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Central Role of Autophagy in Orthodontic Tooth Movement: From Oxidative Stress Regulation to Immune-Matrix Interactions

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Abstract. Autophagy is a highly conserved catabolic process. During orthodontic tooth movement (OTM), it is activated by multiple signals, including mechanical force, hypoxia, oxidative stress, and inflammation, and acts as a core regulatory hub for periodontal tissue remodeling. This review first systematically summarizes the major forms of autophagy (macroautophagy, microautophagy, chaperone-mediated autophagy, and mitophagy), along with their core molecular mechanisms and fundamental roles in bone metabolism. Building on this, it examines the activation and regulation of autophagy by mechanical stimuli (compressive force, tensile force, fluid shear force), hypoxia, oxidative stress and inflammatory signals in the OTM microenvironment, discusses the downstream effects of autophagy on bone remodeling through the immune-matrix interaction network, and summarizes the research progress of targeted intervention strategies involving drugs, nanomaterials and photobiomodulation.

Keywords: Orthodontic tooth movement, Autophagy, Alveolar bone remodeling, Immune-matrix interaction, Targeted therapy

1. Introduction

Orthodontic tooth movement (OTM) depends on the coordinated remodeling of periodontal tissues under mechanical stimulation. In recent years, several reviews have discussed the cellular mechanisms of OTM from different perspectives [1]. Tang and Yang et al. systematically reviewed the role of periodontal ligament stem cell (PDLSC) senescence in age-related orthodontic changes, in which autophagy is implicated as a senescence mechanism [2]. However, autophagy is not merely a downstream event of senescence; it is a central hub linking mechanical force, oxidative stress and immune-matrix interactions. Focusing on autophagy, this review integrates its specific functions and multi-level regulatory networks in different OTM-related cells (PDLSCs, cementoblasts, osteocytes, immune cells), and discusses intervention strategies such as drugs, nanomaterials and photobiomodulation, to provide preliminary ideas and references for subsequent research in this field.

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2. Overview of autophagy

Autophagy is a conserved cellular degradation process that operates in many organisms. When cells are under stress, autophagy is initiated. It serves to remove damaged organelles and other cellular debris, thereby helping cells to stay healthy and prevent damage [3]. Depending on how cargo reaches the lysosomes, autophagy falls into threecategories. They are macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA) [4]. In macroautophagy, phagophores expand and engulf damaged organelles or cytoplasmic components,forming double-membrane autophagosomes that later fuse with lysosomes to finish degradation. In microautophagy, the lysosomal or vacuolar membrane invaginates and directly takes in cargo,wrapping the waste directly [5]. CMA relies on chaperone proteins to recognize specific proteins and movethem across the lysosomal membrane into the lysosome, where they are degraded [6].

The ULK1 complex controls the start of autophagy. When nutrients are sufficient, mTOR inhibits off the ULK1 complex, so autophagystays off. Under stress or nutrient deprivation, mTOR is inhibited, and the ULK1 complexbecomes activated to initiate autophagy. The ULK1 complex also recruits the class III PI3K complex, which includes Beclin-1. This complex promotes phagophore membrane nucleation and expansion. Next, ATG proteins work with LC3,.During this step, cytosolic LC3-I conjugates to phosphatidylethanolamine to form LC3-II on the membrane. LC3-II is a marker of autophagosome formation. Finally, the mature autophagosome fuses with a lysosome to form an autolysosome. The cargo inside is degraded and recycled, which helps the cell maintain health [7].

In addition, mitophagy, as a specific form of selective autophagy, has received considerable attention in bone metabolism research in recent years. By specifically recognizing and clearing damaged or dysfunctional mitochondria, mitophagy maintains mitochondrial network homeostasis and regulates cellular energy metabolism and redox balance [8].

3. Autophagy activation in the OTM microenvironment

During OTM, periodontal tissues are subjected to multiple stress signals such as mechanical force, oxidative stress, hypoxia and inflammation. As a core response mechanism, autophagy integrates these signals and coordinates cellular functional responses.

3.1. Mechanical microenvironment in OTM and induced cellular stress

3.1.1. Compressive force (CF)

Recent studies indicate that CF regulates autophagy in a bidirectional and cell-dependent manner. In bone remodeling, CF can contribute to bone loss while also protecting the root. It promotes bone resorption and suppresses bone formation, which reduces alveolar bone volume.In some settings,however, it activates autophagy in ways thathelp protect the root.

