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Review

The Role of Macrophages in Orthodontic Tooth Movement: A Review

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Abstract: Orthodontic tooth movement (OTM) is facilitated by the induction of mechanical force, which triggers a sterile inflammatory response in the periodontal tissues. This response, in turn, coordinates the processes of bone resorption and formation. Through an extensive review of the existing literature on the biology of OTM, it becomes evident that macrophages play a pivotal role in all stages of the process. Furthermore, researchers have identified various emerging drugs and biological agents that target the behavior of macrophages, aiming to regulate and control the rate of OTM. To date, most studies have primarily focused on investigating the effects of anti-inflammatory drugs on the rate of OTM and elucidating their specific mechanisms. However, there is a notable absence of reports specifically addressing drugs capable of accelerating tooth movement. Nonetheless, in other fields, such as the promotion of fracture healing, techniques for modulating macrophage function using bio-scaffolds or sustained-release formulations loaded with cytokines or drugs have demonstrated significant advancements. Thus, these techniques hold promise as important avenues for future research and development, exploring the potential of macrophages in regulating the rate of OTM.

Keywords: orthodontic tooth movement; macrophage; biological principle; drug;inflammation

1. Introduction

The skeletal and immune systems are intricately interconnected, engaging in mutual interactions through the sharing of various cells and mediators, including cytokines, receptors, and signaling molecules [1]. Orthodontic tooth movement (OTM) exemplifies this interplay, with a specific focus on the role of macrophages [2]. Orthodontic forces applied to the occlusion result in hypoxia within the periodontal membrane (PDL), leading to periodontal vasodilation and recruitment of immune cells, which subsequently induce changes in immune factors within the periodontal tissues. These factors include chemokines, growth factors, and cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor- α (TNF- α), interferon- γ (IFN- γ), and prostaglandin E2 (PGE2) [3, 4]. Many of these inflammatory mediators are intricately involved in regulating osteoclasts and osteoblasts [5, 6]. As integral components of the immune system, macrophages are increasingly recognized for their pivotal role in OTM. Thus, understanding how macrophages influence OTM through polarization, differentiation, and intercellular communication is of utmost importance, as it has implications for the development of novel strategies utilizing drugs and biological agents to modulate the rate of OTM.

2. Biological Principles of Orthodontic Tooth Movement

The classical pressure-tension theory suggests that periodontal tissues can be divided into a compression side (osteoblastic side) and a tension side (osteogenic side) under orthodontic forces [7]. However, this theory does not fully explain the occurrence of osteoclastic activity on the tension side during the initial stage of tooth movement. Therefore, a biphasic theory was proposed, which suggests that OTM consists of two consecutive phases: an initial catabolic phase with bone resorption by osteoclasts at both compression and tension sites, followed by an anabolic phase in which alveolar bone density returns to its pre-treatment level [8]. Inflammation plays a crucial role in the biphasic theory, with macrophages being central to the immune response and playing critical roles in tissue damage repair and inflammation during OTM [9].

3. Role of Macrophages in Orthodontic Tooth Movement

The role of macrophages in OTM has been recognized since early studies in animal models. Vandevska-Radunovic et al. in 1997 observed macrophage recruitment in the periodontium during tooth movement in rats [10]. Further studies by He et al. in 2015 demonstrated the critical role of macrophages by depleting monocytes/macrophages in mice, which resulted in a significant reduction in the distance of OTM [11]. A previous study has demonstrated that macrophages in orthodontic tooth movement (OTM) possess the ability to perceive mechanical forces through the activation of Piezo1. This mechanosensitive receptor facilitates the intranuclear transport of cytokine D1 via the AKT signaling pathway, thereby promoting macrophage proliferation on the tonic side of the alveolar bone in a mouse model of OTM. As a result, accelerated remodeling of the periodontal tissues is observed [12]. In summary of the available literature, the current understanding suggests that macrophages regulate orthodontic tooth movement through a molecular mechanism. This mechanism entails the macrophages' ability to sense mechanical stimulation and perceive alterations in the local microenvironment. Subsequently, they modulate the delicate balance between osteoblasts and osteoclasts by undergoing phenotypic shifts towards M1 or M2 states or undergoing spectral differentiation into osteoclasts. These intricate actions effectively stimulate bone remodeling, ultimately contributing to the process of tooth movement. So the role of macrophages in OTM can be summarized in three aspects: (1) Macrophage phenotype switching mediates alterations in the local inflammatory microenvironment; (2) Macrophages serve as precursor cells for osteoclasts, differentiating into osteoclasts and facilitating bone resorption; (3) Macrophages directly guide osteoblast accumulation and maturation through paracrine cytokines (Figure 1).

