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Function of Orofacial Stem Cells in Tooth Eruption: An Evolving Perspective

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Tooth eruption is closely linked to the normal development of dentition and proper establishment of occlusion. Disturbances in tooth eruption may affect oral physiological functions, facial contour and aesthetics; it is therefore important to understand the eruption process. This process is a complex biological event involving dynamic changes at the tissue and cellular levels. It is guided by anatomical structures as well as biological and molecular factors that result in the movement of the tooth to its final functional position in the oral cavity. Evidence increasingly suggests that stem cells contribute to tooth development and eruption. Multiple stem cell populations have been discovered in teeth and in their supporting tissues, such as dental follicle precursor cells, orofacial bone–/bone marrow–derived mesenchymal stem cells, periodontal ligament stem cells, stem cells from the apical papilla and dental pulp stem cells. These stem cells exhibit distinct differentiation capacities and are closely linked to alveolar bone remodelling, periodontium development and root formation during the eruption process. The present review summarises the current knowledge of the characteristics and functions of orofacial stem cells in tooth eruption, with a particular focus on recent discoveries concerning their lineage allocation and regulatory mechanisms.

Key words: *alveolar bone, dental follicle, dental stem cells, motive force, osteoblasts, osteoclasts*
Chin J Dent Res 2021;24(3):143–152; doi: 10.3290/j.cjdr.b1965049

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This work was supported by the Young Elite Scientist Sponsorship Program by CAST 2018QNRC001, NSFC grants 81800928, China Postdoctoral Science Foundation (2018T110982 and 2018M631090), Sichuan Science and Technology Programme (No 2019YJ0054) to Yi Fan.

Tooth eruption is a series of complex physiological processes whereby a tooth moves towards the occlusal plane after formation of the crown and reaches its functional site by penetrating the alveolar bone and oral mucosa[1,2]. Normal tooth eruption promotes the proper establishment of occlusion, which is beneficial to facial contour, oral physiological function and aesthetics[3]. Tooth eruption is a continuous process consisting of five stages: pre-eruptive movement, intraosseous eruption, mucosal penetration, preocclusal eruption and postocclusal eruption[4]. During the eruption process, the dental root of the erupting tooth elongates and resorption of the primary tooth occurs simultaneously. In the meantime, the tooth moves through the jawbone, accompanied by an increase in the alveolar process height[5]. Although the exact process of tooth eruption has not been characterised fully, several theories are proposed. These include the root formation theory, the vascular pressure/hydrostatic pressure theory, the bone remodelling theory, the dental follicle theory and the periodontal ligament traction theory[6]. It is generally recognised that the tooth erupts when an eruption pathway forms on the

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coronal region. The eruption motive force is exerted at the base of the erupting tooth, moving the tooth along the eruption channel. The eruption pathway is formed by primary root resorption and alveolar bone resorption ahead of the coronal portion of a new tooth. Bone formation at the base of the tooth, dental follicle regulation of the permanent tooth germ and interaction with the periodontal membrane as well as the periapical tissue and pulp all play important roles in providing the eruption motive force[7-10]. These biological processes involve multiple tissue changes, including the development of the tooth germ itself and growth of the surrounding tissue. These are guided by anatomical structures, stem cells and chemical and molecular mediators. The current paradigm states that various types of stem cells that reside in the orofacial region are indispensable for tooth development and jaw growth. Orofacial stem cells include dental follicle precursor cells (DFPCs), orofacial bone–/bone marrow–derived mesenchymal stem cells (OMSCs), periodontal ligament stem cells (PDLSCs), stem cells from the apical papilla (SCAPs), dental pulp stem cells (DPSCs), stem cells from human exfoliated deciduous teeth (SHEDs), mesenchymal stem cells (MSCs) from gingiva (GMSCs) and tooth germ progenitor cells (TGPCs)[11-14]. Seminal studies published in the last decade have demonstrated a tight link between orofacial stem cells and tooth eruption. These stem cells are responsible for the differentiation of osteoblasts, periodontal ligament cells, cementoblasts and odontoblasts under specific conditions. They can form cementum, dentine, periodontal ligament (PDL) and intrinsic alveolar bone in the late stage of tooth development, which plays an important role in regulating tooth eruption by providing eruption power[11,15]. In addition, haematopoietic stem cells (HSCs) that surround the tooth germ promote the development of osteoclasts which are pivotal in the resorption of overlying alveolar bone and primary root to form the eruption channel[16]. The present review aims to outline orofacial stem cell function and recent discoveries regarding the regulatory mechanisms for stem cell–mediated processes during tooth eruption.

