Abnormal dental follicle cells: A crucial determinant in tooth eruption disorders (Review)

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Abstract. The dental follicle (DF) plays an indispensable role in tooth eruption by regulating bone remodeling through their influence on osteoblast and osteoclast activity. The process of tooth eruption involves a series of intricate regulatory mechanisms and signaling pathways. Disruption of the parathyroid hormone-related protein (PTHrP) in the PTHrP-PTHrP receptor signaling pathway inhibits osteoclast differentiation by DF cells (DFCs), thus resulting in obstructed tooth eruption. Furthermore, parathyroid hormone receptor-1 mutations are linked to primary tooth eruption failure. Additionally, the Wnt/β-catenin, TGF-β, bone morphogenetic protein and Hedgehog signaling pathways have crucial roles in DFC involvement in tooth eruption. DFC signal loss or alteration inhibits osteoclast differentiation, affects osteoblast and cementoblast differentiation, and suppresses DFC proliferation, thus resulting in failed tooth eruptions. Abnormal tooth eruption is also associated with a range of systemic syndromes and genetic diseases, predominantly resulting from pathogenic gene mutations. Among these conditions, the following disorders arise due to genetic mutations that disrupt DFCs and impede proper tooth eruption: Cleidocranial dysplasia associated with Runt-related gene 2 gene mutations; osteosclerosis caused by CLCN7 gene mutations; mucopolysaccharidosis type VI resulting from arylsulfatase B gene mutations; enamel renal syndrome due to FAM20A gene mutations; and dentin dysplasia caused by mutations in the VPS4B gene. In addition, regional odontodysplasia and multiple calcific hyperplastic DFs are involved in tooth eruption failure; however, they are not related to gene mutations. The specific mechanism for this effect requires further investigation. To the best of our knowledge, previous reviews have not comprehensively summarized the syndromes associated with DF abnormalities manifesting as abnormal tooth eruption. Therefore, the present review aims to consolidate the current knowledge on DFC signaling pathways implicated in abnormal tooth eruption, and their association with disorders of tooth eruption in genetic diseases and syndromes, thereby providing a valuable reference for future related research.

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1. Introduction

A dental follicle (DF) is a connective tissue sac that forms around nonerupting teeth during early tooth eruption, which originates from the ectoderm of the cranial neural crest and differentiates from cranial neural crest cells (1,2). DFs can be the source of periodontal tissues, dominated by cementum, alveolar bone and periodontal membrane, during tooth development (3). In addition, DFs regulate bone remodeling by affecting the activity of osteoblasts and osteoclasts during tooth eruption (4,5). Therefore, DFs serve an indispensable role in the tooth eruption process. With an enhanced understanding of the DF, researchers have increasingly focused on

mesenchymal stem cells (MSCs) located within the DF. MSCS associated with teeth, which have the ability to differentiate, were first isolated from the DFs of human third molars (6). The dental MSCs (DMSCs) found in DFs exhibit similarities to other human MSCs and are specifically referred to as DF progenitor/stem cells (DFPCs) (7). DFPCs can differentiate into cementocytes, osteoblasts, fibroblasts, adipocytes, chondrocytes, neuron-like cells and periodontal ligament cells (5,8-10). Previous research has demonstrated that proper differentiation and functioning of DFPCs are crucial for the normal progression of tooth eruption (11).

Tooth eruption refers to the migration of a tooth from its developmental site within the jaw to its functional position in the oral cavity, thus leading to occlusal contact with the contralateral tooth (12). Recent research has identified five stages of tooth eruption: Pre-eruptive movement, intraosseous eruption, mucosal penetration, pre-occlusal eruption and post-occlusal eruption (13). The resorption of alveolar bone at the apex establishes an eruptive pathway, whereas alveolar bone formation at the root facilitates tooth movement within the jaw (14). Notably, the DF is involved in the tooth eruption process. Studies have shown that different parts of the DF have different functions; specifically, the crown region is responsible for absorbing alveolar bone, whereas the root region regulates alveolar bone formation (15,16). Therefore, a normal DF is an essential factor for tooth eruption.

Failed tooth eruptions include two conditions: Delayed eruption and complete failed eruption (14,17). Delayed eruption is defined as a tooth that deviates from the average eruption time by >2 standard deviations (18). Complete failed eruption can be categorized as primary retention, secondary retention or impaction (19). Primary retention refers to a tooth remaining embedded in the jaw without emerging into the oral cavity (17), whereas secondary retention occurs when teeth erupt but fail to establish occlusion (20). Impaction is the result of physical obstacles that exist in the path of eruption; this barrier constitutes an independent factor, separate from the eruption process itself (19).

Failed eruption of teeth is commonly attributed to physical obstructions or disorders in the tooth eruption mechanism itself (17,19,21). The process of tooth eruption involves a complex array of regulatory mechanisms and signaling pathways. DF cells (DFCs) serve a crucial role in regulating signal transduction between osteoblasts and osteoclasts, thereby governing alveolar bone resorption and formation (5,22). Additionally, a number of syndromes and systemic diseases have been identified as causative factors for tooth eruption disorders (23). Most of these diseases are caused by genetic factors, with certain syndromes also contributing to tooth eruption failure due to DF abnormalities.

A previous study on DFCs primarily focused on their role in normal tooth eruption, with limited research concentrating on abnormal eruptions (24). The role of tooth eruption-related signaling pathways, such as Wnt and TGF-β signaling pathways, in normal tooth eruption has been extensively studied; however, there are few reviews on the mechanisms underlying abnormal signaling pathways in DFCs that result in failed tooth eruption (25,26). Furthermore, numerous studies have summarized the abnormal tooth eruption observed in various genetic diseases and systemic syndrome (23,25,27-29); however, the pathogenesis of these diseases involves multiple causes, with some specifically implicating the DF in the aberrant tooth eruption process. Notably, to the best of our knowledge, there is currently no comprehensive summary available on diseases in which the DF plays a role in pathogenesis. Therefore, the present review aims to elucidate the signaling pathways associated with abnormal DFCs during failed tooth eruption and to explore their molecular impact on eruption mechanisms. Additionally, this review aims to investigate known genetic diseases and syndromes linked to abnormal tooth eruption, thus providing an overview of their clinical manifestations and underlying causes while emphasizing those involving DFCs. The atypical characteristics of DFCs and factors contributing to tooth eruption failure within these disease contexts are also highlighted.

2. Failure of tooth eruption caused by abnormal signal transduction in DFCs

In recent years, significant insights have been gained into the intricate mechanisms underlying tooth eruption. The complex molecular interactions between cells involved in tooth eruption and DFCs are widely acknowledged. To effectively treat dental diseases characterized by abnormal tooth eruption, it is imperative to understand the fundamental molecular mechanisms within DFCs.

Abnormal parathyroid hormone (PTH)-related protein (PTHrP)-PTHrP receptor (PPR) signaling pathway activity in DFCs. PTHrP functions as a local autocrine/paracrine factor capable of regulating cellular proliferation and differentiation. It exerts regulatory control over epithelial-mesenchymal interactions during organ development, including those of the skin, hair follicles, mammary glands, pancreas and developing teeth (30-34). PTHrP has been reported to be highly expressed in DFCs and as a key molecule necessary for tooth eruption (35). DFCs regulate both bone resorption and formation around teeth, thereby promoting tooth eruption. During this process, PTHrP is instrumental in promoting bone resorption while inhibiting the osteogenesis of DFCs. Research has demonstrated that DFCs, when treated with PTHrP and co-cultured, display reduced expression of osteogenic-related genes, including alkaline phosphatase (ALP), Runt-related gene 2 (RUNX2), bone sialoprotein (BSP) and osteopontin (OPN) (36). Additionally, the Wnt/β-catenin pathway serves as a key signaling pathway for tooth morphogenesis (37), and its activation promotes the stabilization and nuclear translocation of β-catenin (38). PTHrP inhibits the osteogenic differentiation of co-cultured DFCs by suppressing activation of the classical Wnt/β-catenin pathway, primarily through its impact on phosphorylated (p)-GSK-3β. P-GSK-3β reduces the phosphorylation of β-catenin, subsequently inducing nuclear translocation of β-catenin (39). In PTHrP-treated DFCs, the expression of p-GSK-3β has been shown to be reduced (36).

