Chapter 13
Molecular Mechanisms Regulating Tooth Number

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Abstract Tooth number, shape, and position are consistent in mammals and are subject to strict genetic control. Multiple signaling pathways including Shh, Tgf, Bmp, Wnt, Fgf, Notch, and NF-kB are known to play critical roles in regulating tooth development. Recent studies show that these signaling pathways interact with each other through positive and negative feedback loops to regulate tooth number, shape, and spatial pattern. Teeth develop via a dynamic and complex reciprocal interaction between dental epithelium and cranial neural crest-derived mesenchyme. These interactions contain a series of inductive and permissive processes that lead to the determination, differentiation, and organization of odontogenic cells, which are controlled by these signaling pathways. It is believed that dozens of different molecules together form complex molecular networks that regulate tooth development. Studies of human congenital disease and transgenic mice suggest that disturbance of the molecular network results in abnormal tooth formation. Since molecular mechanisms involved in tooth development should be reproduced in tooth regeneration, knowledge of tooth development from both human and mouse studies is crucial for exploring tooth regenerative therapies. In this paper, we present an overview of the current literature covering the molecular mechanisms of tooth development, especially those regulating tooth number.

Keywords Tooth development • Tooth number • Missing teeth • Supernumerary teeth

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13.1 Introduction

Tooth position, number, size, and shape are consistent in mammals and are determined genetically [6, 10, 13, 41, 80]. Teeth develop via sequential, reciprocal interactions between the oral epithelium and neural crest-derived mesenchyme. The first morphological sign of tooth development is an epithelial thickening (dental placode). The thickened tooth epithelium progressively takes the form of bud, cap, and bell configurations as differentiation and morphogenesis proceed. In addition to thickening of the epithelium, mesenchymal cells condense – a process that has been shown to be critical for organogenesis [44]. Subsequently, epithelial cells and mesenchymal cells (dental papilla) differentiate into enamel-producing ameloblasts and dentin-secreting odontoblasts, respectively. Since substantial research efforts over the last decade – using both human studies and transgenic mouse studies – have elucidated many aspects of the molecular mechanisms in tooth development, our understanding of the control of tooth shape diversity and location in the jaws has advanced considerably.

These research efforts have also elucidated that multiple signaling pathways including Shh, Tgf, Bmp, Wnt, Fgf, Notch, and NF-kB are known to play critical roles in regulating tooth development. The fine-tuning of these signaling pathways has been shown to be crucial in governing odontogenic precision. Recent studies show that crosstalk between these signaling pathways build complex molecular networks that regulate tooth development [6, 10, 13, 26, 28, 41, 80].

Regenerative medicine is one of the revolutionary future therapies in dentistry. Since regeneration of organs starts from initiation, knowledge of the molecular mechanisms involved at this stage is crucial for developing tooth regenerative therapies. Missing and extra teeth have been shown to be caused by disturbance of the developmental mechanisms during the initiation stage. Studying these numerical anomalies in both humans and mice therefore provides invaluable information to understanding the molecular mechanisms of tooth initiation and therefore tooth regeneration. In this paper, we present an overview covering the molecular mechanisms of tooth development, especially those determining tooth number.

13.2 Skin Appendage

The skin serves several functions, including thermoregulation, protection from the external environment, maintaining internal tissue fluid from evaporation, sensation, defense against infection, and supporting scaffold for hair. To fulfill these multiple functions, skin develops many structures as epidermal appendages such as nails, sweat glands, hair, sebaceous glands, tooth, and mammary glands. Although diverse in their structural phenotypes, these organs including teeth and hair share common morphological features in the early stages of development – i.e., epithelial components originate as thickenings that subsequently form buds around which the

underlying mesenchymal cells condense. Interactions between the epithelial and mesenchymal tissues play central roles in regulating the morphogenesis of the skin appendages. When cultured alone, neither the epithelial nor mesenchymal components of these structures can differentiate into specific cells. It is also known that epithelial-mesenchymal interactions are sequential and reciprocal occurring in both directions between the epithelial and mesenchymal tissues.