Dental follicle progenitor cells (DFPCs)

The dental follicle is a layer of loose connective tissue that originates from the ectodermal mesenchyme that surrounds the enamel organ and dental papilla of the developing tooth germ prior to tooth eruption[17]. It is divided into two regions, the crown (coronal) and the root (base). Research suggests that the coronal region of the dental follicle regulates primary root and alveolar bone absorption, whereas the base mediates alveolar bone formation and tooth development[18,19]. The dental follicle contains undifferentiated ectomesenchymal cells known as dental follicle progenitor cells (DFPCs). These are multipotent stem cells that can develop into PDL cells, cementoblasts and osteoblasts[20]. Recent lineage tracing experiments using tamoxifen-inducible *CreER* mouse models identified a variety of mesenchymal progenitor cell populations in the dental follicle. These cells are positive for Osterix (Osx), glioma-associated oncogene homolog 1 (Gli1), and parathyroid hormone-related peptide (PTHrP)21-23. Specifically, a study using *Gli1-CreER;tdTomato* mice at postnatal day 3 (P3) suggested that Gli1+ lineage cells are located in the root pulp, PDL and alveolar bone[21]. Furthermore, a study using a constitutively active *Osx-Cre* showed a great majority of Osx-positive mesenchymal cells in the dental follicle and papilla at postnatal day 5 (P5)[22]. However, tamoxifen injection at P3 in *Osx-CreER;tdTomato* mice and chased to P5 showed that Osx was predominantly expressed in odontoblasts, alveolar bone osteoblasts and osteocytes, but only sparsely expressed in dental papilla and dental follicle cells. The descendants of these cells contributed to all cell types involved in dental root development at later stages[22]. More recently, Takahashi et al[23] generated a novel *PTHrP-CreER* mouse model and used it to find that PTHrP+ cells mark dental follicle mesenchymal progenitors during tooth root formation.

It has been shown that DFPCs can differentiate into PDL fibroblasts that secrete collagen and generate PDL-like tissue upon in vivo transplantation[24]. Moreover, DFPCs are able to differentiate into cementoblasts in vitro and generate cementum when transplanted in vivo[17,25]. Notably, these cells maintain mesenchymal stem cell (MSC) features in a long-term culture system and form single or complex tissues in the periodontium[26]. Importantly, DFPCs exhibit a greater tendency to form mineralised nodules and a higher potential for cementoblast/osteoblast differentiation compared to MSCs derived from other tissues. Several signalling pathways, such as those for bone morphogenic protein (BMP), Notch, wingless/integrated (Wnt) and parathyroid hormone 1 receptor (PTH1R) are crucial for osteogenic differentiation of DFPCs[27]. For instance, PTH1R in the dental follicle has been shown to act in a PTHrP-PTH1R autocrine manner to maintain physiological cell fates of DFPCs. Deletion of PTH1R specifically in PTHrP+ dental follicle progenitors leads to loss of the periodontal attachment apparatus and primary failure of tooth eruption[23]. Moreover, WNT5a, a ligand that activates both canonical and non-canonical Wnt pathways, is expressed in the dental epithelium and mesenchyme regions during the early developmental

