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Review

Teeth are bones: Signature genes and molecules that underwrite odontogenesis

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Understanding the molecular genetics of odontogenesis (tooth development) can unlock innovative avenues to genetically engineer teeth for therapy. In this review, emerging insights into the genetic and molecular bases of tooth development are presented. Four conserved signature genes express master molecules (fibroblast growth factors, bone morphogenetic proteins, wingless integrated ligands and sonic hedgehog protein) that underwrite odontogenesis. Five homeobox genes (Barx1, Dlx, Pax9, Msx and Pitx) and many secondary molecules (notably transcription factors) mediate signalling pathways that drive tooth initiation, morphogenesis and differentiation. The role of at least 57 genes and signalling molecules are presented in this work.

Key words: Genes, signalling molecules, odontogenesis.

INTRODUCTION

There is a lot of interest in the molecular genetics of odontogenesis mainly because the development of teeth is a model system for understanding organogenesis, and secondly, teeth congenital abnormalities account for approximately 20% of all inherited disorders (Koussoulakou et al., 2009). Also, our improved understanding of the genetic and molecular foundations of odontogenesis may bring about novel treatments for and biological restoration of teeth abnormalities *in vivo*. Knowledge of how teeth are made in nature may also provide leads towards the synthesis of teeth *in vitro*.

Due to advances in technology, new genes and intriguing molecules associated with tooth development are being discovered, hence, the primary literature on this subject is still widely scattered in various journals. Consequently, the focus of this review is to consolidate emerging insights into the molecular genetic bases and signalling molecules that drive odontogenesis. The ultimate goal is to provide an inventory of signature genes and signalling molecules that underwrite tooth development.

FORMATION OF TEETH

Teeth are highly mineralized appendages found in the entrance of the alimentary canal of both invertebrates and vertebrates (Koussoulakou et al., 2009). Typically, teeth are the dentition or elements of the dermal skeleton present in a wide range of jawed vertebrates (Huysseune et al., 2009). They are associated mainly with chewing and processing of food, but they also frequently serve other functions, such as defense, display of dominance and vocalization in humans.

Teeth are vertebrate organs that arise from complex and progressive interactions between an ectoderm, the oral epithelium and an underlying mesenchyme (Sartaj and Sharpe, 2006). Each tissue layer instructs the other to differentiate in a precisely programmed manner leading to the formation of highly specialized structures, such as incisors, canines, premolars and molars (Bei, 2009). Each of these groups of teeth derives from different parts of the oral epithelium and, depending on the species, teeth can be formed from both endoderm and ectoderm or from ectoderm only (Bei, 2009).Tooth development involves reciprocal interactions between the dental epithelium and the neural crest derived mesenchyme starting with the epithelial condensation and subsequent invagination into the mesenchyme (Thesleff, 2006). These interactions transform the tooth primordial into mineralized structures with various cell types (Mitsiadis and Smith, 2006). In mice, odontogenesis is induced by

by the epithelium around embryonic day 10, and 2 days later, the odontogenic potential switches to the mesenchyme (Lumsden, 1988; Mina and Koller, 1987).

Klein et al. (2007) documented the four stages of developing tooth. First, the epithelium thickens to form a placode. Then, the epithelium invaginates into the underlying mesenchyme, while the prospective dental mesenchyme condenses around it, forming a tooth bud. Subsequently, the epithelium folds and extends into the mesenchyme, surrounding the dental mesenchyme to form a cap and then a bell stage tooth germ.

EVOLUTIONARY ORIGINS OF DENTITION

Teeth originated in stem gnathostomes approximately 450 to 460 million years ago. Since their recruitment into the oral cavity, teeth have been subjected to strong selective constraints due to the crucial role that they play in species survival (Davit-Béal et al., 2009). Two theories have emerged to explain the evolution of teeth. The first theory states that teeth were derived from skin odontodes (dermal denticles) that came to reside within the oral cavity when competent odontode-forming cells invaded the mouth in conjunction with the origin of jaws; this is called the 'outside-in' theory (Smith, 2003; Huysseune et al., 2009). Thus, teeth are hypothesized to have evolved from scale-like epidermal structures, the odontodes, which migrated into the mouth after enough mutations (Koussoulakou et al., 2009).

