate stimulations with these cytokines[74]. Thus, one can assume that certain inflammatory cytokines activate only specific immunomodulatory parameters. In this case, priming with different cytokines might hypothetically activate only specific immunomodulatory functions in dental MSCs.

REGULATION OF THE IMMUNOMODULATORY PROPERTIES OF DENTAL TISSUE-DERIVED MSCS BY BACTERIAL PATHOGENS

The oral cavity is a habitat for different microorganisms, and host-microbial homeostasis is a crucial factor for maintaining oral health[75,76]. Oral diseases are often associated with the disruption of this homeostasis and bacterial invasion into the oral tissues. The mobilization of MSCs to the inflamed area is assumed to be an important factor contributing to the progression of the inflammatory response, but the exact role of these cells in inflammatory processes *in vivo* still needs to be clarified. During inflammatory processes, dental MSCs are exposed to different bacterial and viral products. The expression of TLR family members in different dental MSCs is well described, but their contribution to immunomodulation by dental MSCs is not yet well understood[77-79]. Initially, it was believed that the priming of MSCs with TLR-2 or TLR-4 agonists conferred a pro-inflammatory phenotype that allowed these primed MSCs to stimulate the immune response; in contrast, MSCs primed with TLR-3 agonists were thought to adopt an anti-inflammatory phenotype and exhibit immunosuppressive properties[80]. However, a recent study showed that the ability of bone marrow MSCs to induce T_{reg} differentiation is enhanced by both TLR-3 and TLR-4 activation[81]. Another study reported that TLR-3 and TLR-4 activation abolishes the ability of MSCs to suppress T cell activation[82]. These findings imply that the roles of different TLRs in MSC-mediated immunomodulation still need to be clarified. Unfortunately, there are only a limited number of studies in which the effects of different TLR agonists on the interactions of dental MSCs with different immune cell subsets have been investigated.

One report investigated the effect of TLR-3 and TLR-4 agonists on the ability of DPSCs and DFSCs to suppress the proliferation of PBMCs[61]. This study found that the TLR-3 agonist enhances the inhibitory effects of both types of MSC on PBMC proliferation. In contrast, the TLR-4 agonist augmented the immunosuppressive properties of DFSCs but inhibited those of DPSCs[61]. The treatment of human PDLSCs with the TLR-4 agonist LPS did not influence the inhibitory effect of the PDLSCs on the PHA-stimulated proliferation of CD4+ T cells or the ratio of CD4+ CD25high /CD4+ CD25low lymphocytes[51]. The LPS-treated PDLSCs did not change the frequencies of CD34+ and CD45+ cells but decreased the frequencies of CD33+ and CD14+ myeloid cells within the PBMC population[51]. The pre-treatment of GFs with *P. gingivalis*-derived LPS stimulated their ability to suppress PBMC proliferation, but this effect was rather small compared to the effects of IFN-γ-primed cells[70]. Interestingly, *P. gingivalis*-derived LPS enhanced the IFN-γ-induced immunosuppressive ability of GFs[70].

As shown by some studies, different TLR agonists and bacterial compounds may stimulate the expression of various immunomodulatory proteins in dental MSCs. The expression of IDO seems to be influenced by different TLR agonists, but there are some controversies in the existing data. In human PDLs, *Escherichia coli* (*E. coli*)-derived LPS enhances *IDO* gene expression levels and IDO activity, as measured by kynurenine production[83]. In contrast, another study showed that the TLR-2 agonist Pam3CSK4 only increases the gene expression of IDO and does not have any effect on protein expression, as measured by intracellular staining[68]. In addition, Pam3CSK4

was able to enhance IFN-γ-induced IDO protein expression[68]. The same study did not find any effect of the TLR-4 agonist *E. coli*-derived LPS on the expression of IDO at either the gene or protein level[68]. A study of DPSCs found that Pam3CSK4 and *E. coli*-derived LPS have no effect on IDO protein expression but are able to enhance IFN-γ-induced IDO expression[69]. Another study found that the expression of IDO in DPSCs is enhanced by *E. coli*-derived LPS at both the gene and protein levels after prolonged stimulation for up to 48 h[31]. In GFs, *P. gingivalis*-derived LPS induces a significant increase in the gene expression of IDO but has no effect on IDO activity[71]. In a further study, the same group reported that the mRNA expression of IDO in gingival cells can be induced by bacterial LPS, the TLR-3 agonist Poly I:C, and the TLR5 agonist flagellin but not by the TLR-7 agonist loxoribine, and the effect of Poly I:C was significantly higher than that of the other TLR agonists[70]. In STRO-1+ GMSCs, IDO mRNA expression is induced only by a TLR-3 agonist and not by agonists of TLR-1, 2, 4, 6, or 7[77]. The effect of TLR agonists on IDO expression in dental MSCs might also depend on the origin of the MSCs. For example, IDO expression is not affected by LPS in DFSCs but is inhibited by LPS in DPSCs[61]. In addition to their direct effects, different bacterial products can induce IDO expression in MSCs indirectly through the activation of different immune cells. For example, conditioned medium from LPS-stimulated PBMCs induces the expression of IDO and COX-2 in PDLSCs[67].

The expression of other immunomodulatory factors in dental tissue-derived MSCs is also influenced by bacterial products and TLR agonists. LPS enhances the production of PGE-2 by PDLSCs[51]. The periodontal pathogens *P. gingivalis* and *Fusobacterium nucleatum* (*F. nucleatum*) induce the production of IL-10 by DFSCs under anaerobic conditions[84]. Interestingly, *F. nucleatum*-induced IL-10 production in DFSCs is significantly higher than that in BM-MSCs[84]. The expression of PD-L1 in human PDLSCs is upregulated by various periodontal pathogens, such as *P. gingivalis*, *P. intermedia* and *F. nucleatum*, as well as LPS[73]. It should be noted that bacterial products and TLR agonists also induce the expression of inflammatory mediators such as IL-1β, IL-6, IL-8 and monocyte chemoattractant protein 1 in various craniofacial MSCs[51,68,85-88]. Thus, TLR agonists might activate both the pro-inflammatory and anti-inflammatory properties of dental MSCs, and the exact role of these cells in the inflammatory response is determined by other factors, such as the degree of inflammation and the microenvironment.

