■ CANCER

Taking ALK from bench to bedside and back

Targeting cancers according to their underlying genetic alterations might be a promising therapeutic route, as illustrated by recent reports of the success of the anaplastic lymphoma kinase (ALK) inhibitor crizotinib.

Rearrangement or amplification of *ALK* is associated with several cancers. Eunice Kwak *et al.* (*New Engl. J. Med.* **363**, 1693–1703) and James Butrynski *et al.* (*New Engl. J. Med.* **363**, 1727–1733) respectively found that treatment of non–small-cell lung cancers (NSCLCs) and myofibroblastic tumors bearing *ALK* rearrangements with crizotinib led to tumor shrinkage or stable disease in most cases.

A concern with the therapeutic use of kinase inhibitors is the rapid emergence of tumor resistance. Butrynski *et al.* observed resistance after only eight months, and, in a separate study (*New Engl. J. Med.* **363**, 1734–1739), Young Lim Choi *et al.* characterized two *de novo* independently evolved mutations responsible for crizotinib resistance in a case of NSCLC with an *EML4-ALK* fusion. Both mutations were in the kinase domain of ALK, and one occurred at a 'gatekeeper' position essential for inhibitor binding.

These studies highlight crizotinib as a viable therapeutic strategy in patients genotyped for *ALK* and also provide insights into the mechanisms of crizotinib resistance, which might allow the development of improved next-generation ALK inhibitors.—*MS*

Fresh boost for old cancer drug

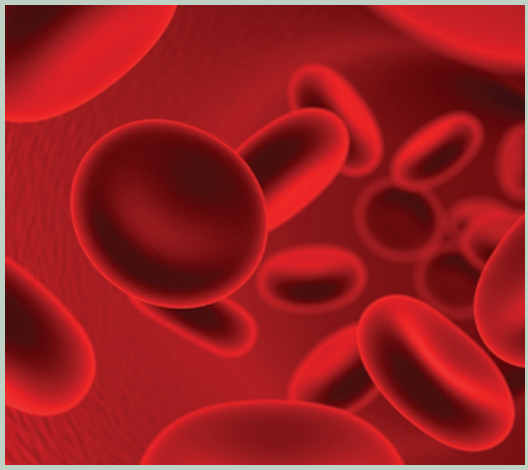
Irinotecan is widely used in colon cancer, but it has an undesirable side effect—it causes severe diarrhea. This inconvenience is caused by further processing of the inactive metabolite of the drug into the active form by a β-glucuronidase enzyme made by commensal bacteria in the gut. But good news comes from a new study reporting that inhibitors of these enzymes protected mice from diarrhea induced by irinotecan and related drugs (*Science* **330**, 831–835).

Using high-throughput screening, Bret Wallace *et al.* identified potent inhibitors of β-glucuronidase that bound its so-called 'bacterial loops'—structural motifs not present in the human enzyme that are required for enzymatic efficacy in bacteria. Crucially, the inhibitors worked in living cells without killing the gut flora or mammalian cells, which is important to avoid opportunistic infections in people treated with chemotherapy.

Mice orally treated with the β-glucuronidase inhibitor and the chemotherapeutic agent showed less diarrhea, as well as healthier gut tissue, compared with control mice. Although reduction in active metabolites and improved efficacy of irinotecan in cancer after treatment with these inhibitors has yet to be proven *in vivo*, they open a door to increasing the dosage and efficacy of irinotecan against human cancers.—*CP*

HEMATOLOGY

Red blood cells by the numbers



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The life story of a red blood cell goes something like this: after its release into the circulation, the cell undergoes an initial rapid reduction in volume and hemoglobin content, followed by a prolonged phase of slower reduction in both of these parameters and the cell's eventual clearance from the circulation. Reporting in the *Proceedings of the National Academy of Sciences USA* (doi:10.1073/pnas.1012747107), John Higgins and L. Mahadevan apply concepts from statistical physics to develop a mathematical model of the population dynamics of this process in humans and show that this model may be useful for diagnosing anemia.

