Japanese Dental Science Review (2016) **52**, 75—83

Contents lists available at ScienceDirect

Japanese Dental Science Review

journal homepage: www.elsevier.com/locate/jdsr

Review Article

Role of the Wnt signaling molecules in the tooth

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Received 12 January 2016; received in revised form 29 March 2016; accepted 1 April 2016

KEYWORDS
Tooth;
Periodontal tissue;
Wnt signaling;
Canonical Wnt;
Tooth development;
Tooth agenesis;
Hypodontia;
Oligodontia

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.

Contents

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http://dx.doi.org/10.1016/j.jdsr.2016.04.001

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 noncanonical 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) 3β, and β-catenin causes the phosphorylation of β-catenin by GSK3β 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-3β, 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 osteoprotegrin (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/Ca^{2+} pathway, a pathway that promotes intracellular calcium transients to regulate cell movements [27]. In the Wnt/Ca^{2+} pathway, Wnt5a triggers intracellular Ca^{2+} release to activate protein kinase C and Ca^{2+}/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