

■ CANCER

microRNA switcheroo

Researchers studying chronic myelogenous leukemia (CML) have identified a microRNA that functions in an unusual way—as a ‘decoy’ that interferes with the function of an RNA-binding protein (*Cell* **140**, 652–665).

Anna Eiring *et al.* found that expression of miR-328 is lost during blast-crisis CML, the acute form of the cancer. Restoration of miR-328 took the edge off of blast-crisis cells, causing them to differentiate.

miR-328 worked in this context in two ways. Typical of most miRNAs examined so far, miR-328 bound the 3′ untranslated region of its target—in this case a survival factor—and prevented its translation. But miR-328 also veered from the established script for miRNAs—binding to hnRNP E2, a regulatory RNA-binding protein that normally blocks the translation of a protein that prompts myeloid differentiation, called C/EBP α . miR-328 binding resulted in translation of C/EBP α and differentiation of blast-crisis cells.

Future studies should reveal whether other microRNAs have similar decoy functions. —CS

■ AGING

Defending mitochondria

People with a form of premature aging suffer from defects in mitochondrial DNA (mtDNA) repair, according to a new report (*J. Exp. Med.* **207**, 379–390).

Individuals with Cockayne syndrome (CS) often die between the ages of 10 and 20 and also have low levels of subcutaneous fat. The syndrome is caused by mutations in genes encoding CSA or CSB, proteins known to mediate repair of DNA damage in the nucleus.

York Kamenisch *et al.* found that CSA and CSB localized to mitochondria and bound mtDNA in cells subjected to oxidative stress. Furthermore, CSA and CSB expression was necessary to prevent ultraviolet A–induced mutations in mtDNA in subcutaneous fat cells and apoptosis. Taken together, these findings suggest that CSA and CSB proteins protect mtDNA from stress-induced damage and may prevent apoptotic loss of subcutaneous fat cells in people with CS.

The findings dovetail with studies suggesting that declines in mitochondrial function might underlie normal aging and shed light on the role of the CS proteins in mtDNA repair. —AK

METABOLISM

Seeking heat

Mom’s milk activates a pathway that turns on brown fat cells, the heat-generating cells in young animals, according to new work in mice (*Cell Metab.* **11**, 206–212).

Elayne Hondares *et al.* found that concentrations of fibroblast growth factor-21 (FGF21)—known for mediating the response to starvation in adults—spike in the liver and bloodstream in newborn mice. FGF21 expression could be quashed by preventing mice from suckling and initiated by substituting lipids for the mother’s milk. FGF21, they found, turns on genes related to activation of brown fat and was also able to activate brown adipocytes in culture.

The researchers provide evidence that FGF21 activation occurs through the lipid-sensing molecule PPAR- α , which is thought to mediate some of the other adaptations to life outside the womb, such as the switch to burning lipids instead of glucose. —CS



J.M. Gallego-Escudero & V. Carreño

■ NEUROSCIENCE

Schizophrenia in utero

A new way to transiently knock down genes in mouse embryos may become a useful tool to understand neurodevelopmental disorders (*Neuron* **65**, 480–489).

A popular idea about schizophrenia and other psychiatric illnesses is that they may ensue, at least in part, from developmental abnormalities. There is also an increasing number of molecules thought to be involved in schizophrenia, but their contribution during brain maturation has been difficult to establish. Minae Niwa *et al.* now report on a potential way around this limitation—a strategy to transiently knock down genes *in utero* in small populations of cells to study the effect of this manipulation on adult mice.

They used their technique, which involves the intracerebral injection of a construct followed by electroporation, to assess the effect of transiently inactivating the gene encoding DISC-1—a well-known schizophrenia susceptibility gene—with a short-hairpin RNA. They observed that knocking down the gene in a small population of neurons in the cerebral cortex of the embryos led to phenotypes similar to what has been found in humans with schizophrenia. Anatomically, there were abnormalities in the maturation and connectivity of the cortical dopaminergic system of the adult mice. Behaviorally, the adult mice showed disturbances in tests such as a novel-object recognition task, deficits that responded to treatment with psychostimulant drugs.

Beyond the potential use of this strategy to discover pathophysiological mechanisms

of neurodevelopmental disorders, mice like these may also be useful screening tools in the search for new psychoactive drugs. —JCL

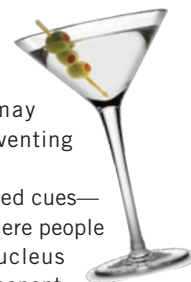
Relapse redux

New insight into the molecular mechanisms underlying addiction may point to new ways of preventing relapse.

In response to drug-related cues—such as being at a party where people are taking drugs—the nucleus accumbens (NAcb), a component of the brain’s reward system, is activated. Antonello Bonci and his colleagues report that pharmacologic inhibition of firing within the NAcb lowers the motivation for alcohol during abstinence (*Neuron* **65**, 682–694).

The researchers observed increased activation of neurons within the NAcb after prolonged periods of abstinence from alcohol. The culprit seems to be small-conductance calcium-activated potassium (SK) channels, as their activity was reduced during abstinence from alcohol, and activation of these channels decreased firing of neurons. Treatment of addicted rats with a drug that activates SK channels lowered their motivation to seek alcohol.

These findings dovetail with recent clinical findings in which deep brain stimulation of the NAcb in alcoholic subjects decreased drug-seeking behavior. The findings provide hope that chlorzoxazone, a centrally acting muscle relaxant and activator of SK channels, might diminish alcohol-seeking behavior and prevent relapse. —KDS



New from NPG

Vitamin D controls T cell antigen receptor signaling and activation of human T cells.

von Essen, M.R. *et al. Nat. Immunol.* **4**, 344–399.

