Lineage Tracing Identified Cell Populations within Adult Stem Cell Niches for Oral Maxillofacial Hard Tissue Formation

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The regeneration of oral maxillofacial hard tissues is currently one of the issues of most concern in public health. This complex process involves a variety of cell types residing in a specialised microenvironment known as the adult stem cell niche in living organisms. Within this niche, adult stem cells are considered to play a central role in the regeneration of hard tissues, which undergo rapid proliferation and differentiation into progenitor cells to replace lost tissue, throughout postnatal life. Their fate is tightly regulated by the niche factors secreted by the non-stem niche cells present within the same microenvironment. Over the past decades, the advent of lineage tracing techniques has revolutionised the in vivo study of cell dynamics. Through tissue- and temporally-specific labelling of Cre-expressing cells, this method enables researchers to depict the defined cell fates and differentiation trajectories. The present review summarises the progress made in lineage tracing studies of hard tissue formation cell populations residing in the oral and maxillofacial regions, with a focus on stem cells, progenitor cells and niche cells. The aim is to provide new clues for future research endeavours.

Keywords: *adult stem cell niche, hard tissue formation, lineage tracing, niche cell, oral maxillofacial region, progenitor cell, stem cell*

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The oral maxillofacial region is a prominent anatomical area with the jaw as the principal skeletal support. Its complex structures, including the teeth, jawbones, temporomandibular joints and various soft tissues, confer significant physiological functions. However, the global prevalence of oral diseases, such as dental caries, periodontal disease and tumours, is increasing, primarily resulting in the destruction of hard tissues in this region.[1,2] This leads to alterations in facial appearance and dysfunctions in chewing and speech. Consequently, enhancing the regeneration of oral maxillofacial hard tissues has become a critical focus in clinical interventions.[3,4]

Adult stem cells play a central role in the homeostasis and regeneration of postnatal tissues.[5] They reside within a specific anatomical location called the adult stem cell niche, which supports their normal function and fate determination through various intercellular interactions.[5] Typically, the adult stem cell niche is composed of cellular components (such as stem/progenitor cells and non-stem niche cells) and acellular components (such as extracellular matrix and long-distance signals from blood vessels, neurons and immune cells) (Fig 1).[6] When hard tissue is lost due to trauma, stem cells undergo asymmetrical division and differ-

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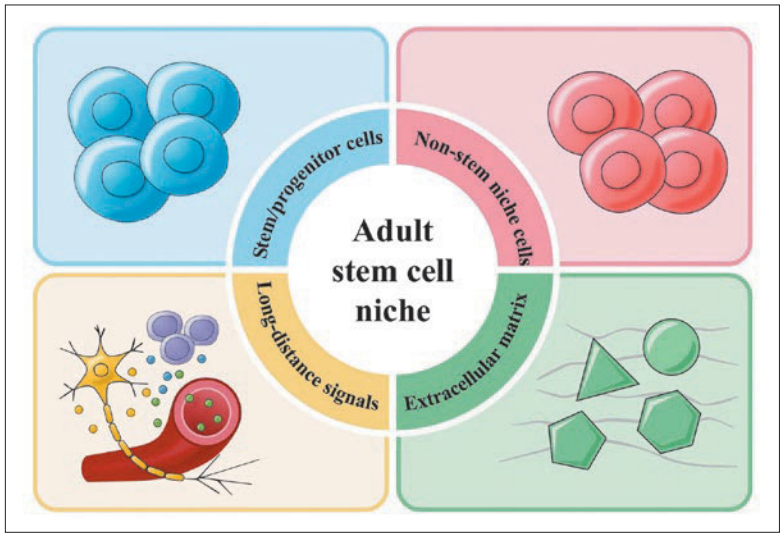

Fig 1 Components of the adult stem cell niche.

entiate into lineage-committed progenitor cells that further differentiate into specific hard tissue–forming cells, contributing to the repair of damaged tissues.[7] Moreover, niche cells play a vital role in regulating stem cell activity through paracrine signalling pathway during this process.[6] However, due to the inability to replicate the intricate microenvironment within a living organism, previous in vitro studies failed to accurately capture the characteristics of the cell population in vivo.[8] As a consequence, some stem cells exhibit enhanced plasticity and proliferation capabilities when isolated from the in vivo environment, even if they are not normally involved in homeostasis maintenance.[9,10]

Advances in transgenic animals have revolutionised the investigation of cell fate in vivo.[11] The lineage tracing technique utilising the Cre/loxP system has been widely employed in the study of oral maxillofacial hard tissues. Targeted gene-driven Cre recombinase enters the nucleus and specifically recognises the loxP sequences.[12] The stop codon flanked by loxP sequences is then removed to allow downstream fluorescent protein gene expression, achieving spatial-specific labelling of cell populations.[12] When the Cre recombinase is further fused with the ligand-binding domain of oestrogen receptor (ER), CreER recombinase can change conformation and enter the nucleus to exert recombinase activity only with the addition of tamoxifen, further realising the temporal-specific regulation of cell labelling.[13] This method enables the permanent labelling and visualisation of Cre- or CreER-expressing cells and their progeny. By virtue of its high efficiency, specificity, continuity and controllability, lineage tracing provides fresh perspectives on realistic cell activities in vivo, thus expanding understanding of cell fate determination during tissue formation and regeneration.

Currently, the lineage tracing technique has identified various cell populations within adult stem cell niches that are involved in the formation of oral maxillofacial hard tissues (Fig 2). In this review, the present authors summarise discoveries obtained through lineage tracing regarding the cellular components of adult stem cell niches, including stem, progenitor and niche cells. The aim of this review is to enhance comprehension of the ongoing research on adult stem cell niches in vivo, and to provide insight into the processes of development, homeostasis and regeneration of hard tissues in the oral maxillofacial region.

Stem cells

Adult stem cells possess the unique ability to undergo continuous self-renewal and differentiate into specific cell types associated with particular tissues.[14] The identification of stem cells through lineage tracing typically requires that all cells within the hierarchy be permanently labelled over an extended tracing period.[14] Current findings have led to the recognition of several well-defined populations of stem cells in the oral maxillofacial regions.

Sox2$^+$ cells

Sox2 is a member of the Sox family of transcription factors with highly conserved HMG-box DNA-binding domains.[15] It is expressed prominently in epithelial tissues across various organs and is established as an iconic marker of epithelial stem cells.[16,17] Recent studies have highlighted the pivotal role of Sox2$^+$ dental epithelial stem cells (DESCs) in tooth development.

