Chapter 2

Immunomodulatory Properties of Dental-Derived Mesenchymal Stem Cells

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Abstract

Mesenchymal stem cells are considered as an attractive tool for tissue regeneration. Almost all dental tissues contain a population of MSC-like cells, which were extensively studied within the last few years. Besides their ability to differentiate into different cell types, dental MSCs also possess strong immunomodulatory properties. Dental MSCs modulate both innate and adaptive immune response and influence the activity of almost all components of the immune system. The interaction between dental MSCs and the immune system is reciprocal because immunomodulatory activity of MSCs is strongly regulated by cytokines produced by immune cells. MSCs isolated from inflamed tissues might exhibit impaired immunomodulatory capacity, suggesting a potential role of these cells in inflammatory diseases and particularly periodontitis. Recent studies suggest that immunomodulatory properties of MSCs can also play an important role in their tissue regenerative capacity. The therapeutic effects of MSCs, including their immunomodulatory capacity, are largely explained by their tropic activity, including production of immunomodulatory proteins and growth factors. Summarizing, dental MSCs play an important role in tissue homeostasis under healthy and diseased conditions.

Keywords: mesenchymal stem cells, immune response, immunomodulation, T cells, dendritic cells, natural killer cells, B cells, macrophages, polymorphonuclear neutrophils

1. Introduction

Mesenchymal stem cells (MSC) are defined as cells that fulfill at least three criteria: adherence to culture plastic under standard cell culture condition; surface expression of mesenchymal

markers CD73, CD90 and CD105 as well as lacking expression of hematopoietic markers CD11b, CD14, CD34, CD45 and HLA-DR; ability to differentiate into osteoblasts, adipocytes and chondrocytes *in vitro* [1]. Originally, MSCs were isolated from bone marrow, but later MSC-like cells were found in different postnatal tissues [2]. MSC-like cells were isolated from numerous dental tissues: dental pulp stem cells (DPSCs) [3]; stem cells of human exfoliated deciduous teeth (SHED) [4]; periodontal ligament stem cells (PDLSCs) [5]; stem cells from apical papilla (SCAP) [6]; dental follicle stem cells (DFSCs) [7]; gingival mesenchymal stem cells (GMSCs) [8] and bone marrow MSCs from orofacial bones [9]. One peculiarity of most dental tissue-derived MSCs is that these cells express several neural lineage markers, which can be explained by their neural crest origin [10, 11].

MSCs in dental tissues reside in perivascular niches, where they are maintained in quiescent nondifferentiated state by specific microenvironment [12]. Upon tissue injury, these cells are recruited to the damaged area and participate in wound healing by proliferation and differentiation into tissue-specific cells [13]. Another important function of MSCs is modulation of immune and inflammatory response. Perivascular localization of MSCs is an essential factor, which enables their interaction with a wide range of cells during the process of their recruiting *in vivo*, as well as transvascular migration and modulation of the functional acticity of these cells. Furthermore, inflammation is characterized by chemotaxis of MSCs to inflamed area where they can perform their immunomodulatory function.

Although the exact mechanisms underlying immunomodulatory properties of MSCs are not fully understood, it is known that they depend on expression of enzymes, production of soluble factors and cell-to-cell contact. The most important factor involved in MSC-mediated immunosuppression is indolamine-2,3-dioxygenase (IDO). This intracellular enzyme catalyzes the catabolism of tryptophan into kynurenine. The resulted tryptophan depletion leads to suppression of different immune cells [14]. The expression of IDO is very low in resting MSCs and is drastically upregulated by interferon (IFN)-γ [15, 16]. The most important soluble factors mediating immunomodulatory effects of MSCs are prostaglandin E2 (PGE-2), transforming growth factor (TGF)-β, and interleukin (IL)-10. PGE-2 is a metabolic product of arachidonic acid cascade, which production is controlled by cyclooxygenase 2, and is involved in regulation of both innate and adaptive immune system by MSCs [17]. Potent immunomodulatory cytokine TGF-β is continuously produced by MSCs, and its production can be enhanced by other anti-inflammatory factors such as IL-4 and IL-13 [18]. IL-10 is an anti-inflammatory cytokine, which can be produced either by MSCs themselves or by MSC-instructed immune cells [19]. Further soluble factors are also reported to be involved in MSC-mediated immunomodulation: human leukocyte antigen (HLA)-G5, galectins, hepatocyte growth factor, tumor necrosis factor α-stimulated gene 6 [20]. Direct cell-to-cell contact mediates immunosuppression effect of MSCs at least partially. This mechanism acts mainly through programmed death ligand 1 (PD-L1), which expression is upregulated by IFN-γ [21]. The membrane-bound HLA-G1 is another factor involved in direct interaction between MSCs and immune cells [21]. Summarizing, the mechanisms involved in MSC-mediated immunosuppression are complicated; they are specific for individual cell types and are largely determined by degree of inflammation and microenvironment (**Figure 1**).

