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Review Article

Role of the Wnt signaling molecules in the tooth



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Summary Wnt signaling plays a central role in many processes during embryonic development and adult homeostasis. At least 19 types of Wnt ligands, receptors, transducers, transcription factors, and antagonists have been identified in mammals. Two distinct Wnt signaling pathways, the canonical signaling pathway and the noncanonical signaling pathway, have been described. Some Wnt signaling pathway components are expressed in the dental epithelium and mesenchyme during tooth development in humans and mice. Functional studies and experimental analysis of relevant animal models confirm the effects of Wnt signaling pathway on the regulation of developing tooth formation and adult tooth homeostasis. Mutations in some Wnt signaling pathway components have been identified in syndromic and non-syndromic tooth agenesis. This review provides an overview of progress in elucidating the role of Wnt signaling pathway components in the tooth and the resulting possibilities for therapeutic development. © 2016 Japanese Association for Dental Science. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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1. Introduction

The first Wnt gene Wnt1, originally named integration site-1 (int-1), was identified by Nusse and Varmus in 1982 as a gene activated by the integration of mouse mammary tumor virus (MMTV) in virally induced breast tumors [1]. Int-1 encodes a secreted, cysteine-rich protein that is difficult to purify in its biologically active form. The initial identification of the signaling pathway associated with this protein was based on genetic systems. In 1987, the fly *Wingless* gene, which controls segment polarity during larval development in *Drosophila melanogaster* [2], was shown to be a homolog of int-1 [3]. Because of the homology between int-1 and *Wingless*, the gene was renamed Wnt1 (*Wingless plus int1*) [4] and was eventually recognized as the founding member of a large Wnt gene family. The Wnt proteins of molecular weight approximately 40,000 are cysteine-rich, glycosylated lipid-modified secreted proteins that regulate embryonic development, cell proliferation, differentiation, and migration [5,6].

The first direct connection between the Wnt signaling pathway and tooth formation was reported in the late 1990s [7]. In this review, we discuss our current understanding of Wnt signaling pathway components and functions in tooth development and homeostasis.

2. Wnt signaling pathway and their components

At least 19 Wnt proteins have been identified in mammals [8]. Two distinct Wnt signaling pathways, the canonical signaling pathway and the noncanonical signaling pathway, have been characterized. Two types of Wnt proteins have been identified. One class of Wnt proteins comprises the β -catenin-dependent canonical Wnts, such as Wnt1, Wnt2, Wnt3, Wnt3a, and Wnt7a. The other class comprises the non-canonical Wnts, such as Wnt4, Wnt5a, Wnt5b, Wnt6, and Wnt11, which act independently of or inhibit the canonical Wnt signaling pathway [8]. Single knockout of Wnt2b, Wnt5b, Wnt6, Wnt8b, and Wnt16 in mice resulted in no detectable phenotype [9]. Functional redundancy of some Wnts has been described in reports of double knockout mice [9,10]. For example, Wnt1–Wnt3a double knockout mice show a more severe phenotype of defects in neural crest development and somite patterning that are not observed in either single-mutant animals [10].

Canonical Wnt signaling is initiated by the binding of Wnt proteins to the receptors of the seven-transmembrane domain-spanning Frizzled (Fz) family (Fz1–10) as well as to the co-receptors lipoprotein receptor-related proteins (LRP) 4, 5, and 6 [11,12]. In the absence of Wnt ligands, a complex between Axin, adenomatous polyposis coli (APC) tumor suppressor protein, casein kinase (CK) 2, glycogen synthase kinase (GSK) 3 β , and β -catenin causes the phosphorylation of β -catenin by GSK3 β and targets it for subsequent degradation by the proteasome [13,14] (Fig. 1). Axin is a negative regulator of the canonical Wnt signaling pathway and a scaffold protein that brings together GSK-3 β , APC, and β -catenin to form a complex [11,15,16]. The binding of Wnt to receptor Fz leads to the activation of Dishevelled (DVL) and causes inactivation of a complex of proteins that degrades cytoplasmic β -catenin. β -Catenin accumulates in the cytoplasm, translocates to the nucleus, and forms active transcriptional complexes with the transcription factor T-cell-specific factor/lymphoid enhancer binding factor 1 (TCF/Lef1) and with transcriptional coactivators that regulate the expression of certain target genes, including cyclin D1 and osteoprotegerin (Fig. 1) [16–20].

