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REVIEW



# The Genes Involved in Dentinogenesis

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**ABSTRACT**

The development and repair of dentin are strictly regulated by hundreds of genes. Abnormal dentin development is directly caused by gene mutations and dysregulation. Understanding and mastering this signal network is of great significance to the study of tooth development, tissue regeneration, aging, and repair and the treatment of dental diseases. It is necessary to understand the formation and repair mechanism of dentin in order to better treat the dentin lesions caused by various abnormal properties, whether it is to explore the reasons for the formation of dentin defects or to develop clinical drugs to strengthen the method of repairing dentin. Molecular biology of genes related to dentin development and repair are the most important basis for future research.

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## Introduction

Dentin constitutes the main body of the tooth and is located in the inner layer of enamel and cementum, the side wall of the pulp cavity and root canal. Dentin acts as a barrier to prevent exposure of the dental pulp, reduce the conduction of hot and cold stimuli to the pulp, and protect the living pulp. In addition, it also provides a hard tissue foundation for later dental restoration.

Odontoblasts are the only known cells that form dentin, and they are involved in the synthesis of primary, secondary, and reactionary dentin. A recent study showed that odontoblasts activate the innate immune response in the pulp.[1] Although the function of odontoblasts is unique, studies have not advanced new information likely because they are end-stage differentiated cells that are difficult to isolate and culture. To study the dentin formation process, it would be necessary to study gene regulation during the development and migration of odontoblasts.

In this review, we present information on 300 genes involved in dentinogenesis (Table 1) and to date, the related regulatory processes of dentinogenesis has not been fully elucidated. However, new signaling molecules and transcription factors have recently been identified and shown to constitute a complex signaling network that participates in dentin formation. Understanding and mastering this signal network is of great significance to the study of tooth development, tissue regeneration, aging, repair and the treatment of dental diseases.

### *Extracellular matrix proteins and related*

Extracellular matrix (ECM) proteins could be directly involved in the construction of dentin because the mutation, deletion, or abnormal regulation of these proteins often leads to serious dentin-related diseases. Presently, all ECM proteins have been identified; however, their functional regulation still needs to be comprehensively studied. Furthermore, new regulatory mechanisms and key regulatory molecules are still being discovered.

Osteogenesis imperfecta (OI) with systemic skeletal dysplasia is a genetic systemic connective tissue disorder involving the bone, dentin, sclera, ear, blood vessels, skin, and other tissues. Type I collagen (*COL1*) gene mutations(COL1A1 and COL1A2)[2,3,4] are the main cause of this disease.

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Bone and dentin have similar mineralization processes, during which osteoblasts and odontoblasts first secrete unmineralized matrices termed osteoid and anterior dentin, respectively. The organic component of osteoid and anterior dentin consists of an ECM primarily composed of COL1 and several non-collagen proteins that play essential roles in the mineralization of collagen fibers during the conversion of osteoid and anterior dentin to bone and dentin, respectively.[9] Bone- and odontoblast-expressed gene 1 (*Bono1*) is a gene expressed in functional odontoblasts that is associated with regions of matrix mineralization.[31] BSP may play an important role in the formation and mineralization during dentinogenesis.[9]

Dentin sialoprotein (DSP) and dentin phosphoprotein (DPP) are encoded by dentin sialophosphoprotein (Dspp) and its deficiency may lead to dentin hypoplasia or dysplasia and opalescent, shell, and abnormal deciduous teeth with short roots. Therefore, Dspp is an important marker of odontoblasts[6] and is the first direct target of distal-less homeobox 3 (Dlx3), which was identified in odontoblasts.[7]

In addition, TM14 has significant roles in the differentiation and maintenance of odontoblasts, and in dentin formation.[8] As a nucleus, bone sialoprotein (BSP) promotes crystal formation and in developing teeth it is well documented to form acellular cementum and periodontal attachments. However the expression and function of BSP in odontoblasts and dentin are uncertain.[9] Dentin matrix acidic phosphoprotein 1/2 (Dmp1/2) participates in odontoblast differentiation and dentin formation.[10,11] Rat Dmp3 is a compound protein of rat DSP and phosphophoryn.[12] The formation of Dmp4 affects the growth and arrangement of hydroxyapatite crystals and promotes the differentiation of osteoblasts, ameloblasts, and odontoblasts.[13]

Matrix metalloproteinase 1 (MMP1) regulates tooth agenesis; MMP2 causes multiple cleavages near the DSP C terminus, releasing larger forms of DGP; and MMP8 may be involved in the alteration of dentin matrix during the development of human and rat tooth germ. In addition, MMP9 is important for tooth development and targets DSP during dentinogenesis, whereas MMP14 functions in tooth root formation, dentinogenesis, and tooth eruption. Furthermore, MMP20 cleaves DSP-DGP to generate DSP and DGP, and MMP1, 2, 9, 10, 11, 13, 14, 15, 16, 17, 19, 20, 23, 24 and 25 are expressed in odontoblasts.[18–20]

The dentin organic matrix is secreted by odontoblasts during dentinogenesis and mineralized in the predentin area.[149] In dental attrition, hardened molds and highly mineralized layers were detected in sclerotic dentin. During the process of sclerotic dentin formation and long-term aging, the MMP content in dentin changes.[150] The process of dentinogenesis is similar to bone formation and many genes are involved in both processes.