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stages of teeth[28]. It is also one of the few Wnt molecules expressed in the mature periodontium. DFPCs' ability to induce mineralisation shows that WNT5a plays an important role in cytodifferentiation[29,30]. Odontogenic ameloblast-associated protein (ODAM) is another interesting candidate for regulating the differentiation capacity of DFPCs. It is encoded by a secretory calcium-binding phosphoprotein cluster gene and plays a critical role in mineralisation[31]. ODAM is expressed in DFPCs and may promote their osteogenic differentiation, thus contributing to alveolar bone formation in the tooth crypt during the eruption process. A study found that culturing DFPCs in osteogenic induction medium resulted in calcium deposition and increased expression of the osteoblast-related gene Runx2[32]. ODAM cooperated with Runx2 to modulate mineralisation and increased the expression of osteogenic-related genes[33]. In addition to signalling pathways, chemical factors can affect the physiological function of DFPCs during tooth eruption. Administering PTHrP (1-34) can accelerate tooth eruption, for example, and inhibit osteogenesis of DFPCs by inactivating the Wnt/β-catenin pathway[18]. A recent study also demonstrated that injection of Bleomycin into the dental follicle at an early stage of development interrupts tooth eruption[34].

OMSCs

The intraosseous phase of eruption, in which the tooth moves out of its bony crypt to pierce the gingiva, requires the two processes of osteoclastogenesis and osteogenesis[35]. The newly formed alveolar bone at the base of the tooth socket during tooth eruption has been studied extensively. One investigation used temporarily impacted dog premolars and observed extensive bone growth at the base of the socket after release[36]. Later experiments confirmed alveolar bone growth during tooth eruption in rats[37,38]. Moreover, evidence suggests that teeth do not erupt without alveolar bone growth, implying that alveolar bone formation is causal[39-41]. For instance, delayed tooth eruption was observed in a knockout mouse model of membrane type 1 matrix metalloproteinase (MT1-MMP)[42]. Although alveolar bone resorption occurs in these mice, the lack of MT1-MMP affects the degradation of collagen and periodontal ligament fibres, thus affecting bone reconstruction, inhibiting the formation of alveolar bone and delaying tooth eruption. MT1-MMP expression was also significantly decreased in the tooth capsule of mice with tooth eruption disorder[43]. Moreover, an in vivo study found that despite the formation of an eruption pathway, the formation of new alveolar bone at the base of mandibular molars can be significantly reduced by interfering with BMP6 expression, leading to delayed or non-eruption of teeth[38].

OMSCs are stem cells that reside in alveolar bone marrow and can give rise to osteoblasts and osteocytes to produce the mineralised matrices of alveolar bone. Human OMSCs are distinct from long bone-derived bone marrow MSCs (BMMSCs) in terms of differentiation traits[44]. Jawbones are composed of the cranial neural crest–derived mandible and maxilla, whereas long bone originates from mesoderm[45]. OMSCs exhibit enhanced osteogenic differentiation ability, as indicated by their higher levels of alkaline phosphatase (ALP) activity, elevated capability for forming mineralised nodules and increased expression levels of osteoblastic markers such as *Runx2*, *Alp* and *osteocalcin* (*Ocn*)[46,47]. OMSCs are also distinct from BMMSCs with respect to regulation of T-lymphocyte survival and proliferation, suggesting that OMSCs are a unique population of MSCs and play an important role in systemic immunity[46]. It has recently been demonstrated that *Prx1-Cre*, which targets early limb bud and craniofacial mesenchymal cells, can be utilised as a marker for OMSC lineage cells in vivo[48]. Lineage tracing experiments demonstrate that $Prx1^{+}$ cells contribute to alveolar osteoblasts and osteocytes surrounding the incisors and at the molar base[49]. Conditional ablation of PTH1R in $Prx1^{+}$ progenitor cells leads to arrested tooth eruption. Mandibular incisor eruption in mutant mice was completely blocked due to aberrant PDL development and alveolar bone formation. Molar eruption was also delayed, mainly due to a lack of eruption motive force since the alveolar bone growth at the base of the crypt was significantly reduced; however, the eruption pathway was unaffected. These data imply that PTH1R signalling in OMSCs plays a critical role in alveolar bone development during tooth eruption[49].