POTENTIAL ROLE OF IMMUNOMODULATION MEDIATED BY DENTAL TISSUE-DERIVED MSCS IN ORAL DISEASES

Although the immunomodulatory ability of dental MSCs is widely recognized, its exact roles in the pathogenesis of various oral diseases remain rather obscure and only hypothetical. MSCs are located in a region that can occasionally be exposed to different bacterial challenges, and this inflammatory milieu might have a substantial effect on their immunomodulatory properties. PDLSCs isolated from inflamed tissue exhibit higher proliferative and migratory capacities than those isolated from healthy tissue[41,89]. Additionally, "inflamed" PDLSCs exhibit impaired abilities to promote T$_{reg}$ induction and suppress Th17 differentiation compared to cells isolated from healthy tissue[39]. PDLSCs from inflamed tissue are less effective in suppressing PBMC proliferation than those isolated from the healthy tissue of matched donors after 72 h of co-culture but not after 24-48 h of co-culture[41]. The same study found higher levels of IL-2, TNF-α and IFN-γ but similar levels of IL-10 in a co-culture of PBMCs and PDLSCs isolated from inflamed tissue compared to a co-culture containing healthy tissue cells[41]. "Inflamed" PDLSCs induce less PBMC apoptosis than "healthy" PDLSCs. In contrast to the above-mentioned studies, one study did not find any differences in the ability to suppress PBMC proliferation or in the expression of COX-2 and IL-10 between PDLSCs isolated from healthy tissue and those from inflamed periodontal tissue[40]. The same study found that upon co-culture with Con A-activated PBMCs, "healthy" PDLSCs exhibited lower IDO and significantly higher TSG-6 expression than "inflamed" PDLSCs[40]. DPSCs derived from teeth with pulpitis fail to suppress PBMC proliferation, but this ability might be restored with IFN-γ treatment[90]. In contrast to the above studies, no difference is found in the ability to modulate macrophage functions between DPSCs isolated from healthy and inflamed tissues[31].

Only a few *in vivo* studies have investigated the expression of immunomodulatory factors in dental tissue under inflammatory conditions. In a mouse model, the severity of periodontal disease induced by the injection of *P. gingivalis* was negatively correlated with the expression of PD-L1 in the periodontal tissue[73]. IDO expression is significantly augmented in macrophages and MSCs in inflamed human pulp tissue[31].

In rats with experimental periodontitis, topical and systemic application of MSCs transfected with TSG-6 leads to significantly lower bone loss, osteoclast formation and systemic levels of the inflammatory cytokines IL-1β and TNF-α[12]. These observations suggest a potential role for immunomodulation mediated by dental tissue-derived MSCs in the progression of different oral diseases, such as pulpitis, gingivitis and periodontitis, and this topic still needs to be intensively explored in future studies.

CONTRIBUTION OF THE IMMUNOMODULATORY EFFECT OF DENTAL TISSUE-DERIVED MSCS ON TISSUE REGENERATION

Although the multilineage differentiation ability of MSCs *in vitro* is largely recognized, the mechanisms of their differentiation *in vivo* are not yet understood, and their clinical application for tissue regeneration is still limited. Transplanted MSCs have a rather short lifespan; for example, after intravenous injection MSCs accumulate in the lungs and disappear within 24 h[91]. The interaction of transplanted MSCs with the host immune system seems to be one of the key elements in the regeneration process[92]. Immunomodulatory and tropic capacity of transplanted MSCs contribute to the creation of a microenvironment, promote the activation of endogenous tissue repair mechanisms and are now considered to be the major mechanism of their therapeutic effect *in vivo*[93].

The healing and regeneration of different dental tissues, similar to the healing and regeneration of other tissues, consists of four overlapping phases: Haemostasis, inflammation, proliferation, and maturation/remodelling[94]. A recent review appreciated the essential role of inflammatory cytokines in the different stages of periodontal wound healing[95]. Inflammatory cytokines might have both positive and negative impacts on the tissue regeneration process[95]. Immune cells are involved in each stage of tissue regeneration, and modulating the immune system is considered a promising approach to promote tissue regeneration[96]. Therefore, the immuno-modulatory properties of dental MSCs are hypothesized to be involved in tissue regeneration[97].

Several studies have investigated the levels of different inflammatory cytokines after MSC application for the regeneration of craniofacial tissue. The transplantation of human PDLSC-conditioned medium improves the healing process of surgically created periodontal defects in rats and is accompanied by a decreased mRNA level of TNF-α in the healing periodontal tissue[44]. The local administration of allogenic bone marrow MSCs into periodontal defects is not only beneficial for tissue regeneration but is also accompanied by decreased local levels of IL-1β, TNF-α and IFN-γ[98]. The transplantation of SHEDs into periodontal defects after experimentally induced periodontitis stimulates the regeneration of the periodontal tissue, which is accompanied by an increased proportion of M2 macrophages[60]. Moreover, SHED application is characterized by lower levels of IL-1β and higher levels of IL-10 in the gingival crevicular fluid[60]. Although these studies do not provide any evidence that the immunomodulatory ability of MSCs is necessary for tissue regeneration, they unequivocally suggest that the MSC-based regeneration of dental tissues is accompanied by the modulation of the inflammatory response.

In addition, few experimental studies have investigated the effect of immuno-modulatory factors on periodontal tissue regeneration. PDLSCs transfected with HGF improve periodontal bone regeneration in swine[99]. Intragingival injection of TSG-6 promotes early wound healing after gingival resection in rats and results in lower levels of the inflammatory markers IL-1β and myeloperoxidase[100]. The transplantation of IFN-γ-pre-treated bone marrow-MSC sheets into mouse calvarial bone defects induces bone regeneration, which is not observed with non-treated cell sheets[101]. Moreover, the transplantation of non-treated bone marrow-MSC sheets induces T cell infiltration into the grafted area[101]. Some studies have also implied that the activation of the complement system by DPSCs can contribute to pulp regeneration[37,38].

The regenerative and immunomodulatory abilities of MSCs are supposed to be tightly interconnected, but the exact relationship between these two functions still needs to be established. Some factors mediating the immunomodulatory effects of MSCs also influence their differentiation potential. Particularly, osteogenic, adipogenic and neural differentiation in human MSCs are altered upon IDO activation by IFN-γ[102]. The differentiation ability of MSCs is also influenced by TSG-6[103,104]. Both, regenerative and immunomodulatory functions of MSCs are influenced by their TGF-β production[105]. One *in vitro* study showed that the differentiation potential of human PDLSCs depends on the inflammatory microenvironments and

correlates with their immunomodulatory properties[106]. TSG-6 production in hPDLCS is induced by BMP-2, which is widely used for bone regeneration in clinic[107]. Furthermore, BMP-2 decreases the inflammatory response in the human macrophage THP-1 cell line[108].

CONCLUSIONS, OPEN QUESTIONS AND FURTHER PERSPECTIVES

Dental tissue-derived MSCs, similar to MSCs from other tissues, influence the properties of both the innate and adaptive immune systems. Numerous *in vitro* studies have shown that dental MSCs influence the functional activities of key components of the immune system, namely, T cells, dendritic cells, natural killer cells, B cells, macrophages, and neutrophils. However, knowledge about MSC-dependent immunomodulation *in vivo* is limited and originates mostly from animal models, which are usually mouse models. Although the principles of immune defence are quite similar among all mammalian species, there are some differences between the mouse and human immune systems[109]. Differences have been found for almost all components of both innate and acquired immunity, and therefore, the translation of data obtained in mice to humans must be done cautiously. Moreover, there are also some differences in the mechanisms of MSC-mediated immunomodulation between humans and mice. Nevertheless, animal studies will be especially important for deepening our knowledge of the *in vivo* mechanisms of MSC immunomodulation. Studies with conditional knockout mice, in which the expression of different proteins involved in immunomodulation can be eliminated in a tissue-specific manner, are especially important.

