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PROGRESS IN STUDIES RELATED TO M2-TYPE MACROPHAGE POLARIZATION FOR BONE REPAIR IN PERIODONTITIS

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ABSTRACT

Periodontitis, a difficult problem in dentistry that has been difficult to overcome, is characterized by alveolar bone resorption, and bidirectional immunoregulation by macrophages is an important influence on the degree of periodontal bone resorption. With the onset of inflammation, macrophages can polarize into two different functional phenotypes, M1 and M2, with M2-type macrophages thought to have anti-inflammatory effects and M1-type macrophages promoting inflammatory responses and accelerating bone resorption. Therefore, in this paper, we will review the regulation of macrophage polarization in periodontal tissues with the expectation that it will improve the efficacy of bone restoration in periodontitis in the future therapeutic field of periodontitis.

Keywords: Macrophage polarization, periodontitis, bone repair

INTRODUCTION

The treatment of periodontitis has been troubling clinical and scientific researchers in dentistry, and periodontitis has been jeopardizing the general health and quality of life of patients, and its main symptom is alveolar bone resorption after the periodontal tissues are infected by bacteria. Therefore, improving or even reversing bone resorption in periodontitis has been a medical problem that has attracted much attention in recent years. Periodontitis is associated with macrophage-mediated immunoregulation from development to tissue repair [1], and it is now widely believed that macrophages can be polarized to M1 and M2 types, and that M1-type macrophages promote the inflammatory response, whereas M2-type macrophages reduce inflammation-related indexes, and periodontitis is an inflammatory disease characterized by bone resorption. Periodontitis is an inflammatory disease characterized by bone resorption; therefore periodontitis is aggravated when macrophages are more polarized toward M1 type, and conversely increased polarization of M2 type macrophages can promote periodontal bone tissue repair. Therefore, in this paper, we will review the regulation of macrophage polarization in periodontal tissues, and hope that it can be equipped with biomaterials to achieve faster and better bone repair treatment in the future periodontitis treatment field.

1. Cellular immune dysregulation in periodontitis bone resorption

Periodontitis is a series of inflammatory reactions that occur in response to infection by specific microbial colonies by the body's immune system, and the main signs of the disease are resorption of alveolar bone and damage to periodontal fibrous tissue. Currently, more than 11% of the world's population suffers from varying degrees of periodontitis [2], and for those who suffer from periodontitis, problems such as occlusal pain and tooth loss caused by

periodontal bone resorption seriously affect their quality of life [3]. Alveolar bone loss is the most characteristic basis of differentiation between periodontitis and gingival inflammation, when inflammation affects the alveolar bone, osteoclasts increase in response to a variety of cytokines and inflammatory mediators thereby achieving bone resorption [4]. In periodontitis, there is an increased cellular inflammatory infiltration of T-cells, B-cells, neutrophils and macrophages in the gingival connective tissue along with increased secretion of inflammatory mediators [5]. Macrophages play an important role throughout the immune response, recognizing pathogen-associated molecular patterns (PAMPs) or risk-associated molecular patterns through specific receptors expressed on Toll-like receptors (TLRs) [6]. triggers periodontal inflammation [6], which results in periodontal bone resorption. Neutrophils and lymphocytes appear sequentially in the inflamed areas of periodontitis, which cause immune dysregulation and also have a role in macrophages, which in turn affects the progression of bone resorption. Existing scholars have found that neutrophils in the inflammatory region can be polarized into N1 and N2 types, N1 type secretes a variety of inflammatory factors that can promote the polarization of macrophages to the pro-inflammatory type, thus exacerbating the periodontal inflammation of bone resorption, and the N2 type inhibits the progression of inflammatory bone resorption, which is a similar polarization reaction to macrophage polarization [7]. The direction of macrophage polarization determines, to a certain extent, the rate and effectiveness of bone resorption repair in periodontitis.

