ORAL SCI HOMEOST MED

Open Access
REVIEW

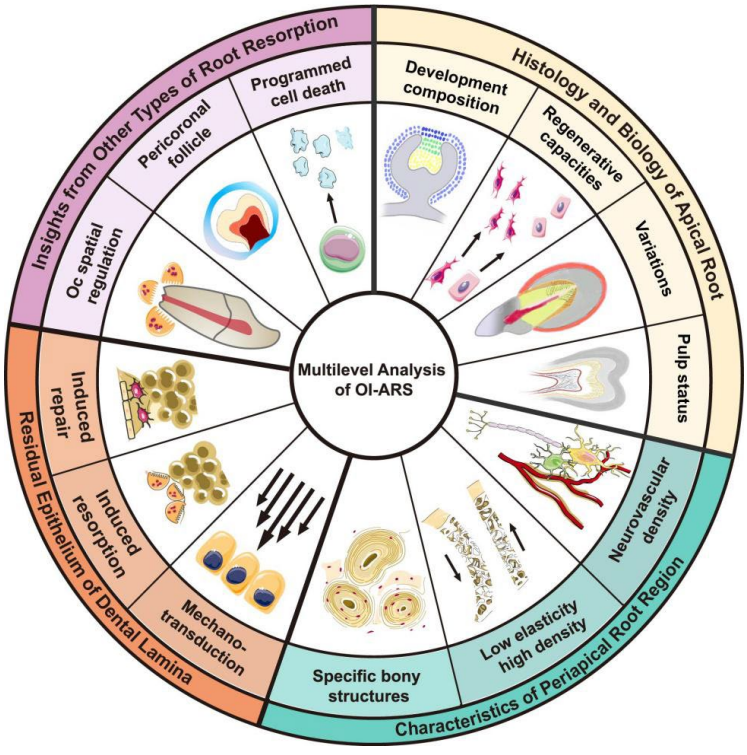
Orthodontically induced apical root shortening: a multilevel analysis of anatomical vulnerabilities, cellular crosstalk, and molecular regulation

Jie Zhang[1,2], Xiao Yuan[1,2], Hong Ding[1], Xi Chen[2], and Chunmiao Jiang[1,2] ✉

[1] *Department of Orthodontics, The Affiliated Hospital of Qingdao University, Qingdao, 266003, China*
[2] *School of Stomatology, Qingdao University, Qingdao, 266023, China*

Cite This: *Oral Sci Homeost Med*, **2026**, 2, 9610039 Read Online

ABSTRACT: Orthodontically induced apical root shortening (OI-ARS) poses a significant clinical challenge, characterized by asymptomatic yet progressive resorption of apical hard and soft tissues, ultimately leading to irreversible root structure loss. Despite its clinical prevalence, the mechanistic underlying of OI-ARS remains poorly understood, with current research predominantly focused on the extensive resorption of dental tissues by osteoclasts rather than apical-specific pathobiology. Additionally, several terminologies have emerged to characterize OI-ARS. However, conceptual ambiguities persist, particularly in distinguishing between reversible cemental remodeling and irreversible apical root shortening. This review systematically examines OI-ARS through an integrative anatomical-cellular-molecular framework, emphasizing how the unique vulnerability of the apical microenvironment arises from its histological and biology, developmental remnants of the dental lamina epithelium, and characteristic of the periapical root region. Furthermore, this review draws parallels between OI-ARS and similarly resorption patterns observed in deciduous teeth and adjacent teeth of impacted teeth, proposing shared regulatory mechanisms involving spatiotemporal control of osteoclastogenesis. Finally, this review identifies critical research directions for elucidating the mechanisms of OI-ARS, aiming to provide novel insights for the prevention and clinical management of this complication.



KEYWORDS: orthodontically induced root resorption, apical root shortening, cellular cementum, neurovascular network, epithelial cell rests of Malassez

1 Introduction

The terminology surrounding root resorption has undergone significant evolution since its initial conceptualization by Scholar Albin Oppenheim in 1942[1]. Subsequent terminologies have emerged based on anatomical location and pathological mechanisms, including external root resorption (ERR), internal root resorption (IRR), external cervical resorption (ECR), cementum resorption, external inflammatory (infection-related) resorption (EIR), and external replacement resorption[2]. Particularly in the field of orthodontics, the terminology has become increasingly specialized, with terms such as orthodontically induced root resorption (OIRR), orthodontically induced inflammatory root resorption (OIIRR), and orthodontically induced external apical root resorption (OI-EARR) being introduced[3-5]. However, these terms have led to some conceptual ambiguities.

It is crucial to differentiate between root resorption and root

Received: December 8, 2025; **Revised:** January 12, 2026
Accepted: January 19, 2026

✉Address correspondence to Chunmiao Jiang, jiangcm@qdu.edu.cn

shortening, as they represent distinct biological processes with different clinical implications. Root resorption generally refers to the pathological process where the root structure is progressively destroyed by osteoclasts and other resorptive cells. This can occur due to various factors such as inflammation, infection, or orthodontic forces. In contrast, root shortening specifically denotes the reduction in the length of the tooth root, often as a result of apical resorption. While root resorption can lead to root shortening, not all resorption processes result in clinically significant shortening. The distinction is important because root shortening can have more severe clinical consequences, such as increased tooth mobility and potential tooth loss, whereas some forms of root resorption may be less clinically significant.

A critical distinction exists between two fundamentally different biological processes during orthodontic force application. One is the physiological cemental resorption-remodeling cycle, and the other is pathological apical root resorption that results in irreversible structural damage[6]. These processes differ markedly in their clinical manifestations, prognostic implications, and long-term impacts on dental integrity. To address this, Naphtali Brezniak proposed the terms "instrumental orthodontitis" and "instrumental detrimental orthodontitis" in 2016[6]. Instrumental orthodontitis describes the sterile inflammation that occurs in the periodontal ligament (PDL) after orthodontic force application, which involves physiological cementum remodeling on the root surface without clinically or radiographically detectable root shortening. Instrumental detrimental orthodontitis specifically denotes apical root shortening, which is radiographically detectable and clinically significant as a primary contributor to tooth mobility, potential tooth loss, and patient-clinician disputes. However, current basic research on the specific mechanisms of orthodontic-induced root resorption still focuses on the extensive resorption of dental tissues by osteoclasts, with no effective research on the mechanisms underlying orthodontically induced apical root shortening (OI-ARS).

The process of OI-ARS represents a fascinating biological phenomenon worthy of in-depth investigation. During this process, both hard tissues (cementum and dentin) and soft tissues (PDL and dental pulp) in the apical region undergo progressive resorption, remarkably without eliciting pain symptoms in patients. Although the neurovascular tissues in the apical region were absorbed, the neurovascular function in the crown portion remained normal, which resulted in the delayed diagnosis of OI-ARS, with orthodontists only identifying the root shortening through radiographic examination during treatment and upon treatment completion. Interestingly, this process shares remarkable similarities with physiological root resorption patterns observed in deciduous teeth and adjacent teeth of impacted teeth, where painless, targeted osteoclastic activity progressively resorbs root structures[7,8]. These parallels may provide valuable mechanistic insights for understanding OI-ARS. Elucidating the underlying mechanisms, including the fate of resorbed apical tissues and the precise spatial regulation of osteoclasts activity in the apical region, holds significant promise for developing preventive strategies against OI-ARS.

The unique anatomical structure of the apical region may be one of the reasons for its susceptibility to resorption. The apical region is where cementum and dentin meet, and the cementum in this area is cellular cementum. The dental pulp enters pulp chamber through the apical foramen in this region, and this area is surrounded by a rich network of blood vessels and nerves[9]. Following root development, residual epithelial components, including epithelial cell rests of Malassez (ECRM), persist within the PDL[10,11]. However, the role of these epithelial remnants in mediating and repairing orthodontically induced root resorption within the inflammatory microenvironment remains poorly understood. Similarly, the response of the apical neurovascular network to mechanical forces and its potential contribution to root resorption requires further investigation.

To address the lack of understanding of the mechanisms underlying OI-ARS, this current review has examined the potential causes from four aspects: (a) the histology and biology of the apical region, (b) the role of residual epithelium of dental lamina, (c) characteristics of periapical root region and susceptibility to OI-ARS and (d) the reflections from root resorption in primary teeth and adjacent teeth of impacted teeth (Fig. 1). By synthesizing current evidence across these domains, this review aims to stimulate further research into effective strategies for preventing and controlling OI-ARS.

2 Histology and biology of apical root

The apical root exhibits complex anatomical structures, with dentin and cementum converging to form the physiological apical foramen—the sole channel connecting the pulp cavity to external tissues, through which nerves, blood vessels, and lymphatic tissues traverse. This junction, however, becomes a biomechanical and biological weak point due to disparities in developmental origin, tissue composition, and regenerative capacity between dentin and cementum. These inherent anatomical and histological vulnerabilities predispose it to resorption under mechanical stress or inflammatory insults. Below, this review examines the developmental origins, structural heterogeneity, regenerative limitations, and pulp interactions at the apical root to elucidate the pathogenesis of OI-ARS and propose novel strategies for its prevention and treatment.

2.1 Development and composition

In terms of developmental origins, cementum is derived from dental follicle mesenchymal stem cells (DFSCs) and Hertwig's epithelial root sheath (HERS), whereas dentin is developed from mesenchymal stem cells within the dental papilla[12,13]. Specifically, after root dentin formation, the HERS disintegrates into a mesh-like structure, allowing dental follicle cells to migrate through it and differentiate into cementoblasts on the dentin surface. A portion of the fragmented HERS contributes to cementum formation, while the remainder persists in the developing periodontal ligament as ECRM[12]. Concurrently, odontoblasts derived from the dental papilla gradually migrate centripetally during the formation of dentin, and the volume of the dental papilla gradually decreases. Once the primary dentin is fully formed, the remaining blood vessels and connective tissues in the pulp cavity constitute the dental pulp[14]. This developmental divergence compromises the apical region's ability to resist external damage and complicates regeneration (Fig. 2a).

In terms of tissue composition, dentin contains approximately 70% inorganic content (primarily hydroxyapatite), whereas cementum comprises only 65%[15-18]. Researchers reported that the hardness and elastic modulus were positively correlated with mineral content in cementum and dentin[19-22]. Poolthong found that

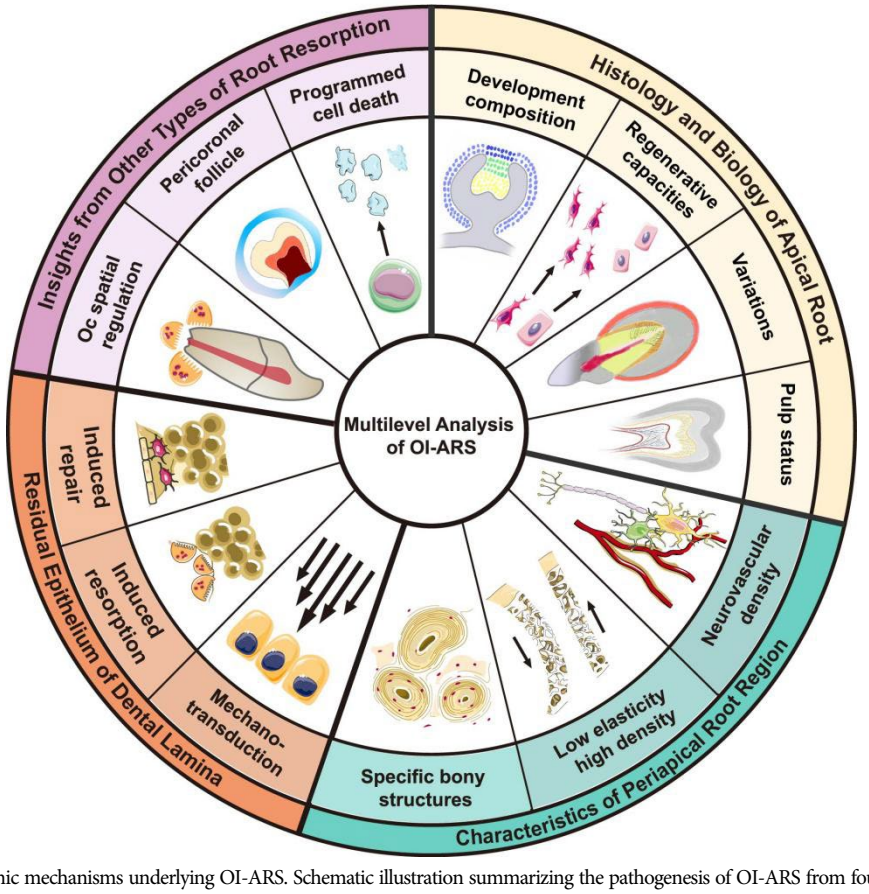


Figure 1 Multilevel pathogenic mechanisms underlying OI-ARS. Schematic illustration summarizing the pathogenesis of OI-ARS from four major aspects: a) Histology and biology of the apical region, including differences in developmental origins, tissue composition, regenerative capacities, and the role of dental pulp. b) Unique characteristics of periapical root region, such as high neurovascular density, variations in bone elasticity and density, and anatomical peculiarities (e.g., incisive canals, bone islands). c) Role of residual epithelium of dental lamina in apical root resorption, highlighting their functions in root repair, root resorption, and mechanotransduction. d) Insights from other types of root resorption, including programmed cell death, the regulatory of pericoronal epithelium, and spatially precise osteoclast regulation.

the elastic modulus of dentin ranged from 17.5 to 22.9 GPa, while the elastic modulus of cementum ranged from 8.6 to 12.0 GPa, and the hardness of dentin ranged from 0.88 to 1.13 GPa, while the hardness of cementum ranged from 0.57 to 0.63 GPa[18]. Compared with dentin, cementum has a lower stiffness or elastic modulus to compensate for the movement of the root when functioning (Fig. 2b)[23]. Besides, this reduced mineral content and elastic modulus of cementum weakens its resistance to orthodontic force and osteoclast resorption. Consequently, if cementum is resorbed, dentin loses its protective buffering layer, leading to stress concentration. However, it remains unclear whether the dentin-cementum complex provides greater resistance to orthodontic forces compared to the dentin layer alone. Future studies could utilize three-dimensional finite element analysis to investigate the stress distribution in various regions of the tooth root following cementum resorption, thereby investigating the risk factors contributing to OI-ARS.