The interaction of MSCs with the immune system is reciprocal, and the immunomodulatory ability of MSCs is highly regulated by different inflammatory cytokines. The priming of dental MSCs with IFN-γ, TNF-α and IL-1β usually enhances their immunosuppressive ability and could be considered a feedback mechanism that dampens exacerbated immune responses (Figure 1). This reciprocal interaction between immune cells and MSCs could be considered an important mechanism contributing to tissue homeostasis and regeneration as well as the progression of different inflammatory diseases. However, the interaction between MSCs and immune cells seems to be more complex. An interesting paradox regarding the immunomodulation mediated by dental MSCs is that this ability might be impaired in cells isolated from an inflammatory environment. This is rather surprising because MSCs in inflamed areas are continuously exposed to numerous inflammatory mediators, which should enhance the immunosuppressive properties of the MSCs. Therefore, the immunomodulation mediated by MSCs could be influenced by other factors and/or chronic inflammation, and these issues need to be further explored.

It is also possible that the impairment of MSC immunomodulation might contribute to the progression of various inflammatory diseases. Dental MSCs express numerous TLRs, and different TLR ligands are thought to influence the immunomodulatory ability of MSCs. Furthermore, bacterial ligands can influence MSCs indirectly through the activation of inflammatory cytokine production in different immune cells. Nevertheless, there is still an insufficient number of experimental studies investigating the effects of different TLR ligands and bacterial products on the ability of MSCs to modulate different immune cell subsets. Importantly, the regulation of immunity by MSCs in different inflammatory diseases might play dual roles and influence both pathogen elimination abilities and collateral tissue damage. The activation of MSCs by TLRs has been shown to have both immunoactivating and immunosuppressive effects, and the physiological and pathophysiological relevance of these effects still needs to be understood.

In addition, the regulation of the immune system by MSCs is thought to largely contribute to tissue regeneration processes. However, the interplay between the immunomodulatory function of MSCs and their regenerative potential in different dental tissues still needs to be investigated. There is already a first report showing that priming MSCs with IFN-γ can enhance their regenerative potential, presumably through the activation of their immunomodulatory potential. As mentioned above, different inflammatory mediators might differentially activate various immunomodulatory proteins in MSCs and thus their immunomodulatory activity. Different populations of immune cells are involved in different time-separated stages of wound healing. Therefore, the activation of a specific "immunomodulatory profile" by MSCs may enhance the efficiency of their application at different stages of the healing process and should be tested in further studies.
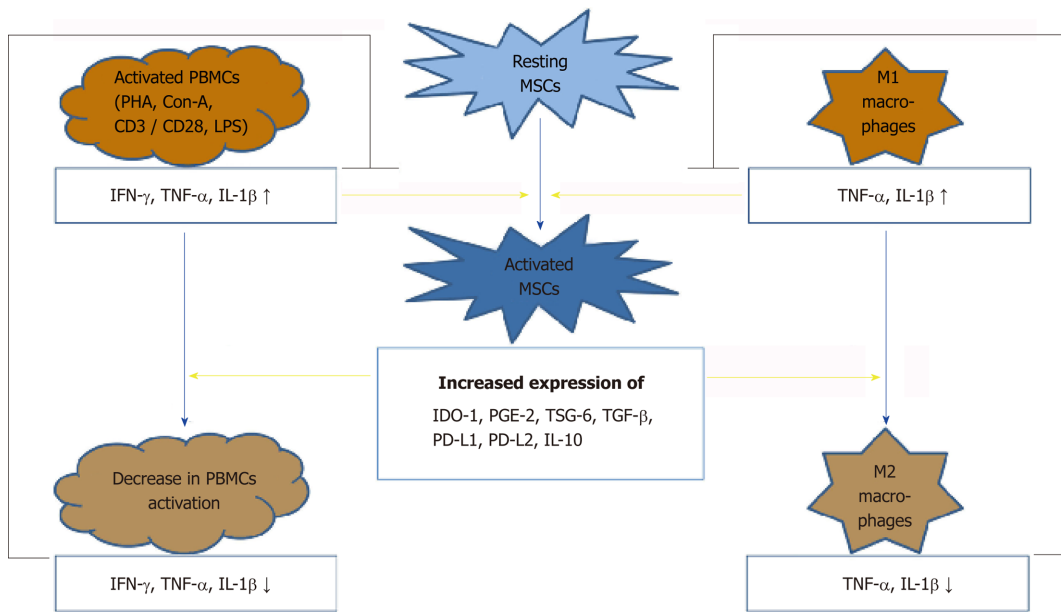
Figure 1 Reciprocal interaction between dental tissue-derived mesenchymal stem cells and immune cells. While the immunomodulatory ability of resting mesenchymal stem cells (MSCs) is usually low, inflammatory cytokines such as interferon-γ, tumour necrosis factor-α, and interleukin-1β lead to strong activation of this ability. Large amounts of these cytokines are produced by immune cells, such as peripheral blood mononuclear cells (PBMCs) or macrophages, under inflammatory conditions. *In vitro* cytokine production can be activated by either mitotic stimuli or bacterial pathogens. Inflammatory cytokines increase the expression of different immunomodulatory proteins in MSCs, which leads to the suppression of the activity of PBMCs or directs macrophage polarization towards the M2 phenotype *via* paracrine mechanisms or direct cell-to-cell contact. The resulting lower levels of the inflammatory cytokines produced by PBMCs or macrophages diminish the ability of these cells to activate MSC-dependent immunosuppression. Thus, the continuous interaction between immune cells and dental tissue-derived MSCs determines the intensity of the immune response and hypothetically plays an important role in tissue homeostasis.

REFERENCES

1	**Dominici M**, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, Deans R, Keating A, Prockop Dj, Horwitz E. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy* 2006; **8**: 315-317 [PMID: 16923606 DOI: 10.1080/14653240600855905]

2	**Zhang Q**, Shi S, Liu Y, Uyanne J, Shi Y, Shi S, Le AD. Mesenchymal stem cells derived from human gingiva are capable of immunomodulatory functions and ameliorate inflammation-related tissue destruction in experimental colitis. *J Immunol* 2009; **183**: 7787-7798 [PMID: 19923445 DOI: 10.4049/jimmunol.0902318]

3	**Chamberlain G**, Fox J, Ashton B, Middleton J. Concise review: mesenchymal stem cells: their phenotype, differentiation capacity, immunological features, and potential for homing. *Stem Cells* 2007; **25**: 2739-2749 [PMID: 17656645 DOI: 10.1634/stemcells.2007-0197]

4	**Gronthos S**, Mankani M, Brahim J, Robey PG, Shi S. Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. *Proc Natl Acad Sci U S A* 2000; **97**: 13625-13630 [PMID: 11087820 DOI: 10.1073/pnas.240309797]

5	**Miura M**, Gronthos S, Zhao M, Lu B, Fisher LW, Robey PG, Shi S. SHED: stem cells from human exfoliated deciduous teeth. *Proc Natl Acad Sci U S A* 2003; **100**: 5807-5812 [PMID: 12716973 DOI: 10.1073/pnas.0937635100]

6	**Seo BM**, Miura M, Gronthos S, Bartold PM, Batouli S, Brahim J, Young M, Robey PG, Wang CY, Shi S. Investigation of multipotent postnatal stem cells from human periodontal ligament. *Lancet* 2004; **364**: 149-155 [PMID: 15246727 DOI: 10.1016/S0140-6736(04)16627-0]