2. Macrophage polarization mediates immune regulation in periodontitis bone resorption

There is a strong correlation between bone resorption in periodontitis and macrophage-mediated immunoregulatory responses. Macrophages are highly plastic as immune cells and can polarize from M0 to M1 and M2 types. Macrophages involve heterogeneous cell populations with extensive plasticity and differentiation kinetics. In response to the inflammatory environment, they can favor either pro-inflammatory M1 type or anti-inflammatory pro-healing M2 type during TLR connection [6], where M2 macrophages are divided into four subtypes, M2a, M2b, M2c and M2d, although these subtypes are functionally nuanced, e.g., M2d maintains virulence in addition to promoting wound healing, all of these M2 subtypes in All of these M2 subtypes play a role in inhibiting the development of inflammation in periodontitis, and these subtypes have highly similar protein expression profiles [8], so that all types of M2 macrophage subtypes in periodontitis can be generalized to anti-inflammatory macrophages for discussion. Gene expression profiles of circulating monocytes by periodontal ligation experiments showed higher levels of TNF-α and IL-6 than controls, indicating that periodontitis induces polarization of M1-type macrophages [9]. In addition, periodontitis bone resorption is also strongly associated with Helper T cells 1 (Th1) type of immune response, as the Receptor activator of nuclear factor -κB ligand (RANKL), which stimulates bone resorption, seems to be predominantly on Th1 type cells M1-type macrophages are mainly involved in the Th1 immune response, producing inflammation-associated factors during the inflammatory phase, interleukin IL-1β, IL-6, IL-12, IL-23, tumor necrosis factor α (TNF-α), tumor necrosis factor α (TNF-α) and tumor necrosis factor α (TNF-α). α), etc [11], these inflammatory factors are involved in the activation of osteoclasts, which are responsible for bone resorption in periodontitis, whereas M2-type macrophages involved in Th2-type immune response are mostly found in the quiescent and restorative phases of periodontitis, which have an inhibitory effect on the process of bone resorption in periodontitis. In addition, a number of signaling pathways are involved in regulating macrophage polarization and thus affecting the level of bone resorption in periodontitis.

3. Molecular mechanisms of periodontitis-associated macrophage polarization

3.1 The NF-κB pathway

In the periodontal environment, osteoclasts involved in bone resorption activities rely on the activation of osteoclast precursors differentiated from osteoblasts by the binding of Receptor activator of nuclear factor-κB (RANK) to its ligand RANKL [12]. Macrophage colony stimulating factor (M-CSF) and RANKL are part of extracellular signaling. During osteoclastogenesis, the interaction of RANKL and RANK initiates dynamic intracellular signaling pathways, including the NF-κB and mitogen-activated protein kinase (MAPK) signaling pathways. Among the inflammatory factors produced by M1-type macrophages, IL-1β, IL-6, and TNF-α are all potent activators involved in the binding of NF-κB to RANKL, which accelerates osteoclast activation, and proliferation [13].The NF-κB pathway is also an important pathway that promotes macrophage polarization toward the M1 type, and Jessica D Cecil et al [14] demonstrated that the outer membrane vesicles (OMV) of Porphyromonasgingivalis (Pg), the main causative agent of periodontitis, are involved in the immune-regulatory aspects of periodontitis, and that they are involved in the immunoregulatory aspects of periodontitis by stimulating proinflammatory factor formation and activation of the NF-κB pathway, which exerts a facilitating effect on M1-type macrophage polarization while inhibiting M2-type polarization.

3.2.Wnt/β-catenin pathway

The Wnt signaling pathway plays an extremely important role in the repair of bone resorption in periodontitis, and it has been experimentally demonstrated that activation of the Wnt pathway can repair alveolar bone resorption defects caused by periodontitis [15]. It is Periodontal ligament stem cells (PDLSCs) that have a tissue-repairing role in periodontal tissues, and LiCl, an agonist of the Wnt pathway, can specifically up-regulate Wnt signaling in PDLSCs to restore the negative effects of bone resorption caused by periodontitis [16].Wnt/ β-catenin signaling pathway can also promote macrophage polarization towards M2-type thereby enabling the repair of periodontal bone defects [17].