2.2 Regenerative capacities

Differences in developmental origins and tissue composition result in differences in regenerative capacity (Fig. 2c). In dentin resorption due to physiological wear or carious insults, dentin exhibits two repair mechanisms: (1) under mild stimuli, odontoblast activity increases to form reactive dentin; (2) under severe stimuli, odontoblasts undergo apoptosis, triggering a complex process involving the recruitment and differentiation of dental pulp stem/progenitor cells into odontoblast-like cells, which produce reparative dentin[24-26]. Furthermore, odontoblasts exhibit morphological heterogeneity. Coronal odontoblasts in young permanent teeth are tall columnar cells reflecting high activity, whereas radicular odontoblasts become cuboidal and flatten near the apex, entering a quiescent state[27-30]. Thus, once osteoclasts breach the cementum and resorb dentin, the lack of functional odontoblasts in apex limits regeneration to poorly mineralized reparative dentin, creating a vicious cycle of "resorption-destruction" under sustained mechanical forces.

Cementum, located on the outermost layer of the root, has a structure similar to bone tissue, comprising cells and mineralized extracellular matrix. Cementum exhibits stronger resistance to resorption compared to the alveolar bone proper, forming the basis for tooth movement during clinical orthodontic treatment. However, the hardness and the elastic modulus of cementum were reported to decrease from the cervical to the apical third[18]. This may render the cementum in the apical region more susceptible to root resorption. During cementum resorption, cementoblasts at the apex differentiate new cementum, and ECRM in the periodontal ligament differentiates into cementoblasts to facilitate repair (Fig. 2c)[31]. However, compared to the porous and highly vascularized alveolar bone, cementum demonstrates weaker regenerative capacity[32]. This may be related to the absence of blood vessels

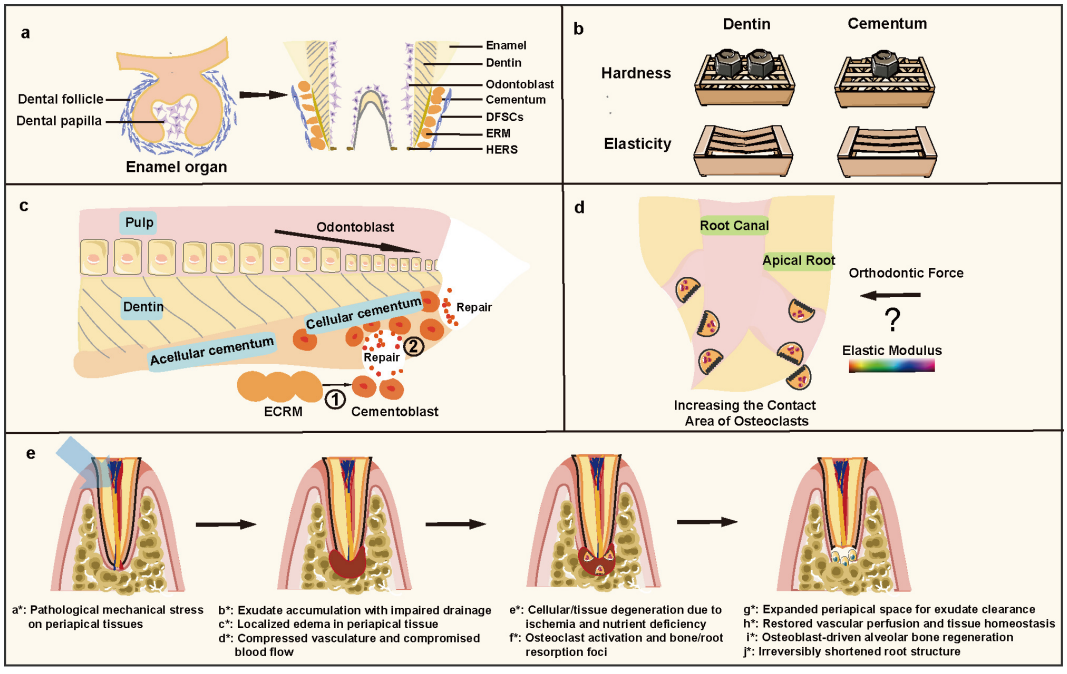


Figure 2 The complexity and heterogeneity in the apical region. (a) Cementum is derived from DFSCs and HERS, whereas dentin is developed from mesenchymal stem cells within the dental papilla. (b) Compared with dentin, cementum has a lower stiffness and elastic modulus. (c) In cementum resorption, cementoblast at the apex differentiate new cementum, and ECRM in the periodontal ligament differentiate into cementoblasts to facilitate repair. (d) Cross-sectional anatomy of apical root canal system variations. Anatomical variations increase the surface area for osteoclast attachment and activity, facilitating apical resorption. The elastic modulus between apical ramification regions and the main root canal under orthodontic forces is still not clear. (e) Excessive or prolonged mechanical loading induces pathological stress in periapical tissues (a*), triggering exudate accumulation with impaired drainage, localized edema, and vascular compression (b*-d*). Resultant ischemia and nutrient deprivation provoke cellular degeneration. In response, host defenses recruit osteoclasts to resorb alveolar bone and root structure (e*-f*), expanding periapical spaces to alleviate inflammatory pressure and restore vascular perfusion. Subsequent osteoblast activity regenerates alveolar bone volume, while irreversible root shortening persists due to limited reparative capacity of dental hard tissues (g*-j*).

within cementum, leading to insufficient nutrient supply, as well as the limited mobility and differentiation potential of cementoblasts embedded within the cementum. Consequently, the repair process following cementum damage is slow. Statistically, root resorption continued at 4 weeks after the completion of orthodontic treatment. During this period, osteoclasts persisted in removing necrotic tissue, and root resorption occurred simultaneously with repair. However, resorption lacunae were still evident, and it was found that the majority of cementum repair activity occurred after 4 weeks of retention[33]. Therefore, in clinical orthodontic treatment, it is generally recommended to suspend treatment for teeth with moderate to severe orthodontically induced root resorption. A 3-month resting period is advised to allow sufficient time for cementum self-repair before resuming treatment or monitoring for potential progression of root resorption. Additionally, mechanical forces can stimulate osteoblast differentiation to promote bone formation. However, whether differences in the responses of cementoblasts, periodontal ligament cells, and osteocytes to mechanical stimuli contribute to the slower repair rate of cementum requires further investigation.

2.3 Variations

Additionally, anatomical variations in root canals may arise due to developmental anomalies in HERS[34]. These variations are particularly prevalent in the apical region, often manifesting as apical ramifications (AR) or apical delta branches. Lobo et al. found that most of the ARs are located in the apical 1 and 2 mm of the root[35]. Gao et al. reported that the median vertical distance of the apical delta was 1.87 mm, with 13% exceeding 3 mm, and the median diameter and length of the apical delta branches were 132.3 and 934.5 μm. Apical delta branches were not straight, with non-circular cross-sectional shapes[36]. These structural features increase the surface area for osteoclast attachment and activity, facilitating apical resorption. Furthermore, whether differences in the elastic modulus between apical ramification regions and the main root canal predispose the former to microcracks under orthodontic forces, thereby promoting the migration of osteoclast precursors, warrants further investigation (Fig. 2d).

2.4 Pulp status

The dental pulp serves as a critical mediator of internal root resorption, and its correlation with external root resorption has been substantiated by multiple studies[37-40]. Clinical evidence showed that the external apical root resorption (EARR) of endodontically treated teeth was reduced by approximately 0.75 mm compared with vital pulp teeth in the fixed orthodontic treatment group. Similarly, in clear aligner treatment group, endodontically treated teeth show approximately 0.5 mm less EARR than vital pulp teeth[41]. This phenomenon may be attributed to the compensatory hyperplasia of cementum, reduced inflammatory response, structural changes in dentin and cementum. In terms of compensatory hyperplasia of cementum, after root canal treatment, the pulp tissue is removed and root canal is filled with artificial material, the dentin loses its nutrient supply. The cementum undergoes compensatory hyperplasia, which can enhance the stability of the tooth within the alveolar socket[42]. This increased

cementum thickness can act as a protective barrier against mechanical forces and reduce the susceptibility to resorption. In terms of reduced inflammatory response, the removal of the pulp tissue eliminates the inflammatory sources and infected substances. At the same time, root canal therapy blocks the invasion of bacteria and inflammatory factors through strict root canal filling and sealing, thereby reducing the inflammatory response of the periapical tissue. This closure helps to maintain the healthy state of periapical tissues, ultimately reducing the possibility of root resorption. In terms of structural changes in dentin and cementum, endodontic treatment can result in depletion of the organic components of root dentine and alteration in the chemical composition, result in lower fracture toughness, decrease in resistance to fatigue failure[43]. However, the impact of structural changes on the resistance to osteoclastic resorption still requires further investigation.

During orthodontic tooth movement in vital pulp teeth, the pulp or periodontal tissues at the root apex are subjected to increased pressure, leading to local tissue edema. On one hand, there is an increase in exudates such as inflammatory cytokines. On the other hand, small arteries are compressed, resulting in a reduction of blood supply within the pulp. According to research reports, as a self-protective mechanism, the capillary network within the crown is denser than that of the root apex[44]. Therefore, once the blood supply is reduced, the blood supply at the root apex becomes extremely limited. Deprived of nutritional support and simultaneously exposed to a variety of inflammatory cytokines, the dental tissues at the root apex undergo resorption. This resorption phenomenon can be regarded as a defensive behavior of the body. After resorption at the root apex, the pressure in the apical region is reduced, the apical foramen enlarges, and consequently, the blood supply within the tooth is allowed to increase (Fig. 2e)[45].

3 Residual epithelium of dental lamina

Root development is orchestrated through dynamic interactions between epithelial and mesenchymal cells. During this process, the apical region contains dental papilla cells that progressively differentiate into pulp tissue. Simultaneously, the HERS extends apically to direct root morphogenesis. The coronal portion of HERS undergoes fragmentation, creating pathways for dental follicle cells to infiltrate the disassembled epithelial network. These migrating cells subsequently differentiate into cementum-forming cells and periodontium[46,47]. This spatiotemporal coordination establishes a microenvironment where epithelial cells and mesenchymal cells within the apical region throughout root development. Clinically, young permanent teeth with incomplete root development exhibit a lower incidence of root resorption during orthodontic treatment, and the less root resorption may result from the effects of dental follicle cells and HERS in repairing resorption by differentiation toward cementoblast and odontoblast[48]. This suggests that attention should be paid to the functions of epithelial and mesenchymal cells around the root, which may play a role in the repair of OI-ARS.

Despite this complexity, current research on the pathogenesis of root resorption predominantly focuses on mesenchymal-derived periodontal ligament cells, largely neglecting the potential contributions of epithelial components[49,50]. To address this gap, this review next synthesizes evidence regarding developmentally critical epithelial populations and their potential associations with root resorption mechanisms.