3.1. Mediating Alterations in the Local Inflammatory Microenvironment

Previous studies have suggested that macrophages are heterogeneous cells whose function is closely linked to alterations in the local microenvironment. This heterogeneity allows them to respond appropriately to pathogens or signaling molecules [13]. Macrophages in a resting state (M0Mφs) are polarized into a "classically activated" state (M1Mφ), which promotes inflammation, and an alternative activated phenotype (M2Mφ), an anti-inflammatory state that aids in tissue repair [14]. Prior studies have noted phenotypic changes of macrophages in orthodontic tooth movement. Generally, on day 3 after orthodontic force application, the number of M1 macrophages increases, and this polarization towards the pro-inflammatory phenotype is crucial for bone resorption and orthodontic tooth movement (OTM) activation. Furthermore, macrophages are subjected to compression and stretching forces in the early stages of OTM, leading to the expression of pro-inflammatory genes such as Tnf- α, Cox-2, and Il-6, producing a variety of pro-inflammatory cytokines that affect the activity of periodontal membrane fibroblasts and enhance osteoclastogenesis [15]. Conversely, until day 14, the number of M2-like macrophages gradually increases on the compressed side of the periodontal tissue [16]. Their secretion of tissue repair signals, such as IL-10 and TGF-β, causes the inflammation to slowly subside.

Despite the conceptual framework provided by the M1/M2 macrophage dichotomy in understanding their role in tissue injury, the precise mechanisms underlying their regulation of inflammation and tissue repair remain incompletely elucidated. Recent advancements in cellular and molecular techniques have facilitated the identification of functionally distinct macrophage subsets within this heterogeneous cell population. Notably, through the construction of a single-cell map of macrophages in the alveolar bone of

mice, which served as a model for orthodontic tooth movement, Xu et al. observed that the CCR2+ subpopulation, constituting the predominant subset among macrophages, exhibited a notable influence on the efficacy of tooth movement. Furthermore, other researchers have suggested that CD301b+ macrophages may play an active role in orthodontic treatment, particularly in an inflammatory environment[18]. These emerging findings highlight the complexity of macrophage heterogeneity and underscore the need for further investigations to unravel their precise contributions to the processes involved in orthodontic tooth movement.