Several genes control alveolar bone remodelling around the tooth. It has been shown that during rat molar eruption, the alveolar bone at the base of the alveolar fossa begins to form on the third day after birth and completes rapid formation on the ninth day[37]. The expression pattern of BMP2 is consistent with alveolar bone development. BMP2 is first expressed on the third day after birth and reaches its highest expression level on the ninth day. Additionally, BMP2 expression levels are stronger in the root of the tooth capsule than in the crown[37]. BMP2 can not only promote differentiation of osteoblasts but can also downregulate the expression of receptor activator of nuclear factor kappa-B ligand (RANKL) to promote the formation of new alveolar bone at the tooth base[50]. BMP2 may therefore be involved in the regulation of alveolar bone

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formation[37,51]. In addition, TNF-α expressed in the dental capsule can promote alveolar bone remodelling by upregulating the expression of BMP2[52]. Moreover, studies have found that BMP9 can induce the differentiation of tooth capsule cells into bone cells, which plays an important role in promoting bone formation. The canonical Wnt/β-catenin signalling pathway has been previously shown to play a critical role in BMP9 induced osteogenic differentiation of MSCs[53]. Furthermore, patients with a chromosome 12q14 aberration have a tooth phenotype of size and eruption timing with a bone growth anomaly[54]. A study examining the expression and function of Hmga2, which is encoded at chromosome 12q14, found that Hmga2 regulates the growth, sizing and eruption of teeth as well as stem cell-related factor expression and is associated with mandibular bone growth[54].

PDLSCs

The PDL is fibrous connective tissue located between the root cementum and the inner wall of the alveolar bone. It links the teeth to the surrounding alveolar bone, providing support, protection and provision for the sensory input to the masticatory system[55]. One study suggests that PDL fibroblasts may play a key role in pulling the tooth axially by means of the network of collagen fibres[56]. However, tooth eruption still occurs in humans despite genetic disorders such as dentinal dysplasia type I. This disorder severely affects the PDL, but tooth eruption still occurs, indicating that other tissues contribute to the eruption process[8]. Additionally, when the collagen turnover was experimentally inhibited or interaction between the PDL and the tooth was abrogated, there were no alterations in the eruption velocity[57]. It is therefore more likely that the PDL is not the basic source for motility in tooth eruption but provides eruption force after the tooth has pierced the gingiva and not during the intraosseous stage[58]. It may also play a key role in sensing bite force and guiding bone remodelling of the alveolar socket as part of the eruption process[3,59].

The PDL consists of several cell types. The main structural cells are fibroblasts, which occupy approximately 35% of the volume of the PDL space[60]. It also contains defence cells, aggregations of epithelial cells and undifferentiated mesenchymal cells called PDLSCs. PDLSCs play an important role in the maintenance and regeneration of periodontal tissue structure and function[61]. PDLSCs can differentiate into PDL cells. PDL cells display an osteoblastic phenotype and osteoblast-analogous behaviour in response to hormonal stimulation, which implies the involvement of PDL cells in the regulation of the remodelling processes of the alveolar bone during tooth eruption[62-64]. Human PDLSCs can differentiate into fibroblasts, osteoblast-like cells and cementoblast-like cells to generate natural periodontium-like connective tissue, osteoid tissue and cementoid tissue[65]. Upon in vitro culture, these progenitor cells express osteoblastic or cementoblastic differentiation factors including osteoprotegerin (OPG) and RANKL and can form mineralised nodules. When transplanted in vivo, PDLSCs exhibit the capacity to form PDL-like and cementum-like structures[61].

