Nature Reviews Rheumatology **8**, 247 (2012); published online 27 March 2012; doi:10.1038/nrrheum.2012.46

BONE

Two Notches in osteoclastogenesis

Notch receptors are implicated in regulating osteoclastogenesis—an important process in driving bone erosion during rheumatoid arthritis (RA). The role of individual Notch receptors and ligands in osteoclastogenesis, however, are currently undefined. Now, Sekine *et al.* have identified differential roles for the Notch2 receptor and its ligand Delta-like protein 1 (DLL1) and the Notch1 receptor and its ligand Jagged1 in the regulation of osteoclastogenesis.

The group used a panel of antibodies that block the activity of mouse and human Notch ligands, as well as agonists of mouse and human Notch receptors. "We found that, *in vitro,* in cells derived from both mice and humans, DLL1 promotes osteoclastogenesis through Notch2 whereas Jagged1 suppresses osteoclastogenesis through Notch1," explains Chiyoko Sekine, author. Moreover, inhibition of Notch signaling suppressed osteoclastogenesis suggesting that the Notch2–DLL1 signaling pathway is dominant. *In vivo,* in a mouse model of RA, an antibody that blocked DLL1 activity reduced the number of osteoclasts in affected joints and suppressed bone erosion in these mice. This antibody also reduced bone loss in ovariectomized mice.

The group are now confirming the effect of this blocking antibody in further mouse models of RA to fully characterize the potentially beneficial effects. "Interestingly, as the differential regulation of osteoclastogenesis was observed in both mice and humans, agonists of the Notch1–Jagged1 pathway or antagonists of the Notch2–DLL1 pathway could be useful for amelioration of bone erosion in patients with RA," explains Sekine.

Katherine Smith

Original article Sekine, C. *et al.* Differential regulation of osteoclastogenesis by Notch2/Delta-like 1 and Notch1/Jagged1 axes. *Arthritis Res.* Ther. doi.10.1186/ar3758