Intolerance for corticosteroids

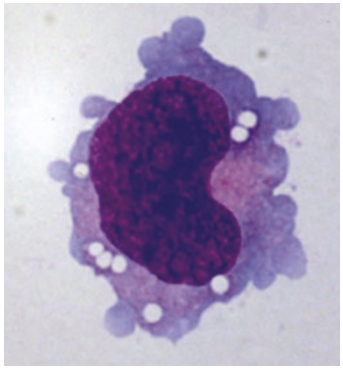
Young children treated with corticosteroids have an increased chance of developing asthma later in life. Findings in mice hint at why. It seems as if the drugs block the development of tolerance to inhaled antigens, report Philippe Stock and colleagues in the 1 December *Journal of Immunology* (**175**, 7380–7387, 2005).

The researchers examined tolerance in a standard experimental regimen. In this regimen, repeated inhalation of ovalbumin enables mice to develop tolerance to the antigen—so that subsequent exposure to ovalbumin does not result in airway inflammation or dysfunction. The researchers found that administering the corticosteroid dexamethasone during the tolerizing regimen affected dendritic cells. The drug blocked the development of a population of these cells in the lung that secrete the cytokine interleukin-10 (IL-10). IL-10 induces regulatory T cells that dampen overactive immune responses in asthma.

Paradoxically, corticosteroids are the most effective treatment for asthma. Corticosteroids control acute lung inflammation by blocking the production of inflammatory cytokines and preventing recruitment of inflammatory cells to the airways. But finding that the drugs may also thwart the development of protective immune mechanisms suggests that they should be used with caution, for short periods at low doses. *–CT*

Leukemia gets smaller

Boosting levels of a microRNA stimulates blood cells to differentiate, according to a study in *Cell* (123, 819–831, 2005). The findings hint at new ways to treat leukemia and uncover an intricate regulatory system in developing blood cells.



Expression of a microRNA promotes granulocyte maturation, shown here.

Retinoic acid is used to treat some forms of leukemia because it triggers maturation of leukemic cells. Francesco Fazi *et al.* found that retinoic acid treatment also boosted levels of the microRNA, miR-233, in these cells. miR-233 was expressed only in mature myeloid cells of the bone marrow, where it may promote their differentiation.

The researchers went on to show that treating with retinoic acid and increasing the expression of miR-233 resulted in greater maturation of leukemic cells than either manipulation alone. A complex network of transcription factors underlies this observation—for instance, retinoic acid prompts a shift in the type of transcription factor binding to the promoter of miR233, resulting in upregulation of the microRNA. Developing agents to bump up miR233 production and stimulate cell differentiation might be helpful for treating some leukemias. *–AF*

Two hits against glioblastoma

A molecularly targeted approach shrinks tumors in some patients with one of the most hard-to-treat cancers, glioblastoma according to a report in *The New England Journal of Medicine* **353**, 2012–2024 (2005).

The vast majority of individuals with this brain cancer die shortly after diagnosis. But some patients are known to respond to kinase inhibitors directed against the epidermal growth factor receptor (EGFR). Ingo Mellinghoff and colleagues asked why.

The researchers found that the tumors of patients who responded clinically to EGFR inhibitors co-expressed a form of EGFR that persistently activates the phosphatidylinositol 3-kinase (PI3K) pathway and the tumor suppressor PTEN, which inhibits PI3K signaling. So, in patients that respond to therapy, two factors concurrently inhibit the PI3K pathway—the EGFR kinase inhibitor and the action of PTEN.

If these observations are validated prospectively, screening for the presence of PTEN may be useful to identify patients with glioblastoma who are more likely to respond to EGFR kinase inhibitors. In addition, inhibitors of the PI3K pathway could be tested in combination with EGFR inhibitors in patients that do not express PTEN. *–JCL*

Stroke bASICs

Cross-talk between glutamate receptors and acid-sensing ion channels (ASICs) causes neuronal death after stroke, report Jun Gao *et al.* in *Neuron* (48, 635–646, 2005).

During a stroke, the environment in which a neuron lives changes drastically. Excess glutamate, an excitatory neurotransmitter, bombards the neuron and causes excitotoxic death. The pH of the ischemic tissue also drops, which activates neuronal acid-sensing ion channels (ASICs). But whether glutamate receptors and ASICs signal to each other to exacerbate neuronal death during stroke was unclear.

The researchers found that activation of glutamate receptors during stroke increased ASIC channel phosphorylation; phosphorylation caused calcium ions to flow through the channels into the neuron, eventually killing it.

This neuronal cell death could be thwarted in cell culture experiments. For instance, pharmacological blockade of glutamate receptors or ASICs decreased cell death in oxygen and glucose-deprived neuron cultures grown in an acidic medium. Death was also prevented by other means, such as blocking CAMKII, a kinase activated by glutamate receptors that phosphorylates ASIC channels.

Whether *in vivo* blockade of the cross-talk between ASICs and glutamate receptors decreases brain injury after stroke remains an open question. *–EC*

HCV hijacks tumor suppressor

A protein expressed by the hepatitis C virus (HCV) interferes with the function of a crucial tumor suppressor protein, retinoblastoma (Rb). These findings could help explain why the virus can trigger liver cancer.

Rb plays a vital role in preventing cancers by repressing certain transcription factors that would otherwise signal cells to divide. But DNA tumor viruses, such as human papillomaviruses, have evolved strategies to inactivate Rb and trigger cell proliferation. Now Tsubasa Munakata *et al.* show that an RNA virus—HCV—can also hijack Rb for its own ends (*PNAS* **102**, 18159–18164, 2005).

The researchers observed that levels of the Rb protein were reduced in cells containing replicating viral RNA. The HCV protein NS5B proved to be the culprit. It shares a motif with the DNA virus proteins that bind and inactivate Rb. And, like the DNA virus proteins, NS5B binds to Rb and targets it for degradation—stimulating cell division.

The findings reveal that RNA and DNA viruses could share some common mechanisms for triggering cancer. The study also adds to the list of viral tricks that HCV might use to edge cells toward tumor formation. *—CT*

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