Mice are the most highly studied mammals for investigating the mechanisms of tooth development. Initiation begins before the organ anlagen are morphologically visible. The first odontogenic signals derive from the tooth epithelium. Bmps-, Fgfs-, Wnts-, NF-kB-, and Shh-related genes are expressed in the presumptive tooth epithelium before the thickening process. Unlike humans, rodent incisors grow continuously throughout life and the stem cell niche is known to be located at the apical end of the incisor tooth. In the laboratory, hair can be initiated from murine dental stem cells, suggesting that tooth epithelium also retains the ability to form hair [84].

13.3 Missing Teeth

13.3.1 Missing Teeth in Humans

Congenital dental anomalies can occur either as non-syndromic familial cases or as part of a syndrome. Missing teeth are one of the most common human developmental anomalies. It has been shown that more than 20 % of humans lose at least one of the third molar teeth [36, 45, 53]. 1.6–9.6 % of the population suffers from hypodontia, with loss of one or two teeth (except the third molar). Oligodontia, with loss of more than six teeth (except the third molar), ranges from 0.0 % to 1.1 %, depending on the population studied. Loss of all teeth is referred to as anodontia. Missing teeth are more common in the permanent dentition than those in the primary dentition. However, it is believed that hypodontia in the primary dentition is correlated to hypodontia in the permanent dentition [36, 45]. Additionally, a higher prevalence ratio of hypodontia has been identified in women, with a 3:2 ratio [9].

13.3.1.1 Non-syndromic (Isolated) Familial Missing Teeth

Non-syndromic familial hypodontia has been reported to probably be inherited either as an autosomal dominant, autosomal recessive, or X-linked trait [1, 2, 15, 22, 65, 79].

It has been shown that mutation in *MSX1* is associated with hypodontia that predominantly affects second premolars and third molars which all have normal primary dentition [31, 45]. Mutation in *PAX9* results in hypodontia in the form of lost molars. Maxillary and/or mandibular second molars and central incisor are often affected in some individuals [37, 46]. The frequency of tooth loss is found to be

Table 13.1 Abnormal tooth numbers in human

Loss of tooth	
Syndrome	Mutation
Hypohidrotic/anhidrotic ectodermal dysplasia	*EDA, EDAR, and EDARADD*
Odonto-onycho-dermal dysplasia	*WNT10A*
Ectrodactyly ectodermal dysplasia cleft lip/palate syndrome	*P63*
Ellis-van Creveld syndrome	*EVC*
Incontinentia pigmenti	*IKKγ*
Van der Woude syndrome	*IRF6*
Rieger syndrome	*PITX2, FOXC1*
Oral facial digital syndrome type I	*OFD1*
Enamel renal gingival syndrome	*FAM20*
Extra tooth	
Cleidocranial dysplasia	*RUNX2*
SOX2 anophthalmia syndrome	*SOX2*
Gardner syndrome	*APC*
Opitz G/BBB syndrome	*MID1*
Tricho-rhino phalangic syndrome	*TRPS1*
Ehlers-Danlos syndrome type III	*Tenascin-XB, COL3A1*
Robinow syndrome	*ROR2*
Nance-Horan syndrome	*NHS*
Fabry syndrome	*a-galactosidase A*
Rothmund-Thomson syndrome	*RECQL4*
Hallermann-Streiff syndrome	*GJA1*

higher for second premolars and maxillary first premolars in association with *MSX1* mutation compared to *PAX9* mutation [53]. Each tooth type thus shows their different response to these gene mutations. Defects identified in *MSX1* and *PAX9* include gene deletion, as well as nonsense, frameshift, and missense mutation. In addition, it has been indicated that a nonsense mutation in *AXIN2* (a molecule essential for canonical Wnt signaling) leads to oligodontia [40]. Here, patients display an absence of at least eight permanent teeth, while primary dentition remains intact.

