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REVIEW

Wnts' fashion statement: from body stature to dysplasia

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Bone is constantly being made and remodeled to maintain bone volume and calcium homeostasis. Even small changes in the dosage, location and duration of int/Wingless (Wnt) signaling affect skeletal development and homeostasis. Wnt/β-catenin signaling controls cell fate determination, proliferation and survival by affecting a balance between bone-forming osteoblast and bone-resorbing osteoclast cell differentiation. During early skeletal development, Wnt/β-catenin signaling is required in directing mesenchymal progenitor cells toward the osteoblast lineage. Later, Wnt/β-catenin in chondrocytes of the growth plate promotes chondrocyte survival, hypertrophic differentiation and endochondral ossification. Gain- or loss-of-function mutations in the Wnt signaling components are causally linked to high or low bone mass in mice and humans. Inactivation of Wnt/β-catenin signaling leads to imbalance between bone formation and resorption because of accelerated osteoclastogenesis due to decline in the levels of osteoprotegerin (OPG) secreted by osteoblasts or directly via Frizzled 8 (Fzd8). In this review, we provide a landscape of the Wnt pathway components in influencing progenitor cell differentiation toward osteoblasts or osteoclasts under physiological conditions as well as pathological disorders resulting in various skeletal dysplasia syndromes.

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Wnt Signaling Pathway

Wingless (Wnt) proteins are a highly conserved[1] family of 22 secreted cysteine-rich glycoprotein morphogens (long-range signaling molecules that work in a concentration-dependent manner) that activate several receptor-mediated signaling cascades. The Wnt signaling pathways regulate cell differentiation, proliferation, survival, migration and polarity, and they have pivotal roles in embryonic development and adult physiology. Abnormal Wnt signaling causes devastating diseases including cancer. Wnt ligands activate at least three different pathways: canonical (β-catenin-dependent), and noncanonical: planar cell polarity and Wnt-$Ca2^+$. In canonical Wnt signaling, Wnt ligands bind to cell surface receptor complexes composed of one of the ten Frizzled (Fzd) receptors and one of the two low-density lipoprotein-related protein (Lrp) co-receptors, which ultimately lead to the stabilization and nuclear translocation of β-catenin. β-catenin also has a role in cell–cell adhesion of binding to cadherins. In Wnt signaling, its levels are tightly regulated by the protein destruction complex composed of Axin1/2, APC, Casein kinase1 (Ck1), Glycogen synthase kinase 3β (Gsk3β) and Wilms tumor on the X chromosome (WTX) that phosphorylates β-catenin. Phosphorylated β-catenin is then degraded by the proteasome. In the presence of Wnt ligands, such as Wnt1 and Wnt3a, Gsk3β and Ck1 phosphorylate Lrp5/6, which recruits Axin2 to the plasma membrane. This leads to the inactivation of the destruction complex such that β-catenin is unphosphorylated, stabilized in the cytosol and translocated to the nucleus to activate downstream target genes by binding to lymphoid enhancer factor/T-cell factor[2,3] transcription factors.

A second group of Wnt ligands represented by Wnt5a and Wnt11, signal through the 'noncanonical' Wnt pathways *in vivo*.[4] The Wnt-$Ca2^+$ pathway involves $Ca2^+$ mobilization and activation of the $Ca2^+$/calmodulin-dependent protein Kinase II and the Protein Kinase C-driven cytosolic signaling pathway.[5] The planar cell polarity (PCP) pathway is evolutionally conserved, which is controlled by a group of core PCP components that include Dishevelled (Dvl), Fzd, and Vangough-like (Vangl1/2). PCP is required to regulate the collective orientation of cells or cell extensions such as cilia and axon.

Skeletal Dysplasia

The skeleton is a dynamic organ that consists mainly of two types of tissues, the cartilage and the bone, which are

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formed by chondrocytes and osteoblasts, respectively.[6] During development, bones are formed by two different processes: intramembranous and endochondral ossification, both of which start from mesenchymal condensation. In endochondral ossification, mesenchymal progenitor cells first differentiate into chondrocytes that are replaced by osteoblasts later to form mature bone. In intramembranous ossification that happens in the skull and lateral halves of clavicles for example, the mesenchymal progenitor cells directly differentiate into osteoblasts to form bone. In adults, bone undergoes active remodeling conducted by two types of cells: osteoblasts that form bone and osteoclasts that resorb bone matrix.[6]