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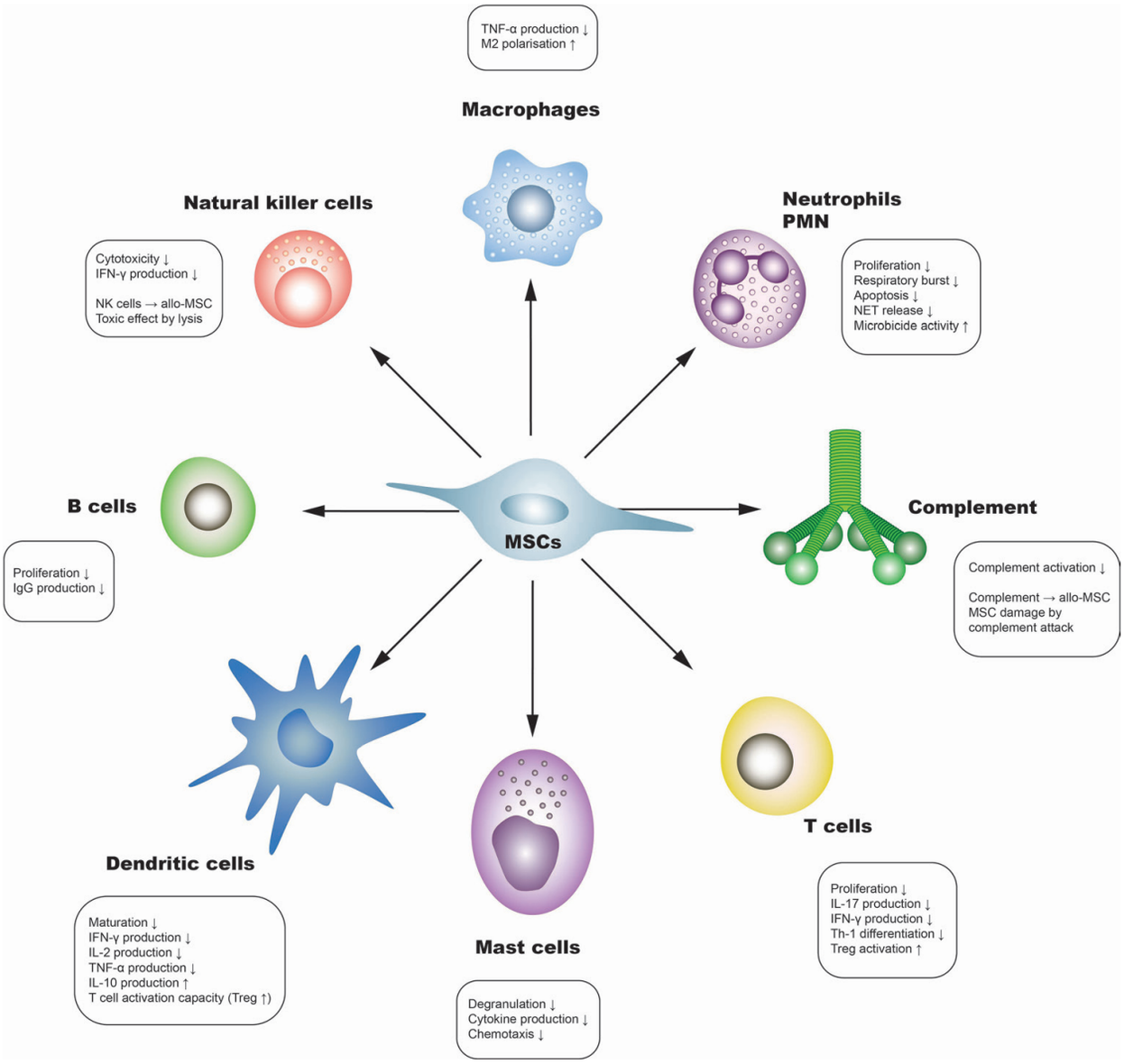

Figure 1. Immunomodulatory effects of MSCs on different components of innate and adaptive immunity.

2. Immunomodulatory effect of MSCs on different components of immune system and their role in dental tissues

2.1. T cells

T cells are one of the most important effector cells of the adaptive immune system, involved in the cell-mediated immune response. Antigen-specific activation of T cells via specialized antigen-presenting cells (APC) leads to clonal selection and differentiation of antigen-specific naïve T cells into different effector subtypes. Depending on which major histocompatibility complex (MHC) the antigen is presented, two different T cell subtypes evolve: CD4+ T-helper cell (MHC class II) with its different phenotypes (Th1/Th2/Th17/Treg) or CD8+ cytotoxic T cell

(MHC class I). The subtypes/phenotypes differ in their surface marker expression, their cytokine secretion profiles and their functions. CD8+ cytotoxic T cells are involved in destruction of virus-infected and tumor cells. Th1 cells are involved in eliminating pathogens, residing in vesicular compartments, whereas Th2 cells participate in B lymphocyte activation, leading to antibody producing plasma cells. In addition, Th17 cells detect extracellular pathogens, recruiting neutrophil granulocytes. Regulatory T cells exhibit a suppressive function, involved in the self-tolerance process and in diminishing inflammatory processes [22].

Although there are a lot of studies investigating the multiple roles of T lymphocytes in periodontitis, the function of T cells in the pathogenesis of periodontitis is still to be clarified [23]. Both Th1 and Th2 cells are detected concurrently in inflamed periodontal tissue [24] and seem to be directly involved in alveolar bone destruction, mainly by producing RANKL [25]. Recently discovered, Th17 cells play an essential role in periodontitis and are one of the primary sources of RANKL [23, 26]. Regulatory T cell-produced IL-10 inhibits RANKL expression of T cells [27]. Periodontitis is shown to be associated with both increased and decreased number of Treg cells [27, 28].