3.3. The Trem1/STAT3/HIF-1α axis

Triggering receptor expressed on myeloid cells-1 (Trem1) is a cell-surface receptor expressed on the surface of immune cells such as macrophages, and researchers have found that Trem1 expression is significantly upregulated in gingival tissues of periodontitis patients [18].D. Wu and Y. Weng et al. [19] observed a decrease in M1 polarization and an increase in M2 polarization by knocking down Trem1 in RAW264.7, while inhibition of Trem1 suppressed the expression of IL-1β, a characteristic inflammatory factor of periodontitis, and signal transducer and activator of transcription 3 (STAT3), which is an essential component of periodontitis. transcription 3 (STAT3) signaling pathway activation was involved in bone defect repair in a periodontitis model [20], whereas overexpression of STAT3 significantly upregulated the expression level of M2-type macrophages, representing that it is also a regulator of macrophage polarization [21]. Hypoxia-inducible factors 1-α (HIF-1α) is often recognized as a reverse activator of osteoclasts [22].HIF-1α cooperates with vascular endothelial growth factor (Vascular endothelial growth factor, VEGF) plays a key role in vascularized osteogenesis and is expected to be an important factor in promoting bone repair in periodontitis [23]. And Trem1 is also regulated by macrophage polarization through the STAT3/HIF-1α pathway, so the Trem1/STAT3/HIF-1α axis is considered to be an important signaling pathway that regulates bi-directional macrophage polarization.

3.4. the RhoA/ROCK pathway

ROCK (Rho-associated coiled-coil protein kinase) is a pro-apoptotic factor that mediates an extracellular milieu that may regulate macrophage M1-type versus M2-type activation [24], and selective inhibition of the RhoA/ROCK signaling pathway increases M1-type macrophages and decreases the proportion of M2-type macrophages [25].ROCK signaling plays an important role in periodontal bone remodeling, and studies have showed that activation of the ROCK signaling pathway can reduce the formation of osteoclasts and thus promote bone regeneration [26], and PDZ combined with motif transcriptional co-activator (TAZ) can promote the proliferation and osteogenic differentiation of periodontal membrane stem cells by up-regulating the ROCK signaling [27], which is of great significance for us to explore the direction of macrophage polarization regulation in assisting the treatment of bone repair in periodontitis.

3.5. kynurenine-AhR-NrF2 pathway

Kynurenine (KYN) is an active metabolite in the degradation of tryptophan by indoleamine 2,3-dioxygenase (IDO) involved in the process of tryptophan, and according to a clinical cross-sectional study by Shivge Kurgan et al. found that salivary levels of KYN were significantly higher in patients with periodontitis than in those without periodontitis [28]. Arylhdrocarbon receptor (AhR) is thought to signal the inhibition of bone resorption in periodontitis, which may be achieved by blocking the NF-κB binding site to inhibit inflammation, whereas Porphyromonasgingivalis (Pg) can promote bone resorption in periodontitis by inhibiting the AhR signaling pathway [29]. Nuclear factor erythroid-2-related actor 2 (NrF2) can inhibit oxidative stress in periodontitis and thus inhibit the development of periodontitis [30].The Kynurenine-AhR-NrF2 pathway is a novel signaling pathway that regulates macrophage polarization in periodontitis [31]. , which is important for regulating macrophage polarization to inhibit bone resorption in periodontitis.

Among the many macrophage polarization signaling pathways regulating periodontitis, the NF-κB pathway is the classical signaling pathway with the widest involvement, and is often regarded as the key to the treatment of bone resorption in periodontitis because of its close relationship with osteoclast differentiation and its antagonistic relationship with Wnt and the newly discovered Kynurenine-AhR-NrF2 pathway.

4. Macrophage polarization regulation and bone repair in periodontitis

4.1. NF-κB pathway-associated regulation of macrophage polarization

Progranulin precursor (PGRN) is a highly expressed protein in periodontal inflammatory tissues [32]. Experimenters reconstructed PGRN to obtain rPGRN and applied it to the periodontal inflammatory environment simulated by Porphyromonasgingivalis LPS to observe that the direction of M1-type macrophage polarization was markedly inhibited and that rPGRN was inhibited through the NF- κB signaling pathway to inhibit M1 polarization [33]. Human β-defensin 3 (hBD3), as a cationic peptide, can be involved in the regulation of human immune responses. hBD3 was used as a single agent in the treatment of periodontitis in mice by researchers, who observed that hBD3 inhibited macrophage polarization toward the M1-type, mainly by decreasing the signaling of the NF-κB pathway and thus inhibiting macrophage polarization toward the M1-type [34]. Periodontitis macrophage polarization regulation through the NF-κB pathway was also performed by Wang Z et al. using exosomes obtained by cyclic tensile force treatment of periodontal membrane cells, and the purified exosomes inhibited the production of IL-1β in macrophages up-regulated by LPS by inhibiting NF-κB nuclear translocation to achieve a reduction in M1 macrophage polarization [35].