7	**Sonoyama W**, Liu Y, Yamaza T, Tuan RS, Wang S, Shi S, Huang GT. Characterization of the apical papilla and its residing stem cells from human immature permanent teeth: a pilot study. *J Endod* 2008; **34**: 166-171 [PMID: 18215674 DOI: 10.1016/j.joen.2007.11.021]

8	**Morsczeck C**, Götz W, Schierholz J, Zeilhofer F, Kühn U, Möhl C, Sippel C, Hoffmann KH. Isolation of precursor cells (PCs) from human dental follicle of wisdom teeth. *Matrix Biol* 2005; **24**: 155-165 [PMID: 15890265 DOI: 10.1016/j.matbio.2004.12.004]

9	**Sharpe PT**. Dental mesenchymal stem cells. *Development* 2016; **143**: 2273-2280 [PMID: 27381225 DOI: 10.1242/dev.134189]

10	**Bakopoulou A**, About I. Stem Cells of Dental Origin: Current Research Trends and Key Milestones towards Clinical Application. *Stem Cells Int* 2016; **2016**: 4209891 [PMID: 27818690 DOI: 10.1155/2016/4209891]

11	**Wada N**, Gronthos S, Bartold PM. Immunomodulatory effects of stem cells. *Periodontol 2000* 2013; **63**: 198-216 [PMID: 23931061 DOI: 10.1111/prd.12024]

12	**Yang H**, Aprecio RM, Zhou X, Wang Q, Zhang W, Ding Y, Li Y. Therapeutic effect of TSG-6 engineered iPSC-derived MSCs on experimental periodontitis in rats: a pilot study. *PLoS One* 2014; **9**: e100285 [PMID: 24979372 DOI: 10.1371/journal.pone.0100285]

13	**Yang R**, Yu T, Zhou Y. Interplay between craniofacial stem cells and immune stimulus. *Stem Cell Res Ther* 2017; **8**: 147 [PMID: 28646913 DOI: 10.1186/s13287-017-0607-1]

14	**Glenn JD**, Whartenby KA. Mesenchymal stem cells: Emerging mechanisms of immunomodulation and

therapy. *World J Stem Cells* 2014; **6**: 526-539 [PMID: 25426250 DOI: 10.4252/wjsc.v6.i5.526]

15   **Ma OK**, Chan KH. Immunomodulation by mesenchymal stem cells: Interplay between mesenchymal stem cells and regulatory lymphocytes. *World J Stem Cells* 2016; **8**: 268-278 [PMID: 27679683 DOI: 10.4252/wjsc.v8.i9.268]

16   **Li Z**, Jiang CM, An S, Cheng Q, Huang YF, Wang YT, Gou YC, Xiao L, Yu WJ, Wang J. Immunomodulatory properties of dental tissue-derived mesenchymal stem cells. *Oral Dis* 2014; **20**: 25-34 [PMID: 23463961 DOI: 10.1111/odi.12086]

17   **Munn DH**, Mellor AL. Indoleamine 2,3 dioxygenase and metabolic control of immune responses. *Trends Immunol* 2013; **34**: 137-143 [PMID: 23103127 DOI: 10.1016/j.it.2012.10.001]

18   **Fontaine MJ**, Shih H, Schäfer R, Pittenger MF. Unraveling the Mesenchymal Stromal Cells' Paracrine Immunomodulatory Effects. *Transfus Med Rev* 2016; **30**: 37-43 [PMID: 26689863 DOI: 10.1016/j.tmrv.2015.11.004]

19   **Kalinski P**. Regulation of immune responses by prostaglandin E2. *J Immunol* 2012; **188**: 21-28 [PMID: 22187483 DOI: 10.4049/jimmunol.1101029]

20   **Nemeth K**, Keane-Myers A, Brown JM, Metcalfe DD, Gorham JD, Bundoc VG, Hodges MG, Jelinek I, Madala S, Karpati S, Mezey E. 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* 2010; **107**: 5652-5657 [PMID: 20231466 DOI: 10.1073/pnas.0910720107]

21   **Najar M**, Raicevic G, Fayyad-Kazan H, De Bruyn C, Bron D, Toungouz M, Lagneaux L. 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* 2015; **11**: 442-452 [PMID: 25326368 DOI: 10.1007/s12015-014-9567-3]

22   **Tipnis S**, Viswanathan C, Majumdar AS. Immunosuppressive properties of human umbilical cord-derived mesenchymal stem cells: role of B7-H1 and IDO. *Immunol Cell Biol* 2010; **88**: 795-806 [PMID: 20386557 DOI: 10.1038/icb.2010.47]

23   **Kleiveland CR**, Verhoeckx K, Cotter P, López-Expósito I, Kleiveland C, Lea T. Peripheral Blood Mononuclear Cells. Verhoeckx K, Cotter P, López-Expósito I, Kleiveland C, Lea T. *The Impact of Food Bioactives on Health: in vitro and ex vivo models [Internet]*. Cham (CH): Springer; 2015; Chapter 15 [PMID: 29787062 DOI: 10.1007/978-3-319-16104-4_15]

24   **Peng L**, Ye L, Zhou XD. Mesenchymal stem cells and tooth engineering. *Int J Oral Sci* 2009; **1**: 6-12 [PMID: 20690498 DOI: 10.4248/ijos.08032]

25   **Wada N**, Menicanin D, Shi S, Bartold PM, Gronthos S. Immunomodulatory properties of human periodontal ligament stem cells. *J Cell Physiol* 2009; **219**: 667-676 [PMID: 19160415 DOI: 10.1002/jcp.21710]

26   **Özdemir AT**, Özgül Özdemir RB, Kırmaz C, Sarıboyacı AE, Ünal Halbutoğlları ZS, Özel C, Karaöz E. The paracrine immunomodulatory interactions between the human dental pulp derived mesenchymal stem cells and CD4 T cell subsets. *Cell Immunol* 2016; **310**: 108-115 [PMID: 27576175 DOI: 10.1016/j.cellimm.2016.08.008]

27   **Kwack KH**, Lee JM, Park SH, Lee HW. Human Dental Pulp Stem Cells Suppress Alloantigen-induced Immunity by Stimulating T Cells to Release Transforming Growth Factor Beta. *J Endod* 2017; **43**: 100-108 [PMID: 27871783 DOI: 10.1016/j.joen.2016.09.005]

28   **Zhao Y**, Wang L, Jin Y, Shi S. Fas ligand regulates the immunomodulatory properties of dental pulp stem cells. *J Dent Res* 2012; **91**: 948-954 [PMID: 22904205 DOI: 10.1177/0022034512458690]

29   **Demircan PC**, Sariboyaci AE, Unal ZS, Gacar G, Subasi C, Karaoz E. Immunoregulatory effects of human dental pulp-derived stem cells on T cells: comparison of transwell co-culture and mixed lymphocyte reaction systems. *Cytotherapy* 2011; **13**: 1205-1220 [PMID: 21905956 DOI: 10.3109/14653249.2011.605351]

