## Glucose-sensing neurons

Neurons react to glucose to control whole-body glucose levels, according to a recent study (*Nature* **449**, 228–232), which may have implications for the pathogenesis of diabetes.

Hypothalamic pro-opiomelanocortin (POMC) neurons respond to high levels of glucose by raising intracellular concentrations of ATP upon excess burning of this fuel. The increase in ATP then closes ATP-sensitive ion channels, inducing neuronal firing. However, it was unclear whether disturbances in this glucose-sensing mechanism contributed to disease.

In POMC neurons, Laura Parton *et al.* overexpressed a mutant form of the channel that is much less sensitive to ATP. When stimulated with glucose, these neurons were unable to increase their firing rate, and the mice could no longer control their systemic glucose levels. This effect could be replicated when normal mice were fed a high-fat diet, indicating that these neurons become desensitized by chronically high glucose levels caused by high-fat diet–induced obesity. These results suggest that proper glucose sensing by the brain is needed to control whole-body glucose levels and may partly explain why an improper diet can lead to diabetes. —*RL*

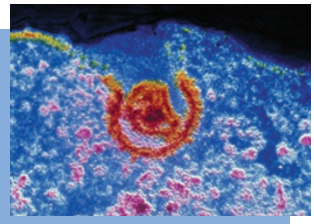
## Mind the gap

**Craniosynostosis, the fusion of cranial sutures to prematurely close the gap between the skull bones, is a common genetic disorder that is often treated by repeatedly operating on affected infants. Now, a paper in *Nature Genetics* (39, 1145–1150) reports that it may be possible to target the fibroblast growth factor receptor (FGFR) signaling pathway to develop less invasive therapies for this condition.**

**Some forms of craniosynostosis, such as Apert syndrome, are caused by activating mutations in FGFR2. In the new study, Vivek Shukla, Xavier Coumoul *et al.* showed that a small hairpin RNA targeting the mutant FGFR2 prevented Apert-like syndrome in mice by reducing receptor expression.**

**FGFR2 regulates the activity of extracellular signal-regulated kinases 1 and 2 (ERK1/2), so the authors inhibited the activation of ERK1/2 with a molecule that prevents their phosphorylation. This also resulted in a marked inhibition of craniosynostosis. These results implicate the ERK signaling pathway in forms of craniosynostosis linked to FGFR mutations and raise the possibility that ERK1/2 inhibitors may be used therapeutically** —*JCL*

## Neutralizing HIV



Neutralizing antibodies prevent HIV infection in more than one way *in vivo*, report Ann Hessell *et al.* (*Nature* **449**, 101–104).

*In vitro*, neutralizing antibodies are usually assessed for their ability to prevent virus entry into cells, but they could have other antiviral effects. The Fc portion of an antibody can bind Fc receptors (FcRs) on phagocytic cells, or it can activate the complement pathway. Either interaction can trigger the destruction of the infected cell or of the virus particle.

To work out whether these non–entry-blocking mechanisms contribute to antibody protection against HIV infection *in vivo*, the authors engineered versions of the b12 neutralizing antibody that lack the FcR- and/or complement-binding regions. Only the variant defective for both functions was less able to protect macaques from infection compared with the wild-type b12 or complement-disabled antibody, indicating that FcR-mediated effector functions are important *in vivo*. The doubly defective antibody did protect some of the monkeys, however, indicating that entry-blocking mechanisms are also important. The entry-blocking function seems to work at lower concentrations of antibody than the FcR-mediated function, suggesting that high concentrations of neutralizing antibody might not be needed from a vaccine if the FcR-mediated effects could be substituted with robust cell-mediated immunity. —*CT*

## Mast cells say 'enough!'

Mast cells temper inflammation during allergic contact dermatitis and ultraviolet B (UVB) irradiation, promote the resolution of these responses and reduce the associated skin pathology (*Nat. Immunol.*, doi:10.1038/ni1503).

UVB irradiation or allergic antigens from poison oak and related plants can set off inflammatory responses that last for days. T cells and other immune cells enter the site and attack the tissue, causing skin hyperplasia and necrosis.

Michele Grimbaldeston *et al.* found that mast cells are necessary to curb tissue damage. This immune modulation is dependent on production of the anti-inflammatory cytokine interleukin (IL)-10, which can regulate T-cell migration and proinflammatory cytokine production. In allergic contact dermatitis from plant antigens, the mast cells were stimulated by antibody binding to Fc receptors, but UVB-induced inflammation appeared to promote mast-cell IL-10 production in a different, but unknown way. Perhaps mast cell activity, in particular IL-10 production, could be manipulated therapeutically to diminish the inflammatory response and prevent tissue damage. —*KS*

## Pain in the brain

**Chemokine release by the injured spinal cord activates distant brain microglia to maintain chronic pain (*J. Neurosci.* 27, 8893–8902).**

**Spinal cord injury often leads to chronic pain, but the mechanism by which this happens has been unclear. Peng Zhao *et al.* found that the chemokine CCL21 is upregulated in the spinal cord after injury and that some CCL21 may be transported to the thalamus, a sensory relay station in the brain. There, CCL21 activates thalamic microglia, which then signal to local neurons, causing the sensation of pain. The investigators injected CCL21 into the thalamus of rats with an intact spinal cord, which triggered microglial activation and pain. When they blocked CCL21 in the thalamus of rats with an injured spinal cord, this reversed microglial activation and pain behaviors.**

**These findings highlight a key role of microglia during the maintenance of chronic pain, which could perhaps be targeted to manage pain after spinal cord injury.** —*EC*

## Absorbent CGG repeats

Sequestration of RNA-binding proteins (RBPs) leads to neurodegeneration and may cause fragile X–associated tremor/ataxia syndrome (FXTAS) (*Neuron* **55**, 556–564; 565–571).

Fragile X syndrome arises when there are >200 CGG repeats in the fragile X mental retardation (*FMR1*) gene, preventing its expression. Pre-mutation carriers, who have 55–200 CGG repeats, continue to make FMR1 transcripts and are developmentally normal, but may acquire FXTAS later in life. Peng Jin *et al.* and Oyinkan Sofola *et al.* found that the CGG repeats of the pre-mutation allele transcript bind to and soak up intracellular RBPs. Expression of CGG repeats led to neurodegeneration in *Drosophila melanogaster*, but overexpression of the RBPs prevented this phenotype. One of these RBPs, Pur α, was found in the inclusions of FXTAS-affected individuals, suggesting that loss of free RBPs may result in neuronal cell death and FXTAS. —*KS*

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