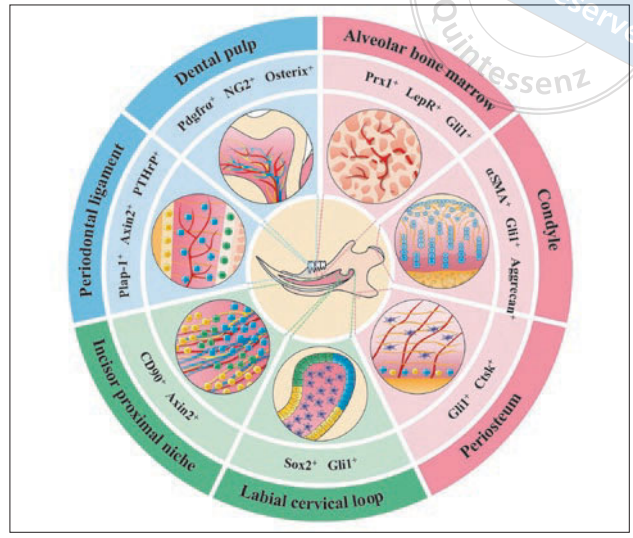

Fig 2 Lineage tracing identified representative cell populations within different adult stem cell niches in the oral maxillofacial region.

Rodent incisors retain the ability of continuous growth after birth due to the presence of the labial cervical loop (laCL), a well-known adult stem cell niche at the proximal end of the incisor.[18,19] Research by Juuri et al[20] indicated a gradual localisation of Sox2 expression from the entire oral epithelium to the laCL, followed by postnatal generation of all epithelial cell lineages, including ameloblasts, outer enamel epithelium, stellate reticulum and stratum intermedium, which were also generated by Sox2$^+$ cells in adult mouse incisors. Conversely, in mouse molars, Sox2$^+$ cells are transiently present during the embryonic period and contribute to all epithelial cell lineages, but disappear after birth synchronously with the loss of cervical loops.[21] Therefore, the different fates of Sox2$^+$ DESCs in the murine incisor and molar provide an acceptable explanation for different postnatal growth potential at the cellular level.

Prx1$^+$ cells

Paired related homeobox 1 (Prx1 or Prrx1) is a transcription factor expressed in the mesenchymal tissues.[22] Prx1$^+$ cells are well recognised as important mesenchymal stem cells (MSCs) in long bones and calvaria.[23,24] Application of lineage tracing in oral maxillofacial hard tissues has yielded valuable insight into the functions of Prx1$^+$ MSCs.

Prx1$^+$ cells may be responsible for tooth morphogenesis

Teeth are different shapes to accommodate a wide variety of functions.[25] In tapered mouse incisors, Prx1$^+$ cells nest in the dental follicle and dental pulp, but not in epithelial lineage cells.[26,27] Intriguingly, Prx1$^+$ cells exhibit varying distributions in different molars: they are widely present within the dental pulp of the first molar (M1), have a reduced distribution in the second molar (M2) and are nearly absent in the third molar (M3) during early tooth development.[26,28] Given the morphological differences among murine molars, it is tempting to speculate about a potential correlation between Prx1$^+$ MSCs and tooth morphogenesis.

Prx1$^+$ cells support the formation of jawbone

Prx1$^+$ cells also engage in jawbone development and the maintenance of homeostasis after birth. Cui et al[27] identified a large number of Prx1$^+$ cells surrounding incisors and at the molar base that subsequently differentiated into osteocytes in neonatal Prx1-Cre mice. However, in adult Prx1-CreER mice, only a few Prx1$^+$ cells were detected in the periodontal ligament (PDL), supporting the turnover of periodontal tissues.[29] Overall, the contribution of Prx1$^+$ cells to alveolar bone formation appears to be more significant in infancy.

Nevertheless, Prx1$^+$ cells remain crucial for alveolar bone remodelling and regeneration in adulthood. The most recent study by Feng et al[30] demonstrated the necessity of Prx1$^+$ cells for implant osseointegration. To investigate the role of Prx1$^+$ cells in jawbone regeneration, Zhao et al[31] established a full-thickness mandibular defect model by osteotomy, and found that Prx1$^+$ cells were activated and clustered on the surface of trabecular bone in the defect area. In contrast, ablation of Prx1$^+$ cells by inducing endogenous cytotoxic diphtheria toxin A resulted in impaired alveolar bone repair in non-critical size periodontal defects, suggesting the significance of Prx1$^+$ MSCs in the process of jawbone damage repair.[29]

LepR$^+$ cells

The leptin receptor (LepR) has been identified as a marker of adult bone marrow mesenchymal cells in long bones.[32,33] LepR$^+$ cells serve as a significant source of osteoprogenitor cells and are capable of secreting various cytokines to maintain a conducive microenvironment for hematopoietic stem cells, thereby supporting the maintenance of adult bone homeostasis and facilitating timely fracture repair.[34,35] In the oral maxillofacial region, the functions of LepR$^+$ cells have also garnered increasing attention.

LepR$^+$ cells play a minor role in cementum formation

Under physiological conditions, LepR$^+$ cells are predominantly located in the apical region of the PDL in 4-week-old juvenile LepR-Cre mice, with a smaller presence in the gingiva, alveolar bone marrow cavity and dental pulp.[9,36] Remarkably, all cementocytes are negative for LepR at the juvenile stage.[36] Extending the tracing period up to 1 year, the progeny of LepR$^+$ PDL cells gradually increase and differentiate into cementocytes at a low frequency.[36] In adult LepR-CreER mice, LepR$^+$ cells also show minimal contribution to cementocytes, even though the ablation of LepR$^+$ cells lead to disturbances in periodontium homeostasis and ultimately result in cementum dysplasia.[9] Based on the existing findings, the contribution of LepR$^+$ cells to cementum formation is minor.

LepR$^+$ cells have a limited effect on the formation of alveolar bone

A quiescent population of LepR$^+$ cells within the bone marrow (BM) can give rise to osteoblastic lineage cells physiologically and contribute to the regeneration of alveolar bone after tooth extraction.[37,38] Ablation of LepR$^+$ BM cells brought about attenuated healing of extraction sockets.[37]

PDL stem cells (PDLSCs) have a high differentiation potential to promote alveolar bone regeneration.[39] The role of LepR$^+$ PDLSCs in the development and homeostasis of alveolar bone has been revealed recently.[9,36] However, research by Oka et al[36] demonstrated a definite but limited effect of LepR$^+$ PDLSCs on new bone formation in tooth extraction sites, with the LepR$^-$ PDL cell subpopulation showing a greater contribution to alveolar bone regeneration. Taken together, the insignificant contribution of LepR$^+$ PDLSCs to both cementum and alveolar bone indicates that they are not the primary source of cells forming oral maxillofacial hard tissues.