Teeth are modified skin denticles (Huysseune et al., 2009) that served various functions, such as protection, sensation and hydrodynamic advantage on the outer body surface of jawless fishes (Koussoulakou et al., 2009). Over the course of 500,000,000 years of evolution, the odontodes moved into the oral cavity creating buccal teeth which covered the entire surface, but later were restricted to jaw margins (Koussoulakou et al., 2009).

According to Huysseune et al. (2009), the 'outside-in' theory is largely based on the anatomical resemblance of shark skin denticles to teeth. These workers state that the 'outside-in' theory has the following principles: (a) odontodes originated from ectoderm, on the external surface of an organism in the form of skin denticles; (b) in order for oral teeth to have evolved, ectodermal cells that form denticles on the surface must have mixed and incorporated into the oro-pharyngeal cavity during development; and (c) only ectodermal cells have the capacity to form odontodes and thus all derivatives must have originated via ectodermal organogenesis.

The second theory is that teeth were derived from pharyngeal denticle whorls which moved up into the mouth (Smith, 2003; Huysseune et al., 2009). This 'inside out' hypothesis suggests that teeth evolved prior to the origin of jaws, with oral teeth being co-opted from endodermally derived pharyngeal denticles (Smith and Coates, 2001; Johanson and Smith, 2005). This theory is supported by data from fossil records and embryological studies of extant species.

Ecological adaptations of teeth form and function

Dietary habits and ecological adaptations have contributed to the repertoire of teeth anatomical forms and shapes. Thus, diet and mastication are seen as key factors in teeth evolution (Koussoulakou et al., 2009). These authors contend that teeth form (cardiform, villiform, incisor, canine and molariform) is strongly related to feeding habits. It is believed that mammal-like reptiles (Cynodonts) changed their teeth design to reflect their switch from catching and swallowing whole prey to a newer dentition meant for better mastication using cusps (Polly, 2000).

In essence, evolution favoured an increase in teeth complexity as seen in the diversity of cusps which provides for novel surfaces that can deal with an enormous variety of foods (Koussoulakou et al., 2009). Thus, while evolution selected for dental diversity, the number of teeth per dentition decreased. On one hand, the evolutionary journey from fish to reptiles to mammals was a classic switch from polyodonty to oligodonty (decrease in teeth numbers), but on the other hand, it was an increase in morphological complexity from homodonty to heterodonty (Koussoulakou et al., 2009). Some organisms develop teeth once in their lifetime (e.g. killer whales, rats and elephants) while others (e.g. turtles, birds, toothless whales and anteaters) have lost their dentition, a phenomenon known as adontia (Keränen et al., 1999).

Master molecules for tooth development: Four conserved molecular circuits

Odontogenesis is a complex process under tight genetic and molecular controls. Growth molecules such as the fibroblast growth factors (FGFs) and the bone morphogenetic proteins (BMPs), and transcription factors such as the wingless integrated (Wnt) and sonic hedgehog (Shh) proteins play a crucial role in tooth initiation, morphogenesis and differentiation (Thesleff, 2006). BMPs and FGFs, master molecules of odontogenesis, are expressed in both the ectoderm and ectomesenchyme, whereas Shh and Wnts are expressed only in the ectoderm (Klein et al., 2007).

According to Bei (2009), the conserved signalling pathways mediated by FGFs, BMPs, Wnt and Shh ligands and their receptors constitute the key pathways that are reiteratively invoked during tooth development. The plethora of molecules that underwrite odontogenesis (>300 genes and >100 transcription factors) and the intricacy of their interactions (activation, inhibition and

regulatory loops) frequently lead to homeostatic errors, which in turn result in congenital aberrations, such as tooth agenesis, the most commonly inherited tooth disorder (Koussoulakou et al., 2009). A summary of the master molecules that drive odontogenesis is as shown in Table 1.

Fibroblast growth factors

FGF is a representative growth factor family involved in the repair and regeneration of tissues (Yun et al., 2010). FGFs act as signal molecules that bind and activate FGF receptors (FGFRs). Activated FGFRs mediate signalling by recruiting specific molecules that bind to phosphorylated tyrosine at the cytosolic part of the receptor, cascading a number of signalling pathways leading to specific cellular responses (Yun et al., 2010). The FGF family comprises of 23 members, although, there are only 18 FGFR ligands (Yun et al., 2010). There are mesenchymal (FGF3 and FGF10) as well as epithelial (FGF4 and FGF9) FGFs (Klein et al., 2007).

