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Turning genetic discoveries into new treatments: The Wnt/LRP-5 system as a source of new drug targets for skeletal diseases

P.V.N. Bodine

Women's Health and Musculoskeletal Biology, Wyeth Research, Collegeville, PA, USA

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Wnts are a large family of growth factors that control many important biological processes including bone formation. These secreted, lipid-modified glycoproteins bind to a membrane receptor complex composed of a frizzled (FZD) G-protein coupled receptor and a low-density lipoprotein (LDL) receptor-related protein (LRP)[1,2]. The formation of this ligand-receptor complex activates one of several intracellular signaling pathways including the beta-catenin, calcium and c-Jun NH_2-terminal kinase (JNK) pathways. These pathways are controlled by numerous extracellular and intracellular regulatory proteins, many of which suppress Wnt activity. Among these are a diverse group of secreted antagonists that bind and sequester Wnts (e.g., secreted frizzled-related proteins or SFRPs) or block signaling at the level of LRP (e.g., dickkopfs or DKKs and SOST/sclerostin)[3-5].

Research over the past 7 years has firmly established canonical Wnt signaling or the beta-catenin pathway as playing a key role in modulating bone formation and remodeling[6-12]. The initial human genetic discoveries of loss-of-function and gain-of-function mutations of LRP-5 causing osteoporosis pseudoglioma syndrome (OPPG) and high bone mass (HBM), respectively, have been followed up by a large number of mouse genetic studies that have provided mechanistic insights into how these mutations affect osteoblast physiology and coupling to osteoclastogenesis. These investigations have identified and validated several potential drug targets for the treatment of metabolic bone diseases and other skeletal pathologies. These targets include extracellular modulators of Wnt signaling such as DKK-1, SOST/sclerostin and SFRP-1 as well as intracellular regulators like the enzyme glycogen synthase kinase-3beta (GSK-3beta).

HBM mutations of LRP-5 lead to increased bone formation by preventing secreted antagonists like DKK-1 and SOST/sclerostin from binding and blocking the canonical Wnt pathway in osteoblasts. SOST was initially identified as a gene that was inactivated in another human HBM syndrome, bone dysplasia sclerosteosis. Although a member of the DAN family of proteins that contains bone morphogenetic protein (BMP) inhibitors, sclerostin is now considered to be a direct suppressor of LRP-5/6 function[13]. Because DKK-1 and sclerostin are secreted proteins, they are good targets for neutralizing antibodies that are currently in clinical development for the treatment of osteoporosis as well as the skeletal complications of multiple myeloma. A monoclonal antibody that inhibits sclerostin has been shown to increase serum markers of bone formation in healthy postmenopausal women[14]. A neutralizing antibody to DKK-1 was reported to increase bone formation and bone mineral density in intact rats and mice[15]; it has also been shown to blunt joint destruction in a mouse model of rheumatoid arthritis[16] and to prevent bone loss and increase bone formation in a mouse model of multiple myeloma[17].

Although potentially less cost effective than orally active compounds, biotherapeutics like humanized monoclonal antibodies have the advantage of circumventing many of the technological hurdles to developing small molecular drugs. Nevertheless, some Wnt pathway components are being targeted for orally active compounds. Small molecular weight inhibitors of DKK-1 have been reported[18]. LiCl, which is used to treat bi-polar disorders, has been shown to inhibit GSK-3beta, increase canonical Wnt signaling *in vitro* and elevate bone formation in mice[19]. While controversial[20],

The author is a full-time employee of Wyeth Research and owns stock and holds stock options in the company.

Corresponding author: Peter Bodine, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, USA
E-mail: bodinep@wyeth.com

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there is also some clinical data to suggest that use of LiCl may reduce fracture risk[21]. In addition, a potent and orally active small organic compound that inhibits GSK-3beta has been reported to reverse the effects of ovariectomized-induced bone loss in rats[22]. While GSK-3beta inhibitors have been developed for non-skeletal indications like type-2 diabetes and Alzheimer's, none has entered the clinic for osteoporosis. Finally, because deletion of SFRP-1 in mice leads to increased trabecular bone accrual in ageing animals, small molecular weight inhibitors of this Wnt pathway antagonist have also been described[23].

In summary, through the efforts of many academic, biotechnology and pharmaceutical scientists, research on the role of Wnt pathways in skeletal biology have rapidly progressed from the initial human genetic discoveries to translation studies and drug discovery. It is hoped that these hard won efforts will soon bring important new therapies to patients that suffer from debilitating and pervasive diseases like osteoporosis and arthritis.

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