PTHrP is also involved in regulating tooth root development. Cementum covers the surface of the mineralized tissue of the root, and its formation is crucial for root development. Cementoblasts express the PTH/PTHrP receptor. PTHrP stimulation can inhibit the expression of BSP and osteocalcin (OCN) in cementoblasts *in vitro*, thereby blocking

cementoblast-mediated mineralization (40). In a previous study, after the knockout of PTHrP in tooth tissues, including DFs, the surviving mice exhibited tooth eruption failure and abnormal root formation (41). By contrast, the injection of PTHrP can accelerate tooth eruption and inhibit the osteogenesis of DFCs (36). Additionally, PTHrP signaling in the DFC may regulate osteoclast differentiation by influencing the colony-stimulating factor 1 (CSF-1)-receptor activator of NF-κB (RANK)-RANK ligand (RANKL)-osteoprotegerin (OPG) pathway (11,42,43), which is predominantly expressed by DFCs (35). CSF-1 and RANKL stimulate osteoclast formation, whereas OPG inhibits it by competing with RANKL for binding, thereby blocking its activity (44,45). Osteoclasts serve a crucial role in alveolar bone resorption, thus facilitating tooth eruption. PTHrP can promote bone resorption to create a pathway for tooth eruption, whereas the expression of RANKL and OPG serve as a key determinant of osteoclast activity around the teeth (42). Studies have demonstrated that PTHrP treatment increases the expression of osteoclastogenic factors in DFC. Specifically, PTHrP has been shown to elevate the expression of RANKL and reduce the expression of OPG, thereby increasing the RANKL/OPG ratio in DFCs (36); this increased ratio promotes osteoclast differentiation, thus accelerating the process of tooth eruption. Previous studies have constructed RANKL-null mouse models that exhibit impaired tooth eruption, thus suggesting that RANKL plays an integral role in tooth eruption (46). PTHrP can also reduce osteoclastogenesis through the downregulation of CD200, which is closely related to RANKL (11,47). Therefore, abnormal PTHrP expression in DFCs may be closely associated with tooth eruption failure (Fig. 1).

PTH receptor-1 (PTH1R), which is also known as the PTH/PPR (35), is a class B G protein-coupled receptor composed of seven transmembrane helices that is abundantly expressed in DFCs (48). PTH1R can interact with both PTH and PTHrP (49,50). PPR can regulate the differentiation of cementoblasts, as PPR-deficient progenitors have been shown to exhibit both accelerated bone fibroblast differentiation and upregulation of NFIC, leading to irregular cellular cementum formation on the surface of roots that normally form acellular cementum; this defect results in abnormal root development (48). Mutations in PTH1R have been associated with primary failure of eruption (PFE) (51-53). PFE is characterized by incomplete or absent tooth eruption despite the presence of an unobstructed pathway for eruption due to dysfunction in the eruption mechanism (54). The association between PFE and PTH1R was initially identified by Decker *et al* (55). Despite the incomplete understanding of PFE pathogenesis, further investigation of PTH1R has increasingly implicated an aberrant PTHrP-PTH1R signaling pathway in DFCs as being a contributing factor to the development of PFE (29,35). Tooth eruption depends on an unobstructed pathway and sufficient force (56,57). A characteristic of PFE is its unimpeded pathway, thus suggesting that a lack of adequate force may be the underlying cause. The eruption force is driven by the coordinated actions of the DF, alveolar bone formation at the tooth root, and periodontal tissue (29). DFCs serve a vital role in this intricate process, particularly through their involvement in the PTHrP-PTH1R pathway, which directly governs DFPC proliferation, and subsequent DFPC differentiation into cementoblasts, alveolar osteoblasts and periodontal ligament cells (35,58). PTH1R is abundant in DFCs and is particularly enriched in PTHrP$^+$ DFPC (48,51). These findings highlight the importance of the PTHrP-PTH1R signaling pathway in guiding PTHrP$^+$ DFPC differentiation during tooth eruption (51). To confirm that PTH1R deletion leads to PFE, a previous study specifically utilized PTHrP-CreER to delete the receptor in PTHrP$^+$ DFC (59). Due to the fact that the PFE of the first molar in mice shows a similar phenotype to human PFE in adulthood (specifically that of open occlusion) (52,60), mice were selected to establish a model to determine the role of PTH1R in tooth eruption. The results showed that, compared with in the control mice, the PTH1R-deficient mice exhibited a phenotype characteristic of PFE. Subsequent examination demonstrated that PTH1R deficiency in PTHrP$^+$ DFPCs resulted in the abnormal formation of cementoblasts, thus leading to premature cellular cementum formation on the root surface and subsequent loss of periodontal attachment (59). Although previous studies have traditionally considered tooth eruption to be a distinct process from root formation (61), previous studies have established an interrelationship between them (48,59). These findings provide information on the involvement of DFCs in the mechanisms underlying PFE; however, further exploration is necessary to elucidate additional underlying mechanisms (Fig. 2).

Abnormal Wnt/β-catenin signaling pathway activity in DFCs. The Wnt signaling pathway comprises two distinct pathways: The classical β-catenin-dependent pathway and the nonclassical pathway (62). Wnt/β-catenin signaling serves a crucial role in tooth development and eruption, with active expression of Wnt/β-catenin signaling observed in MSCs, including DFCs (63). Wnt signaling is crucial in multiple stages of tooth development and it guides tooth development during fetal formation (64). Aberrant Wnt signaling can impede tooth development, while overactivation can lead to misplaced tooth eruption. After birth, normal tooth root and periodontal tissue formation depend on Wnt signaling. Inactivation of Wnt/β-catenin signaling causes tooth root loss or short roots with increased periodontal space. Proper bone resorption and formation are essential for normal tooth eruption, and Wnt/β-catenin signaling is crucial (63,65). In MSCs, classical Wnt signaling promotes the differentiation of DFPCs into osteoblasts rather than chondrocytes and adipocytes (63). Studies have highlighted the dual role of the Wnt signaling pathway in osteoclast formation; β-catenin activation promotes the proliferation of osteoclast progenitor cells at an early stage, after which β-catenin is inactivated to promote osteoclast differentiation (66,67). This process ensures that osteoclasts perform normal functions and supports smooth bone resorption.

Studies have demonstrated that excessive Wnt/β-catenin signaling in MSCs can result in tooth eruption disorders (68,69). Activation of β-catenin in DFPCs and osteoblasts, under the influence of Wnt/β-catenin signal transduction, leads to upregulation of OPG expression (70), and OPG inhibits the RANK-RANKL pathway, thereby suppressing osteoclast differentiation and maturation, and ultimately contributing to tooth eruption disorder. Conversely, the constitutive activation of β-catenin (Ocn-cre; Ctnnb$^{LOX\ (EX3)/+}$, Col1a1-cre; Ctnnb$^{LOX\ (EX3)/+}$) or the homozygous deletion of Axin2, which