Runt-related transcription factor 2 (Runx2) participates in dentin formation, mineralization, and the development of odontoblasts.[32] Runx2 is also essential for the differentiation of osteoblasts and odontoblasts, and it regulates the expression of numerous bone- and tooth-related genes. Runx2 determines the lineage of osteoblasts and odontoblasts in the mesenchymal cells. Osterix (*OSX*), a downstream gene of Runx2 in the osteoblast differentiation signaling pathway, is involved in the differentiation, maturation, and intercellular signal transduction of odontoblasts.[41] Osteoprotegerin (OPG) is expressed in both the thickened and bud epithelium, as well as in combination with receptor activator of nuclear factor-κB (RANK) in both the enamel and papillary stroma. Although RANK ligand (RANKL) was not detected in the tooth epithelium or mesenchyme, it was expressed in pre-osteogenic mesenchymal cells near the developing tooth germ.[46]

### Mineralization related pathway

Followed by the pre-section, we reviewed some key proteins related with odontoblasic differentiation or dentinogenesis. In further, the mineralization related pathways those could upregulate the mentioned proteins also can affect odontoblastic differentiation.

### Wnt signaling pathway

The Wnt signaling pathway could currently be considered the most thoroughly studied pathway and drug research related to dentin regeneration has also achieved significant breakthroughs recently. However, the involvement of the Wnt

**Table 1.** The genes involved in dentinogenesis.

| Pathway | Gene | Main function in dentinogenesis |
|---|---|---|
| Extracellular matrix proteins and related | COL1A1/2, COL2A1, COL4A1/2/3/4/5/6 | The COL1A1/2 [2,3] and COL2A14 mutation results in dentinogenesis imperfecta; Type IV collagen alpha subunits occur during molar germ development and that these changes are essential for molar morphogenesis and cytodifferentiation.5 |
| | DSPP, DPP, DSP, DGP | Dentin hypoplasia or dysplasia. It is an important marker of odontoblast.[6] |
| | DLX3 | Deletion of Dlx3 leads to major dentin defects through down-regulation of Dspp.[7] |
| | TM14 | Mainly expressed in odontoblasts,and participates in the formation and mineralization of dentin.[8] |
| | BSP | As the crystal nucleus, promotes the crystal formation, and participate in dentinogenesis.[9] |
| | Dmp1/2/3/4 | Dmp1/2 participates in the differentiation and dentin formation of odontoblasts.[10,11] Rat Dmp3 is a compound protein of rat DSP and phosphophoryn.[12] Dmp4 forms and affects the growth and arrangement of hydroxyapatite crystals, and promotes the differentiation of osteoblasts, ameloblasts and odontoblasts.[13] |
| | EMILIN-1/2/3 | EMILIN-1 and −2 staining appears to increase in the pre-dentin and in the ECM surrounding odontoblasts. EMILIN-3 was significantly increased in inflamed odontoblasts.[14] |
| | SSUH2 | Decrease of collagen in the teeth of mice, which makes the dentin mineralization abnormal.[15] |
| | GRP78 | SSUH2 binds to the Dank domain of GRP78 through DanJ, which affects the transport of collagen and DMP1, there by affecting the mineralization of teeth.[16] |
| | Sulf1/2 | Sulf1/Sulf2 double null mutant mice exhibit a thin dentin matrix and short roots.[17] |
| | MMP1/2/7/8/9/10/11/13/14/15/16/17/19/20/23/24/25 | MMP1 regulate tooth agenesis; MMP2 makes multiple cleavages near the DSP C terminus, releasing larger forms of DGP; MMP8 may be involved in the alteration of dentin matrix during the development of human and rat tooth germ; MMP9 is important for tooth development and DSP is a target of MMP9 during dentinogenesis; MMP14 functions in tooth root formation, dentinogenesis, and tooth eruption; MMP-20 cleaves DSP-DGP to generate DSP and DGP; MMP1, 2, 9, 10, 11, 13, 14, 15, 16, 17, 19, 20, 23, 24 and 25 expressed in odontoblasts.[18–20] |
| | TIMP1/2/3 | Expression was detected in odontoblasts.[21] |
| | Osteocalcin | Both crown and root odontoblasts and dentin stained for Osteocalcin.[20] |
| | Osteonectin | Osteonectin was present mostly in the nonmineralized predentin.[22] |
| | MEPE | It plays an important role in the formation of dentinal tubules and pulpal homeostasis.[23] |
| | PHEX | A decrease in PHEX expression could suppress dentin formation.[24] |
| | Versican, Decorin, Appican, Biglycan, Glypican, Syndecan-1/3 | Decorin, biglycan, syndecan-1 and syndecan-3 showed gene expressions overlapping with OASIS. Especially the expression pattern of decorin and syndecan-3 coincided temporally and spatially exactly with that of OASIS.[25] |
| | Tenascin | Association with dentinal tubules, particularly prominent in the tooth crown.[26] |
| | Tuftelin | Tuftelin could be secreted by preodontoblast cells and preameloblast cells.[27] |
| | Reelin | Reelin may promote adhesion between dental nerve endings and odontoblasts.[28,29] |
| | S100-A7 | S100-A7 released from dentin by MMP20 might play a key role in dentin pulp regeneration.[30] |

