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The future of bone formation: pharmacological manipulation of the Wnt signaling pathway

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One pathway identified by human genetics as a major player in the control of bone formation is the Wnt signaling pathway [1]. This pathway is crucial for the specification of cell fates, regulation of cell growth, differentiation, and apoptosis. Wnt ligands are secreted lipid-modified glycoproteins that signal through a receptor complex comprising a member of the Frizzled family of seven transmembrane domain receptors, and the co-receptor lipoprotein-receptor related proteins (LRPs) 5 or 6. Inactivating mutations in the gene for LRP5 result in impaired bone mass and severe osteoporosis, with heterozygous carriers also having reduced bone mass and an increased incidence of osteoporotic fractures. On the other hand, an activating mutation of the same gene is associated with a greatly increased bone mass.

Activation of Wnt signaling by the interaction of LRP5 with the Wnt-Frizzled ligand-receptor complex results in inhibition of β -catenin phosphorylation by a kinase called GSK-3 β . Inhibition of GSK protects β -catenin from degradation and allows this protein to reach the nucleus and activate gene transcription. Activation of Wnt signaling pathway results in inhibition of chondrocyte differentiation and promotion of bone formation.

Pharmacological manipulation of the Wnt signaling is a possible way to promote bone formation: inhibition of extracellular proteins which prevent Wnt-LRP5/6 interaction should increase bone mass.

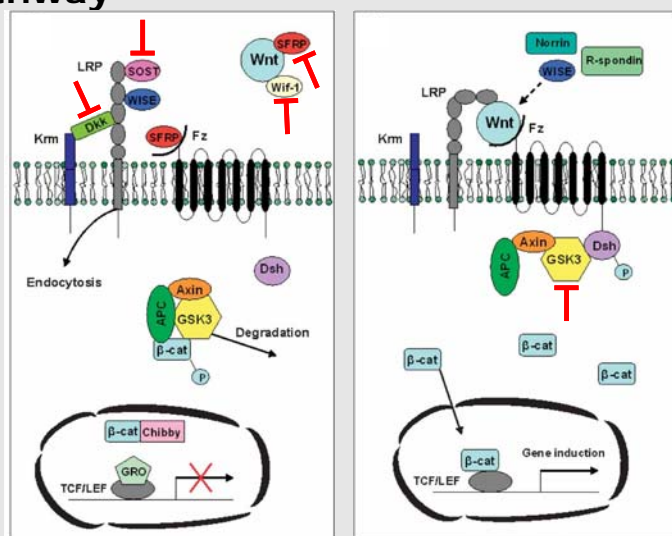
1. Martin TJ et al. Osteoporos Int. 2008;19:1125-1138.
2. Macsai CE et al. J Cell Physiol. 2008;215:578-587.

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The "classical" pathway is inactivated through a variety of inhibitors, mediating the degradation of β -catenin via its phosphorylation and inhibiting gene transcription. Dkk and sclerotin (SOST), can bind to the LRP component of the Wnt receptor complex, preventing Wnt from forming a complex with LRP and Fz. SFRP antagonizes Wnt signaling by directly binding to Wnt proteins.

Activation of the pathway is initiated when Wnt binds to Frizzled (Fz) receptors and low-density lipoprotein LRP5-6 (LRP-5/6) coreceptors. This interaction inhibits a cytoplasmic complex composed of GSK-3, Axin, and APC, leading to a block in β -catenin phosphorylation by GSK-3. β -Catenin accumulates in the cytoplasm and then enters the nucleus, where it stimulates gene transcription.



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