For instance, the proximal dental epithelium secretes FGF8, which induces the expression of homeobox genes (*Pax9, Barx1, Dlx1* and *Dlx2*) that drive the construction of molariform teeth (Koussoulakou et al., 2009). Normal tooth development is also dependent on the presence of a functional enamel knot mediated by FGF4 and FGF9 (Klein et al., 2007). FGF4 protects neighbouring epithelial and mesenchymal cells from apoptosis (Koussoulakou et al., 2009). FGF4 and FGF9 activate the mesenchyme-specific “c” isoform of FGFRs and are thought to maintain *Fgf3* expression in the dental mesenchyme (Klein et al., 2007).

Loss of *Fgf3* function leads to defective enamel (Wang et al., 2007); hence, the FGF proteins play a critical role in controlling ameloblast development. Decreased FGF signaling leads to arrested tooth development at the bud stage (Celli et al., 1998), whereas increased FGF signaling (due to lack of an FGF antagonist) in *sprouty* (*spry*) null mice leads to several abnormalities in tooth development including the formation of supernumerary teeth in the diastema (Klein et al., 2007). The differential expression and tight control of FGFs is therefore paramount to the formation of normal dentition.

Bone morphogenetic proteins (BMPs)

BMPs are part of the TGF-β superfamily (Kingsley, 1994) and comprised of a large and evolutionarily conserved family of secreted signalling molecules that are required for numerous developmental processes including the development of teeth. BMP4 is secreted by the distal epithelium and serves a regulatory role by inhibiting FGF8 secretion, and by so doing produces localized sites that express *Pax9* and that express *Pax9* and specify where teeth will develop (Peters et al., 1998). BMP4 is necessary for normal tooth cyto-differentiation and maturation (Gluhak-Heinrich et al., 2010).

BMP4 also induces, in the distal mesenchyme, the expression of genes (*Msx1* and Msx2) that direct incisor formation (Koussoulakou et al., 2009). Increased expression of *Msx1* changes the developing tooth to an incisor (Plikus et al., 2005), but loss of *Msx1* arrests tooth development at the bud stage. A weak BMP signal, ensuing from a loss of BMP receptors or overexpression of BMP inhibitors, results in various defects in different cusps and teeth, suggesting differential requirements for the level of BMP signalling (Plikus et al., 2005). A lack of BMP4 signal leads to the down-regulation of *Msx1* expression and distal extension of *Barx1* into the incisor region (Neubüser et al., 1997). Down-regulation of the *Barx1* gene transforms the developing tooth to a molar (Plikus et al., 2005).

BMP4 signalling from the condensing mesenchyme mediates the induction of the enamel knot. Addition of BMP4 to the oral epithelium increases the production of enamel knot markers, such as p21 (Jernvall et al., 2000). Loss of BMP4 signalling in the dental epithelium by conditional knockout of the receptor *Bmpr1a* gene leads to arrest of tooth development at the bud stage, confirming the signalling role of BMP4 from the mesenchyme to the epithelium at this stage (Andl et al., 2004). Deletion of the *Bmp4* gene early in the odontogenic process leads to decreased expression of the *Dlx5* and *Osterix* genes in odontoblasts (Gluhak-Heinrich et al., 2010). *Dlx5* has been shown to regulate collagen type I (*col1*) transcription; thus, this could explain the decreased *col1a*1 expression seen in both the odontoblasts and associated osteoblasts in the periodontium (Gluhak-Heinrich et al., 2010).

Expression of *Msx1* and *Bmp4 genes is* closely linked during tooth development, acting as part of a positive feedback loop, and addition of BMP4 can partially rescue a tooth defect in *Msx1* mutant mice (Zhao et al., 2000). On the other hand, BMP4 and FGF8 negatively regulate each other so that loss of BMP4 function leads to an expansion of FGF8 action into the distal epithelium (Wilson and Tucker, 2004). This mutual antagonism acts to further delineate the boundary between the presumptive molar- and presumptive incisor-forming regions.

Wingless integrated (*Wnt*) gene family

Wnt proteins are a large family of about 19 secreted ligands that activate several receptor-mediated pathways (Logan and Nusse, 2004). Wnt signaling drives multiple stages of odontogenesis, from the initiation stage to tooth differentiation. Several *Wnt* genes are broadly expressed in oral and dental epithelium. Wnt pathways work through several mediators.

Table 1. Master genes that control odontogenesis.