30   **Hossein-Khannazer N**, Hashemi SM, Namaki S, Ghanbarian H, Sattari M, Khojasteh A. Study of the immunomodulatory effects of osteogenic differentiated human dental pulp stem cells. *Life Sci* 2019; **216**: 111-118 [PMID: 30465790 DOI: 10.1016/j.lfs.2018.11.040]

31   **Lee S**, Zhang QZ, Karabucak B, Le AD. DPSCs from Inflamed Pulp Modulate Macrophage Function via the TNF-α/IDO Axis. *J Dent Res* 2016; **95**: 1274-1281 [PMID: 27384335 DOI: 10.1177/0022034516657817]

32   **Omi M**, Hata M, Nakamura N, Miyabe M, Kobayashi Y, Kamiya H, Nakamura J, Ozawa S, Tanaka Y, Takebe J, Matsubara T, Naruse K. Transplantation of dental pulp stem cells suppressed inflammation in sciatic nerves by promoting macrophage polarization towards anti-inflammation phenotypes and ameliorated diabetic polyneuropathy. *J Diabetes Investig* 2016; **7**: 485-496 [PMID: 27181261 DOI: 10.1111/jdi.12452]

33   **Jewett A**, Man YG, Tseng HC. Dual functions of natural killer cells in selection and differentiation of stem cells; role in regulation of inflammation and regeneration of tissues. *J Cancer* 2013; **4**: 12-24 [PMID: 23386901 DOI: 10.7150/jca.5519]

34   **Tseng HC**, Cacalano N, Jewett A. Split anergized Natural Killer cells halt inflammation by inducing stem cell differentiation, resistance to NK cell cytotoxicity and prevention of cytokine and chemokine secretion. *Oncotarget* 2015; **6**: 8947-8959 [PMID: 25860927 DOI: 10.18632/oncotarget.3250]

35   **Martinez VG**, Ontoria-Oviedo I, Ricardo CP, Harding SE, Sacedon R, Varas A, Zapata A, Sepulveda P, Vicente A. Overexpression of hypoxia-inducible factor 1 alpha improves immunomodulation by dental mesenchymal stem cells. *Stem Cell Res Ther* 2017; **8**: 208 [PMID: 28962641 DOI: 10.1186/s13287-017-0659-2]

36   **Chmilewsky F**, Jeanneau C, Laurent P, About I. Pulp fibroblasts synthesize functional complement proteins involved in initiating dentin-pulp regeneration. *Am J Pathol* 2014; **184**: 1991-2000 [PMID: 24814102 DOI: 10.1016/j.ajpath.2014.04.003]

37   **Cardoso CR**, Garlet GP, Moreira AP, Júnior WM, Rossi MA, Silva JS. Characterization of CD4+CD25+ natural regulatory T cells in the inflammatory infiltrate of human chronic periodontitis. *J Leukoc Biol* 2008; **84**: 311-318 [PMID: 18451325 DOI: 10.1189/jlb.0108014]

38   **Rufas P**, Jeanneau C, Rombouts C, Laurent P, About I. Complement C3a Mobilizes Dental Pulp Stem Cells and Specifically Guides Pulp Fibroblast Recruitment. *J Endod* 2016; **42**: 1377-1384 [PMID: 27497510 DOI: 10.1016/j.joen.2016.06.011]

39   **Liu D**, Xu J, Liu O, Fan Z, Liu Y, Wang F, Ding G, Wei F, Zhang C, Wang S. Mesenchymal stem cells derived from inflamed periodontal ligaments exhibit impaired immunomodulation. *J Clin Periodontol* 2012; **39**: 1174-1182 [PMID: 23005571 DOI: 10.1111/jcpe.12009]

40   **Li C**, Wang X, Tan J, Wang T, Wang Q. The immunomodulatory properties of periodontal ligament stem

cells isolated from inflamed periodontal granulation. *Cells Tissues Organs* 2014; **199**: 256-265 [PMID: 25471814 DOI: 10.1159/000367986]

41   **Tang HN**, Xia Y, Yu Y, Wu RX, Gao LN, Chen FM. Stem cells derived from "inflamed" and healthy periodontal ligament tissues and their sheet functionalities: a patient-matched comparison. *J Clin Periodontol* 2016; **43**: 72-84 [PMID: 26719165 DOI: 10.1111/jcpe.12501]

42   **Shin C**, Kim M, Han JA, Choi B, Hwang D, Do Y, Yun JH. Human periodontal ligament stem cells suppress T-cell proliferation via down-regulation of non-classical major histocompatibility complex-like glycoprotein CD1b on dendritic cells. *J Periodontal Res* 2017; **52**: 135-146 [PMID: 27021598 DOI: 10.1111/jre.12378]

43   **Liu O**, Xu J, Ding G, Liu D, Fan Z, Zhang C, Chen W, Ding Y, Tang Z, Wang S. Periodontal ligament stem cells regulate B lymphocyte function via programmed cell death protein 1. *Stem Cells* 2013; **31**: 1371-1382 [PMID: 23553748 DOI: 10.1002/stem.1387]

44   **Nagata M**, Iwasaki K, Akazawa K, Komaki M, Yokoyama N, Izumi Y, Morita I. Conditioned Medium from Periodontal Ligament Stem Cells Enhances Periodontal Regeneration. *Tissue Eng Part A* 2017; **23**: 367-377 [PMID: 28027709 DOI: 10.1089/ten.TEA.2016.0274]

45   **Kang H**, Lee MJ, Park SJ, Lee MS. Lipopolysaccharide-Preconditioned Periodontal Ligament Stem Cells Induce M1 Polarization of Macrophages through Extracellular Vesicles. *Int J Mol Sci* 2018; **19** [PMID: 30513870 DOI: 10.3390/ijms19123843]

46   **Silvério KG**, Rodrigues TL, Coletta RD, Benevides L, Da Silva JS, Casati MZ, Sallum EA, Nociti FH. Mesenchymal stem cell properties of periodontal ligament cells from deciduous and permanent teeth. *J Periodontol* 2010; **81**: 1207-1215 [PMID: 20476882 DOI: 10.1902/jop.2010.090729]

47   **Tzach-Nahman R**, Nashef R, Fleissig O, Palmon A, Shapira L, Wilensky A, Nussbaum G. Oral fibroblasts modulate the macrophage response to bacterial challenge. *Sci Rep* 2017; **7**: 11516 [PMID: 28912533 DOI: 10.1038/s41598-017-11771-3]

48   **Cianci E**, Recchiuti A, Trubiani O, Diomede F, Marchisio M, Miscia S, Colas RA, Dalli J, Serhan CN, Romano M. Human Periodontal Stem Cells Release Specialized Proresolving Mediators and Carry Immunomodulatory and Prohealing Properties Regulated by Lipoxins. *Stem Cells Transl Med* 2016; **5**: 20-32 [PMID: 26607175 DOI: 10.5966/sctm.2015-0163]

49   **Wang Q**, Ding G, Xu X. Periodontal Ligament Stem Cells Regulate Apoptosis of Neutrophils. *Open Med (Wars)* 2017; **12**: 19-23 [PMID: 28401196 DOI: 10.1515/med-2017-0004]