3.1 Characteristics of epithelial cells

Epithelial cells and mesenchymal cells exhibit significant differences in tissue structure and function. Epithelial cells exhibit the capacity for epithelial-mesenchymal transition (EMT), maintaining apical-basal polarity and forming specialized intercellular junctions, including tight junctions, adherens junctions, and desmosomes. With the loss of apical-basal polarity and cell-cell contact structure, epithelial cells exhibit increased migration (Fig. 3a)[51]. After root development is complete, the epithelial root sheath disintegrates, leaving epithelial cells within the periodontal tissues. When tooth is subjected to stimuli, these cells can migrate to the affected area, participating in tissue repair or exacerbating disease progression. For instance, in cases of apical periodontitis, inflammatory products stimulate the proliferation of ECRM. When these proliferations form larger masses, the central epithelial cells, due to a lack of nutrients, undergo degenerative changes, necrosis, and liquefaction, forming a radicular cyst[52]. When the dental lamina remnant is stimulated, it can form odontogenic keratocysts and gingival cysts[52,53]. Ameloblastoma is one of the most common benign epithelial tumors of odontogenic origin. The epithelium of ameloblastoma is derived from odontogenic epithelium, such as residual epithelium of the tooth germ and epithelium of the enamel organ[54]. When tumor invades the alveolar, the involved root may be absorbed in a large area, leading to tooth loosening, displacement or loss[55,56].

The characteristics of EMT and migration enable epithelial cells to reaching the affected areas for proliferation and differentiation. However, the proliferation, migration, EMT, and outcomes of epithelial cells during root resorption are not yet clear. The structures and signaling pathways by which epithelial cells perceive mechanical stimuli during orthodontic forces are also unknown. Therefore, this review subsequently concludes the epithelial components associated with tooth development, and explored the outcomes of these epithelial components following stimulation, as well as their association with OI-ARS.

3.2 Epithelial remnants and root resorption

3.2.1 Reduced enamel epithelium

After the completion of enamel development, ameloblasts, stratum intermedium, and stellate reticulum combine with the outer enamel epithelium to form a layer of squamous epithelium covering the enamel organ, known as the reduced enamel epithelium. When the tooth erupts into the oral cavity, the reduced enamel epithelium forms the junctional epithelium of the gingiva at the cervical region of the tooth. If the tooth has not yet erupted, the reduced enamel epithelium can become the origin of dentigerous cysts, eruption cysts, or lateral periodontal cysts[57]. The reduced enamel epithelium may mediate in the root resorption of neighboring teeth and the alveolar bone. In cases of dentigerous cysts, contact between the reduced enamel epithelium and the roots of adjacent teeth can easily lead to root resorption of the neighboring teeth. This phenomenon is similar to orthodontically induced apical root resorption, characterized by the progressive resorption of apical tissues such as the dental pulp and periodontal ligament. Mechanistically, reduced enamel epithelial cells have been reported to express various factors and receptors, including transforming growth factor beta (TGF-β) receptor 1, TGF-β-inducible

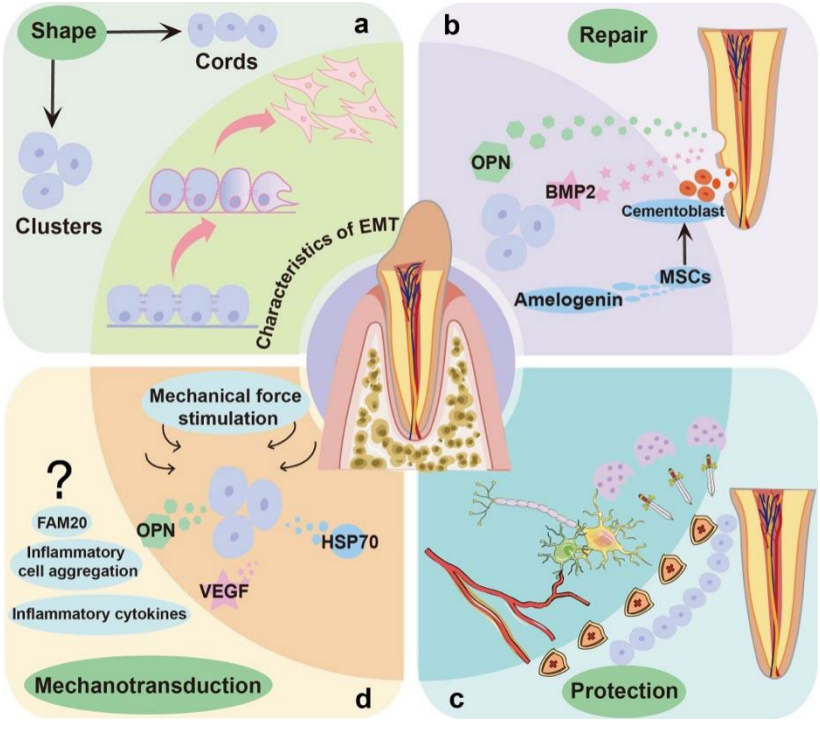


Figure 3 Schematic diagram of the role of ECRM in apical root resorption. (a) Epithelial cells exhibit the capacity for EMT. During this process, apical-basal polarity is redirected into front-rear polarity, cytoskeletal changes occur, and downregulation of epithelial junctions. The shape of ECRM in periodontal ligament is small epithelial cords or clusters. (b) ECRM have the potential to repair cementum. (c) The integrity of ECRM prevent the invasion of blood vessels, nerves and osteoclasts. (d) The mechanoresponsive properties of ECRM. The expression of FAM20, induction of inflammatory cell aggregation and secretion of inflammatory cytokines is still not clear.

transcription factor 1, NADPH oxidase 4, cytochrome c, caspase-3, β-catenin and parathyroid hormone-related protein (PTHrP)[57-60]. Among these, PTHrP plays a critical role in promoting alveolar bone resorption, which is essential for tooth development and eruption. This process is mediated through the RANK/RANKL (receptor activator of nuclear factor-kappa B/receptor activator of NF-κB ligand) signaling pathway[57,61,62]. Resorption of the tooth root by the reduced enamel epithelium can be induced in the same manner as the alveolar bone during the process of eruption pathway formation[57]. The cell component and mechanism by which the reduced enamel epithelium induces root resorption requires further investigation, which may provide insights into OIARS.

3.2.2 Epithelial cell rests of malassez (ECRM)

ECRM are odontogenic epithelial cells that remain in the periodontium after the eruption of teeth[10]. In the periodontal ligament, small epithelial cords or clusters can be observed in the fibrous spaces near the root surface (Fig. 3a). These structures, which are arranged parallel to the root surface, are known as ECRM[31,63]. ECRM possesses functions such as preventing root resorption, maintaining the periodontal ligament space, preventing ankylosis, regulating cementoblast differentiation and formation of radicular cysts[11,64]. In terms of root resorption, ECRM might change their morphological structure and exist in connective tissue of the resorption lacunae. An ultrastructural study showed epithelial cell clusters similar to ECRM were present in repairing resorption lacunae subsequent to orthodontic tooth movement in humans[65]. Another study showed that ECRM were observed in resorption areas on root surfaces of extracted premolars after rapid palatal expansion using transmission electron microscopy with 3-dimensional reconstruction[66]. In terms of cementum repair, ECRM have the potential to contribute to this process by secreting enamel proteins, bone morphogenetic protein 2 (BMP2), and osteopontin (OPN). Additionally, ameloblastin may play a role in inducing the differentiation of mesenchymal cells into cementoblasts (Fig. 3b)[31,67]. However, they found that ECRM did not increase in number, and epithelial cells were not observed in the connective tissue of resorption lacunae. It is suggested that proliferated epithelial cells from ECRM might be transformed and directly participate in cementum repair[31]. Mechanistically, ECRM cells express osteoprotegerin (OPG), and OPG deficiency leads to the destruction of ECRM, characterized by irregular morphology and reduced numbers[63]. In addition, the integrity of ECRM can prevent the invasion of blood vessels and osteoclasts (Fig. 3c), which plays a positive role in preventing root resorption[68,69].

Epithelial cells exhibit mechanoresponsive properties. ECRM respond to mechanical stretching forces by expressing heat shock protein 70 (HSP70), vascular endothelial growth factor (VEGF), and osteopontin (OPN) (Fig. 3d)[70]. FAM20A, a kinase responsible for orchestrating the phosphorylation of secreted proteins and proteoglycans, has been implicated in various dental pathologies, including amelogenesis imperfecta, intrapulpal calcification, gingival hyperplasia, and delayed or failed tooth eruption. In epithelial-specific FAM20A knockout (KO) mice, delayed tooth eruption primarily occurs during the intraosseous eruption stage. This delay is associated with a postponed peak in osteoclast activity, leading to a later formation of the eruption canal and, consequently, delayed tooth eruption. Additionally, the development of HERS is disrupted in FAM20A KO mice, resulting in the activation of the WNT signaling pathway and downregulation of tooth root development-related pathways, ultimately causing shortened tooth

roots[71]. Although FAM20A may play a role in root resorption by modulating epithelial cell functions, no direct studies have yet investigated this potential mechanism.

In summary, the role of epithelial cells in root resorption should not be ignored given their migratory properties, epithelial-mesenchymal transition properties, mechanotransduction properties, and important role in cementum repair. However, the spatiotemporal distribution of epithelial cells within the tooth root and the mechanisms underlying their induction of inflammatory cell aggregation or cytokines under orthodontic force remain to be further explored. Elucidating the spatiotemporal coding patterns of epithelial-mesenchymal communication and developing epithelial-specific targeted delivery systems may hold significant importance for the prevention and treatment of OI-ARS.

4 Characteristics of periapical root region and susceptibility to OI-ARS

4.1 Blood vessels

Blood vessels in the PDL provide nutrients, immune cells, and hormones required for orthodontic-induced remodeling[72]. Young permanent teeth with incomplete apical development and large apical foramina have an abundant blood supply in the apical region, resulting in a low probability of root resorption during orthodontic treatment. This indicates that the presence of blood vessels around the root is a factor in regulating root resorption. Next, this review explores the mechanisms by which blood vessels influence apical root resorption from two aspects: the regulation of surrounding stem cells affecting bone remodeling and the mechanotransduction capacity of vascular endothelial cells (ECs) (Fig. 4b).

There are a large number of undifferentiated stem cells around the blood vessel wall, which can participate in tissue regeneration and repair. Shen et al. discovered osteogenic progenitor cells surrounding the peri-arteriolar region in bone marrow, which were specifically LepR+ cells expressing Osteolectin. These peri-arteriolar LepR+Osteolectin+ cells are rapidly dividing, short-lived osteogenic progenitors that are poised for osteogenic differentiation. Their numbers increase following fracture and diminish with age. The maintenance of these cells requires mechanical stimulation[73]. In addition, type H vessels, which high expression of cluster of differentiation 31 (CD31) and endomucin (Emcn), have a dense arrangement of osteoprogenitors[74]. Runx2+ osteoprogenitors and collagen type 1α+ (Col1α1+) osteoblasts are densely arranged around the CD31+ vessels[75]. In alveolar bone, H-type vessels increased at the healing site in tooth extraction model, and with perivascular accumulation of Runx2+ osteoprogenitors[76]. In PDL, neural crest-derived mesenchymal stem cells such as prx1+ cells overlap with perivascular cells and are involved in angiogenesis[77]. The phenomenon of osteoprogenitors close to vessels is to absorb the nutrients and oxygen required for osteogenic metabolism, and can also take the vessel as a vehicle to migrate to the bone remodeling area[78].