SCAPs

Tooth eruption is closely related to tooth development per se, particularly regarding root development which increases the overall length of the tooth. Root development has previously been considered as the force responsible for eruption. Much evidence seemed to indicate that rootless teeth in humans, monkeys, dogs and rodents can erupt into the oral cavity, suggesting that root development is not the fundamental process for tooth eruption[66]. Nevertheless, experiments with mouse models suggested that defective root formation is closely related to arrested tooth eruption[22,23]. For instance, loss of PTH1R in Osx^{+}-progenitors results in complete failure of tooth eruption, accompanied by truncated roots[22]. Similarly, ablation of PTH1R in PTHrP^{+}-progenitors leads to the malformation of molar roots and, ultimately, undereruption[23].

Root formation in developing teeth begins with the apical proliferation of epithelial cells from the cervical loop. It is well documented that the interaction between the Hertwig epithelial root sheath (HERS) and the apical papilla is the driving force for root elongation[67]. The apical papilla is a distinct zone of the dental mesenchyme surrounded by the dental sac[68]. The apical papilla tissue only exists during root development and the MSC-like populations isolated in the apical papilla are termed SCAPs. SCAPs are a unique population of dental stem cells and exhibit MSC properties such as clonogenicity and multidifferentiation ability[69]. It is believed that SCAPs contribute to the developing radicular pulp and periodontium during tooth formation. Isolated SCAPs can differentiate into odontoblasts and osteoblasts in vitro and exhibit higher proliferation and enhanced mineralisation ability when compared to BMMSCs and DPSCs[70]. Recent studies demonstrated that BMP9 and BMP2 effectively induce osteo-/odontoblastic differentiation of SCAPs[71,72]. When transplanted in vivo, SCAPs have been shown to regenerate new vascularised pulp-like tissue with the deposition of a

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new layer of dentine-like tissue[73]. Moreover, they can regenerate a typical PDL-/cementum-like complex and form a periodontal/root complex when co-transplanted with PDLSCs[68,69].

HSCs

HSCs can self-renew and give rise to all the different types of blood cells in the body[74]. The population of HSCs consists of long-term (LT-HSCs) and short-term HSCs (ST-HSCs). These differentiate into multipotent progenitors (MPPs) and late MMPs. These cells further commit to a common myeloid progenitor, and then differentiate into monoblasts in the bone marrow. These monoblasts enter the circulation and give rise to immature promonocytes and mature monocytes. Monocytes can differentiate into osteoclast precursors and macrophages. Osteoclast precursors and macrophages can then differentiate into osteoclasts[75,76]. Osteoclasts are multinucleated giant cells that resorb bone, ensuring development and continuous remodelling of the skeleton and the bone marrow haematopoietic niche[77]. Although the postnatal contribution of HSC-derived cells is important for optimal osteoclast maintenance and function, a recent discovery revealed other precursors that originate from the embryonic erythro-myeloid progenitor (EMP) lineage of resident macrophages that also contribute to osteoclast development[78]. These EMP-derived embryonic osteoclasts play an essential role in tooth eruption, as well as skull and long bone development. HSC-derived osteoclasts are associated with the maintenance of bone mass after birth[78,79].