The molecular secret behind why it's good to have some fun in the sun. A key human T cell protein depends on vitamin D and its receptor for expression.

**Circulating mitochondrial DAMPs cause inflammatory responses to injury.**

Zhang, Q. *et al. Nature* **464**, 104–107.

Traumatic injury spills bits of mitochondria into the body, to which it reacts as it does to bacteria, mitochondria's ancient ancestors. Recognition of bacteria-like molecular components of mitochondria activates immune cells and prompts inflammatory organ injury.

Consolidation of the cancer genome into domains of repressive chromatin by long-range epigenetic silencing (LRES) reduces transcriptional plasticity.

Coolen, M.W. *et al. Nat. Cell Biol.* **3**, 235–246.

A comprehensive map of the prostate cancer epigenome suggests that epigenetic changes induce a repressive state across large domains. A substantial proportion of the genome is affected.

Telomere elongation in induced pluripotent stem cells from dyskeratosis congenital patients.

Agarwal, S. *et al. Nature* **464**, 292–296.

Researchers created induced pluripotent stem (iPS) cells from individuals with a disorder that affects telomere maintenance. The process of creating iPS cells restored telomere elongation despite genetic lesions affecting telomerase.

Neural bases for addictive properties of benzodiazepines.

Tan, K.R. *et al. Nature* **463**, 769–774.

Benzodiazepines such as valium can become addictive through a system involving dopamine and binding of the drugs to a particular type of GABA_A receptor. Perhaps drugs can be designed that bypass this binding.

■ METABOLISM

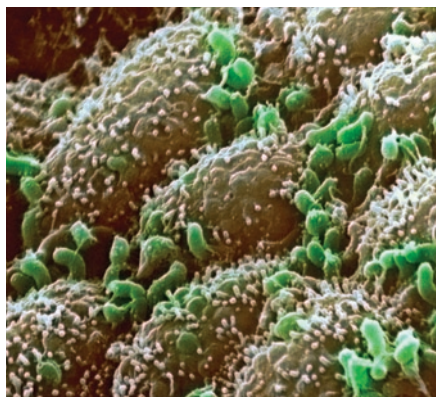
Stay lean with TLR5

A molecule that recognizes bacteria, Toll-like receptor 5 (TLR5), is required to keep mice lean and healthy, according to work by Matam Vijay-Kumar *et al.* The findings add to accumulating evidence that the bacterial composition of the gut has an effect on weight.

The researchers examined mice deficient in TLR5, which is expressed on intestinal epithelium and immune cells and binds flagellin, the main component of bacterial flagella. They found that the mice were obese, owing to overeating, and had features of metabolic syndrome, such as high blood pressure and insulin resistance. On a high-fat diet, these mice developed fatty liver and diabetes (*Science* doi:10.1126/science.1179721).

The defects could be traced to alterations in the composition of gut bacteria. For instance, treating the TLR5-deficient mice with antibiotics caused their metabolic syndrome to disappear. The researchers also transferred the resident gut bacteria from TLR5-deficient mice into wild-type, germ-free mice—causing these mice to overeat and develop obesity, high blood sugar and insulin resistance.

Outstanding questions include how TLR5 deficiency changes bacterial composition, how such changes result in metabolic syndrome and whether the findings are relevant to humans. —AF



Bacteria (green) on surface of intestine (raised bumps are villi, white structures are microvilli).

Biomedical Imaging, Southampton General Hospital, SPL

■ MUSCLE PHYSIOLOGY

Sore headline

Findings in mice provide insight into why muscles get sore after strenuous exercise—and why such soreness often doesn't appear until a day or two after a workout. The culprit is the peptide bradykinin, which is

released during exercise and seems to bump up expression of nerve growth factor (NGF), resulting in increased sensitivity to pain (*J. Neurosci.* **30**, 3752–3761).

Shiori Murase *et al.* examined bradykinin because it is known to cause pain sensitization and can alter expression of neuropeptides in various cell types. They first determined that injection of a B₂ bradykinin receptor antagonist before (but not after) exercise prevented exercise-induced pain sensitivity in rats. They next found that NGF mRNA and protein were upregulated starting 12 hours after exercise, and when they injected NGF-specific antibodies into the rats 6 hours after exercise, pain sensitivity was blocked. Furthermore, injection of the B₂ receptor antagonist suppressed upregulation of NGF mRNA and protein.

The cellular source of the NGF, and how bradykinin induces it, remain unknown. Further exploration of this pathway may lead to treatments for diseases such as myofascial pain syndrome. —KG

■ HEART DISEASE

Sealing muscular dystrophy

People with Duchenne muscular dystrophy (DMD) often die of heart failure, precipitated by small tears in the membrane of heart muscle cells followed by heart enlargement to compensate for the weakness. Using a dog model of DMD, DeWayne Townsend *et al.* now show that continual treatment with a membrane sealant can stabilize myocytes and alleviate some DMD symptoms (*J. Clin. Invest.* doi:10.1172/JCI41329).

The researchers treated golden retrievers with DMD with a continuous infusion of P188, a polymer that can insert into lipid bilayers and repair damaged biological membranes. Dogs treated with the sealant had decreased levels of a cardiac injury indicator, fewer fibrotic lesions in cardiac muscle (hallmarks of DMD) and improved heart and myocyte function as compared to dogs treated with saline. The effects of P188 were reversible in myocytes isolated from P188-treated dogs, highlighting the need for continuous administration. Chronic P188 treatment had no effect on renal or hepatic systems, suggesting that prolonged administration of the polymer is safe.

These results build on previous studies of P188 in the mouse model of DMD and suggest a therapeutic approach to the treatment of DMD-associated heart disease. —AK

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