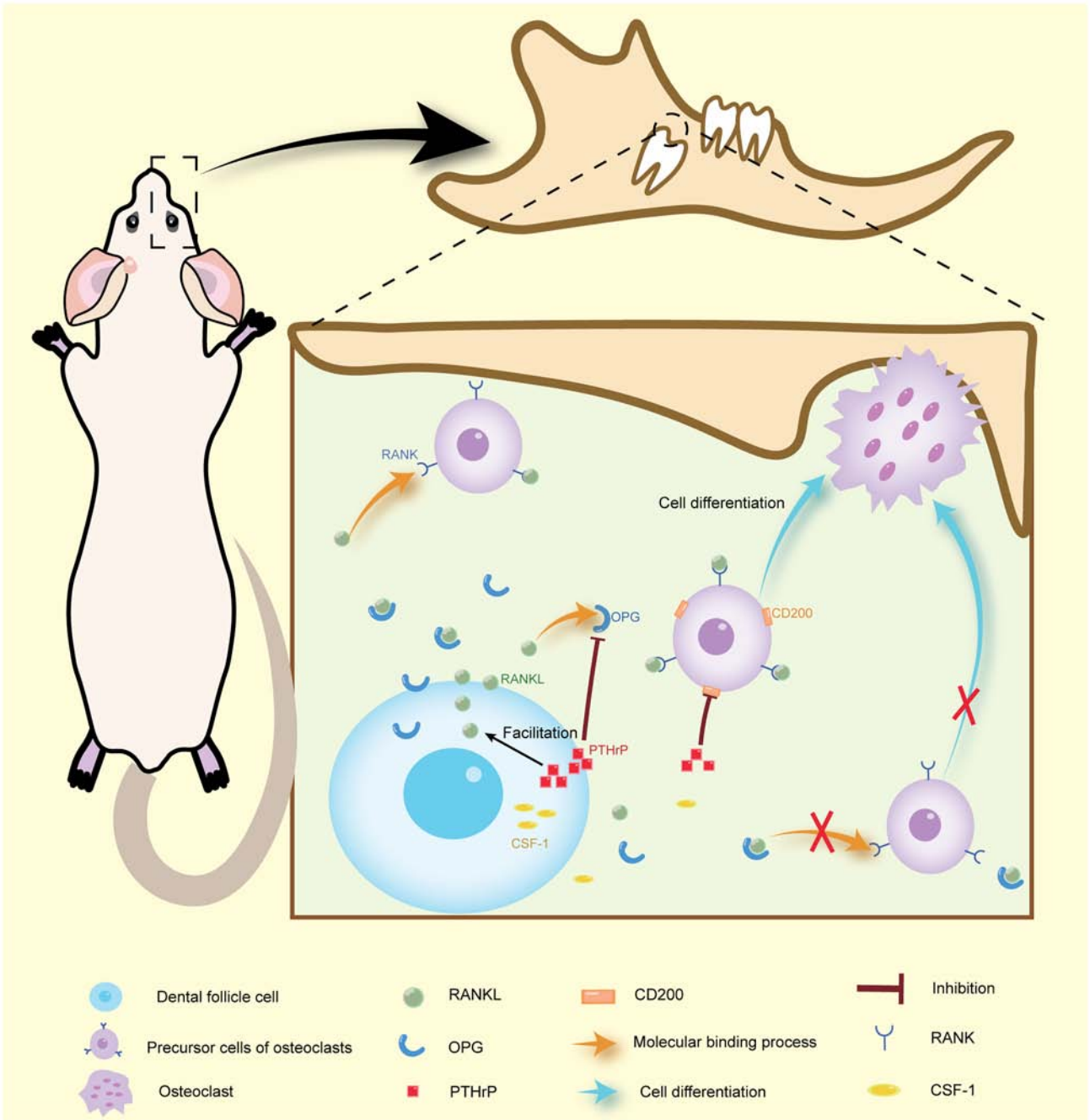

Figure 1. RANK-RANKL-OPG pathway is an important pathway for osteoclast differentiation. RANKL secreted by dental follicle cells can promote osteoclast differentiation when it acts on the RANK of osteoclast precursor cells. PTHrP affects tooth eruption by regulating osteoclast differentiation. When PTHrP is underexpressed, the formation and function of osteoclasts are abnormal, leading to insufficient alveolar bone absorption in the eruption pathway and abnormal tooth eruption. In addition, PTHrP can inhibit the expression of CD200, leading to the block of osteoclast differentiation. CSF-1, colony-stimulating factor 1; OPG, osteoprotegerin; PTHrP, parathyroid hormone-related protein; RANK, receptor activator of NF-κB; RANKL, RANK ligand.

is a negative regulator of Wnt signaling, can promote DFC differentiation, and increase cementoblasts and cellular cementogenesis. Eventually, excessive cementum and tooth stiffness can occur (63,68,71,72). Therefore, the upregulation of Wnt/β-catenin signaling in DFCs can impair tooth eruption by disrupting osteoclast function and promoting the excessive formation of cementoblasts. The latter effect can be reflected in the distortion of periodontal tissue. As the DF is crucial for periodontal tissue formation, Wnt/β-catenin signaling within the DF is indispensable for periodontal tissue homeostasis. Previous studies have shown that mice with continuous Wnt/β-catenin signaling upregulation in dental tissues fail to exhibit tooth eruption (68,71). Upon excluding cases not attributed to disrupted osteoclast activity, it was observed that these mice experienced calcification of the periodontal ligament and functional periodontal ligament, which obliterated the distinction between alveolar bone and cellular cementum, thus leading to tooth rigidity and subsequent failure of tooth eruption (72). Additionally, aberrant osteoblast differentiation can result in tooth eruption failure. Osteoblasts are derived from DFPCs, and their differentiation is also regulated by the Wnt pathway (73). Overexpression of Wnt10b in the Ocn

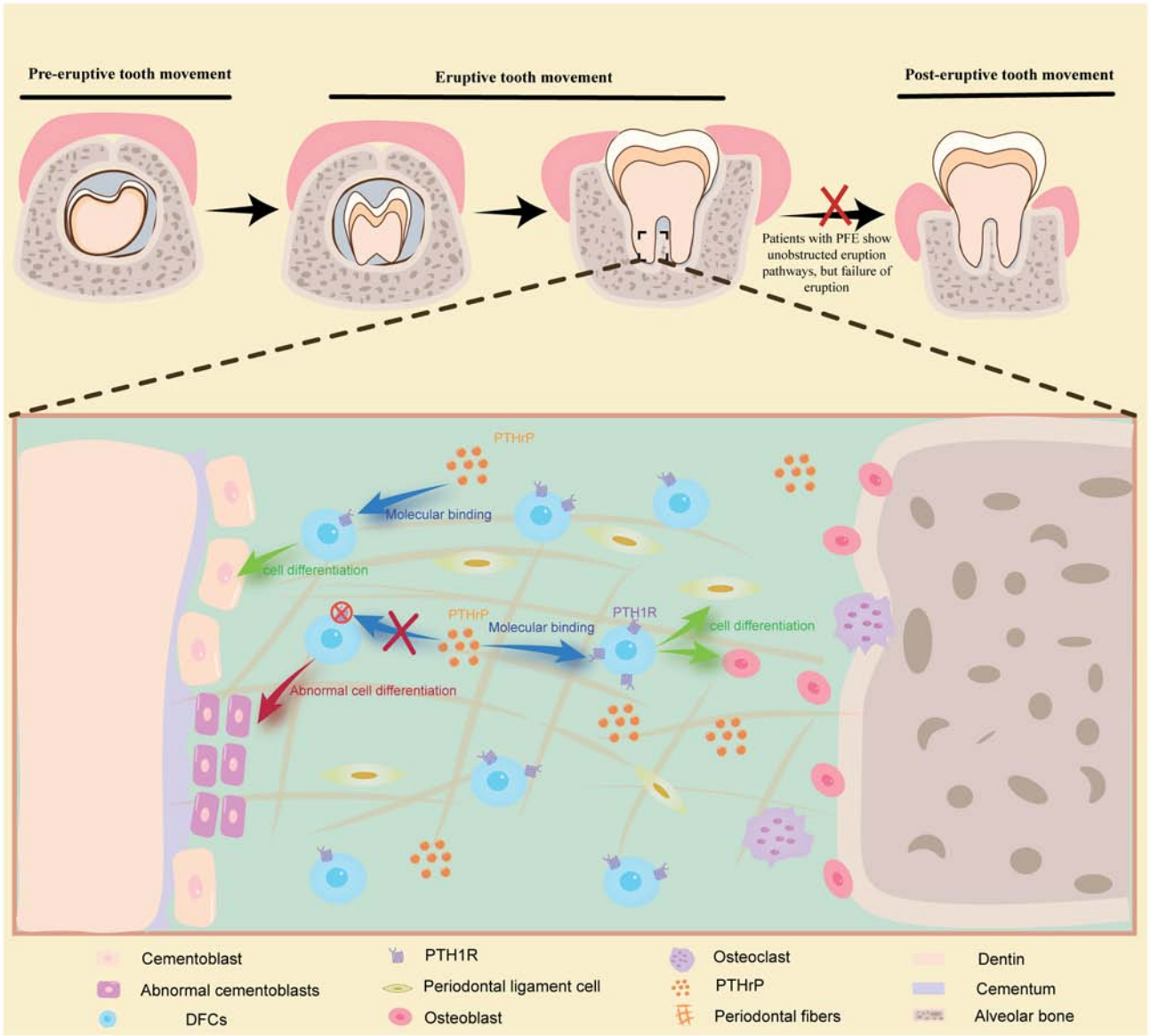

Figure 2. PFE is caused by the dysfunction of the tooth eruption mechanism. It is clinically manifested as the failure of tooth eruption despite the smooth passage of tooth eruption and no obstruction of alveolar bone and mucosa. PTH1R gene mutations are the main cause of the disease. PTHrP is mainly expressed in DFCs. PTH1R-deficient DFC differentiate into abnormal cementoblasts, which lead to the premature formation of cellular cementum on the surface of the root, lead to the loss of periodontal attachment and affect tooth eruption. DFCs, dental follicle cells; PFE, primary failure of eruption; PTH1R, parathyroid hormone receptor-1; PTHrP, parathyroid hormone-related protein.

promoter in mice was shown to enhance postnatal bone mass by promoting osteoblast differentiation, which consequently impairs tooth eruption (74).

Abnormal TGF-β signaling pathway activity in DFCs. The interaction between the epithelium and mesenchyme is crucial for tooth morphogenesis and eruption (75,76). This process involves multiple signaling pathways, including the TGF-β signaling pathway, with members of the TGF-β family playing crucial roles in normal and pathological tooth development. Among these members, TGF-β type 2 receptor (Tgfbr2), which is one of the receptors for TGF-β, is expressed in both epithelial and neural crest-derived mesenchyme. A mouse model with conditional deletion of Tgfbr2 in mesenchymal cells using Osterix (Osx) promoter-driven Cre recombinase exhibited delayed tooth eruption. Simultaneously, aberrant differentiation of osteoblasts and dentinal cells was observed, along with a significant decrease in the number of osteoclasts (77). The expression of Osx is primarily localized in the dental mesenchyme, specifically in the apex of the dental papilla and DFC (48). Therefore, it may be hypothesized that Osx is localized in DFCs, thus the Osx-driven Cre recombinase can result in the deletion of Tgfbr2 and the inhibition of TGF-β signaling in the aforementioned models. This leads to the abnormal differentiation of DFCs into osteoblasts and dentinogenic cells, as well as the abnormal formation of osteoclasts, which ultimately causes tooth eruption disorders. Additionally, aberrant expression of Smad4 can disrupt tooth development through the TGF-β signaling pathway, as Smad acts as an intracellular mediator within the TGF-β signaling pathway (78). The conditional deletion of Smad4 in mesenchymal cells derived from the neural crest has been shown to

halt tooth development (79). In addition, in a previous study, the deletion of Smad4 in the dental mesenchyme using Ocn-Cre led to abnormal root formation and delayed odontoblast differentiation (80). Due to the fact that MSCs, such as DFPCs, are critical for tooth root development, Smad4 deficiency in DFCs is likely to lead to abnormal tooth development with impaired eruption. Moreover, due to the fact that Smad4 impacts the bone morphogenetic protein (BMP) signaling cascade, it has been implicated in the regulation of the BMP signaling pathway.