CF activates autophagy in ways that supports osteoclast formation,leading to alveolar bone loss. CF also acts on osteoblasts, inducing them to secrete RANKL, which subsequently promotes osteoclast formation [9]. Similar effects have been reported in PDLSCs, where CF activatesmitophagy in these cells. This alters the RANKL/OPG ratio and further promotes osteoclast formation [10]. CF also acts through FER1L4 and the ROCK/ROS pathway to increase autophagy levels in PDLSCs,which promotes bone resorption [11, 12]. CF can also inhibit autophagy. When that occurs, cells cannot form new bone effectively. In bone marrow mesenchymal stem cells, prolonged CF exposure gradually suppresses autophagy, increases cell death,and impairs osteogenic

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differentiation, which reduces bone formation [13]. In cementoblasts, CF turns up the LincRNA-p21/FoxO3 pathwayand thereby inhibits autophagy. MMP9 and MMP13 levels then decrease. Consequently,cementoblasts cannot migrate to resorption pits or mineralize properly, resulting in impaired new cementum formation [14, 15].

However, CF does not always exert detrimental effects cells through autophagy. In some cases, it appears to be protective instead. One study found that CF upregulates S1PR1 in cementoblasts and activates mitophagy under heavy pressure. ROS levels were reduced as a result,and root resorption was attenuated [16].

3.1.2. Tensile force (TF)

TF promotes alveolar bone formation and mineralization by upregulating autophagy in several supporting cell types. Firstly, in cementoblasts, TF enhances autophagy and upregulates Postn, which promoyesmineralization [15]. Secondly, TF acts through multiple signaling pathways, with autophagy as a central hub. In osteocytes, TF activates autophagy, andthe cells then secrete FGF23. FGF23 supportsosteoblast maturation and differentiation and contributes tobone formation [17]. TF also induces PDLSCs to secrete CCN1. Through the PI3K/Akt and MAPK/ERK pathways, CCN1 activates autophagy, increases cell migration, and speeds up bone formation [18]. A similar pattern is seen in osteoblasts.TF upregulates Klotho in these cells and,throughthe NF-κB and PI3K/Akt pathways, promotes osteogenic differentiation on the tension side, leading to new bone formation [19]. Cyclic TF also induces mitophagy in PDLSCs.The cells shift their metabolism toward glycolysis during this process, which supplies energy for osteogenesis. In summary, these findings suggest that TF positions autophagy as a central hub between signaling pathways and metabolicchanges that support bone formation and mineralization [20].

3.1.3. Fluid shear force (FSS)

FSS is a key mechanical signal. It triggersautophagy in severalcell types, which helps protectcells and restorebone mass. In osteocytes, FSS increasesautophagic flux and raisesATP production and release, which supportsosteocyte survival [21]. In osteoblasts from osteoporotic bone, FSS upregulates lncRNA NEAT1. NEAT1 binds miR-466f-3p and reduces its inhibition of hexokinase 2.As a result, autophagy in osteoblastsincreases, and the osteoporotic bone phenotype improves [22]. FSS also activates the AnxA6 pathway in osteoblasts.This enhances autophagy as well asALP and Col1 expression, which promotes bone formation. Bonemass is therefore restobluein osteoporotic patients [23].

3.2. Oxidative stress: ROS-mediated autophagy

Oxidative stress leads to excessive ROS production,andROS also acts as a critical signal that regulatesautophagy. Studies so farhave investigated how ROS regulates autophagy in both bone cells and gingival cells..

In bone cells, Zhu et al. examinedmultiple pathways bywhich ROS regulates autophagy. These include the ROS/FOXO3, ROS/AMPK, ROS/Akt/mTOR, and ROS/JNK/c-Jun pathways in osteoblasts, osteocytes, and osteoclasts under oxidative stress, which then affectthe balance between bone formation and bone resorption [24]. Further studies suggestthat this regulationdiffers by cell type. In osteoclasts, oxidative stress exerts dual effects. When ROS is reduced,mitophagy gene activity falls, and this impairs osteoclast formation through the AKT and p38/MAPK pathways.By

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contrast, when RANKL upregulates Nox4, ROS is generated extramitochondrially, activating the PERK/eIF-2α/ATF4 stress pathway and inducing autophagy, thereby promoting osteoclast maturation and differentiation [25, 26]. In osteoblasts pretreated with H2O2 and then subjected to TF, the autophagy genes LC3 and BECN1 increased markedly. The inflammatory genes COX2 and IL8 alsorise together with PGE2 release. This pattern suggests that oxidative stress may regulate mechanical force-induced autophagy through inflammatory gene activation [27].