Skeletal dysplasia (dysplasia with Latin roots meaning bad growth) or osteochondrodysplasia is a large heterogeneous group of over 450 different clinical and genetic conditions that results in abnormal shape, growth, maintenance and integrity of the bones, cartilage and associated connective tissue, along with complications in other organs due to skeletal malformation.[7] Historically, three main categories of skeletal dysplasia were described to include osteodysplasia, chondrodysplasia and dysostoses.[8] While the osteodysplasias involve alterations in bone strength and mineralization, such as osteopenia and osteosclerosis, chondrodysplasias are cartilage defects that affect the shape and longitudinal growth of the skeleton, which often cause short stature. Malformations of individual bones or group of bones define dysostoses. But, recent discoveries have left these distinctions blurred, with genetic mutations in certain loci producing compound phenotypes of skeletal dysplasia. A plethora of the signaling pathways including but not limited to Wnt, peroxisome proliferator-activated receptors (PPAR), fibroblast growth factor (FGF), parathyroid hormone, bone morphogenetic protein, transforming growth factor β, Notch and Hedgehog are essential for proper skeletogenesis and adult bone homeostasis,[9] whereas defects in these pathways correlate genetically and molecularly with various skeletal complications leading to different forms of skeletal dysplasia.[10] Mutations in components of these pathways disrupt normal signaling processing and lead to deregulation of skeletal patterning, skeletal cell proliferation, differentiation and survival leading to skeletal dysplasia. Here, we have comprehensively reviewed the genes of the Wnt signaling pathway for their roles in bone mass physiology and their specific mutations in skeletal dysplasia syndrome pathology.

Canonical Wnt/β-Catenin Pathway in Osteoblastogenesis/Osteoclastogenesis

Wnt/β-catenin signaling in conjunction with other signal transduction pathways such as PPARs, Notch and Parathyroid hormone receptor pathways controls mesenchymal progenitor identity, proliferation and survival. Under embryonic skeletal development, Wnt/β-catenin signaling directs mesenchymal progenitor cells toward the osteoblast lineage.[11,12] Postnatal Wnt/β-catenin signaling in chondrocytes of the growth plate promotes hypertrophic differentiation and endochondral ossification.[13,14] In a reciprocal relationship with the Wnt/β-catenin pathway, PPARγ modulates mesenchymal progenitor differentiation from osteoblasts toward adipogenesis[15] and partly by modulating the mammalian target of rapamycin pathway.[16] PPARγ also catabolically regulates bone mass by suppressing bone-forming osteogenesis, while promoting differentiation of bone-resorbing osteoclasts, decreasing overall bone mass.[17] A recent article by Scholtysek *et al.*[18] provided evidence for a novel role of PPARβ/δ in amplifying Wnt/β-catenin signaling and osteoprotegerin (OPG) production from osteoblasts for attenuation of osteoblast-mediated osteoclastogenesis, suggesting them as alternate treatments for skeletal dysplasia such as osteoporosis. Bone-resorbing cells, osteoclasts, develop from the monocyte/macrophage lineage under tight control of osteoblasts. On one hand, osteoblast-secreted cytokines, colony-stimulating factor-1 and receptor activator of nuclear factor κB ligand (RANKL) promote osteoclast differentiation; another osteoblast-secreted molecule, OPG, acts as a decoy receptor for RANKL, inhibiting inappropriate osteoclastogenesis in a Wnt/β-catenin-dependent manner.[19] Moreover, a recent article also established an OPG-independent role of Wnt/β-catenin-mediated inhibition of osteoclastogenesis regulated by the Wnt receptor, Fzd8.[20] Wnt3a is also known to strongly inhibit Vitamin 1,25-D3-induced osteoclast formation.[21] Bone formation is induced by the anabolic function of the parathyroid hormone via suppression of the Wnt/β-catenin pathway inhibitors, Dkk1 and Sclerostin.[22]

Lrp5/6, Dkk1 and Wnt Signaling in Bone Formation and Skeletal Dysplasias

Human and mouse developmental genetic studies have demonstrated that Lrp5/6 and the Wnt signaling pathway are key players in bone formation and the risk of osteoporosis, and that Lrp5/6-Wnt signaling is essential for normal bone development and homeostasis.[23–26] The Wnt/β-catenin pathway is a major signaling pathway in skeletal biology.[27,28] Wnt/β-catenin signaling is required for osteoblast cell fate determination in embryonic development.[28] Later, it has a critical role in bone mass acquisition and maintenance as revealed by human and mouse genetic studies.[29] As one of the co-receptors for Wnt signaling, Lrp5 is expressed in osteoblasts and regulates their proliferation, survival and function. The risks for skeletal dysplasia such as osteoporosis are majorly determined genetically,[30] and, through candidate gene analysis and genome-wide linkage studies, Lrp5 locus has been identified to be associated with bone density and fracture risk.[31,32] Mechanistically, Lrp5 signals in the duodenum by inhibiting serotonin synthesis by modulating the expression of its rate-limiting synthesis enzyme, Tryptophan hydroxylase 1 and promoting bone mass.[33] Additional studies by Cui *et al.*[34] with osteocyte and gut-specific expression of Lrp5 gain-of-function mutants revealed that only osteocyte-specific Lrp5 mutants exhibit increased bone mass, whereas osteocyte-specific Lrp5 loss-of-function mutants show low bone mass independent of serotonin levels. Recently, Esen *et al.*[35] demonstrated an Lrp5-dependent metabolic regulation of osteoblast differentiation by Wnt3a in a β-catenin-independent manner via modulation of glucose metabolism through mammalian target of rapamycin C2-AKT signaling. This finding implicates a new route of Lrp5-mediated regulation of bone mass with glucose metabolism as a probable target for skeletal diseases associated with loss of Lrp5.

