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Research Progress on the Immunomodulatory Effect of Mesenchymal Stem Cells on Chronic Periodontitis

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Abstract

Periodontal disease is an inflammatory and destructive disease of periodontal support tissue caused by microorganisms in dental plaque. During the development of periodontal disease, host immune regulation plays an important role, and unnecessary excessive immune regulation often exacerbates the course of chronic periodontal disease. Mesenchymal stem cells (MSCs) are adult stem cells with self replication ability and multi-directional differentiation potential. Many studies have found that MSCs have strong immunosuppressive effects on both adaptive and innate immunity. In recent years, literature has reported that MSCs are involved in the immune regulatory effect of chronic periodontal disease, inhibiting its inflammatory response and alveolar bone resorption, but the specific regulatory mechanism has not been elucidated. This article reviews the current research status of the immune regulatory effects of MSCs on chronic periodontitis.

Keywords

Mesenchymal Stem Cells, Chronic Periodontal Disease, Inflammatory Response, Bone Resorption, Immune Regulation

1. Introduction

Chronic periodontal disease is an inflammatory osteolytic disease caused by the interaction between periodontal pathogens and host immune responses. In the pathogenesis of periodontal disease, the difficulty of immune cells recognizing "self" and "non self", as well as the large amount of pro-inflammatory factors produced, are the main reasons for the inflammatory response and sustained al-

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veolar bone resorption in periodontal disease. This response is considered by scholars to be excessive immunity. MSCs can secrete rich bioactive molecules, such as growth factors and chemokines, and regulate the microenvironment of the injured site through paracrine effects, thereby inhibiting apoptosis and inflammation, promoting angiogenesis, and ultimately promoting tissue repair. Studies have found that the immunomodulatory and anti-inflammatory effects of odontogenic mesenchymal stem cells can help reduce reactive oxygen species in periodontal tissues of patients with periodontitis, thus alleviating periodontitis symptoms MSCs have low immunogenicity and have immunomodulatory effects in both innate and adaptive immune systems [1]. However, the regulatory mechanism of MSCs in chronic periodontitis is still unclear, and its detailed mechanism is still under further research. The current research status of the immune regulatory effect of MSCs on chronic periodontitis is summarized as follows.

2. Understanding the Immune Response in Chronic Periodontal Disease

Subgingival plaque is the initiating factor of periodontal disease, and unnecessary excessive immune response from the host can exacerbate the progression of chronic periodontal disease. A thorough study of the pathogenesis of periodontitis is beneficial for guiding clinical doctors in better treatment of periodontitis. During the pathogenesis of periodontal disease, periodontal pathogens induce a large amount of infiltration of neutrophils, macrophages, B lymphocytes, and T lymphocytes. These inflammatory cells express RANKL, TNF-α, IL-1β, Inflammatory factors such as IL-17 and MMP-6 promote osteoclast activation, alveolar bone resorption, and periodontal collagen degradation [2]. In recent years, a large number of studies have shown that immune regulatory cells such as M2 macrophages, Treg cells, and Breg cells can be induced or transplanted by drugs to inhibit the expression of periodontal inflammatory factors, thereby reducing osteoclast activation and alveolar bone resorption in animal models of periodontitis [3] [4] [5]. Especially the B lymphocytes in periodontal tissue can induce pro-inflammatory factor TNF-α, IL-17, IL-1β, IL-6 and MMPS are significantly elevated compared to healthy periodontal tissue [6] [7] [8]. B cells are the main source of RANKL in periodontal tissue. RANKL is a member of the TNF superfamily (also known as osteoclast differentiation factor), which binds to RANK expressed on the surface of osteoclasts or osteoclast precursor cells, promoting osteoclast differentiation and activation, and causing bone resorption. IL-1β Induce neutrophil and macrophage infiltration and secretion of PGE2 and lysosomal enzymes, leading to bone resorption. TNF-α, IL-6 and IL-17 act on osteoclasts, exacerbating alveolar bone resorption. The latest research shows that B10 cells secrete IL-10 factors, which are a class of anti-inflammatory factors that inhibit the expression of pro-inflammatory factors. Researchers established a periodontitis mouse model using IL-10 gene knockout mice, and the results showed that IL-10 knockout mice had significantly higher alveolar bone resorp-

tion than wild-type mice [9]. Transplanting immunomodulatory cells, such as Treg and Breg, into animal models of periodontitis can inhibit IL-1 in periodontal tissue β. The expression of inflammatory factors such as RANKL, while inhibiting periodontal inflammation and alveolar bone resorption [10] [11] [12]. Therefore, the host's immune response is a double-edged sword in periodontitis. When the immune response is excessive, it exacerbates the development of inflammation, indicating that immune regulation is crucial in controlling the occurrence, development, and prognosis of periodontitis.

