Much ado about IDO

A synthetic metabolite of the amino acid tryptophan reverses paralysis in a mouse model of multiple sclerosis (*Science* **310**, 850–855). By mimicking a natural immune-suppressive molecule, the metabolite quells the hyperactive immune response that shears myelin from neurons and leads to disease.

Tryptophan catabolism by the enzyme indoleamine 2,3-dioxygenase (IDO) is known to dampen T-cell responses. Michael Platten *et al.* observed that an altered myelin peptide known to subdue myelin-reactive T cells also switched on expression of IDO in the T cells—a clue that tryptophan metabolites might be beneficial in multiple sclerosis.

To test this idea, the authors fed a synthetic tryptophan metabolite to mice with experimental autoimmune encephalomyelitis, a multiple sclerosis–like disease. Mice treated with the compound had fewer disease relapses and milder symptoms. The drug seemed to work by suppressing the proliferation of myelin-reactive T cells, and by dampening the ability of microglial cells in the central nervous system to present antigen to the T cells.

Tryptophan metabolites are structurally related to two drugs—linomide and laquinimod—which have shown some efficacy, albeit by an unknown mechanism, in people with multiple sclerosis. Unfortunately those drugs are toxic to the heart. The new results suggest that other orally active derivatives of tryptophan metabolites could potentially treat multiple sclerosis and perhaps other autoimmune diseases. — *CT*

Alcohol blocks innate immunity

A dampened immune response leaves alcoholics susceptible to lung infections and pneumonia. This effect is now traced to deficits in a growth factor receptor that regulates macrophages (*J. Immunol.* 175, 6837–6845).

Pratibha Joshi *et al.* found that macrophages in the lungs of ethanol-fed rats had reduced levels of the receptor for granulocyte-macrophage colony-stimulating factor (GM-CSF). This receptor normally receives signals from GM-CSF, which recruits macrophages and prompts their differentiation.

The researchers showed that the lung macrophages from rats fed ethanol were unable to properly secrete cytokines or phagocytose bacteria. Such changes may explain why alcoholics have diminished immunity against lung pathogens.

In an experiment with implications for therapy, the researchers found that the immune deficits could be reversed by recombinant GM-CSF. In ethanol-fed rats, this treatment increased cell-surface expression of the GM-CSF receptor, enhanced cytokine secretion by lung macrophages and restored macrophage bacterial phagocytosis. GM-CSF is already in clinical trials for sepsis and lung injury. — *AA*

Modifying myc

The myc oncoprotein is switched on and off by ubiquitination, according to a new report. Proper regulation of this process may help guard against cancer (*Cell* **123**, 409–421).

Sovana Adhikary *et al.* identified a ubiquitin ligase, HectH9, that modifies myc. Rather than targeting myc for degradation, ubiquitination enables the transcription factor to recruit transactivating proteins to the promoters of myc target genes. Expression of a myc mutant that could not be ubiquitinated decreased transcription of target genes and blocked cell proliferation. What's more, a repressor of myc (Miz1) blocked myc ubiquitination by inhibiting the myc-HectH9 interaction.

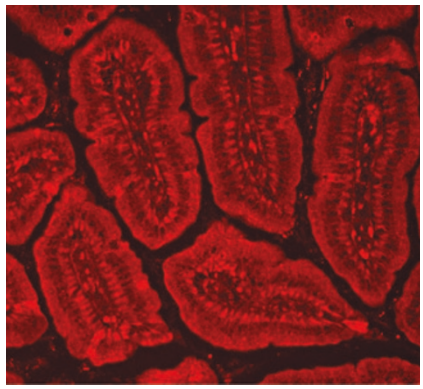
The researchers also report that expression of HectH9 is increased in certain tumor cells. Experimentally reducing levels of HectH9 in some cancer cells blocked proliferation and anchorage-independent growth.

These findings suggest HectH9 activity may underlie the cell proliferation that contributes to cancer. Understanding, in more detail, how HectH9 regulates myc may provide clues for the design of new cancer drugs. — *AA*

Written by Allison Alcivar, Jasmine Bhatia, Randy Levinson and Clare Thomas.

No iron-clad rules

A mouse model uncovers a twist to the molecular basis of a toxic iron-overload disorder (*Cell Metabolism* 2, 309–319).



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Ceruloplasmin (red), an enzyme involved in iron transport, accumulates in gut epithelial cells.

In people with aceruloplasminemia, a rare inherited disease, iron dangerously accumulates in the tissue due to a deficiency in the enzyme ceruloplasmin. The enzyme is thought to assist release of iron from tissue when the body demands it, so its loss leads to excess storage and eventually cell damage.

Srujana Cherukuri *et al.* tested the mouse ceruloplasmin knockout, putting an extreme request on its body for iron by bloodletting and an iron-poor diet. Unexpectedly, the knockout mice did not show a defect in releasing iron from tissue stores under these conditions—instead, the mice had a deficiency in iron absorption from food in the gut.

Under normal conditions, ceruloplasmin may well release iron from tissue. But the findings suggest that under conditions of extreme iron demand, the enzyme also assists in sucking up iron from the gut. On the basis of their findings, the researchers suggest that creating extreme demand for iron in people with the disease might ease symptoms, which could be accomplished by mild bloodletting coupled with an iron-deficient diet — *RL*

Nitric oxide in Alzheimer disease

Dampening production of nitric oxide seems to protect against brain pathology and prolong lifespan in a mouse model of Alzheimer disease (*J. Exp. Med.* **202**, 1163–1169).

To show this, Carl Nathan *et al.* examined mice deficient for inducible nitric oxide synthase (iNOS) that also express mutant forms of two proteins with a role in Alzheimer disease, APP and presenilin 1.

The researchers found that the mice lived longer and had fewer plaques in their brains than Alzheimer mice expressing iNOS. The mice also had less β-amyloid, a protein that accumulates in the brains of individuals with the disease. The researchers suggest that the next step should be to assess whether selective inhibitors of iNOS have an effect in mouse models of Alzheimer disease. — *JB*