The non-canonical pathways require Fz but not LRP, β -catenin, or TCF transcription factors. Noncanonical Wnt ligands interact with alternative Wnt receptors, such as receptor tyrosine kinase-like orphan receptor (Ror) 2 or receptor tyrosine kinase Ryk [11,21,22]. Noncanonical Wnt signaling is mediated by at least two mechanisms. The first is the planar cell polarity (PCP) pathway, which controls tissue polarity, a process in which cells orient themselves within a plane perpendicular to the apical–basal axis [23–25]. Activation of small GTPases, such as Rho and Rac, by noncanonical Wnt/Fz is a key mechanism that regulates the Wnt-PCP pathway to promote reorganization of the actin cytoskeleton [25,26]. The second mechanism is the Wnt/Ca²⁺ pathway, a pathway that promotes intracellular calcium transients to regulate cell movements [27]. In the Wnt/Ca²⁺ pathway, Wnt5a triggers intracellular Ca²⁺ release to activate protein kinase C and Ca²⁺/calmodulin-dependent kinase II [22]. Alternatively, binding of Wnt5a to Ror2 can activate c-Jun-N-terminal kinase and inhibit canonical Wnt signaling [21,28,29].

Several secreted Wnt antagonists have been reported, including secreted frizzled related protein (sFRP), Dickkopf (Dkk), Sclerostin (*Sost* gene product), Wnt inhibitory factor-1 (WIF-1), and Wise (Fig. 1) [30]. Members of the sFRP family and WIF-1 bind primarily to Wnt proteins, inhibiting

