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Review article

The role of the wnt/β-catenin signaling pathway in formation and maintenance of bone and teeth

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ABSTRACT

The Wnt signaling pathway is known as one of the important molecular cascades that regulate cell fate throughout lifespan. The Wnt signaling pathway is further separated into the canonical signaling pathway that depends on the function of β-catenin (Wnt/β-catenin pathway) and the noncanonical pathways that operate independently of β-catenin (planar cell polarity pathway and Wnt/Ca^{2+} pathway). The Wnt/β-catenin signaling pathway is complex and consists of numerous receptors, inhibitors, activators, modulators, phosphatases, kinases and other components. However, there is one central, critical molecule to this pathway, β-catenin. While there are at least 3 receptors, LRP 4, 5 and 6, and over twenty activators known as the wnts, and several inhibitors such as sclerostin, dickkopf and secreted frizzled-related protein, these all target β-catenin. These regulators/modulators function to target β-catenin either to the proteasome for degradation or to the nucleus to regulate gene expression. Therefore, the interaction of β-catenin with different factors and Wnt/β-catenin signaling pathway will be the subject of this review with a focus on how this pathway relates to and functions in the formation and maintenance of bone and teeth based on mainly basic and pre-clinical research. Also in this review, the role of this pathway in osteocytes, bone cells embedded in the mineralized matrix, is covered in depth. This pathway is not only important in mineralized tissue growth and development, but for modulation of the skeleton in response to loading and unloading and the viability and health of the adult and aging skeleton.

Contents

Abbreviations: APC, adenomatous polyposis coli; BMP, bone morphogenic protein; Col1a1, alpha 1 type 1 collage; Cx43, connexin 43; DKK, dickkopf; Dmp1, dentin matrix acidic phosphoprotein 1; DVL, disheveled; FGFs, fibroblast growth factors; GSK3β, glycogen synthase kinase 3β; int 1, integration 1; LRP, low density lipoprotein receptor-related protein; OPG, osteoprotegerin; PCP, planar cell polarity; PDL, periodontal ligament; PGE2, prostaglandin E2; RANKL, receptor activator of nuclear factor kappa B ligand; sFRP1, secreted frizzled-related protein 1; Shh, sonic hedgehog; SOST, sclerostin; TCF/LEF, T-cell factor/lymphoid enhancer-binding factor; VEGFR2, vascular endothelial growth factor receptor 2.

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1. Introduction

The protein β-catenin is the central target and an essential component of the Wnt/β-catenin signaling pathway. This pathway is involved in numerous aspects of growth and development in many organs and tissues, ranging from cell fate determination, polarity and differentiation to migration, proliferation, and function (Moon et al., 2002; Visweswaran et al., 2015). For example, during embryonic development, Wnt/β-catenin critically contributes to the establishment of the body axis and the orchestration of tissue and organ development. After development, Wnt/β-catenin has been shown to play an essential role in self-renewing tissues such as the hair follicle, the intestinal crypt, and the hematopoietic system. Under pathological conditions, mutations resulting in the activation of this pathway are commonly observed in cancers, such as colon cancer, hair follicle tumors, and leukemia (Clevers, 2006) (For review see Baron and Kneissel, 2013). As several reviews have summarized and updated the progress of the Wnt signaling pathway in human skeletal disease (For review see Rudnicki and Williams, 2015; Baron and Kneissel, 2013), the focus in this review will be on the role of this pathway in mineralized tissue, both bone and tooth, development and function based on the recent discoveries using animal models and cell lines. This pathway not only plays a critical role in growth and development but in the maintenance of the mature skeleton and response to conditions of loading such as exercise and conditions of unloading such as space flight and patient immobilization.

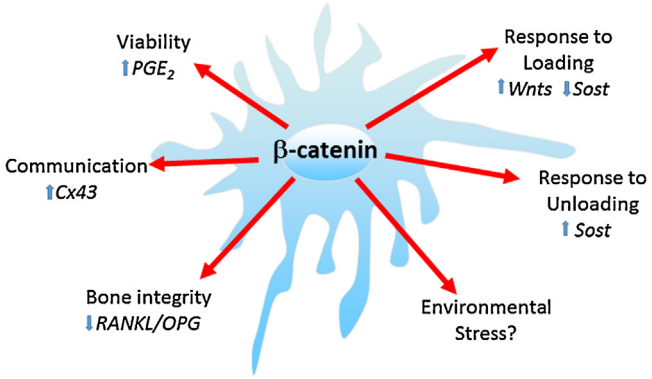

Fig. 1. In the osteocyte, β-catenin is essential for 1). Maintenance of osteocyte viability and protection from apoptotic factors such as glucocorticoids through PGE_2 (Kitase et al., 2010); 2). Communication between osteocytes potentially through the regulation of Connexin 43 (Xia et al., 2010); 3). Bone integrity as loss of β-catenin in osteocytes leads to elevated bone resorption through the increase of RankL/OPG ratios (Kramer et al., 2010); 4). Response to anabolic loading through the upregulation of Wnts (Javaheri et al., 2014); 5). Response to unloading leads to an increase in inhibitors of the wnt/β −catenin pathway such as sclerostin (Robling et al., 2008) and 6). Gender effects are observed in response to unloading and potentially environmental stress (Maurel et al., 2016). The target gene involved in sensing environment stress is still unclear. It will be important to determine if β-catenin also plays a role in these functions in other cells embedded in a mineralized matrix such as cementocytes.