Among all immune cells, the effect of MSCs on T cells is studied at most [29]. It is already known that MSCs influence the activation, proliferation and differentiation of T cells, modulating T cell-mediated immune response [30]. MSCs are potent suppressors of T cell proliferation, including CD4+ T-helper and CD8+ cytotoxic T cells [29, 31]. This suppressive effect of MSCs is enhanced by priming with IFN-γ and TNF-α is mediated by IDO, PGE-2, HLA-G5 [32–34] as well as by cell-to-cell contact through PD-L1 and HLA-G1 [35, 36]. In addition, MSCs suppress proliferation of naïve but not maturated CD8+ T cells [37]. Furthermore, MSCs modulate CD4+ T-helper cell differentiation, their cytokine production and the balance between different CD4+ T-helper subtypes [38, 39]. The effect of MSCs on T cell polarization might depend on their activation state [40]. Interestingly, nonprimed MSCs stimulate proliferation of nonactivated T cells, but retain their ability to promote Treg formation [41].

MSCs from different dental tissues also show the ability to modulate T lymphocytes. T cell proliferation is inhibited by different IFN-γ primed dental MSCs, particularly DPSCs, PDLSCs, GMSC, and SCAP [8, 42–44]. DPSCs can also induce T cell apoptosis [45]. The inhibitory effect of dental MSCs on T cell proliferation is mediated mainly by IDO, hepatocyte growth factor (HGF), and TGF-β [29, 46]. Furthermore, DPSCs, PDLSCs, and SHED inhibit IL-17 production by T cells and stimulate formation of Treg cells, which might dampen periodontal inflammation [42, 44, 47]. Interestingly, immunomodulatory properties of PDLSCs on T cells are impaired under inflammatory conditions. PDLSCs isolated from inflamed tissue exhibit lower inhibitory effect on T cell proliferation, Th17 differentiation, and IL-17 production as well as induce lower number of regulatory Treg cells and IL-10 production [44]. Moreover, PDLSCs from inflamed tissue also inhibit IFN-γ production by T cells and Th1 cell differentiation, whereas PDLSCs from healthy tissue have no effect on these parameters [44].

2.2. Dendritic cells

Dendritic cells constitute a critical interface between innate and adaptive immune response and are responsible for initiating antigen-specific immune response [48]. The major function of

classical dendritic cells is detection of invading pathogens and their presentation to the adaptive immune system, which results in initiation of long-lasting antigen-specific response. Besides antigen detection and presentation to T cells, classical DCs also produce pro-inflammatory cytokines, which plays a crucial role in T cell differentiation into different subsets. Classical DCs (cDCs) derive from bone marrow precursors and can be found in lymphoid tissue, bone marrow, and most nonlymphoid tissues. In the absence of pathogens, cDCs are immune tolerogenic and induce expansion of Treg [49]. Activation of cDCs by pattern recognition receptors induces their maturation, migration to lymph node and priming of T cells. Besides cDCs, there are several nonclassical DCs subsets: monocyte-derived DCs, plasmacytoid DCs and Langerhans cells [50].

In recent years, an importance of dendritic cells in both maintaining of periodontal health and progression of periodontal disease was recognized [51]. Under healthy conditions, immature DCs of periodontal tissue promote production of Treg cells and thus are involved in induction of immune tolerogenic state. Langerhans cells, which are present in sulcular and junctional epithelium, are also involved in maintenance of periodontal health homeostasis via induction of Treg cells [51]. Upon exposure to periodontal pathogens, DCs can contribute to different types of adaptive immune response. Activation of Th1, Th2, or Th17 response by DCs might be both beneficial and destructive for the host [52]. The activation and maturation of dendritic cells is influenced by periodontal pathogen *Porphyromonas gingivalis* [53], which is thought to lead to subversion of local immunity and alteration of host immune homeostasis.

The functional activity of dendritic cells is substantially affected by MSCs. Bone marrow MSCs inhibit differentiation of DCs from their precursors. This concerns both classical DCs and monocyte-derived DCs [54–56]. Furthermore, DCs differentiated in the presence of bone marrow MSCs exhibit impaired maturation upon stimulation with pattern recognition receptors and/or inflammatory cytokines [54, 57, 58]. Interestingly, no impaired maturation is observed when DCs are differentiated in the presence of MSCs isolated from inflamed tissue." ocktail [59]. In contrast to DCs differentiation, the effect of MSCs on the maturation of differentiated DCs is less obvious. On the one hand, some studies show that MSCs inhibit maturation of differentiated DCs [60, 61]. On the other hand, some studies show that MSCs have no effect on maturation of differentiated DCs [54] or even can potentiate this process [62, 63]. The process of DCs maturation is also stimulated by MSCs originating from inflamed tissue [59]. The effect of MSCs on DCs is often associated with production of IL-6 and PGE-2, which are known to inhibit DCs differentiation [64, 65] and stimulate their maturation [66]. Another important factor for interaction between MSCs and DCs is TNF-stimulated gene 6 protein (TSG-6), which is produced by MSCs and might inhibit DCs maturation [67].

