Suppressive CpG

A study by Hessel et al. (page 1563) explains how a potent immune activator shuts down allergic inflammation. CpG-rich DNA sequences, common in microbial DNA, are best known as agents that bind to the innate receptor Toll-like receptor (TLR)-9 on immune cells, triggering their activation and alerting the host to the pathogenic invasion.

Clinicians have taken advantage of the immune-activating qualities of CpG-rich DNA molecules, which are in a clinical trial as immunostimulatory agents such as adjuvants. However, treatment with these synthetic DNAs also inhibits allergic airway inflammation in mice, a phenomenon commonly attributed to the CpG-induced production of T helper (Th)-1–promoting cytokines, which counteract the effects of allergy-promoting Th2 cytokines.

But Hessel and colleagues now show that antiallergy CpG DNA treatment works not by antagonizing the effects of Th2 cytokines, but by preventing the Th2 response from ever getting started. CpG treatment inhibited the early production of the Th2 cytokine interleukin-4 from basophils and mast cells, and crippled the function of lung dendritic cells (DCs). DCs from CpG-treated mice had reduced levels of MHC class II and costimulatory molecules and were thus unable to activate Th2 cells. These results were unexpected as, in most contexts, CpG molecules and were thus unable to activate Th2 cells.

What determines whether CpG sequences will activate or inhibit DCs remains an open question, and one that will be important to resolve in order to ensure that CpG DNAs—now also in clinical trials as asthma inhibitors—generate the desired response in humans. JEM

Constipation kills

Cellular constipation can be deadly, according to a study on page 1587. Wang and colleagues show that cells get clogged with absorbed secretory cargo when they lack an enzyme that helps form vesicles. Deletion of this enzyme proved lethal in mice, halting brain, bone and vascular development.

The enzyme in question is a protein tyrosine phosphatase (PTP) called MEG2. MEG2 binds lipids and resides on intracellular vesicle membranes, where it clips phosphate residues from the fusion protein NSF. Once dephosphorylated, NSF initiates homotypic fusion between immature secretory vesicles, a critical step in protein secretion.

Knocking out MEG2, the team found, prevented T cells (isolated from chimeric mice) from secreting the autocrine growth factor interleukin–2, stunting T cell proliferation in response to stimulation. Electron micrographs of the deficient T cells revealed that the cells lacked mature secretory vesicles and were clogged with the dense remains of fusion-incompetent vesicles.

Platelets that lacked MEG2 were also dysfunctional, failing to aggregate when exposed to the clotting factor thrombin. But the MEG2 defect spared neutrophils and macrophages, although these cells rely on the same cellular machinery for vesicle release.

Cell type–specific PTPrms might compensate for MEG2’s absence in neutrophils and macrophages. Besides looking for these PTPrms, the group is also investigating the mechanism behind the developmental defects in the MEG2-deficient mice, which they suspect result from an inability to produce growth factors that direct the migration and differentiation of progenitor cells. JEM

No entry for adenosine

The body has evolved a variety of ways to limit the destructive effects of low oxygen, one of which is to ramp up extracellular levels of the nucleoside adenosine. High extracellular adenosine limits hypoxia–driven vascular leakage by promoting the barrier function of endothelial cells and helps dampen inflammatory responses by inhibiting immune cell activation and cytokine production. Now, on page 1493, Eltzschig and colleagues find that hypoxia keeps extracellular adenosine high by switching off production of its cellular importer.

How the body accumulates extracellular adenosine, which is normally pumped rapidly back into cells by equilibrative nucleoside transporters (ENTs), is not completely clear. Hypoxia increases the expression of cell surface enzymes that hydrolyze ATP to adenosine and also increases the expression of adenosine receptors. But neither of these facts explains how extracellular adenosine avoids being rapidly shuttled back into cells by the ENT transporters.

Hypoxia increases extracellular adenosine by shutting off the production of the adenosine transporter ENT1.

HIF-1α

Hypoxia dampens the transcription of ENT1, which encodes the primary transporter of adenosine in endothelial cells, thereby decreasing the cell’s adenosine importing capacity. The transcription factor HIF-1α (hypoxia inducible factor-1α) bound to the ENT1 promoter and was required for the repressive effect. The authors are now investigating how HIF-1α, best known for its ability to induce gene expression, shuts down the expression of ENT1. JEM