nerve branch is performed several days before actual axotomy[6,7]. Candidate mechanisms that may account for enhanced regeneration after such conditioning include neurotrophic signaling, increases in cyclic nucleotides (cAMP) or magnified polyamine metabolism[8,9]. Using the conditioning paradigm, Hanz *et al.* also show that the effectiveness of such conditioning lesions depends on retrograde signaling mediated by the importin-dynein complex.

Several important questions arise from this study. For those most concerned about the prospects for manipulating human injury responses, a pressing question is whether the importin/dynein network is also involved in central nervous system (CNS) and spinal cord axonal regeneration. Regeneration in the adult CNS is substantially more limited than in the peripheral nervous system. Moreover, some axonal populations, such as corticospinal tract axons in the spinal cord, are particularly refractory to regrowth after injury. Although CNS myelin harbors several growth-inhibitory proteins, corticospinal axons show only minimal regrowth even in an environment free of myelin-associated inhibitors. Insufficient regenerative responses of these and other CNS neurons might be due to an insufficient amount of retrograde injury signal reaching the cell body from the lesioned axon, or to the long distance over which this signal must travel (up to a meter in humans).

Long distances could carry the risk of signal dampening or loss[10]. On the other hand, CNS neurons might lack the appropriate intracellular machinery to convey the retrograde signal. Experiments similar to those of Hanz *et al.* now need to be conducted within CNS neurons.

It is also important to identify the actual injury signals that are transported by importins, and to discover what they do once they reach the cell body. The expression of growth-associated genes is upregulated after injury in some neurons, yet the overexpression of these proteins is only partially effective in enhancing regeneration in some neuronal populations[11–13]. Array analyses of gene expression and analyses of changes in protein translation in injured and uninjured neurons might provide some insight.

Cumulatively, answers to these questions could provide a means of experimentally enhancing the injury signal or its transport machinery, thereby augmenting the regenerative state of CNS neurons. Such an approach would represent a new opportunity for increasing CNS regeneration and plasticity.

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Laying down the bone

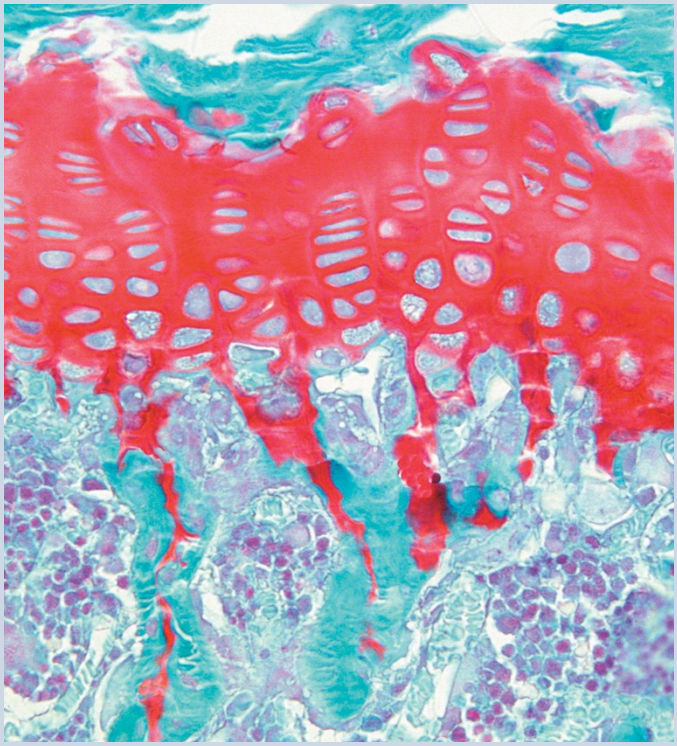
A plate of rapidly dividing chondrocytes—cartilage-forming cells—controls elongation within the bone (cartilage of mouse tibia stained orange here). Previous work has shown that the versatile molecule gp130 influences bone formation, but the data have not yielded a clean story. In the 2 February *Journal of Clinical Investigation*, Natalie Sims *et al.* clear the air.

Previous studies had found that gp130-knockout mice ramp up production of osteoclasts, bone-resorbing cells. But the picture quickly becomes more complicated. In cell culture, for instance, antibodies that neutralize gp130 also increase osteoclast formation.

gp130 dimers can activate two signaling pathways: the STAT-1/3 transcription pathway and the SHP-2/Ras/MAPK pathway. To dissect the influence of each of these pathways, Sims *et al.* took advantage of mice containing mutations that knocked out each pathway independently. The investigators found that STAT-1/3-mediated proliferation of chondrocytes and bone-forming osteoblasts. The SHP-2/Ras/MAPK pathway inhibited formation of bone-eating osteoclasts.

The authors speculate that the output could depend on gp130 binding partners. For instance, the cytokine IL-6, previously implicated in arthritis, was found to stimulate osteoblast generation through gp130/STAT-1/3 signaling.

Charlotte Schubert



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