MSCs derived from different dental tissues also exhibit an ability to modulate the function of DCs. Periodontal ligament STRO1+ CD146+ stem cells inhibit expression of nonclassical major histocompatibility complex-like glycoprotein CD1b, which results in inhibition of DC-mediated T cell proliferation [68]. Gingiva-derived MSCs are shown to inhibit maturation and activation of DCs resulting in attenuation of the inflammatory response, associated with PGE-2-dependent mechanisms [69]. MSCs derived from SHED are shown to influence differentiation, maturation, and T cell activation ability of monocyte-derived DCs [70]. Particularly, after exposure to SHED-derived MSC, DCs induce higher proportion of Treg cells, exhibit

decreased production of pro-inflammatory cytokines IL-2, TNF-α, and IFN-γ and produce increased levels of anti-inflammatory IL-10 protein [70].

2.3. Natural killer cells

Natural killer cells (NK cells) are originally thought to be a component of innate immune system, but studies of last few years show that these cells have attributes of both innate and adaptive immune system [71]. NK cells can directly induce the death of tumor and virus-infected cells. Additionally, NK cells are considered as a major source of IFN-γ and also produce other cytokines. This makes them important players of immune system, regulating the function of other immune cells like DCs, macrophages, neutrophils, T cells and B cells [72–76]. Two major populations of NK cells are present in peripheral blood. Predominant population of NK cells is $CD56^{dim}CD16^{+}$ and exhibits moderate expression of CD56. Approximately 5% of all NK cells show $CD56^{bright}CD16^{-}$ phenotype and exhibit high expression of CD56 [77].

Although NK cells play an important role in both innate and adaptive immune response, their role in periodontal disease remains obscure [78]. Chronic periodontitis is associated with an increased number of NK cells in human gingiva [79, 80]. NK cells are considered as one of the major sources of IFN-γ [81], which can be associated with increased tissue destruction and periodontal disease severity [82, 83]. Besides, NK cells can directly interact with some periodontal pathogens. Interaction between *P. gingivalis* and NK cells leads to enhanced IFN-γ production and is involved in production of *P. gingivalis* specific IgG2 [84]. Another periodontal pathogen *A. actinomycetemcomitans* promotes IFN-γ production by NK cells either directly or mediated by DCs [85]. Direct recognition of *Fusobacterium nucleatum* by NK cells through their receptor NKp46 contributes to increased tissue destruction in experimental periodontitis [86].

NK cells and MSCs interact in a complex reciprocal manner. Cultured MSCs are recognized and lysed by NK cells that are activated by IL-2 or IL-15, which could be explained by low MHC class I expression on MSCs' surface. Interestingly, priming of MSCs by IFN-γ induces upregulation of MHC class I expression and prevents them from being killed by activated NK cells. The susceptibility of MSCs for NK cells mediated killing is also regulated by toll lile receptor (TLR) activation [87]. MSCs primed with TLR-3 are protected from being killed by activated NK cells, whereas priming with TLR-4 and TLR-7/-8 has no significant effect on MSCs susceptibility to NK cell mediated lysis [88]. In turn, MSCs also influence activity of NK cells. Particularly, MSCs suppress cytokine production and cytotoxicity of freshly isolated NK cells but not those of activated NK cells [37, 89, 90]. The effect of MSCs on NK cells is largely mediated by IDO and PGE-2 [89].

Information about interaction of dental MSCs and NK cells is rather limited. Similarly to bone marrow MSCs, dental pulp stem cells are susceptible to lysis by activated NK cells [91]. NK cells exert the strongest cytotoxic effect on undifferentiated DPSCs, whereas differentiated cells are less susceptible to lysis [92]. DPSCs could be protected from NK cell mediated cytotoxicity by co-culture with monocytes [92] or by overexpression of hypoxia-inducible factor 1 [93].

2.4. B cells

B cells are an indispensable component of the adaptive immune response, which is mainly involved in antibody production. B cells develop from hematopoietic progenitor cells in the fetal liver and in the bone marrow postnatal [94]. After exiting bone marrow, immature B cells migrate to secondary lymph organs like the spleen or lymph nodes, where they may encounter antigens through interaction with antigen-presenting cells like dendritic cells and macrophages. After interaction with antigen, B cells differentiate into short-lived antibody-producing plasma cells. Alternatively, B cells may enter a germinal center, where they undergo clonal expansion, class switch recombination and somatic hypermutation resulting in differentiation into high affinity antibody-producing plasma cells and memory B cells [95]. Recent studies revealed that beside antibody production, B cells are also involved in the processes of antigen presentation and cytokine production [96–98].

B cells and plasma cells are the major leukocytes in periodontal lesions and represent 18% and 50% of all infiltrating cells, respectively [99]. Despite this fact, the role of B cells in periodontitis is not characterized sufficiently. B cells comprise several functionally different subsets and their distribution is altered in patients with severe periodontitis [100]. The major function of B cells is producing specific antibodies against periodontal pathogens, which is an important step of bacteria elimination [101]. However, B cells are also considered as major source of deleterious effects of immune response. Particularly, B cells are known to be one of the major sources of RANKL, which plays a central role in bone resorption by osteoclasts [102]. Mice with B cells immunoglobulin D deficiency exhibit lower alveolar bone loss upon oral infection, suggesting an important role of B cells in tissue destruction [103]. Some B cells subsets are also involved in the autoimmune response in periodontitis [99].

