Joint remodelling in inflammatory disease

Georg Schett

Ann Rheum Dis 2007;**66**(Suppl III):iii42–iii44. doi: 10.1136/ard.2007.078972

Correspondence to:
Georg Schett, Department of
Internal Medicine 3 and
Institute for Clinical
Immunology, University of
Erlangen-Nuremberg,
Krankenhausstrasse 12, D-
91054 Erlangen, Germany;
georg.schett@med3.imed.
uni-erlangen.de

Accepted 11 July 2007

Bone and the immune system share multiple interactions. The skeleton harbours the bone marrow and provides the niche for development of haematopoietic cells including the immune system. The immune system provides cells as well as molecular signals, which regulate bone homeostasis. Understanding the cellular and molecular regulation of the tight interaction between bone and the immune system is crucial for understanding the changes of skeletal architecture during inflammation. Whereas a short and self-limited activation of the immune system has no clinically meaningful effect on bone, prolonged immune activation as found in chronic inflammatory disease inevitably leads to bone wasting.

Inflammation is the main contributor to bone loss and to increased fracture risk in patients with chronic inflammatory rheumatic disease and chronic inflammatory bowel disease and adds to the deleterious effect of high-dose and/or prolonged treatment with glucocorticoids.^{1–3} At a systemic level, it is now known that inflammation tightly regulates fracture risk and even a small rise in the parameters of inflammation results in an increased risk of fracture.⁴

In the case of chronic joint disease such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) the inflammatory process is localised in the close vicinity to skeletal structures (fig 1). This allows inflammatory tissue to directly engage bone and cartilage in the disease process leading to a change and remodelling of the joint architecture, creating an irreversible damage and an impairment or even loss of function of the affected joints. In fact, the clinical picture of chronic inflammatory joint disease is a composite of inflammatory lesions and structural damage.⁵ Since structural damage is usually irreversible and accumulates during the course of disease, its contribution to the global clinical picture continuously increases over time.⁶ Synovial inflammation can create profoundly different patterns of joint remodelling.⁷ The hallmark of structural damage in RA is bone erosion, which is the consequence of local bone resorption along the joint surface. In contrast, AS is dominated by local bone formation, which is reflected by bony spurs called osteophytes at the joint ends and spondylophytes at the edges of the vertebral bodies. Though, also RA can show some radiological evidence for local bone formation, such as sclerosis of bone erosions and vice versa, AS can show some signs of local bone resorption such as erosions in the sacroiliac joint or as “anterior spondylitis”; these changes do not dominate the clinical picture of disease over time. PsA combines features of bone formation and bone resorption and thus forms a distinct entity. The molecular mechanisms determining these different forms of joint remodelling are not fully clarified, but novel insights suggest that regulation of osteoclast and osteoblast formation in joints determines the quality and quantity of structural changes in the joint.

The normal joint comprises a thin synovial membrane, which spans between the joint ends and constitutes the inner layer of the joint capsule. The inner layer of the synovium, which is directed to the synovial space containing the synovial fluid, is a fine mesodermal membrane composed of one to two cell layers.

The synovial membrane inserts at the periosteum of both joint ends and is in close connection with neighbouring ligaments and tendons. In the case of arthritis this synovial membrane faces a dramatic structural change, which is based on the influx of immune cells such as monocytes/macrophages and neutrophils, as well as T and B lymphocytes. In addition, proliferation of resident synovial fibroblasts occurs, contributing to synovial hyperplasia. Based on the close relationship of the synovial membrane to cartilage and bone, these structures are severely damaged during arthritis and face structural remodelling during the course of the disease.

Cytokines expressed by inflammatory cells in the synovial membrane regulate local bone homeostasis and enable joint remodelling during disease.⁸ Rheumatoid arthritis is characterised by bone erosions, which are the result of an enhanced bone resorption. In rheumatoid arthritis osteoclasts, the primary bone reabsorbing cells, accumulate and degrade the periarticular bone as well as the mineralised cartilage.⁹ Osteoclasts are specialised cells that reabsorb bone and their local accumulation in the joint by far outweighs bone formation and reflects a catabolic state.¹⁰ Osteoclasts form locally in the joint and differentiate from mononuclear precursor cells abundantly present in the inflamed joint due to the influx of monocytes in the context of inflammation. The differentiation of monocytes into the osteoclast lineage goes along with fusion of mononuclear osteoclast precursors, which already express osteoclast markers such as cathepsin K and tartrate-resistant acid phosphatase, to multinucleated giant cells. These cells then acquire final differentiation makers such as the calcitonin receptor and undergo polarisation to attach to the surface of mineralised tissue, which allows them to start resorption.