(*Continued*)

**Table 1.** (Continued).

| Pathway | Gene | Main function in dentinogenesis |
|---|---|---|
| Mineralization related pathway | Bono1 | Expressed in functional odontoblasts and was associated with regions of matrix mineralization.[31] |
| | Runx2 | Participation in dentin formation, mineralization, and development of odontoblasts.[32] |
| | Msx2 | Msx2 expressed in the odontoblast.[33] |
| | PAX9 | Tooth agenesis.[34] |
| | Opn | Essential for type I collagen secretion in reparative dentin.[35] |
| | Vdr | Vitamin D receptors deficiency compromises dentin maturation.[36] |
| | Smpd3 | Deletion of smpd3 induces dentinogenesis imperfecta in mice.[37] |
| | Osad | Osad may play an important role during tooth development and biomineralization of dentin.[38] |
| | SOST | Sclerostin deficiency hastened reparative dentinogenesis after pulp injury.[39] |
| | ANKH | Direct mineralization in cementum and likely other mineralized tissues.[40] |
| | OSX | Involved in the differentiation, maturation and intercellular signal transduction of odontoblasts.[41] |
| | SMOC2 | Dentin dysplasia, small teeth, missing teeth.[42] |
| | CCN2 | Associated with reparative dentinogenesis.[43] |
| | PACE4 | PACE4 plays a crucial role in dentinogenesis, especially via the activation of BMPs.[44] |
| | Alp/Alpl | Tooth mineralization.[45] |
| | RANK/RANKL | Associated with delayed permanent tooth emergence and tooth development.[46] |
| | OPG | Resulted in reduced mineralization.[46] |
| Wnt Signaling Pathway | Timp1 | Play crucial roles in reactivation of immature pulp cells for tertiary dentinogenesis.[47] |
| | CTNNB1 | Tooth agenesis.[48] |
| | APC | Supernumerary tooth; Odontoma.[49] |
| | Kremen1 | Ectodermal dysplasia including oligodontia.[50] |
| | LRP6 | Oligodontia.[51] |
| | Axin2 | Axin2-expressing cells differentiate into new odontoblast-like cells that secrete reparative dentine.[52] |
| | Ctbp1 | Hypotonia.[53] |
| | SFRP2 | Key factor in maintaining cell survival following dentinogenic commitment.[54] |
| | Lef1 | Play a key role in odontoblast differentiation through regulating Dspp expression.[55] |
| | Wnt1/2/3a/4/5a/5b/6/7a/7b/8a/8b/9b/10a/10b/11/13/14/16 | Tooth agenesis.[56,57] mediation of dentinogenesis.[58,59] |
| | VPS4B | Regulate tooth development.[60] |
| Shh Signaling Pathway | Shh | Shh regulates growth and determines the shape of the tooth.[61] |
| | Ptch1/2 | Regulate teeth stem cell maintenance and differentiation.[62] |
| | MSX1/2 | Msx1 and Msx2 play a major role in tooth formation.[63] |
| | Gli1/2/3 | $Gli1^{+}$ cells in mature teeth appear to contribute to the regeneration of dental pulp and periodontal tissues. Gli2 mutants were found to have abnormal development of maxillary incisors, whereas Gli3 mutants had no major tooth abnormalities. Gli2/Gli3 double homozygous mutants did not develop any normal teeth.[64,65] |
| | Sufu | Modulating the tooth germ morphogenesis during the bud-to-cap stage transition.[61] |
| | Nfic | Nfic has an essential role in tooth root formation.[66] |
| | Kif3a | Kif3a-deficient mice results in tooth dysplasia.[67] |

(*Continued*)