The information about the effect of MSCs on B cells is rather controversial: it seems that this effect depends on several factors like B cells maturation state, stimuli used for B cells proliferation and differentiation and ratio between MSCs and B cells. Thus, MSCs inhibit B cell proliferation at MSC:B cell ratio 1:1 to 1:2 [104], but stimulate B cell proliferation at ratio 1:5 to 1:10 [104]. Interestingly, under highly proliferative conditions, MSCs inhibit B cell proliferation even at low MSC:B cells ratio [104]. MSCs stimulate proliferation of naïve and memory B cells [105]. MSCs enhance IgG production by B cells upon stimulation with lipopolysaccharide or cytomegalovirus [106], but inhibit production of IgG, IgA and IgM in mixed lymphocyte culture [107]. Pre-exposure of MSCs to IFN-γ enhances their inhibitory effect on B cell proliferation and IgG production [108, 109] but eliminate their ability to induce regulatory B cells [109]. The inhibitory effect of MSCs on B cells largely depends on cell-to-cell contact, in which interaction between programmed death-1 (PD-1) and its ligand PD-1 L takes place [108, 110].

The information about the effect of dental MSCs on functional activity of B cells is rather limited. The only one report shows that PDLSCs influence B cells both *in vitro* and *in vivo* [111]. Particularly, PDLSCs inhibit proliferation, differentiation and chemotaxis of B cells *in vitro* as well as fail to activate humoral immunity *in vivo* in miniature pig models [111]. This inhibitory effect of PDLSCs on B cells is achieved by interaction of PD-1 and its ligand PD-1 L [111].

2.5. Macrophages

Macrophages are phagocytic tissue resident cells of the innate immune system, which are generated from peripheral blood monocytes. Macrophages are found almost in all tissues and their differentiation is determined by specific tissue environments in physiological or inflammatory conditions [112]. The major function of macrophages is the elimination of pathogens by phagocytosis and antigen presentation to cells of the adaptive immune system [113]. In addition to pathogen elimination, macrophages are involved in regulation of immune response, inflammation resolution and immune suppression [114]. Besides their role in immunity, macrophages also play a central role in the clearance of apoptotic cells and damaged tissue [115]. In the early 1990s, a concept for classically activated pro-inflammatory M1 macrophages and alternatively activated anti-inflammatory M2 macrophages emerged. Nowadays, the M1-M2 concept of macrophages activation is extensively revisited since it became obvious that macrophages exhibit extremely high plasticity [116]. Upon activation, macrophages adapt an intermediate state which exhibits some features of both M1 and M2 types, which are considered as extreme states. The activation state of macrophages is driven by the environment and thereby, macrophages are thought to provide an optimal progression of the immune response.

Macrophages activation and polarization to M1-like or M2-like phenotypes play an essential role in the progression of periodontal disease. Upon infection, macrophages are polarized into M1-like phenotype, promote inflammatory response and are correlated with bone resorption [117]. These macrophages produce high amount of cytokines such as IL-1, TNF-α, IL-6, MMP-9, which are associated with periodontal tissue destruction. Moreover, M1 macrophages produce high amount of IL-12 and IL-23. These cytokines stimulate differentiation and proliferation of Th17 cells, which promote further tissue destruction [118]. In case of successful pathogen elimination, a switch into M2-like phenotype occurs. These macrophages play a crucial role in the clearance of apoptotic cells and damaged tissue as well as in wound healing promotion. The increased level of IL-10, which is produced by M2 macrophages, is associated with decreased severity of periodontitis. The ratio between M1 and M2 macrophages is increased in periodontal disease compared to the healthy state and gingivitis [119, 120]. Moreover, the enhanced levels of M1 macrophages correlate with the pocket depth and the levels of tissue destructive cytokines IL-1β and MMP-9 [120].

MSCs modulate the polarization of macrophages. Co-culture of macrophages with MSCs induces their polarization towards regulatory M2 phenotype and is characterized by decreased production of pro-inflammatory TNF-α and IL-12, increased production of IL-10, increased expression of M2 marker CD206 and enhanced phagocytic activity [121, 122]. The polarization of macrophages into M2 phenotype by MSCs is mediated mainly by PGE-2 and IDO [122, 123]. However, the contribution of direct cell-to-cell contact to MSC-mediated macrophage polarization cannot be excluded as well [124]. Induction of macrophages regulatory phenotype is also observed upon systemic or local MSCs administration [122, 125]. Macrophages co-cultured with MSCs are described as a novel type and called MSC-educated macrophages [121]. These macrophages are currently considered for potential clinical application in the treatment of myocardial infarction, graft rejection, diabetes mellitus, ischemic disease and so on [126].

Macrophages polarization is also influenced by different dental MSCs. Human gingiva-derived MSCs induce macrophages polarization into M2 phenotype, which can be associated with an acceleration of wound healing [127]. Human DPSCs isolated from both healthy and inflamed tissue markedly suppress LPS-induced TNF-α production by macrophages through IDO-dependent mechanism [128]. Transplantation of DPSCs into the unilateral hindlimb skeletal muscle suppresses inflammation of sciatic nerves by promoting macrophages M2 polarization [129]. Conditioned medium of periodontal ligament stem cells enhances periodontal regeneration, which was accompanied by alteration of macrophages activity [130]. Recently, SCAP is shown to attenuate neuro-inflammation, which was accompanied by regulation of macrophages activity [131].

