■ METABOLISM

Autophagy regulates food intake

Autophagy in hypothalamic neurons regulates food intake in mice, according to Qingyuan Meng and Dongsheng Cai (*J. Biol. Chem.* doi:10.1074/jbc.M111.254417) and Susmita Kaushik *et al.* (*Cell Metab.* **14**, 173–183).

Meng and Cai found that chronic high-fat feeding and obesity was associated with reduced expression of autophagy-related protein 7 (Atg7) and other markers of autophagic activity in the hypothalamus. Genetic knockdown of Atg7 by shRNA injection resulted in increased food intake and obesity, as well as increased nuclear factor-κB–mediated inflammation. When this inflammation was abrogated by knocking out IκB kinase-β in all neurons, Atg7 deficiency no longer resulted in increased food intake and obesity versus wild type controls.

In contrast, Kaushik *et al.* found that genetic knock out of *Atg7* in AgRP neurons, an orexigenic cell type, reduced body weight and reduced food intake upon refeeding. Mechanistically, they found that hypothalamic autophagy mobilizes stored lipids in the neurons to generate intracellular fatty acids, which then increases AgRP protein expression. It is unclear, however, whether increased food intake is due to this effect on AgRP protein expression or due to the enlarged free fatty acid pool that would provide more energy for increased AgRP neuronal activity.

It is also not clear why these groups found what seem to be opposite results. It may be a matter of which hypothalamic neuron subtype the autophagy is occurring in and the particular experimental systems used.—*RL*

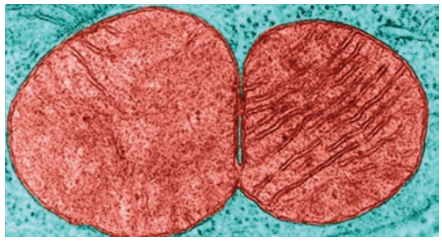
■ NEUROSCIENCE

A path to pain

Some antiretroviral drugs and anticancer drugs induce pain by increasing oxidative stress in peripheral nerves. Oxidative stress can cause changes in mitochondrial fission and fusion, which can, in turn, lead to more oxidative stress. Now, Luiz F. Ferrari *et al.* report that inhibiting the enzyme Drp1, which has a key role in mitochondrial fission, can reduce pain caused by antiretroviral and anticancer drugs in rats (*J. Neurosci.* **31**, 11404–11410).

Peripheral nerves extend from a sensory organ, such as the skin, into the spinal cord. When the researchers reduced Drp1 expression in the rat spinal cord or infused a Drp1 antagonist in the skin, they reduced pain induced by intravenous infusion of an antiretroviral drug. This suggests that Drp1 has a role at both ends of the sensory neuron in modulating pain.

The Drp1 inhibitor could also block pain induced by intravenous infusion of an anticancer drug or by intradermal administration of inflammatory proteins or reactive oxygen species. The findings suggest that blocking mitochondrial fission could be a promising approach to treat pain.—*EC*



Don W. Fawcett / Photo Researchers, Inc.

■ CANCER

Salinomycin acts through Wnt in CSCs

Basic research into the biological features of cancer stem cells (CSCs) is progressing in parallel with translational efforts to target them therapeutically. A recent study (*Proc. Natl. Acad. Sci. USA* **108**, 13253–13257) may provide a mechanistic intersection between the two areas by showing that a CSC-specific drug targets 'stemness' regulation pathways.

The antibiotic salinomycin was previously identified in a screen for CSC-specific lethality, but the basis for its effect remained poorly understood. Now, Desheng Lu *et al.* uncover that salinomycin inhibits the activity of the Wnt signaling pathway, recently appointed as an essential regulator of CSC properties in leukemia.

The authors present preliminary evidence suggesting that salinomycin can reduce the levels of LRP6, a Wnt co-receptor necessary for the pathway activity in tumors, and, at high doses, salinomycin may have broader effects on Wnt signaling.

Although the exact mechanism for LRP6 or Wnt regulation remains to be elucidated, the report further confirms that salinomycin can regulate Wnt and induce death in cultured leukemic cells from patients, further supporting the need to unravel the drug's therapeutic potential.—*VA*

Written by Victoria Aranda, Michael Basson, Eva Chmielnicki, Alison Farrell, Juan Carlos López and Meera Swami.

New from NPG

HIV-1 adaptation to NK-cell-mediated immune pressure
Alter, G. *et al. Nature* **476**, 96–100.
The authors show that natural killer (NK) cells can mediate immune pressure on HIV-1 *in vivo* in humans. The virus can evolve to evade this immune mechanism by selecting for alternative sequence polymorphisms that favor binding to inhibitory killer-cell immunoglobulin-like receptors on NK cells.

Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis
The International Multiple Sclerosis Genetics Consortium & The Wellcome Trust Case Control Consortium 2. *Nature* **476**, 214–219.
This study identifies 29 new susceptibility loci for multiple sclerosis. These genes contain many involved in immune function and particularly implicate T helper cell differentiation in multiple sclerosis pathogenesis.

Brain cannabinoid CB_2 receptors modulate cocaine's actions in mice
Xi, Z.-X. *et al. Nat. Neurosci.* doi:10.1038/nn.2874 (24 July).
The authors show that CB_2 receptors in the brain mediate the effects of cocaine and suggest that these receptors could be a target for developing therapies to treat drug abuse and addiction.

Astrocytes from familial and sporadic ALS patients are toxic to motor neurons
Haidet-Philips, A.M. *et al. Nat. Biotechnol.* doi:10.1038/nbt1957 (10 August).
Astrocytes are known to be important in pathology of familial amyotrophic lateral sclerosis (ALS). The authors show that astrocytes from individuals with sporadic ALS are toxic to motor neurons and that SOD1 is also a target in this form of the disease, revealing common mechanisms of pathogenesis.

Indoleamine 2,3-dioxygenase is a signaling protein in long-term tolerance by dendritic cells
Pallotta, M.T. *et al. Nat. Immunol.* doi:10.1038/ni.2077 (31 July).
IDO participates in immunosuppression by virtue of its enzymatic activity in tryptophan metabolism. These authors now show it induces tolerance through a separate mechanism by acting as a signaling protein in response to transforming growth factor-β.