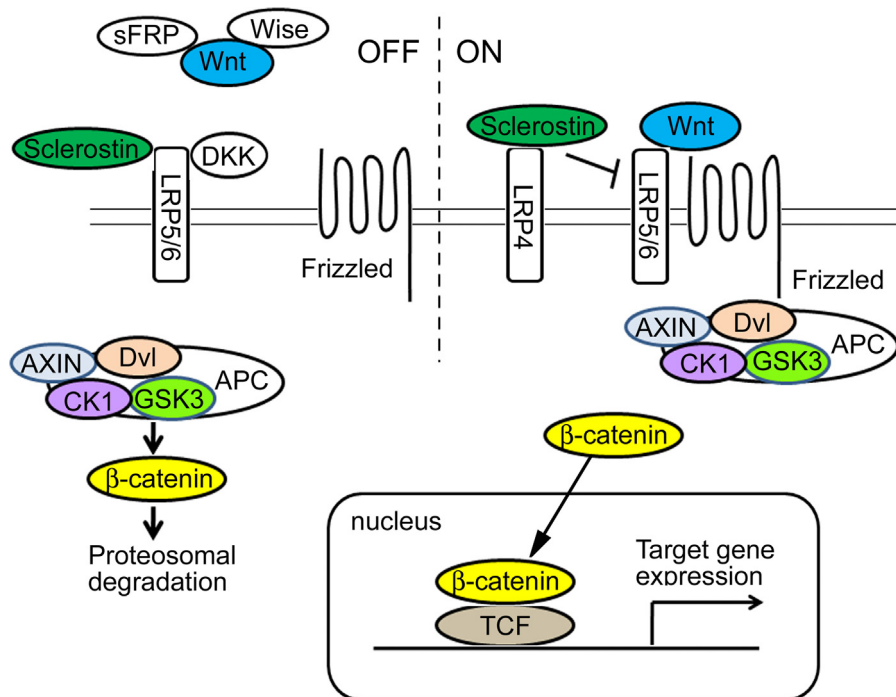


Figure 1 The canonical Wnt signaling pathway. The secreted Frizzled-related protein (sFRP) family or Wise bind to Wnt proteins, leading to inhibition of the interaction between Wnt and the Frizzled receptor. Sclerostin or Dickkopf (DKK) binds to lipoprotein receptor-related proteins (LRP) 5/6 to inhibit Wnt signaling. Cytosolic accumulation of β -catenin in response to a canonical Wnt signal is a crucial step in the signaling pathway. Left: In the absence of Wnt ligand, β -catenin associates with the destruction complex composed of Axin, adenomatous polyposis coli (APC), casein kinase (CK) 2, and glycogen synthase kinase (GSK)-3. GSK-3 phosphorylates β -catenin, inducing rapid degradation of β -catenin via the ubiquitin/proteasome pathway. Right: The canonical Wnt signaling is initiated by the binding of the Wnt ligand to Frizzled and LRP5/6. Subsequently, Wnt ligand blocks β -catenin degradation, allowing transportation to the nucleus, where β -catenin interacts with the transcription factor T-cell-specific factor (TCF) and activates target gene expression.

the interaction between Wnts and Fz [31]. LRP5/6 binds to DKK and sclerostin to inhibit Wnt signaling [32,33]. Sclerostin has also been shown to bind to LRP4 [34], and different regions of sclerostin interact with LRP5/6 and LRP4 [35]. The secreted protein Wise and its orthologs [Sostdc1, uterine sensitization-associated gene-1 (USAG-1), and Ectodin] reportedly inhibit Wnt signaling through an interaction with LRP6 [36]. Recently, Notum was identified as a secreted Wnt antagonist that belongs to the α/β hydrolase superfamily. Notum deacylates Wnt proteins to suppress signaling activity [37].

The Wnt signaling pathway is reportedly involved in regulation of bone mass and formation of bone and tooth tissues [19]. In fact, Wnt signaling plays a critical and evolutionarily conserved role in tooth development at many stages. In this review, we discuss the current understanding of Wnt signaling components and its functions in the tooth.

3. Canonical Wnt signaling pathway components in the tooth and periodontal tissue

3.1. Tooth development

Several Wnt signaling components, including Wnt ligands, receptors, transducers, transcription factors, and

antagonists, are expressed in the dental epithelium and mesenchyme during tooth development in humans and mice (Table 1) [38,39]. Wnt 3, Wnt4, Wnt6, Wnt7b, and Wnt10b are expressed in the epithelium. Wnt5a shows localized expression in the mesenchyme and dental papilla. Wnt3, Wnt5a, LRP5, Fz6, β -catenin, Lef1, and Dkk1 exhibit similar expression patterns during tooth development in humans and mice [39]. Targeting components of the canonical Wnt pathway influences tooth formation.

During tooth development, nuclear β -catenin is detected in both the dental epithelium and the underlying mesenchyme, and the canonical Wnt signaling pathway is activated at multiple stages of tooth morphogenesis [40]. The effects of canonical Wnt signaling at the early bud stage are mediated through the suppression of *Msx1* and *Bmp4* gene expression. Inhibition of canonical Wnt signaling results in the development of aberrantly shaped teeth, indicating an essential role of canonical Wnt signaling in early tooth development [40]. Disruption of canonical Wnt signaling either by ectopic expression of DKK1 or deletion of β -catenin or Lef1 in the oral epithelium arrests tooth morphogenesis at the early (DKK1 and β -catenin) or late bud stage (Lef1) [40–42]. Tissue-specific deletion of β -catenin in developing odontoblasts produced molars lacking roots and aberrantly thin incisors [43]. Inactivation of *Gpr177*, the mouse ortholog of *Drosophila* *Wls/Evi/Srt*, which is essential for proper secretion of Wnt, in the dental epithelium leads to the arrest

Table 1 Expression of Wnt signaling pathway components in the tooth.

Classification	Function	Name	References
Canonical	Ligand	Wnt3	[38,39]
		Wnt3a	[63,107]
		Wnt4	[38,107,108]
		Wnt6	[38,107]
		Wnt7a	[107]
		Wnt7b	[38]
		Wnt10a	[46,107]
	Receptor	Wnt10b	[38,109]
		Fz4	[39]
	Coreceptor	Fz6	[38,39]
		LRP4	[107,110]
		LRP5	[39,111]
	Transducer	LRP6	[111]
		Axin2	[47,107]
	Transcription factor	APC	[112,113]
		β -Catenin	[39,114]
		LEF1	[107,115]
		TCF1	[107]
	Antagonist	TCF4	[39]
		DKK1	[107,116,117]
DKK2		[107,117]	
DKK3		[107,117]	
DKK4		[107,117]	
SFRP1		[118]	
Sclerostin		[67,68]	
Noncanonical	Ligand	Wise (Sostdc1)	[111,119]
		Gpr177	[44]
Noncanonical	Ligand	Wnt5a	[39,72,75,107]
		Wnt5b	[107]
	Receptor	Ror2	[73]
		YAP	[106]