Vascular endothelial cells secrete a variety of cytokines to regulate the function of osteocytes in the bone marrow microenvironment, and conversely, osteocytes can also regulate angiogenesis. In osteogenesis, Type H ECs secrete growth factors that have been demonstrated to promote osteoprogenitor survival and proliferation, such as platelet-derived growth factor subunit A (PDGFA), TGFβ1, TGFβ3, and fibroblast growth factor (FGF) 1[75]. After co-culture with vascular endothelial cells, the osteogenic differentiation ability of osteoblasts was enhanced, and the expression of osteogenic markers such as ALP, runx2 and osterix (OSX) was increased[79]. In bone resorption, MMP-9 and RANKL, released from type H ECs is critical for bone resorbing by regulating osteoclasts[78]. Perivascular osteoclasts protect the neighboring vascular cells against senescence by secreting angiogenin (ANG), a ribonuclease with pro-angiogenic activity[80]. Besides, osteoblast and osteoclast promote angiogenesis by secreting platelet-derived growth factor BB (PDGF-BB), VEGF, and slit guidance ligand 3 (slit3). In periodontium, periodontal ligament cells (PDLCs) secrete slit3 to promote the growth of H-type blood vessels, thereby regulating alveolar bone homeostasis[81]. However, excessive vascularization can exacerbate inflammatory responses. Denser

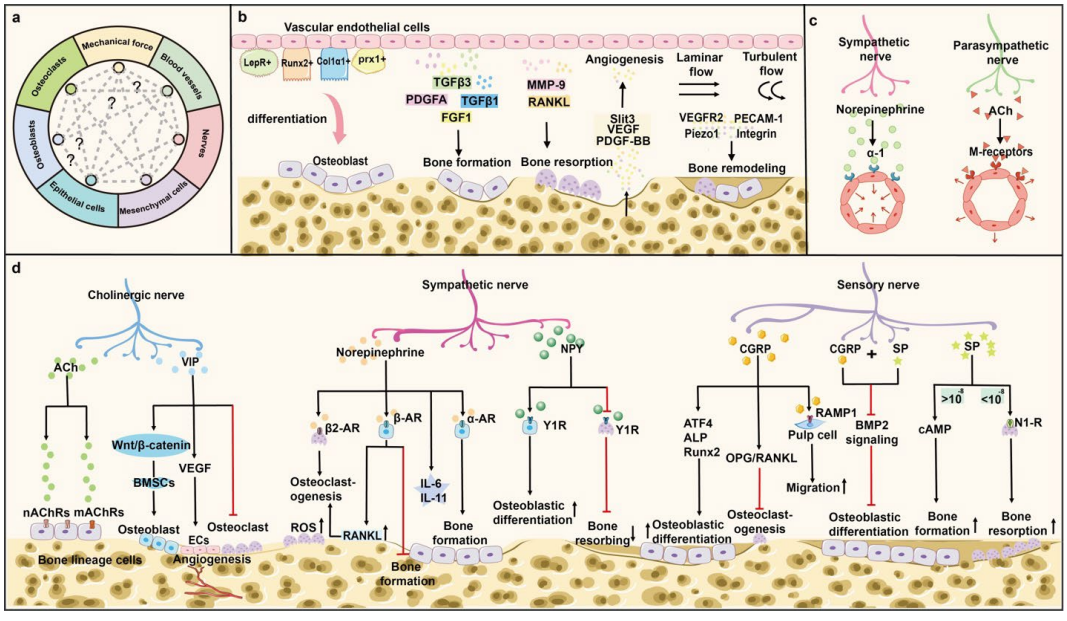


Figure 4 Blood vessels and neural regulatory mechanisms in bone linked to OI-ARS. (a) The interrelationships between the components present around the apical root. (b) The role of blood vessels in bone remodeling. (c) Regulation of blood vessels by nerves. (d) Neural regulatory in bone remodeling.

vasculature with enlarged vessel diameters enhances inflammatory infiltration, which in turn disrupts angiogenesis and bone remodeling[82]. For example, in the microenvironment of periodontitis and osteoarthritis, PDLCs or chondrocytes secrete a large number of pro-angiogenic factors such as VEGF, leading to increased vascular infiltration and aggravated bone resorption[83-85]. These findings highlight the critical interplay between angiogenesis, osteogenesis, and bone resorption in maintaining bone remodeling homeostasis. Disruption in any of these processes can destabilize the balance of bone remodeling.

Vascular endothelial cells possess the ability to sense and transduce mechanical stimuli. In response to physical mechanotransduction forces from blood flow, such as laminar flow, turbulent flow, or cyclic stretching mediated by blood pressure, endothelial cells convert these mechanical stimuli into biochemical signals through receptor tyrosine kinases (e.g., VEGFR2 and VEGFR3), ion channels (e.g., Piezo1 and TRPV4), integrins, and junction proteins (e.g., PECAM-1 and VE-cadherin), thereby regulating adaptive changes in vascular structure and function[86,87]. The dysfunction of mechanotransduction in endothelial cells is closely associated with the progression of diseases such as atherosclerosis and hypertension[88]. During tooth movement, the vessels surrounding the root are also subjected to mechanical stimulation. However, little attention has been paid to the blood vessels in the model of root resorption, especially OI-ARS, and the interaction between endothelial cells and osteogenic precursor cells or osteoclasts under mechanical stimulation has not been studied (Fig. 4a).

In the apical region, blood vessels occupy approximately 47% of the space within the PDL, in comparison with 4% at the cervical area of the root[89]. During orthodontic tooth movement, the blood vessels in PDL are subjected to pressure or stretch, and the blood supply is affected. Especially in the apical region, the apex moves the most (root wise), since this part is at the edges of the moving levers[9]. This means the adequate blood supply becomes poor, the adjacent tissues in apical region are less able to adapt to the sudden decrease in blood supply. When orthodontic forces are excessive or long-lasting, the blood vessels around the tooth root are subjected to excessive compression or traction, leading to local ischemia or bleeding that forms acellular areas with hyaline degeneration or thrombosis. To eliminate this necrotic tissue, immune cells are recruited to the damaged area. During this process, the release of chemicals such as histamine and serotonin increases vascular permeability, triggering a more severe inflammatory response, and releasing more inflammatory cytokines, causing tissue edema and cell infiltration, which further affects blood flow. Unlike compression at the cervical area, which is adjacent to the gingiva and oral cavity, tissue fluid can quickly find this pathway to seep out or transfer, often manifesting clinically as gingival redness and swelling[9]. However, edema occurring at the apex is not easily drained, leading to increased local pressure. Under such an adverse microenvironment, endothelial cell dysfunction occurs, on the one hand, leading to impaired differentiation function of adjacent stem cells and abnormal cementum function at the apex, and on the other hand, inducing an increase in osteoclasts that absorb necrotic tissue at the apex, including the apical area surrounded by tissue fluid. These may be one of the reasons why the apex is prone to root resorption. In addition, the abnormal mechanosensing and mechanoconduction of endothelial cells may also play an important role in the progression of apical resorption. In the future, more basic research can focus on the functional changes of blood vessels in the process of OI-ARS to further explore its pathogenesis.

4.2 Nervous system

In craniofacial system, trigeminal nerve is the primary neural source regulating the development of teeth and the maxillofacial bones[90-92]. Its branches enter the dental pulp through the apical foramen or distribute within the corresponding periodontal ligament and alveolar bone. The neural distribution in the dental pulp and periodontal tissues is crucial for sensing and transmitting pain signals. When orthodontic forces are applied to the periodontal ligament, mechanical pressure activates mechanoreceptors within the ligament, such as Ruffini endings and Pacinian corpuscles. These receptors convert mechanical stimuli into neural impulses, which are transmitted to the central nervous system via afferent nerve fibers. The presence of the nervous system represents a protective response of the body to mechanical stimuli. However, if mechanical stimulation persists and is not promptly removed, inflammatory mediators released by the nerves can trigger an inflammatory response, potentially leading to traumatic periodontitis or root resorption. Nerves and blood vessels are highly co-localized, sharing numerous signals and receptors during growth, differentiation, and navigation. Additionally, neurotransmitters can directly or indirectly regulate the functions of bone remodeling-related cells and epithelial cells. These findings suggest that the nervous system may play a regulatory role in apical root resorption. Next, this review specifically examines the potential mechanisms by which nerves may regulate OI-ARS (Fig. 4c, 4d).

4.2.1 Neurovascular axis

Nerves and blood vessels form a complex network structure to supply nutrients to tooth and periodontal tissues. There is an obvious overlap between the two networks. Nerves rely on blood vessels to ensure sufficient oxygen supply, while blood vessels require neural control and regulation. These two systems mutually guide each other and participate in each other's neogenesis and directional migration. Considering the role of vessels in root resorption mentioned above, nerves may indirectly contribute to root resorption by modulating blood vessels within the inflammatory and mechanical stimulation microenvironment.

Upon sympathetic excitation, neurotransmitters such as norepinephrine are released, which cause vasoconstriction by binding to alpha-1 (α-1) receptors on vascular smooth muscle cells[93]. Upon parasympathetic excitation, neurotransmitters such as acetylcholine are released, which cause vasodilation by binding to M-receptors on vascular smooth muscle cells[94]. Additionally, the nervous and vascular systems employ similar axon guidance factors, such as netrins, slits, semaphorins, and ephrins, which play important roles in angiogenesis through different receptors. For example, netrin-1 inhibits angiogenesis through the UNC5B receptor, while promoting angiogenesis through the CD146 receptor[95].

In the microenvironment of inflammation and mechanical stress associated with OI-ARS, it remains unclear whether sympathetic or parasympathetic nerve fibers are activated within the PDL and periapical tissues. Additionally, the effects of neurotransmitters on the function of vascular endothelial cells have not been investigated. Further research is required to determine whether the nervous system influences root resorption by modulating the vascular system, thereby altering oxygen and nutrient delivery around the

tooth root, as well as affecting the chemotaxis and aggregation of immune cells.

4.2.2 Neuro-bone axis

Bone is richly innervated with sympathetic and parasympathetic nerve fibers. Acetylcholine (ACh), the primary neurotransmitter secreted by cholinergic nerves, exerts its effects by binding to nicotinic acetylcholine receptors (nAChRs) or muscarinic acetylcholine receptors (mAChRs) expressed on bone lineage cells. ACh modulates bone remodeling through the regulation of osteoblast and osteoclast proliferation and differentiation[96]. Vasoactive intestinal peptide (VIP), co-released with ACh from cholinergic nerves, exerts its biological functions by interacting with VPAC1 and VPAC2 receptors on target cells[97]. VIP has been shown to promote osteogenic differentiation of bone marrow stromal cells (BMSCs) through activation of the Wnt/β-catenin signaling pathway and stimulate angiogenesis by enhancing the secretion of the angiogenic factor VEGF[98]. Regarding osteoclastic activity, existing evidence indicates that VIP suppresses osteoclastogenesis[99].

The sympathetic nerves release several neurotransmitters, including norepinephrine and neuropeptide Y (NPY). Norepinephrine acts on target cells through α-adrenergic receptors (α-AR) and β adrenergic receptors (β-AR)[100]. Among these receptors, β-AR is expressed on both osteoblasts and osteoclasts, playing a pivotal role in bone metabolism regulation[101]. Activation of β-adrenergic signaling directly stimulates osteoclastogenesis through β2-AR on osteoclasts, primarily via reactive oxygen species (ROS) generation[102]. Norepinephrine inhibits bone formation by activating β-AR receptors on osteoblasts, while also increasing the secretion of RANKL from osteoblasts, thereby promoting osteoclast differentiation[103,104]. Furthermore, β-AR activation induces the secretion of pro-inflammatory cytokines, including interleukin-6 (IL-6) and interleukin-11 (IL-11). Notably, local adrenergic β-receptor blockade has been shown to effectively enhance bone defect treatment by promoting osteogenic differentiation and suppressing osteoclastogenesis[105]. In contrast to β-AR, α-AR has been reported to promote bone formation by upregulation of osteogenic differentiation-related proteins in MC3T3-E1 cells[106]. NPY is an another neural signaling molecule secreted by sympathetic nerves. NPY receptors, Y1R and Y2R, are primarily involved in bone remodeling. Central regulation of bone metabolism mainly occurs through Y2R receptors, while peripheral regulation is primarily mediated via Y1R receptors. Inhibition of the Y1 receptor increases osteoblastic differentiation in MC3T3-E1 osteoblast cells[107]. NPY-deficient BMSCs exhibit enhanced osteogenic differentiation[108]. Besides, lack of Y1Rs stimulates the formation of larger multinucleated osteoclasts in vitro, which have reduced bone-resorbing activity[109]. These findings suggest that NPY negatively regulates bone formation. However, whether sympathetic nerves regulate root resorption through NE or NPY remains unexplored, and their distribution in periodontal tissues warrants further investigation.

Sensory nerves secrete the neuropeptide calcitonin gene-related peptide (CGRP), which stimulates osteoblast differentiation by upregulating transcription factor-4 (ATF4) and osteocalcin, and also inhibits osteoclastogenesis mediated by OPG/RANKL, thereby regulating bone metabolism[110]. In a rat model of mandibular distraction osteogenesis, CGRP accelerates bone regeneration by targeting BMSCs. CGRP promotes the migration and proliferation of BMSCs, as well as the expression of osteogenic differentiation markers ALP and Runx2[111]. In a model of dental pulp injury, sensory nerves within the pulp release CGRP, which binds to receptor activity modifying protein 1 (RAMP1) on dental pulp cells, promoting the migration of dental pulp stem cells to injured area to repair pulp tissue[92]. Sensory nerves also secrete substance P (SP), which promotes bone formation by enhancing cAMP, and can also promote bone resorption by acting on the N1 receptors on osteoclasts[112,113]. The dual role of SP in bone formation and resorption may be related to its concentration. When the concentration of SP is higher than 10^{-8} M, bone matrix mineralization is enhanced[114,115]. Conversely, bone formation is blocked when SP concentrations is lower than 10^{-8} M[116]. When CGRP and SP are present simultaneously, their effects on bone metabolism are more complex. SP or CGRP alone could promote bone mineralization through enhancing BMP2 signaling in vitro. However, co-stimulation of CGRP and SP in osteoblasts suppressed BMP2 signaling induced osteogenic differentiation[117]. This suggests that when studying the role of sensory nerves in apical root resorption, it is necessary to determine which neuropeptides are dominant, as different neuropeptides may have different effects and mechanisms on apical resorption.