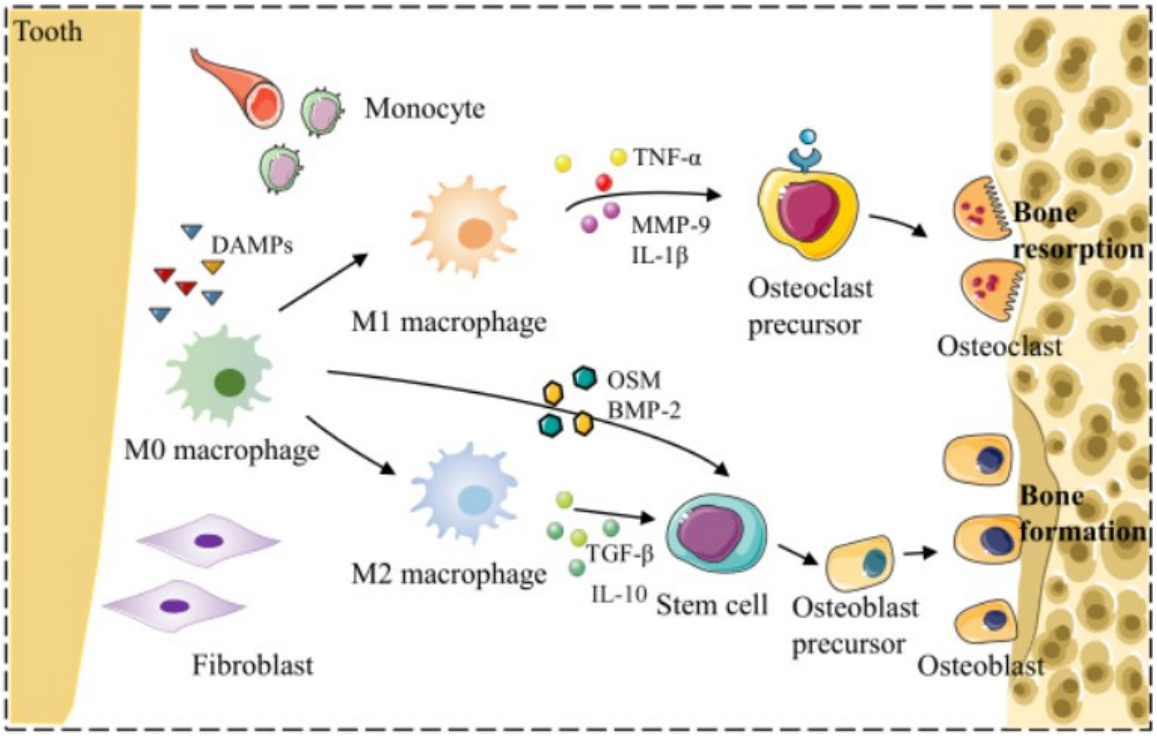

Figure 1. Macrophage polarization regulates alveolar bone remodeling in orthodontic tooth movement.

3.2. Lineage-differentiating into Osteoclasts to Execute Bone Resorption

Osteoclasts are well-defined and unique cells in bone. They are tissue-specific multinucleated cells produced by the differentiation of monocytes/macrophage precursor cells on or near the bone surface that are responsible for bone resorption. In general, orthodontic forces trigger sterile inflammation, followed by local inflammation that recruits monocyte/macrophage precursors into the periodontal ligament (PDL). Local inflammatory cells and osteoblasts differentiate them into osteoclasts by secreting osteoclast differentiation factors or directly expressing receptor activator of nuclear factor-κ B ligand (RANKL) [19]. RANKL, a type II transmembrane protein that is expressed on the cell surface in a soluble form released by protein hydrolysis and whose receptor, receptor activator of nuclear factor kB (RANK), is located on the surface of macrophages, prompts macrophages to change their phenotype to multinucleated osteoclasts [20]. There is evidence that the absence of RANKL impedes the movement of orthodontic teeth [21]. In addition, local cells can produce the RANKL decoy receptor osteoprotegerin (OPG) to downregulate RANK-RANKL-induced osteoclastogenesis [22]. RANK and RANKL, together with OPG, act as important components of the RANK/RANKL/OPG signaling axis to regulate osteoclast differentiation and activation, and are the main drivers of orthodontically induced bone remodeling [23]. Furthermore, it has commonly been assumed that the number and activity of osteoclasts have a direct impact on the rate of tooth movement [8]. Therefore, the ratio of OPG, RANKL, and RANK plays an important role in controlling the rate of tooth movement.

3.3. Directly Instructing Osteoblast Maturation and Mesenchymal Stem Cell Differentiation

As previously mentioned, M1Mφ secrete inflammatory factors such as TNF-α/IL-1/IL-6, which mediate the acute inflammatory response after teeth are subjected to orthodontic forces [24]. It is believed by many

investigators that longer M1Mφ infiltration is detrimental to bone remodeling as it may enhance damage and affect the later regenerative process [25]. However, moderate inflammatory infiltration mediated by M1Mφ is necessary to recruit stem cells to specific areas and alter the microenvironment [22]. Glass et al. found that low concentrations of TNF-α enhance the recruitment of mesenchymal progenitor cells by increasing CCL-2 and CXCL-12 [26]. Additionally, IL-6 increases ALP activity and accelerates MSC osteogenesis through the gp130-STAT-3 pathway [27,28]. In the later stages of tooth movement, the dominant proportion of M1Mφ has a stronger ability to promote tissue regeneration [29]. Anti-inflammatory factors secreted by M2Mφ, such as IL-10 and TGF-β, suppress the inflammatory response [30,31]. Some indispensable osteoinductive signals, such as BMP-2, BMP-4, BMP-5, and BMP-6, are also secreted more by M2Mφ than M1Mφ, which facilitates osteogenic differentiation of BMSCs [32]. BMP-2 enhances nuclear translocation of RUNX2 and upregulates ALP expression in BMSCs by activating the Smad1 signaling pathway [33,34].