of early tooth development, and deletion of *Axin2* rescued this phenotype [44]. Tissue-specific inactivation of β -catenin in developing odontoblasts produced molars lacking roots and aberrantly thin incisors [43]. Constitutively expressing active β -catenin in the oral epithelium results in formation of multiple teeth after transplantation to the kidney capsule [45].

Wnt10a is specifically expressed in the epithelial signaling centers and the primary and secondary enamel knots [46]. The spatial and temporal distribution of Wnt10a mRNA expression shows that the expression shifts from the secondary enamel knots to the underlying preodontoblasts. In addition, Wnt10a was shown to induce dentin sialophosphoprotein expression. *Axin2*, which is a direct target of Wnt/ β -catenin signaling activity, is also expressed in developing odontoblasts and dental pulp cells [47], indicating that canonical Wnt signaling is associated for dentinogenesis [48]. The tissue-specific inactivation of β -catenin in developing odontoblasts resulted in development of molars lacking roots [49]. Moreover, constitutive activation of β -catenin in the dental mesenchyme leads to differentiation

of odontoblasts and cementoblasts and induces excessive dentin and cementum formation in mice [50]. The effects of canonical Wnt in dental pulp injury have also been described. A liposome-reconstituted Wnt3a protein protected pulp cells from cell death and stimulated proliferation of undifferentiated pulp cells, which improved pulp healing in rats [51]. On the other hand, Wnt1 negatively regulates the differentiation of dental pulp stem cells into odontoblasts by the inhibition of alkaline phosphatase (ALP) activity and the formation of mineralized nodules in dental pulp stem cells [52]. This suggests that odontogenesis is regulated through spatial and temporal expression of Wnt1 during odontogenic differentiation.

WIF1, a secreted Wnt antagonist, is strictly expressed in the enamel knot at embryonic day 14.5 (E14.5) and E16.5. Upon knockdown of WIF1, the promotion of apoptosis leads to a delay in an early event during tooth development [53]. WIF1 and *Dkk2* are much more abundantly expressed in the mandibular than in the maxillary molar mesenchyme [54]. Other recent reports have claimed that noggin inhibits canonical Wnt and that canonical Wnt signaling functions primarily to control the odontogenic fate of the dental epithelium by sustaining *Pitx2* expression and partly to regulate cell proliferation during early odontogenesis [55].

3.2. Periodontal tissue

The roles of canonical Wnt signaling in the development and homeostasis of periodontal tissue have been described [43,56–59]. Experiments with conditional β -catenin-stabilized mice have shown that constitutive stabilization of β -catenin in the dental mesenchyme leads to excessive formation of cementum [43,57]. Disruption of Wnt/ β -catenin signaling in odontoblasts and cementoblasts in conditional knockout mice arrests tooth root development [58]. Cells showing Wnt responsiveness are distributed adjacent to the cementum in the periodontal ligaments of continuously erupting incisor teeth and are coincident with the distribution of proliferating cells [56]. Using OCCM-30 cells, an immortalized murine cementoblast cell line, Wnt3a was shown to suppress the expression of ALP, bone sialoprotein, and osteocalcin expression [60]. Wnt3a also increases the expression of cyclin D1, a known cell cycle regulator, suggesting that Wnt3a inhibits cementoblast differentiation and promotes cell proliferation [60]. Amelogenin, an enamel matrix protein that is secreted by ameloblasts, has been implicated in cementogenesis [61]. Amelogenin activates the canonical Wnt signaling pathway in human periodontal ligament cells in culture, although the mechanism remains unclear [62].

