

Addendum

How Does Joint Remodeling Work?

New Insights in the Molecular Regulation of the Architecture of Joints

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Addendum to:

Dickkopf-1 Is a Master Regulator of Joint Remodeling

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ABSTRACT

Remodeling of joints is a key feature of inflammatory and degenerative joint disease. Bone erosion, cartilage degeneration and growth of bony spurs termed osteophytes are key features of structural joint pathology in the course of arthritis, which lead to impairment of joint function. Understanding their molecular mechanisms is essential to tailor targeted therapeutic approaches to protect joint architecture from inflammatory and mechanical stress. This addendum summarizes the new insights in the molecular regulation of bone formation in the joint and its relation to bone resorption. It describes how inflammatory cytokines impair bone formation and block the repair response of joints towards inflammatory stimuli. It particularly points out the key role of Dickkopf-1 protein, a regulator of the Wingless signaling and inhibitor of bone formation. This new link between inflammation and bone formation is also crucial for explaining the generation of osteophytes, bony spurs along joints, which are characterized by new bone and cartilage formation. This mechanism is largely dependent on an activation of wingless protein signaling and can lead to complete joint fusion. This addendum summarized the current concepts of joint remodeling in the limelight of these new findings.

Joints face profound remodeling in the course of arthritis. In humans, pathologic joint remodeling manifests as (i) destruction of joints due to bone erosion (rheumatoid arthritis), (ii) fusion of joints due to formation of bony spurs such as osteophytes, spondylophytes and syndesmophytes (ankylosing spondylitis) or (iii) a mixture of both changes (psoriatic arthritis). The molecular mechanisms determining these different forms of joint remodeling are not fully clarified, Insights in these mechanisms however are a clue to a deeper understanding of the architectural changes of human joints.

Similar to systemic bone turnover, which most is most prominent in the trabecular bone compartment of the spine and long bones, joints are hot spots of bone remodeling during inflammatory disease. Cytokines expressed by inflammatory cells in the synovial membrane regulate local bone homeostasis and enable to remodel joints during disease—a process which can either lead to crippling and functional loss or to fusion and stabilization of the affected joint. Rheumatoid arthritis is characterized by bone erosions, which are the result of an enhanced bone resorption. In rheumatoid arthritis osteoclasts, the primary bone resorbing cells, accumulate and degrade the periarticular bone as well as the mineralized cartilage.¹ Molecularly increased osteoclast formation is based on the expression of macrophage colony-stimulating factor (M-CSF) and receptor-antagonist of NFκB ligand (RANKL) in the synovial tissue, which both drive the differentiation of osteoclasts from monocytic precursors.²⁻⁴ Osteoclasts are specialized cells to resorb bone and their local accumulation in the joint leads to a catabolic state, which by far outweighs bone formation resulting in a negative net effect of bone remodeling. Inflammatory cytokines, such as TNF, IL-1, IL-6 and IL-17 induce osteoclast formation by enhancing the expression of RANKL and promoting differentiation of osteoclast precursor cells to mature osteoclasts.⁵⁻⁸ Abundance of proinflammatory cytokines in the synovial membrane of patients with RA, their induction of molecules involved in osteoclast formation and the influx of monocytes/macrophages serving as osteoclast precursor cells represent ideal prerequisites for osteoclast formation in joints.⁹

The fact that appropriate repair strategies are virtually absent in patients with RA and that bone is hardly rebuilt when bone erosions have emerged, suggests activation of molecular signals, which blunt bone formation. Bone formation itself is regulated by growth factors and hormones, which stimulate differentiation and activity of osteoblasts. Typical regulators of bone formation constitute parathyroid hormone, prostaglandins, bone morphogenic proteins (BMPs) and wingless proteins (Wnt). Particularly the role

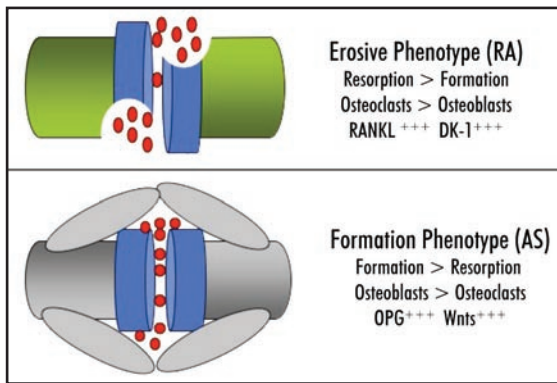


Figure 1. Patterns of joint remodeling.

of Wnt proteins in bone formation have achieved growing interest during the past few years, leading to identification of the LRP5/6 receptor as a key molecule for anabolic skeletal responses. Wnt proteins bind to the LRP5/6 receptor and lead to activation of a signal pathway involving GSK3 and β -catenin, which drive differentiation of mesenchymal cells into osteoblastogenesis.¹⁰ Regulators of Wnt-induced bone formation are Dickkopf (DKK) proteins, which competitively bind to LRP5/6 and prevent signaling activation by additionally engaging a negative coreceptor termed Kremen-1.^{11,12} DKK proteins thus regulate bone homeostasis by interference with Wnt signaling.¹³

We recently showed that inflammatory cytokines such as TNF induce DKK-1, a member of the DKK-family, which inhibits Wnt signaling. DKK-1 is highly expressed in inflammatory lesions of experimental arthritis and human rheumatoid arthritis.¹⁴ Moreover, increased levels can be detected in the serum of patients with RA, which depend on TNF. This is supported by the normalization of elevated DKK-1 levels in RA patients upon initiation of systemic TNF-blockade. Inhibition of DKK-1 in mice completely abolishes bone erosions in different models of experimental arthritis and leads to increased bone growth, which manifests as osteophyte formation in the joint.

DKK-1 links the inflammation with bone formation as RANKL links inflammation with bone resorption. The fact that TNF and presumably also other inflammatory mediators induce both proteins explains the profound negative effect of inflammation on bone. Inflammation uncouples the balance between bone resorption and formation, enhancing the former by inducing RANKL and by repressing the latter by DKK-1. Also appears to be a tight cross talk between the Wnt- and RANKL-pathways.¹⁵ Inhibition of DKK-1 in arthritic mice lead to protection from bone erosions and osteoclasts did not appropriately form. This effect is based on the induction of osteoprotegerin (OPG) a natural decoy receptor for RANKL, which blocks RANKL and thus osteoclast formation. OPG is induced by Wnt proteins and shifts the balance from bone resorption to bone formation.

In contrast to rheumatoid arthritis joints in ankylosing spondylitis and also in degenerative joint disease (osteoarthritis) show an attempt towards joint fusion rather than joint destruction. These bony spurs are the result of endochondral bone formation starting from the periosteum close to the joints, where osteoblasts differentiate build up bone matrix. We could demonstrate that Wnt proteins are crucially involved in this process since inhibition of DKK-1 lead to emergence of osteophytes and even complete fusion of joints. Taken

together these data suggest that the balance of the Wnt/DKK system determines the remodeling of joints by governing bone destruction as well as osteophyte formation in joints (Fig. 1).

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