CD90$^+$ cells

CD90, also known as Thy1, is a glycophosphatidylinositol-anchored cell membrane protein essential for the pluripotency of MSCs.[40] An et al[41] identified a CD90$^+$ MSC subset responsible for supplying cells for the rapid growth of incisors during early postnatal development and adult clipped incisors regeneration, while only very few were detected during homeostasis. Notably, the reappearing CD90$^+$ cells in clipped incisors were generated by a small and quiescent Celsr1$^+$ cell population located proximal to MSCs, suggesting a potential role of Celsr1$^+$ cells as a stem cell reservoir.[41] Although researchers hypothesised that the blooming of CD90$^+$ cells during incisor regeneration might be related to the loss of occlusal force, the unloaded incisor did not exhibit accelerated growth when clipping the opposing incisor, indicating that Celsr1$^+$ cells were likely triggered by other currently unidentified signals rather than occlusal force change.[41]

Apart from the incisor pulp, a recent study by Zhao et al[42] demonstrated the differentiation of CD90$^+$ cells into cementoblasts in the developing molar PDL and the decreased number in adults. In mild periodontitis, CD90$^+$ cells regain their ability to differentiate into cementoblasts.[42] However, Nagata et al[43] reported no detectable upregulation of CD90 in cementoblasts based on single-cell transcriptomic analysis. This discrepancy may be attributed to variations in experimental methodologies, necessitating further investigation to definitively delineate the lineage hierarchy of cells in periodontal tissues.

Pdgfrα$^+$ cells

Platelet-derived growth factor receptor α (Pdgfrα) is a common marker of stem cells.[44] Adult Pdgfrα-CreER; tdTomato mice could label the majority of dental pulp cells, whereas only a small number of osteocytes in the alveolar bone and very few PDL cells were labelled.[45] Specifically, Yao et al[46] identified a population of CD51$^+$Pdgfrα$^+$ cells that gradually declined with age in the odontoblast layer and pulp core in murine molars. However, the specific role of these cells in tooth homeostasis and age-related changes remains largely unexplored, warranting further research to decipher the mechanisms involved.

Stem/progenitor cells

The characterisation of stem cell markers is notably intricate, making it challenging to differentiate these cells accurately based solely on a single marker.[47] Consequently, the cells labelled by a singular recombinase system are expected to represent a heterogeneous population exhibiting stem-like properties. Furthermore, the absence of data from long-term lineage tracing complicates the direct classification of certain cells as stem cells. Therefore, this review will collectively address these cells in this section for further discussion.

αSMA$^+$ cells

As a characteristic protein of myofibroblasts, alpha-smooth muscle actin (αSMA) is engaged in the movement and contraction of blood vessels.[48,49] Additionally, αSMA is commonly used as a molecular marker for mesenchymal stem/progenitor cells.

αSMA$^+$ cells are responsive to dental tissues injury

Minor subsets of αSMA$^+$ cells have been detected in dental pulp, PDL and the alveolar bone surrounding incisors or molars.[45,50,51] CD31 antibody staining indicated that αSMA$^+$ cells typically reside in perivascular regions.[52] These cells are recognised for their significant involvement in the process of tissue repair. Roguljic et al[50] observed the proliferation and differentiation of αSMA$^+$ PDL cells into various cell types, including cementoblasts, osteoblasts and fibroblasts, in a murine PDL injury model. Additionally, Vidovic et al[51-53] also demonstrated that αSMA$^+$ cells in dental pulp were substantially activated and differentiated into odontoblasts in response to experimental dentine injury and pulp exposure.

αSMA$^+$ cells are fibrocartilage stem cells residing in the condyle cartilage superficial zone

The condylar cartilage is characterised by highly organised cellular zones, which are sequentially arranged from the surface to the interior as the fibrous superficial zone, the proliferative zone, the chondrocyte zone and the mature hypertrophic chondrocyte zone.[54] Research by Embree et al[55] indicated that undifferentiated αSMA$^+$ cells in the superficial zone could spontaneously differentiate into mature chondrocytes, thus maintaining the steady state of condylar cartilage. Therefore, this observation provides powerful evidence for the notion that the superficial zone may serve as a conducive adult stem cell niche for fibrocartilage stem cells (FCSCs).

Gli1$^+$ cells

Hedgehog (Hh) signalling regulates the proliferation and differentiation of stem cells in the nervous, skeletal, digestive and reproductive systems.[56] As an essential transcription factor in Hh signaling, Gli1 serves as a reliable stem/progenitor cell marker.[57] Recently, a series of studies have demonstrated the significance of Gli1$^+$ stem/progenitor cells in the formation, homeostasis and regeneration of oral maxillofacial hard tissues.

Gli1$^+$ cells are heterogeneous populations involved in tooth formation

Tooth formation is a complex process involving reciprocal interactions between the epithelium and mesenchyme.[58] As mentioned above, the laCL is recognised as a niche for DESCs in the mouse incisor.[18,19] Seidel et al[59] identified the label-retaining Gli1$^+$ DESCs in the laCL that gave rise to ameloblasts. The neurovascular bundle (NVB) situated in the mesenchyme adjacent to laCL also harbours Gli1$^+$ MSCs, which continuously generate transit-amplifying progenitors that actively undergo mitosis and differentiate into odontoblasts or dental pulp cells to maintain dental homeostasis.[60] In summary, Gli1$^+$ cells play a crucial role in both epithelial and mesenchymal cell lineages during incisor formation.

Moreover, Gli1$^+$ cells are also involved in the development of molar roots. Wen et al[61] reported the distribution of Gli1$^+$ cells in the molar apical mesenchyme and dental epithelium in postnatal 7.5-day-old mice. Upon completion of root development at 3 weeks old, the main structures, including odontoblasts, dental pulp, PDL and the remaining dental epithelium, were found to be tdTomato$^+$ cells derived from Gli1$^+$ cells.[61] Additionally, a study by Xie et al[62] also asserted the involvement of Gli1$^+$ cells in the formation of both cellular and acellular cementum. Ablation of Gli1$^+$ cells resulted in a noticeable cementum hypoplasia phenotype.[62] Overall, these results provide compelling evidence to support the heterogeneity of Gli1$^+$ stem/progenitor cells in the formation of dental hard tissues.