Abnormal BMP signaling pathways in DFCs. The BMP signaling pathway is an essential component of osteoblast differentiation and bone development, and it exhibits extensive interplay with TGF-β signaling (81,82). Research has demonstrated that selective knockout of BMP2 in DFPC leads to impaired formation of tooth tissue and periodontal tissue, thus suggesting that the BMP signaling pathway in DFPCs serves an important role in maintaining the normal physiological function of DFPCs (83). In addition, mouse models with deletion of the BMP1 and TLL1 genes have shown impaired tooth eruption (84). BMP1 and TLL1 are encoded by distinct genes, but share similar structures and functions, and belong to a small family of extracellular metalloproteinases (85). Following gene knockout of BMP1 and TLL1, mice with impaired tooth eruption displayed reduced osteoclasts, which was potentially due to impaired osteoclast induction. Mesenchymal cells exhibit high levels of BMP7, and the removal of BMP7 from these cells can lead to impaired tooth eruption and abnormal mineralization (86). One possibility for this effect is that the timing of tooth eruption is directly related to mineralization onset. Another plausible explanation is that BMP7 function in dental pulp and DFPCs affects tooth eruption; however, the specific mechanism involved remains unclear. Additionally, muscle segment homeobox like 2 (Msx2), which is a target of BMP signaling, has been reported to be expressed in mesenchymal cells (87,88), and Msx2-null mice also exhibited tooth eruption failure (89). Experiments have suggested the alteration of the RANK osteoclast differentiation pathway in Msx2-null mice, thus implying the effect of Msx2 on the potential regulation of this pathway, which impacts osteoclast function and causes tooth eruption failure. These findings suggest that dysregulation of the TGF-β and BMP signaling pathways within DFCs often results in abnormal tooth eruption.

Abnormal Hedehog (Hh) signaling pathways in DFCs and other cells. Hh signaling has a crucial role in the development of various organs, including teeth, by mediating interactions between epithelial and mesenchymal cells. Hertwig's epithelial root sheath is surrounded by dental papilla and DFPCs that express receptor patched 1 (Ptch1) for Hh. During tooth development, Hh-expressing cells are strictly localized in the dental epithelium, whereas Ptch-positive cells are found in dental mesenchymal cells without Sonic hedgehog protein (Shh) expression (90). Analysis of mice with mesoblastic dysplasia revealed abnormalities in the C-terminus of the Ptch1 protein. In these mutants, the proliferation of mesenchymal cells around the teeth was inhibited. Additionally, they exhibited disrupted molar eruption and shorter roots. These findings indicate that abnormal transmission of the Shh signal between the epithelium and DF mesenchyme may impact tooth root development and eruption (91). The involvement and functions of DFCs in tooth eruption exhibit temporal and spatial variations. Temporal variations divide tooth eruption into intraosseous and extraskeletal stages, with DFCs playing distinct roles (92). Intraosseous eruption mainly results from alveolar bone resorption and remodeling. During this period, different regions of the DF are thought to play different roles, and DFCs around the crown induce different types of osteoclast differentiation by upregulating the expression of factors such as CSF-1, VEGF and RANKL (24), which leads to an increase in the number of osteoclasts, thus facilitating crown bone resorption to establish unobstructed eruption pathways. By contrast, the DF tissue near the developing root apex serves a key role in alveolar bone formation, thus providing upward force for tooth eruption. This process is intricately linked to the differentiation of DFCs into osteoblasts. Spatial effects on DFs may be the result of regional differences in gene expression. In a previous study, DFCs were isolated from both the crown and basal regions of rat teeth, and RNA was extracted from each region for analysis. The expression of RANKL in the crown region was greater than that in the basal region, whereas the expression of BMP-2 in the basal region was greater than that in the crown region (24). Thus, the spatial localization of gene expression in the DF may modulate osteoclast generation and osteoblast differentiation. The coordinated activity of different regions of the tooth, which is mediated by DFCs, facilitates tooth movement toward the oral cavity. However, the removal of the crown or root region of DF can impede successful eruption; specifically, crown removal disrupts pathway formation, whereas root removal inhibits bone formation (16). The DFs in the two regions exert influences on tooth eruption through distinct signaling pathways. In the crown region, the main pathways involved are the Wnt/β-catenin pathway, TGF-β signaling pathway and BMP signaling pathway. In the root region, in addition to the aforementioned pathways, the Hh signaling pathway also serves a significant role (Figs. 3 and 4). When the tooth is exposed to the oral cavity, it enters the stage of extraosseous eruption. In this stage, the force of tooth upward eruption is mainly derived from the periodontal ligament (93). Furthermore, periodontal tissue derived from DFs and normal follicle development crucially support the tooth eruption progression outside the alveolar bone.

3. Syndromes and genetic disorders

Abnormal tooth eruption can be classified into two main categories, failed and delayed tooth eruption, and is associated with numerous systemic syndromes and genetic diseases, the majority of which are caused by pathogenic gene mutations. Table I presents a comprehensive list of syndromes and genetic disorders associated with aberrant tooth eruption. According to the data, 48 diseases are known to be linked to abnormal tooth eruption (23,25,28,29). There is convincing evidence for a strong relationship between abnormal tooth eruption and the presence of DFs in seven of these diseases. Furthermore, five of these disorders have been attributed to mutations in specific genes: Cleidocranial dysplasia (CCD), osteopetrosis, mucopolysaccharidosis VI, enamel renal syndrome and dentin dysplasia (DD). Moreover, regional odontodysplasia (RO)