**Table 1.** (Continued).

| Pathway | Gene | Main function in dentinogenesis |
|---|---|---|
| TGFβ Signaling Pathway | TGF-β | Matrix formation and pulpal obliteration.[68] |
| | Activin βA | Activin βA by follistatin may allow odontoblast terminal differentiation to occur.[69,70] |
| | Follistatin | Activin-follistatin system regulates odontoblast differentiation during tooth development.[69] |
| | Islet1 | Exclusively expressed in epithelial cells of the developing incisors during odontogenesis.[71] |
| | Ectodin | Ectodin inhibited the activity of BMP2, BMP4, BMP6, and BMP7.[72] |
| | BMP1/2/3/4/5/7/9 | Play a crucial role in organogenesis, including tooth development.[73,74] Participates in the process of cell differentiation, mineralization and dentinogenesis.[75] |
| | KLF4 | Klf4 promotes dentinogenesis and odontoblastic differentiation via modulation of TGF-β signaling pathway and interaction with histone acetylation.[22] |
| | p300, HDAC3 | p300- and HDAC3-regulated odontoblast differentiation through upregulating histone acetylation.[76] |
| Notch Signaling Pathway | Notch 1/2/3 | Upregulation of Notch signaling pathway after tooth injury.[77] |
| | TSPEAR | Mutations in TSPEAR, encoding a regulator of Notch signaling, affect tooth morphogenesis.[78] |
| | DLK1 | Inhibited the odontoblastic differentiation of hDPSCs.[79] |
| TNF Signaling Pathway | Eda, Edar, Edaradd | Tooth agenesis.[80] |
| | Traf6 | Regulate cuspal morphogenesis.[81] |
| | TNFRSF19 | Expressed in an overlapping domain with Edar in the tooth.[82] |
| Ion channel | Nav1.1/1.2/1.3/1.4/1.5/1.6/1.7/1.8/1.9 | Nine voltage-gated sodium channels are all expressed in odontoblasts, and their expression location depends on the tooth position and tooth maturity. Related to tooth sensitivity.[83] |
| | TRPC1/2/3/4/5/6/7 | TRPC1-7 belongs to the calcium channel family and were mainly expressed in odontoblasts.[84] |
| | CLCN1/2/3/4/5/6/7 | Regulated tooth development through effects on cell proliferation and cell cycle signal pathway.[85] |
| | TRPM3/7/8 | Both odontoblasts and dental pulp cells express TRPM channels in rat, mouse and human tooth.[86] |
| | Piezo1/2 | Expressed in odontoblasts.[87] |
| | TRPV1/2//3/4 | TRPV1/2//3/4 channels expressed in odontoblasts.[88] |
| | P2X3/4/5/7, P2Y1 /2/4/6/11/12/13/14 | Extracellular ATP activates P2 receptors and downstream signaling events that induce cell odontogenic differentiation.[89] |
| | AQP4/5 | AQP4 and AQP5 immunostaining was observed in the odontoblasts and their processes.[90] |
| | AHR | Tooth mineralization.[91] |
| Growth factor | FGF1/2/3/4/7/8/9/10/11/12/13/15/17/20, FGFR1/2/3 | Function in dentinogenesis.[92–96] |
| | COUP-TFII | Matrix mineralization in odontoblast-lineage cells.[97] |
| | β2AR | The sympathetic nervous system decreases tertiary dentin formation via β2AR.[98] |
| | PTH/PTHrP/PTH1R | Essential signal in the formation of the eruption pathway.[99] |
| | IGF-1 | IGF-1 can weaken odontogenic differentiation and dentinogenesis capability.[100] |
| | EXT-1 | Function in the dentin formation.[101] |
| | Oxytocin | Promote odontoblast-like cell differentiation, resulting in increased dentin formation.[102] |
| | IGFBP5/6/7 | IGFBP5/6/7 may play independent and redundant regulatory roles in late-stage odontogenesis.[102] |

(*Continued*)

**Table 1.** (Continued).

| Pathway | Gene | Main function in dentinogenesis |
|---|---|---|
| Stress response | HSP25/70 | Hsp25 is involved in reinforcement of the cell layer following cell movement during odontogenesis. Hsp70 might play an important role during reparative dentin formation.[103] |
| | Ape1 | Promote the odontogenic differentiation capacity.[104] |
| | DRP1 | DRP1 inhibition accelerates dentin formation through mitochondrial elongation and activation.[105] |
| | MTCO2 | Age-related changes marker in odontoblasts.[106] |
| | PPARα/γ | Active PPARα signaling is required to achieve normal mineralization of molar enamel. PPARγ in pulp cells increases cell viability, odontoblastic differentiation, and dentin mineralization under oxidative stress.[107,108] |
| | LAMP2 | Lysosomal (LAMP2) markers, ageing and stress related in odontoblasts.[106] |
| | SIRT4 | Sirt4 knockdown resulted in reduced odontogenic differentiation and mineralization.[109] |
| Nervous system related pathway | GDNF | Function in odontoblasts develop, differentiate, and the matrix and predentin layers formation.[110] |
| | Nestin | The original odontoblasts may differently regulate Nestin expression.[111] |
| | NRG-1, ErbB3/4 | NRG-1 and the receptors ErbB3/4 are expressed locally during rodent tooth development.[112] |
| | Lhx8 | Regulates dentin development and regeneration.[113] |
| Cell junction related genes | OCLN, CLDN1, Zo1/2 | Play an important role in the differentiation of odontoblasts.[114] |
| | CNRs, Pcdh-γ, Reelin | Related to both morphogenesis and cell differentiation events.[28] |
| | E-cadherin, P-cadherin | Differential and specific roles for E-cadherin and P-cadherin during the morphogenesis.[115] |
| | Connexin26/32/43 | Expressed in odontoblasts.[116] |
| Bile secretion pathway | SLC2A1, SLC4A4, ADCY5, ATP1B1, SLC10A1, ABCC3 | Expressed in tooth germ odontoblasts.[117] |