50   **Misawa MYO**, Silvério Ruiz KG, Nociti FH, Albiero ML, Saito MT, Nóbrega Stipp R, Condino-Neto A, Holzhausen M, Palombo H, Villar CC. Periodontal ligament-derived mesenchymal stem cells modulate neutrophil responses via paracrine mechanisms. *J Periodontol* 2019; **90**: 747-755 [PMID: 30644104 DOI: 10.1002/JPER.18-0220]

51   **Kukolj T**, Trivanović D, Djordjević IO, Mojsilović S, Krstić J, Obradović H, Janković S, Santibanez JF, Jauković A, Bugarski D. Lipopolysaccharide can modify differentiation and immunomodulatory potential of periodontal ligament stem cells via ERK1,2 signaling. *J Cell Physiol* 2018; **233**: 447-462 [PMID: 28295277 DOI: 10.1002/jcp.25904]

52   **Grawish ME**. Gingival-derived mesenchymal stem cells: An endless resource for regenerative dentistry. *World J Stem Cells* 2018; **10**: 116-118 [PMID: 30310530 DOI: 10.4252/wjsc.v10.i9.116]

53   **Chen M**, Su W, Lin X, Guo Z, Wang J, Zhang Q, Brand D, Ryffel B, Huang J, Liu Z, He X, Le AD, Zheng SG. Adoptive transfer of human gingiva-derived mesenchymal stem cells ameliorates collagen-induced arthritis via suppression of Th1 and Th17 cells and enhancement of regulatory T cell differentiation. *Arthritis Rheum* 2013; **65**: 1181-1193 [PMID: 23400582 DOI: 10.1002/art.37894]

54   **Zhang QZ**, Su WR, Shi SH, Wilder-Smith P, Xiang AP, Wong A, Nguyen AL, Kwon CW, Le AD. Human gingiva-derived mesenchymal stem cells elicit polarization of m2 macrophages and enhance cutaneous wound healing. *Stem Cells* 2010; **28**: 1856-1868 [PMID: 20734355 DOI: 10.1002/stem.503]

55   **Zhang X**, Huang F, Li W, Dang JL, Yuan J, Wang J, Zeng DL, Sun CX, Liu YY, Ao Q, Tan H, Su W, Qian X, Olsen N, Zheng SG. Human Gingiva-Derived Mesenchymal Stem Cells Modulate Monocytes/Macrophages and Alleviate Atherosclerosis. *Front Immunol* 2018; **9**: 878 [PMID: 29760701 DOI: 10.3389/fimmu.2018.00878]

56   **Su WR**, Zhang QZ, Shi SH, Nguyen AL, Le AD. Human gingiva-derived mesenchymal stromal cells attenuate contact hypersensitivity via prostaglandin E2-dependent mechanisms. *Stem Cells* 2011; **29**: 1849-1860 [PMID: 21987520 DOI: 10.1002/stem.738]

57   **Du L**, Yang P, Ge S. Isolation and characterization of human gingiva-derived mesenchymal stem cells using limiting dilution method. *J Dent Sci* 2016; **11**: 304-314 [PMID: 30894989 DOI: 10.1016/j.jds.2016.03.010]

58   **Yamaza T**, Kentaro A, Chen C, Liu Y, Shi Y, Gronthos S, Wang S, Shi S. Immunomodulatory properties of stem cells from human exfoliated deciduous teeth. *Stem Cell Res Ther* 2010; **1**: 5 [PMID: 20504286 DOI: 10.1186/scrt5]

59   **Silva Fde S**, Ramos RN, de Almeida DC, Bassi EJ, Gonzales RP, Miyagi SP, Maranduba CP, Sant'Anna OA, Marques MM, Barbuto JA, Câmara NO, da Costa Maranduba CM. Mesenchymal stem cells derived from human exfoliated deciduous teeth (SHEDs) induce immune modulatory profile in monocyte-derived dendritic cells. *PLoS One* 2014; **9**: e98050 [PMID: 24846008 DOI: 10.1371/journal.pone.0098050]

60   **Gao X**, Shen Z, Guan M, Huang Q, Chen L, Qin W, Ge X, Chen H, Xiao Y, Lin Z. Immunomodulatory Role of Stem Cells from Human Exfoliated Deciduous Teeth on Periodontal Regeneration. *Tissue Eng Part A* 2018; **24**: 1341-1353 [PMID: 29652608 DOI: 10.1089/ten.TEA.2018.0016]

61   **Tomic S**, Djokic J, Vasilijic S, Vucevic D, Todorovic V, Supic G, Colic M. Immunomodulatory properties of mesenchymal stem cells derived from dental pulp and dental follicle are susceptible to activation by toll-like receptor agonists. *Stem Cells Dev* 2011; **20**: 695-708 [PMID: 20731536 DOI: 10.1089/scd.2010.0145]

62   **Hieke C**, Kriebel K, Engelmann R, Müller-Hilke B, Lang H, Kreikemeyer B. Human dental stem cells suppress PMN activity after infection with the periodontopathogens Prevotella intermedia and Tannerella forsythia. *Sci Rep* 2016; **6**: 39096 [PMID: 27974831 DOI: 10.1038/srep39096]

63   **Ding G**, Liu Y, An Y, Zhang C, Shi S, Wang W, Wang S. Suppression of T cell proliferation by root apical papilla stem cells in vitro. *Cells Tissues Organs* 2010; **191**: 357-364 [PMID: 20090301 DOI: 10.1159/000276589]

64   **Krampera M**. Mesenchymal stromal cell 'licensing': a multistep process. *Leukemia* 2011; **25**: 1408-1414 [PMID: 21617697 DOI: 10.1038/leu.2011.108]

65   **Bernardo ME**, Fibbe WE. Mesenchymal stromal cells: sensors and switchers of inflammation. *Cell Stem Cell* 2013; **13**: 392-402 [PMID: 24094322 DOI: 10.1016/j.stem.2013.09.006]

66   **Moonen CGJ**, Alders ST, Bontkes HJ, Schoenmaker T, Nicu EA, Loos BG, de Vries TJ. Survival, Retention, and Selective Proliferation of Lymphocytes Is Mediated by Gingival Fibroblasts. *Front Immunol* 2018; **9**: 1725 [PMID: 30140265 DOI: 10.3389/fimmu.2018.01725]

67   **Kim JH**, Jo CH, Kim HR, Hwang YI. Comparison of Immunological Characteristics of Mesenchymal Stem Cells from the Periodontal Ligament, Umbilical Cord, and Adipose Tissue. *Stem Cells Int* 2018; **2018**: 8429042 [PMID: 29760736 DOI: 10.1155/2018/8429042]

68   **Andrukhov O**, Hong JS, Andrukhova O, Blufstein A, Moritz A, Rausch-Fan X. Response of human periodontal ligament stem cells to IFN-γ and TLR-agonists. *Sci Rep* 2017; **7**: 12856 [PMID: 28993635 DOI: 10.1038/s41598-017-12480-7]

69   **Takegawa D**, Nakanishi T, Hirao K, Yumoto H, Takahashi K, Matsuo T. Modulatory roles of interferon-γ through indoleamine 2, 3-dioxygenase induction in innate immune response of dental pulp cells. *J Endod* 2014; **40**: 1382-1387 [PMID: 25146019 DOI: 10.1016/j.joen.2014.03.018]