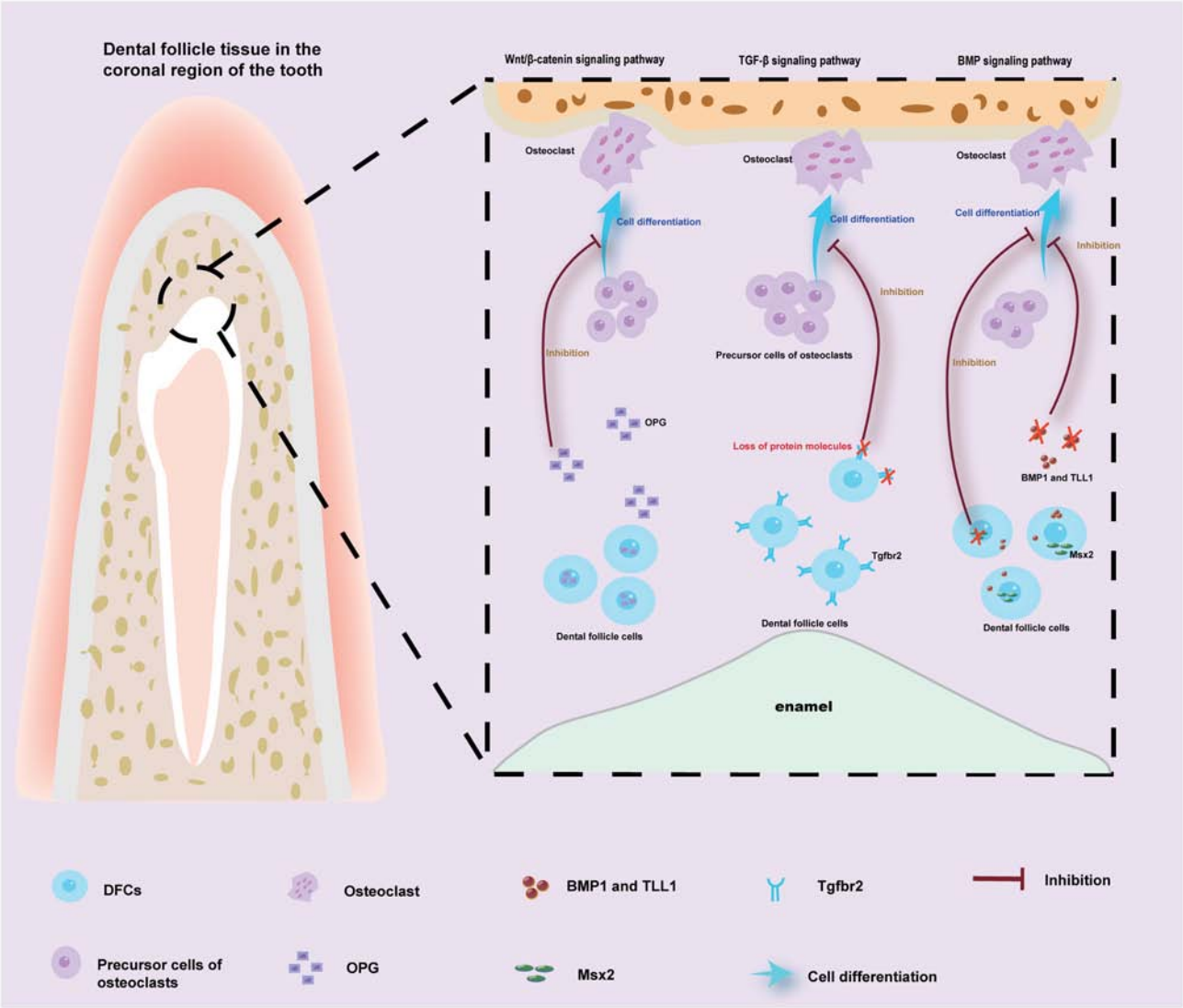

Figure 3. Disturbance of DFC signaling pathways results in disorders of osteoclast differentiation. The depicted regions in this figure are primarily situated within the crown dental follicle tissue. Wnt/β-catenin signaling pathway: Activation of the Wnt/β-catenin pathway leads to an upregulation of OPG expression, which subsequently inhibits osteoclast differentiation. TGF-β signaling pathway: Deficiency of Tgfbr2 receptor in DFCs inhibits osteoclast differentiation. BMP signaling pathway: Suppression of BMP1, TLL1 and Msx2 proteins associated with this pathway inhibit osteoclast differentiation. BMP, bone morphogenetic protein; DFC, dental follicle cell; Msx2, muscle segment homeobox like 2; OPG, osteoprotegerin; Tgfbr2, TGF-β type 2 receptor.

and multiple calcifying hyperplastic DFs are two distinct types of tooth eruption disorders that are not associated with genetic mutations.

CCD. CCD, which was identified by Marie and Sainton in 1897, is an autosomal dominant disorder characterized by hypoplasia of the clavicle and skull, widening of the suture and fontanelle, and short stature (49). In addition to skeletal abnormalities, patients with CCD often have dental issues, such as supernumerary teeth accompanied by severe malocclusion and crossbite, retention of primary dentition, impacted teeth and failed tooth eruption (94,95). In a recent study, 50 patients with CCD were examined, 41 of whom had symptoms of tooth eruption failure. These patients presented with a total of 665 teeth displaying abnormal eruption patterns. The most commonly affected teeth were canines (79.5%), followed by permanent premolars (71.0 and 62.5%, first and second permanent premolars, respectively), and superdeciduous teeth and/or retained primary teeth were often observed in this area. Conversely, the first and second molars were less affected (6.0 and 24.0%, respectively) (27).

Genetic studies have shown that mutations in a single allele of RUNX2 cause CCD. These mutations commonly arise from deletions, missense mutations and substitutions occurring within the DNA binding region of RUNX2. The RUNX2 gene, also known as core binding factor a1 (Cbfa1), is located on chromosome 6p21 (96). RUNX2 acts as a crucial transcriptional regulator of osteoblast differentiation during bone formation (97). In addition, heterozygous Runx2-knockout mice were found to exhibit the majority of bone abnormalities observed in human patients with CCD. It has been reported that Runx2 is expressed in preosteogenic mesenchyme and active osteogenesis sites in mice (98-100). Mice with complete deficiency of Runx2 [Runx2 (-/-)] have been shown to exhibit severe osteogenesis imperfecta and often succumb to respiratory distress at birth due to defects in

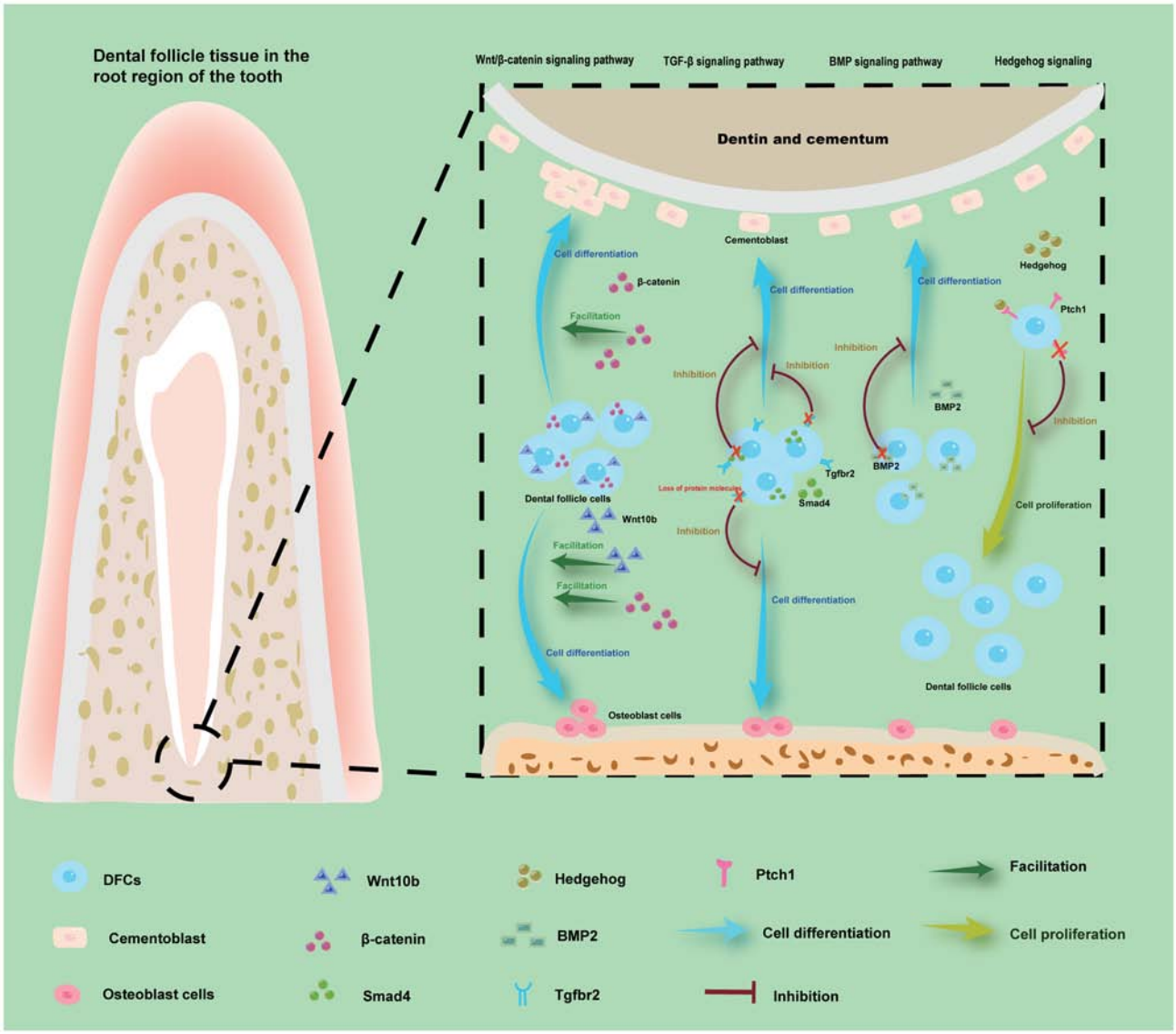

Figure 4. Depicted regions primarily reside within the dental follicle tissue surrounding the root apex. Overexpression of β-catenin in the Wnt/β-catenin signaling pathway promotes differentiation of DFCs into cementoblasts, thereby enhancing cementum formation. Conversely, loss of Tgfbr2 and Smad4 in the TGF-β signaling pathway, as well as BMP2 deficiency in the BMP signaling pathway inhibits the formation of cementoblasts, Eventually, an excess or deficiency of cementum can result in abnormal root development. The excessive upregulation of Wnt10b and β-catenin in the Wnt/β-catenin signaling pathway leads to a significant increase in bone mass by promoting osteoblast differentiation. The loss of the Tgfbr2 in the TGF-β signaling pathway inhibits the differentiation of DFC into osteoblasts, leading to the block of alveolar bone formation. Loss of Ptch1 receptors inhibits the proliferation of DFCs, thereby affecting tooth eruption. BMP, bone morphogenetic protein; DFC, dental follicle cell; Ptch1, patched 1; Tgfbr2, TGF-β type 2 receptor.

the ribs. Heterozygous mutant mice [Runx2 (+/-)] can survive but exhibit skeletal abnormalities, including an open fontanelle and clavicular defects. This phenotype suggests that a mutation in one allele of Runx2 in mice is sufficient to produce an osteogenic malformation (101). These mice recapitulate the bone abnormalities that are commonly observed in most cases of CCD. To investigate whether these mice can also replicate tooth eruption abnormalities similar to those found in CCD, a heterozygous Runx2-knockout mouse model was generated to observe tooth eruption (101). Compared with wild-type mice, mutant mice exhibited a significant delay in tooth eruption. Further investigations into the impact of Runx2 on skeletal and dental anomalies, and its primary cellular targets, have demonstrated that Runx2 is expressed in osteoblasts and DFs but not in osteoclasts (102,103). Therefore, the abnormal tooth eruption in Runx2 (+/-) young adult mice may be attributed to two factors: i) Due to the inhibition of DF-mediated osteoclast signaling during tooth eruption in Runx2 (+/-) mice; and ii) due to the impaired osteogenic differentiation of DFCs leading to defective bone deposition in osteoblasts and consequently resulting in abnormal eruption.