3. The Immunomodulatory Effect of MSCs

MSCs were first discovered in the bone marrow by Friedenstein in 1974 [13]. Subsequently, a large number of *in vivo* and *in vitro* studies have shown that MSCs are a type of pluripotent stem cells that can differentiate into tissues such as fat, bone, cartilage, muscle, tendon, ligament, nerve, myocardium, and endothelium under different induction conditions [14] [15]. With the follow-up research, MSCs not only have the potential of multi-differentiation, but also participate in the progression of infectious diseases and injurious diseases through immune regulation. Recent studies have shown that MSCs have low expression of MHC-I and no expression of MHC-II, which protects them from attacks by NK and T cells. They have strong anti rejection ability and therefore have low immunogenicity, and can exert immune regulatory effects through direct contact with cells or secretion of cytokines.

3.1. The Immunosuppressive Effect of MSCs in Inflammatory Tissues

Under the induction of inflammatory factors, MSCs can homing from peripheral blood to inflamed and damaged tissues, inhibiting inflammation and tissue repair through immune regulation and tissue regeneration ability, but the mechanism of action is very complex. Al Kharboosh and Wei found that in inflammatory diseases, MSCs express VCAM-1, ICAM-1, and LFA-3 and reach the inflammatory site with the assistance of these factors [16]. Then, through VLA-4/VCAM-1 interaction with endothelial cells, they migrate to the lesion site and exert immune regulation and tissue repair functions. Transplantation of MSCs with high expression of VCAM-1 promotes hematopoietic reconstruction and immune regulation [17]. MSCs exert immunosuppressive effects mainly through the following two pathways: firstly, inhibiting inflammation through paracrine anti-inflammatory factors such as NO, IDO, PGE2, TSG6, and CCL-2 [18] [19]. Through exosomes and SAF-1 α/The CXCR7 signaling pathway, FAS-L pathway, and other pathways regulate other pro-inflammatory cells, thereby exerting immune regulatory effects [20] [21] [22]. Extracellular vesicles contain IL-10 and TGF-β inhibiting the immune effects of T lymphocytes, B lymphocytes, and dendritic cells. Among them, the exosomes secreted by MSCs reduced the proliferation rate of B cells and T cells by 18% and 23%, respectively [23]. Extracellular vesicles derived from MSCs during infusion alleviate graft

versus host disease (GVHD) and increase the survival rate of GVHD mice [24].

3.2. Immunomodulatory Effects of MSCs on B Cells

B10 cells are an important class of immune regulatory cells in B cells, which inhibit inflammation and bone resorption by secreting IL-10. *In vitro* studies have shown that MSCs pass through SDF-1 α/CXCR7 signaling pathway induces the expression of $CD19^{+}IL\text{-}10^{+}$regulatory B cells [21], and MSCs can also promote the increased expression of CD24hiCD38hi regulatory B cells, promoting the expression of IL-10 [25]. Research has found that MSCs from different sources have immunomodulatory abilities. Human placental amniotic membrane derived MSCs inhibit CpG induced differentiation of B cells into CD138+ plasma cells, and reduce gene expression of IRF-4, PRDM1, and XBP-1 [26]. MSCs derived from fat induce an increase in CD19+38hi24hiIL10+regulatory B cells from 3.35% to 16.75%, participating in immune regulation [27]. *In vivo* experiments have shown that regulatory B cells treated with MSC can inhibit colitis in mice, and intraperitoneal transplantation of MSC can also inhibit colitis in mice [28]. Therefore, MSCs may promote immune regulatory B cell proliferation by inhibiting inflammatory B cell proliferation and exerting immune regulatory effects.

