PHYSIOLOGY

Receptor becomes a ligand

The protein RANKL is released by bone-forming cells called osteoblasts, and binds to its receptor, RANK, on osteoclast cells to trigger bone removal. It emerges that the pathway can act in reverse to stimulate bone formation. SEE ARTICLE P.195

MONE ZAIDI & CHRISTOPHER P. CARDOZO

The integrity of the adult skeleton must be maintained by tightly coupled bone-remodelling processes: old bone is resorbed by cells called osteoclasts and is replaced by new bone, which is synthesized by cells called osteoblasts[1]. Osteoblasts become buried within the newly formed bone and morph into a third cell type, osteocytes. Osteoblasts and osteocytes secrete the signalling protein RANKL, which activates the RANK receptor on haematopoietic stem cells, triggering their differentiation into osteoclasts and so promoting osteoclast function[2,3]. But it is less clear how osteoclasts signal to osteoblasts to modify bone formation. On page 195, Ikebuchi *et al.*[4] provide compelling evidence that osteoclasts regulate osteoblasts using the same RANKL–RANK system acting in reverse — in this setting, it is the RANKL ligand that modulates intracellular signalling, rather than the RANK receptor.

The authors first confirmed previous data[5] indicating that osteoclasts release small extracellular vesicles that harbour RANK on their surface (Fig. 1a). They showed that overlaying a layer of isolated RANK-bearing vesicles on a layer of mouse osteoblasts in culture activated the expression of the differentiation-promoting genes *Col1a1, Runx2* and *Osx* in the cells. The presence of RANK-containing vesicles also triggered mineral deposition by osteoblasts, both *in vitro* and in mouse skulls *in vivo*. Mineral deposition, indicative of bone formation, was promoted by the Runx2 protein.

Runx2 is known[6] to be activated by a signalling pathway involving the proteins PI3K, Akt and mTOR. Indeed, Ikebuchi *et al.* found that Runx2 activation in mouse osteoblasts was blocked by the mTOR-inhibitor molecule rapamycin. The authors then showed that RANKL activates the PI3K–Akt–mTOR pathway through a region in its cytoplasmic tail that is rich in the amino acid proline; this proline-rich domain interacts with kinase enzymes that activate PI3K. Mutations in crucial proline residues within this domain abrogated the effects of RANK–RANKL reverse signalling.

Finally, Ikebuchi and colleagues established that RANKL monomers are not activated by RANK. Instead, crosslinking of individual RANKL proteins to produce multimers is a prerequisite for downstream signalling. The authors showed that genetically modified anti-RANKL antibodies containing structures called leucine zippers, which are known to induce trimer formation, could activate RANKL reverse signalling in osteoblasts (Fig. 1b).

