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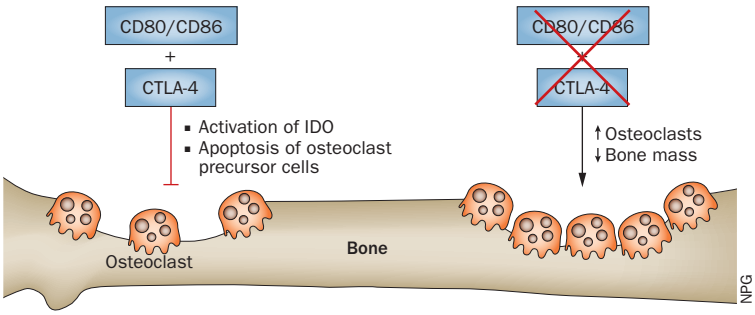
BONE

The immune system takes control of bone homeostasis



New research published in *Science Translational Medicine* further demonstrates the close links between the immune system and bone homeostasis as the field of osteoimmunology becomes more established. The authors show that the immune co-stimulatory molecules CD80 and CD86 negatively regulate bone resorption by controlling osteoclastogenesis.

Bone is dynamic and bone remodelling is therefore tightly controlled. The immune system can influence osteoclastogenesis, and the interaction between T cells and osteoclast lineage cells is particularly important. Georg Schett and colleagues hypothesized that T cell–osteoclast crosstalk during bone homeostasis is akin to the interaction between antigen-presenting cells (APCs) and T cells—an important checkpoint in immune regulation—for which co-stimulatory signals between APCs and T cells are crucial. Thus, they reasoned that co-stimulatory molecules might be involved in immune–bone interactions.

The researchers first confirmed that, compared with wild-type mice, *Cd80*$^{-/-}$*Cd86*$^{-/-}$ mice had reduced bone mass and increased numbers of osteoclasts overall, as well as increased numbers of osteoclasts at the bone surface. *In vitro* studies indicated that *Cd80*$^{-}$*Cd86*$^{-}$ osteoclasts resisted physiological inhibition by cytotoxic T-lymphocyte protein 4 (CTLA-4) or regulatory T cells. Engagement of CD80/CD86 by CTLA-4 was, therefore, crucial to the negative regulation of osteoclastogenesis.

Next, they showed that the interaction of CTLA-4 with CD80/CD86 activated indoleamine 2,3-dioxygenase (IDO), which has a role in mediating the suppressive effects of regulatory T cells. Crucially, IDO induction led to enhanced apoptosis in osteoclast precursors.

Finally, the investigators analysed the number of osteoclast precursor cells in peripheral blood (as a measure of osteoclastogenesis) in patients who had been treated with either abatacept (a CTLA-4–Ig fusion protein) or ipilimumab (an anti-CTLA-4 antibody). Importantly, the findings in humans were consistent with the mouse data. Ipilimumab increased, whereas abatacept decreased, the number of osteoclast precursor cells.

"We can now explain why abatacept has a strong potential to protect bone in patients with arthritis," says author Georg Schett, who postulates that fast protection of bone by abatacept might be advantageous when treating arthritis early in the disease course.

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Original article Bozec, A. *et al.* T cell costimulation molecules CD80/86 inhibit osteoclast differentiation by inducing the IDO/tryptophan pathway. *Sci. Transl. Med.* **6**, 235ra60 (2014)