Further elucidation of the molecular basis of the abnormal eruption observed in Runx2 (+/-) mice is required to test these two possibilities. First, impaired osteoclast recruitment is a possible cellular mechanism for delayed tooth eruption in patients with CCD. Previous research has demonstrated active resorption of alveolar bone and an increase in osteoclasts during eruption in both wild-type mice and Runx2 (+/-) mutant mice; however, this increase was significantly inhibited in the mutant mice. Additionally, this previous study

Table I. Syndromes and genetic disorders associated with abnormal tooth eruption.

Disease name	OMIM number(s)[a]	Orphanet number[b]	Association with the DF	Risk factors[b]	Tooth eruption status	(Refs.)
Cleidocranial dysplasia	119600; 620099	1452	Yes	RUNX2 gene mutation	Delayed eruption	(23,25,27-29)
Albers-Schönberg osteopetrosis	166600	53	Yes	CLCN7 gene heterozygous mutations	Failure of eruption	(25,28)
Mucopolysaccharidosis VI	253200	583	Yes	ARSB gene mutation	Delayed eruption	(23)
Enamel renal syndrome	204690	1031	Yes	FAM20A gene mutation	Failure of eruption	(27)
Dentin dysplasia	125400; 125420	1653	Yes	VPS4B gene mutation	Failure of eruption	(27,29)
Regional odontodysplasia	/	83450	Yes	Local circulatory disorders, viral infections, local trauma, pharmacotherapy during pregnancy, facial asymmetry or a combination of these factors	Failure or delay in eruption	(28,29)
Multiple calcifying hyperplastic dental follicles	/	/	Yes	Unknown	Failure of eruption	(25)
Gorlin syndrome	109400	377	Unknown	Ptch1 gene mutation	Failure of eruption	(27,29)
Oculodental syndrome, Rutherfurd type	180900	2709	Unknown	Unknown	Failure of eruption	(28)
Cherubism	118400	184	Unknown	SH3BP2 gene mutation in ~80% of cases	Failure of eruption	(27-29)
Albright hereditary osteodystrophy	612462	79444	Unknown	GNAS gene mutation	Delayed eruption	(25)
Gardner syndrome	175100	79665	Unknown	APC gene mutation	Failure of eruption	(23,27,29)
Osteoglophonic dysplasia	166250	2645	Unknown	FGFR1 gene mutation	Failure of eruption	(28,29)
Nance-Horan syndrome	302350	627	Unknown	NHS gene mutation	Failure of eruption	(28)
McCune-Albright syndrome	174800	562	Unknown	Somatic mutations of the GNAS gene	Failure of eruption	(28)
Hypodontia-dysplasia of nails syndrome	189500	2228	Unknown	MSX1 gene mutation	Failure of eruption	(28)

Table I. Continued.

Disease name	OMIM number(s)[a]	Orphanet number[b]	Association with the DF	Risk factors[b]	Tooth eruption status	(Refs.)
GAPO syndrome	230740	2067	Unknown	Homozygous nonsense or splicing mutations in the ANTXR1 gene	Failure of eruption	(23,25,27-29)
Osteopathia striata with cranial sclerosis	300373	2780	Unknown	Mutations in the Wilms tumor gene on the X chromosome	Failure of eruption	(25)
Singleton-Merten syndrome	182250; 616298	85191	Unknown	Unknown	Delayed eruption	(25,27,29)
Aarskog syndrome	100050; 305400	915	Unknown	FGD1 gene mutation	Delayed eruption	(25,27,29)
Acrodysostosis	101800; 614613	950	Unknown	Heterozygous mutations in either the PRKAR1A or PDE4D genes	Delayed eruption	(25)
Apert syndrome	101200	87	Unknown	FGFR2 gene mutation	Delayed eruption	(25,27,29)
Chondroectodermal dysplasia	225500; 617088; 618123	289	Unknown	EVC and EVC2 gene mutations	Delayed eruption	(25)
Cockayne syndrome	133540; 214150; 216400; 216411; 278780; 610756; 610758; 616570	191	Unknown	ERCC6 and ERCC8 gene mutations	Delayed eruption	(25)
Dubowitz syndrome	223370	235	Unknown	Unknown	Delayed eruption	(25)
Frontometaphyseal dysplasia	305620; 617137	1826	Unknown	Unknown	Delayed eruption	(25)
Goltz syndrome	305600	2092	Unknown	PORCN gene mutation	Delayed eruption	(25)
Hunter's syndrome	309900	580	Unknown	Iduronate-2-sulfatase deficiency	Delayed eruption	(25)
Incontinentia pigmenti	308300	464	Unknown	IKBKG gene mutation	Delayed eruption	(25,29)
Levy-Hollister syndrome	149730; 620192; 620193	2363	Unknown	Unknown	Delayed eruption	(25)
Osteogenesis imperfecta	166200; 166210; 166220; 166230; 259420; 259440; 610682; 610915; 610967; 610968; 613848; 613849; 613982; 614856; 615066; 615220; 616229; 616507; 619131; 619795	666	Unknown	COL1A1 and COL1A2 gene mutations	Delayed eruption	(25,27,29)

Table I. Continued.

Disease name	OMIM number(s)[a]	Orphanet number[b]	Association with the DF	Risk factors[b]	Tooth eruption status	(Refs.)
Hutchinson-Gilford syndrome	176670	740	Unknown	Unknown	Delayed eruption	(25)
Pyknodysostosis	265800	763	Unknown	Encoding cathepsin K gene mutations	Delayed eruption	(25)
Carpenter syndrome	201000; 614976	65759	Unknown	RAB23 and MEGF8 gene mutations	Failure of eruption	(27,29)
Down syndrome	190685	870	Unknown	Additional independent chromosome 21 (47,+21)	Failure of eruption	(29)
Hypertrichosis lanuginosa congenita	145700; 145701; 307150	2222	Unknown	Unknown	Failure of eruption	(29)
Costello syndrome	218040	3071	Unknown	HRAS gene mutation	Failure of eruption	(27,29)
Junctional epidermolysis bullosa	/	305	Unknown	mutations in various genes, including COL17A1, ITGA6, ITGB4, LAMA3, LAMB3, LAMC2 and ITGA3	Failure of eruption	(27,29)
Gaucher disease	230800; 230900; 231000; 231005; 608013; 610539	355	Unknown	GBA gene mutation	Failure of eruption	(29)
Hereditary gingival fibromatosis	135300; 605544; 609955; 611010; 617626	2024	Unknown	Unknown	Failure of eruption	(27,29)
Hallermann-Streiff syndrome	234100	2108	Unknown	Unknown	Failure of eruption	(27,29)
Hyperimmuno-globulinemia	252500	576	Unknown	GNPTAB gene mutation	Failure of eruption	(29)
Menkes disease	309400	565	Unknown	ATP7A gene mutation	Failure of eruption	(29)
Neurofibro-matosis type 1	162200; 162210; 613675	636	Unknown	NF1 gene mutation	Failure of eruption	(29)
Parry-Romberg syndrome	141300	1214	Unknown	Unknown	Failure of eruption	(29)
Sclerosteosis	269500; 614305	3152	Unknown	Unknown	Failure of eruption	(29)
SHORT syndrome	269880	3163	Unknown	PIK3R1 gene mutation	Failure of eruption	(27,29)
Infantile spasms syndrome (West Syndrome)	300672; 308350; 613477; 613722; 615006; 616139; 616341; 617065; 617929; 618298	3451	Unknown	Gene mutation of STXBP1, TSC1, TSC2 and trisomy 21	Failure of eruption	(29)

[a]Data from https://omim.org; [b]data from https://www.orpha.net. DF, dental follicle.

indicated that Runx2 may serve a role in osteoclastogenesis by activating the expression of RANKL and receptor activators of RANK-RANKL signaling (101). It may be hypothesized that the two alleles of Runx2 promote RANK-RANKL signaling, which is essential for active osteoclast recruitment in the tooth germination pathway, and that DFCs play a crucial role in osteoclast recruitment and express Runx2. This finding suggested that Runx2 mutations in DFCs may hinder active alveolar bone resorption by affecting osteoclast numbers, thus contributing to abnormal tooth eruption. Additionally, the effect of Runx2 mutations on osteoblasts was investigated by examining its effect on the osteogenic differentiation of DFCs. The findings demonstrated that a Runx2 mutation decreased the mineralization capacity of DFCs and downregulated the expression of genes associated with osteoblast function, such as ALP, Osx, OCN, ColIα1 and OPN. Furthermore, it disrupted bone formation during tooth eruption, consequently diminishing the osteogenic potential of DFCs. These effects may contribute to abnormal tooth eruption in patients with CCD (104).