Using standard measurements of red blood cell size and hemoglobin content, the authors found that parameters derived from their mathematical model differed in characteristic ways between normal individuals and people with three different types of anemia—anemia of chronic disease, thalassemia trait and iron-deficiency anemia. The researchers then showed that specific model parameters could be used diagnostically in two ways: first, to identify individuals with latent iron-deficiency anemia several weeks before the anemia became clinically detectable; and second, to distinguish between iron deficiency anemia and thalassemia trait, the two most common forms of microcytic anemia.—*MB*

■ NEUROSCIENCE

Vagrant amyloid

The synaptic alterations triggered by amyloid-β in one brain region could spread trans-synaptically to other regions, according to Julie Harris *et al.* (*Neuron* **68**, 428–441).

The entorhinal cortex is one of the brain regions that are affected at early time points during the progression of Alzheimer's disease. Harris and her colleagues overexpressed mutant amyloid precursor protein (APP) in the entorhinal cortex to trigger the accumulation of amyloid-β characteristic of the disease. The transgenic mice showed the same behavioral abnormalities that are seen in other Alzheimer's mouse models in which there is more widespread overexpression of APP.

Remarkably, APP overexpression in the entorhinal cortex altered synaptic function in downstream structures, including the dentate gyrus, the CA1 hippocampal region and even the parietal cortex. Moreover, the researchers found substantial levels of amyloid-β in the hippocampus, pointing to the trans-synaptic propagation of disease in this model. The relevance of these results to the cortical and hippocampal dysfunction in individuals with Alzheimer's disease remains to be established.—*JCL*

Dysregulated development

Alterations in excitatory synapse development are associated with psychiatric disorders. Two new studies shed light on divergent ways in which synapse formation can be altered.

In the first one, Seth Margolis *et al.* (*Cell* **143**, 442–455) studied factors that constrain synapse development. They identified

a RhoA guanine nucleotide exchange factor—ephexin-5—that negatively regulates excitatory synapse development. Activation of the EphB2 receptor leads to phosphorylation of ephexin-5, targeting it for degradation by the proteasome through the E3 ligase Ube3A and triggering synapse formation. Ube3A is deleted in Angelman's syndrome and is also altered in some forms of autism spectrum disorders, suggesting a link between altered excitatory synapse formation and neurodevelopmental disorders.

Phelan-McDermid syndrome is caused by deletions in the terminal portion of chromosome 22, leading to developmental delay. In the second study, Joanna Giza *et al.* (*J. Neurosci.* **30**, 14805–14816) found that targeted deletion of one gene in this region, that encoding islet brain-2, alters excitatory neurotransmission and Purkinje cell arborization. Behaviorally, mice lacking this gene show deficits in exploration and motor performance.

Collectively, these studies support the hypothesis that alterations in synaptic development underlie common developmental brain disorders.—*KDS*

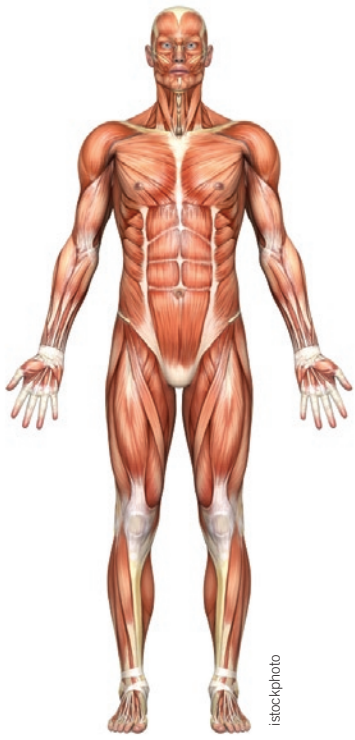
■ IMMUNOLOGY

DCs from monocytes

Although dendritic cells (DCs) can be derived from monocytes using specific combinations of cytokines *in vitro*, monocytes and DCs are typically considered to develop independently from a common precursor *in vivo*. Using an antibody that recognizes a specific receptor on monocyte-derived DCs (Mo-DCs), Cheolho Cheong *et al.* (*Cell* **143**, 416–429) now report that Mo-DCs with antigen-presenting activity do indeed exist *in vivo*.