4.2. Wnt pathway-associated modes of macrophage polarization regulation

The TNF-α pretreated gingival MSC exosome CD73 induces M2 macrophage polarization, which contributes to the resolution of inflammation and prevents bone resorption in periodontal tissues, and its other exosome, miR-1260b, is essential for the inhibition of osteoclastogenesis through the Wnt pathway. mesenchymal stem cell (GMSC)-derived exosomes may be important modulators of macrophage polarization toward M2 in periodontitis [36].Jiayin Liu et al. transplanted a large number of PDLSCs into periodontitis bone defect areas and finally detected that PDLSCs could promote macrophage polarization toward M2 type and thus stimulate periodontal bone regeneration [37].Since PDLSCs can achieve bone repair through the Wnt pathway, we can speculate that the mechanism relies on the Wnt pathway to promote M2 polarization assisted by periodontitis bone repair.

4.3. Trem1/STAT3/HIF-1α axis-associated macrophage polarization regulation

Dimethyl oxalylglycine (DMOG), an activator of HIF-1α, inhibited the polarization of RAW264.7 cells stimulated by Pg.LPS toward the M1-type and facilitated VEGF production in in vitro experiments thereby promoting periodontitis bone repair [38]. The expression of Recombinant Serum/Glucocorticoid Regulated Kinase1 (SGK1) is directly correlated with STAT3, which was found to be downregulated when SGK1 was inhibited, and the expression of M2-type macrophage-associated secretions including Arg-1, Ym-1 and other secretions including Arg-1, Ym-1, etc. were down-regulated, so SGK1 can promote the polarization of M2-type macrophages through the STAT3 pathway and thus participate in the bone repair process in periodontitis [21].

4.4. ROCK pathway-associated macrophage polarization regulation

Yang Yang and other researchers constructed micro-nanonets and conducted in vitro and in vivo experiments, and found that this material can promote the polarization of macrophage M2 type in inflammation sites through ROCK signaling, and increased the formation of blood vessels and bone mass [39], which is very important for the promotion of vascularized osteogenesis in periodontitis.Donghua Huang et al. applied superparamagnetic nanoparticles in hydrogel The formation of superparamagnetic magnetic nanoparticles (SPMNPS) in hydrogels can regulate the direction of M1/M2 type macrophage polarization through dynamic magnetic response to achieve better bone repair, and this regulatory process is also achieved through the ROCK signaling pathway [40].

4.5. Kynurenine-AhR-NrF2 pathway related macrophage polarization regulation

Adipose-derived stromal stem cells (ASCs) can produce KYN under the enzymatic action of IDO to activate AhR to increase its binding to NrF2, which ultimately promotes M2-type macrophage polarization [41]. Therefore, it is also believed that ASCs inhibit bone resorption in periodontitis by regulating macrophage polarization to M2 type through IDO-dependent Kynurenine-AhR-NrF2 pathway. Related studies on KYN have also shown that KYN can inhibit early osteoclast differentiation, and its downstream AhR is also involved in the regulation of osteogenic and osteoblastic activities [42], so this pathway could be an important signaling pathway for future studies on the association between macrophage polarization regulation and periodontal bone repair.

5. Prospect

Macrophage polarization is an observable phenomenon in the immunomodulation of periodontitis, and a large number of studies have confirmed that macrophage polarization toward M2-type can promote periodontitis bone tissue repair. Therefore, inhibition of M1-type macrophages and promotion of directed macrophage polarization toward M2-type is the

current favorable direction for repairing bone defects caused by periodontitis. Many scholars have discovered drugs that regulate the direction of macrophage polarization balance under different mechanisms to achieve the inhibition of periodontitis bone resorption (see Figure 1), and these studies are valuable for future clinical breakthroughs in periodontitis bone resorption, which is difficult to treat. It is hoped that this review will summarize the existing macrophage polarization modulation therapies for the treatment of periodontitis bone resorption, and inspire more dentists and research scholars to combine reagents and materials with M2-type macrophage polarization modulation, and to study the repair effect and mechanism of periodontitis bone resorption, especially the latest report on the mechanism of periodontitis bone resorption related to the kynurenine (KYN) pathway, with a view to overcome the clinical challenge of periodontitis bone resorption. In order to overcome the clinical problem of difficult repair of bone resorption in periodontitis.

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