In gingival cells as well,higher oxidative stress is linked to greater autophagy. On one hand, nutrient deprivation increases ROS, which activates autophagy. AMPKα is phosphorylated at Thr172, a key step in autophagy initiation. ROS can also enhance autophagy via the AMPK pathway [28]. Under starvation conditions such as EBSS treatment, mitophagy is induced. This process requires ROS and depends on the PINK1/Parkin pathway [29]. On the other hand, Sanhuang Decoction reduces ROS and MDA and increases SOD and GSH-Px in gingival cells. This activates the PI3K/Akt/mTOR pathway, which typically inhibits autophagy, thereby decreasing autophagy [30].

3.3. Hypoxia and inflammation

Oxidative stress is not the only signal. Hypoxia and inflammation may also regulate autophagy independently.

Hypoxia can activate autophagy through more than one pathway,and this pattern has been reportedin differentmodels. In rats with nasal obstruction and in hypoxic cells, the FOXO1-HDAC6 interaction in bone marrow stem cells dissociates. FOXO1 then enhances autophagy,whileHDAC6 inhibits osteogenic differentiation [31]. In addition, $CoCl_2$-simulated hypoxia upregulates HIF-1α and circCDK8 in PDLSCs, and autophagy is activated through the circCDK8/mTOR pathway,which inhibits osteogenic differentiation [32]. Similarly, in malignant tumors such as glioblastoma, pancreatic cancer, hepatocellular carcinoma and oral squamous cell carcinoma, hypoxia regulates the activity of mTOR, Beclin-1 and autophagy-related genes through HIF-1α to induce autophagy activation [33].

Regarding inflammatory signals, multiple cytokines regulate autophagy in osteoclast precursors through non-ROS-dependent pathways, thereby affecting osteoclast differentiation. IL-17 is one such cytokine, and its effect is dose-dependent. Low levels of IL-17 activate autophagy in osteoclast precursors and promote osteoclast formation via Beclin-1, TAB3, and ERK. In contrast, high levels of IL-17 exert the opposite effect [34]. In addition, PDLSCs undergoing osteogenic differentiation secrete TGF-β3, which acts on osteoclast precursors, leading to increased LC3-II and activated autophagy. Consequently, osteoclast formation is impaired and bone resorption is reduced [35].

4. Autophagy regulates immune-matrix interactions: downstream effects of autophagy

When activated, autophagy alters cellular function andthe way immune cells communicate with supporting cells, which in turn shapes the direction of bone remodeling. In supporting cells, autophagy regulates the release of inflammatory factors,which mediates intercellular communication and affects neighboring cells and immune regulation. On the loaded side of the tooth, PDLSCs upregulate LC3and activate autophagy while inhibiting the AKT pathway; at the same time,M1 macrophage markers TNF-α and iNOS increase, macrophages shifttoward the M1 phenotype, osteoclastogenesis rises, and bone remodeling becomes unfavorable [36, 37].

Immune cells also influencebone through autophagy, but the outcome is highly cell-type-dependent. During macrophage polarization, higherautophagy is usually linked to less bone

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resorption. More specifically,enhanced autophagy or mitophagy clears damaged mitochondria, reduces ROS accumulation, inhibits the NLRP3 inflammasome, decreases IL-1β release, and promotes M2 polarization. Together these changes create microenvironment that is more favorable for bone regeneration [38]. Conversely, inhibiting macrophage autophagy has the opposite effect.For example, CF inhibits macrophage autophagy via cGAS and P2X7R, activatesthe NLRP3 inflammasome, and promotesmacrophage differentiation into osteoclasts [39].

But pattern in neutrophils is different. Increased autophagy in these cells promotes bone resorption: S100A9 activates autophagy and leads to the formation of extracellular traps that promote macrophage differentiation into osteoclasts and enhance bone resorption [40]. These findings indicate that autophagy can exert opposite effects in different immune cell types.