(*Continued*)

**Table 1.** (Continued).

| Pathway | Gene | Main function in dentinogenesis |
|---|---|---|
| Other related genes | IFT140 | IFT140 is essential in promoting dentin formation and reparation.[118] |
| | EphrinB1, EphB2 | Regulates odontogenic differentiation and the early stages of tooth injury.[119] |
| | KDM1A, KDM5A | KDM1A have function for the dentinogenesis.[120] Inhibits the odontogenic differentiation and plays an important role in reparative dentinogenesis.[121] |
| | PrP | Odontoblasts showed prominent staining for PrP at levels comparable to those of nerve fibers.[122] |
| | HtrA1 | HtrA1 might positively regulate odontoblastic differentiation.[123] |
| | PP1 | PP1 might be a potent regulator of odontoblastic differentiation and dentinogenesis.[124] |
| | Sema3A | Play an important role in dentin regeneration via canonical Wnt/β-catenin signaling.[125] |
| | CPNE7 | CPNE7 induced odontoblast differentiation in vitro and promoted dentin formation in vivo.[126] |
| | MAP1B | MAP1B could be involved in the terminal differentiation of odontoblasts.[127] |
| | Phospho1 | Function in the early mineralization of mantle dentin.[128] |
| | Midkine | Midkine promotes odontoblast-like differentiation and tertiary dentin formation.[129] |
| | Cdc42 | Is particularly required for cell survival and tooth morphogenesis.[130] |
| | Sp1/3/6/7 | Sp1 promotes the odontoblastic differentiation and mineralization of dental papilla cells[131]; Sp3 is essential for post-natal survival and late tooth development[132]; Sp6 has been found to present striking dental abnormalities[133]; Sp7 is required for proliferation and differentiation of odontoblasts.[134] |
| | Zeb1 | Promoted odontoblast differentiation in the early stage.[135] |
| | Fubp1 | Plays a modulating role during dentinogenesis.[136] |
| | GATA4 | Important for root formation and odontoblast polarity.[137] |
| | ADAMTS2 | Mutation in ADAMTS2 causes multiple tooth agenesis and focal dysplastic dentin defects.[138] |
| | Trps1 | Trps1 functions as a repressor of later stages of dentinogenesis.[139] |
| | OASIS | Play an important role in the differentiation of the odontoblast.[25] |
| | Hand2 | Essential for odontoblasts cells during development.[140] |
| | RICK | Regulates odontogenic differentiation of dental pulp stem cells.[141] |
| | WWP2 | Promotes Odontoblastic Differentiation.[142] |
| | TANGO1 | Severe dentinogenesis imperfecta.[143] |
| | Mdm2 | Promotes the odontoblast-like differentiation. |
| | Glut1/2/4 | Dentinogenesis.[32,144] |
| | MTOR | Reparative dentinogenesis.[32] |
| | CB1 | Enhance the dentinogenic differentiation ability.[145] |
| | Parp-1 | Involved in the regulation of continuous dentinogenesis in the incisors at an advanced age.[146] |
| | Usp34 | USP34-dependent deubiquitination is critical for root morphogenesis by stabilizing NFIC.[147,148] |
| | mTORC1 | mTORC1 involed in odontoblast proliferation and mineralization.148 |

non-classical signaling pathway in the dentin formation process has not been elucidated. This pathway plays a crucial role in the reactivation of immature pulp cells for tertiary dentinogenesis.[47] TIMP1 plays a crucial role in the formation of tertiary dentin.

In addition, cavity preparation may activate the Wnt/β-catenin pathway.[47] Wnt signaling is essential to both the epithelium and stroma, whereas heterologous inactivation of β-catenin leads to stagnation of early tooth germ development. The elimination of mesenchymal-specific β-catenin stagnated tooth germ development, which indicates that Wnt signaling plays a role in the transition from the bud stage to the cap stage during tooth germ mesenchymal development. [50]

Wnt10a was shown to be strongly expressed in the odontoblast layer and was specifically expressed in the secretory odontoblasts co-expressed with DSPP.[56] The role of the Wnt/β-catenin signaling pathway in odontoblast differentiation and dentin formation is mediated through its component proteins.[56] Phenotype-related diseases are sometimes caused by paralog genes, which may explain the dental abnormalities in patients with Wnt10a and Wnt10b mutations.[57] Wnt signaling is essential for normal tooth development and its persistent activation leads to the continuous renewal of teeth and supernumerary teeth, whereas its inhibition stagnates tooth development. Abnormal Wnt signaling has been shown to cause a variety of human developmental disorders ranging from the lack of a tooth to life-threatening cancer.[57]