Gene or protein	Function	References
FGF3	FGF3 induces primary enamel knots; *Fgf3*$^{-/-}$ mice display smaller molars with several morphological anomalies compared to wildtype and *Fgf3*$^{+/-}$ molars; *fgf3* expression plays an important role in dental development by controlling the size of teeth and regulating the number, position, and interrelation of cusps in molar teeth; humans carrying *fgf3* mutations have similar dental morphology to primitive primates	Charles et al. (2009)
FGF8	Induces expression of *Pax9*, *Barx1*, *Dlx1* and *Dlx2* homeobox genes in the proximal mesenchyme and direct the formation of molariform teeth; Required for postnatal tooth development; constitutes an epithelial inductive signal capable of inducing the expression of downstream signaling molecules in dental mesenchyme via Msx1	Catón and Tucker (2009)
FGF10	Important for formation and maintenance of stem cells in the development of incisors; essential for development of mouse incisors and maintenance of incisor cervical loops during prenatal development	Klein et al. (2008)
FGF23	An important hormone for maintaining phosphate homeostasis; seems to function as a vitamin D counter-regulatory hormone, the primary “phosphaturic” hormone, and in a bone–kidney axis to coordinate the renal phosphate handling and bone mineralization	Quarles (2003)
FGFR1/FGFR2	FGFR1 promotes proliferation of dental epithelial cells; ablation of *Fgfr2* genes in the dental epithelium leads to defective maxillary incisors that lack ameloblasts and the enamel; thus FGFR2 signaling axis plays a role in maintaining the constant supply of dental epithelial cells (from stem cell niches) required for incisor development and lifelong growth	Lin et al. (2009)
BMP2; BMP4	BMP2 and BMP4 stimulate odontoblast differentiation; BMP4 secreted by the distal epithelium induces in the distal mesenchyme the expression of genes (Msx1, Msx2, and Alx4) that direct incisor formation; thus BMP4 directs bone mineralization and incisor formation; BMP4 signaling from the condensing mesenchyme plays a critical role in the induction of enamel knot; BMP4 inhibits FGF8 secretion	Catón and Tucker (2009)
Wnt/β-catenin	Wnt signaling is required early in tooth germ formation and interference with signaling via addition of an antagonist results in retarded development and formation of smaller teeth; mutation of β-catenin causes formation of large, misshapen teeth buds and ectopic teeth; forced activation of Wnt/β-catenin signaling promotes the formation of ectopic teeth; thus Wnt/β-catenin initiates tooth neogenesis and promotes continuous tooth development when activated in embryos	Liu and Millar (2010)
Shh	Involved in lateral and planar signaling in early tooth development; up-regulation of shh activity causes the formation if ectopic premolar-shaped teeth in the diastema, mesial to the first molars; act as a morphogen involved in the patterning of teeth	Ohazama et al. (2010)

For instance, expression of *Eda,* a Wnt signaling mediator, is regulated by the Wnt family of proteins (Laurikkala et al., 2001). If Wnt signalling is blocked at the early bell stage when the secondary enamel knots are forming, the expression of *Eda* is reduced and molars form with flattened cusps (Liu et al., 2008). Wnt signaling is therefore important in the development of molar cusps (Liu et al., 2008).

But *Eda*, when overexpressed, leads to the formation of supernumerary teeth. Thus, overexpression of the canonical Wnt signaling, either through loss of function of its inhibitors or by overexpression of its effectors, leads to supernumerary teeth (Bei, 2009). Multiple teeth have also been shown to arise from the molar field in mice where *β-catenin* has been overexpressed (Jarvinen et al., 2006). The number of teeth that can develop from the molar field, therefore, would appear to be restricted by Wnt signalling.

Sonic hedgehog (Shh) signalling

The Shh protein is secreted by the epithelium and then signals to the underlying mesenchyme (Hardcastle et al., 1998). Shh signalling acts as a mitogen during early growth of the tooth germ (Cobourne et al., 2001). High levels of Shh in odontogenic epithelium arrests tooth development at the bud stage and increased Shh signalling in the epithelial component causes hypodontia (Cobourne et al., 2009). Inhibition of Shh pathways after the early epithelial-thickening stage stops tooth development, inhibition of Shh at the bud stage results in malformed teeth, and later inhibition of Shh at the bell stage affects the timing of tooth growth (Jackman et al., 2010).