Mutation in *EDA* has been shown to be linked to non-syndromic hypodontia, although mutation in *EDA* can also lead to syndromic dental anomalies [83]. Mutation of *WNT10A* is found in patients with isolated hypodontia, even though mutation of the gene is also linked to odonto-onycho-dermal dysplasia [77]. Additionally, *GREM2* mutations have been found to exist within families with absent teeth [30].

13.3.1.2 Syndromic Missing Teeth

There are about eighty syndromes showing hypodontia (Table 13.1; [36]).

Ectodermal dysplasia consists of variable defects in the morphogenesis of ectodermal derivatives such as teeth, skin, hair, sweat glands, and nails, although more than 150 clinically distinct ectodermal dysplasias have been identified. Ectodermal dysplasia syndromes can be inherited in an autosomal dominant, autosomal recessive, or X-linked form. Disruption of the *EDA*, *EDAR*, and *EDARADD* loci has been causally identified for the onset of hypohidrotic/anhidrotic ectodermal dysplasia [56]. Odonto-onycho-dermal dysplasia is an autosomal recessive ectodermal syndrome, which is caused by mutation in *WNT10A*. It is characterized by hyperkeratosis, smooth tongue, dry hair, nail dysplasia, and hyperhidrosis of palms and soles. The dysplasia also presents with severe hypodontia [36]. Ectrodactyly ectodermal dysplasia cleft lip/palate syndrome is an autosomal dominant disorder characterized by ectrodactyly, ectodermal dysplasia, and cleft lip/palate. Patients with this syndrome also exhibit oligodontia/anodontia. Heterozygous mutation in *P63* has additionally been shown to be responsible for ectrodactyly ectodermal dysplasia cleft lip/palate syndrome [73]. Incontinentia pigmenti is an X-linked dominant disorder, which is characterized by abnormal skin pigmentation and hair loss. It is caused by mutation of *IKKγ* (*NEMO*) [56]. Incontinentia pigmenti is recognized as a form of ectodermal dysplasia by many societies, since ectodermal structures (hair, skin, nails, and teeth) as well as the eyes and nervous system are affected. Hypodontia is a common feature of the disorder [73].

Ellis-van Creveld syndrome is characterized by polydactyly, chondrodysplasia, nail dysplasia, and cardiac defects and is caused by mutation of *EVC*. Missing teeth are frequently observed in Ellis-van Creveld syndrome patients [5]. Van der Woude syndrome is characterized by cleft lip and/or cleft palate, paramedian lip pits and sinuses, and conical elevations of the lower lip. It is caused by mutation in the *IRF6* gene. Hypodontia is a common feature of the syndrome [55, 72]. Rieger syndrome is an autosomal dominant disorder, which consists of malformations in the anterior chamber of the eye and umbilical anomalies. Rieger syndrome patients also show hypodontia or anodontia. Mutations in *PITX2* and *FOXC1* have additionally been shown to be responsible for Rieger syndrome. Oral facial digital syndrome type I is an X-linked disorder which is caused by mutation of *OFD1*. The syndrome is characterized by malformation of the face, oral cavity, digits, central nervous system, and kidneys. Missing teeth are often observed in oral facial digital syndrome type I patients [23]. Enamel renal gingival syndrome is caused by the mutation of *FAM20*, and patients display impaired calcium metabolism and hypodontia [29].

It is generally accepted that hypodontia is often accompanied by clefts of the lip and palate. Hypodontia has been shown to be observed in 80% of patients with clefts [36, 74]. The prevalence ratio of hypodontia is also correlated to the severity of the cleft [69].

13.3.1.3 Sporadic Missing Teeth

It is believed that sporadic hypodontia is caused by environmental factors such as trauma to the jaws, surgical procedures on the jaws, traumatic extraction of the primary teeth, chemotherapy, and radiation therapy [52, 71]. In common with environmental factors, mutation of *PAX9* has been shown to be associated with sporadic hypoplasia [62].