In addition to the nerve fibers mentioned above, bone microenvironment also contains various axon guidance factors and neurotrophic factors, which have been found to be involved in bone remodeling. Axon guidance factors include sema3A, sema4D, netrin-1, and slit3. Among them, mice with neuron-specific sema3A deficiency have significantly reduced bone mass, indicating that neuron-derived sema3A is responsible for bone remodeling[118]. Sema4D has been reported to alleviate the inhibitory effect of bisphosphonates on osteoclast formation[119]. Netrin-1 injection protected the mice against autoimmune bone destruction in vivo[120]. However, an excess amount of netrin-1 can promote osteoclastogenesis. Blockade of netrin-1 prevents bone destruction and reduces the severity of K/BxN serum transfer-induced arthritis[121]. Slit-3 stimulates the migration and proliferation of osteoblasts by activating β-catenin and can also inhibit bone resorption by suppressing the differentiation of osteoclasts[122].

The neurotrophins family encompasses nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), neurotrophin 3 (NT-3), and neurotrophin 4/5 (NT4/5)[123]. NGF and BDNF promote new bone formation by inducing osteoblast proliferation and differentiation[124]. BDNF also enhances RANKL secretion by human BMSCs, which contributes to osteoclastogenesis[125]. However, in the inflammatory and mechanical microenvironment of OI-ARS, the source and target cells of axon guidance factors and neurotrophic factors have not been studied.

In conclusion, while studies have demonstrated the interrelation between the nervous system and bone metabolism-related cells, little research has been conducted in root and alveolar bone metabolism-related diseases. The apical region is rich in cells related to bone metabolism, such as periodontal ligament stem cells, dental follicle stem cells, cementoblasts, and osteoclasts. Moreover, the apical area has a dense nerve distribution, suggesting potential direct and indirect interactions between nerves and bone metabolism-related cells. Several critical questions warrant further investigation: (1) the precise distribution patterns of sensory and cholinergic nerve fibers surrounding the root and alveolar bone; (2) the identification of specific cell populations responsible for

secreting axon guidance factors and neurotrophic factors; (3) the characterization of stimuli triggering these secretory responses; and (4) the identification of targeted cells response to the secreted factors. Elucidation of the molecular mechanisms underlying these neural-bone interactions in the apical region may provide novel insights into the pathogenesis of OI-ARS and facilitate the development of targeted therapeutic strategies.

4.2.3 Neural-epithelial crosstalk

Experimental studies have shown that inferior alveolar nerve transection can lead to a decreased density of epithelial distribution within the periodontal ligament, concurrently with an increased number of resorption lacunae on the root surface, where cellular cementum is observed within the lacunae[69]. This phenomenon suggests that the nervous system may indirectly influence the pathological process of root resorption by regulating the spatial distribution and functional status of epithelial tissues.

During embryogenesis, the dental lamina originates from neural crest (NC) cells, which transiently emerge from the dorsal neural tube and migrate extensively to populate diverse tissues. These pluripotent NC cells differentiate into both neural lineages and non-neural cells[126]. This shared developmental ancestry between neural crest-derived neurons and dental epithelial cells provides a mechanistic basis for neuroepithelial crosstalk. At the structural and functional levels, epithelial cells share many of the properties associated with neural systems. At the anatomical level, studies have indicated direct synaptic communication between colon epithelial cells and surrounding neurons, providing morphological evidence for the direct transmission of neural signals to epithelial cells[127,128]. At the molecular regulation level, neurotransmitters released from nerve terminals—including norepinephrine, acetylcholine, and substance P (SP)—bind to G protein-coupled receptors or ion channels on epithelial cell membranes through either paracrine signaling or synaptic contact, thereby activating downstream signaling pathways. Additionally, acetylcholine released by cholinergic nerves controls epidermal structure and function via the M3 muscarinic acetylcholine receptor. These morphologic changes are associated with upregulation of cell proliferation genes and downregulation of genes contributing to epidermal differentiation, extracellular matrix formation, intercellular adhesion, and cell arrangement[129]. In contrast, NPY secreted by sympathetic nerves has been shown to inhibit keratinocyte proliferation[130]. Collectively, these studies suggest that the nervous system finely regulates epithelial homeostasis through neurotransmitter-receptor specific dialogues.

In recent years, targeting neuro-epithelial interactions has emerged as a novel therapeutic strategy. Local application of β-2 receptor antagonists has improved the healing of combined burn and radiation wounds[131]. Targeting SP have shown significant therapeutic efficacy in atopic dermatitis[132,133]. Therefore, future research may focus on utilizing spatial transcriptomics to map the molecular interactions between nerves and epithelium in the apical region of the root. Additionally, establishing animal models with nerve supply deficiencies could elucidate the causal relationship between epithelial abnormal differentiation and root resorption. Finally, developing sustained-release hydrogel systems targeting specific neurotransmitter receptors may achieve precise modulation of the periodontal microenvironment. These breakthroughs will propel the neuroregulatory therapies for root resorption from basic research towards clinical translation.

4.3 Alveolar bone

The interaction between root and cortical bone during tooth movement may lead to different resorption phenomena. Specifically, when the cervical or middle portion of the tooth root collides with the cortical bone, alveolar bone resorption typically occurs, manifesting as fenestration or dehiscence. However, resorption in the apical region was more common when the apex collided with the cortical bone. This difference raises questions about the susceptibility of the apical region: Why is the root apex more prone to damage.

In addition to the structural characteristics of the root itself, factors such as the density, thickness, and remodeling rate of the alveolar bone play a crucial role in the occurrence of apical resorption. However, their relationship with the occurrence of OI-ARS needs to be further investigation (Fig. 5). The apical one-third region of the alveolar bone exhibits increased thickness, reduced elasticity modulus, and higher mineral density compared to its

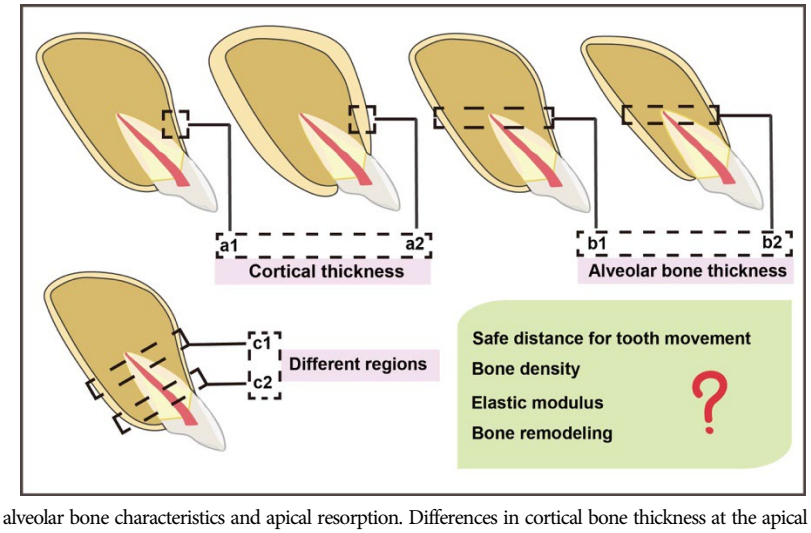


Figure 5 Relationship between alveolar bone characteristics and apical resorption. Differences in cortical bone thickness at the apical region, variations in alveolar bone thickness, and distinct anatomical locations of alveolar bone between the apical and cervical root zones (a1 vs. a2, b1 vs. b2, c1 vs. c2) may serve as key determinants of OI-ARS susceptibility, mediated by their divergent biomechanical properties in safe tooth movement distance, bone mineral density, elastic modulus, and bone remodeling rates.

cervical counterpart[134,135]. The increased thickness of cortical bone prolongs mechanical stress exposure on the root surface by extending the bone remodeling lag phase, rendering the apical region more susceptible to root resorption compared to the middle third of the root. Furthermore, patients with thin alveolar bone exhibit a narrower safe zone for orthodontic tooth movement, as direct root-cortical bone contact predisposes to apical root resorption through concentrated stress transmission[136].

Certain specific bony structures may also contribute to apical resorption during orthodontic treatment. For example, the incisive canal is located posterior to the central incisors. When the anterior teeth are retracted or intruded, the maxillary central incisors may conflict with the dense cortical bone of the incisive canal, leading to apical resorption[137,138]. Similarly, special attention should be paid to the positional relationship of maxillary molars and premolars with the maxillary sinus during orthodontic movement. Contact between the tooth root and the maxillary sinus wall also poses a risk of root resorption[139]. Additionally, when teeth come into contact with hard tissues such as bone islands, root resorption is more likely to occur[140].

Based on the above factors, it is recommended to develop a CBCT-based three-dimensional bone density analysis to construct risk prediction models in future. When the bone density, cortical thickness, and alveolar bone thickness in the apical region exceed certain values, clinicians should be alerted to reduce orthodontic forces and adopt an intermittent force application mode to allow sufficient time for root repair. For high-risk areas such as the maxillary sinus wall or incisive canal, the use of local ultrasonic bone scalers for minimally invasive resistance reduction can be combined to reduce the incidence of apical resorption.

5 Root resorption in deciduous teeth and adjacent teeth of impacted teeth

Root resorption is not exclusive to orthodontic treatment. During the physiological shedding of deciduous teeth, gradual root resorption occurs, and when impacted teeth collide with adjacent permanent teeth, resorption of the permanent teeth may also arise. These phenomena share certain similarities with OI-ARS, such as being painless progressive processes where all hard and soft tissues in the root area, including the periodontal ligament, cementum, dentin, and pulp, are resorbed and ultimately replaced by alveolar bone[141]. However, when deciduous teeth lack underlying successor permanent teeth, their roots typically do not undergo resorption or exhibit significantly slower resorption rates[7]. This observation raises two critical questions: First, how do the dental tissues disappear during resorption progression. Could inhibiting this disappearance process mitigate or prevent apical resorption. Second, unerupted successor permanent teeth and impacted teeth are often enveloped by pericoronal follicle. Does this structural configuration mediate the initiation of root resorption.

During the physiological resorption of deciduous tooth roots, both soft and hard tissues are eliminated through dual mechanisms: (1) apoptosis of the tissues themselves and (2) active resorption of hard tissues (cementum and dentin) by odontoclasts[142-145]. Following the resorption of hard tissues, odontoclasts undergo apoptosis and are subsequently phagocytosed by macrophages or leukocytes for lysosomal degradation[146]. However, the lifespan of odontoclasts under physiological conditions remains poorly explored, and future research should delve deeper into this area to analyze the state of osteoclasts under physiological and pathological conditions, which may be significant for the prevention and treatment of root resorption. In addition to the resorption of hard tissues, the dental pulp within deciduous teeth disappears through apoptosis, and the presence of apoptosis in pulp of deciduous teeth with advanced-stage resorption is more intense than in the pulp of young permanent teeth[147,148]. Despite this, the unabsorbed portion of the pulp retains its structural integrity and continues to mediate pain perception, healing, and reparative functions until the final stages of resorption[147,149]. This parallels OI-ARS, where residual dental tissues remain functional.

The physiological root resorption of deciduous teeth mainly mediated by the permanent teeth beneath them. In areas where some permanent teeth are missing, the roots of deciduous teeth may persist for months or even years. This is because of the presence of pericoronal follicle in the unerupted permanent teeth. Pericoronal follicle is an important epithelial part, consisting of the reduced epithelium of the enamel organ adhered to the crown, and of the epithelial remnants of the dental lamina. The epithelial cells secrete epidermal growth factor (EGF), which stimulates pericoronal bone resorption of teeth for the purpose of opening the way for tooth eruption[7]. The prevalence of external root resorption in patients with impacted third molars ranges from 0.3% to 24.2%[150]. These findings underscore the critical role of epithelial tissues and their secretions in apical resorption, particularly their ability to recruit osteoclasts and precisely target the apical region. Identifying the key regulatory factors or cell populations involved could hold significant therapeutic potential for preventing or mitigating root resorption.

The recruitment and origin of osteoclasts during root resorption have been extensively studied. Periodontal ligament cells secrete various chemokines such as monocyte chemotactic protein-1 (MCP-1) and C-X-C motif chemokine ligand 12 (CXCL12) under mechanical stress, recruiting macrophages to migrate to the root resorption area and polarize into the M1 type[50,151]. Besides, periodontal ligament cells stimulated by mechanical forces also regulate the RANKL/OPG ratio through multiple signaling pathways to promote osteoclast differentiation and resorption[152]. Intriguingly, during the progression of apical resorption, the surrounding alveolar bone maintains its structural integrity through balanced bone remodeling, whereas the resorbed root surface fails to regenerate and is ultimately replaced by new bone. This raises unresolved questions: Do bioelectrical gradients, pH differences, or topographical cues at the root-bone interface guide osteoclast localization. Furthermore, a paradoxical bidirectional regulation exists in orthodontic inflammatory root resorption. Under the same inflammatory microenvironment, osteoclastic activity dominates at the root apex, while osteoblasts deposit new bone in the resorbed region. This coordinated yet spatially segregated activity of osteoclasts and osteoblasts demands further investigation.