### SHH signaling pathway

Sonic hedgehog signaling molecule (SHH) has been shown to regulate dentin formation mainly during embryo development. GLI family zinc finger 1 (Gli1)-positive cells in mature teeth have been found to have stem cell properties that contribute to the regeneration of pulp and periodontal tissue. SHH, a secreted protein that plays a significant role in mammalian embryogenesis, regulates growth and determines the tooth shape. Dental epithelial SHH regulates tooth morphogenesis through epithelial mesenchymal signal transduction. Many studies have analyzed the function of SHH signaling in different stages of tooth development, and have reported that it regulates the formation of various tooth components, including the enamel, dentin, cementum, and other soft tissues.[61] SHH is mainly expressed in the dental epithelium during tooth development.[64]

The stratum intermedium is a highly dynamic and SHH-expressing structure that undergoes marked and transient changes in the histological organization and phenotype during odontogenesis. The stratum intermedium is involved in the development of the tooth germ, which has not been previously reported.[151] This delicate cell group has undergone an amazing process of evolution and degradation, which is closely related to the process of development from the dental cusp to the cervix. SHH is one of the signaling molecules for which the intermediate layer may play a role in mediated its function.[151] The primary cilia are essential for the integration of Wnt and Hh signals and in their functional absence, SHH signals decrease in the dental stroma, whereas those of Wnt increase in the dental mesenchyme.[67]

### TGFβ signaling pathway

The transforming growth factor β (TGFβ) signaling pathway is mainly involved in the differentiation and regulation of odontoblasts and includes the BMP family of molecules, which showed the most remarkable effects.

The TGFβ family plays an important role in matrix formation and pulpal obliteration, especially in pulp-dentin pathophysiology. TGFβ induces the secretion of ECM components related to primary and tertiary dentin formation. TGFβ isoforms are also expressed by mature odontoblasts, leading to the isolation of these growth factors in the dentin matrix. This process provides a matrix-associated TGFβ library that can be released in matrix changes associated with caries injury or trauma.[68] BMPs are signaling molecules secreted by the TGF superfamily and more than 30 types are known to regulate embryonic development in almost all tissues and organs of all animals and Fine-tuning of BMP is very important for its various functions.[72]

### Notch signaling pathway

The Notch signaling molecule expression and activation are critical not only for the development of tooth embryos, but also for the regeneration of damaged tissues of adult teeth. Notch is an important regulator of stem cell fate and can induce cell proliferation and differentiation. There is a close relationship between dental pulp mesenchymal cells and neovascularization in dental pulp diseases and the Notch signaling pathway is upregulated after tooth injury.[77]

### TNF signaling pathway

The specific role of the tumor necrosis factor (TNF) family of molecules identified in tooth morphogenesis suggests that this pathway plays an important role in the development and evolution of the tooth number and shape.[82] Ectodysplasin A (EDA), a member of the TNF superfamily, and its receptor, EDAR, are an essential part of ectodermal organ development. Analysis of their expression patterns and mutant phenotypes has shown that they may participate in signal transduction between different epithelial cells during hair and tooth development in mice.[82]

### Ion channel

Ion channels play an important role in various kinds of proprioception, pain, and conduction of hot and cold stimuli in teeth, as well as in calcium transport, deposition, and loss of teeth.

Voltage- and ligand-gated ion channels play a significant role in toothaches. The sensory fibers of the trigeminal nerve possess different types of voltage-gated ion channels expressed in common nerve cells and odontoblasts. Previous studies have shown that small molecules such as 5 '- adenosine triphosphate (ATP) and its ion receptor of the P2X family play an essential role in the sensory system of mediating toothaches. [88]

### Growth factor

It is involved in the development of teeth and the formation of secondary and reactionary dentins.

Although there is evidence that tooth morphogenesis and innervation are independent, the role of nerve fibers in tooth development or dentin and enamel formation remains controversial. In our study, the first molar tooth germ neurons of glial -derived neutrotrophic factor (GDNF)-deficient and wild-type mice were almost identical in structure and Schwann cell density.[110] This suggests that GDNF, similar to other members of the GDNF family such as neurturin, is not involved in guiding or maintaining the neural structure during tooth development or in the survival of Schwann cells.[110]

Among the members of the BMP family, the biological function of BMP 2 in root development has been widely studied and it promotes the differentiation of dental pulp stem cells into odontoblasts. IGF-1 promotes osteogenic differentiation and osteogenesis of bone, but can also reduce its odontogenic differentiation and ability, suggesting that IGF-1 could be as a candidate material for bone tissue engineering. The osteogenic differentiation signaling pathway of stem cells from apical papilla (SCAP) induced by IGF-1 requires further study, whereas IGF-2 appears to preferentially play a role in enamel deposition.[152]

