■ NEUROSCIENCE

Noradrenaline rush in schizophrenia

A study in mice indicates that schizophrenia might involve defects in noradrenaline-mediated signaling, underscoring the potential of this neurotransmitter system as a therapeutic target (*PLoS Biol.* **8**, e1000393).

Michael Siuta *et al.* discovered the link between schizophrenia and noradrenaline while examining mice with defects in the mammalian target of rapamycin complex-2 (mTORC2) pathway. Previous work had shown that defective mTORC2-mediated phosphorylation of Akt is associated with the disease. Siuta *et al.* knocked out the mTORC2 regulatory protein rictor in neurons to create mice with the same defect in Akt phosphorylation.

Rictor-null mice showed hallmarks of schizophrenia such as deficits in prepulse inhibition, a well-characterized schizophrenia-associated behavior, and reduced dopamine in the cerebral cortex. The mice also had high levels of cortical noradrenaline and enhanced expression of the noradrenaline transporter. Crucially, blocking this transporter reversed the schizophrenia-like phenotypes.

These results point to a functional link between Akt, dopamine and noradrenaline, the mechanistic and anatomical bases of which remain to be established. —*JCL*

■ CARDIAC BIOLOGY

Rejecting biopsies

Expression profiling of blood samples can substitute for invasive biopsies to evaluate people with cardiac transplants, but with limitations, according to a clinical report (*N. Engl. J. Med.* **326**, 1890–1900).

During the first year after cardiac transplant, almost 35 percent of patients experience acute cellular rejection, which can lead to loss of the transplant. To help prevent rejection, patients are monitored through invasive biopsies deep into the heart.

Michael Pham *et al.* instead monitored subjects with a gene chip that assesses 11 genes with a role in immunity during organ rejection. These subjects needed fewer biopsies to confirm risk of rejection than those undergoing biopsy—and reported that they were much more comfortable. After two years, the risk for graft dysfunction, death or retransplantation was similar in both groups.

The noninvasive procedure, however, was tested only in low-risk patients at least six months after transplantation and was limited to detecting the absence of rejection. —*CP*

NEUROSCIENCE

Chaos-causing clots

Cardiovascular diseases such as stroke and atherosclerosis enhance the likelihood that an individual will get Alzheimer's disease. A study in *Neuron* may explain why—formation of fibrin clots and aggregates of amyloid along brain blood vessels adversely affect each other, and this could lead to the development of dementia (*Neuron* 66, 695–709).

Marta Cortes-Canteli *et al.* found that Aβ, the neurotoxic molecule that accumulates in the brain during Alzheimer's disease, causes abnormal formation of fibrin clots that can't be easily degraded. They observed abnormal blood clots in brain blood vessels of mice with high Aβ levels and in humans with Alzheimer's disease.

Depletion of fibrinogen—the fibrin precursor—from Alzheimer's model mice, either pharmacologically or genetically, led to reduced amyloid deposition along the brain blood vessels of the mice and to improved cognitive performance.

Future work is needed to determine the mechanism by which fibrinogen affects vascular amyloid formation, which could lead to new approaches to treat Alzheimer's disease. —*EC*

Aβ deposits (red) in blood vessels (green) may synergize with fibrin clots to promote Alzheimer's disease.

■ REPRODUCTION

Puberty peptide

The onset of puberty depends on proper fuel reserves—starvation, for instance, can delay puberty. Research in rats now suggests that the brain peptide nesfatin-1—a suppressor of food intake—links energy levels to the onset of puberty (*J. Neurosci.* **30**, 7783–7792).

David García-Galiano *et al.* report that levels of nesfatin-1 in the hypothalamus also rise as female rats go through puberty. This expression was reduced by 48 hours of fasting, hinting that Nesfatin-1 might convey information about energy levels during the transition to puberty. To test this idea, the researchers injected the peptide into the brains of young female rats and found that it bumped up concentrations of sex hormones called gonadotropins. What's more, knocking out nesfatin-1 expression with an antisense oligonucleotide delayed the onset of puberty.