These cells localize to the T cell areas of peripheral lymph nodes of mice exposed to lipopolysaccharide (LPS) or to Gram-negative bacteria. The researchers showed that the LPS-mediated induction of Mo-DCs requires L-selectin and CCR7, and that these cells cross-present bacterial antigens to T cells at least as efficiently as the classical DCs that exist in inflamed lymph nodes.

The cytokine requirements for the *in vivo* differentiation of Mo-DCs have yet to be determined, and the importance of these antigen-presenting cells during bacterial infection is unknown. Their identification and characterization nevertheless contribute new insights into the developmental relationship between monocytes and dendritic cells and the distinct roles of DC subsets in mediating immune responses.—*AF*



■ METABOLISM

Uncoupled muscle

Two transcriptional regulators act on mitochondrial function to regulate energy metabolism in muscle, report Delphine Duteil *et al.* (*Cell Metab.* **12**, 496–508).

Steroid receptor coactivator-1 (SRC-1) and transcriptional intermediary factor-2 (TIF2), members of the p160 family of transcription factors, exert important regulatory functions in fat and liver. Duteil *et al.* analyzed TIF2's functions in skeletal muscles by selectively knocking it out in adult mice. The mutant mice showed increased mitochondrial uncoupling in myocytes, which protected them from the switch from slow- to fast-twitching muscle fibers that often results from prolonged lack of physical activity.

Mechanistically, the effects of the TIF2 ablation involved an increase in the protein levels of SRC-1 and the dual modulation of the mitochondrial molecule uncoupling protein-3 (UCP3). As the lack of TIF2 also delayed the appearance of type 2 diabetes and protected the mice from diet-induced obesity, the authors raise the possibility of harnessing these transcriptional co-regulators to treat metabolic disorders.—*JCL*

Written by Michael Basson, Kevin Da Silva, Alison Farrell, Juan Carlos López, Carolina Pola and Meera Swami

New from NPG

Suppression of inflammation by a synthetic histone mimic.
Nicodeme, E. *et al. Nature* doi:10.1038/nature09589 (10 November).
A pharmacological approach that interferes with the recognition of acetylated histones protects against sepsis and endotoxic shock in mice.

Glioblastoma stem-like cells give rise to tumour endothelium.
Wang, R. *et al. Nature* doi:10.1038/nature09624 (21 November).

Tumour vascularization via endothelial differentiation of glioblastoma stem-like cells.
Ricci-Vitiani, L. *et al. Nature* doi:10.1038/nature09557 (21 November).
Two studies showing that brain cancer cells can turn into blood vessel cells that then form part of the tumor vasculature, disclosing a new mechanism of tumor angiogenesis.

ZAPS is a potent stimulator of signaling mediated by the RNA helicase RIG-I during antiviral responses.
Hayakawa, S. *et al. Nat. Immunol.* doi:10.1038/ni.1963 (21 November).
ZAPS, a shorter isoform of poly(ADP-ribose) polymerase-13, stimulates interferon production in response to viral infection and could constitute a new therapeutic target.

Extensive spontaneous plasticity of corticospinal projections after primate spinal cord injury.
Rosenzweig, E.S. *et al. Nat. Neurosci.* doi:10.1038/nn.2691 (14 November).
Spontaneous recovery in primates after spinal cord injury may be due to growth of new nerve fibers and not to regeneration of the severed axons.

Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci.
Franke, A. *et al. Nat. Genet.* doi:10.1038/ng.717 (21 November).
A meta-analysis of six genome-wide association studies for Crohn's disease discloses 30 genomic regions newly associated with this pathology.