The Dkk family of extracellular proteins consisting of four members (Dkk1, Dkk2, Dkk3 and Dkk4) is a negative regulator of the Wnt/β-catenin pathway by competing for binding Lrp5/6.

Dkk1 and Dkk2 are the best-characterized members of this family. Gene deletion of Dkk1 in mice increases bone mass,[36,37] whereas the induction of Dkk1 in osteoblasts leads to osteopenia.[38] Lytic bone lesions in patients with multiple myeloma are associated with increased Dkk1 expression, suggesting that Dkk1 inhibits osteoblast differentiation and/or function.[39] The role of Dkk2 in regulating bone development was shown in a study, in which mice lacking Dkk2 developed osteopenia.[40] Clinical trials with anti-Dkk1 antibodies are underway for osteoporosis and other skeletal diseases.

Secreted Frizzled-Related Protein-1 (sFRP-1)

The deletion of sFRP-1 activates Wnt signaling in osteoblasts, which enhances trabecular bone formation.[41] Mechanistically, it has been determined that the deletion of sFRP-1 inhibited osteoblast lineage cell apoptosis, while enhancing the proliferation and differentiation of these cells *in vitro*.[42] Activation of the Wnt pathway in osteoblasts by removing sFRP-1 has important implications in maintaining bone architecture in the aging skeleton.

Secreted Frizzled-Related Protein-3 (sFRP-3)

Polymorphisms in the sFRP-3 gene are associated with multiple epiphyseal dysplasias, characterized by shorter stature and frail articular cartilage that disassociates easily from the underlying bone.[43] In addition, sFRP-3 has been reported to be associated with osteoarthritis.[44]

Wnt-Induced Signaling Protein 3 (WISP-3)

WISP genes are members of the CCN family involved in cell growth and differentiation and have been proposed to have roles in cancer.[45] WISP-3 is a secreted protein expressed by synoviocytes and chondrocytes and is essential for human cartilage integrity. Recessive mutations in WISP-3 cause a mild chondrodysplasia called progressive pseudorheumatoid arthropathy of childhood (OMIM #208230). Affected individuals present, with progressive small and large joint polyarthritis, stiffness and decreased mobility. In addition, polymorphisms in WISP-3 have been shown to confer susceptibility to Juvenile Idiopathic Arthritis.[46]

Sclerostin

Rare recessive or dominant sclerosing (an inflammatory response leading to a fibrotic process) disorders are caused by mutations in genes involved in the Wnt pathway, which regulates osteoblast differentiation.[47] Among these genes, inactivating mutations in sclerostin, a Wnt antagonist that is specifically expressed in osteocytes and regulates osteoblast differentiation, have been shown to cause sclerosteosis and Van Buchem diesease.[48,49]

Human Porcupine Locus MG61/PORC (PORCN)

PORCN is thought to encode an O-acyltransferase that catalyzes cysteine N-palmitoylation and serine O-acylation in the endoplasmic reticulum, which allows membrane targeting and secretion of several Wnt proteins that have key roles in embryonic tissue development.[50] Mutations in the PORCN gene have been reported as causative for focal dermal hypoplasia (OMIM #305600).[51,52] Focal dermal hypoplasia is an X-linked dominant disorder of ecto-mesodermal development.[53] Digital deformities such as syndactyly, ectrodactyly or brachydactyly are frequently seen in affected individuals who develop striated areas of reduced bone density (osteopathia striata).

Wilms Tumor on the X chromosome (WTX)

Osteopathia striata with cranial sclerosis (OMIM #166500) is an X-linked dominant condition marked by linear striations in the metaphyseal region of the long bones and pelvis in combination with cranial sclerosis owing to increased osteoblast activity.[54] The disease-causing gene was identified as the WTX gene (FAM123B), an inhibitor of WNT signaling.[55]