Control of tooth position involves a combination of Shh signalling at initiation sites and antagonism in edentulous regions, such as the mouse diastema (Cobourne et al., 2004). Shh is also part of a molecular pre-pattern for the serial induction of sequential cusps on the mouse molar, predicting the cusp topography more than a day in advance in muroid rodents (Jernvall et al., 2000). Temporal and spatial differences in Shh expression dictate the order of appearance and spacing of teeth (Smith et al., 2009). In fact, profiling Shh expression provides information on progressive pattern formation of the dentition, especially for timing and location of tooth loci, and for timing and position of tooth cusps (Smith et al., 2009). Furthermore, the Shh pathway plays a critical role in ameloblast differentiation, the cells that co-ordinate enamel formation (Ohazama et al., 2010). Scaling down of Shh activity in postnatal ameloblasts leads to localized loss of enamel (Ohazama et al., 2010).

Shh signal networks with other pathways. *Shh* expression in the enamel knot is induced and maintained by signaling from mesenchyme to epithelium via FGF3 and FGF10 (Kratochwil et al., 2002). BMP4 inhibits *Shh* expression in tooth primordia (Zhao et al., 2000). The BMPs appear to inhibit growth in two ways: by affecting the Shh and/or FGF signaling pathways and by promoting cell cycle arrest (Peterkova et al., 2009). The expression of *Fgf8* and *Bmp4* in the oral epithelium is initially induced by *Shh* signalling from the pharyngeal endoderm during pharyngeal arch formation (Haworth et al., 2007; Brito et al., 2008). At the same time, Lrp4 is a direct mediator of both Wnt and Bmp signaling and an indirect mediator of Shh (Ohazama et al., 2010). Mice with a null mutation of *Lrp4* develop extra cusps on molars and have incisors that exhibit clear molar-like cusp and root morphologies (Ohazama et al., 2010).

Homeobox genes that mediate odontogenesis

Table 2 shows an inventory of homeobox genes that function during odontogenesis. These genes are *Barx1*, *Dlx1*/*Dlx2*, *Pax9*, *Pitx1/Pitx2* and *Msx1*. *Barx1* and *Dlx* genes direct the formation of molars; *Pax9* makes odontogenesis proceed beyond the bud stage; *Pitx* is essential for cusp formation; and *Msx1* works through BMP4 to amplify the signal for incisor development.

Secondary molecules that mediate odontogenic networks

Table 3 presents details of about 37 different molecules (mostly transcription factors) that mediate tooth development. Briefly, some of these molecules are involved in enamel formation and mineralization (Eda, ENAM, amelin, amelogenin, FoxJ1, Ae2, p120, GEP, Col17, p21, Eve1, Nr0b1, Phex and Tbx), tooth morphogenesis and differentiation (Prx, Six, DMP1, cadherins, Runx2, Dspp, Notch and csCSF1) and teeth patterning (Lhx, Lrp4 and Nfic). The protein HERS mediates the formation of cementum; Spry genes are negative regulators of FGF; Islet-1 and p21 mediate BMP4 expression; Lef-1 and Dact1-3 relay Wnt signals; Alk8 and microRNAs regulate mesenchymal tooth tissues; Osr2 defines the tooth morphogenetic space; Gli genes are required for normal teeth development; and Activin βA is necessary for the formation of incisors and mandibular molars.

CONCLUSION

This review discusses several genes and protein molecules that mediate odontogenesis at various stages. It is clear that several gene networks and signalling molecules are invoked at different stages of odontogenesis, thus bringing about multiple tooth phenotypes. The major genetic circuits are under the control of the BMP, FGF, Wnt and Shh molecules. Odontogenesis is also regulated by the homeobox genes

Table 2. Homeobox genes that regulate odontogenesis.