Molecularly increased osteoclast formation is based on the expression of macrophage colony-stimulating factor (MCSF) and receptor-antagonist of NF- κ B ligand (RANKL) in the synovial tissue, which both drive the differentiation of osteoclasts from monocytic precursors.^{11–13} Whereas MCSF is responsible for early osteoclast differentiation and binds to c-Fms, a surface receptor on monocytes, RANKL is additionally involved in late osteoclast differentiation and their activation. RANKL binds a receptor termed RANK on the plasma

Abbreviations: AS, ankylosing spondylitis; BMPs, bone morphogenic proteins; DKK, Dickkopf; MCSF, macrophage colony-stimulating factor; OPG, osteoprotegerin; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RANKL, receptor-antagonist of NF- κ B ligand; Wnt, wingless proteins

Figure 1 Joint remodelling in arthritis. "RA-like" joint remodelling is based on the resorption of juxta-articular bone by osteoclasts (OC, red cells). Molecules involved in osteoclast formation such as the receptor antagonist of NK- κ B ligand (RANKL) dominate, whereas those important for osteoblasts (OB) and bone formation are suppressed. "AS-like" joint remodelling is based on bone formation at the joint ends leading to osteophytes, which are bony spurs, built by osteoblasts (orange cells). Molecules involved in osteoblast formation such as Wingless (WNT) and bone morphogenic proteins (BMP) dominate, whereas those important for osteoclasts and bone resorption are suppressed.

membrane of monocytes. The major cellular source of MCSF and RANKL expression are the synovial fibroblasts and activated T cells. It is not fully clear whether it is predominantly the Th1 T cell phenotype that promotes osteoclast formation, or if Th17 cells might be more important, which are also known as potent promoters of osteoclast formation.^{14–15} The production of IL17 by Th17 cells may be considered a major inducer of TNF and IL1.¹⁶ Both cytokines drive inflammation in arthritic joints and are also responsible for bone and cartilage damage. TNF and IL1 induce expression of RANKL and promote osteoclast formation, and they also directly regulate osteoclast formation via TNF-receptor 1 and, in the case of IL1, by modulating the expression of the RANK on osteoclast precursors.^{17–19} Furthermore, TNF appears to influence the distribution of osteoclast precursor cells in the body by increasing their efflux from the bone marrow into the bloodstream, secondary lymphatic organs and inflammatory sites such as the synovium.²⁰ IL6 is another major link between inflammation and bone damage in arthritis since IL6 has also been identified as one of the pro-inflammatory cytokines, which induce RANKL expression and thus promote osteoclastogenesis.²¹ In contrast, anti-inflammatory mediators such as IL4, IL10 and presumably also TGF- β inhibit osteoclast formation and in line with these observations recent data also suggest that regulatory T cells suppress osteoclastogenesis via contact-dependent CTLA-4-triggered mechanisms.²²

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). The role 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.²³ Regulators of Wnt-induced bone formation are Dickkopf (DKK) proteins, which competitively bind to LRP5/6 and prevent signalling activation by additionally engaging a negative co-receptor termed Kremen-1.^{24–25} DKK proteins thus regulate bone homeostasis by interference with Wnt signalling.²⁶

We recently showed that inflammatory cytokines such as TNF induce DKK-1, a member of the DKK-protein family, which inhibits Wnt signalling. DKK-1 is highly expressed in inflammatory lesions of experimental arthritis and human RA.²⁷ Moreover, increased levels can be detected in the serum of patients with RA, which depend on TNF. This is supported by the normalisation of elevated DKK-1 levels in RA patients on initiation of the 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. This suggests that TNF induces molecules that block bone formation and prevent formation of osteophytes in response to inflammatory stress. It also indicates that blockade of TNF, although highly effective at inhibiting inflammation and bone erosion, is unlikely to be considered as a suitable method to block osteophyte formation. Indeed, failure of the TNF blockade to block osteophytes has been demonstrated in a murine arthritis model with a high rate of osteophyte formation.²⁸