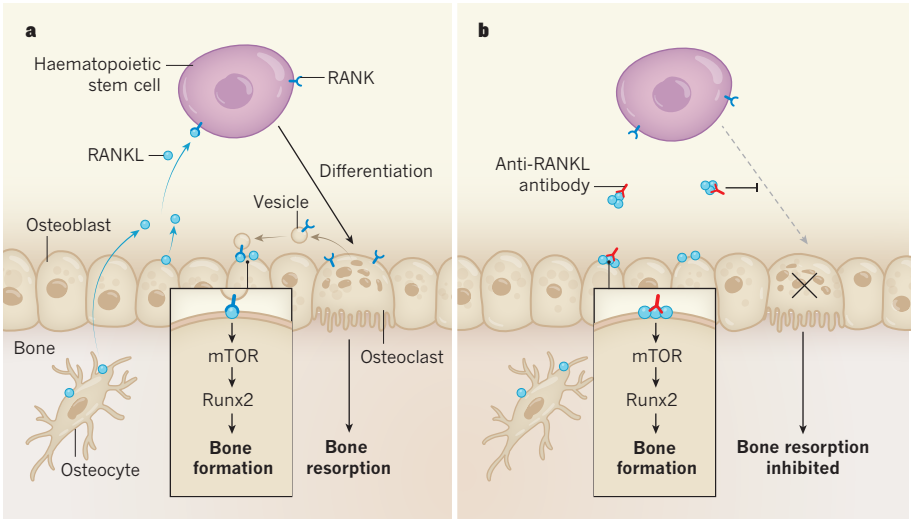

Figure 1 | Uncoupling bone formation and resorption. **a**, The signalling molecule RANKL is released by bone-producing cells called osteoblasts and their descendants, osteocytes. RANKL binds to the RANK receptor on haematopoietic stem cells, triggering their differentiation into cells called osteoclasts that resorb bone. Ikebuchi *et al.*[4] report that osteoclasts release extracellular vesicles that have RANK on their surface. Binding of vesicular RANK to RANKL on the surface of osteoblasts (and perhaps osteocytes, not shown) triggers intracellular signalling; the mTOR pathway is activated, which triggers production of proteins such as Runx2 that promote bone formation. **b,** The authors developed an anti-RANKL antibody, which binds and inactivates multiple RANKL monomers, thus reducing the formation of osteoclasts from their precursors. These antibodies also activate signalling in osteoblasts by binding cell-surface RANKL. Thus, they trigger bone formation while inhibiting bone resorption.

These intriguing data reveal a plausible physiological explanation for why RANK would be released from osteoclasts as cargo in extracellular vesicles[5]; they also establish that RANKL can act as a signal-transducing molecule at the cell surface, rather than merely as a secreted signalling protein. More broadly, this is the first demonstration of signal transduction by vesicular cell-surface receptors interacting with membrane-bound ligands. Finally, and perhaps most importantly, the study provides a mechanism by which osteoclasts in the process of resorbing bone communicate with nearby osteoblasts to regulate the extent to which new bone is formed. It remains unclear whether RANK-containing vesicles can activate cell-surface RANKL on osteocytes, which might not be in close proximity to osteoclasts.

On the therapeutic front, the anti-RANKL antibody denosumab is widely used to prevent and treat both osteoporosis and skeletal problems caused by the spread of cancers to bone. By preventing RANKL–RANK forward signalling, denosumab inhibits bone resorption by osteoclasts. But, in doing so, it transiently lowers bone formation, because of the tight coupling between osteoclasts and osteoblasts[7]. Ikebuchi and colleagues' newly engineered anti-RANKL antibody could potentially uncouple resorption and formation, and so be a more-effective alternative to denosumab. Notably, the authors found that, in mice whose ovaries had been removed (a model for post-menopausal osteoporosis), the antibody reduced bone resorption, but did not suppress bone formation.

It is difficult to speculate on whether Ikebuchi and co-workers' anti-RANKL

antibody would have untoward side effects. This is certainly possible, because RANK and RANKL have many roles elsewhere in the body. For instance, immune cells called T cells express RANKL, and RANK is found on dendritic cells, with which T cells interact to trigger immune responses; in this setting, the interaction between RANK and RANKL enhances T-cell immunity[8]. The proteins have also been identified in the brain, notably in some neurons and neuron-supporting cells, in brain-specific immune cells called microglia, and in brain tissue deprived of oxygen[9]. They have also been implicated as mediators of fever-related responses to infections[10].

That said, a decade's worth of clinical studies using denosumab has revealed no discernible effects on the immune system or the brain. There is also no evidence yet for reverse RANK signalling in immune cells or neurons. Nonetheless, given that nearly all nucleus-bearing cells release extracellular vesicles, further studies of RANK–RANKL signalling in non-skeletal tissues are imperative. Given nature's propensity for reusing principles of intercellular signalling in many ways, the possibility of reverse signalling by other receptors must also be explored. ■

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CONDENSED-MATTER PHYSICS

Spins travel far in an antiferromagnet

Controlled long-distance transport of electron spins is required for a kind of electronics known as spintronics. Such transport has been realized in an antiferromagnet, the most common type of magnetic material. SEE LETTER P.222

SERGIO M. REZENDE

Strongly magnetic materials called antiferromagnets have an intriguing property. Below a certain temperature, the spins (intrinsic angular momenta) of neighbouring atoms in the material point in opposite directions, so that the material exhibits no response to an external magnetic field. The discovery and pioneering studies of antiferromagnets were made by the physicist Louis Néel, who stated in his 1970 Nobel Lecture that the materials "are extremely interesting from the theoretical viewpoint, but do not seem to have any applications" (see go.nature.com/2lzrly8). This pessimistic view of antiferromagnets would change dramatically a few decades later. Today, the materials have practical applications, and promise to deliver several more. On page 222, Lebrun *et al.*[1] report the observation of long-distance spin transport in an antiferromagnetic insulator, demonstrating that such materials could be used for spin-based electronics (spintronics).