α Subunit of Stimulatory G-protein (GNAS) and Fibrous Dysplasia

Fibrous dysplasia (OMIM #174800) presents with low-to-moderately cellular fibrous stroma surrounding irregularly shaped bone trabeculae without osteoblastic rimming.[56] Gain-of-function mutations in GNAS locus are involved in the pathogenesis of fibrous dysplasia, associated with osteoblastic differentiation defects in skeletal progenitor cells, and characterized by bone marrow fibrosis, intramedullary and immature woven bone, failure of mature lamellar bone formation and abnormal bone resorption.[57] Bone tissue itself is associated with fusiform fibroblast-like cells, corresponding to poorly differentiated osteoblasts due to increased proliferation but lack of differentiation of progenitor cells. The bone lesions may be associated with endocrine dysfunction and skin spots, known as the McCune–Albright syndrome.[58] A recent article from our lab demonstrated a causative role of the Wnt/β-catenin pathway upregulation due to gain-of-function mutation in GNAS, in the pathology of fibrous dysplasia.[59]

Fibroblast Growth Factor Receptor-3 (FGFR-3)

Mutation in FGFR-3 leading to hyperactivated FGFR-3 constitutes an important underlying mechanism in thanatophoric dysplasia type II and potentially other skeletal disorders due to the disruption of Wnt/β-catenin-Sox9 homeostasis.[60]

Noncanonical Wnt Pathway and Skeletal Dysplasia

In mammals, Ror2, a member of the Ror-family receptor tyrosine kinases, has been shown to act as a receptor for Wnt5a to mediate noncanonical Wnt signaling. Wnt5a-Ror2 crosstalk between bone cells enhances bone resorption and negatively regulates skeletal homeostasis.[61] Mutations in the human Ror2 gene have been found to be responsible for skeletal dysplasias as dominant brachydactyly type B[62] and recessive Robinow syndrome.[63,64] Wnt5a induces RANK expression that is critical for osteoclastogenesis for osteoblast-generated RANKL binding and promoting osteoclast generation.[61] Loss-of-function mice mutants for PKCδ and Wnt7b also exhibit impaired bone formation.[65]

Concluding Remarks

We have written this review to summarize the various roles of the Wnt pathway components in the regulation of bone mass in

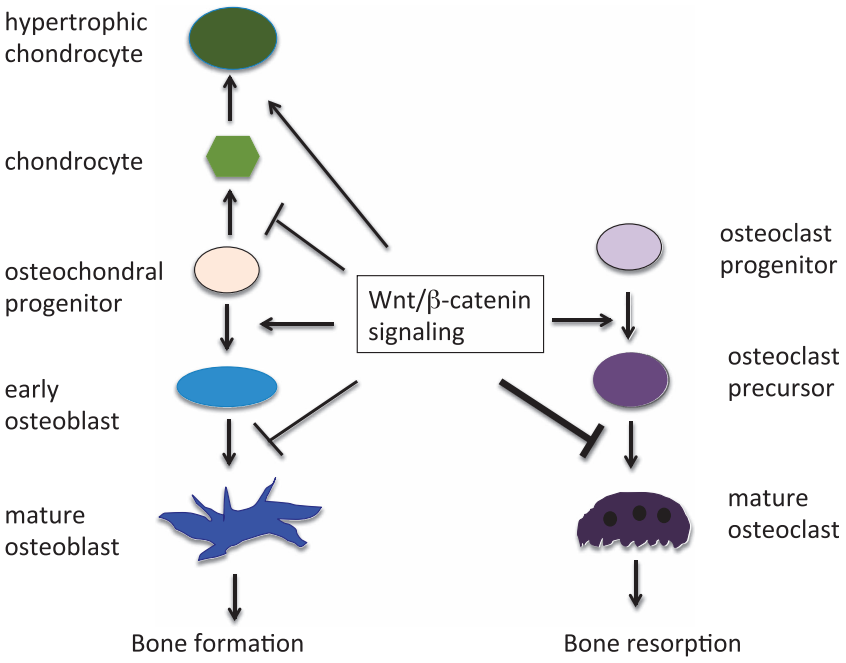

Figure 1 A graphic summary of the multiple roles of Wnt/β-catenin signaling in bone formation and resorption. Disruption of Wnt/β-catenin signal transduction leads to skeletal malformations or diseases by affecting at least one of the regulatory steps.

skeletal development and remodeling.[66–71] The Wnt signaling pathways influence body stature and their deregulation leads to a plethora of pathological conditions expressed as different skeletal diseases ranging from epiphyseal dysplasia to spondyloepimetaphyseal dysplasia. Proper Wnt signaling activity is critical to normal bone development and homeostasis as either gain or loss of Wnt signaling activities adversely affects the skeleton resulting in skeletal dysplasias as summarized in **Figure 1**.

As a major signaling pathway in skeletal biology, Wnt signaling acts on many different aspects of bone development and disease. Global understanding of these various aspects of Wnt signaling in skeletal biology will help to delineate molecular interactions of other pathways with the Wnt signaling pathway and to develop effective therapeutic interventions to treat skeletal disease by modulating the activities of Wnt signaling components.

Conflict of Interest

The authors declare no conflict of interest.

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