70   **Mahanonda R**, Sa-Ard-Iam N, Montreekachon P, Pimkhaokham A, Yongvanichit K, Fukuda MM, Pichyangkul S. IL-8 and IDO expression by human gingival fibroblasts via TLRs. *J Immunol* 2007; **178**: 1151-1157 [PMID: 17202379 DOI: 10.4049/jimmunol.178.2.1151]

71   **Nisapakultorn K**, Makrudthong J, Sa-Ard-Iam N, Rerkyen P, Mahanonda R, Takikawa O. Indoleamine 2,3-dioxygenase expression and regulation in chronic periodontitis. *J Periodontol* 2009; **80**: 114-121 [PMID: 19228097 DOI: 10.1902/jop.2009.080315]

72   **Issaranggun Na Ayuthaya B**, Satravaha P, Pavasant P. Interleukin-12 modulates the immunomodulatory properties of human periodontal ligament cells. *J Periodontal Res* 2017; **52**: 546-555 [PMID: 27663623 DOI: 10.1111/jre.12421]

73   **Zhang J**, Wang CM, Zhang P, Wang X, Chen J, Yang J, Lu W, Zhou W, Yuan W, Feng Y. Expression of programmed death 1 ligand 1 on periodontal tissue cells as a possible protective feedback mechanism against periodontal tissue destruction. *Mol Med Rep* 2016; **13**: 2423-2430 [PMID: 26847035 DOI: 10.3892/mmr.2016.4824]

74   **Konermann A**, Beyer M, Deschner J, Allam JP, Novak N, Winter J, Jepsen S, Jäger A. Human periodontal ligament cells facilitate leukocyte recruitment and are influenced in their immunomodulatory function by Th17 cytokine release. *Cell Immunol* 2012; **272**: 137-143 [PMID: 22119482 DOI: 10.1016/j.cellimm.2011.10.020]

75   **Devine DA**, Marsh PD, Meade J. Modulation of host responses by oral commensal bacteria. *J Oral Microbiol* 2015; **7**: 26941 [PMID: 25661061 DOI: 10.3402/jom.v7.26941]

76   **Olsen I**, Lambris JD, Hajishengallis G. *Porphyromonas gingivalis* disturbs host-commensal homeostasis by changing complement function. *J Oral Microbiol* 2017; **9**: 1340085 [PMID: 28748042 DOI: 10.1080/20002297.2017.1340085]

77   **Mekhemar MK**, Adam-Klages S, Kabelitz D, Dörfer CE, Fawzy El-Sayed KM. TLR-induced immunomodulatory cytokine expression by human gingival stem/progenitor cells. *Cell Immunol* 2018; **326**: 60-67 [PMID: 28093098 DOI: 10.1016/j.cellimm.2017.01.007]

78   **Fawzy El-Sayed KM**, Klingebiel P, Dörfer CE. Toll-like Receptor Expression Profile of Human Dental Pulp Stem/Progenitor Cells. *J Endod* 2016; **42**: 413-417 [PMID: 26769027 DOI: 10.1016/j.joen.2015.11.014]

79   **Chatzivasileiou K**, Lux CA, Steinhoff G, Lang H. Dental follicle progenitor cells responses to Porphyromonas gingivalis LPS. *J Cell Mol Med* 2013; **17**: 766-773 [PMID: 23560719 DOI: 10.1111/jcmm.12058]

80   **Delarosa O**, Dalemans W, Lombardo E. Toll-like receptors as modulators of mesenchymal stem cells. *Front Immunol* 2012; **3**: 182 [PMID: 22783256 DOI: 10.3389/fimmu.2012.00182]

81   **Rashedi I**, Gómez-Aristizábal A, Wang XH, Viswanathan S, Keating A. TLR3 or TLR4 Activation Enhances Mesenchymal Stromal Cell-Mediated Treg Induction via Notch Signaling. *Stem Cells* 2017; **35**: 265-275 [PMID: 27571579 DOI: 10.1002/stem.2485]

82   **Liotta F**, Angeli R, Cosmi L, Filì L, Manuelli C, Frosali F, Mazzinghi B, Maggi L, Pasini A, Lisi V, Santarlasci V, Consoloni L, Angelotti ML, Romagnani P, Parronchi P, Krampera M, Maggi E, Romagnani S, Annunziato F. 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* 2008; **26**: 279-289 [PMID: 17962701 DOI: 10.1634/stemcells.2007-0454]

83   **Moon JS**, Cheong NR, Yang SY, Kim IS, Chung HJ, Jeong YW, Park JC, Kim MS, Kim SH, Ko HM. Lipopolysaccharide-induced indoleamine 2,3-dioxygenase expression in the periodontal ligament. *J Periodontal Res* 2013; **48**: 733-739 [PMID: 23488665 DOI: 10.1111/jre.12063]

84   **Biedermann A**, Kriebel K, Kreikemeyer B, Lang H. Interactions of anaerobic bacteria with dental stem cells: an in vitro study. *PLoS One* 2014; **9**: e110616 [PMID: 25369260 DOI: 10.1371/journal.pone.0110616]

85   **Bindal P**, Ramasamy TS, Kasim NHA, Gnanasegaran N, Chai WL. Immune responses of human dental pulp stem cells in lipopolysaccharide-induced microenvironment. *Cell Biol Int* 2018; **42**: 832-840 [PMID: 29363846 DOI: 10.1002/cbin.10938]

86   **Chang J**, Zhang C, Tani-Ishii N, Shi S, Wang CY. NF-kappaB activation in human dental pulp stem cells by TNF and LPS. *J Dent Res* 2005; **84**: 994-998 [PMID: 16246929 DOI: 10.1177/154405910508401105]

87   **Andrukhov O**, Andrukhova O, Özdemir B, Haririan H, Müller-Kern M, Moritz A, Rausch-Fan X. Soluble CD14 Enhances the Response of Periodontal Ligament Stem Cells to P. gingivalis Lipopolysaccharide. *PLoS One* 2016; **11**: e0160848 [PMID: 27504628 DOI: 10.1371/journal.pone.0160848]

88   **Zhang J**, Zhang Y, Lv H, Yu Q, Zhou Z, Zhu Q, Wang Z, Cooper PR, Smith AJ, Niu Z, He W. Human stem cells from the apical papilla response to bacterial lipopolysaccharide exposure and anti-inflammatory effects of nuclear factor I C. *J Endod* 2013; **39**: 1416-1422 [PMID: 24139265 DOI: 10.1016/j.joen.2013.07.018]

89   **Park JC**, Kim JM, Jung IH, Kim JC, Choi SH, Cho KS, Kim CS. Isolation and characterization of human periodontal ligament (PDL) stem cells (PDLSCs) from the inflamed PDL tissue: in vitro and in vivo evaluations. *J Clin Periodontol* 2011; **38**: 721-731 [PMID: 21449989 DOI: 10.1111/j.1600-051X.2011.01716.x]

90   **Sonoda S**, Yamaza H, Ma L, Tanaka Y, Tomoda E, Aijima R, Nonaka K, Kukita T, Shi S, Nishimura F, Yamaza T. Interferon-gamma improves impaired dentinogenic and immunosuppressive functions of irreversible pulpitis-derived human dental pulp stem cells. *Sci Rep* 2016; **6**: 19286 [PMID: 26775677 DOI: 10.1038/srep19286]

