OSTEOARTHRITIS

TGF- β overload at bones of cartilage degeneration

Recruitment of mesenchymal stem cells (MSCs) and aberrant bone formation, uncoupled from resorption, is stimulated by an increase in subchondral bone concentration of transforming growth factor β (TGF- β) during osteoclastic resorption, in response to abnormal mechanical load. This alteration in bone microarchitecture leads—despite the protective effect of TGF- β expression in cartilage—to cartilage degeneration and osteoarthritis (OA), and can be attenuated by inhibition of TGF- β 1 activity in subchondral bone. Thus, as work now published by Zhen *et al.* in *Nature Medicine* suggests, targeting TGF- β in subchondral bone could be a therapeutic strategy in OA.

Subchondral bone pathology is linked to cartilage degeneration in OA. Divergent effects of signalling molecules in different joint tissues might partly explain why biologic therapies have so far been of limited effectiveness in the disease.

Articular cartilage structural integrity is known to depend on TGF- β signalling, and bone-marrow MSCs are recruited to resorption pits via TGF- β activation during new trabecular bone formation. Whereas lack of endogenous TGF- β aggravates cartilage degeneration in mouse models of OA, therefore, it also suppresses osteophyte formation.

To investigate functions of TGF- β in articular cartilage and subchondral bone in OA, Zhen and colleagues used the anterior cruciate ligament transection (ACLT) mouse model, in which surgery creates abnormal joint loading. ACLT induced osteoclastic bone resorption, clustering of nestin-positive MSCs, formation of bone-marrow osteoid lesions and altered subchondral bone morphology, accompanied by increased TGF- β signalling and followed by cartilage degeneration. Similar bone and cartilage disruptions occurred in mice expressing mutant active TGF- β 1 in subchondral bone marrow. Subchondral bone concentrations of active TGF- β 1 were substantially higher in affected joints of patients with OA than in healthy controls.

Inhibition of TGF- β receptor 1 normalized osteoid localization in ACLT mice and protected articular cartilage. Anti-TGF- β antibody beads implanted into the subchondral tibia of ACLT rats suppressed aberrant bone formation, without altering TGF- β signalling in cartilage. Together with gene targeting results indicating that MSCs respond to subchondral bone TGF- β signalling during OA progression, the findings reinforce this pathway as a potential therapeutic target.

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Original article Zhen, G. *et al.* Inhibition of TGF- β signaling in mesenchymal stem cells of subchondral bone attenuates osteoarthritis. *Nat. Med.* doi:10.1038/nm.3143