2.6. Polymorphonuclear neutrophils

Polymorphonuclear neutrophils are the major fraction of leukocytes circulating in blood (50–70%) and form the first line of host defense against pathogens [132]. Under physiological conditions, up to 2×10^{11} neutrophils are generated from myeloid precursors in the bone marrow daily. To fulfill their key role in the innate immune response, neutrophils must be recruited from bloodstream to the sites of inflammation. Transendothelial migration of neutrophils is a complex process initiated upon activation of tissue-resident leukocytes by invading pathogens [133]. Neutrophils are rather short-lived cells and their lifespan in peripheral blood is thought to be up to 7 h and might be prolonged under inflammatory conditions [134]. Upon tissue migration, the lifespan of neutrophils might be extended up to 2 days [135]. Neutrophils possess several pathogen elimination mechanisms. First, pathogens can be phagocytized and exposed to reactive oxygen species or antibacterial proteins released from the neutrophils granules [136]. Another possibility is the elimination of pathogens via neutrophil extracellular traps (NETs), which consist mainly of DNA and are capable of direct degradation and elimination of bacteria [137]. Recently, a regulatory role of neutrophils in inflammatory response and inflammation resolution has been emerged [138].

Neutrophils play an important role in the homeostasis of periodontal tissue in both healthy and diseased conditions [139]. Neutrophils comprise more than 95% of all leukocytes recruited into the gingival sulcus by dental biofilm [140] and prevent potential bacterial invasion into gingival tissue under healthy conditions. Nevertheless, they are not sufficiently effective in control of dysbiotic microbiota [141]. In addition, keystone pathogen *P. gingivalis* can subvert neutrophil-mediated immunity and promote the conversion of symbiotic microbiota to dysbiotic one [142]. Congenital disorders associated with either neutrophil deficiency or impairment of their life cycle are characterized by the development of aggressive forms of periodontal disease [143]. The maintenance of periodontal health is critically dependent on number and distribution of neutrophils: both insufficient and unrestrained neutrophils recruitment is associated with periodontal inflammation [142].

The knowledge about the interaction of MSCs and neutrophils is rather limited. So far, MSCs were found to exhibit some modulating effects on polymorphonuclear neutrophils. Both resting and TLR-3 primed MSCs have been shown to exert antiapoptotic effects on neutrophils mediated by IL-6, IFN-β and granulocyte macrophage colony-stimulating factor (GM-CSF) [144].

These antiapoptotic effects have also been observed at very low MSC:neutrophil ratio of up to 1:500 in naïve and IL-8 activated neutrophils [145]. Additionally, MSCs dampened the N-formyl-l-methionin-l-leucyl-l-phenylalanine (f-MLP)-induced respiratory burst [145]. Furthermore, MSCs augment antibacterial activity of neutrophils [146]. Human MSCs from amniotic membrane inhibit NET release by neutrophils through a TSG-6 dependent mechanism [147]. The efficacy of MSCs to suppress neutrophils recruitment might also partially depend on MSCs' origin [148].

MSCs of dental origin were also shown to influence neutrophils' functional properties. Particularly, PDLSCs significantly reduce neutrophil apoptosis and enhance their antimicrobial function [149]. PDLSCs exhibit antiapoptotic and proliferation promoting effects on IL-8 activated neutrophils through IL-6 production [150]. The effect of PDLSCs on neutrophils seems to be independent on cell-to-cell contact. Human DFSCs infected with periodontal pathogens *P. intermedia* or *T. forsythia* reduce neutrophil chemotaxis, phagocytic activity and NET formation [151]. Further investigations are needed to clarify the interactions between MSCs of dental origin and polymorphonuclear neutrophils as well as their underlying mechanisms.

2.7. Mast cells

Mast cells are bone marrow-derived granule-containing immune cells, which are present in almost all tissues, including several dental tissues. Upon activation, mast cells release numerous inflammatory mediators from their granules, which are either preformed (histamine, TNF-α, cathepsin G, etc.) or synthesized de novo (interleukins, platelet activating factor, macrophage inhibitory factor 1α) [152]. Mast cells are recognized to be involved in allergic reaction and autoimmunity, but also play an important role in pathogenesis of some inflammatory diseases, particularly arthritis and multiple sclerosis [153, 154]. The functions of mast cells are phagocytosis, antigen presentation and regulation of other cells of the immune system, particularly monocytes, T cells and B cells [155]. Beside inflammatory mediators, mast cells also secrete different growth factors such as VEGF, FGF, TGF-β and PDGF [156].

The role of mast cells in periodontitis is investigated rather poorly and the existing data are sometimes controversial [157]. Two studies show that the density of mast cells is increased in patients with gingivitis and further increased in periodontitis patients suggesting a potential role of these cells in disease progression [158, 159]. In contrast, a decrease in mast cells density or even lack of these cells is reported for marginal chronic gingivitis and acute necrotizing gingivitis [160]. In human, degranulation of mast cells correlates with periodontal disease severity underlying the role of these cells in disease progression [161].