3.3. Immunomodulatory Effects of MSCs on T Cells

T cells are one of the main immune cells in the inflammatory response, and pro-inflammatory T lymphocytes are mainly Th1 and Th17 cells. Studies have shown that MSCs inhibit the differentiation of CD4+T lymphocytes into Th1 and Th17 type T cells, and upregulate the expression of CD4+CD25+FOXP3+regulatory T cells [29]. Treg is a type of T lymphocyte that plays an immune regulatory role through IL-10 and TGF-β Animal experiments have shown that transplanted MSCs upregulate the expression of Treg in mice and inhibit the severity of disease in EAE mouse disease models by exerting immunosuppressive effects [29]. Research has shown that MSCs induce T lymphocyte apoptosis through FAS-L, inhibit T cell and NK cell proliferation and function, and downregulate the maturation and function of dendritic cells [22].

Overall, MSCs secrete anti-inflammatory factors through paracrine pathways to participate in immune regulation. They can also inhibit the proliferation of immune cells such as B cells, T cells, NK cells, and dendritic cells, and recruit other immune regulatory cells such as Breg and Treg to jointly create a suitable environment for regulating immune response tolerance.

4. Immunomodulatory Effects of MSCs in Periodontal Disease

For MSCs, as early as 2004, Kawaguchi demonstrated that transplantation of MSCs can promote the recovery of periodontal tissue in chronic periodontal disease [30]. With in-depth research on MSCs, scholars have found that MSCs

exert effects on the adaptive and innate immune systems through direct cellular contact and secretion of soluble cytokines or extracellular vesicles. Christian *et al.* found that in IL-1 and IFN-γ In the presence of PDLSC, periodontal derived mesenchymal stem cells (PDLSC) can inhibit the proliferation of CD4+T lymphocytes [31]. In the environment of periodontitis, due to the abundant presence of inflammatory factors, the aggregation of MSCs is weakened, affecting their immune regulatory ability. This also demonstrates the potential of stem cell transplantation in periodontal treatment from another perspective. Tang *et al.*'s research also supports this idea, finding that under low concentrations of Pg-LPS stimulation, the proliferation, osteogenesis, and inhibition of T cell activation of MSCs are enhanced. However, high concentrations of Pg-LPS can inhibit MSC proliferation, osteogenesis, and weaken their ability to inhibit T cell activation [32]. The mechanism may be that MSCs can activate the WNT/CasL signaling pathway through DKK-I methylation to achieve immune regulatory function [33]. FasL is an important molecule that induces T cell apoptosis by MSCs. Its expression is reduced in gingival tissue of elderly mice, and MSCs infiltration is also reduced. On the contrary, inflammatory T cell infiltration is increased [22]. In periodontitis tissues, a large number of pro-inflammatory B lymphocytes and T lymphocytes infiltrate, which is the main source of RANKL in periodontitis. RANKL interacts with RANK on the surface of osteoclasts and precursor cells to activate osteoclasts, leading to alveolar bone resorption. Nakao found that the miR-1260b in the extracellular vesicles of gingival derived MSCs can regulate periodontitis and inhibit osteoclast gene activation through the Wnt5a-RANKL signaling pathway. Local transplantation of bone marrow mesenchymal stem cells into the gingiva of periodontitis mice significantly reduces the inflammatory factor TNF in low periodontal tissue-α, IL-1β [34].

5. Outlook

In recent years, the research of odontogenic mesenchymal stem cells has gradually progressed from animal experiments to human experiments. Safety is an unavoidable topic in stem cell application research [35]. The potential tumorigenic and tumorigenic risks of stem cells have attracted much attention, including gene changes during *in vitro* expansion, tumor formation after implantation, and promotion of the development of existing tumors [36]. Compared with embryonic stem cells and induced pluripotent stem cells, mesenchymal stem cells have a low risk of tumorigenesis, but there have been reports of proto-stem cell-derived tumors several years after stem cell transplantation, suggesting that long-term observation and evaluation of the safety of stem cells is needed [37]. In addition, immune rejection after transplantation is also a problem in stem cell applications. The low immunogenicity of odontogenic stem cells and their own immunomodulatory capacity make allogeneic stem cell transplantation possible. The immunomodulatory effect of MSCs can intervene in the formation of certain inflammatory factors during the development of chronic periodontitis, in-

itiating the progression of periodontitis from destructive to reparative. However, the specific mechanism remains to be further studied by scholars, and MSCs are expected to become a new direction for the treatment of chronic periodontitis.

Conflicts of Interest

No other author has reported a potential conflict of interest relevant to this article.

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