6 Conclusions and perspectives

OI-ARS remains a significant clinical challenge in modern orthodontics, characterized by irreversible structural consequences. Current clinical management, which relies on radiographic monitoring and passive treatment pauses, fails to address the biological complexity of OI-ARS, resulting in prolonged treatment durations and compromised long-term tooth prognosis. Persistent nosological confusion surrounding root resorption terminology

further complicates both research and clinical practice, particularly in distinguishing between adaptive cemental remodeling and pathological apical resorption. The apical region's unique anatomical signature, including cellular cementum's limited regenerative capacity, dentin-cementum junctional fragility, and neurovascular-epithelial interactions, creates a microenvironment uniquely susceptible to mechanical stress-induced resorption. Besides, parallels between OI-ARS and physiological root resorption patterns in deciduous or impacted teeth suggest conserved regulatory mechanisms involving programmed cell death and spatiotemporal control of osteoclastogenesis. However, direct experimental validation of these hypotheses remains lacking. To bridge this knowledge gap and transform clinical practice, future efforts should focus on two strategic domains.

6.1 Mechanistic decoding of apical vulnerability

From the perspective of dental structural biomechanics, three-dimensional finite element analysis can be used to investigate the map stress distribution and elastic modulus variations across diverse dental structures under orthodontic loading, including comparisons of cementum layer thickness, apical bifurcations, and single-canal root configurations. Additionally, the alterations in the organic and inorganic composition of dental tissues following root canal treatment, and their impact on osteoclastic activity, warrant systematic investigation.

Regarding the response of cells and tissues in the apical region to orthodontic forces, comparative studies are needed to elucidate differential mechanotransduction mechanisms among cementoblasts, periodontal ligament cells, and osteocytes. RNA sequencing of these populations could identify differentiation-related gene networks, potentially revealing therapeutic targets to restore cementoblast function. Spatial transcriptomics should be applied to resolve dynamic changes in epithelial, vascular, and neural distributions during OI-ARS progression, with particular emphasis on metabolite-mediated regulation of vascular-neural-cementoblast crosstalk. Single-cell sequencing of coronal epithelium may uncover key molecular drivers of osteoclast recruitment, while scanning ion conductance microscopy could delineate biophysical gradients (e.g., bioelectric potentials, surface topography) at the root-alveolar bone interface that guide osteoclast localization.

6.2 Clinical exploration

Clinically, artificial intelligence (AI)-driven risk prediction models integrating CBCT radiomic features—such as apical bifurcation complexity, cortical bone density gradients, and anatomical proximity to critical structures (incisive canal, maxillary sinus)—should be developed. Machine learning algorithms could optimize force delivery in real time using strain data from piezoelectric microsensors embedded in orthodontic appliances, automatically reducing applied forces when resorption risk thresholds are exceeded.

Therapeutic innovation should prioritize localized drug delivery systems loaded with dual-action agents that concurrently suppress osteoclastogenesis and enhance cementogenesis. Regenerative strategies could involve biomimetic scaffolds replicating cementum's hierarchical structure, surgically implanted to restore lost root length. These scaffolds may incorporate piezoelectric materials to convert mechanical stimuli into pro-regenerative electrical signals, mimicking natural tissue responses.

Overall, success in addressing OI-ARS will require multidisciplinary convergence, uniting orthodontists, bioengineers, and computational biologists to decode the apical region's "biological fingerprint". By harmonizing mechanistic insights with precision clinical tools, next-generation orthodontic therapies may achieve efficient tooth movement while preserving root integrity, ultimately advancing the dual goals of aesthetic excellence and biological preservation.

Acknowledgments

This research was funded by National Natural Science Foundation of China (Grant No. 82401066) and Natural Science Foundation of Shandong Province (Grant No. ZR2024QC169, ZR2022MH215).

Data available statement

N/A

Author contribution

J.Z. and C.J. formulated the topic and drafted the manuscript. X.Y., H.D. revised the manuscript. X.C. polished the text. The authors read and approved the final manuscript.

Ethics approval and consent

N/A

Consent for publication

All authors agree to publish.

Conflict of interest

The authors have no competing interests to declare that are relevant to the content of this article

References

[1] Oppenheim, A. Human tissue response to orthodontic intervention of short and long duration. *Am. J. Orthod. Oral Surg.* **1942**, *28*, 263–301.

[2] Patel, S.; Krastl, G.; Weiger, R.; et al. ESE position statement on root resorption. *Int. Endod. J.* **2023**, *56*, 792–801.

[3] Lund, H.; Gröndahl, K.; Ken, H. S.; et al. Apical root resorption during orthodontic treatment: A prospective study using cone beam CT. *Angle Orthod.* **2012**, *82*, 480–487.

[4] Deng, L. Z.; Guo, Y. W. Estrogen effects on orthodontic tooth movement and orthodontically-induced root resorption. *Arch. Oral Biol.* **2020**, *118*, 104840.

[5] Pereira, S.; Nogueira, L.; Canova, F.; et al. IRAK1 variant is protective for orthodontic-induced external apical root resorption. *Oral Dis.* **2016**, *22*, 658–664.

[6] Brezniak, N.; Wasserstein, A. Orthodontic root resorption: A new perspective. *Angle Orthod.* **2016**, *86*, 1056–1057.

[7] Consolaro A; Rodrigues M T; Consolaro R B; et al. The two extremes of physiological tooth resorption in primary tooth with or without the permanent successor tooth. *Dental Press J Orthod* **2021**, *26*, e21ins26.

[8] Guarnieri R; Cavallini C; Vernucci R; et al. Impacted maxillary canines and root resorption of adjacent teeth: A retrospective observational study. *Med Oral Patol Oral Cir Bucal* **2016**, *21*, e743–e750.

[9] Brezniak, N.; Wasserstein, A. Root resorption revisited: The

paradigm of force effect on root resorption: *Is a 'paradigm shift' needed in order to learn more about the phenomenon*? *Angle Orthod.* **2019**, *89*, 518–520.
[10] Rincon, J. C.; Young, W. G.; Bartold, P. M. The epithelial cell rests of Malassez–a role in periodontal regeneration? *J. Periodontal Res.* **2006**, *41*, 245–252.
[11] Xiong, J. M.; Gronthos, S.; Bartold, P. M. Role of the epithelial cell rests of Malassez in the development, maintenance and regeneration of periodontal ligament tissues. *Periodontol. 2000* **2013**, *63*, 217–233.
[12] Li, J. Y.; Parada, C.; Chai, Y. Cellular and molecular mechanisms of tooth root development. *Development* **2017**, *144*, 374–384.
[13] Cho, M. I.; Garant, P. R. Development and general structure of the periodontium. *Periodontol. 2000* **2000**, *24*, 9–27.
[14] Rothová, M.; Peterková, R.; Tucker, A. S. Fate map of the dental mesenchyme: Dynamic development of the dental papilla and follicle. *Dev. Biol.* **2012**, *366*, 244–254.
[15] Ali Saghiri, M.; Vakhnovetsky, J.; Vakhnovetsky, A.; et al. Functional role of inorganic trace elements in dentin apatite tissue: Part 1: Mg, Sr, Zn, and Fe. *J. Trace Elem. Med. Biol.* **2022**, *71*, 126932.
[16] Rex, T.; Kharbanda, O. P.; Petocz, P.; et al. Physical properties of root cementum: Part 4. *Quantitative analysis of the mineral composition of human premolar cementum. Am. J. Orthod. Dentofac. Orthop.* **2005**, *127*, 177–185.
[17] Arzate, H.; Zeichner-David, M.; Mercado-Celis, G. Cementum proteins: Role in cementogenesis, biomineralization, periodontium formation and regeneration. *Periodontol. 2000* **2015**, *67*, 211–233.
[18] Srivicharnkul, P.; Kharbanda, O. P.; Swain, M. V.; et al. Physical properties of root cementum: Part 3. Hardness and elastic modulus after application of light and heavy forces. *Am. J. Orthod. Dentofac. Orthop.* **2005**, *127*, 168–176.
[19] Hodgskinson, R.; Currey, J. D.; Evans, G. P. Hardness, an indicator of the mechanical competence of cancellous bone. *J. Orthop. Res.* **1989**, *7*, 754–758.
[20] Malek, S.; Darendeliler, M. A.; Swain, M. V. Physical properties of root cementum: Part I. A new method for 3-dimensional evaluation. *Am. J. Orthod. Dentofacial Orthop.* **2001**, *120*, 198–208.
[21] Mahoney, E.; Holt, A.; Swain, M.; et al. The hardness and modulus of elasticity of primary molar teeth: An ultra-micro-indentation study. *J. Dent.* **2000**, *28*, 589–594.
[22] Break, K.; Currey, J. D.; Pond, C. M.; et al. The mechanical properties of the dentine and cement of the tusk of the narwhal *Monodon monoceros* compared with those of other mineralized tissues. *Arch. Oral Biol.* **1990**, *35*, 615–621.
[23] Darendeliler, M. A.; Darendeliler, H.; Uner, O. The drum spring (DS) retractor: Constant and continuous force for canine retraction. *Eur. J. Orthod.* **1997**, *19*, 115–130.
[24] Galler, K. M.; Weber, M.; Korkmaz, Y.; et al. Inflammatory response mechanisms of the dentine–pulp complex and the periapical tissues. *Int. J. Mol. Sci.* **2021**, *22*, 1480.
[25] Almushayt, A.; Narayanan, K.; Zaki, A. E.; et al. Dentin matrix protein 1 induces cytodifferentiation of dental pulp stem cells into odontoblasts. *Gene Ther.* **2006**, *13*, 611–620.
[26] Yin, J. X.; Xu, J.; Cheng, R.; et al. Role of connexin 43 in odontoblastic differentiation and structural maintenance in pulp damage repair. *Int. J. Oral Sci.* **2021**, *13*, 1.
[27] Ruch, J. V. Odontoblast commitment and differentiation. *Biochem. Cell Biol.* **1998**, *76*, 923–938.
[28] Ruch, J. V.; Lesot, H.; Begue-Kirn, C. Odontoblast differentiation. *Int. J. Dev. Biol.* **1995**, *39*, 51–68.
[29] Linde, A.; Goldberg, M. Dentinogenesis. *Crit. Rev. Oral Biol. Med.* **1993**, *4*, 679–728.
[30] Bleicher, F. Odontoblast physiology. *Exp. Cell Res.* **2014**, *325*, 65–71.
[31] Hasegawa, N.; Kawaguchi, H.; Ogawa, T.; et al. Immunohistochemical characteristics of epithelial cell rests of Malassez during cementum repair. *J. Periodontal Res.* **2003**, *38*, 51–56.
[32] Ma, R.; Xie, X. D.; Xu, C. M.; et al. Loss of β-catenin causes cementum hypoplasia by hampering cementogenic differentiation of Axin2-expressing cells. *J. Periodontal Res.* **2023**, *58*, 414–421.
[33] Cheng, L. L.; Türk, T.; Elekdağ-Türk, S.; et al. Physical properties of root cementum: Part 13. Repair of root resorption 4 and 8 weeks after the application of continuous light and heavy forces for 4 weeks: A microcomputed-tomography study. *Am. J. Orthod. Dentofac. Orthop.* **2009**, *136*, 320.e1–320.e10.
[34] Mazzi-Chaves, J. F.; Silva-Sousa, Y. T. C.; Leoni, G. B.; et al. Micro-computed tomographic assessment of the variability and morphological features of root canal system and their ramifications. *J. Appl. Oral Sci.* **2020**, *28*, e20190393.
[35] Lobo, N. S.; Wanderley, V. A.; Nejaim, Y.; et al. Assessment of ramifications in the apical region of root canals: A micro-CT study in a Brazilian population. *Braz. Dent. J.* **2020**, *31*, 505–510.
[36] Gao, X. H.; Tay, F. R.; Gutmann, J. L.; et al. Micro-CT evaluation of apical delta morphologies in human teeth. *Sci. Rep.* **2016**, *6*, 36501.
[37] Berbari R; Nassif N; Sfeir E. Inflammatory Status of Excavated Pulp Tissue and Internal Root Resorption in Pulpotomized Primary Molars. *J Dent (Shiraz)* **2022**, *23*, 284–291.
[38] Zheng, Y.; Chen, M.; He, L.; et al. Mesenchymal dental pulp cells attenuate dentin resorption in homeostasis. *J. Dent. Res.* **2015**, *94*, 821–827.
[39] Zhao, D. N.; Xue, K.; Meng, J. Y.; et al. Orthodontically induced external apical root resorption considerations of root-filled teeth vs vital pulp teeth: A systematic review and meta-analysis. *BMC Oral Health* **2023**, *23*, 241.
[40] Kolcuoğlu, K.; Oz, A. Z. Comparison of orthodontic root resorption of root-filled and vital teeth using micro–computed tomography. *Angle Orthod.* **2020**, *90*, 56–62.
[41] Kurnaz, S.; Buyukcavus, M. H. Panoramic evaluation of external root resorption in mandibular molars during orthodontic treatment: A comparison between root-filled and vital teeth treated with fixed appliances or clear aligners. *BMC Oral Health* **2024**, *24*, 1152.
[42] Elsayed, S.; Alolayan, A.; Farghal, L.; et al. Generalised hypercementosis in a young female seeking extraction: Revision and update of surgical technique. *J. Coll. Physicians Surg. Pak.* **2019**, *29*, 1111–1113.
[43] Patel, S.; Bhuva, B.; Bose, R. Present status and future directions: Vertical root fractures in root filled teeth. *Int. Endod. J.* **2022**, *55*, 804–826.
[44] Dzeletovic, B.; Grga, D.; Krsljak, E.; et al. Dental pulp blood flow and its oscillations in women with different estrogen status. *J. Endod.* **2012**, *38*, 1187–1191.
[45] Brezniak, N.; Wasserstein, A. Does pulp have a role in root resorption? *Angle Orthod*. **2022**, *92*, 815–817.
[46] Li, X. B.; Zhang, S. C.; Zhang, Z. R.; et al. Development of immortalized Hertwig's epithelial root sheath cell lines for cementum and dentin regeneration. *Stem Cell Res. Ther.* **2019**, *10*, 3.
[47] Guo, Y. W.; Guo, W. H.; Chen, J.; et al. Are Hertwig's epithelial root sheath cells necessary for periodontal formation by dental follicle cells? *Arch. Oral Biol.* **2018**, *94*, 1–9.
[48] Li, X. Y.; Xu, J. C.; Yin, Y. Y.; et al. Notch signaling inhibition protects against root resorption in experimental immature tooth movement in rats. *Am. J. Orthod. Dentofac. Orthop.* **2021**, *159*, 426–434.e5.
[49] Li, X. Y.; Men, X. R.; Ji, L.; et al. NLRP3-mediated periodontal ligament cell pyroptosis promotes root resorption. *J. Clin. Periodontol.* **2024**, *51*, 474–486.
[50] Fang, X. Y.; Zhan, Y. X.; Zhou, X. M.; et al. CXCL12/CXCR4 mediates orthodontic root resorption *via* regulating the M1/M2 ratio.