13.3.2 Missing Teeth in Mice

Mice are the most highly studied mammals for investigating the molecular mechanisms of tooth development, since the most common application of gene targeting is to produce knockout mice. Mice however only have incisor and molar teeth and as such their use is limited as a model for human tooth development.

The first odontogenic signal is derived from the epithelium. Prior to this, there is no prespecification of the cells into different populations within the mandibular arch. All ectomesenchyme cells in the arch are therefore equally responsive toward any signals, including those which instigate hair and limb development. After receiving appropriate signaling, the underlying mesenchyme becomes independent of the epithelial cues. From the bud stage, the direction of cellular communication is reversed and signals pass from the condensing mesenchyme to the epithelium.

Many genes have been shown to play a critical role in regulating tooth number (Table 13.2). In common with humans, mice with mutations in *Msx1* and *Pax9* mutation exhibit missing teeth, driven by an arrest of tooth development at the bud stage [64, 70]. Mutation of other molecules such as *Fgfr2*, *Lef1*, and *Runx2* also shows an arrest of tooth development at the bud stage [16, 18, 78]. Transition to cap stage from bud stage is thus a critical point in tooth development. In common with humans, *p63* and *Pitx2* mutant mice show missing teeth, but this is caused by an arrest of tooth development at stages preceding the bud stage [39, 42, 43]. Together, these data suggest that *p63* and *Pitx2* are essential for developmental signaling before the requirement of *Msx1*, *Pax9*, *Fgfr2*, *Lef1*, and *Runx2*. However *Msx1/2* mutants also show an arrest of tooth development at stages preceding the bud stage, suggesting that *Msx1* has a role in tooth initiation for which *Msx2* can compensate for gene loss in the mutant mouse [7].

It is believed that Shh, Tgf, Bmp, Wnt, and Fgf signaling are known to play critical roles in tooth initiation. *Gli2/3* (transcription factors mediated by Shh) mutants show an arrest of tooth development at stages prior to bud formation [24]. Mice with epithelial conditional deletion of *Bmpr1a* lead to an arrest of tooth development at the bud stage [4]. Additionally, *Fgf3/10* mutants show an arrest of tooth development preceding the bud stage, whereas mutation of *Fgfr2* results in an arrest of tooth development at the bud stage [16, 82]. Downregulation of Wnt signaling by overexpression of *Dkk1* (an antagonist of Wnt signaling) shows an arrest of tooth develop-

Table 13.2 Abnormal tooth numbers in mice

Loss of tooth		Extra tooth	
Tooth type	Mutation/Tg	Tooth type	Mutation/Tg
All tooth	*Msx1*	All tooth	*Apc*
	Pax9		*Sp6*
	Runx2		
	p63	Incisor	*Lrp4*
	Pitx2		*Wise*
	Msx1/Msx2		*K5-Ikkβ*
	Lef1		*Lhx6/Lhx7*
	Gli2/Gli3		
	K14-Dkk1	Diastema	*Ift88*
	Bmpr1a		*Lrp4*
	Fgf3/Fgf10		*Wise*
	Fgfr2		*Sprouty2*
	Dicer		*Sprouty4*
			R-Spondin2
Incisor	*Activinβa*		*Eda*
			K14-Eda
Molar	*Eda*		*K5-Edar*
	K14-Noggin		
	Bmp4	Molar	*Osr2*
	IkBα		
	Dlx1/Dlx2		

ment at stages prior to bud formation, whereas *Lef1* (a Wnt-related molecule) mutation results in an arrest of tooth development at the bud stage [3, 78]. In common with *Msx1* and *Msx2*, it is likely that there is redundancy between molecules within the same signaling pathway during tooth initiation events.

The term "epigenetics" refers to the covalent modification of DNA, protein, or RNA, resulting in changes to the function and/or regulation of these molecules without altering the genomic sequence. MicroRNAs (miRNAs) represent one of these epigenetic factors. These noncoding small single-stranded RNAs are 19–25 nucleotides in length and negatively regulate gene expression by binding target sequences in mRNA molecules. Absence of miRNAs in neural crest-derived cells, driven by deletion of *Dicer* (an essential molecule for microRNA processing), have been shown to lead to an absence of tooth development – although exact phenotypes vary between animals from lack of tooth development to almost normal tooth development [61]. This suggests that epigenetic factors also play a critical role in the regulation of tooth formation, but the exact mechanism is as yet unclear.