During tooth eruption, primary root and alveolar bone resorption functions to accurately establish the eruption channel and is therefore of vital importance. This process requires the differentiation of osteoclasts to accomplish subsequent resorption[80]. Inhibition or enhancement of osteoclast-forming factors may affect osteoclast activity, leading to aberrant primary root and alveolar bone resorption during eruption[81]. Dental follicles have a high concentration of chemical mediators for osteoclastogenesis, such as prostaglandins, epidermal growth factor (EGF), interleukin-1 (IL-1), BMP4, colony-stimulating factor 1 (CSF-1) and transforming growth factor (TGF-β)[82]. Osteoclast precursor cells in the dental follicle are derived from monocytes/macrophage lineage cells[83]. Cytokines, such as CSF-1, monocyte chemotactic protein-1 (MCP-1), myeloid differentiation factor 88 (MyD88) and RANKL, have been shown to participate in osteoclastgenesis during tooth eruption[84]. The dental follicle cells first synthesise and secrete CSF-1 and MCP-1, which promote the accumulation of monocytes into the dental follicle where they differentiate into osteoclast precursors[16,85]. For instance, during rat molar eruption, CFS-1 and MCP-1 are expressed in the dental follicles on the third day after birth when the monocytes in the dental follicles accumulate in large numbers[85]. CSF-1 not only promotes the survival and proliferation of osteoclast precursor cells, but also upregulates the expression of receptor activator of nuclear factor-kappa B (RANK) and downregulates OPG[86-88]. Osteoclast differentiation, maturation and function are largely regulated by intercellular RANKL/RANK/OPG signalling. RANKL is a type II transmembrane protein and member of the tumour necrosis superfamily that is expressed in BMSCs, osteoblasts, osteocytes and bone marrow adipose tissue[89-91]. The binding between RANKL and its receptor RANK promotes monocyte–macrophage progenitor differentiation into mature osteoclasts and stimulates bone resorption. CSF-1 and RANKL have been shown to play an essential role in osteoclast formation during the eruption process. This is supported by animal models that show that teeth lacking CSF-1 or RANKL do not erupt[92,93]. In addition, a study suggested that Semaphorin 3A (Sema3A), a neuronal guidance molecule, mediates osteoclast activity in occlusal alveolar bone resorption during the intraosseous phase of eruption[94]. Furthermore, isorhamnetin 3-O-neohesperidoside has been shown to interfere with resorption of the crown-covered bone of erupting teeth by mediating the RANKL-induced osteoclastogenesis of bone marrow macrophages[95]. More recently, a genetic study tested the correlation between gene expression of RANK/RANKL/OPG in children and delayed tooth emergence with persistent primary teeth. The result suggested that polymorphism rs9594738 in RANKL is associated with delayed permanent tooth eruption. Additionally, children with persistent primary teeth have decreased RANKL gene expression in periapical tissue compared with control subjects[96]. Notably, antiresorptive drugs have recently been applied to treat paediatric patients with bone diseases. A study using a mouse model evaluated the effect of these drugs on tooth eruption and found that the anti-human-RANKL antibody denosumab had no adverse effect on tooth growth and eruption despite increased alveolar bone volume[97]. Conversely, zoledronic acid (ZOL), a nitrogen-containing bisphosphonate with a known affinity for hydroxyapatite, significantly delayed tooth root formation and eruption[98]. These data emphasise that the possible detrimental effects on tooth eruption of bone disease–related drugs in growing children need to be considered.

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Other stem cells (DPSCs, TGPCs, SHEDs, GMSCs)

DPSCs are multipotent stem cells that reside in the cell-rich zone of both adult pulp tissue and the primary tooth pulp[99,100]. They display self-renewal capability and multilineage differentiation potential. They can differentiate along multiple cell lineages and promote the regeneration of dental pulp, dentine and cementum. They thus play a fundamental role in postnatal tooth homoeostasis and repair[101]. During tooth eruption, DPSCs function to maintain the normal growth of teeth by differentiating into odontoblasts, which express both dentine matrix protein 1 (DMP1) and dentine sialophosphoprotein (DSPP) and produce dentine. Intraflagellar transport 80 (IFT80) is a recently discovered protein expressed in DPSCs that is required for maintaining DPSC properties. IFT80 controls tooth development and eruption by influencing DPSC proliferation and differentiation. Mice with conditional ablation of IFT80 in odontoblasts show delayed incisor eruption and impaired molar root formation[102]. DPSCs exhibit a more profound role in stem cell–based bone and dental regeneration therapy as they can generate complete or partial tooth structures[103]. Hung et al[104] utilised DPSCs to form tooth-like structures in rabbit alveolar sockets but there was no visible tooth eruption in any of the graft sites. This indicates that DPSCs are not the driving force for initiating the eruption process.