Gli1$^+$ cells function in alveolar bone regeneration

In the jawbone, Gli1$^+$ BM cells mainly reside along blood vessels within the furcation area of the molar roots.[63] Additionally, a minor population of Gli1$^+$ cells scatter in the periosteum of the mandible.[64] These two distinct

populations of Gli1$^+$ cells participate in the maintenance of local bone homeostasis. Despite lacking various differentiation markers physiologically, Gli1$^+$ BM cells possess the potential to be stimulated into proliferation and differentiation into osteocytes following tooth extraction, contributing to extraction socket healing and implant osseointegration.[63] As a complement, the ablation of Gli1$^+$ BM cells leads to a significant reduction in bone volume around the implant, emphasising the importance of Gli1$^+$ cells in alveolar bone regeneration.[63]

The engagement of Gli1$^+$ PDL cells should not be ignored. Shalehin et al[10] transplanted the maxillary first molars from Gli1-CreERT2 mice into the abdominal subcutaneous connective tissues of wild-type mice, and the results showed that Gli1$^+$ PDL cells were capable of osteogenic differentiation. They also demonstrated that Gli1$^+$ cells in the tooth socket were positive for Periostin 1 day after tooth extraction, indicating the contribution of Gli1$^+$ cells originating from PDL to alveolar bone regeneration.[65]

A notable characteristic of PDLSCs is their responsiveness to mechanical forces.[66] Orthodontic tooth movement (OTM) serves as a well-defined model for investigating the regulatory factors in mechanical-force mediated bone remodelling.[67] Liu et al[68] first revealed a substantial increase in the number of Gli1$^+$ PDL cells on the tension side following 7 days of OTM, contrasting with restricted decreased Gli1$^+$ cells on the pressure side. Subsequent evidence from Seki et al[69] also suggested that Gli1$^+$ PDL cells on the tension side exhibited immediate proliferation in response to tensile stress and further differentiated into mature osteoblasts. Intriguingly, a similar level of increased Gli1$^+$ PDL cells on the pressure side was observed 10 days after OTM, with these cells differentiating into fibroblasts to contribute to PDL reconstruction.[69] Conversely, when unloading the occlusal forces by extracting the opposing teeth, Men et al[45] observed a significant decrease in Gli1$^+$ PDL cells, accompanied by notably reduced alveolar bone height and relative bone density. Collectively, these studies provide sufficient evidence for the diverse responses of Gli1$^+$ stem/progenitor cells to distinct mechanical forces.

Gli1$^+$ cells orchestrate the osteogenesis and chondrogenesis of the condyle

Postnatal Gli1$^+$ cells in the condyle are spatially distributed in two different domains, namely the superficial zone of the cartilage and the subchondral bone immediately beneath the cartilage (chondro-osseous junction).[70,71] The superficial zone provides a niche for FCSCs.[72] Gli1$^+$ FCSCs here could proliferate and migrate into two to four cell layers deeper.[71] However, they do not typically migrate into the mature hypertrophic chondrocyte zones even after 1-year tracing.[71] In contrast, Gli1$^+$ cells at the chondro-osseous junction lack expression of Sox9 and Aggrecan, indicating that they do not belong to the cartilage lineage.[71] Instead, they extend towards the trabecular bone and subsequently exhibit colocalisation with Osterix$^+$ osteoblasts, which verify their osteogenic differentiation ability in the subchondral bone.[70,71] In summary, two unique populations of Gli1$^+$ cells contribute to the growth and development of the condyle, each with distinct characteristics and functions.

Building upon this groundwork, researchers have delved into the contribution of these two Gli1$^+$ cell populations to tissue repair and the adaptive remodelling process. Firstly, Chen et al[70] conducted experiments on a murine condylar fracture model and found that Gli1-lineage cells originating from the chondro-osseous junction could differentiate into osteoblasts and chondrocytes at the fracture site. In a separate study involving a murine model of temporomandibular joint osteoarthritis (TMJOA) induced by partial discectomy, Lei et al[71] demonstrated that the abnormal mechanical loading triggered osteoclast-mediated subchondral bone resorption. This subsequently led to aberrant subchondral bone formation due to the overexpansion of Gli1$^+$ cell progeny, highlighting the significant function of Gli1$^+$ cells at the chondro-osseous junction in response to mechanical stress.[71] Meanwhile, investigations focusing on Gli1$^+$ FCSCs in a murine TMJOA model induced by anterior disc displacement surgery also revealed the activation of the chondrogenic capacity of Gli1$^+$ FCSCs.[73] Collectively, these findings underscore the indispensable role played by Gli1$^+$ stem/progenitor cells in preserving the structural and functional integrity of the condyle.

Plap-1$^+$ cells

PDL associated protein-1 (Plap-1) is an extracellular matrix protein that is highly expressed in the PDL and participates in balancing bone metabolism.[74,75] Iwayama et al[76] documented Plap-1 as a molecular marker that selectively labelled the lineage of periodontal fibroblasts. Through lineage tracing, Plap-1$^+$ cells were detected within the fibroblastic zone in a 3-month tracing period when the PDL turnover was completed, which indicated their identity as stem/progenitor cells involved in PDL homeostasis.[76] Moreover, they were also observed in the cementoblastic and osteoblastic zone during homeostasis maintenance and periodon-

titis repair, suggesting that this is a heterogeneous cell population.[76] As a result, a "PDL single-cell atlas" was conducted and eventually identified a distinct population of Ly6a$^+$ Plap-1 clusters situated in the apical region of the PDL that might represent PDLSCs to serve as a potential source for other PDL cells.[76]

NG2$^+$ cells

Neuron-glial antigen 2 (NG2) is a proteoglycan that is predominantly expressed in mammalian glial cells and pericytes.[77] In recent years, the heterogeneity of NG2$^+$ cells has garnered increasing interest. Lineage tracing investigations have provided compelling evidence that NG2$^+$ pericytes serve as the cellular origin for a minor population of MSCs within the odontogenic mesenchyme.[78] Throughout the development and maintenance of mouse incisors, NG2$^+$ cells primarily contribute to the vascular system, with only a sparse distribution in the pulp and odontoblast layers.[60,78,79] These observations are similarly applicable to mouse molars.[45,60] In response to incisor tooth injury, NG2$^+$ cells exhibit a rapid reaction by proliferating and differentiating into odontoblast-like cells, thereby producing reparative dentine-like tissue.[60,78,80] Nevertheless, the degree to which blood vessels and nerves contribute to the population of stem/progenitor cells remains largely unexplored.