13.4 Supernumerary Teeth

Teeth are found in most vertebrates and have played a central role in their evolution. Change in tooth number is a significant evolutionary adaptation to accommodate novel feeding strategies. Reduction in tooth number is a well-known evolutionary trend of the dentition within eutherians. The total number of teeth per dentition has generally decreased, whereas tooth morphological complexity has increased during tooth evolution. Findings in tooth evolution are therefore a key feature to understanding the molecular mechanisms in regulating tooth number.

13.4.1 Supernumerary Teeth in Humans

The prevalence ratio of supernumerary teeth ranges from 0.2 % to 0.8 % in the deciduous dentition and from 0.3 % to 5.3 % in the permanent dentition [80]. The incidence of supernumerary teeth in men is higher than those in women (1.8:1–4.5:1, female/male) [53, 80].

13.4.1.1 Syndromic Extra Teeth in Humans

Multiple supernumerary teeth are usually a syndromic symptom, and the prevalence for non-syndromic multiple supernumerary teeth have been reported to be less than 1 % (Table 13.1; [68]).

Cleidocranial dysplasia (dysostosis) is characterized by general bone dysplasia, short stature, delayed closure of the cranial sutures, and hypoplastic or aplastic clavicles. Cleidocranial dysplasia is known to be associated with supernumerary dentition. Mutations in *RUNX2* are responsible for the dysplasia [36, 80]. *SOX2* anophthalmia syndrome is caused by mutations in the *SOX2* gene and is characterized by anophthalmia or microphthalmia, with various extraocular symptoms such as hypogonadotropic hypogonadism, brain anomaly, and esophageal abnormalities. Again, patients show supernumerary tooth formation [54]. Gardner syndrome is a rare autosomal dominant disorder which is caused by mutations in *APC*. The syndrome consists of gastrointestinal polyps, multiple osteomas, and skin and soft tissue tumors including a characteristic retinal lesion. Variant tooth anomalies including supernumerary teeth are observed in these patients. In addition, Opitz G/BBB syndrome, tricho-rhino phalangic syndrome, Ehlers-Danlos syndrome type III, Robinow syndrome, Nance-Horan syndrome, Fabry syndrome, Rothmund-Thomson syndrome, and Hallermann-Streiff syndrome are all known to be syndromes where supernumerary teeth occur [13, 73, 80].

As with hypodontia, syndromic extra tooth formation is often accompanied by cleft lip/palate. In this instance, splitting of the tooth germs due to cleft lip and/or palate is the cause of the formation of supernumerary teeth [38, 80].

13.4.1.2 Missing and Extra Teeth in Humans

The concomitant occurrence of hypodontia and supernumerary teeth is observed in Down syndrome, oral facial digital syndrome type I, Ellis-van Creveld syndrome, and Ehlers-Danlos syndrome [76]. These suggest that single gene mutation can lead to these opposite tooth phenotypes in same patients.

13.4.2 Supernumerary Teeth in Mice

It is widely accepted that modern eutherian mammals evolved from a common ancestor that had three incisors, one canine, four premolars, and three molars. Mice possess only one incisor and three molars in each jaw quadrant, separated by a toothless region called the "diastema." It is believed that mice lost the remaining teeth during evolution. Genetically modified mice therefore provide some limited information on the determinant of non-murine tooth types. However, it has been shown that mice have retained the genetic potential for the development of teeth lost during evolution, such as the premolars.