TGPCs are a novel stem cell population that was identified in the dental mesenchyme of the third molar tooth germ during the late bell stage. TGPCs can be expanded and maintained for nearly 60 population doublings, during which they retain their spindle-shaped morphology and high proliferation rate. TGPCs show a similar multilineage differentiation capacity to that of other dental MSCs, including the ability to differentiate into adipocytes, osteoblasts/odontoblasts, chondrocytes and neurons[105,106]. TGPCs can differentiate into osteoblasts to form new alveolar bone, which may provide the motive force during the eruption process of the third molars.

SHEDs are derived from the pulp tissue of exfoliating primary teeth[107]. They represent a postnatal stem cell population with easy accessibility, high viability and multilineage differentiation potential that includes odontoblasts, osteoblasts, neuronal and glial cells under specific conditions[108,109]. Compared to DPSCs, SHEDs display higher proliferative activity and odonto-/osteogenic differentiation, as well as osteoinductive ability[110]. GMSCs are a new population of stem cells isolated from human gingiva[111]. GMSCs have been shown to exhibit clonogenicity, self-renewal and multipotent differentiation capacity, and possess both stem cell-like and immunomodulatory properties[112]. High expression levels of Ocn, Opn and ColαI were detected in GMSCs, indicating their potential to differentiate into osteoblasts[113,114]. SHEDs and GMSCs show region-specific functions during tooth development; however, their putative role in the eruption process needs further investigation.

Interactions among stem cells during tooth eruption

The initiation of tooth development involves a series of interactions between the epithelium and the underlying mesenchyme. For instance, a recent study demonstrated that the eruption process involved the release of mechanical stress inside the mandible[115]. The mechanical stress inhibited Wnt signalling in the mesenchyme between the primary and permanent tooth and upregulated Wnt signalling in the epithelium of the permanent tooth, thus initiating its development[115]. During the eruption stage, the dental follicle regulates both alveolar bone resorption and formation using the well characterised regulatory network of RANKL/RANK/OPG interaction between osteoblasts and osteoclasts[51]. RANKL is expressed by osteoblast lineage cells and then combines with the osteoclast precursor cell cytokine RANK to form RANK-RANKL. This combination orchestrates the differentiation of osteoclasts and odontoclasts in alveolar remodelling and physiological root resorption during the eruption process[116]. In addition, osteoblast expressed RUNX2 modulates osteoclast differentiation by controlling the expression of RANKL and OPG. In cleidocranial dysplasia, a RUNX2 mutation led to defects in formation of the tooth eruption pathway due to aberrant osteoclast differentiation and bone remodelling[117].

Moreover, HERS provides a structural boundary between the dental follicle and dental papilla, creating an epithelial–mesenchymal interaction during root development[118]. DFPCs and their progeny have been shown to interact with HERS cells[119-121]. For instance, HERS cells have been shown to promote osteogenic differentiation of DFPCs in a Wnt signalling-dependent manner[122]. Furthermore, DFPCs can be regulated by SCAPs. Signalling from the apical papilla downregulate the osteogenesis and fibrogenesis properties of DFPCs[123].

Conclusion

The precise regulatory mechanisms underlying the tooth eruption process are largely unknown. In general, it is suggested that a tooth erupts when resorption of the