Progenitor cells

Progenitor cells, which exhibit a more defined differentiation trajectory while retaining a degree of stemness, can be labelled with multiple lineages during short-term lineage tracing experiments as well.[14] Nevertheless, the absence of unlimited self-renewal capacity in these labelled progenitor cells results in their eventual disappearance following prolonged tracing periods, thereby differentiating them from stem cells.[14]

Axin2$^+$ cells

The canonical Wnt/β-catenin signalling is indispensable for the development of hard tissues, and Axin2 is the direct transcriptional target gene within this pathway.[81-83] Thus far, Axin2$^+$ cells have been acknowledged as important progenitor cells in the formation and regeneration of oral maxillofacial hard tissues.

Axin2$^+$ cells are widely involved in tooth formation and restoration

Axin2-LacZ reporter mice have become a valuable tool for in vivo studies of Axin2 expression patterns.[84,85] In incisors, X-gal staining showed the extensive expression of Axin2 in the dental mesenchyme, particularly in the proximal regions of incisors.[86,87] After a 1-week lineage tracing in 3 week-old mice, almost all odontoblasts were labelled as tdTomato$^+$ cells, indicating that Axin2$^+$ cells were important cell sources for odontoblasts during postnatal tooth development.[86] However, the fluorescent signals vanished upon prolonging the tracing duration to 1 month.[87] Thus, Axin2$^+$ cells in the mouse incisor mesenchyme represent a rapidly proliferating, non-self-renewing population of progenitors.

In mouse molars, Axin2 also labels odontoblasts and dental pulp cells during homeostasis.[88,89] In addition, Axin2$^+$ cells present in the PDL are essential for cementum formation because the ablation of Axin2$^+$ PDL cells leads to severe cementum hypoplasia.[42,90-92] A study by Xie et al[90] further demonstrated that Axin2$^+$ PDL cells were a shared progenitor source of both cellular and acellular cementum, which promotes a better understanding of the cell origin and formation processes of dental hard tissues.

The pathological change in dentine due to damage is the formation of tertiary dentine at the injury site, which can be further divided into reactionary dentine and reparative dentine according to the degree of damage.[93] Specifically, Axin2$^+$ odontoblasts are triggered to secrete more matrix for reactionary dentine formation following superficial dentine trauma.[88] Under severe pulp exposure, however, a substantial number of odontoblasts undergo cell death.[93] Axin2$^+$ pulp cells proliferate and differentiate into new odontoblast-like cells to form reparative dentine as a protective response to injury.[94] These observations highlight the pronounced contribution of Axin2$^+$ progenitor cells in both tooth development and reparative processes following tooth injury.

Axin2$^+$ cells are supporting actors in alveolar bone regeneration

In addition to pulp Axin2$^+$ cells, PDL-derived Axin2$^+$ cells contribute to alveolar bone regeneration in multiple models. Following tooth extraction, Yuan et al[95] found that Axin2$^+$ PDL cells proliferated, migrated to the tooth socket and subsequently differentiated into osteoblasts to generate new bone. Additionally, Wang et al[96] delineated the property of Axin2$^+$ PDL cells to

be activated in response to mechanical force in mice that underwent OTM. Despite the osteogenic potential demonstrated by Axin2$^+$ PDL cells in multiple models, Xie et al[92] pointed out that their contribution to alveolar bone regeneration was very limited, suggesting Axin2$^+$ cells might not function as the dominant driving force in this process.

Aggrecan$^+$ cells

Aggrecan (Acan) is an important proteoglycan in cartilage extracellular matrix, known for its interaction with hyaluronic acid, which endows cartilage with its elasticity and load-bearing properties.[97,98] Recent lineage tracing studies utilising Acan-CreER mice have revealed the developmental trajectory of chondrocyte progenitor cells within the condyle.

Aggrecan$^+$ cells contribute to chondrocytes in all layers of the condyle

The distribution of Acan$^+$ cells in condylar cartilage is non-uniform during homeostasis, characterised by a higher density observed in the anterior and middle regions compared to the posterior region.[99-101] Additionally, the interspaced patches of Acan$^+$ cells and Acan$^-$ cells respectively extend deeply into the cartilage and reach the hypertrophic chondrocyte layer.[101] These observations indicate the ability of Acan$^+$ cells to generate chondrocytes across different layers and suggest a regional variation in cellular composition in condylar cartilage. In line with this phenomenon, the reduction in chondrocyte count is more pronounced in the anterior and middle regions of Acan$^+$ cells ablation mice.[100,101] More importantly, despite the surviving cells subsequently initiating proliferation to restore the cell count, these newly-formed cells exhibit a clustered distribution on the surface without extending into the cell-depleted areas in the hypertrophic chondrocyte layers.[101] Further study of the mechanisms involved may enrich knowledge of the pathogenesis of osteoarthropathy.

Aggrecan$^+$ cells transdifferentiated into osteocytes

It was traditionally believed that chondrocytes underwent apoptosis prior to endochondral ossification.[102] However, by tracing Acan$^+$ cell lineage, Jing et al[103] demonstrated that chondrocytes could directly transdifferentiate into bone lineage cells in vivo, bypassing apoptosis, which greatly promoted understanding of cartilage cell transdifferentiation. Furthermore, in a study conducted on mice with unstable mandible ramus fracture, Wong et al[104] also observed the transdifferentiation of Acan$^+$ chondrocyte cells into osteoblasts contributing to the formation of fracture callus, which underscored the significance of Acan$^+$ progenitor cells in the regeneration process of condylar fractures.

Osterix$^+$ cells

Osterix (Osx), also known as specificity protein 7 (Sp7), is an osteoblast-specific transcription factor that determines the directional differentiation of osteoblasts.[105] Recent research has expanded understanding of Osx$^+$ cells beyond their involvement in osteoblast differentiation to their contribution to root morphogenesis.

Tracing Osx-Cre mice from birth until postnatal day 30, cells originating from the odontogenic mesenchyme within the dental follicle and dental papilla of incisors/molars were predominantly labelled, whereas odontogenic epithelium-derived cells, such as ameloblasts and epithelial root sheaths, remained unmarked.[106-108] Additionally, Rakian et al[109] observed the temporal emergence of the Osx$^+$ cells from M1 to M3, suggesting a strong link between Osx activity and tooth development stage.