In wild-type mice, tooth germ-like structures are observed in the diastema at early stages of development, which disappear during later stages [63]. Both mutation and overexpression of *Eda* are known to lead to extra tooth formation in the diastema, suggesting that the precise signaling regulated by *Eda* is essential for controlling odontogenesis in the diastema [48, 63]. Extra tooth formation in the diastema is also observed in mice with mutation of *Gas1* (an inhibitor of Shh), *R-spondin2* (activators of Wnt signaling), *Ift88* (molecules present in the primary cilia where Shh signaling is activated), *Wise* (a secreted BMP antagonist and Wnt modulator), *Lrp4* (a negative Wnt co-receptor), *Sprouty2* (a negative feedback regulator of Fgf), and *Sprouty4* (a negative feedback regulator of Fgf) [32, 33, 35, 59, 60]. Evolutionary tooth loss in the diastema is likely to be associated with changes in these signaling pathways. These also suggest that odontogenic activity in the diastema is mainly controlled by inhibitors of signaling pathways.

Mammals have single-rowed dentitions, whereas many other vertebrates have dentition which consists of multiple rows. It is believed that mammals lost this additional dentition during evolution. *Osr2* is expressed in the molar tooth germ area with a lingual-to-buccal gradient and restricts expression of *Bmp4* – which is also mediated by *Msx1*. Mice with mutations in *Osr2* develop supernumerary teeth lingual to the endogenous molars due to expansion of *Bmp4* expression [85]. The interaction between *Osr2*, *Bmp4*, and *Msx1* thus plays a critical role in regulating molar tooth initiation in the buccolingual axis [41].

In common with the diastema and molar region, extra incisor tooth formation is also observed in mice with mutations in *Wise*, *Lrp4*, *Lhx6/7* and *Sprouty2/4*, and overexpressing *Ikkβ* [8, 11, 17, 32, 59]. Single extra incisor in a jaw quadrant is thus formed by changes in the Wnt, Bmp, Fgf, and NF-kB pathways.

Constitutive stabilization of β-catenin in the epithelium results in numerous supernumerary tooth formation in the mouse [25]. *Apc* is known to play a critical role in regulating the Wnt signaling pathway and conditional deletion of *Apc* in the epithelium also results in multiple supernumerary tooth formation [81]. Mice with overexpression of *Lef1* (a Wnt-related molecule) have been associated with ectopic tooth formation [86]. Numerous extra teeth are also observed in *Epiprophin* (*Sp6*)-deficient mice, which show upregulation of Wnt signaling [49]. Taken together, numerous extra tooth formation is thus directly related to over-activation of Wnt signaling. Wnt inhibitors, Dkks, are known to be expressed in wild-type developing tooth germs, suggesting that Wnt signaling activity is regulated by the balance between ligands and inhibitors [21].

13.5 Odontogenic Activity Between Tooth Germs

Each tooth type is known to show different developmental timing in humans. In mice, the second and third molars start to develop after the first molar reach the bell stage. It has been shown that the first molar tooth germs inhibit development of the second molar at an early stage [34]. The development of the second molar tooth initiates only when inhibitory factors from the first molar are sufficiently reduced. Odontogenic activity is thus regulated by the interaction between tooth germs. Bmp signaling is likely to be involved in this interaction. Indeed, mice with mesenchymal conditional deletion of *Bmp4* and mice overexpressing *Noggin* (Bmp antagonist) present with an absence of second and/or third molars [27, 67]. Mice with mutation of *Eda* and with reduction of NF-kB also exhibit loss of the second and/or third molars, suggesting that Eda-NF-kB cascade is also involved in the interaction between tooth germs [57, 66].

13.6 Tooth Initiation and Tooth Type

It has been shown that more than 20 % of humans lose at least one of the third molars [36, 45, 53]. Apart from the third molars, lower second premolars and/or upper lateral incisors are most commonly affected, followed by the upper second premolars [53]. Most of the common supernumerary teeth (46.9–92.8 % of supernumerary teeth) are observed between the upper central incisors – the so-called mesiodens [20, 68, 87]. Supernumerary teeth are also observed in the premolar region (10 % of the total supernumerary cases) and almost 75 % of those are in the mandible [80]. Supernumerary teeth are also found in the molar region as a distomolar (fourth molar). Furthermore, mice with targeted null mutations of both *Dlx1* and *Dlx2* homeobox genes have a tooth patterning phenotype where development of maxillary molar teeth is inhibited but development of all other teeth is normal. *ActivinβA* mutants show the opposite tooth phenotype, where maxillary molar teeth

are present and other teeth are absent [19]. Odontogenic activities are thus differently regulated between regions of the maxillary and mandibular jaw.