4. Drugs or Biological Agents to Modulate Macrophages for Controlling OTM

In the clinical work of orthodontists, the control of orthodontic tooth movement consists of three core scientific issues: target position, efficiency, and precision. During orthodontic treatment, precise positioning of each tooth in the dental arch is crucial and tailored to the specific dental and skeletal characteristics of each patient. For instance, in cases where a patient exhibits a normal molar relationship and a convex facial profile, maintaining the molar position unchanged while retracting the anterior teeth is often desired. However, in the practical realm of orthodontic practice, achieving the exact target tooth positions predetermined before treatment can be challenging due to individual variations. This concept of precision represents the degree of alignment between the actual tooth positions achieved and the intended target positions. On the other hand, the efficiency of orthodontic treatment is determined by the time it takes for the teeth to reach their desired locations. The size of orthodontic force significantly influences treatment efficiency.

To address the unique malocclusion issues of each patient, orthodontists develop individualized treatment plans that establish target positions for each tooth in the dentition. Achieving these target positions rapidly and precisely necessitates effective methods. While Periodontally Accelerated Osteogenic Orthodontics (PAOO) can expedite tooth movement, its invasive nature often deters patients from accepting this approach. Consequently, there is a growing interest in pharmacological interventions as a means to enhance orthodontic tooth movement. Notably, several studies have highlighted the pivotal role of macrophages in this process, presenting them as convincing targets for targeted manipulation. By summarizing the advancements in current drug research, we aim to provide valuable insights for orthodontic clinical work.

4.1. Naturally Occurring Compounds

A growing number of studies have shown that some naturally occurring compounds (Table 1) are able to affect macrophage polarization [35]. However, studies on their ability to affect tooth movement are still relatively few. Only a natural small molecule product called fucoidan has been reported [36]. By establishing an orthodontic tooth movement model in mice treated with rockweed polysaccharide, the investigators found a significant decrease in tooth movement distance and a significant increase in surrounding bone density. Additionally, the percentage of pro-inflammatory macrophages as well as IL-1β protein level was significantly decreased after treatment with rockweed polysaccharide, while the percentage of restorative macrophages was significantly increased. In short, it affected the polarization of macrophages towards M2 via the STAT3 pathway.

4.2. ResolvinD1 (*RvD1*)

Resolvins are endogenous lipid mediators derived from eicosapentaenoic and docosahexaenoic acids that possess dual properties, namely, anti-inflammatory effects and prevention of the progression of acute inflammatory responses to chronic inflammation. RvD1 is produced by sequential oxidation of docosahexaenoic acid by 15- and 5-lipoxygenases and has been shown to inhibit inflammation, promote the production of anti-inflammatory mediators, and modulate macrophage function. In a rat model of orthodontic

tooth movement (OTM), local injection of RvD1 was found to decrease the expression of pro-inflammatory cytokines, such as IL-6 and IL-7, and increase the expression of anti-inflammatory cytokines, such as IL-4, IL-10, and IL-13. In vitro experiments also revealed that RvD1 strongly inhibited the differentiation of macrophages into osteoclasts [37]. These findings suggest that RvD1 is a promising biologic agent for controlling OTM-related inflammation and reducing the adverse movement of teeth and post-treatment relapse.

Table 1. Natural compounds regulating M1 & M2 polarization.

	Natural Compounds
regulating Mφ/M1 polarization	Diosgenin glucoside (Dios)、Polysaccharides、Pentacyclic triterpene Lup-20(29)-en-3β-ol (Lupeol)
regulating Mφ/M2 polarization	Celastrol、Luteolin (3′,4′,5,7-tetrahydroxy flavone)、Curcumin、Isoliquiritigenin (ISL)、Punicalagin (PUN)、Crocin
regulating both Mφ/M1 and Mφ/M2 polarization	Emodin、Lycium barbarum polysaccharide (LBP)
regulating M1/M2 polarization	Salidroside (SLDS)、Trichosanthes kirilowii lectin (TKL)、1,3,6,7-tetrahydroxy-8-prenylxanthone (TPX)、fucoidan