The effect of MSCs on mast cells function is investigated only by few studies. Bone marrow MSCs suppress mast cells degranulation, cytokine production and chemotaxis through production of PGE-2 by COX-2 [162, 163]. MSCs derived from human umbilical cord blood inhibit mast cells degranulation in pre-clinical model through PGE-2- and TGF-β1-dependent mechanisms [164]. The effect of dental MSCs on mast cells function is not investigated to date.

2.8. Complement

The complement system is a component of the innate immune system comprising more than 40 plasma proteins, which are primarily produced in the liver as inactive precursors [165]. The complement could be activated through three different pathways: classic, alternative and lectin pathway. All three pathways are converged at C3 complement component and lead to the generation of different effectors. Complement system components are involved in pathogen destruction, amplification of immune response through synergy with TLRs, mobilization of hematopoietic stem cells from the bone marrow and regulation of T cells subsets activation [166].

The complement system plays an important role in pathogenesis of periodontal disease [167, 168]. Component of complement system is present in the gingival crevice, and its concentration is increased in periodontitis. As the first defense line of immune system, complement system is involved in the control of oral microbiota and maintenance of host-microbial homeostasis in the oral cavity [169]. Exploitation of complement components by periodontal pathogens, particularly *P. gingivalis*, leads to dysregulation of host immune system, dysbiosis of oral microbiota and triggering destructive inflammatory processes [169, 170].

Interaction of MSCs with complement system is bilateral and not yet completely investigated. Upon intravenous injection, MSCs activate complement system, which leads to their damage by membrane attack complex [171]. However, MSCs might inhibit complement activation and associated damage by secreting factor H, which is increased by pro-inflammatory cytokines TNF-α and IFN-γ [172]. Bone marrow MSCs can also synthesize some components of complement system and thus influence some immune cells. Particularly, mycoplasma-induced production of C3 protein is shown to inhibit Ig production by B cells [173].

To date, only interaction of dental pulp cells with complement system was investigated. Upon stimulation with lipoteichoic acid, dental pulp progenitor cells produce almost all components required for activation of complement system [174]. Moreover, DPSCs express C3a- and C5a receptors, which are activated by complement system and induce cell proliferation and mobilization [174, 175].

3. Immunomodulatory effect of MSCs on different components of immune system and their role in dental tissues

Similarly to bone marrow MSCs, immunomodulatory properties of dental MSCs are not constitutive and are affected by surrounding microenvironment. Immunomodulation capacity of quiescent MSCs is usually low and can be drastically enhanced upon stimulation with inflammatory cytokines such as IFN-γ, TNF-α and IL-1β [176]. These cytokines are mainly produced by activated immune cells and thus MSCs and immune cells regulate each other reciprocally. This interaction plays an important role in tissue homeostasis as well as in the processes of inflammation and tissue repair. Upon activation with inflammatory cytokines, MSCs usually adapt an immunosuppressive phenotype and might dampen excessive inflammatory response [177]. However, under low levels of inflammation, MSCs might also stimulate immune response

and promote inflammation [177]. In dental MSCs, inflammatory cytokines usually increase the expression of immunomodulatory proteins. Activated PBMCs enhances the expression of TGF-β1, hepatocyte growth factor and IDO-1 in PDLSCs, DPSCs, and gingival MSCs [178]. IDO expression is drastically upregulated by IFN-γ in different dental MSCs [16, 178].

The immunomodulatory capacity of MSCs is also influenced by different pathogen-associated molecular patterns through activation of TLRs, but the role of MSCs priming by TLR is rather controversial to date. In some cases, priming of MSCs by TLR-3 and TLR-4 ligands enhances their immunosuppressive effect [179]. Another report shows that TLR-3 and TLR-4 activation results in abolishment of MSCs ability to suppress T cells activation [180]. These differences could be explained by the fact that activation of TLRs in MSCs induces production of both anti-inflammatory and pro-inflammatory mediators. The role of TLRs in immunomodulatory capacity of dental MSCs is currently under investigation and might be tissue specific. TLR-3 agonist augments immunosuppressive potential of DPSCs and dental follicle stem cells, whereas TLR-4 agonist augments immunosuppressive properties of dental follicle stem cells but inhibits those of DPSCs [181]. Different bacterial lipopolysaccharides induce production of proinflammatory mediators IL-6, IL-8 or MCP-1 in PDLSCs and DPSCs [16, 182–184]. TLR-2 and TLR-4 agonists fail to induce the expression of IDO-1 on protein level in PDLSC, but TLR-2 agonist enhances IFN-γ-induced IDO-1 expression [16]. In turn, LPS also enhances production of anti-inflammatory PGE-2 by PDLSCs [184]. Thus, TLR agonist might activate both proinflammatory and anti-inflammatory properties of dental MSCs and their exact role in inflammatory response is determined by other factors, like degree of inflammation and microenvironment.

Dental MSCs are located in the region which is continuously exposed to different bacterial challenges. Inflammatory milieu has a substantial effect on immunomodulatory properties of dental MSCs. PDLSCs isolated from inflamed tissue exhibit higher migratory capacityas well as impaired ability to promote Treg induction and suppress Th17 differentiation compared to cells isolated from healthy tissue [44, 185]. Similarly, DPSCs derived from teeth with pulpitis fail to suppress proliferation of PBMCs, but this ability might be restored by IFN-γ [186]. In contrast to above data, one study found no difference between DPSCs isolated from normal and inflamed tissues in their ability to modulate macrophage function [128]. To summarize, the alteration of immunomodulatory properties of dental MSCs under inflammatory conditions might play an essential role in the progression of different inflammatory disease such as pulpitis, gingivitis and periodontitis.