Barx1	If Barx1 is mis- expressed in the presumptive incisor region, the tooth germs that develop in the presumptive incisor region will develop as molars with the formation of multiple cusps; Barx1 is a key molar determinant; *Barx1* is a gene that has a direct role in directing predental ectomesenchymal cells to follow a morphogenetic pathway leading to multicuspid tooth development	Miletich et al. (2005)
Dlx1/Dlx2	Expressed in first branchial arch prior to initiation of tooth development; if Dlx1 and Dlx2 are knocked out in mice, then molars fail to develop in the maxilla but incisors and mandibular molars still form; loss of both *Dlx1* and Dlx*2* results in complete agenesis of maxillary molars, whereas mandibular molars and incisors appear normal; Dlx2 and FoxJ1 also activate the amelogenin promoter, and amelogenin is required for enamel formation and late stage tooth development; Dlx1/Dlx2 are important in the development of upper molar teeth; Dlx3 is important for ondotoblast polarization and dentin formation; deletion of Dlx3 is etiologic for Tricho-dento-osseous (TDO) syndrome, an autosomal dominant disorder characterized by abnormalities in the thickness and density of bones and teeth	Choi et al. (2010) and Venugopalan et al. (2011)
Pax9	*Pax* genes play important roles in mammalian development and organogenesis; *Pax9* is required for tooth development to proceed beyond the bud stage; *Pax9* is required for the mesenchymal expression of *Bmp4, Msx1,* and *Lef1,* suggesting a role for *Pax9* in the establishment of the inductive capacity of the tooth mesenchyme; lack of canines and premolars in the mouse upper diastema is due to weak expression of *Pax9* gene	Peters et al. (1998)
Msx1	Loss of either Msx1 causes the arrest of tooth development at the bud stage; Msx1 is most likely a presumptive incisor marker, expressed in the distal part of the jaw; mice lacking *Msx1* exhibit loss of *Bmp-4* expression in the dental mesenchyme and molar developmental arrest at the bud stage; thus Msx1 amplifies the Bmp-4 tooth-generating signal; mutations in *Pax9/Msx1* genes cause non-syndromic oligodontia	Catón and Tucker (2009) and Li et al. (2009)
Pitx1; Pitx2	Loss of *Pitx1* function leads to a reduction of the cusps in the mandibular molars, thus changing the shape of the tooth, with molars taking on a more premolar appearance; Pitx2, a homeodomain transcription factor, is the earliest marker of tooth development, and it may be possible that it regulates signaling molecules and transcription factors expressed in the early dental epithelium; Pitx2 is essential for normal development of teeth, and *Pitx2* mutation causes Axenfeld-Rieger syndrome, a human genetic disorder characterized by dental hypoplasia; Pitx2 activates and may be required for the sustained expression of *Lef-1*, which is absolutely required for later stages of tooth development	Venugopalan et al. (2011)

and mediated by several transcription factors and ligands. These molecules work by activating or inhibiting specific odontogenic genes at various stages of tooth initiation, differentiation and morphogenesis. Genetic aberrations during odontogenesis may occur from time to time, and this might result in unusual dentition. Givenadvances in technology, it will not be surprising if more genes and signalling molecules are unravelled in the near future. This will increase our knowledge of teeth development, and possibly open new vistas to treat

Table 3. Secondary molecules that mediate various odontogenic pathways.

Eda; Edar; Edaradd	Missense mutations in *Eda* are associated with tooth agenesis; causes congenital oligodontia inherited in X-linked manner; high levels of Eda lead to supernumerary teeth (pre-molar-like) and low Eda activity leads to missing molars; loss of Edar, Edaradd and Eda leads to defects in the enamel knot; loss of Eda leads to fewer, reduced cusps and fewer, smaller teeth; Edar causes shovel-shaped incisors	Kimura et al. (2009)
ENAM gene/enamelin	*ENAM* gene provides instructions for making enamelin, a protein essential for the formation of enamel	Smith et al. (2009)
Ameloblastin/amelin	Ameloblastin cell layer is adjacent to and responsible for enamel formation; directs enamel mineralization; enhances pulp repair and cementum regeneration; truncated ameloblastin causes dental and junctional epithelium defects	Hu et al. (2008) and Wazen et al. (2010)
Amelogenin	Amelogenin (AMG) is a protein found in developing tooth enamel, and it belongs to a family of extracellular matrix proteins. Deletion of AMG causes amelogenesis imperfecta and abnormal formation of enamel; thus amelogenin protein has a role in biomineralization of tooth enamel	Barron et al. (2010)
FoxJ1	Expressed in ameloblasts and odontoblasts; it is a transcription factor in embryonic development and differentiation; together with Dlx2, it activates the transcription of amelogenin; *FoxJ1(-/-)* mice maxillary and mandibular incisors are reduced in length and width and have reduced amelogenin expression; *FoxJ1(-/-)* mice show a reduced and defective ameloblast layer	Venugopalan et al. (2011)
Zmpste24	*Zmpste24*-deficient mice had dental dysplasia features such as reduced cusps in molars, shorter and more curved/thicker teeth, and smaller ameloblasts	de Carlos et al. (2008)
Ae2 protein	Anion exchanger Ae2 protein is involved in pH regulation during maturation stage amelogenesis; thus Ae2 is required for enamel maturation; disruption of Ae2 leads to poorly formed bone and the failure of teeth to erupt	Lyaruu et al. (2008)
p120	p120-mediated cadherin stability is important for dental enamel formation; p120 directs the attachment and detachment of the secretory stage ameloblasts as they move in rows	Bartlett et al. (2010)
GEP	GEP plays an important role in amelogenesis and tooth formation during postnatal development; the hypothesis is that GEP acts as a local growth factor which controls the expression levels of DSPP, ALP, DMP1, AMELX, ENAM and AMBN during postnatal tooth development	Cao et al. (2010)
Col17	*Col17* deficiency disrupts the epithelial-mesenchymal interactions, leading to both defective ameloblast differentiation and enamel malformation; $Col17^{-/-}$ mouse incisors have poorly differentiated ameloblasts that lack enamel protein-secreting Tomes' processes and reduced mRNA expression of amelogenin, ameloblastin, and of other enamel genes	Asaka et al. (2009)