Osteopetrosis. Osteopetrosis is a disease caused by disruption of the bone remodeling process with osteoclastic bone resorption defects, and can be divided into intermediate autosomal recessive osteopetrosis (global incidence, 1/250,000) and autosomal dominant osteopetrosis (global incidence, 1/20,000) (105) depending on how it occurs. The clinical manifestations of osteopetrosis commonly include fractures, scoliosis, osteoarthritis, bone marrow insufficiency, developmental delays, tooth eruption disorders and a range of neurological symptoms. Additionally, heightened bone density can lead to compression of cranial nerves and subsequent abnormal innervation (106,107). The eruption of teeth may be delayed or completely absent due to decreased bone resorption and abnormal opening of tooth eruption pathways. Additionally, dental deformities, enamel hypoplasia, dentin abnormalities, inadequate mineralization of enamel and dentin, and defects in the periodontal membrane have been observed (108). A statistical analysis of patients with osteopetrosis demonstrated that the maxillary second molars (66.7%) and mandibular second molars (58.3%) exhibited the highest incidence of tooth eruption failure, whereas anterior teeth and first premolars were rarely affected (27).

Osteopetrosis arises from gene mutations that cause abnormalities in the rough marginal region and dysfunction of osteoclasts, which fail to mediate extracellular acidification in this area, thus resulting in obstructed osteolysis (23). The genes involved in the formation and function of the rough marginal region of osteoclasts include CLCN7, TCIRG1, OSTM1, SNX10 and PLEKHM1. Mutations in these genes impair the transport of endosomal and lysosomal vesicles, thereby disrupting rough marginal regions, as well as osteoclast formation and function (109). Osteoclasts serve a crucial role in tooth eruption, and abnormal tooth eruption in patients with osteopetrosis may be attributed to dysfunctional osteoclasts. Among the aforementioned mutated genes, CLCN7 mutations are the most common cause of osteopetrosis (110), and their impact on osteoclasts is closely related to DFCs. A CLCN7-deficient mouse model was established via injection of chitosan-CLCN7-small interfering RNA nanoparticles, and the mice exhibited abnormal tooth eruption. Coincidentally, these dental changes have also been observed in patients with CLCN7 mutations (111,112). Subsequent experiments have demonstrated that CLCN7 regulates tooth eruption through the DFC-mediated osteoclast pathway by decreasing CLCN7 expression in the DFC, thus leading to reduced numbers of osteoclasts and bone resorption pits (111). Therefore, the lack of CLCN7 in DFCs may inhibit osteoclast formation. This relationship may be mediated through the RANKL-OPG pathway. The RANK-RANKL-OPG signaling axis and downstream transcription factors are important pathways through which DFCs regulate osteoclast generation. OPG secreted by DFCs may inhibit osteoclast generation (45,113), whereas RANKL secreted by DFCs is an important positive regulator of osteoclast differentiation (114,115). RANKL and OPG have been reported to be expressed in DFCs, and CLCN7-deficient mice exhibited downregulated RANKL expression and upregulated OPG expression, which inhibited osteoclast generation (111). Thus, mutations in CLCN7 may result in diminished osteoclasts and aberrant tooth eruption through the RANK-RANKL-OPG signaling pathway mediated by DFCs.

Furthermore, *in vitro* investigations of DFCs have demonstrated that defects in CLCN7 can impede DFC differentiation. Previous research has indicated that DFCs can differentiate into various cell types, including osteoblasts (116). Normally, induced DFCs exhibit upregulation of osteoblast-related genes, such as ALP, BSP, OPN and TGFB1, thus confirming their potential for osteoblastic differentiation. However, the expression levels of these proteins have been shown to be reduced in a CLCN7-deficient cell group (111). Thus, CLCN7 mutations may be involved in regulating the osteogenic differentiation of DFCs to influence tooth eruption.

Mucopolysaccharidosis VI. Mucopolysaccharidosis represents a cluster of hereditary disorders characterized by impaired degradation of mucopolysaccharides [also known as glycosaminoglycans (GAGs)] due to deficiency of specific enzymes, thus resulting in increased accumulation of mucopolysaccharides across diverse tissues (117). Mucopolysaccharidosis types I-VII are classified based on clinical and biochemical characteristics, and exhibit a high degree of variability. Clinical manifestations include developmental delay, growth retardation and skeletal abnormalities (118). Initially, the accumulation of mucopolysaccharides in various organs leads to progressive intellectual disability and neurodevelopmental deficiency. The most severe consequences occur when excessive GAG accumulation affects the heart, thus resulting in severe cardiovascular disease and even death. Additionally, an excessive buildup of GAG in the DF can impede tooth eruption (23).

Maroteaux-Lamy syndrome (mucopolysaccharidosis type VI), which was initially reported in 1965 (119), is an uncommon autosomal recessive disorder, with a global incidence ranging from 0.0132:100,000 to 20:100,000 (120,121). This disorder arises due to a deficiency of arylsulfatase B (ARSB), which is a crucial gene involved in the degradation of dermatan sulfate. Mutations in this gene lead to the accumulation of undegraded or partially degraded mucopolysaccharides that disrupt cellular function and give rise to various symptoms. Patients with mucopolysaccharidosis

VI exhibit physical characteristics resembling those of other types of mucopolysaccharidosis, including short stature, joint stiffness, corneal opacity, and cardiac and respiratory dysfunction (122). However, in contrast to patients with other subtypes, patients with this condition exhibit normal cognitive abilities, metachromatic inclusions in white blood cells and deficiencies in ARSB (123). Furthermore, dental abnormalities are significant manifestations of Maroteaux-Lamy syndrome. These abnormalities are commonly described as dysplastic and widely spaced permanent molars with abnormal root eruption and calcification. Such aberrant teeth often coincide with DF irregularities, wherein excessive deposition of dermatan sulfate impairs the normal morphology and function of the DF. Consequently, the DF becomes tougher and thicker due to the dense fibrous connective tissue observed upon histopathological examination. This abnormal DF increases resistance to tooth eruption, thus ultimately leading to failed tooth eruption (23,118,123).

Enamel renal syndrome. Enamel renal syndrome is an uncommon genetic disorder inherited in an autosomal recessive pattern due to biallelic mutations in the FAM20A gene (124). It is characterized by amelogenesis imperfecta (AI), delayed tooth eruption, intramedullary calcification, gingival enlargement, gingival fibromatosis and nephrocalcinosis (125). Among them, AI and nephrocalcinosis are the most common characteristics of these patients. AI refers to a group of genetic disorders ranging in incidence from 1:700 to 1:14,000 in the United States that affects both the quality and quantity of enamel. Symptoms can be observed in some or all teeth, with AI uniformly affecting enamel across individuals, thus resulting in either hypoplastic or undermineralized enamel. The affected teeth may exhibit discoloration, sensitivity, or increased susceptibility to disintegration prior to or after eruption (126). Nephrocalcinosis is a disease characterized by calcium salt deposition in the kidney, which may be predominantly cortical or medullary in nature; it is often associated with primary hyperparathyroidism, distal renal tubular acidosis and other diseases (127). In addition to enamel and kidney lesions, abnormal tooth eruption is also a prevalent clinical manifestation. Patients with enamel renal syndrome exhibit an aberrant eruption pathway for their posterior teeth (125). Although the root is fully formed, the eruption of the tooth stops halfway, and pericoronal radiolucency manifests around the impacted teeth. Previous case studies have demonstrated that the DF associated with mandibular posterior molars exhibits an atypical structure that is characterized by dense connective tissue and mineralized tissue (128-130). Therefore, delayed tooth eruption can be attributed to the pathological condition of the DF. One possibility for this effect is that DFs may exhibit impaired synthesis of essential molecular components required for proper tooth eruption. Previous studies have demonstrated that FAM20A is localized in the DF above the cusp, and its deficiency has been linked to unsuccessful tooth eruption, thus suggesting a potential role for FAM20A-catalyzed phosphorylation in regulating the pathway involved in shaping the pathway of tooth eruption. Additionally, the presence of pericoronal radiolucency around the impacted teeth can be associated with mutations in FAM20A within the DF (130-132). Another factor is that tooth eruption may be hindered by the DF due to mechanical retention caused by cystic or fibrous transformation. Additionally, the presence of calcification in the DF of patients could contribute to abnormal eruption (133). FAM20A mutations are responsible for enamel renal syndrome and are also associated with calcification in the DF. The gene normally suppresses mineralization; however, in patients with homozygous FAM20A mutations, increased promoter activity and reduced inhibition of oxalate crystal growth cause mineralization of the DF, thus impairing its ability to support normal tooth eruption (127).