2. Discovery and structure of β-catenin

Catenin, beta 1 (β-catenin; *Ctnnb1*) was first named in the late 1980s by Ozawa and colleagues along with α-catenin and γ-catenin as these proteins linked E-cadherin to cytoskeletal structures in Ca^{2+}-dependent cell adhesion (Ozawa et al., 1989). It was reported as a component of a mammalian cell adhesion complex even though the protein can also be located in both the cytoplasm and nucleus (McCrea et al., 1991). The gene *int 1* (integration 1) in mouse and the gene *wg* (wingless) in drosophila were reported, found to be homologues and later named as Wnt (Clevers, 2006). In the middle 1990s, several groups independently found that b-catenin in the nucleus triggered Wnt-mediated transcription via T-cell factor/Lymphoid enhancer-binding factor (TCF/LEF) transcription factors (Valenta et al., 2012). The studies eventually supported a dual function of β-catenin, one of crucial importance in the cadherin adhesion complex and a second playing a central role in the Wnt-signaling pathway (Fig. 1).

The crystal structure of β-catenin was determined in 2008 (Xing et al., 2008). The structure includes the N-terminal region, the armadillo or Arm domain (total 13 amino acid repeat), the far C-terminal region adjacent to the Arm domain, the end of C-terminal region, Helix C, and unstructured sequences distal to Helix C, each with specific functions. The N-terminal region mediates the degradation of β-catenin, the inner surface of the Arm domain serves as a ligand binding site, the C-terminal segment acts as a strong transactivator by recruiting both effectors and inhibitors, and the Helix C is required for Wnt signaling by potentially recruiting various coactivators. The function of β-catenin closely relies on the molecular structure, though the binding domain or amino acids may vary in the different β-catenin signaling pathways. It is not clear how the unstructured sequences contribute to signaling, therefore studies using new techniques and approaches are still needed to explore the dynamic structure of β-catenin (Gottardi and Peifer, 2008).

3. Components of the canonical wnt/β-catenin pathway

There are several pathways in which Wnt plays a role such as the planar cell polarity pathway, the Wnt/Ca^{+2} pathway and a Protein Kinase A pathway involving CREB, but we will be addressing the best studied pathways referred to as the canonical pathway or the Wnt/β-catenin signaling pathway (Bonewald and Johnson, 2008). Under normal homeostasis, phosphorylated β-catenin is part of a degradation complex consisting of adenomatous polyposis coli (APC), glycogen synthase kinase 3β (GSK3β), and axin where it becomes ubiquinated and targeted to the proteasome for degradation. However, with receptor activation (the low density lipoprotein receptor-related proteins, LRP, 4, 5 or 6), β-catenin is freed from its degradation complex in a monomeric form for translocation to the nucleus to initiate gene transcription. The secreted Wnts initiate receptor activation and signaling by binding to the transmembrane receptor Frizzled and LRP coreceptors 4, 5, or 6, inducing phosphorylation of the cytoplasmic tail of the LRPs which recruits axin from the degradation complex to bind to this phosphorylated site. With axin removed, the degradation complex is dissociated by cytoplasmic protein disheveled (DVL) to release β-catenin. Thus, β-catenin accumulates in the cytoplasm and ultimately translocates to the nucleus where it binds with TCF/LEF, leading to the activation of target genes. Antagonists of the Wnt receptors, including Sclerostin (SOST), Dickkopf (DKK) 1, 2, and 3, and secreted frizzled-related protein 1 (sFRP1) protein prevent β-catenin translocation by binding to Wnt proteins (as sFRP1) or by interfering with interactions between Wnt proteins and their receptors and coreceptors (as Sclerostin and Dkk-1)(Burgers and Williams, 2013; Canalis, 2013; Chen et al., 2007; Dallas et al., 2013). In the absence of wnts, the cytoplasmic levels of β-catenin remain low (Aberle et al., 1997).

New components of this pathway are constantly being discovered and therefore, understanding how this pathway operates is not completely known. This pathway has been expanding in number of Wnts, Wnt receptors, coreceptors, soluble inhibitors, modulators, and other molecules thereby increasing the complexity of