Still unclear is how nesfatin-1 operates mechanistically and how it might work with other regulators of puberty, such as leptin. Curiously, knocking down nesfatin-1 in the hypothalamus did not have an effect on food intake or weight gain in adult female rats—in contrast to previous results in male rats and mice. Perhaps female and male animals respond differently to this peptide.—*CS*

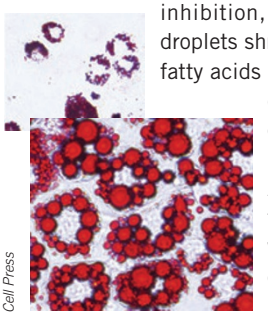
■ METABOLISM

Macrophages take aim

A macrophage-derived protein blocks the synthesis of new fatty acids to help break down fat droplets, new research shows (*Cell Metab.* **11**, 479–492, 2010).

Macrophages are known to infiltrate fat tissue, where they may contribute to the development of insulin resistance. But the new findings suggest that macrophages also secrete a protein that counteracts obesity, called apoptosis inhibitor of macrophages (AIM). Toru Miyazaki discovered this protein more than ten years ago and found that its expression levels increased with the progression of obesity in mice.

The researchers now report that fat cells endocytose AIM, which, in turn, can bind and inhibit fatty acid synthase. As a result of this inhibition, intracellular fat droplets shrink, causing free fatty acids and glycerol molecules to spew out of the cells. Mice deficient in AIM had larger fat cells and were heavier than ordinary mice, phenotypes that were reversible by injecting the mice with AIM.



AIM shrinks lipid droplets (red) in fat cells (untracted cells on bottom).

It remains to be seen whether AIM can counteract weight gain in wild-type mice. —*ED*

■ AUTOIMMUNITY

Dueling T cell receptors

A study in mice provides a new explanation for how infections may trigger autoimmunity. The findings suggest a key role for T cells expressing two types of T cell receptors, recognizing both a pathogen and a self protein (*Nat. Immunol.* doi:10.1038/ni.1888).

Qingyong Ji *et al.* studied multiple sclerosis, an autoimmune disease that targets myelin and is associated with viral infection. They found that mice expressing a transgenic $CD8^+$ T cell receptor specific for myelin basic protein developed multiple sclerosis–like disease after infection with a vaccinia virus.

This onset of autoimmunity was not due to poor viral clearance or cross-reactivation of the transgenic T cell receptor with viral antigens. Instead, the researchers found that a subset of the transgenic T cells specific for myelin basic protein in normal mice also expressed a virus-specific T cell receptor. These cells expanded after infection with vaccinia and lost tolerance to self antigens.

These findings suggest that $CD8^+$ T cells expressing both myelin and virus-specific T cell receptors are activated by viral infection, leading in turn to a loss of tolerance and the onset of autoimmune disease. —*AK*

Patterns in Crohn's

Polymorphisms in the pathogen recognition receptor gene *NOD2*, found in 10–20% of North American individuals with Crohn's disease, increase the risk of developing the condition. Findings by Meher Rahman *et al.* hint at why, suggesting that such polymorphisms result in dysregulated activation of regulatory T cells, cells that can shield the body from excess immune activation (*J. Immunol.* **184**, 7247–7256).

Individuals with Crohn's disease homozygous for a disease-associated variant of *NOD2* have decreased numbers of T_{reg} cells in their intestines. Normally, stimulation of NOD2 protects T_{reg} cells from Fas ligand–mediated apoptosis by upregulating anti-apoptotic machinery. The researchers found that this mechanism seems to go awry in human T_{reg} cells either deficient in NOD2 or expressing disease-associated variants. Such cells showed increased susceptibility to apoptosis in cell culture. The findings suggest that activation of wild-type NOD2 is protective.