4. Contribution of the immunomodulatory effects of MSCs in their tissue regenerative potential

Although the regenerative potential of MSCs is largely recognized, their application for tissue regeneration in clinic is still limited. The major hurdle for clinical application of MSCs is the fact that the mechanisms of their differentiation *in vivo* are largely unknown. Preclinical studies and clinical trials with MSCs transplantation show that the rate of MSCs engraftment

is rather poor and does not correlate with the clinical outcome of MSC-based therapy. The lifetime of transplanted MSCs is rather short: for example, intravenously injected MSCs are accumulated in the lung, where they disappear within 24 h [187]. Although the exact mechanisms of MSCs differentiation *in vivo* are unknown, it is a fact that differentiation is regulated by the local microenvironment and interaction of transplanted MSCs with the hosts′ immune system is one of the key elements in this process [188]. The mechanisms underlying MSCs differentiation *in vivo* are also altered by diseased microenvironments [189]. Moreover, transplanted MSCs themselves contribute to the creation of the microenvironment through their immunomodulatory function and the production of different growth factors, which in turn promote activation of endogenous tissue repair mechanisms [190]. Immunomodulatory and tropic capacity of MSCs are now considered as the major mechanisms of their therapeutic effect *in vivo*. This statement is supported by the observations that the secretome of MSCs exert similar tissue regenerative effects as transplanted MSCs [191]. Furthermore, the secretome of MSCs possess also strong immunomodulatory effects [20, 192].

It is rather difficult to discriminate between the role of regenerative potential and immunomodulatory abilities in the output of MSC-based therapies. Tissue regeneration is a complex process, which consists of several timely overlapping phases and involves interaction between different cell types. The immune system plays an important role in the processes of tissue repair and regeneration. Different immune cells are involved in the different stages of tissue regeneration processes [193]. Neutrophils and macrophages are the major cells involved in the inflammatory phase and are responsible for bacteria phagocytosis and removal of tissue debris. Regenerative M2 macrophages and regulatory T cells secrete anti-inflammatory cytokines, which create microenvironments promoting tissue repair. Therefore, the modulation of the immune response by MSCs might be an important mechanism underlying their regenerative potential. Regenerative potential of MSCs and their immunomodulatory properties are tightly interconnected. Many factors mediating immunomodulatory effects of MSCs are also influencing their differentiation potential. Particularly, activation of IDO by IFN-γ alters osteogenic, adipogenic and neural differentiation of human MSCs [194]. TSG-6, another immunomodulatory factor produced by MSCs, plays a crucial role in their differentiation ability [195, 196]. TGF-β produced by MSCs is potentially involved in both regenerative and immunomodulatory function of these cells [197].

Immunomodulatory properties of dental MSCs also seem to play an important role in the regeneration of dental tissues [198]. The major information about the potential role of immunomodulatory properties in therapeutic efficacy of dental MSCs arise from animal studies. Most studies suggest that allogenic transplantation of dental MSCs is well tolerated by recipients' immune system and does not induce any immune rejection [199]. Systemic transplantation of SHED cells ameliorates ovariectomy-induced osteopenia presumably through induction of Treg cells and reducing Th1 and Th17 cells number [200]. Transplantation of allogenic bone marrow MSCs into periodontal defects suppressed local levels of pro-inflammatory cytokines IL-1β, TNF-α and IFN-γ, which indicates their immunomodulatory function *in vivo* [201]. An *in vitro* study shows that the differentiation potential of PDLSCs is influenced by inflammatory microenvironments and is largely determined by their immunomodulatory properties [202].

5. Conclusions

Dental MSCs, similarly to MSCs from other tissues, influence the properties of both the innate and the adaptive immune system. Particularly, dental MSCs change the functional activities of all components of the immune system: T cells, dendritic cells, natural killer cells, B cells, macrophages, neutrophils, mast cells and complement system. The effects of MSCs are mostly immunosuppressive, but in some cases, MSCs might also enhance the immune response. The immunomodulatory mechanisms of MSCs include both production of soluble mediators and cell-to-cell contact. The interaction between MSCs and the immune system is reciprocal: immunomodulatory ability of resting MSCs is rather low and is substantially enhanced by proinflammatory cytokines IFN-γ, TNF-α and IL-1β. This circumstance suggests a tight interaction between MSCs and the immune system, which plays an important role in the maintenance of local tissue homeostasis.

In some cases, dental MSCs isolated from inflamed tissues exhibit impaired immunomodulatory capacity. Furthermore, immunomodulatory properties of dental MSCs might also be influenced through activation of their TLRs by different pathogen-associated bacterial patterns. These observations suggest that dental MSCs might also play an important role in the pathogenesis of different inflammatory diseases and particularly periodontitis.

Although dental MSCs exhibit significant differentiation capacity *in vitro*, the mechanisms underlying their regenerative potential *in vivo* are still unclear. Since the immune system plays one of the key roles in tissue repair processes, immunomodulatory capacity of dental MSCs could be considered as one of the major mechanisms of their effects *in vivo*.

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Conflict of interest

All authors declare no conflict of interest.

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