■ OBESITY

Is beige the new brown?

Fat tissue comes in different colors—white, brown and beige. The two latter types express the gene encoding mitochondrial uncoupling protein 1 (*Ucp1*), allowing them to burn excess fuel. Strategies to increase brown and beige fat *in vivo* are therefore being intensively explored to combat obesity. A recent report in *Nature* (doi:10.1038/nature10777) offers new hope in this direction.

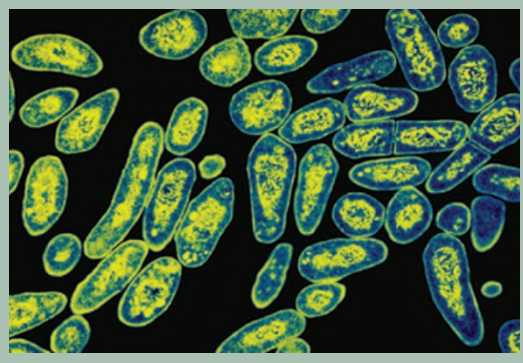
Boström *et al.* found that mice on an exercise regimen or those that transgenically overexpress the peroxisome-proliferator–activated receptor γ coactivator 1α (PGC-1α) in the muscle (to mimic exercise) showed *Ucp1* upregulation in their subcutaneous fat and, thus, fat 'beiging'. They then took a systems biology approach to identify factors released by the muscle in response to PGC-1α activity. One of these factors, a shed fragment of fibronectin type III domain containing 5 (FNDC5), which they named irisin, acts as a hormone on subcutaneous white fat cells to induce *Ucp1* expression, thus increasing energy expenditure. Genetic overexpression of FNDC5 modestly raised serum concentrations of irisin and reduced body weight in obese mice while improving their insulin sensitivity.

The team also showed that irisin plasma concentrations are higher in people who exercise, suggesting a mechanism by which exercise improves metabolism.

One aspect missing from the report is the identification of the cell-surface receptor for irisin. Once identified, it is possible that small chemical compounds could be developed that target this receptor, thus providing a drug platform to turn white fat beige and reduce obesity in the clinic. —*RL*

ANTIMICROBIALS

Mycobacterial asymmetry



Kwangshin Kim / Photo Researchers, Inc.

A new study provides insights into how variable antibiotic susceptibility may arise in mycobacterium populations, which may have implications for our understanding of how to best apply antibiotic treatments to eliminate infection in individuals with tuberculosis.

Aldridge *et al.* (*Science* 335, 100–104) investigated the growth and division of single *Mycobacterium smegmatis* and *Mycobacterium tuberculosis* cells and found that, compared to *Escherichia coli*, the mycobacterial cells had more variable elongation rates. *E. coli* cells divide symmetrically and elongate along the lateral cell body; in contrast, mycobacterial cells divide asymmetrically and elongate in a unipolar manner from the growth pole. The authors found that these characteristics result in two different daughter cells after *M. smegmatis* division: an 'accelerator cell', which inherits the old growth pole and grows more rapidly, and an 'alternator cell', which must assemble a new growth pole and therefore grows more slowly than the accelerator cell.

Antibiotics target bacterial processes crucial to growth and division, and Aldridge *et al.* found that, consistent with their faster growth rate, accelerator cells were more sensitive than alternator cells to antibiotics that inhibit cell-wall synthesis. Future studies will be necessary to determine whether these variations observed in *M. smegmatis* populations also apply to *M. tuberculosis* and whether there are consequences for antibiotic resistance of mycobacteria *in vivo*. —*MS*

■ INFLAMMATION

Burning up the brain

Several hypotheses have been put forth to describe how production of the cytokine interleukin 1β (IL-1β) in the periphery induces fever, including activation of neurons and microglia, direct stimulation of hypothalamic neurons and peripheral activation of the vagus nerve.

Now, Markus Schwaninger and his colleagues (*J. Exp. Med.* **208**, 2615–2623) report that brain endothelial cells are the target of IL-1β in fever. *In vitro* IL-1β activates the MAP kinase kinase kinase TAK1. This induces cyclooxygenase-2 and results in prostaglandin E2 production in brain endothelial cells, leading to fever and lethargy. Conditional deletion of TAK1 specifically in brain endothelial cells in mice reduced the IL-1β–induced fever response and lethargy. TAK1 ablation in neurons, astrocytes and oligodendrocytes did not alter this response, ruling out a contribution by these cell types.

In addition to fever and lethargy, the IL-1β–induced sickness response also includes anorexia, weight loss and activation of the hypothalamic-pituitary axis in mice. However, these latter characteristics were not affected by TAK1 deletion in brain endothelial cells, suggesting that IL-1β may affect different elements of the sickness response by acting on distinct cell populations. —*KDS*

■ BRAIN

Anxious about your meal?

The sirtuin SIRT1 functions in the brain to regulate several metabolic processes, as well as affecting memory and learning. A new study in mice shows that this deacetylase can also influence anxiety and behavior (*Cell* **147**, 1459–1472).

Sergiy Libert and his colleagues showed that brain-specific knockout of SIRT1 decreased anxiety, promoted exploratory drive and resulted in increased amounts of the neurotransmitter serotonin in the brain. SIRT1-overexpressing mice had the opposite phenotype, which could be corrected using inhibitors of monoamine oxidase A (MAO-A)—an enzyme that metabolizes serotonin. The authors also characterized how SIRT1 can regulate the amount of serotonin—SIRT1 boosts *MAOA* transcription by deacetylating the transcription factor nescient helix loop helix 2 (NHLH2) on Lys49, thus increasing its activity on the *MAOA* promoter and decreasing the amount of serotonin in the brain.

Large-scale genetic analyses revealed an association between certain *SIRT1* human polymorphisms and an increased risk of anxiety, social and panic disorders. Furthermore, two of the most common *SIRT1* variants found in people at risk of developing anxiety disorders enhanced SIRT1 activity and its ability to activate MAO-A *in vitro*.

SIRT1-mediated regulation of anxiety probably has a role in adaptation to environmental variations, such as food abundance, which suppresses SIRT1. The results from this study suggest that targeting SIRT1 in the brain may also be promising for the treatment of human anxiety. —*CP*

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