DKK-1 links 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. There also appears to be a close crosstalk between the Wnt and RANKL pathway.²⁹ Inhibition of DKK-1 in arthritic mice led 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 RA, joints in AS and also in degenerative joint disease (OA) show an attempt towards joint fusion rather than joint destruction. These bony spurs are the results of endochondral bone formation starting from the periosteum close to the joints, where osteoblasts differentiate and build up bone matrix. One of the pathways that drives joint fusion is that of bone morphogenic proteins (BMPs). Inhibitors of BMPs such as noggin can prevent joint fusion.³⁰ Also Wnt proteins and their inhibitors are known to be crucially involved in this process. Taken together these data suggest that the balance of the RANKL/OPG system, the Wnt/DKK-1 system and the BMP/noggin system determines the remodelling of joints by governing bone destruction as well as osteophyte formation.

Competing interests: None declared.

REFERENCES

- 1 Gough AK, Liley J, Eyre S, Holder RL, Emery P. Generalized bone loss in patients with early rheumatoid arthritis. *Lancet* 1994;**344**:23–7.
- 2 Schett G, Redlich K, Smolen JS. Inflammation-induced bone loss in the rheumatic diseases. In: Favus MJ, eds. *Primer on the metabolic bone diseases and disorders of mineral metabolism*, 6th edn. USA: Lippincott Williams & Wilkins, 2006:310–3.
- 3 Card T, West J, Hubbard R, Logan RF. Hip fractures in patients with inflammatory bowel disease and their relationship to corticosteroid use: a population based cohort study. *Gut* 2004;**53**:251–5.