4.3. Itaconate

Itaconate is a metabolite produced by the tricarboxylic acid cycle in pro-inflammatory macrophages. It has been shown that local injection of the itaconic acid derivative Four-Octyl itaconate (4-OI) in periodontal tissue can cause alkylation of KEAP1 cysteine residues in macrophages, resulting in the dissociation of the KEAP1-Nrf2 polymer and activation of the Nrf2 signaling axis. This, in turn, reduces inflammation and oxidative stress and decreases periodontal destruction [38]. Other studies have revealed that itaconate can also exert its unique anti-inflammatory activity by acting as an SDH inhibitor and inducing ATF3 protein and ATF3-driven stress response [39]. These findings suggest that itaconic acid, either alone or by increasing endogenous itaconic acid by increasing IRG1 activity or using its derivatives, may have great potential as an effective strategy to alter the rate of tooth movement.

4.4. Antihistamines

The effect of antihistamine treatment on OTM has not been fully studied to date. However, histamine has been reported to increase the expression of OPG in macrophages under simulated orthodontic compression strain. Cetirizine was found to significantly decrease the expression of the aforementioned genes following the application of various histamine receptor antagonists [30]. Augmentation of OPG reduces the rate of tooth movement by inhibiting osteoclast differentiation. Hence, it could be hypothesized that the application of antihistamines may have good prospects for controlling the rate of OTM in the future.

4.5. Scaffolds or Sustained-release Loaded with the Active Immune Agent or Drug

Scaffolds or sustained-release systems loaded with active immune agents or drugs are a potential future direction for research to target macrophages in periodontal tissue. Systemic use of macrophage-targeted drugs may have adverse effects on the immune system, making local delivery of small molecules a promising strategy. To promote osteoblast differentiation of stem cells, delivering drugs or cytokines with nanoparticles is a common method [40, 41]. Sequential delivery of immunomodulatory cytokines via scaffolds is also widely used in tissue engineering [42,43], with examples such as acellular bone modifications for short-term release of interferon-gamma (IFN-ɣ) to promote M1 phenotype, followed by more sustained release of interleukin-4 (IL-4) to promote M2 phenotype [44]. To control the rate of orthodontic tooth movement, controlled release PECE hydrogel was used to carry parathyroid hormone (PTH) or parathyroid hormone-related protein (PTH-rP) locally, which enhanced the OTM of rats [45]. The delivery of growth factor or cell therapy has potential safety concerns, such as burst release-induced hyperphysiological dose administration or unexpected immune responses that need to be further verified.

5. Discussion

During orthodontic tooth movement, biological tissues in the dentoalveolar complex undergo complex remodeling. Skeletal and immune systems interact during this period by sharing multiple cells and mediators such as cytokines, receptors and other signaling molecules. Macrophages have come into prominence with accumulating understanding of their multi-layered contributions in OTM. Previous research has established that the macrophage polarization, cytokines, potential to differentiate into osteoclasts and their crosstalk with osteoblasts play an integral role in orthodontic tooth movement.

Thus, macrophages are a compelling target to manipulate as apex regulatory cells, which provides a clear motivation for the development of various drugs to modulate this autologous force that affects the rate of tooth movement. Unfortunately, the drugs studied at this stage are mainly anti-inflammatory drugs, which play an important role in a small percentage of teeth that do not need to be moved clinically and function as a branch resistance, but even have a reverse effect in most of the teeth that need to be moved rapidly. Precisely because of this complexity of the need for the rate of movement of different teeth in the same dentition during orthodontic treatment, it also brings a tremendous difficulty in drug discovery. Systemic administration does not ensure that each tooth in the dentition moves at the desired rate and may provoke undesired systemic side effects, whereas local administration makes it difficult to maintain an optimal dose of the agent in the PDL due to rapid flushing of the drugs by the circulation, thereby requiring frequent injections. Surprisingly, the local use of biological scaffolds containing immunomodulatory cytokines to control the transformation of macrophage phenotype at different time points has recently yielded promising results in animal models. Although their efficacy and safety have yet to be proven, it is believed that one day this method will move from the bench to the chair.

In the future, we need to further identify the molecular mechanisms and potential targets of macrophages that regulate the rate of tooth movement in order to safely and effectively employ drugs locally against their targets to control OTM rate.

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