Root morphogenesis commences with the formation of a bilayered epithelial structure known as the Hertwig epithelial root sheath (HERS).[110] Notably, some Osx$^+$ cells were observed in close proximity to the HERS of neonatal mice.[111,112] A long-term tracing experiment revealed that these Osx$^+$ cells eventually differentiated into odontoblasts and cementoblasts, contributing to root maintenance even after the completion of root development.[112]

PTHrP$^+$ cells

Parathyroid hormone-related protein (PTHrP) is a locally acting autocrine/paracrine ligand that is widely expressed in a variety of tissues, including teeth and bones.[113,114] It plays a unique biological role by binding to parathyroid hormone type 1 receptor (PTH1R).[115] Recent in-depth studies have progressively elucidated an inseparable relationship between PTHrP$^+$ cells and Osx$^+$ cells.

PTHrP$^+$ cells represent a more localised subpopulation of dental mesenchymal cells compared to Osx$^+$ cells. To be specific, PTHrP$^+$ cells are exclusively found in the dental follicle but absent from the dental papilla and pulp.[43,111,116] At postnatal day 7, when molar root formation begins, PTHrP$^+$ cells show active

proliferation in the immediate vicinity of the HERS in the dental follicle and then differentiate into PDL cells, cementoblasts and alveolar cryptal bone osteoblasts.[111,116] Even after tooth eruption, PTHrP$^+$ cells persist on the root surface, predominantly on the acellular cementum.[111,116]

Ctsk$^+$ cells

Cathepsin K (Ctsk), a member of the papain family of cysteine proteases, was initially discovered as a collagenase expressed by activated osteoclasts to degrade collagen and other matrix proteins during bone resorption.[117,118] Remarkably, Ctsk$^+$ cells exemplify the heterogeneity of osteogenesis progenitor cells.

Under physiological conditions, Ctsk-Cre extensively labelled periosteum cells in the mandible, with a fraction of Ctsk$^+$ cells present in the bone marrow and a small number in the dental pulp and odontoblasts.[119,120] Notably, Ctsk$^+$ cells in the periosteum were positive for stem cell markers and osteogenic markers.[120] The diphtheria toxin receptor-mediated ablation of Ctsk$^+$ cells resulted in decreased Ctsk$^+$ cells and delayed bone defect healing.[120] Thus, Ctsk$^+$ cells are considered to be an important population responsible for intramembranous osteogenesis in the jawbone.

The identification of Ctsk$^+$ cell subtype significantly advocates the heterogeneity within Ctsk$^+$ cells. For example, Ding et al[120] identified a specific subset of Ly6a$^+$Ctsk$^+$ cells restricted to the jawbone periosteum. These Ly6a$^+$Ctsk$^+$ periosteal cells could aggregate in the callus and differentiated into osteogenic lineages in response to jaw defects.[120] Given the reported involvement of Ly6a$^+$ cells in angiogenesis, whether Ly6a$^+$Ctsk$^+$ cells make more multifaceted contributions to the repair of hard tissue injury requires further research. Additionally, Weng et al[121] documented a subpopulation of Krt14$^+$Ctsk$^+$ osteoprogenitor cells with dual epithelial and mesenchymal properties around the mucosa–bone interface. These Krt14$^+$Ctsk$^+$ cells contributed to alveolar bone homeostasis and especially osteogenesis induced by maxillary sinus floor lifting, which highlighted the potential contribution of epithelium-derived cells to the process of bone formation.[121] Intriguingly, during the formation and maturation of new bone tissue, these Krt14$^+$Ctsk$^+$ cells underwent a transformation into Krt14$^-$Ctsk$^+$ cells, accompanied by enhanced osteogenic capacity.[121] To investigate the physiological significance of this shift in cellular identity and function, further studies are warranted regarding the unidentified regulatory mechanisms involved in this process.

Niche cells

In contrast to stem cells and progenitor cells, certain cell types within the stem cell niche lack the characteristic properties of stemness.[6] Although these cells do not engage in tissue homeostasis and repair through direct differentiation into terminally differentiated cells, they play a crucial role in supporting the survival and functionality of stem and progenitor cells via paracrine signalling and other mechanisms.[6] Consequently, these cells warrant particular consideration in the study of stem cell biology.

Runx2$^+$ cells

Runt-related transcription factor 2 (Runx2) is a bone-specific transcription factor that is essential for the differentiation commitment of MSCs to osteoblasts.[122] Surprisingly, Chen et al[123] found a subpopulation of Runx2-expressing mesenchymal cells in the proximal region of mouse incisors, located adjacent to MSCs and transit-amplifying progenitors. Under physiological conditions, these Runx2$^+$ cells maintain a quiescent state.[123] Additionally, no significant changes were observed in their distribution or quantity during the injury repair process for clipped incisors.[123] Furthermore, EdU staining also revealed their low proliferative activity.[123] Thus, Runx2$^+$ cells were identified as non-stem niche cells. Mechanistic studies further revealed that these Runx2$^+$ cells can secret insulin-like growth factor binding-protein-3 (Igfbp3) to activate insulin-like growth factor-2 (IGF-2) signalling, regulating the proliferation and differentiation of transit-amplifying cells, to maintain niche homeostasis and promote incisor growth.[123]

SM22α$^+$ cells

Smooth muscle protein 22-α (SM22α) is a 22 kDa globular protein primarily present in vascular smooth muscle, visceral smooth muscle and myofibroblasts.[124,125] Previous studies have demonstrated the important role played by SM22α$^+$ cells in vascular homeostasis and remodelling.[126] However, understanding of the behaviour of SM22α$^+$ cells in oral maxillofacial hard tissues is still in its inception. A recent study by Zhou et al[127] demonstrated the proliferation of a physiologically quiescent SM22α$^+$ cell population at the tooth extraction socket, engaging in intramembranous bone regeneration. However, these SM22α$^+$ cells did not express classical MSC markers or differentiate into osteocytes for new bone formation.[127] Instead, they were identified as niche cells indirectly supporting bone regeneration by

secreting H_2S in a Pdgfrβ-dependent manner.[127] Overall, these findings serve as a reminder to emphasise the indispensable contribution of niche cells to the regeneration of oral maxillofacial hard tissues.

Discussion

In this review, the present authors have discussed lineage tracing-identified cell populations in the oral maxillofacial region. In addition to these extensively studied cells, recent years have also witnessed other scattered reports on potential stem and progenitor cell populations associated with oral and maxillofacial hard tissue formation, such as rapidly dividing $Lgr5^+$ cells in laCL,[128] $Bmi1^+$ epithelial stem cells in incisors[129] and glia-derived PLP^+ mesenchymal stem cells.[130] These findings further contribute to the growing body of research in stem cell biology. The present authors' objective is to delineate a framework for the adult stem cell niche in the context of hard tissue homeostasis and regeneration. These findings are underpinned by advancements in lineage tracing methodologies, which continuously update comprehension of adult stem cells and guide us in the pursuit of future investigative endeavours.

