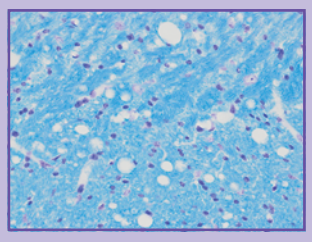
For TLR ligands, 3 is better than 2

Adjuvants are frequently used to increase the quantity of vaccine-induced T cell immune responses. Stimulating certain pairs of TLRs, a family of microorganism-sensing receptors, has a synergistic effect on the magnitude of such immune responses in preclinical models. TLR ligands therefore represent potential new vaccine adjuvants. However, the quality of a T cell response can be more important than its quantity, and Zhu and colleagues have now determined that a specific combination of three TLR ligands increases the quality but not the quantity of a vaccine-induced T cell response in mice (607–616). When mice were immunized with an HIV envelope peptide together with three TLR ligands — MALP2, which binds TLR2/6 heterodimers; polyI:C, which binds TLR3; and CpG DNA, which binds TLR9 — they mounted a more effective protective T cell response than did mice immunized with the HIV envelope peptide together with any two of the ligands. Further analysis determined that the increased protection correlated with peptide-specific T cell responses of enhanced quality, primarily due to augmented functional avidity for cells presenting the HIV envelope peptide, rather than enhanced quantity. The authors therefore suggest that select TLR ligand combinations could be used to separately manipulate the quality and quantity of vaccine-induced T cell responses.

Separating bone formation and destruction

Researchers developing new treatments for osteoporosis are looking to design therapeutics that increase the amount and/or quality of bone. However, osteoblast-mediated bone formation is tightly coupled to osteoclast-mediated bone destruction. Identifying ways to separate these two processes is therefore crucial to designing anabolic approaches to treat osteoporosis. Walker and colleagues have now identified one potential way to do this in mice (582–592). Specifically, they determined that the gp130-signaling cytokine oncostatin M (OSM) induces distinct functions in mice when using two receptors, OSM receptor (OSMR) and leukemia inhibitory factor receptor (LIFR). When OSM bound a receptor complex including OSMR, it stimulated expression of RANKL, a pro-osteoclastic factor. In contrast, when OSM bound a receptor complex including LIFR, it lowered production of sclerostin, an inhibitor of bone formation produced by osteocytes, but did not stimulate RANKL production. Consistent with this, mice lacking OSMR were found to have increased bone mass. Importantly, mouse OSM enhanced bone formation in *Osmr*$^{-/-}$ mice by inhibiting sclerostin production. These data indicate the existence of two pathways through which mouse OSM can act and reveal the existence of a pathway by which bone formation can be stimulated independently of bone destruction.

Modeling inherited stroke faithfully



Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common inherited form of stroke and vascular dementia. Although it is known to be caused by dominant mutations in *NOTCH3*, how these mutations promote disease pathogenesis has not been determined, largely because there is no good animal model of the disease. However, Joutel and colleagues have now generated a mouse model of CADASIL by using a large P1-derived artificial chromosome to overexpress a large genomic segment containing a CADASIL-causing *Notch3* point mutation in an endogenous-like expression pattern in mice (433–445). Initial analysis determined that the mice developed the hallmarks of CADASIL, including deposition of granular osmiophilic material in brain vessels, progressive damage to the white matter, and reduced cerebral blood flow. Further analysis uncovered evidence that cerebrovascular dysfunction and microcirculatory failure are very early events triggered by the CADASIL-causing mutant Notch3 and that they ultimately lead to key features of the CADASIL-like disease, specifically hypoperfusion and white matter damage. The authors hope that additional studies using these mice will identify other pathogenic mechanisms and provide insight into potential therapeutics for the treatment of CADASIL.

N-WASP helps hair growth

Many physiological processes in the skin, including wound healing and hair follicle (HF) cycling, involve actin cytoskeleton reorganization regulated by the Rho family GTPases Cdc42 and Rac1. Consistent with this, aberrant regulation of the cytoskeleton is associated with various human skin disorders. In this issue (446–456), Lyubimova and colleagues have determined that neural Wiskott-Aldrich syndrome protein (N-WASP), which acts downstream of Cdc42 to regulate actin cytoskeleton reorganization, has a key role in skin function and HF cycling, by generating and analyzing mice lacking N-WASP in skin. Analysis of the mice indicated that N-WASP is critical for keratinocyte proliferation and hair growth but is dispensable for epidermal differentiation and wound healing. The role of N-WASP in hair growth was found to be a result of its key role in HF cycling and in the maintenance and differentiation of HF progenitor cells. As N-WASP deficiency resulted in decreased nuclear localization of β-catenin in follicular keratinocytes and decreased Wnt-dependent transcription, the authors suggest that N-WASP promotes β-catenin–dependent transcription, thereby promoting the differentiation of HF progenitor cells.