reduce GABA receptor activity led to social deficits.

The findings suggest that decreased inhibitory neurotransmission could cause behavioral dysfunction across the autism spectrum and may lead the way toward a potential therapy for the disorder. —*EC*

■ METABOLISM

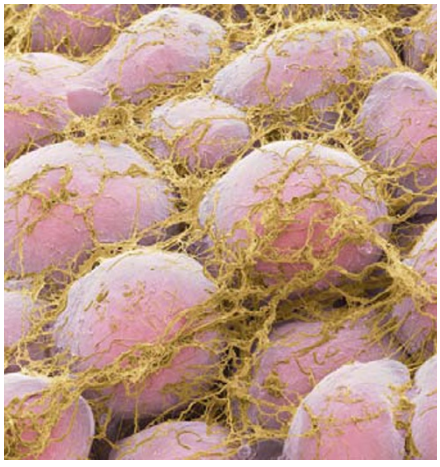
An energizing flux

A new study in mice shows that the enzyme nicotinamide N-methyltransferase (Nnmt) is a key mediator of obesity and its metabolic complications (*Nature* **508**, 258–262, 2014).

Nnmt expression and activity is known to be upregulated in the fat tissue of obese humans and rodents. Barbara Kahn and her colleagues now find that knockdown of *Nnmt* expression in adipose tissue in mice increased their energy expenditure, protecting them from diet-induced obesity and insulin insensitivity.

They also dissect the metabolic pathways altered by the lack of Nnmt to explain the increase in energy expenditure in these animals. The absence of this enzyme results in increased cellular amounts of its substrate nicotinamide (Nam) as well as *S*-adenosylmethionine (SAM), which Nnmt uses as a methyl donor to metabolize Nam. This boost in Nam levels led to activation of sirtuins, which are known to increase energy expenditure, and SAM was shown to feed into the polyamine flux pathway, which results in the same metabolic effect.

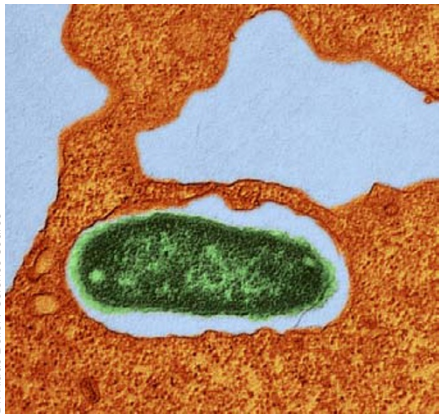
These findings provide a metabolic explanation of how upregulation of Nnmt may contribute to development of disease in obese individuals and suggest that this enzyme may be a potent target to treat obesity. —*RL*



Steve Gschmeissner / Science Source

■ INFECTIOUS DISEASES

Destroying Salmonella's camouflage



Dr. Klaus Boller / Science Source

Intracellular pathogenic bacteria, such as *Salmonella*, evade the immune response by hiding inside vacuoles of macrophages to ensure replication and survival. A new study uncovers a family of GTPases induced by interferon that destroy these hiding places so that bacteria can be recognized and inflammasome immune complexes can be activated in the host cell (*Nature* doi:10.1038/nature13157).

Using a mouse model of infection with intracellular bacteria, including *Salmonella*, Ettiene Meunier and colleagues found that guanylate-binding proteins (GBPs), a class of GTPases, were induced by interferon, which is required for activation of the immune system in infected macrophages. GBPs, particularly GBP2, limited bacterial replication and activated the non-canonical caspase-11 inflammasome, although they were not involved in the detection of the bacteria. The authors found that GBPs are recruited to the vacuole containing the bacteria to induce lysis of the vacuole, resulting in *Salmonella* release into the cytosol so that immune sensors can recognize the bacterial lipopolysaccharide.

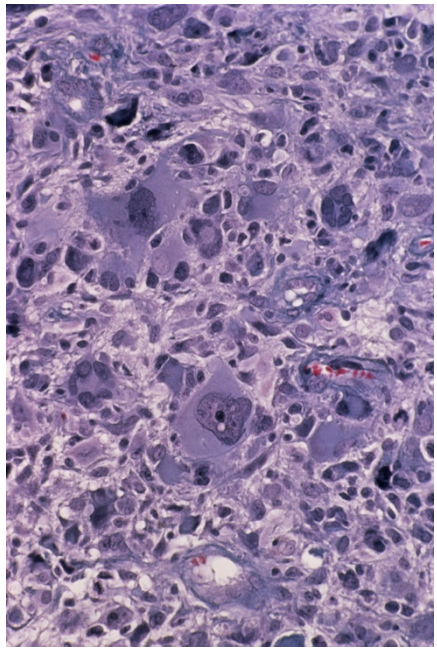
It is still unclear how the vacuoles are lysed or how these GBPs distinguish between vacuoles containing pathogens and those that don't inside macrophages. Modulation of the pathways described in this study could be used to control inflammation during sepsis. —*CP*

■ CANCER

Reconstructing glioblastoma hierarchy

A recent study shows that four transcription factors (TFs) dictate reprogramming of human differentiated glioblastoma cells into stem-like cells that can give rise to tumors in animals, as cancer-propagating cells do in human glioblastoma. The findings point toward a unidirectional, but potentially plastic, cellular hierarchy in glioblastoma (*Cell* **157**, 1–15, 2014).

Mario Suvà and his colleagues derived both stem-like propagating tumor cells and differentiated tumor cells from human proneuronal glioblastomas. By comparing their epigenetic signatures, the authors identified several TFs that are differently expressed and direct the phenotypic state of the stem-like cells. A cocktail of the TFs SOX2, OLIG2, POU3F2 and SALL2 is sufficient to reprogram differentiated glioblastoma cells into stem-like cells with unlimited self-renewal that can propagate tumors in mice and show epigenetic characteristics of tumor-propagating cells from patients. These four TFs and the associated epigenetic circuits were also found in a small population of cells from fresh human primary glioblastoma that express a stem cell marker, validating the relevance of the results in human tumors.



CNRI / Science Source

A key target of this core set of TFs is a histone demethylase complex that may be a candidate therapeutic target to induce death in stem-like tumor cells, which are usually drug resistant. Future studies should confirm this hierarchical model in other subtypes of glioblastoma. —*CP*

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