91   **Eggenhofer E**, Luk F, Dahlke MH, Hoogduijn MJ. The life and fate of mesenchymal stem cells. *Front Immunol* 2014; **5**: 148 [PMID: 24904568 DOI: 10.3389/fimmu.2014.00148]

92   **Liu Y**, Wang L, Kikuiri T, Akiyama K, Chen C, Xu X, Yang R, Chen W, Wang S, Shi S. Mesenchymal stem cell-based tissue regeneration is governed by recipient T lymphocytes via IFN-γ and TNF-α. *Nat Med* 2011; **17**: 1594-1601 [PMID: 22101767 DOI: 10.1038/nm.2542]

93   **Wang Y**, Chen X, Cao W, Shi Y. Plasticity of mesenchymal stem cells in immunomodulation: pathological and therapeutic implications. *Nat Immunol* 2014; **15**: 1009-1016 [PMID: 25329189 DOI: 10.1038/ni.3002]

94   **Hämmerle CH**, Giannobile WV; Working Group 1 of the European Workshop on Periodontology. Biology of soft tissue wound healing and regeneration--consensus report of Group 1 of the 10th European Workshop on Periodontology. *J Clin Periodontol* 2014; **41** Suppl 15: S1-S5 [PMID: 24640995 DOI: 10.1111/jcpe.12221]

95   **Morand DN**, Davideau JL, Clauss F, Jessel N, Tenenbaum H, Huck O. Cytokines during periodontal wound healing: potential application for new therapeutic approach. *Oral Dis* 2017; **23**: 300-311 [PMID: 26945691 DOI: 10.1111/odi.12469]

96   **Julier Z**, Park AJ, Briquez PS, Martino MM. Promoting tissue regeneration by modulating the immune system. *Acta Biomater* 2017; **53**: 13-28 [PMID: 28119112 DOI: 10.1016/j.actbio.2017.01.056]

97   **Wada N**, Tomokiyo A, Gronthos S, Bartold PM. Immunomodulatory Properties of PDLSC and Relevance to Periodontal Regeneration. *Curr Oral Health Rep* 2015; **2**: 245-251 [DOI: 10.1007/s40496-015-0062-y]

98   **Du J**, Shan Z, Ma P, Wang S, Fan Z. Allogeneic bone marrow mesenchymal stem cell transplantation for periodontal regeneration. *J Dent Res* 2014; **93**: 183-188 [PMID: 24226426 DOI: 10.1177/0022034513513026]

99   **Cao Y**, Liu Z, Xie Y, Hu J, Wang H, Fan Z, Zhang C, Wang J, Wu CT, Wang S. Adenovirus-mediated transfer of hepatocyte growth factor gene to human dental pulp stem cells under good manufacturing practice improves their potential for periodontal regeneration in swine. *Stem Cell Res Ther* 2015; **6**: 249 [PMID: 26670567 DOI: 10.1186/s13287-015-0244-5]

100   **Beltran SR**, Svoboda KK, Kerns DG, Sheth A, Prockop DJ. Anti-inflammatory protein tumor necrosis factor-α-stimulated protein 6 (TSG-6) promotes early gingival wound healing: an in vivo study. *J Periodontol* 2015; **86**: 62-71 [PMID: 25269522 DOI: 10.1902/jop.2014.140187]

101   **Takeshita K**, Motoike S, Kajiya M, Komatsu N, Takewaki M, Ouhara K, Iwata T, Takeda K, Mizuno N, Fujita T, Kurihara H. Xenotransplantation of interferon-gamma-pretreated clumps of a human mesenchymal stem cell/extracellular matrix complex induces mouse calvarial bone regeneration. *Stem Cell Res Ther* 2017; **8**: 101 [PMID: 28446226 DOI: 10.1186/s13287-017-0550-1]

102   **Croitoru-Lamoury J**, Lamoury FM, Caristo M, Suzuki K, Walker D, Takikawa O, Taylor R, Brew BJ. Interferon-γ regulates the proliferation and differentiation of mesenchymal stem cells via activation of indoleamine 2,3 dioxygenase (IDO). *PLoS One* 2011; **6**: e14698 [PMID: 21359206 DOI: 10.1371/journal.pone.0014698]

103   **Lee RH**, Yu JM, Foskett AM, Peltier G, Reneau JC, Bazhanov N, Oh JY, Prockop DJ. TSG-6 as a biomarker to predict efficacy of human mesenchymal stem/progenitor cells (hMSCs) in modulating sterile inflammation in vivo. *Proc Natl Acad Sci U S A* 2014; **111**: 16766-16771 [PMID: 25385603 DOI: 10.1073/pnas.1416121111]

104   **Qi Y**, Jiang D, Sindrilaru A, Stegemann A, Schatz S, Treiber N, Rojewski M, Schrezenmeier H, Vander Beken S, Wlaschek M, Böhm M, Seitz A, Scholz N, Dürselen L, Brinckmann J, Ignatius A, Scharffetter-Kochanek K. TSG-6 released from intradermally injected mesenchymal stem cells accelerates wound healing and reduces tissue fibrosis in murine full-thickness skin wounds. *J Invest Dermatol* 2014; **134**: 526-537 [PMID: 23921952 DOI: 10.1038/jid.2013.328]

105   **Ng F**, Boucher S, Koh S, Sastry KS, Chase L, Lakshmipathy U, Choong C, Yang Z, Vemuri MC, Rao MS, Tanavde V. PDGF, TGF-beta, and FGF signaling is important for differentiation and growth of mesenchymal stem cells (MSCs): transcriptional profiling can identify markers and signaling pathways important in differentiation of MSCs into adipogenic, chondrogenic, and osteogenic lineages. *Blood* 2008; **112**: 295-307 [PMID: 18332228 DOI: 10.1182/blood-2007-07-103697]

106   **Zhang J**, Li ZG, Si YM, Chen B, Meng J. The difference on the osteogenic differentiation between periodontal ligament stem cells and bone marrow mesenchymal stem cells under inflammatory microenviroments. *Differentiation* 2014; **88**: 97-105 [PMID: 25498523 DOI: 10.1016/j.diff.2014.10.001]

107   **James AW**, LaChaud G, Shen J, Asatrian G, Nguyen V, Zhang X, Ting K, Soo C. A Review of the Clinical Side Effects of Bone Morphogenetic Protein-2. *Tissue Eng Part B Rev* 2016; **22**: 284-297 [PMID: 26857241 DOI: 10.1089/ten.TEB.2015.0357]

108   **Um S**, Kim HY, Lee JH, Song IS, Seo BM. TSG-6 secreted by mesenchymal stem cells suppresses immune reactions influenced by BMP-2 through p38 and MEK mitogen-activated protein kinase pathway. *Cell Tissue Res* 2017; **368**: 551-561 [PMID: 28247086 DOI: 10.1007/s00441-017-2581-4]

109   **Mestas J**, Hughes CC. Of mice and not men: differences between mouse and human immunology. *J Immunol* 2004; **172**: 2731-2738 [PMID: 14978070 DOI: 10.4049/jimmunol.172.5.2731]