It has been established that instructive signals are involved in the determination of tooth type. Homeobox genes have been found to regulate patterning in the development of many tissues including the maxillae and mandibles. In the developing jaws, several homeobox genes show highly restricted expression patterns in the ectomesenchyme along the proximodistal axis. For example, *Barx1* are expressed in mesenchymal cells of the presumptive molar region, whereas *Msx1* and *Msx2* are expressed in mesenchymal cells where the incisors develop. Spatially restricted gene expression is also observed in the epithelium. *Bmp4* is expressed in the presumptive incisor region, while *Fgf8* expression is restricted to the presumptive molar region. In the epithelium, these molecules have been shown to be responsible for regulating mesenchymal homeobox gene expression. Mis-expression of *Barx1* in the murine presumptive incisor mesenchyme results in a transformation of tooth shape, with molars developing from incisor primordia. Transposition of teeth (i.e., adjacent teeth switching positions) is an extremely rare dental anomalies in humans [12, 75]. However, examples of molar-like teeth in the maxillary central incisor region and premolar-like teeth in the maxillary lateral incisor region have previously been reported [28]. It is believed that the maxillary canine is most frequently involved in the transposition event [51]. Tooth identity is believed to be determined by complicated mechanisms, such as spatially restricted homeobox gene expression, and the gradient and overlap of signaling molecules [13, 14, 47]. Although the etiology of transposed teeth remains unclear, it is possible that changes in the balance of the determinant molecules results in the switching of tooth types.

13.7 The Midline and Tooth Development

Holoprosencephaly is a relatively common defect of the forebrain and midface in humans and is caused by impaired midline cleavage of the embryonic forebrain. It is believed that the holoprosencephaly spectrum is associated with the appearance of a solitary median maxillary central incisor. Single maxillary central incisors are also a feature of single median maxillary central incisor syndrome, which is caused by a failure in growth at the midline [10, 50]. Craniofacial development is thus linked to tooth development.

13.8 Conclusion

Tooth number, shape, and position are consistent in mammals and are subject to strict genetic control. Here, we highlight an overview covering the molecular mechanisms of tooth development, especially those regulating tooth number. Dozens of different molecules together form complex molecular networks creating positive

and negative feedback loops, and a series of inductive and permissive processes that regulate tooth number. Multiple signaling pathways such as Shh, Tgf, Bmp, Wnt, Fgf, Notch, and NF-kB – and crosstalk between them – are known to play critical roles in regulating tooth development. Activity of signaling pathways is also regulated by the balance of ligands, activators, inhibitors, and receptors. Teeth develop via a dynamic and complex reciprocal interaction between dental epithelium and cranial neural crest-derived mesenchyme. It has been shown that transcription factors are involved in epithelial-mesenchymal interactions through the signaling loops between tissue layers by responding to inductive signals and regulating the expression of other signaling molecules. It has been shown that all these factors function as distinct role between tooth type, timing, location, and gender in mammals.

Studies of human congenital disease and transgenic mice suggest that disturbance of the molecular network results in abnormal tooth formation. Since molecular mechanisms involved in tooth development should be reproduced in tooth regeneration, knowledge of tooth development from both human and mouse studies provides crucial information for the advancement of tooth regenerative therapy. Among the molecular mechanisms involved in tooth development, those regulating tooth number are the most critical for tooth regeneration, as replacement dentition should start from tooth initiation. Rodent incisors grow continuously throughout life by utilizing a stem cell niche located at the apical end of the incisor tooth. As such, this structure is also able to provide crucial information pertinent to the study of tooth regeneration.

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