Table 3 Cont.

p21	Target of Bmp signaling; the expression of p21 in the enamel knot is followed by Bmp-4 expression, and subsequently by apoptosis of the differentiated enamel knot cells; p21 transcripts were detected in the restricted area of the inner dental epithelium during late cap and initial bell stages and then confined to the post-mitotic odontoblasts and ameloblasts; p21 inhibits cyclin-dependent GI kinases and does not allow enamel knot cells to enter the S-phase; therefore p21 facilitates the elimination of enamel knot cells by apoptosis	Catón and Tucker (2009)
Eve1; Nr0b1	*Eve1* has been shown to be associated with the primary tooth and early ameloblast development, the enamel organ precursor; *Nr0b1* is an early marker for ameloblastoma formation and tooth development, being expressed in the fifth branchial arch 10 hours earlier than *Pix1* during embryogenesis; thus these genes co-promote primary tooth development in zebra fish	Powers et al. (2009)
Phex	Loss of *Phex* function is related to a defect of type II sodium-dependent phosphate co-transporter (Npt2) expression in teeth; *Phex* mutation causes a disorder in phosphate homeostasis, and display hypomineralization in bones and teeth; *Phex* mutation causes over-expression of FGF23 in teeth	Onishi et al. (2008)
Tbx1	A transcription factor essential for the maintenance of ameloblast progenitor cells in incisors and its deletion results in the absence of enamel formation	Catón et al. (2009)
Prx1, Prx2	Critical for molar tooth morphogenesis; loss of function leads to medially located incisor; *Prx1*(-/-) *Prx2*(-/-) mutants have reduced expression of Shh and abnormal morphogenesis of the mandibular arch	Mitchell et al. (2006)
Six1, Six2, Six4, Six5	Six family genes may participate in tooth germ morphogenesis and the proliferation and/or differentiation of the incisor ameloblast stem/progenitor cells	Nonomura et al. (2010)
DMP1	DMP1 initiates osteoblast differentiation by transcription in the nucleus and orchestrates mineralized matrix formation extracellularly, at later stages of osteoblast maturation; produced by osteoblasts and osteocytes, DMP1 regulates cell attachment and cell differentiation, activates matrix metalloproteinase-9, and affects biomineralization; mice that are null for Dmp1 develop a bone phenotype characterized by hypomineralization	Turan et al. (2010)
Cadherins	E-cadherin is involved in the differentiation and function of the ameloblasts and other cells supporting amelogenesis; N-cadherin is important for odontoblast function in normal development and under pathological conditions	Heymann et al. (2002)
Runx2	Transcription factor *Runx2* is necessary for osteoblast and odontoblast differentiation and regulates many bone- and tooth-related gene expressions; *Runx2* determines the lineage of osteoblasts and odontoblasts from mesenchymal cells; persons with *Runx2* gene mutations display dental disorders, with supernumerary teeth, abnormal tooth eruption, and tooth hypoplasia; *Runx2* and *Osx* are necessary for osteoblast and odontoblast differentiation	Chen et al. (2009)

Table 3 Cont.