- 4 **Schett G**, Kiechl S, Weger S, Mayr A, Oberhollenzer S, *et al*. High-sensitivity C-reactive protein and risk of non-traumatic fractures in the Bruneck Study. *Arch Int Med* 2006;**166**:2495–501.
- 5 **Firestein GS**. Evolving concepts of rheumatoid arthritis. *Nature* 2003;**423**:356–61.
- 6 **Aletaha D**, Smolen J, Ward MM. Measuring function in rheumatoid arthritis: identifying reversible and irreversible components. *Arthritis Rheum* 2006;**54**:2784–92.
- 7 **Schett G**, Landewé R, Desiree van der Heijde D. TNF blockers and structural remodeling in ankylosing spondylitis: what is reality and what is fiction? *Ann Rheum Dis* 2007;**66**:709–11.
- 8 **McInnes I**, Schett G. Cytokines in the pathogenesis of rheumatoid arthritis. *Nat Immunol* 2007;**7**:429–42.
- 9 **Gravallese EM**, Harada Y, Wang JT, Gorn AH, Thornhill TS, Goldring SR. Identification of cell types responsible for bone resorption in rheumatoid arthritis and juvenile rheumatoid arthritis. *Am J Pathol* 1998;**152**:943–51.
- 10 **Teitelbaum SL**. Bone resorption by osteoclasts. *Science* 2000;**289**:1504–8.
- 11 **Seitz M**, Loetscher P, Fey MF, Tobler A. Constitutive mRNA and protein production of macrophage colony-stimulating factor but not of other cytokines by synovial fibroblasts from rheumatoid arthritis and osteoarthritis patients. *Br J Rheumatol* 1994;**33**:613–9.
- 12 **Gravallese EM**, Manning C, Tsay A, Naito A, Pan C, Amento E, *et al*. Synovial tissue in rheumatoid arthritis is a source of osteoclast differentiation factor. *Arthritis Rheum* 2000;**43**:250–8.
- 13 **Shigeyama Y**, Pap T, Kunzler P, Simmen BR, Gay RE, Gay S. Expression of osteoclast differentiation factor in rheumatoid arthritis. *Arthritis Rheum* 2000;**43**:2523–30.
- 14 **Kong YY**, Feige U, Sarosi I, Bolon B, Tafuri A, Morony S, *et al*. Activated T cells regulate bone loss and joint destruction in adjuvant arthritis through osteoprotegerin ligand. *Nature* 1999;**402**:304–9.
- 15 **Sato K**, Suematsu A, Okamoto K, Yamaguchi A, Morishita Y, Kadono Y, *et al*. Th17 functions as an osteoclastogenic T helper cell subset that links T cell activation and bone destruction. *J Exp Med* 2006;**2203**:2673–82.
- 16 **Lubberts E**, van den Bersselaar L, Oppers-Walgreen B, Schwarzenberger P, Coenen-de Roo CJ, Kolls JK, *et al*. IL-17 promotes bone erosion in murine collagen-induced arthritis through loss of the receptor activator of NF-kappa B ligand/osteoprotegerin balance. *J Immunol* 2003;**170**:2655–62.
- 17 **Lam J**, Takeshita S, Barker JE, Kanagawa O, Ross FP, Teitelbaum SL. TNF-alpha induces osteoclastogenesis by direct stimulation of macrophages exposed to permissive levels of RANK ligand. *J Clin Invest* 2000;**106**:1481–8.
- 18 **Wei S**, Kitaura H, Zhou P, Ross FP, Teitelbaum SL. IL-1 mediates TNF-induced osteoclastogenesis. *J Clin Invest* 2005;**115**:282–90.
- 19 **Zwerina J**, Redlich K, Polzer K, Joosten L, Kroenke G, Distler J, *et al*. TNF-induced structural joint damage is mediated by interleukin-1. *Proc Natl Acad Sci USA* 2007;**104**:11742–7.
- 20 **Ritchlin CT**, Haas-Smith SA, Li P, Hicks DG, Schwarz EM. Mechanisms of TNF-alpha- and RANKL-mediated osteoclastogenesis and bone resorption in psoriatic arthritis. *J Clin Invest* 2003;**111**:821–31.
- 21 **Wei S**, Wang MW, Teitelbaum SK, Ross FP. Interleukin-4 reversibly inhibits osteoclastogenesis via inhibition of NF-kappa B and mitogen-activated protein kinase signaling. *J Biol Chem* 2002;**277**:6622–30.
- 22 **Zaiss M**, Zwerina J, Polzer K, Skapenko A, Schulze-Koops H, Horwood N, *et al*. Regulatory T cells suppress osteoclast formation: a new link between the immune system and bone. *Arthritis Rheum*. In press.
- 23 **Miller JR**. The Wnts. *Genome Biology* 2001;**3**:3001.
- 24 **Glinka A**, Wu W, Delius H, Monaghan AP, Blumenstock C, Niehrs C. Dickkopf-1 is a member of a new family of secreted proteins and functions in head induction. *Nature* 1998;**391**:357.
- 25 **Bafico A**, Liu G, Yaniv A, Gazit A, Aaronson SA, Bafico A, *et al*. Novel mechanism of Wnt signalling inhibition mediated by Dickkopf-1 interaction with LRP6. *Nat Cell Biol* 2001;**3**:683.
- 26 **Morvan F**, Boulukos K, Clement-Lacroix P, Roman Roman S, Suc-Royer I, Vayssiere B, *et al*. Deletion of a single allele of the Dkk1 gene leads to an increase in bone formation and bone mass. *J Bone Min Res* 2006;**21**:934.
- 27 **Diarra D**, Stolina M, Polzer K, Zwerina J, Ominsky MS, Dwyer D, *et al*. Dickkopf-1 is a master regulator of joint remodeling. *Nat Med* 2007;**13**:156–63.
- 28 **Lories RJ**, Derese I, de Bari C, Luyten FP. Evidence for uncoupling of inflammation and joint remodeling in a mouse model of spondylarthritis. *Arthritis Rheum* 2007;**56**:489–97.
- 29 **Glass DA**, Bialek P, Ahn JD, Starbuck M, Patel MS, Clevers H, *et al*. Canonical Wnt signaling in differentiated osteoblasts controls osteoclast differentiation. *Dev Cell* 2005;**8**:751–64.
- 30 **Lories RJ**, Derese I, Luyten FP. Modulation of bone morphogenetic protein signaling inhibits the onset and progression of ankylosing enthesitis. *J Clin Invest* 2005;**115**:1571–9.