J. Dent. Res. **2022**, *101*, 569–579.
[51] Xu, J.; Lamouille, S.; Derynck, R. TGF-β-induced epithelial to mesenchymal transition. *Cell Res.* **2009**, *19*, 156–172.
[52] Rioux-Forker, D.; Deziel, A. C.; Williams, L. S.; et al. Odontogenic cysts and tumors. *Ann. Plast. Surg.* **2019**, *82*, 469–477.
[53] Hornillos-De Villota M; Pampin-Martínez M M; Moran-Soto M J; et al. Peripheral odontogenic keratocyst. *A Case report. J Clin Exp Dent* **2023**, *15*, e169–e172.
[54] Masthan, K. M. K.; Anitha, N.; Krupaa, J.; et al. Ameloblastoma. *J. Pharm. Bioallied Sci.* **2015**, *7*, S167–S170.
[55] Mendenhall, W. M.; Werning, J. W.; Fernandes, R.; et al. Ameloblastoma. *Am. J. Clin. Oncol.* **2007**, *30*, 645–648.
[56] Effiom, O.; Ogundana, O.; Akinshipo, A.; et al. Ameloblastoma: Current etiopathological concepts and management. *Oral Dis.* **2018**, *24*, 307–316.
[57] Suda, N. Role of reduced enamel epithelium in root resorption. *J. Oral Biosci.* **2022**, *64*, 43–48.
[58] Moriguchi, M.; Yamada, M.; Miake, Y.; et al. Transforming growth factor beta inducible apoptotic cascade in epithelial cells during rat molar tooth eruptions. *Anat. Sci. Int.* **2010**, *85*, 92–101.
[59] Lu, X. Y.; Ito, Y.; Atsawasuwan, P.; et al. Ameloblastin modulates osteoclastogenesis through the integrin/ERK pathway. *Bone* **2013**, *54*, 157–168.
[60] Beck, F.; Tucci, J.; Russell, A.; et al. The expression of the gene coding for parathyroid hormone-related protein (PTHrP) during tooth development in the rat. *Cell Tissue Res.* **1995**, *280*, 283–290.
[61] Philbrick, W. M.; Dreyer, B. E.; Nakchbandi, I. A.; et al. Parathyroid hormone-related protein is required for tooth eruption. *Proc. Natl. Acad. Sci. U. S. A.* **1998**, *95*, 11846–11851.
[62] Mekaapiruk, K.; Suda, N.; Hammond, V. E.; et al. The influence of parathyroid hormone-related protein (PTHrP) on tooth-germ development and osteoclastogenesis in alveolar bone of PTHrP-knock out and wild-type mice *in vitro*. *Arch. Oral Biol.* **2002**, *47*, 665–672.
[63] Wang, Y. F.; Liu, M. M.; Deng, S. J.; et al. Osteoprotegerin deficiency causes morphological and quantitative damage in epithelial rests of Malassez. *J. Mol. Histol.* **2018**, *49*, 329–338.
[64] Mizuno, N.; Shiba, H.; Mouri, Y.; et al. Characterization of epithelial cells derived from periodontal ligament by gene expression patterns of bone-related and enamel proteins. *Cell Biol. Int.* **2005**, *29*, 111–117.
[65] Brice, G. L.; Sampson, W. J.; Sims, M. R. An ultrastructural evaluation of the relationship between epithelial rests of Malassez and orthodontic root resorption and repair in man. *Aust. Orthod. J.* **1991**, *12*, 90–94.
[66] Kittel, P. W.; Sampson, W. J. RME-induced root resorption and repair: A computerised 3-D reconstruction. *Aust. Orthod. J.* **1994**, *13*, 144–151.
[67] Rincon, J. C.; Xiao, Y.; Young, W. G.; et al. Production of osteopontin by cultured porcine epithelial cell rests of Malassez. *J. Periodontal Res.* **2005**, *40*, 417–426.
[68] Kat, P. S. P.; Sampson, W. J.; Wilson, D. F.; et al. Distribution of the epithelial rests of Malassez and their relationship to blood vessels of the periodontal ligament during rat tooth development. *Australas. Orthod. J.* **2003**, *19*, 77–86.
[69] Fujiyama, K.; Yamashiro, T.; Fukunaga, T.; et al. Denervation resulting in dento-alveolar ankylosis associated with decreased malassez epithelium. *J. Dent. Res.* **2004**, *83*, 625–629.
[70] Koshihara, T.; Matsuzaka, K.; Sato, T.; et al. Effect of stretching force on the cells of epithelial rests of malassez *in vitro*. *Int. J. Dent.* **2010**, *2010*, 458408.
[71] Liu, L. X.; Yao, L. H.; Lu, Z. Y.; et al. Epithelial-specific deletion of FAM20A leads to short root defects. *Gene* **2023**, *884*, 147731.
[72] Li, Y.; Zhan, Q.; Bao, M. Y.; et al. Biomechanical and biological responses of periodontium in orthodontic tooth movement: Up-date in a new decade. *Int. J. Oral Sci.* **2021**, *13*, 20.
[73] Shen, B.; Tasdogan, A.; Ubellacker, J. M.; et al. A mechanosensitive peri-arteriolar niche for osteogenesis and lymphopoiesis. *Nature* **2021**, *591*, 438–444.
[74] Nakashima, K.; Zhou, X.; Kunkel, G.; et al. The novel zinc finger-containing transcription factor osterix is required for osteoblast differentiation and bone formation. *Cell* **2002**, *108*, 17–29.
[75] Kusumbe, A. P.; Ramasamy, S. K.; Adams, R. H. Coupling of angiogenesis and osteogenesis by a specific vessel subtype in bone. *Nature* **2014**, *507*, 323–328.
[76] Yan, Z. Q.; Wang, X. K.; Zhou, Y.; et al. H-type blood vessels participate in alveolar bone remodeling during murine tooth extraction healing. *Oral Dis.* **2020**, *26*, 998–1009.
[77] Gong, X. Y.; Zhang, H.; Xu, X. Q.; et al. Tracing PRX1+ cells during molar formation and periodontal ligament reconstruction. *Int. J. Oral Sci.* **2022**, *14*, 5.
[78] Peng, Y.; Wu, S.; Li, Y. S.; et al. Type H blood vessels in bone modeling and remodeling. *Theranostics* **2020**, *10*, 426–436.
[79] Liu, Z. K.; Liu, H. H.; Liu, S. B.; et al. SIRT1 activation promotes bone repair by enhancing the coupling of type H vessel formation and osteogenesis. *Cell Prolif.* **2024**, *57*, e13596.
[80] Liu, X. N.; Chai, Y.; Liu, G. Q.; et al. Osteoclasts protect bone blood vessels against senescence through the angiogenin/plexin-B2 axis. *Nat. Commun.* **2021**, *12*, 1832.
[81] Chen, Y. L. Occlusal force maintains alveolar bone homeostasis *via* type H angiogenesis. *Int. Dent. J.* **2025**, *75*, 104423.
[82] Wei, W.; An, Y. L.; An, Y.; et al. Activation of autophagy in periodontal ligament mesenchymal stem cells promotes angiogenesis in periodontitis. *J. Periodontol.* **2018**, *89*, 718–727.
[83] Zhang, Z.; Shuai, Y.; Zhou, F.; et al. PDLSCs regulate angiogenesis of periodontal ligaments *via* VEGF transferred by exosomes in periodontitis. *Int. J. Med. Sci.* **2020**, *17*, 558–567.
[84] Hu, W. H.; Chen, Y. Q.; Dou, C.; et al. Microenvironment in subchondral bone: Predominant regulator for the treatment of osteoarthritis. *Ann. Rheum. Dis.* **2021**, *80*, 413–422.
[85] Kirschneck, C.; Thuy, M.; Leikam, A.; et al. Role and regulation of mechanotransductive HIF-1α stabilisation in periodontal ligament fibroblasts. *Int. J. Mol. Sci.* **2020**, *21*, 9530.
[86] Augustin, H. G.; Koh, G. Y. A systems view of the vascular endothelium in health and disease. *Cell* **2024**, *187*, 4833–4858.
[87] Dominguez, A.; Iruela-Arispe, M. L. Integration of Chemo-mechanical signaling in response to fluid shear stress by the endothelium. *Curr. Opin. Cell Biol.* **2023**, *85*, 102232.
[88] Ando, J.; Yamamoto, K. Hemodynamic forces, endothelial mechanotransduction, and vascular diseases. *Magn. Reson. Med. Sci.* **2022**, *21*, 258–266.
[89] Blaushild, N.; Michaeli, Y.; Steigman, S. Histomorphometric study of the periodontal vasculature of the rat incisor. *J. Dent. Res.* **1992**, *71*, 1908–1912.
[90] Mei, H. X.; Li, Z. Z.; Lv, Q. Y.; et al. Sema3A secreted by sensory nerve induces bone formation under mechanical loads. *Int. J. Oral Sci.* **2024**, *16*, 5.
[91] Sijaona, A.; Luukko, K.; Kvinnsland, I. H.; et al. Expression patterns of Sema3F, PlexinA4, -A3, Neuropilin1 and-2 in the postnatal mouse molar suggest roles in tooth innervation and organogenesis. *Acta Odontol. Scand.* **2012**, *70*, 140–148.
[92] Wang, C. M.; Liu, X. C.; Zhou, J. N.; et al. Sensory nerves drive migration of dental pulp stem cells *via* the CGRP-Ramp1 axis in pulp repair. *Cell. Mol. Life Sci.* **2024**, *81*, 373.
[93] Ma, J.; Li, Y. N.; Yang, X. Y.; et al. Signaling pathways in vascular function and hypertension: Molecular mechanisms and therapeutic interventions. *Signal Transduct. Target. Ther.* **2023**, *8*, 168.
[94] Sheng Y; Zhu L. The crosstalk between autonomic nervous system and blood vessels. *Int J Physiol Pathophysiol Pharmacol* **2018**, *10*, 17–28.

[95] Tu, T.; Zhang, C. X.; Yan, H. W.; et al. CD146 acts as a novel receptor for netrin-1 in promoting angiogenesis and vascular development. *Cell Res.* **2015**, *25*, 275–287.

[96] Wan, Q. Q.; Qin, W. P.; Ma, Y. X.; et al. Crosstalk between bone and nerves within bone. *Adv. Sci.* **2021**, *8*, 2003390.

[97] Juhász, T.; Helgadottir, S. L.; Tamás, A.; et al. PACAP and VIP signaling in chondrogenesis and osteogenesis. *Peptides* **2015**, *66*, 51–57.

