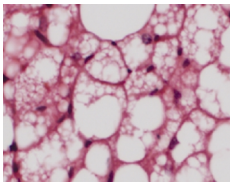
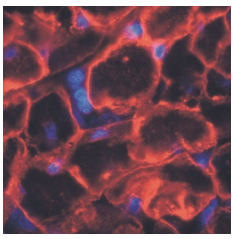
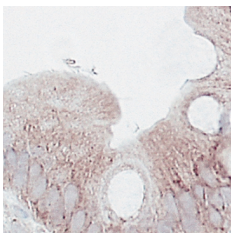


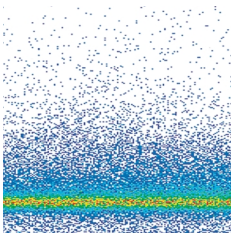
No obesity without UCP1. Energy expenditure through brown adipose tissue (BAT) thermogenesis contributes to the maintenance of body temperature in a cold environment and to the burning of excess food energy. It depends on uncoupling protein 1 (UCP1), which uncouples respiration from ATP synthesis in the mitochondria of brown adipocytes. Studying UCP1 function in mice, Leslie Kozak and colleagues have constructed congenic lines that lack UCP1 on different genetic backgrounds. On pages 399–407 they confirm previous unexpected findings — complicated by a mixed genetic background — that UCP1 mutants are resistant to diet-induced obesity, and proposed that in the absence of BAT nonshivering thermogenesis the animals are forced to employ alternative thermogenic mechanisms that are metabolically more expensive. These alternative mechanisms, which remain to be identified, could also influence metabolism and body weight in adult humans who are largely devoid of BAT and UCP1.



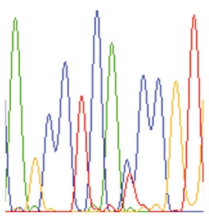
LpL location and lipid uptake in the heart. Cardiomyocytes express lipoprotein lipase (LpL) that dissociates from the cell surface and migrates to the luminal surface of capillary endothelial cells, where it interacts with lipid particles and converts triglycerides to free fatty acids. The latter then cross the endothelial barrier and are taken up by cardiomyocytes and used to generate energy. Ira Goldberg and colleagues have tethered LpL to the cardiomyocyte surface to test whether the enzyme is only active after its translocation. As they report (pages 419–426), LpL anchored to the cardiomyocyte surface also promotes lipid uptake. In fact, mice carrying the transgene exhibited increased lipid accumulation and dilated cardiomyopathy. The authors conclude that some lipid particles must be able to enter the subendothelial space and directly interact with cardiomyocytes, and that this may play a role in normal physiology as well.



Nucleotides and electrolyte transport in the colon. Members of the P2Y family of G protein–coupled receptors regulate ion transport in epithelial cells in response to extracellular nucleotides. Studying NaCl secretion in the colon, Jens Leipziger and colleagues focused on the $P2Y_6$ receptor, which is expressed basolaterally in colonic enterocytes. As they report (pages 371–379), activation of the receptor by UDP leads to sustained NaCl secretion. Comparison with the $P2Y_1$ receptor, which is expressed in a similar pattern, revealed that while ATP-induced activation of $P2Y_1$ stimulates Ca^{2+}-mediated secretion, UDP-mediated activation of $P2Y_6$ elevates both Ca^{2+} and cytosolic cAMP levels. High cAMP levels in turn activate cAMP-regulated ion channels in the apical colonic mucosa, thus ensuring a sustained secretory response.



Mechanisms of diabetes suppression. The CD3 complex, a part of the T cell receptor, plays a central part in the antigen-specific activation of T cells. OKT3, a murine anti-CD3 antibody, has been shown to induce lasting remission of diabetes in mice when administered shortly after disease onset, and initial results with a modified version of the antibody in human patients were encouraging. Interested in the mechanism by which the antibody acts in humans, Kevan Herold and colleagues have examined the response of T cells to the modified antibody hOKT3γ1(Ala-Ala). As they report, beginning on page 409, the structural alterations that lead to the humanized antibody that no longer binds Fc receptors seem to have changed the activation properties of hOKT3γ1(Ala-Ala) compared with other anti-CD3 antibodies. hOKT3γ1(Ala-Ala) treatment promotes the generation of IL-10–secreting T cells that might inhibit the autoimmune response and thus elicit beneficial effects in diabetes patients.



Complex channel genetics. Mutations in the *SCN5A* gene, which encodes a cardiac sodium channel, can cause multiple cardiac diseases including long QT and Brugada syndrome, depending on the resulting specific amino acid change. On pages 341–346, Jeffrey Balser and colleagues report on a boy with congenital heart disease. The patient is homozygous for a novel T512I mutation in *SCN5A* but also carries a common polymorphism (H558R, present in one out of five individuals) on one allele. In vitro comparison of channels encoded by either the allele containing the T512I alteration alone or the H558R/T512I allele revealed a direct functional interaction between the two alterations such that the effects of T512I alone are more severe than when they are present in the context of H558R. Additional examples will be necessary to test whether the common H558R alteration can modulate other *SCN5A* mutations that by themselves cause severe phenotypes.