Recently, Nemoto et al. reported Wnt3a expression in Hertwig's epithelial root sheath (HERS) cells during mouse tooth root development as well as in cultured human epithelial rest cells of Malassez, whereas Wnt3a expression could not be detected in dental mesenchymal cells in culture [63]. In immortalized murine dental follicle cells, Wnt3a induced ALP expression. Moreover, Wnt3a induced Runx2 and Osterix in these cells, suggesting a potential role of HERS in stimulating cementoblast/osteoblast differentiation of dental follicle cells *via* the canonical Wnt signaling pathway [63].

The activation of the canonical Wnt signaling has recently been reported to induce *in vivo* cementum regeneration in the rat periodontal defect model and *in vitro* cementoblast differentiation of human periodontal ligament cells [64]. Also, when lithium ions, which are known activators of canonical Wnt signaling [65], are released from bioactive scaffolds, they enhance the proliferation and differentiation of human periodontal ligament cells on the scaffolds [66]. Sclerostin is a canonical Wnt antagonist expressed by cementocytes [67]. Observations from sclerostin-knockout mice reveal an increased width of the cementum and concomitant moderate decrease in the periodontal space width. No significant differences were observed for the tooth and pulp chamber volume, suggesting that sclerostin alters the cementum phenotype rather than tooth development [68]. These reports indicate that regulation of the canonical Wnt signaling pathway plays critical roles in the differentiation of odontoblasts and cementoblasts and that regulation of canonical Wnt signaling may function in the formation of dentin and cementum during tooth development and tissue regeneration.

4. Noncanonical Wnt signaling pathway components in tooth

Wnt5a is strongly expressed in murine and human dental papilla mesenchyme [69,70]. Overexpression of Wnt5a inhibits the proliferation and migration of human dental papilla cells (hDPCs) [70], and Wnt5a increases mineralization-related gene expression in hDPCs, suggesting that Wnt5a promotes the differentiation of hDPCs [71]. Wnt6 overexpression also induced expression of osteogenesis-related genes while exerting no significant effect on the proliferation of hDPCs, indicating a role of Wnt6 in odontogenic differentiation [72]. The loss of the Wnt5a function experiment, which used Wnt5a-deficient mice to induce the abnormal pattern of cups due to decreased cell proliferation in dental epithelium and mesenchyme, retardation of tooth development, and smaller tooth suggests that Wnt5a regulates growth, patterning, and odontoblast differentiation during odontogenesis [73]. Conversely, the gain of Wnt5a function experiment used exogenous Wnt5a protein to induce cell death in the dental region [74]. Their observations indicate that Wnt5a regulates the balance between cell proliferation and cell death, which involves epithelial and mesenchymal interactions on tooth development.

Wnt5a expression was also detected in tooth lining cells and dental follicle cells during mouse tooth development. Knockdown of Wnt5a using siRNA enhanced the Wnt3a-induced ALP expression in SVF4 cells, an immortalized murine dental follicle cell line, indicating that Wnt5a negatively regulates canonical Wnt-mediated early dental follicle cell differentiation [75]. These results suggest the existence of a feedback mechanism between canonical and noncanonical Wnt signaling during the differentiation of dental follicle cells [75]. Other reports have suggested a similar function for Wnt5a because knockdown of Wnt5a in human PDL stem cells enhanced the ALP activity induced by osteoinductive medium, in which canonical Wnt signaling may be activated [76]. Wnt5a reportedly suppresses osteogenic-related markers of human PDL cells

cultured by osteogenic induction medium [77]. Conversely, Wnt5a signaling functions as a positive regulator in dental follicle cell differentiation triggered by BMP-2 [78], suggesting that the function of Wnt5a may depend on the state of the cell. These diverse responses may be due to multiple options for the transduction of Wnt5a signals [79], including the availability of various receptors and other signaling cascade mediators [80]. The observations described above indicate that the noncanonical Wnt signaling pathway plays critical roles in tooth development and suggest that Wnt regulation may have potential uses in regenerative therapy.