The progress of lineage tracing methodology brings about new insights

Lineage tracing has become the cornerstone technique for studying cellular dynamics in vivo. In its infancy, the non-inducible Cre system was pervasive due to its straightforward operability and high efficiency in genetic recombination.[12] However, the constitutively expressing recombinases are associated with several challenges, such as unspecific postnatal labelling, spatiotemporal administration difficulty and risk of germline leakage.[131,132] To address these issues, there has been a shift towards the adoption of the inducible CreER system, which is exemplified by the tamoxifen administered genetic recombination.[13] Consequently, the extent of labelled cells through these two methodologies exhibits dominant discrepancies. As described by Ono et al,[111] 2 days after tamoxifen injection on postnatal day 3, Osx-CreER tagged Osx^+ cells were primarily distributed in the odontoblast layer of the mandibular M1, with sparse presence in the dental follicle and papilla. Conversely, Osx-Cre labelled most mesenchymal cells in the dental follicle and dental papilla by postnatal day 5.[111] This extent discrepancy amplifies as the mice grow older. Thus, the validity of findings from some non-inducible Cre designated studies in the adult stem cell niche may be questionable (Table 1).

Despite these improvements, the side effects of tamoxifen with regard to interference with bone metabolism remain concerning. As an oestrogen analogue, tamoxifen inevitably stimulates the growth of both cortical and trabecular bone in a dose-dependent manner.[133] The potential adverse impact of β-catenin depletion in $Prx1^+$ cells on osteogenesis was even reversed by higher doses of tamoxifen.[134] The impact of tamoxifen induction is also associated with changes in osteoclast activity.[134] Thus, a systematic tamoxifen injection guideline serves as a necessary basis for obtaining reliable results. Nevertheless, the lack of standardised protocols for tamoxifen administration results in varying administration regimens across different studies, further complicating the interpretation of experimental outcomes (Table 2).

On the other hand, the choice of reporter gene also matters. Initially, the LacZ gene was substantially used in murine embryonic development research, whereas its limitations, such as its technical sensitivity, non-quantitative nature and incompatibility with immunohistochemistry, restricted its broader application.[135,136] The groundbreaking discovery of fluorescent proteins opens up new possibilities for cell labelling, with tdTomato being the most extensively employed reporter protein in diverse studies.[137] However, as research evolves, the limitations of monocolour reporter systems have become apparent. Specifically, these systems are unable to distinguish the differentiation trajectories of individual progeny cells. Thus, the innovation of multicolour reporter gene systems is necessary to accurately depict the lineage origins of each progeny cell.[138] Up to now, a dual recombinases-mediated double labelling lineage tracing approach has allowed researchers to track the transition of $Krt14^+Ctsk^+$ cells into $Krt14^-Ctsk^+$ cells that exhibit a stronger capacity for osteogenic differentiation in the oral and maxillofacial region.[121] Similarly, in the study of long bones, the utilisation of Rainbow mice has facilitated the identification of distinct skeletal stem cell populations that play a critical role in postnatal bone homeostasis and regeneration.[139,140] Given their vast potential, multicolour reporter gene systems are anticipated to serve as a countermeasure to elucidate the hierarchical relationships between different cell populations.

More questions to be addressed

The utilisation of transgenic tools has facilitated the identification of cell populations residing in the adult stem cell niche in the oral maxillofacial region. Nevertheless, some subjects still require additional investigation. First,

Table 1 Genetic recombination system used in oral maxillofacial lineage tracing.

System	Driver	Application fields	References
Non-inducible	Prx1-Cre	Development, homeostasis, regeneration	26-28,31,142
	LepR-Cre	Development, homeostasis, regeneration	36,37,45
	CD90-Cre	Development, homeostasis, regeneration	41,42
	NG2-Cre	Development, homeostasis, regeneration	60,78,79
	Osx-Cre	Development	106,107,109,111,142
	Ctsk-Cre	Development, homeostasis, regeneration, inflammation	119,120
	SM22α-Cre	Regeneration	127
Inducible	Sox2-CreERT2	Development, homeostasis	20
	Prx1-CreER	Development, regeneration	29
	LepR-CreER	Development, homeostasis, mechanical remodelling	9
	Pdgfrα-CreER	Homeostasis, aging	45,46
	Gli1-CreERT2	Development, homeostasis, regeneration, OTM, implant osseointegration, TMJOA, periodontitis	10,59-65,68-73,143,144
	αSMA-CreERT2	Development, homeostasis, dentine injury	45,50-53,55
	Plap-1-CreER	Homeostasis, periodontitis	76
	NG2-CreERT	Homeostasis, regeneration	45,80
	Axin2-CreERT2	Development, homeostasis, regeneration, OTM	86-92,94-96
	Acan-CreERT2	Development, homeostasis, regeneration	99-101,103,104,145-147
	Osx-CreERT2	Development	108,111,112
	PTHrP-CreER	Development	43,116
	Ctsk-CreER	Maxillary sinus floor lifting	121

CreERT and CreERT2 are modified variants of CreER.
OTM, orthodontic tooth movement; TMJOA, temporomandibular joint osteoarthritis.

the heterogeneity of the same marker identified cell population in different niches remains unresolved. In the case of $Gli1^+$ cells, they play diverse roles in the oral maxillofacial region: as DESCs in laCL,[59] as MSCs in the incisor proximal niche,[60] and as FCSCs in the superficial zone of condylar cartilage.[71] While their differentiation trajectories are radically distinct, the elucidation of how divergent cell fate is determined remains insufficient.

Another expansive area of research involves exploring the relationship and interplay between different cell populations within a shared location. As described above, various cell populations identified by distinct markers are frequently detected within the same niche, and they exhibit similar functions in maintaining homeostasis and facilitating regeneration. For instance, Osx^+ cells and $PTHrP^+$ cells within the dental follicle and dental papilla both play crucial roles in postnatal root morphogenesis in a comparable fashion,[111,112] and both αSMA^+ cells and $Axin2^+$ cells in dental pulp are actively engaged in the formation of the tertiary dentine following dentine injury.[51,94] The question of whether they represent distinct cell populations exhibiting synergistic effects, subgroups of the same functional cell population characterised by different markers or derived cells situated at different levels of the differentiation hierarchy requires additional empirical research for clarification.