[98] Shi, L.; Feng, L.; Zhu, M. L.; et al. Vasoactive intestinal peptide stimulates bone marrow-mesenchymal stem cells osteogenesis differentiation by activating Wnt/β-catenin signaling pathway and promotes rat skull defect repair. *Stem Cells Dev.* **2020**, *29*, 655–666.

[99] Liu, X. G.; Liu, H. R.; Xiong, Y. Q.; et al. Postmenopausal osteoporosis is associated with the regulation of SP, CGRP, VIP, and NPY. *Biomed. Pharmacother.* **2018**, *104*, 742–750.

[100] Tank A W; Lee Wong D. Peripheral and central effects of circulating catecholamines. *Compr Physiol* **2015**, *5*, 1–15.

[101] Mulcrone, P. L.; Campbell, J. P.; Clément-Demange, L.; et al. Skeletal colonization by breast cancer cells is stimulated by an osteoblast and β2AR-dependent neo-angiogenic switch. *J. Bone Miner. Res.* **2017**, *32*, 1442–1454.

[102] Kondo, H.; Takeuchi, S.; Togari, A. β-Adrenergic signaling stimulates osteoclastogenesis *via* reactive oxygen species. *Am. J. Physiol. Endocrinol. Metab.* **2013**, *304*, E507–E515.

[103] Yao, Q. Q.; Liang, H. X.; Huang, B.; et al. Beta-adrenergic signaling affect osteoclastogenesis *via* osteocytic MLO-Y4 cells' RANKL production. *Biochem. Biophys. Res. Commun.* **2017**, *488*, 634–640.

[104] Ma, Y.; Nyman, J. S.; Tao, H.; et al. β2-adrenergic receptor signaling in osteoblasts contributes to the catabolic effect of glucocorticoids on bone. *Endocrinology* **2011**, *152*, 1412–1422.

[105] Wu, H.; Song, Y.; Li, J. Q.; et al. Blockade of adrenergic β-receptor activation through local delivery of propranolol from a 3D collagen/polyvinyl alcohol/hydroxyapatite scaffold promotes bone repair *in vivo*. *Cell Prolif.* **2020**, *53*, e12725.

[106] Docherty, J. R. The pharmacology of α(1)-adrenoceptor subtypes. *Eur. J. Pharmacol.* **2019**, *855*, 305–320.

[107] Yahara, M.; Tei, K.; Tamura, M. Inhibition of neuropeptide Y Y1 receptor induces osteoblast differentiation in MC3T3-E1 cells. *Mol. Med. Rep.* **2017**, *16*, 2779–2784.

[108] Wee, N. K. Y.; Sinder, B. P.; Novak, S.; et al. Skeletal phenotype of the neuropeptide Y knockout mouse. *Neuropeptides* **2019**, *73*, 78–88.

[109] Sousa, D. M.; Conceição, F.; Silva, D. I.; et al. Ablation of Y1 receptor impairs osteoclast bone-resorbing activity. *Sci. Rep.* **2016**, *6*, 33470.

[110] He, H. T.; Chai, J. S.; Zhang, S. F.; et al. CGRP may regulate bone metabolism through stimulating osteoblast differentiation and inhibiting osteoclast formation. *Mol. Med. Rep.* **2016**, *13*, 3977–3984.

[111] Jia, S.; Zhang, shi-jian, Wang, xu-dong, et al. Calcitonin gene-related peptide enhances osteogenic differentiation and recruitment of bone marrow mesenchymal stem cells in rats. *Exp. Ther. Med.* **2019**, *18*, 1039–1046.

[112] Niedermair, T.; Schirner, S.; Seebröker, R.; et al. Substance P modulates bone remodeling properties of murine osteoblasts and osteoclasts. *Sci. Rep.* **2018**, *8*, 9199.

[113] Fu, S.; Mei, G.; Wang, Z.; et al. Neuropeptide substance P improves osteoblastic and angiogenic differentiation capacity of bone marrow stem cells *in vitro*. *BioMed Res. Int.* **2014**, *2014*, 596023.

[114] Wang, L. P.; Zhao, R.; Shi, X. Y.; et al. Substance P stimulates bone marrow stromal cell osteogenic activity, osteoclast differentiation, and resorption activity *in vitro*. *Bone* **2009**, *45*, 309–320.

[115] Goto, T.; Nakao, K.; Gunjigake, K. K.; et al. Substance P stimulates late-stage rat osteoblastic bone formation through neurokinin-1 receptors. *Neuropeptides* **2007**, *41*, 25–31.

[116] Adamus, M. A.; Dabrowski, Z. J. Effect of the neuropeptide substance P on the rat bone marrow-derived osteogenic cells *in vitro*. *J. Cell. Biochem.* **2001**, *81*, 499–506.

[117] Tuzmen, C.; Campbell, P. G. Crosstalk between neuropeptides SP and CGRP in regulation of BMP2-induced bone differentiation. *Connect. Tissue Res.* **2018**, *59*, 81–90.

[118] Fukuda, T.; Takeda, S.; Xu, R.; et al. Sema3A regulates bone-mass accrual through sensory innervations. *Nature* **2013**, *497*, 490–493.

[119] Liu, L. L.; Mu, H.; Pang, Y.; et al. Semaphorin 4D promotes osteoclast formation but inhibits osteoblast formation: Implication in bisphosphonate-related osteonecrosis of the jaw. *Pharmacology* **2023**, *108*, 400–408.

[120] Maruyama, K.; Takemura, N.; Martino, M. M.; et al. Netrins as prophylactic targets in skeletal diseases: A double-edged sword? *Pharmacol. Res.* **2017**, *122*, 46–52.

[121] Mediero, A.; Wilder, T.; Ramkhelawon, B.; et al. Netrin-1 and its receptor Unc5b are novel targets for the treatment of inflammatory arthritis. *FASEB J.* **2016**, *30*, 3835–3844.

[122] Kim, B. J.; Lee, Y. S.; Lee, S. Y.; et al. Osteoclast-secreted SLIT3 coordinates bone resorption and formation. *J. Clin. Investig.* **2018**, *128*, 1429–1441.

[123] Scheib, J.; Höke, A. Advances in peripheral nerve regeneration. *Nat. Rev. Neurol.* **2013**, *9*, 668–676.

[124] Cai, X. X.; Luo, E.; Yuan, Q. Interaction between schwann cells and osteoblasts *in vitro*. *Int. J. Oral Sci.* **2010**, *2*, 74–81.

[125] Ai, L. S.; Sun, C. Y.; Zhang, L.; et al. Inhibition of BDNF in multiple myeloma blocks osteoclastogenesis *via* down-regulated stroma-derived RANKL expression both *in vitro* and *in vivo*. *PLoS One* **2012**, *7*, e46287.

[126] Zhang, Q. Z.; Nguyen, P. D.; Shi, S. H.; et al. Neural crest stem-like cells non-genetically induced from human gingiva-derived mesenchymal stem cells promote facial nerve regeneration in rats. *Mol. Neurobiol.* **2018**, *55*, 6965–6983.

[127] Bellono, N. W.; Bayrer, J. R.; Leitch, D. B.; et al. Enterochromaffin cells are gut chemosensors that couple to sensory neural pathways. *Cell* **2017**, *170*, 185–198.e16.

[128] Bohórquez, D. V.; Shahid, R. A.; Erdmann, A.; et al. Neuroepithelial circuit formed by innervation of sensory enteroendocrine cells. *J. Clin. Invest.* **2015**, *125*, 782–786.

[129] Duan, J. Y.; Grando, C.; Liu, S. M.; et al. The M3 muscarinic acetylcholine receptor promotes epidermal differentiation. *J. Investig. Dermatol.* **2022**, *142*, 3211–3221.e2.

[130] Dumont, Y.; Bastianetto, S.; Duranton, A.; et al. Immunohistochemical distribution of neuropeptide Y, peptide YY, pancreatic polypeptide-like immunoreactivity and their receptors in the epidermal skin of healthy women. *Peptides* **2015**, *70*, 7–16.

[131] Albrecht, H.; Yang, H. Y.; Kiuru, M.; et al. The beta 2 adrenergic receptor antagonist timolol improves healing of combined burn and radiation wounds. *Radiat. Res.* **2018**, *189*, 441–445.

[132] Inagaki, N.; Shiraishi, N.; Igeta, K.; et al. Depletion of substance P, a mechanism for inhibition of mouse scratching behavior by tacrolimus. *Eur. J. Pharmacol.* **2010**, *626*, 283–289.

[133] Ohmura, T.; Hayashi, T.; Satoh, Y.; et al. Involvement of substance P in scratching behaviour in an atopic dermatitis model. *Eur. J. Pharmacol.* **2004**, *491*, 191–194.

[134] Leonardi, R.; Ronsivalle, V.; Barbato, E.; et al. External root resorption (ERR) and rapid maxillary expansion (RME) at post-retention stage: A comparison between tooth-borne and bone-borne RME. *Prog. Orthod.* **2022**, *23*, 45.

[135] Feller, L.; Khammissa, R. A. G.; Thomadakis, G.; et al. Apical external root resorption and repair in orthodontic tooth movement: Biological events. *BioMed Res. Int.* **2016**, *2016*, 4864195.

[136] Li, X. Y.; Xu, J. C.; Yin, Y. Y.; et al. Association between root resorption and tooth development: A quantitative clinical study. *Am. J. Orthod. Dentofac. Orthop.* **2020**, *157*, 602–610.

[137] Matsumura, T.; Ishida, Y.; Kawabe, A.; et al. Quantitative analysis of the relationship between maxillary incisors and the incisive canal by cone-beam computed tomography in an adult Japanese population. *Prog. Orthod.* **2017**, *18*, 24.
[138] Chung, C. J.; Nguyen, T.; Lee, J. H.; et al. Incisive canal remodelling following maximum anterior retraction reduces apical root resorption. *Orthod. Craniofacial Res.* **2021**, *24*, 59–65.
[139] Oishi, S.; Ishida, Y.; Matsumura, T.; et al. A cone-beam computed tomographic assessment of the proximity of the maxillary canine and posterior teeth to the maxillary sinus floor: Lessons from 4778 roots. *Am. J. Orthod. Dentofac. Orthop.* **2020**, *157*, 792–802.
[140] Sinnott, P. M.; Hodges, S. An incidental dense bone island: A review of potential medical and orthodontic implications of dense bone islands and case report. *J. Orthod.* **2020**, *47*, 251–256.
[141] Harokopakis-Hajishengallis, E. Physiologic root resorption in primary teeth: Molecular and histological events. *J. Oral Sci.* **2007**, *49*, 1–12.
[142] Takada, K.; Kajiya, H.; Fukushima, H.; et al. Calcitonin in human odontoclasts regulates root resorption activity *via* protein kinase A. *J. Bone Miner. Metab.* **2004**, *22*, 12–18.
[143] Kimura, R.; Anan, H.; Matsumoto, A.; et al. Dental root resorption and repair: Histology and histometry during physiological drift of rat molars. *J. Periodontal Res.* **2003**, *38*, 525–532.
[144] Sasaki, T. Differentiation and functions of osteoclasts and odontoclasts in mineralized tissue resorption. *Microsc. Res. Tech.* **2003**, *61*, 483–495.
[145] Domon, T.; Osanai, M.; Yawaka, Y.; et al. Ultrastructural study of the root dentine surface resuming resorption on human deciduous teeth. *Ann. Anat. Anat. Anz.* **2000**, *182*, 175–184.
[146] Domon, T.; Taniguchi, Y.; Inoue, K.; et al. Apoptosis of odontoclasts under physiological root resorption of human deciduous teeth. *Cell Tissue Res.* **2008**, *331*, 423–433.
[147] Turan, Y.; Akal, N.; Yildirim, B.; et al. Apoptosis in physiological root resorption of primary teeth. *Niger. J. Clin. Pract.* **2023**, *26*, 307–313.
[148] Rodrigues, L. V.; Vasconcelos, A. C.; Campos, P. A.; et al. Apoptosis in pulp elimination during physiological root resorption in human primary teeth. *Braz. Dent. J.* **2009**, *20*, 179–185.
[149] Monteiro, J.; Day, P.; Duggal, M.; et al. Pulpal status of human primary teeth with physiological root resorption. *Int. J. Paediatr. Dent.* **2009**, *19*, 16–25.
[150] Li, D. N.; Tao, Y. W.; Cui, M. Y.; et al. External root resorption in maxillary and mandibular second molars associated with impacted third molars: A cone-beam computed tomographic study. *Clin. Oral Investig.* **2019**, *23*, 4195–4203.
[151] Zhang, J.; Liu, X. Q.; Wan, C. Y.; et al. NLRP3 inflammasome mediates M1 macrophage polarization and IL-1β production in inflammatory root resorption. *J. Clin. Periodontol.* **2020**, *47*, 451–460.
[152] Iglesias-Linares, A.; Hartsfield, J. K. Jr. Cellular and molecular pathways leading to external root resorption. *J. Dent. Res.* **2017**, *96*, 145–152.