The debut of antiferromagnets in technology was made possible through the 1988 discovery of the giant magnetoresistance effect[2,3], which resulted in the 2007 Nobel Prize in Physics. This discovery showed that, in magnetic structures containing nanometre-thick multilayers (stacks of different ultrathin films), electron transport could be controlled by the spin of the electrons — rather than by their electric charge, as in conventional electronics. This finding triggered research into magnetic multilayers, and gave birth to the field of spintronics, which has revolutionized magnetic recording techniques and promises to bring about advances in information technologies[4].

Antiferromagnets proved to be essential in sensors that use the giant magnetoresistance effect. Since the late 1990s, the read heads for computer-disk drives have been based on such sensors. These read heads are much more sensitive to changes in magnetic fields than are conventional ones. However, although antiferromagnets are important for spintronic devices, they have had a passive role. Ferromagnets — materials in which all of the atomic spins are aligned — have had the active role.

In the past decade, this situation has begun to change because of experimental and theoretical results showing that antiferromagnets have several advantages over ferromagnets in spintronic devices. One advantage is the insensitivity of antiferromagnets to perturbations in external magnetic fields. Another is their ultrafast dynamics, which could enable devices to operate at terahertz-scale (10^{12} Hz) frequencies and therefore facilitate faster electronics. Developments in the past few years have given rise to the field of antiferromagnetic spintronics[5–7], which now gains a boost, thanks to Lebrun and colleagues.

The authors used a thin, flat sample of

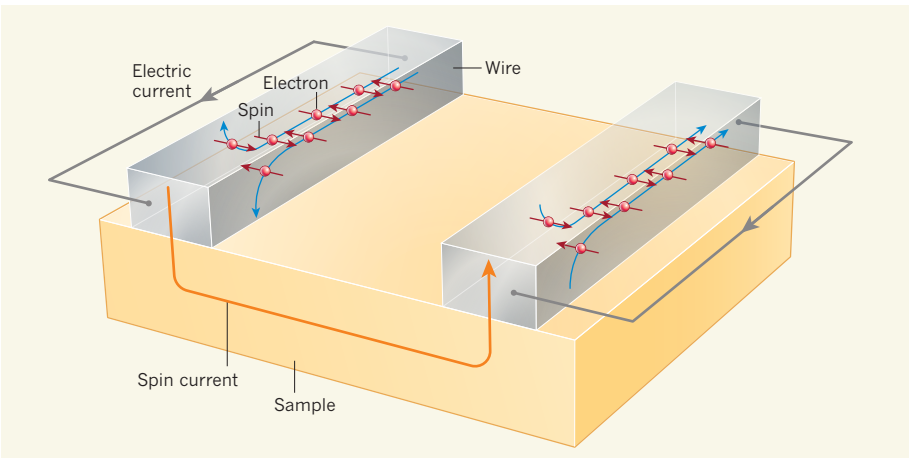

Figure 1 | Spin transport in an antiferromagnetic insulator. Lebrun *et al.*[1] carried out an experiment using a thin, flat sample of an electrically insulating material that exhibits a type of magnetism known as antiferromagnetism. The authors deposited two thin platinum wires on the surface of the sample and injected an electric current into one of the wires (the left wire). This electric current was converted into a spin current, which is produced by electrons with opposite spins (intrinsic angular momenta) moving in opposite directions (blue arrows). The spin current flowed into the sample and was transported laterally towards the second wire, where it was converted into an electric current. The authors demonstrated that the spin current could be transported over a relatively long distance between the wires (tens of micrometres at a temperature of 200 kelvin), which is a requirement for spin-based electronics.