Macrophages chew the fat

Macrophages regulate the insulin sensitivity of fat and muscle, according to two new studies.

Peroxisome proliferator-activated receptor-γ (PPAR-γ) regulates cellular responses to free fatty acids and other signals. Work by Justin Odegaard, Roberto Ricardo-Gonzalez *et al.* showed that macrophages must express PPAR-γ to turn on the anti-inflammatory alternative activation pathway (*Nature* doi:10.1038/nature05894). They report that mice with PPAR-γ-deficient macrophages had abnormal adipocyte metabolism, including insulin resistance. What's more, coculture experiments show that PPAR-γ-deficient macrophages signal directly to adipocytes, suggesting that alternatively activated macrophages maintain adipocyte function through paracrine signaling.

Andrea Hevener *et al.*, in turn, identified a role for macrophages in regulating insulin sensitivity in muscle and liver (*J. Clin. Invest.* **117**, 1658–1669). They found that macrophages infiltrate the muscle and that conditioned media from PPAR-γ-deficient macrophages leads to insulin resistance in cultured myotubes. Conversely, thiazolidinediones, such as rosiglitazone, improved insulin-sensitivity by activating PPAR-γ. Hevener *et al.*, however, reported that diabetic mice with PPAR-γ-deficient macrophages are insensitive to these drugs, suggesting that macrophages may be an important target of thiazolidenedione treatment. —*RL*

Smoking pot addiction

Inhibitors of α_7 nicotinic acetylcholine receptors (nAChR) may treat marijuana addiction (*J. Neurosci.* 27, 5615–5620).

Chronic use of marijuana may cause addiction. Treatment is needed for marijuana addicts—300,000 people in the United States alone.

Marcello Solinas *et al.* taught rats to self-administer a cannabinoid receptor agonist, which mimics marijuana's active compound, Δ^9-tetrahydrocannabinol (THC). When the rats were treated with a α_7 nAChR antagonist, self-administration of the marijuana-like drug was reduced.

Drug reward is linked to dopamine release into a part of the brain called the nucleus accumbens. The authors found that THC induced this dopamine release, which was blocked by the α_7 nAChR antagonist.

If these findings hold true in humans, administering α_7 nAChR antagonists to addicts could block their dependence on marijuana. —*EC*

Insightful cilia

Nature Genetics

Lebercilin lines the basal body of a cilium in a mouse photoreceptor cell.

A new gene encoding a ciliary protein was found for the most common form of congenital blindness, Leber congenital amaurosis (LCA) (*Nat. Genet.* doi:10.1038/ng2066).

Individuals with LCA are born blind or become severely visually impaired shortly after birth. Anneke den Hollander *et al.* identified the gene, *LCA5*, in an LCA-associated locus. The authors named the *LCA5* protein product lebercilin for its similarity to ciliary proteins. The transcript was expressed throughout mouse development, at first broadly and then becoming restricted to ciliated epithelia, including those of the nervous system, the gut and the inner ear. In the adult mouse eye, lebercilin was detected in the basal bodies of cilia of the photoreceptors. Lebercilin interacts with many cytoskeletal components, including scaffolding proteins, molecular motors and the centrosome. This discovery increases the number of LCA-associated genes and reveals LCA to be a ciliopathy. —*KS*

p53 pathway microRNA

A microRNA acts downstream of p53 to induce cell cycle arrest, according to a report in *Nature* (doi:10.038/nature05939).

After DNA damage and during cellular stress, p53 induces growth arrest by regulating the expression of genes involved in the cell cycle, apoptosis and DNA repair. p53 is primarily a transcriptional activator, but some targets are repressed after p53 activation.

Lin He, Xingyue He *et al.* report that three microRNAs in the *miR-34* locus are direct targets of p53 and are induced after DNA damage. Ectopic expression of these microRNAs downregulated expression of multiple cell cycle–regulated genes, including cyclin E2 and cyclin-dependent kinase 4, leading to cell-cycle arrest. p53 is deactivated in most cancer cells, and as expected, low levels of the three microRNAs encoded by *miR-34* are found in human tumors. —*KS*

Give me a SIGN

In dendritic cells (DCs), a unique signaling pathway gives human immunodeficiency virus (HIV) a distinct advantage for its replication and subsequent infection of $CD4^+$ T cells (*Nat. Immunol.* 8, 569–577).

DCs capture foreign antigens with their diverse surface receptors and present the antigens to T cells. One receptor, DC-SIGN, is both an adhesion receptor that brings dendritic cells and T cells together and the recognition receptor for HIV, yet its downstream signaling pathway is unknown.

Ashleigh Hodges *et al.* identified a complex of DC-SIGN, leukemia-associated Rho guanine nucleotide-exchange factor (LARG) and Rho GTPase that forms after HIV binds DCs. This complex kept dendritic cells immature, preventing an effective response to viral infection. Concurrently, the cells released chemokines that are likely to promote specific recruitment of $CD4^+$ T cells, the preferred hosts of HIV. Suppressing LARG reduced virus-cell synapse formation and viral replication.

Members of this complex could be new targets for halting HIV immune escape. —*KJ*

Baby's breath

Death from sudden infant death syndrome (SIDS) is often preceded by a mild viral or bacterial infection that can cause apnea. The proinflammatory cytokine interleukin (IL)-1β impairs respiration during infection in neonates, report Annika Hofstetter *et al.* (*PNAS* **104**, 9894–9899).

IL-1β coordinates central physiological responses to infections, in part by inducing prostaglandin E_2 (PGE_2) synthesis in the vasculature of the blood-brain barrier. Hofstetter *et al.* found that IL-1β induced PGE_2 synthesis in the region of the mouse brainstem that controls respiration. PGE_2 then reduced breath frequency and caused irregular breathing patterns, including apnea, in the newborn mice. The authors then studied the role of IL-1β and PGE_2 in the recovery of breath after hypoxia, such as would occur during apnea. They found that IL-1β-treated mice had fewer and shorter gasps after hypoxia, which correlated with decreased survival rates.

Interestingly, Hofstetter *et al.* also reported a correlation between infection, PGE_2 levels and apnea in human infants, suggesting that the PGE_2 pathway may be a valuable target to steady the breathing of sick babies. —*KS*

Written by Eva Chmielnicki, Kate Jeffrey, Randy Levinson and Katherine Stevens