■ METABOLISM

An obesity hub

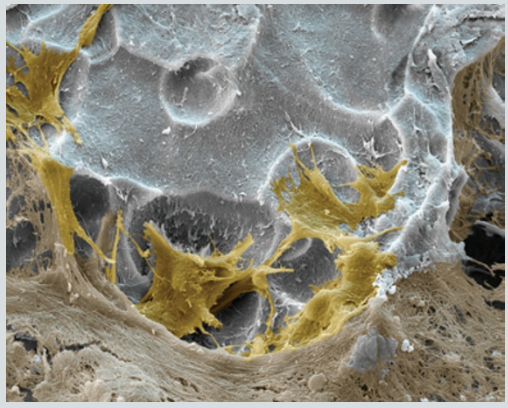
Dysregulation of thermogenesis and inflammation are linked to obesity. A new study in mice shows that a receptor commonly expressed in fat cells controls both programs and functions in a cell-autonomous manner (*Cell* **151**, 96–110).

Li Ye *et al.* used a chemical screen to identify proteins in white adipocytes that increase expression of the gene encoding Pgc1α in these cells, as this reflects activation of the thermogenic program. TRPV4, a calcium-permeable ion channel that is highly expressed in white fat cells, was found to negatively regulate Pgc1α and oxidative metabolism in these cells. Inhibition of TRPV4 increased expression of the gene encoding uncoupling protein 1 (UCP1) and other mitochondrial genes, which caused 'browning' of adipocytes and boosted respiration. Interestingly, this inhibition also dampened proinflammatory pathways, which decreased the expression of chemokines and cytokines and their secretion from fat cells. Mice lacking TRPV4 showed an improved metabolic profile; they were protected from diet-induced obesity owing to increased energy expenditure and had improved insulin sensitivity as a result of reduced inflammation in adipose tissue.

Although the authors found that TRPV4 antagonists could improve glucose tolerance in obese mice, which suggested that they might have potential for treating obesity and type 2 diabetes, further research should investigate the effects of TRPV4 inhibition in other tissues where this channel is expressed.—*CP*

BONE

Regulating bone remodeling



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Increased osteoclast activity is implicated in a number of bone loss conditions; thus, targeting bone resorption by osteoclasts could be a potential therapeutic avenue for these pathologies. A new study shows that the adenosine diphosphate (ADP) receptor P2RY12 regulates osteoclast function and can be therapeutically targeted in mouse models of bone loss (*J. Clin. Invest.* 122, 3579–3592).

ADP is known to increase osteoclast activity, so Xinming Su *et al.* decided to examine the role of P2RY12 in osteoclasts. Mice lacking P2RY12 showed decreased osteoclast activity *in vivo* and were partially protected from age-related bone loss. Bone marrow macrophages from *P2ry12*$^{-/-}$ mice could be differentiated *ex vivo* into mature osteoclasts, but these osteoclasts showed reduced resorption function and could not be stimulated by ADP to increase bone resorption.

The authors then tested the susceptibility of *P2ry12*$^{-/-}$ mice to various types of pathological bone loss and found that they were less susceptible than wild-type mice to arthritis-associated, tumor-associated and ovariectomy-induced bone loss. Su *et al.* also showed that clopidogrel, which inhibits P2RY12 and is a US Food and Drug Administration–approved antiplatelet drug, could partially protect wild-type mice from pathological bone loss.

Although there are currently no prospective data on the effects of clopidogrel on bone in patients being treated with this drug, clinical studies to evaluate this aspect may be useful to better assess the potential for therapeutically targeting P2RY12 in bone loss conditions.—*MS*

■ IMMUNOLOGY

CD8$^+$ T cells mediate elite control

Elite controllers are rare individuals who are infected with HIV-1 yet maintain low to undetectable levels of virus in their blood and have no disease. Many of these people express specific major histocompatibility complex (MHC) class I alleles, which suggests that viral control is mediated by CD8$^+$ T cells. David Watkins and his colleagues now report that in a monkey model of elite control of simian immunodeficiency virus (SIV) infection, CD8$^+$ T cells targeting just three epitopes in the SIV Vif and Nef proteins correlate with control of virus replication (*Nature* doi:10.1038/nature11443).

In these authors' model of elite control—rhesus macaques expressing the MHC class I molecule Mamu-B*08 and infected with a highly pathogenic SIV—Mamu-B*08–restricted CD8$^+$ T cells recognizing three SIV epitopes (two in Vif and one in Nef) have been shown to predominate the T cell response. Watkins and his colleagues have now assessed the importance of these CD8$^+$ T cell responses by vaccinating Mamu-B*08$^+$ macaques with vectors encoding or not encoding the three immunodominant SIV epitopes and subsequently challenging the macaques intrarectally with high doses of pathogenic SIVmac239. They found that all macaques vaccinated with the immunodominant T cell epitopes robustly controlled virus early in infection and showed higher post-infection T cell responses specific for two of the epitopes, Vif RL9 and Nef RI10, than the macaques vaccinated with nonimmunodominant SIV epitopes. In particular, cytotoxic T cells recognizing Nef RL10 were associated with viral control during the chronic phase of infection. A surge in viremia in two macaques vaccinated with the immunodominant epitopes during chronic phase was associated with escape of the immunodominant epitopes, further underlining their importance in T cell maintenance of viral control. This study will encourage further investigation of the relevant mechanisms and increase the potential for targeted vaccines to induce CD8$^+$ T cell mediated control of HIV infection.—*AF*

■ NEUROSCIENCE

Growth factor can shrink reward responses

A recent paper in *Science* (**338**, 124–128) shows that brain-derived neurotrophic factor (BDNF) can reduce the behavioral response to morphine exposure in mice.

Conditioned place preference (CPP) is a commonly used way to measure reward. In this task, animals tend to spend more time in a place they associate with having received a drug of abuse. Ja Wook Koo *et al.* found that chronic administration of morphine to mice led to the reduced expression of BDNF in the ventral tegmental area (VTA), a key component of the brain's reward circuits. Knocking down BDNF expression in the VTA enabled morphine to increase the excitability of dopamine neurons in this brain region and potentiate CPP. By contrast, applying BDNF in the VTA markedly suppressed CPP. Directly stimulating dopamine terminals from the VTA