■ PSYCHIATRIC DISORDERS

Partners in crime

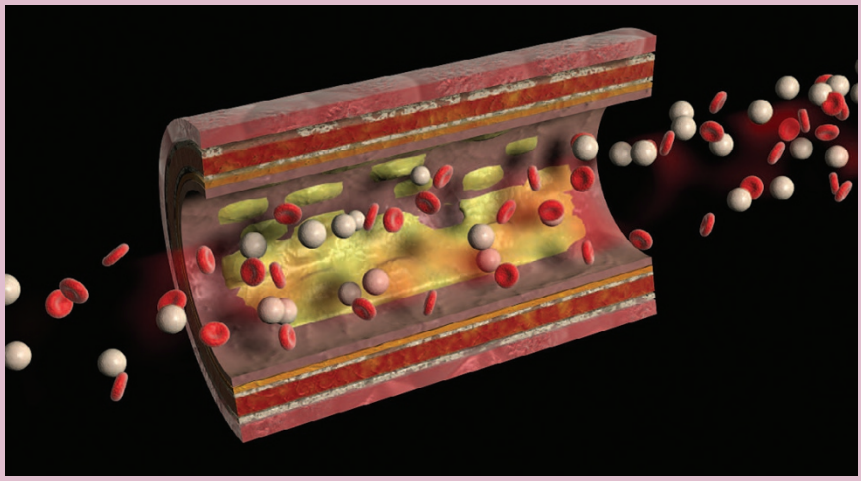
Mutations in the scaffolding protein disrupted in schizophrenia 1 (DISC1) have been linked to schizophrenia and other psychiatric diseases. Now, Eunchai Kang *et al.* report that the interaction between DISC1 and fasciculation and elongation protein zeta-1 (FEZ1) modulates neuronal development in mice (*Neuron* **72**, 559–571).

The researchers found that knocking down FEZ1 expression in mouse hippocampus led to the generation of neurons with more complex dendrites, which is similar to the phenotype observed when DISC1 is knocked down in mice. When they infused a peptide that would block the DISC1-FEZ1 interaction, Kang and colleagues also observed an increase in dendritic complexity, suggesting that this interaction is necessary to maintain normal development of neurons in the hippocampus, a brain structure involved in learning and memory.

Individuals with a particular DISC1 mutation (S704C) have an increased risk of developing schizophrenia. By examining two separate case-control populations, the researchers found that FEZ1 polymorphisms can increase the risk for schizophrenia in individuals who are homozygous for serine at this site in DISC1. However, further work is needed to determine the mechanism behind this observation. —*EC*

METABOLISM

Athero: all but Sirt-ain?



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Genetic overexpression of Sirt1 has been shown to increase insulin sensitivity and improve macrophage cholesterol metabolism in mice. Given these findings and that metabolic syndrome is marked by insulin resistance, dyslipidemia and an increased risk for atherosclerosis, Li Qiang *et al.* (*Cell Metab.* 14, 758–767) hypothesized that a transgenic mouse strain mildly overexpressing Sirt1 would be protected from the development of atherosclerosis when placed on a high-fat and high-cholesterol diet.

However, the team found this was not the case. Although they did see improved glycemic control, they also found evidence that atherosclerosis was worse in these mice compared with wild-type mice fed the same diet. Mechanistically, the authors found that Sirt1 deacetylates, and thus represses, the transcriptional factor Creb, which is known to activate hepatic glucose production but inhibit lipid synthesis.

So, whereas the pharmaceutical industry has been looking for specific and potent activators of Sirt1 to improve metabolism, these new results suggest that such clinical approaches should be approached with care, as these compounds may aggravate the risk for atherosclerosis. —*RL*

■ ANTIMICROBIALS

An alternative strategy

Antibiotics are conventionally used to treat urinary tract infections (UTIs), but increases in bacterial resistance to commonly used antibiotics means that new therapeutic strategies for bacterial infections must be devised. Corrine K. Cusumano *et al.* now describe an alternative approach for treating and preventing infections caused by uropathogenic *Escherichia coli* (UPEC) (*Sci. Transl. Med.* **3**, 109ra115).

The team had previously designed a range of mannoside compounds to target a UPEC adhesin called FimH, which is necessary for the invasion, colonization and the formation of intracellular bacterial communities in the bladder epithelium. Cusumano *et al.* have now investigated the efficacy of these compounds to inhibit UPEC biofilm production *in vitro*, allowing them to identify one that showed the best activity at low doses and was orally bioavailable. This compound treated chronic cystitis in a mouse model, showing improved efficacy compared with the standard antibiotic treatment for UTIs (trimethoprim-sulfamethoxazole; TMP-SMZ), and could also be used prophylactically. In addition, the mannoside compound synergized with TMP-SMZ by trapping the bacteria in the bladder lumen, where they are exposed to maximum doses of the antibiotic.

The authors also developed further mannoside compounds with improved pharmacokinetics and efficacy *in vivo*, which could be further investigated for their therapeutic potential in women with recurrent UTIs. —*MS*

■ IMMUNOLOGY

Dendritic cell demise

Type I interferons (IFN-I) promote dendritic cell death after viral infection.

Plasmacytoid dendritic cell (pDC) activation and release of IFN-I early after infection is important for mounting an effective adaptive response and curtailing viral replication. However, in the course of viral infection, pDC numbers drop precipitously.

Marco Colonna and his colleagues (*J. Exp. Med.* **208**, 2367–2374) have now found that IFN-I itself induces pDC death. Following infection with DNA or RNA viruses, the serum concentration of IFN-I increased in parallel with a decrease in pDC numbers. As the dose of virus was increased, more IFN-I was produced, leading to a more pronounced decline in pDC numbers. The authors found that IFN-I acts directly on pDCs, activating them and inducing the expression of pro-apoptotic molecules, caspase activation and cell death.

Although this mechanism may be beneficial in limiting excessive pDC activation and immunopathology after viral infection, these results suggest that caution is warranted with IFN-α therapy in individuals infected with hepatitis C virus, as this IFN-I may directly reduce pDC numbers and impair antiviral responses. —*KDS*

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