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overlying alveolar bone forms an eruption pathway and a motive force is created by alveolar bone at the tooth base and the root elongates to move the tooth through the eruption pathway. These processes require the molecular networks of stem cells and their progeny. For instance, HSC- and EMP-derived embryonic osteoclasts play critical roles in osteoclast development and account for coronal alveolar bone and deciduous root resorption. Moreover, the coordination of DFPCs, OMSCs, PDLSCs, SCAPs, DPSCs and TGPCs contributes to periodontium and alveolar bone development and remodelling that provide the motive force and maintain the physiological function of the tooth structure (Fig 1 and Table 1). Emerging lineage tracing experiments have identified specific surface markers for these stem cells. By using conditional transgenic mouse models, it is possible to further characterise gene function in orofacial stem cells during the eruption process. Further investigation is needed to unravel the physiological properties of the different stem cell populations in regulating the normal eruption process and shed light on the aetiology of disturbances of tooth eruption. These advances will make it possible to develop novel, biologically based diagnosis and treatment strategies for patients with tooth eruption abnormalities.

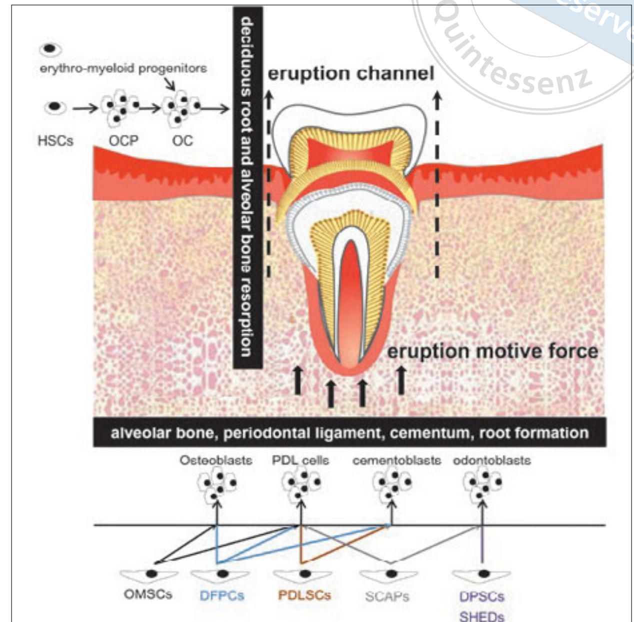

Fig 1 Schematic illustration of various types of orofacial stem cells during tooth eruption. Stem cell function is coordinated to form the tooth eruption channel (primary root and alveolar bone resorption) and the eruption motive force (alveolar bone, periodontal ligament formation, cementum and dentine).

Conflicts of interest

The authors declare no conflicts of interest related to this study.

Author contribution

Drs Yi YU, Chen CUI, Shu Yuan GUAN and Li Wei ZHENG and Yi FAN collected the literature and drafted the manuscript; Drs Xue Dong ZHOU and Yi FAN supervised the procedures and approved the manuscript; Drs Chen CUI and Yi FAN revised the manuscript. All authors gave their final approval and agreed to be accountable for all aspects of the work.

(Received Jun 17, 2020; accepted Nov 17, 2020)

Table 1 Key orofacial stem cells and their roles during tooth eruption

Cell	Distribution	In vivo differentiation capacity	Roles in tooth eruption
DFPCs	Dental follicle	Osteoblasts, cementoblasts, PDL fibroblasts	Involved in tooth root, PDL and alveolar bone formation
OMSCs	Alveolar bone marrow	Osteoblasts, PDL fibroblasts	Form alveolar bone at the base of the tooth socket to provide eruption motive force
PDLSCs	PDL	PDL fibroblasts, cementoblasts	Involved in PDL development and maintenance
SCAPs	Apical papilla	PDL fibroblasts, odontoblasts	Involved in radicular pulp and periodontium development
HSCs	Bone marrow	Osteoclasts	Involved in osteoclast development and establishment of the eruption channel
DPSCs	Pulp tissue	Odontoblasts	Form dentine during tooth development
SHEDs	Pulp tissue of exfoliated primary teeth	Odontoblasts of primary teeth	Form dentine of primary teeth
TGPCs	Tooth germ mesenchyme of the third molar	Potential to differentiate into osteoblasts	Form alveolar bone surrounding the third molar

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