BONE

Bony spur formation in inflammatory arthritis: an active and independent process

Bony spurs (Figure 1) are responsible for much of the pain and limited joint movement experienced by sufferers of some inflammatory joint diseases. The relationship between inflammation, bone erosion and bony spur formation in arthritis is the subject of ongoing investigation, but new research by Georg Schett and colleagues shows that, once arthritis is induced in an experimental setting, bony spur formation does not depend on inflammation and bone erosion.

Much is known about the pathogenic mechanisms responsible for the catabolic processes involved in inflammatory joint destruction, with tumor necrosis factor (TNF) and receptor activator of nuclear factor κB ligand (RANKL) both having key roles in enhancing osteoclastogenesis. Anti-TNF agents have well-established anti-inflammatory properties, but their effect on the anabolic process of bone spur formation is unclear. Not only are the relationships between spur formation, inflammation and bone resorption unclear: so, too, are the kinetics of bony spur formation. Thus, Schett's team first set out to define the kinetics of bony spur formation in adjuvant-induced arthritis (AIA) and collagen-induced arthritis (CIA) rat models of inflammatory arthritis.

As early as 3 days and 5 days after the onset of clinical symptoms and massive synovial infiltration, periosteal proliferation was seen in the hind paws of the CIA and AIA models, respectively. Before the bony spurs emerged, small bone erosions occurred and osteoclast numbers increased, indicating that spur formation might require a prior resorptive stimulus. Bony spur formation in these two models, therefore, occurs subsequently to inflammation, initial osteoclast formation and bone erosion, suggesting that spur formation might indeed represent a response to joint inflammation. In both models, initial lesions were characterized by proliferating mesenchymal cells at periosteal sites near the joint space. By 27 days after disease onset, the bony spurs had grown rapidly and consistently in both models.

As osteoclasts are usually required to remodel mineralized tissue, the researchers next studied whether there was any link between new bone formation and the appearance of osteoclasts. Although the kinetic pattern of bone growth in bony spurs in CIA and AIA models was similar to that of the entire lesion, the actual bony part of the spur was always slightly smaller than the lesion, indicating that fibrous and cartilage-like tissue was consistently being remodeled into bone alongside consistent lesion growth. Even during early disease onset (day 5), small bone deposits appeared in lesions, which then induced the appearance of osteoclasts. The increase in the size of the bone within the bony spurs was then accompanied by an accumulation of osteoclasts in these lesions before a gradual drop in their number.

To address whether the growth of bony spurs is dependent on inflammation or osteoclast generation, the team of researchers inhibited inflammation by blocking TNF, and used osteoprotegerin to inhibit RANKL and thereby prevent osteoclast formation. They started the treatments 3 days after inducing arthritis in both rat models, when bone erosions were already visible. Although inhibiting TNF reduced inflammation, it did not prevent the formation of bony spurs in either model. Similarly, osteoprotegerin markedly reduced the number of osteoclasts but had no effect on the size of bony spurs; notably, preventive treatment with osteoprotegerin could not stop the formation of spurs.

"These data support current pathophysiologic concepts of bony spur formation and ankylosis suggesting that these processes are primarily based on the reactivation of old developmental programs involved in bone and cartilage formation," explains Schett, adding that "bone spur formation, therefore, seems to be an active and independent process, which escapes control from inflammation and bone erosion." Looking forwards, Schett is keen to further define the molecular switches that control bone growth and ankylosis of joints: "It will be interesting to know how joints can sense pathological situations, allowing them to react with bony overgrowth."

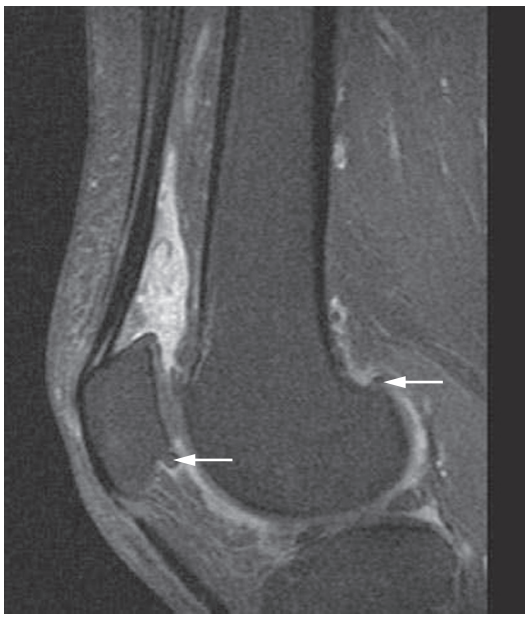

Figure 1 | Bony spurs in a human osteoarthritic knee (arrows). Reproduced from *Nat. Clin. Pract. Rheumatol.* **5**, 149–158 (2009).

Katrin Legg

Original article Schett, G. *et al.* Tumor necrosis factor α and RANKL blockade cannot halt bony spur formation in experimental inflammatory arthritis. *Arthritis Rheum.* **60**, 2644–2654 (2009).