Dspp	*Dspp* is important for odontoblast differentiation; *Dspp* provides instructions for making a protein called dentin sialophosphoprotein which is cut into two smaller proteins (DPS and DSP) that are essential for normal tooth development	Chen et al. (2009)
Notch	Notch proteins are cell surface transmembrane-spanning receptors that initiate a signaling cascade that governs cell fate decisions such as differentiation, proliferation, and apoptosis in numerous tissue types; Notch up-regulation in pulp cells represents one of the early molecular events in the process of dental tissue repair; during tooth development, Notch signaling is associated with the differentiation of dental epithelial and mesenchymal cells and is also involved in the regulation of the stem cells in the continuously growing incisor	Mitsiadis and Smith (2006)
csCSF-1	Cell surface CSF-1 is important for optimal cyto-differentiation and dentin matrix protein expression; it indirectly or directly regulates DMP1; expression of csCSF-1 within the tooth microenvironment is essential for normal tooth morphogenesis and may provide a mechanism for coordinating the process of tooth eruption	Werner et al. (2007)
Lhx6, Lhx7	Critical for craniofacial development and patterning of mammalian dentition; control the patterning of the first branchial arch and odontogenesis	Denaxa et al. (2009)
Lrp4	Lrp4 integrates Bmp and Wnt signaling during tooth development by binding the Bmp antagonist Wise; loss of Lrp4 activity suppresses a developmental program for cuspid crown-like morphogenesis in incisors; Lrp4 is important for maintaining the simple shape of incisors by suppressing cusp formation; Lrp4 via its action on multiple signaling pathways including Shh, Bmp, and Wnt is central to transition between a continuous enamel covering, grooved enamel, and folded enamel	Ohazama et al. (2010)
Nfic	Disruption of *Nfic* causes loss of molar root formation with apparently normal crown formation and severe mandibular incisor disruption with milder maxillary incisor defects; loss of Nfic leads to the suppression of odontogenic cell proliferation and differentiation and induces apoptosis of aberrant odontoblasts during root formation, thereby contributing to the formation of short roots	Lee et al. (2009)
HERS	Participates in cementum development and may differentiate into cementocytes; interact with cranial neural crest derived mesenchyme to guide root development	Huang et al. (2009)
Spry 2, Spry4	Genes of the *Sprouty* (*Spry*) family encode negative feedback regulators of fibroblast growth factor (FGF) and other receptor tyrosine kinase signaling molecules that repress diastema tooth development	Klein et al. (2007)
Islet-1	Mis-expression of Islet-1 in the epithelium overlying the molar region leads to ectopic expression of Bmp4, loss of molar markers in the underlying mesenchyme, and leads to failure in molar development	Catón and Tucker (2009)
Lef-1	Lef1 is a cell-type-specific transcription factor and mediates Wnt signaling pathway by association with its co-activator β-catenin; loss of Lef1 results in arrested tooth development at the late bud stage meaning Lef1 is required for a relay of a Wnt signaling to a cascade of FGF signaling activities to mediate the epithelial-mesenchymal interaction during tooth morphogenesis; Lef1 null mutant mice show a significant increase in apoptotic activity within the dental epithelium	Noh et al. (2009)

Table 3 Cont.

Dact1-3	Contribute to early tooth formation by modulation of Wnt signaling	Kettunen et al. (2010)
Alk8	Essential for dental epithelial and mesenchymal tooth tissues in developing primary and replacement teeth in zebra fish	Chung et al. (2010)
MicroRNAs	Specific microRNAs regulate tooth epithelial stem cell differentiation; thus tooth development is tightly controlled by microRNAs in dental mesenchyme	Cao et al. (2010)
Osr2	*Osr2* knockout mice develop teeth outside of the normal tooth row; thus the tooth morphogenetic field is shaped and restricted by the effect of *Osr2* on the expression of the *Bmp-4* gene within the mesenchymal cell layer; mice lacking both Msx1 and Osr2 grow the first molars, but no additional teeth; thus, without Osr2, enough Bmp-4 was expressed for the first molar teeth to grow, but without Msx1, the bmp4 signal was not amplified to the point where it could kick off the next tooth in the row	Zhou et al. (2011)
Gli1, Gli2, Gli3	Gli1 and Gli2 regulate a similar set of genes; Gli2 mutants were found to have abnormal development of maxillary incisors; Gli2/Gli3 double homozygous mutants did not develop any normal teeth and did not survive beyond embryonic day 14.5; however, Gli2(-/-); Gli3(+/-) did survive until birth and had small molars and mandibular incisors whereas maxillary incisor development was arrested as a rudimentary epithelial thickening	Hardcastle et al. (1998)
Activin βA	Null mutations lead to bud stage arrest, and lack incisors and mandibular molars	Matzuk et al. (1995)

odontogenic disorders.

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