Research News

Insulin booster

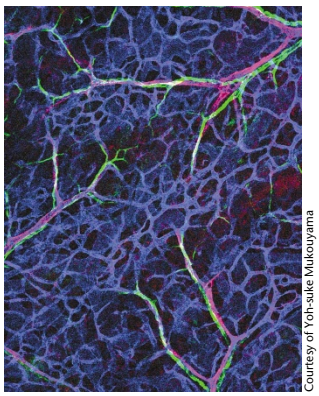
A preclinical study shows promise in stabilizing insulin production in patients with type 1 diabetes. In these patients, T cells turn against insulin-producing β-cells in the pancreas. Immunomodulatory drugs such as cyclosporine reduce diabetic symptoms in human trials, but concerns include toxicity, and the lack of long-term effects without continued drug therapy. Treatment with an antibody against a mediator of T-cell activation, CD3, alleviates symptoms in mouse models of diabetes. In the 30 May *NEJM*, Kevan Herold *et al.* show it works in humans. They treated patients with the antibody shortly after diagnosis, before β-cell destruction is complete. Patient's received an engineered version of the antibody unable to bind the Fc receptor, which recognizes the invariant region of certain immunoglobulins. This antibody did not cause severe side effects in previous trials with kidney transplant patients. The new study also reports minimal side effects after a single 14-day course of treatment. The therapy resulted in a significant long-term clinical response, as 9 of 12 patients receiving the antibody maintained or improved insulin production for at least a year after treatment. Only 2 of 12 controls showed sustained insulin production. An additional phase 2 study is now underway.

Outsmarting myelin

Tricking nerves to grow where they usually do not—such as in the CNS after spinal injury—is one quest for neurobiologists. A big barrier to this goal is myelin, which contains proteins that repel neurite outgrowth and lead to growth cone collapse. One such protein is myelin-associated glycoprotein (MAG), which has been thought to serve as a ligand for two glycolipids, the two major brain gangliosides GD1a and GD1b. Now, Alka Vyas *et al.* confirm this interaction in the 11 June *PNAS*. The authors found that in culture they could promote neuron growth by shaving off sialic acid carbohydrate groups with an enzyme, preventing glycosphingolipid biosynthesis, or adding an anti-ganglioside antibody. Furthermore, mice genetically lacking complex gangliosides were less susceptible to MAG-mediated inhibition. The authors present a model in which clustering of gangliosides by MAG binding results in activation of protein cell signals, perhaps the jack-of-all signals, rhoGTPase.

Nerves first

Nerves and blood vessels are both highly branched structures, and previous studies have provided hints that they may branch together. Now, Yohsuke Mukouyuama *et al.* have seen it up close. The researchers imaged embryonic chick skin labeled with tissue-specific antibodies to endothelia, nerves and arteries. In the 14 June *Cell* they report that arteries, but not veins, run alongside of nerves, as in this confocal microscope image (vessels in blue, arteries in red, nerves in green). And it is the nerves that call the shots: In mutant embryos lacking sensory nerves, arteries failed to properly differentiate. In mutants with disorganized nerves, the blood vessels follow the disorganized nerves. It seems the nerves may beckon the arteries through vascular endothelial growth factor (VEGF). VEGF was expressed at higher levels in nerves than surrounding mesenchymal tissue, and was able to induce arterial differentiation *in vitro*. Why this clever set-up? The authors speculate that the arteries keep the nerves stocked up on oxygen and nutrients. Neurotrophins such as nerve growth factor (NGF) are expressed in arterial vessels, and they appear to promote the survival of growing axons before they arrive at peripheral targets. In other systems, such as in tumor vessels, artery branching can occur independently of nerves, but may require similar signals from other tissue.



Courtesy of Yoh-suke Mukouyama

Cancer dragnet

Researchers have discovered a new oncogene by honing in on a signaling pathway containing RAS, one of the first oncoproteins ever identified, report Andrew Futreal and colleagues at the Sanger Center. The goal of the centers' Cancer Genome Project is bold—they plan to screen all human genes for cancer-related mutations. Their first published hit is *BRAF*, one of three human *RAF* genes in the RAS-RAF-MEK-ERK-MAP kinase pathway. The authors screened genomic DNA from tumors and cancer cell lines for point mutations in *BRAF* and then sequenced regions with genetic lesions, according to an online report in the 9 June *Nature*. They first identified somatic mutations in 3 of 21 cancers and cell lines and then screened 530 cancer-cell lines and 378 primary cancers or short-term cultures. Missense mutations in *BRAF* occur in 66% of malignant melanomas and at a lower frequency in a wide range of human cancers. All mutations occur within a kinase domain, with a single substitution accounting for 80% of lesions. The authors found that these mutations crank up BRAF's kinase activity and transform cells in culture. The researchers have over 30,000 more genes to go, but this study strongly validates the approach.

Clogged arteries? Eat a tree

Extracts of resin of the guggul tree have been used in Ayurvedic medicine since at least 600 BC for obesity, lipid disorders and other ailments. In the 31 May issue of *Science* David Moore and colleagues examine the function of the active agent in this extract, the plant sterol guggulsterone. Previous studies had shown that guggelsterone lowered blood cholesterol in mice gorged on cholesterol. The researchers found that guggelsterone inhibited the farnesoid receptor (FXR), which is involved in cholesterol metabolism. They further implicated FXR by showing that mice genetically lacking FXR and kept plump on cholesterol do not respond to guggelsterone. FXR has diverse functions, including the conversion of cholesterol into bile and the regulation of lipoprotein gene expression. So, what happens after guggulsterone binds FXR is uncertain. Whatever the exact mechanism, it is clearly different from that of the statins, which inhibit cholesterol biosynthesis. Although direct comparisons have not been done, Moore suspects that the statins are more powerful cholesterol-busters than guggelsterone. He cautions against using both together though, as the *Science* study suggested that guggelsterone also inhibited the pregnane X receptor, which puts a brake on drug metabolism.

Charlotte Schubert