Investigating and effectively harnessing the regulatory mechanisms that govern cell activity is essential for translating basic research into practical applications, particularly when considering various identities and functions of different cell types. The challenge arises from the intricate regulatory network of overlapping signalling pathways. While a singular signal can widely influence the biological functions of multiple cell populations, the activity of a specific cell population is concurrently modulated by signals originating from diverse sources.[29,62,90] Furthermore, there has been growing recognition of the role played by neurovascular regulation within the adult stem cell niche. Notable examples include the Hh signal activated by NVB sensory nerves and the PDGF signal provided by arterial cells.[60,141] Consequently, it is imperative that further investigation be carried out into the mechanisms that govern cell behaviour within the niche, as such insights could enhance current clinical attempts substantially.

Conclusion

In summary, current lineage tracing on cell fate determination in the oral maxillofacial region has yielded significant advancements, greatly enhancing comprehension of the adult stem cell niche. However, the potential

Table 2 Tamoxifen administration regimen in the inducible genetic recombination system.

Driver	Application fields	Time of induction	Number of injections	Dosage of tamoxifen	References
Prx1-creER	Development	Postnatal day 3	10 consecutive days	40 mg/kg b.w	29
	Regeneration	7–9 weeks old	10 consecutive days	40 mg/kg b.w	29
LerR-CreER	Development	Postnatal day 5	2 consecutive days	1 mg	9
		Postnatal day 21			
	Mechanical remodelling	6 weeks old	5 consecutive days	1 mg	9
	Homeostasis	3 months old	5 consecutive days	1 mg	9
Pdgfrα-CreER	Homeostasis	5–8 weeks old[45]	1 time[46]	70 mg/kg b.w[46]	45,46
		3 months old[46]	2 consecutive days[45]	1.5 mg/10 g b.w[45]	
	Aging	14 months old[46]	1 time[46]	70 mg/kg b.w[46]	46
Gli1-CreERT2	Development	Postnatal day 0.5[70]	1 time[61,62,70,143] 2 consecutive days[64,72]	75 mg/kg b.w[62,72] 1.5 mg/10 g b.w[61,70,143] 1.5 mM/g b.w[64]	61,62,64,70,72,143
		Postnatal day 3.5[61]			
		Postnatal day 12[72]			
		postnatal day 13[64]			
		Postnatal day 16[143]			
		Postnatal day 21[62]			
	Homeostasis	4–6 weeks old[60]	1 time[59]	10 mg[59,60] 1.5 mg/10 g b.w[45]	45, 59, 60
		5–8 weeks old[45]	2 consecutive days[45]		
		8–10 weeks old[59]	3 consecutive days[60]		
	Tooth extraction	4 weeks old[65]	2 consecutive days[10,65]	10 mg[10,65]	10,65
		8 weeks old[10]			
	OTM	8 weeks old[69]	2 consecutive days[69]	10 mg[69]	68,69
		10–12 weeks old[68]	3 consecutive days[68]	100 μg/g b.w[68]	
	Implant osseointegration	6 weeks old	2 consecutive days	1.5 mg/10 g b.w	63
	TMJOA	4 weeks old[73]	2 consecutive days[73]	75 mg/kg b.w[73]	71,73
		6 weeks old[71]	3 consecutive days[71]	1.5 mg/10 g b.w[71]	
	Periodontitis	6–8 weeks old	2 consecutive days	4 mg	144
αSMA-CreERT2	Development	Postnatal day 16[55]	1 time[55]	75 μg/g b.w[50]	50,55
		3–4 weeks old[50]	2 consecutive days[50]	62.5 mg/g b.w[55]	
	Homeostasis	5–8 weeks	2 consecutive days	1.5 mg/10 g b.w	45
	Dentine injury	Postnatal day 4[51]	2 consecutive days[51]	75 μg/g b.w[51-53]	51-53
		4 weeks old[52,53]	2 at 24-h intervals[52,53]		
NG2-CreER	Homeostasis	5–8 weeks old	2 consecutive days	1.5 mg/10 g b.w	45
	Regeneration	6 weeks old	5 consecutive days	75 mg/kg b.w	80
Axin2-CreERT2	Development	Postnatal day 12[143]	1 time[89,90,92,143] 3 consecutive days[42,86,88,91]	75 mg/kg b.w[86,89,90,92]	42,86,88-92,143
		Postnatal day 14[42]		2 mg/30 g b.w[42]	
		Postnatal day 21[86,89,92]		0.15 mg/g b.w[143]	
		Postnatal day 28[90]		4 mg/25 g b.w[88,91]	
		1 month old[91]			
		Postnatal day 90[88]			
	Homeostasis	Adult[42]	3 consecutive days[42]	2 mg/30 g b.w[42]	42
	Dentine injury	6 weeks[94]	3 consecutive days[88,94]	0.1 mg/g b.w[94]	88,94
		Adult[88]		4 mg/25 g b.w[88]	
	Tooth extraction	Adult	3 consecutive days	4 mg/25 g b.w	95
	OTM	Postnatal day 28	1 time	75 mg/kg b.w	96
Acan-CreERT2	Development	Postnatal day 3[145,147]	1 time[103,145-147] 3 consecutive days[101]	1.5 mg/10 g b.w[101,103]	101,103,145-147
		Postnatal day 7[101]		1 mg/13 g b.w[146]	
		Postnatal day 14[103,146]		75 mg/kg b.w[147]	
	Homeostasis	5 weeks old[99]	3 consecutive days[100]	1 mg/10 g b.w[99]	99,100
		9 weeks old[100]	5 consecutive days[99]	150 mg/kg b.w[100]	
	Regeneration	10–16 weeks old	5 consecutive days	75 mg/kg b.w	104

CreERT2 is a modified variant of CreER with three points mutations.
b.w, body weight; OTM, orthodontic tooth movement; TMJOA, temporomandibular joint osteoarthritis.

systematic errors in the current experiments need to be ruled out by rigorous experimental design. Further questions about the hierarchical relationship and the interaction between different cell populations have not been answered precisely due to the limitations of the tools. It is anticipated that improvements in technology and methodology will further reveal the enigmatic nature of cell populations in the formation of oral maxillofacial hard tissues, thus making a significant contribution to the rapid development of regenerative medicine.

Conflicts of interest

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

Author contribution

Dr Shuang YANG contributed literature collection and manuscript draft; Drs Chang Hao YU, Fei Fei LI, Yu SHI, Hui WANG, Wei Dong TIAN, Quan YUAN and Ling YE contributed to the manuscript revision; Dr Fan Yuan YU contributed to the conception, supervision and revision.

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