5. Regulation of autophagy

5.1. Pharmacological and biologic regulation of autophagy

Multiple drugs and biologics improve the biological functions of periodontal and related cells and promote bone remodeling by activating autophagy. First, melatonin activates autophagy through multiple pathways to improve PDLSC function and bone remodeling. In an inflammatory microenvironment, melatonin activates autophagy by upregulating TMEM110 to promote osteogenic differentiation of PDLSCs [41]. Under senescent conditions, melatonin restores autophagic function of senescent PDLSCs through the MT-PI3K/AKT/mTOR pathway and reverses cellular senescence [42]. Similarly, both proanthocyanidins and psoralen activate autophagy by inhibiting the PI3K/Akt/mTOR pathway, thereby promoting the osteogenic differentiation of PDLSCs and endogenous alveolar bone regeneration [43].

Second, super-activated platelet lysate regulates the mTOR pathway during orthodontic maxillary expansion, regulates PDLSC autophagy and osteoclast activity, promotes bone remodeling, and shortens orthodontic treatment time [44]. In addition, L-arginine, an amino acid-based agent, upregulates the Sirt1 pathway under hypoxic conditions to activate autophagy, decreases Caspase-3 and Bax, and increases Bcl-2, thereby reducing cementoblast apoptosis and attenuating root resorption [45].

However, autophagy must be tightly regulated, as excessive autophagy is detrimental. One study found that prolonged compressive force overactivates PDLSC autophagy and increases cell death, whereas blocking Beclin-1-dependent autophagy reduces cell death. Thus, under orthodontic force, autophagy exerts dual effects [46].

5.2. Nanomaterial regulation of mitophagy

Nanomaterials can target autophagy and improve cellular function. Gold nanoparticles promote the osteogenic differentiation of PDLSCs through two mechanisms. In inflammation, they restore the TFEB autophagy-lysosome system. thereby rescuing impaired autophagic flux [47]. They also activate PINK1 mitophagy, thereby improving mitochondrial function [48]. Subsequently, PDLSCs are mixed with gold nanocomplex and encapsulated in a type I collagen gel, which is implanted into rats with alveolar bone loss. Autophagy is activated, PDLSCs promote bone formation, and bone loss is attenuated [49]. In addition, nanoparticles that sustain drug release can activate mitophagy through the PINK1-Parkin pathway and promote gingival tissue regeneration [50].

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5.3. Photobiomodulation (PBM) regulation of autophagy

PBM is a non-invasive light treatment that modulates bone and gingival tissue by regulating autophagy. PBM blocks the PI3K/Akt/mTOR pathway in preosteoblast, thereby increasing autophagic flux and promoting osteogenic differentiation and matrix production [51]. In osteoporotic disease, 650 nm PBM activates autophagy in bone marrow stem cells, increasing alkaline phosphatase production and mineral deposition [52]. In rats undergoing tooth movement, both 660 nm and 808 nm lasers upregulate Beclin-1 in gingival cells near the loaded molar. Autophagy activating autophagy, reducing osteoclast formation, and increasing bone density [53]. These results indicate PBM can protect teeth during and after treatment by regulating autophagy pathways, and that optimal wavelength, energy, and timing are required for optimal outcomes.

6. Conclusion

In recent years, autophagy in OTM has gradually attracted the attention of orthodontists and researchers. Mechanical stimulation, hypoxia and inflammatory signals together constitute the OTM microenvironment, which induces oxidative stress through multiple pathways and thus activates autophagy. The regulation of autophagy by different signals is cell-type-dependent: compressive force activates autophagy in most periodontal cells but inhibits it in cementoblasts, whereas tensile force, fluid shear force and hypoxia consistently induce autophagy in all studied cells. Following activation, autophagy ultimately determines the direction of bone remodeling by regulating the immune-matrix interaction network. Intervention strategies targeting key nodes in this framework (drugs, nanomaterials, photobiomodulation) have shown potential for clinical translation.

Some limitesremain. Data are still scarce,and real-time observation is limited. Even so,as evidence on autophagy in OTM continues to accumulate,future research may support both basic science and clinical practice and help clarify the mechanism of OTM.

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