Other researchers have observed increased expression of Fas ligand in the inflamed intestine, which could decrease T_{reg} cell numbers in these individuals and lead to excess T cell activation. —*KDS*

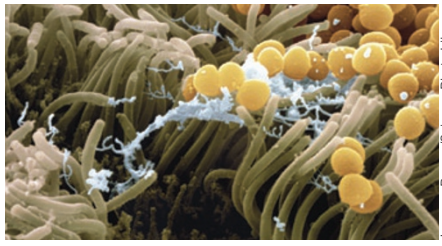
■ MICROBIOLOGY

Resisting *Staph*

The emergence of drug-resistant *Staphylococcus aureus* has spurred researchers to search for a new way to take aim at the bug—and it seems that the commensal bacterium *Staphylococcus epidermidis* has already got it figured out.

Tadayuki Iwase *et al.* (*Nature* **465**, 346–349) examined bacterial species in the nasal cavities of 88 volunteers and found that the absence of *S. aureus* correlated with the presence of an 'inhibitory' type of *S. epidermidis*. In cell culture experiments, the inhibitory *S. epidermidis* blocked biofilm formation by *S. aureus*. The commensal bacterium secretes an inhibitory factor, a serine protease called Esp, necessary for biofilm destruction *in vitro*.

The findings suggest an innovative strategy to interfere with *S. aureus* growth. Notably, *S. aureus* grown in culture with Esp for one year did not develop resistance to the protein.



Juergen Berger/Science Photo Library

Staphylococcus aureus (yellow) on human nasal epithelial cells. The spherical bacteria adhere to mucus (blue) on cilia.

Meanwhile, in *Science*, Morgan Wyatt *et al.* identify two peptides, dubbed auresimines, that regulate the expression of virulence factors in *S. aureus* (*Science* doi:10.1126/science.1188888). Auresimine synthesis bypasses ribosomes, instead relying on nonribosomal peptide synthetases (as does penicillin). The peptides regulate the expression of immunomodulatory proteins, adhesins, lytic proteins and cytotoxins.

An *S. aureus* strain unable to produce the auresimines was attenuated in mice, suggesting that targeting these peptides may be one more strategy to keep *S. aureus* at bay. —*KG*

Written by Eva Chmielnicki, Elie Dolgin, Katherine Gora, Anna Kushnir, Juan Carlos López, Carolina Pola and Charlotte Schubert

New from NPG

An immunoglobulin-like receptor, Allergin-1, inhibits immunoglobulin E–mediated immediate hypersensitivity reactions.
Hitomi, K. *et al. Nat. Immunol.* **11**, 601–607.
An inhibitory receptor expressed by mast cells suppresses severe allergic reactions.

Opposing roles for calcineurin and ATF3 in squamous skin cancer.
Wu, X. *et al. Nature* **465**, 368–372.
Study uncovers why calcineurin inhibitors such as cyclosporin A, immunosuppressants used to prevent organ transplant rejection, greatly increase the risk for squamous cell carcinoma.

Calcium-dependent protein kinase-1 is an essential regulator of exocytosis in *Toxoplasma*.
Lourido, S. *et al. Nature* **465**, 359–362.
New drug target is identified in *Toxoplasma gondii* that is absent in human hosts.

Quiescent haematopoietic stem cells are activated by IFN-γ in response to chronic infection.
Baldridge, M.T. *et al. Nature* **465**, 793–797.
Mouse model of *Mycobacterium avium* infection shows how IFN-γ bumps up production of immune cells to counteract chronic infection.

Acute D_2 receptor blockade induces rapid, reversible remodeling in human cortical-striatal circuits.
Tost, H. *et al. Nat. Neurosci.* published online, doi: 10.1038/nn.2572 (6 June).
An antipsychotic drug that blocks dopamine results in temporary reduction in the volume of certain brain areas. The findings suggest that short-term structural changes in the brain may underly some of the side-effects of antipsychotic medication.

The matricellular protein CCN1 induces fibroblast senescence and restricts fibrosis in cutaneous wound healing.
Jun, J.-I. & Lau, L. F. *Nat. Cell Biol.* published online, doi: 10.1038/ncb2070 (6 June).
Protein expressed at sites of wound repair limits scarring by inducing cellular senescence.