Eating bone or adding it: the Wnt pathway decides

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An inhibitor of the Wnt signaling pathway mediates bone destruction in inflammatory arthritis. The inhibitor may be the key to understanding why in some joint diseases bone is destroyed and in others built up (pages 156–163).

Joint pain comes in many flavors. When it comes to arthritis, however, there is at least one major difference among the various types. In inflammatory conditions such as rheumatoid arthritis, bone destruction kicks into overdrive and there is a shutdown of bone repair[1]. In contrast, in conditions such as ankylosing spondylitis and psoriatic arthritis, the bone destruction is associated with excessive bone formation. What accounts for these two very different ways for the joint to respond to injury?

The answer may lie with Dickkopf-1 (DKK-1), an inhibitor of the wingless (Wnt) signaling pathway. In this issue, Diarra *et al.*[2] show that blocking the activity of DKK-1 reverses bone destruction in joints in mouse models of inflammatory arthritis—tipping the balance in favor of increased bone formation.

The Wnt family of glycoproteins are involved in the regulation of multiple cellular activities, including bone formation and remodeling during growth and development and in the postnatal state (**Fig. 1** and refs. 3, 4). Activation of the canonical pathway by Wnt ligation to its receptors results in dephosphorylation and nuclear translocation of β-catenin, which interacts with T-cell factor (Tcf)/lymphoid-enhancing factor (Lef) transcription factors to control the expression of target genes.

In a major advance in the understanding of bone remodeling, loss of function in low-density lipoprotein receptor-like protein 5 (LRP5), a putative Wnt coreceptor, was shown to result in osteoporosis pseudoglioma syndrome, a human disorder characterized by severely decreased bone mass. In contrast, gain-of-function mutations in LRP5 were associated with high bone mass. On the basis of the assumption that LRP5 is a Wnt coreceptor, these observations established the link between the Wnt pathway and control of bone mass, and focused intense interest on this regulatory system as a potential target for treatment of skeletal disorders such as osteoporosis[5–7].

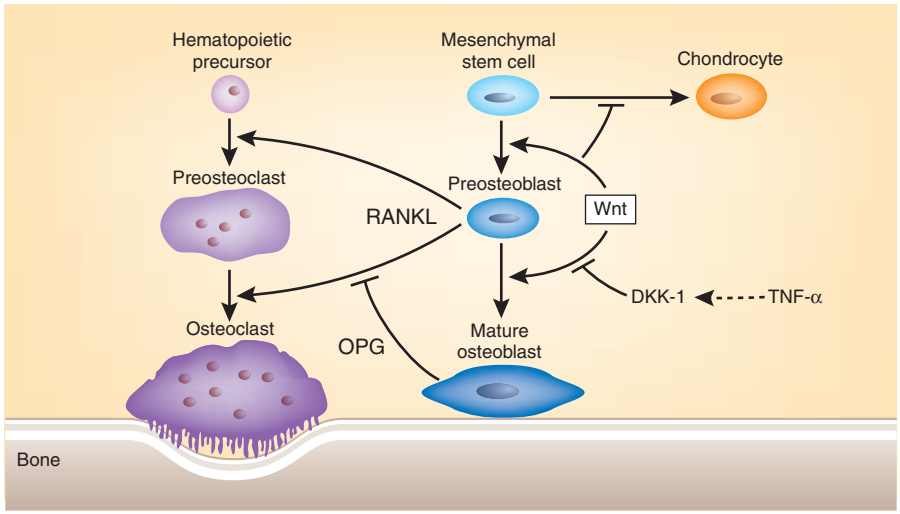

Figure 1 Bifunctional role of the Wnt signaling pathway in regulation of osteoblast (bone-forming cell) and osteoclast (bone-resorbing cell) differentiation. Wnt signaling diverts the mesenchymal stem cells down the pathway of osteoblast differentiation. DKK-1 binds to the Wnt receptor complex on the surface of the osteoblast lineage cell and blocks Wnt signaling, arresting osteoblast proliferation and differentiation. The precursors of the mature osteoblast enhance bone resorption by boosting RANKL-induced osteoclastogenesis. Blockade of DKK-1 permits progression of osteoblast differentiation. Activation of the Wnt signaling pathway in the mature osteoblast upregulates OPG, which blocks RANKL-induced osteoclastogenesis, resulting in inhibition of bone resorption.