### Stress response

Presently, the molecular regulatory mechanism of the stress response in teeth is not well understood, although it is of great significance to tooth development and the formation of secondary and reactionary dentins. The expression of heat shock protein 25 (Hsp25) in odontoblasts could be considered a stress response, which can be achieved by regulating actin dynamics and programmed cell death. Following the development of dentin and its deposition, the odontoblast retreated from the apex to the incisor end and the pulp space in the middle is reduced, forming pseudo-stratification. This histological finding suggests that odontoblasts undergo mechanical stress due to increase cell density during active dentin formation and this environmental change may induce a strong Hsp25 immune response in these cells.[153]

### Nervous system related pathway

Nerve-related genes involved in the regulation of dengtinogenesis have also been reported. Some studies have shown that during pulp regeneration odontoblast cells are likely derived from Schwann cells in the pulp, but the fine regulatory mechanisms involved are still poorly understood.[110] The role of nerve fibers in triggering the development of the teeth or in the onset of dentin and enamel formation is still controversial, although evidence suggests that tooth morphogenesis and innervation are independent. In our study, the first molar tooth germ (FMTG) nerves were almost identical in structure and density to the Schwann cells in GDNF-deficient and wild-type mice. This suggests that glial cell-line derived growth factor (GDNF) and neurturin are not involved in guiding or maintaining the structure of nerves in the developing tooth or in the survival of Schwann cells.[110]

### Cell junction related genes

The role of the cell junction in oral development and disease is poorly understood. Occludin (OCLN), claudin-1 (CLDN1), and zonula occludens-1/2 (Zo1/2) play important roles in odontoblast differentiation.[114] CNRs, protocadherin (Pcdh)-γ, and Reelin are related to both morphogenesis and cell differentiation events.[28] E-cadherin and P-cadherin have differential and specific roles during morphogenesis[115] and connexin 43 is expressed in odontoblasts.[116] The expression patterns of CLDN1, OCLN, ZO-1, and ZO-2 are different. Tight junctions (TJs) of the rat lower incisor odontoblasts may play an important role in the early differentiation of odontoblasts, especially in determining the direction of mineral secretion and establishing the distal membrane domain.[114]

### Bile secretion pathway

Recent studies have shown that this signaling pathway, ostensibly unrelated to teeth, is involved in tooth embryo development, and tooth formation involves strict genetic control procedures.[117] Therefore, exploring the gene network system regulating tooth development has a very positive practical significance in the study of tooth tissue regeneration and the prevention and treatment of tooth abnormalities. The early bell stage is the initial phase of odontoblast formation and dentin matrix deposition in the tooth development process. RNA sequencing and differential gene analysis of rat tooth germ samples at the cap and early bell stages showed that the bile secretion pathway was the most significantly different between the cap and bell stages among related signaling pathway during development, which mainly included SLC10A1, SLC2A1, SLC4A4, ADCY5, ATP1B1 and ABCC3.[117]

### Other related genes

However, the major signaling pathways involved in dentinogenesis and new genes remain to be discovered and elucidated. For instance, IFT140 is essential in promoting dentin formation and reparation.[118] Odontoblasts showed prominent staining for PrP at levels comparable to those of nerve fibers.[122] Glucose supply via GLUT1 might occur before the differentiation of odontoblast-like cells. The transport of glucose via Glut2/Glut4 might contribute to the production of a dentin bridge during wound healing.[32,144] Mdm2 promotes Odontoblast-like differentiation by Ubiquitinating Dlx3 and p53. It will continue to add and classify, because the number is small and not deep enough.

## Conclusion and perspectives

The development and restoration of dentin is a complicated and strict regulatory process and numerous signaling molecules and transcription factors constitute the complex signaling network mediating dentin formation. Understanding these signal networks is of great significance to the study of tooth development, damage repair, and tissue regeneration and to the treatment of abnormal tooth development. We believe that research in this field should focus on the following points in the future.

### Odontoblasts aging

Odontoblast aging is a field that has rarely been studied in the past decade and similar to other major functional cells, odontoblasts have a process of development, maturation, and senescence. To date, the specific genes involved in odontoblast cell aging are unknown. Odontoblast aging is closely related to dentin regeneration. The autophagy-lysosome system of odontoblasts ensures the renewal of organelles and proteins, thereby extending their lifespan. However, the gradual accumulation of lipofuscin in lysosomes reduces the viability of odontoblasts and the ability of dentin to regeneration.[154,155] Moreover, the old dentin structure is also different from that of young dentin, and a study on the mechanical behavior of dentin reported that all stiffness, strength, and fatigue properties tested decreased significantly with age.[156] Scanning electron microscopy revealed that old dentin exhibited more intratubular crystal deposits than the young dentin, which had an 80% lower permeability.[157] We hope that future research will elucidate the process and molecular mechanisms of odontoblast aging, which could provide strategies to regulate odontoblast aging or reverse the aging process.