5. Human diseases in tooth associated with mutations of the Wnt signaling components

5.1. Wnt10a mutation

Wnt10a of the canonical Wnt pathway is expressed in the dental epithelium and mesenchyme. WNT10a mutations have been reported in various ectodermal dysplasia syndromes, rare autosomal-recessive odonto-onycho-dermal dysplasia (OODD) [81,82], and severe autosomal recessively inherited Schöpf–Schulz–Passarge syndrome (SPSS) [83–85]. OODD and SPSS share a common ectodermal dysplasia involving hair, teeth, nails, and skin, characterized by dry hair, hypodontia (tooth agenesis), smooth tongue, nail dysplasia, hyperkeratosis of the skin, and palmoplantar keratoderma. Currently, OODD and SPSS are considered a part of the same disorder within the Wnt10a mutations [86,87]. Wnt10a mutations have also been described to be the most common causes of non-syndromic severe hypodontia with minor signs of ectodermal dysplasia [88] and autosomal-dominant inherited isolated hypodontia [89–91].

5.2. Axin2 mutation

Axin2, which is localized to chromosome 17q21–q25, is a negative regulator of the canonical Wnt pathway that suppresses signal transduction by promoting β -catenin degradation [92]. Axin2 mutations have been described in oligodontia [93,94]. It also reported that three Axin2 gene variants are associated with both hypodontia and oligodontia [95]. Mutations of this gene have also been found in various human cancers, including those of skin, gastrointestinal, liver, and ovary [96]. However, the relationship between tooth agenesis and tumor is still controversial [97,98]. Using Axin2-lacZ mice, Axin2 expression was observed in primary and secondary enamel knots and in the underlying mesenchyme at the development stage [47]. Postnatal Axin2 expression has been detected in developing odontoblasts and in the dental pulp; it has also been found concentrated around the developing roots. These observations suggest roles for Axin2 in defining the regions of enamel formation and in controlling root development during the late stages of tooth development [47].

5.3. LRP6 mutation

LRP6 encodes a transmembrane cell-surface protein that, together with members of the Fz receptor family, functions

as a co-receptor in the canonical Wnt signaling pathway. Recently, Massink et al. reported four heterozygous LRP6 loss-of-function mutations in four independent families affected by non-syndromic autosomal-dominant oligodontia [99]. They also showed that the LRP6 missense variant (c.56C>T) results in altered glycosylation and improper sub-cellular localization of the protein, resulting in abrogated activation of canonical Wnt signaling. Thus, the disruption of canonical Wnt signaling is of importance in the etiology of tooth agenesis [99].

6. Prospective of other Wnt signaling molecules

Yes-associated protein (YAP) and transcriptional coactivator with PDZ binding domain (TAZ) are WW domain-containing transcriptional coactivators originally identified in a proteomic screening for 14-3-3 binding proteins [100] and are well known to be regulated by the Hippo signaling pathway [101]. Azzolin et al. reported that TAZ is a downstream component of the canonical Wnt signaling pathway and a mediator of Wnt biological responses independent of the Hippo pathway [102,103]. Recently, Park et al. reported YAP/TAZ as downstream effectors of the alternative Wnt signaling pathway [104]. The alternative Wnt-YAP/TAZ signaling axis, which consists of Wnt-Fz/Ror-G α 12/13-RhoGTPases-Lats1/2, promotes YAP/TAZ activation and TEAD-mediated transcription [104]. In transgenic mice that overexpress a constitutively active form of YAP in the dental epithelium, the resulting tooth phenotype was deformed tooth morphogenesis with widened dental lamina [105]. In contrast, YAP deficiency in the dental epithelium resulted in development of a small tooth germ with reduced epithelial cell proliferation [106]. Data from the gene expression profiles of an embryonic E14.5 YAP conditional knockout and YAP transgenic mouse tooth germs indicate that YAP regulates the expression of Hoxa1 and Hoxc13 in oral as well as dental epithelial tissues [106]. However, the relationship between Wnt signaling and YAP/TAZ in tooth formation remains to be determined. Direct interactions of YAP/TAZ in the epithelial tissues of the developing tooth may provide insights into the molecular mechanisms of Wnt signaling not only in terms of organism development but also regarding the onset and progression of human diseases.

7. Conclusion

In conclusion, several recent studies have indicated a role of both the canonical and noncanonical Wnt signaling pathways in the regulation of tooth development, maintenance, and turnover. Therefore, strategies to modulate Wnt signaling pathway components are very attractive for the treatment of tooth regeneration. Hopefully, the efforts currently underway to target Wnt signaling will be successful and generate new therapeutics in the future.

Conflict of interest

None declared.

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