In the past several years, studies have revealed that Wnt signaling occurs downstream of additional signaling cascades that involve the bone morphogenetic proteins (BMPs) and Hedgehog (Hh) molecules; the Wnt signaling pathway thus serves as a master controller of bone formation[3,4]. The initial studies established the essential role of Wnt signaling in repressing the differentiation of mesenchymal progenitors into adipocytes and chondrocytes (cartilage-forming cells) and promoting the differentiation of these cells into osteoblasts, the cells that lay down bone[8].

In two recent breakthrough studies, Wnt signaling in osteoblasts through the canonical β-catenin pathway has also been implicated unexpectedly in regulating the formation of osteoclasts, the cells that resorb bone. One study provided evidence that the Wnt pathway positively regulates osteoblast expression of osteoprotegerin (OPG), a soluble receptor in the tumor necrosis factor (TNF) receptor family[9]. OPG inhibits receptor activator of NF-κB ligand (RANKL), a factor essential for formation of osteoclasts[10,11].

Another study took a slightly different approach and came to a similar conclusion: the Wnt pathway can suppress osteoclast-mediated bone resorption—this suppression seems to occur through downregulation of RANKL and upregulation of OPG in osteoblast lineage cells[12]. Thus, it seems that the Wnt pathway not only boosts bone formation by fostering osteoblast activity, but it can also inhibit bone resorption by affecting osteoclasts.

As the pivotal role of the Wnt/β-catenin pathway in the regulation of bone remodeling became clear, attention turned to approaches for manipulating this system to treat bone-remodeling disorders, including the bone loss in rheumatoid arthritis. Secreted regulators, of course, are one focus here, and several have been identified. Diarra *et al.* focused on DKK-1. The DKK family members inhibit the Wnt pathway by binding to the Wnt receptor LRP and a cell surface coreceptor, Kremen-1/2. DKK binding

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induces internalization of the receptor complex, thus reducing Wnt/β-catenin signaling[3,4].

The authors used a rat monoclonal antibody to mouse DKK-1 in three different models of inflammatory arthritis. In all models, the antibody protected against joint structural damage. No effect on inflammation was observed, suggesting that the beneficial effects were related to specific attenuation of osteoclast-mediated bone resorption.

A hallmark of the joint pathology in the three animal models of inflammatory arthritis is not only increased focal bone erosion, but also the suppression of bone formation at sites adjacent to focal osteoclast-mediated bone resorption[1]. Diarra *et al.* implicate DKK-1 in both the enhanced bone resorption as well as the suppression of bone formation in these models, since there was increased formation of bone (osteophytes) at the joint margins in the DKK-1 antibody–treated animals. Levels of DKK-1 were increased in the inflamed synovium (joint lining) and the sera in the animal models. Importantly, the effect of anti–DKK-1 treatment on inhibiting bone resorption was associated with increased expression of OPG. The authors speculate that the protection from bone destruction was caused by the capacity of OPG to block osteoclast-mediated bone resorption.

The authors also placed their findings in the context of other factors that play a role in joint destruction in arthritis. They showed that TNF-α, a potent cytokine produced by inflamed synovium, induced upregulation of DKK-1 in cultured synovial fibroblasts. Finally they showed that DKK-1 levels were also elevated in sera from individuals with rheumatoid arthritis, as well as in their inflamed synovium. In contrast, serum levels of DKK-1 were very low in individuals with ankylosing spondylitis, a form of arthritis associated with excessive bone formation. The findings implicate the Wnt pathway in controlling the pattern of both bone formation and resorption in human joint disease.

The new findings bolster the view that pathological processes in the bone involve regulatory systems that operate in physiological remodeling. As more information is gathered about repair and remodeling of joint tissues under physiologic conditions, it is likely that additional targets will be identified for the treatment of inflammatory arthritis and related diseases.

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