### Odontoblasts immune responses

The odontoblast is the first tissue barrier against invasion of the tooth by caries-related pathogens, and is the starting and effective point of the immune response of the tissue to these pathogens. However, the pattern recognition receptors (PRRs) involved in the responses to pathogen-associated molecular patterns (PAMPs) in odontoblasts have not been fully clarified. Therefore, a deeper understanding of the mechanisms underlying PAMP-induced innate immune responses and the role of PRRs in odontoblasts would help the development of strategies to maintain dental pulp tissues in a healthy condition for as long as possible. Furthermore, the enhanced understanding of these processes may lead to the development of novel therapeutic strategies and treatments for pulpitis.

### Dentin development

Currently, although there is considerable information available on the dentin developmental process and related genes, the details of its complex regulatory network are still unclear. Furthermore, repairing dentin abnormalities or defects that have occurred is challenging. Presently, prenatal or pre-implantation genetic diagnosis is the most effective method of solving dentin developmental problems. Future further studies and understanding of the regulatory network of dentin development would contribute to enabling the modification adult mutant genes for the benefit of patients by combining modern gene modification techniques such as CRISPR/cas9.

### Epigenetics in dentin development and aging

Recent studies have demonstrated the important role of epigenetics in dentin development and the main epigenetic modifications include DNA methylation, histone acetylation, and methylation.[158] However, because of the limitations of in vivo and in vitro models and research techniques, epigenetic research on dentin development has only just begun. A considerable amount of research is still required to reveal rules and interventions in developmental abnormalities.

### Dentin regeneration

Dentin regeneration, especially regenerative restoration after dentin injury, requires an understanding of the occurrence and development of dentin, because the two main signaling pathways are very similar. Dentin regeneration requires dental pulp cells and is closely related to dental pulp regeneration.[159] In addition to previous studies on dentinogenesis, some novel approaches have been explored in the past year. For example, a novel injectable treated dentin hydrogel (TDMH) has been developed for use as a pulp capping material for dentin regeneration.[159] Histological results showed that TDMH allowed the harvesting of thicker formed dentin than that of Biodentine and mineral trioxide aggregate (MTA).[159] Another

study utilized an amphiphilic synthetic polymeric combined with exosomes derived from both dental pulp stem cells and immortalized murine odontoblasts as dental pulp capping material to generate dentin *in vivo*. After 6 weeks, the exosome group exhibited higher quality formation of the dentin bridge than the group treated with glass-ionomer cement.[154] The development of nanotechnology has also led to the application of nanomaterials in new strategies in the field of dentin regeneration. Mesoporous bioactive glass/graphene oxide composites have been shown to improved mineral differentiation of human dental pulp stem cells by upregulating the odontogenesis-specific markers DSPP and DMP-1. This observation suggests that this composite may induce stem cell differentiation into odontoblast-like cells and thereby induce dentin formation.

### *Physical factors*

Some physical factors including ultrasound, static magnetic field(SMF), electric field(EF), and laser irradiation also affect the differentiation of odontoblasts. Ultrasound: In the experimental model of dentin injury without pulp exposure, low-intensity pulsed ultrasound (frequency: 1.5 MHz, 200 μs pulse width, 1 kHz pulse repetition frequency, 30 mW/cm$^2$ spatial averaged temporal averaged intensity) treatment of teeth increased calcium ion transport-related protein (Cav1.2, NCX1 and TRPV1) expression. After 14 days, hematoxylin and eosin (H&E) staining showed more significant dentin formation in the pulse treatment group than that in the other groups and the underlying mechanism may involve inflammatory reactions and mechanical effects.[160]

Static magnetic field (SMF): Recently, SMF has been shown to promote the proliferation, migration, and differentiation of stem cells. Furthermore, SMF at 1 mT has been reported to increase DPSC proliferation, and the gene expression of fibroblast growth factor (FGF)-2, TGF-β, and vascular endothelial growth factor (*VEGF*) by upregulating *MMP-1* and *MMP-2* gene expression. SMF also inhibits the phosphorylation of YAP/TAZ, which continuously induces odontoblast differentiation and mineralization in DPSCs.[161]

Electro filed (EF): A potential method (frequency: 1 Hz, 40 ms pulse length and 70 V) using a pulse EF to deliver growth/differentiation factor 11(GDF11) could promote DPSC differentiation into odontoblasts and induce the expression of dentin sialoprotein (Dsp), a differentiation marker for odontoblasts, in the future. This study suggests that the co-application of physical and gene therapy may achieve the goal of dental tissue repair.[162]

Laser irradiation: Low-level laser irradiation (InGaAsP; 940 nm; 0.2 W, continuous mode) at 8 J/cm$^2$ stimulated cellular proliferation and promoted biomineralization of stem cells from human exfoliated deciduous teeth by upregulating odontogenesis-related genes (DSPP, ALP, BMP-2) .[163] The development of genomics, molecular biology, biophysics, and materials science in the future will provide more alternative and efficient methods for the regeneration and restoration of dentin. Consequently, the "secrets" of dentinogenesis will be gradually unveiled.

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