DD. Genetic dentin disorders have been well documented and include two primary types: Dentinogenesis imperfecta (DI) and DD (134). Based on the clinical classification, DI can be further categorized into three subgroups (types I-III), whereas DD can be divided into two subgroups (135). The present review specifically focused on DD, which was previously referred to as a 'rootless tooth'; however, with advancements in understanding of this disorder, this condition has become known as DD. This disorder is classified into type I (DD1) and type II (DD2) (136). DD1 is a rare autosomal dominant nonsyndromic disorder in human dentinal diseases, with an estimated incidence of 1/100,000 (137). In DD1, the patient's crown exhibits a normal shape, morphology and coloration; however, the patient presents with premature tooth loss, tooth loosening and abnormal tooth eruption (138,139). Imaging demonstrates structural abnormalities, including bulbous crowns, occlusion of the endodontic compartment, shortened roots and periapical radiolucency. Pulp remnants in permanent teeth may show crescent-shaped radiolucence, whereas deciduous teeth show complete pulp occlusion (139). The clinical appearance of teeth in patients with DD2 is also normal; however, the primary teeth may appear to be amber and translucent (140). In DD2, the roots exhibit a normal shape and morphological features. Therefore, delayed tooth eruption is rarely reported as being a feature of DD2, but it is often observed in patients with DD1 (139). This is due to the fact that root development has a certain impact on tooth eruption, thus necessitating further investigations into the potential causes of delayed eruption in DD1.

To date, mutations in the VPS4B, SMOC2 and SSUH2 genes have been identified via genetic screening to be associated with the pathogenesis of DD1 (141-143). Among them, VPS4B has been shown to be closely related to the formation of alveolar bone and cementum, and the normal differentiation of DFCs is also an essential component of cementogenesis and the development and formation of surrounding alveolar bone (144). Therefore, VPS4B mutations may lead to abnormal osteogenesis by affecting the normal differentiation and proliferation of DFCs, and eventually leading to abnormal tooth eruption. Ultimately, a comparative analysis of the proliferation and osteogenic induction capacity of DFCs derived from patients with VPS4B-mutant DD1 and healthy controls was conducted (145). The growth rates of DFCs were found to be significantly greater in patients with DD1 than in controls; however, compared with those from control individuals, DFCs from patients with DD1 exhibited lower expression levels of osteogenic genes, such as ALP, OCN, BSP and RUNX2, as well as fewer calcium nodules,

as observed via Alizarin red S and ALP staining. These findings suggest that VPS4B may have a crucial role in regulating the osteogenic differentiation of DFCs and that mutations in VPS4B could lead to reduced osteogenic capacity in patients with DD1. Consequently, impaired root formation and bone remodeling during development may ultimately contribute to tooth eruption disorders.

RO. RO is a rare developmental anomaly that was first described by Zegarelli *et al* in 1963 (146). The etiology of RO remains incompletely elucidated, although it is not believed to have a hereditary basis (147). Various potential pathogenic factors have been postulated in the literature, including local trauma, radiation exposure, high fever episodes, vascular disorders, prenatal drug administration, localized or systemic viral infections, reactivation of latent viruses, impaired migration or differentiation of neural crest cells, nutritional or metabolic deficiencies, ischemia events and Rhesus disease (148,149). The clinical manifestations of RO include discoloration of teeth (yellow or brown), impaired tooth eruption, atypical tooth morphology, tooth mobility, and the presence of swelling or abscess formation (150). The main radiographic characteristics include an enlarged pulp cavity, open root apices, indistinct borders and a ghost-like appearance of the affected tooth (151). Histologically, enamel and dentin show hypoplasia and insufficient calcification, the pulp is larger than normal, and the DF appears to be calcified (152,153). In general, the disease affects both primary and permanent dentition. The mandible is generally more susceptible than the maxilla. Among the clinical manifestations, tooth eruption failure commonly occurs (149). The failure of tooth eruption may be attributed to dental deformities hindering the process, abnormal calcification and swelling of the DF causing mechanical obstruction, or dysregulation of signaling pathways in DFPCs during the eruption induction pathway resulting from calcification of the DF (154,155). According to the literature, imaging studies have demonstrated abnormal hyperplasia and fibrous tissue swelling in the vicinity of nonerupted teeth (154-156), which is associated with aberrant calcification of the DF tissue. In addition, histological studies have demonstrated various types of calcification within the DF of patients with RO, including fibrous or nonfibrous osteoid chains, as well as fused calcified spheres attached to larger calcified masses or osteoid chains. These calcifications are predominantly located in areas typically occupied by enamel formation, some of which are formed independently of collagen involvement, whereas others result from collagen fiber mineralization (154,157). The accumulation of calcified tissue in the DF is closely associated with both the enlargement of the DF and an increase in periodontal fibrous tissue. These abnormal DF tissues may eventually lead to tooth eruption disorder.

Multiple calcifying hyperplastic DFs (MCHDFs). MCHDFs are rare, and their etiology is still unclear (158); they are clinically defined by multiple unerupted teeth and large DFs (159). Radiographically, these follicles are observed as radiolucency surrounding the crown of the unerupted tooth and may also exhibit radiopaque lesions within the inner part of the DF (160,161). The histological features of this condition include extensive cemento-like calcification and the presence of residual odontogenic epithelium within the fibrous connective tissue matrix (162). The process of calcification is usually performed in DFs because DFPCs in DFs can differentiate into cementoblasts or osteoblasts (163). Impacted teeth may result from incomplete digestion of fibrous tissue (164) and abnormal structure or enlargement of the DF, which obstructs tooth eruption. Additionally, calcified tissue within the DF could disrupt DFPC-related signal transduction pathways that are crucial for proper tooth eruption (162). The reported data have suggested that the incidence of type I calcification is greater in patients with MCHDF than in patients with type II calcification. However, type I calcification may also occur in DFs with hypoplasia and regional odontodysplasia, thus suggesting similar etiologies for tooth eruption disorders in these conditions (165). Following the excision of abnormal DFs, successful eruption of impacted teeth in patients with MCHDF further underscores the pivotal role of diseased DFs in eruption failure (165).

4. Conclusion

The DF serves a crucial role in tooth eruption, and regulates the formation and resorption of alveolar bone. Abnormalities in DFCs are closely associated with abnormal eruption patterns, and disturbances in signaling pathways within the DF represent an important factor contributing to tooth eruption disorders. PTHrP signaling can modulate osteoclast differentiation by influencing the CSF-1-RANK-RANKL-OPG pathway. Moreover, PTH1R is abundantly expressed in DFCs, and interacts with both PTHrP and PTH. Notably, mutations in PTH1R are associated with PFE. Wnt/β-catenin, TGF-β and BMP signaling pathways are essential for tooth development and eruption, with disruptions in these pathways impairing osteoclast and osteoblast functions, and leading to eruption disorders. Furthermore, disrupted Shh signaling transmission between the epithelium and DF mesenchyme may also impact tooth root development and eruption. Moreover, DF abnormalities are clearly associated with various clinical syndromes exhibiting tooth eruption disorder symptoms. These include skull dysplasia, osteopetrosis, mucopolysaccharidosis VI, enamel renal syndrome and DD, which are caused by mutations in related genes. Moreover, conditions such as regional tooth dysplasia, MCHDFs and some odontogenic cysts are not attributed to genetic mutations or have an unknown etiology; instead, they mostly arise from structural anomalies within the DF that mechanically impede normal tooth eruption.

5. Future perspectives

A deeper understanding of the mechanisms involving DFCs in tooth eruption is crucial. This present review may improve knowledge and aid in resolving clinical issues related to the regulation of tooth eruption. The application of single-cell epigenomic technology may facilitate a more comprehensive understanding of the epigenetic regulation governing DFPCs and determine the patterns of epigenetic modifications that are potentially implicated in tooth eruption disorders. Additionally, the DF organoid model has emerged as an experimental paradigm for investigating tooth development and regeneration in recent years (166,167). The application

of the this model is expected to gradually expand. Currently, DF organoid models mainly target tooth development issues in children and adolescents; however, with technological advancements and the increase in clinical practice, this model may also serve a significant role in investigating tooth eruption. By integrating these techniques, we aim to identify the potential molecular mechanisms of DFPCs in tooth eruption disorders, and provide crucial theoretical support and a scientific basis for future developments in tooth regeneration treatments.

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Authors' contributions

WZ, XC and JC conceptualized the study. YY validated the reliability of the topic selection. JC, YY, JL, HL, ZS and YZ performed the literature review and wrote the manuscript. WZ, XC, YoW and YaW completed the review and editing of the manuscript. JC and YZ completed the supervision of the work. HL and ZS participated in generating the figures. WZ conduct the project administration. XC and WZ provided funding. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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