Gassy degeneration

Nitric oxide (NO) gas spurs on brain degeneration, according to a study on page 1163. Nathan and colleagues show that the NO-producing enzyme iNOS accelerates brain destruction and death in a mouse model of Alzheimer’s disease.

Alzheimer’s disease is a lethal neurodegenerative disease that causes progressive memory loss and dementia. The disease is associated with a build-up in the brain of peptide fragments derived from a protein called β-amyloid precursor protein (APP). APP is a protein that normally gets cleaved in the brain, although the functions of APP and of its primary cleavage products are poorly understood.

Mutations in APP, or in the enzymes that chop it up, result in the overproduction of the disease-causing peptide (known as Aβ). Although it is not completely clear how Aβ contributes to disease, it has been shown to trigger iNOS expression in brain cells. This NO-producing enzyme is normally triggered by immune responses and inflammation and is needed to fight off certain infections. But in the brain, iNOS may contribute to mitochondrial and protein damage that destroys neurons.

This group and others found iNOS in brain lesions of patients with Alzheimer's disease, but no studies had investigated whether iNOS contributed to disease progression. Nathan and colleagues now show that Alzheimer’s-prone mice that lack iNOS live twice as long and develop fewer amyloid plaques than iNOS-expressing mice. Both groups of mice developed some plaques initially, but the iNOS-deficient mice were spared the rapid accumulation of plaques later in life.

The delayed effect of the iNOS deficiency was likely due to a positive feedback loop between the enzyme and the Aβ peptide, suggests Nathan. Aβ might have to accumulate before it triggers the production of iNOS. iNOS then exacerbates Aβ accumulation, perhaps in part by blocking proteasomal degradation, a pathway the cell uses to dispose of Aβ. When this loop is interrupted, disease progression is slowed. The group now plans to test iNOS inhibitors in Alzheimer’s-prone mice to see if a pharmacological approach recapitulates the genetic approach.

Based on these results, Nathan suggests that iNOS inhibitors—which have already been produced and tested in humans—might be a promising and thus far overlooked therapy for the treatment of this devastating disease. JEM

Crk gets hijacked

The ulcer-inducing bacterium Helicobacter pylori busts through the cells that line the stomach by hijacking a host protein, suggest Suzuki and colleagues on page 1235. The co-opted protein turns on multiple signaling pathways in gastric cells that cause the normally adhesive cells to pull apart from their neighbors.

Roughly half of all people worldwide have H. pylori living in their stomachs. Most people host the infection without consequence but, in some, H. pylori infection triggers peptic ulcers and gastric cancer. H. pylori encodes a set of proteins that allows it to adhere to and thrive in the stomach and to avoid immune attack. One of these proteins—CagA (cytoxin-associated antigen-A)—helps ward off immune cells but also disrupts the epithelial cells that line the stomach.

Many studies have investigated how CagA, which is injected into gastric epithelial cells through a specialized bacterial secretion system, helps breach the epithelial lining of the stomach. Once inside the cells, CagA binds to a variety of intracellular signaling proteins. But it was not clear which of these proteins is required for CagA-induced cell scattering.

Suzuki and colleagues now identify a new target of CagA: the Crk family of adaptor proteins. CagA–Crk binding in infected epithelial cells triggered the activation of downstream signaling pathways, including the Ras–Raf and Rac1–WAVE pathways, which are normally induced during routine cell turnover. These signals prompted the expulsion of adhesive proteins β-catenin and E-cadherin from the adherens junctions that hold the cells together.

The liberation of β-catenin from adherens junctions not only compromises cell contacts, but likely also induces aberrant proliferation of the cells, as nuclear β-catenin drives the expression of cell cycle–promoting genes such as cyclin D1. Both cell scattering and proliferation compromise the integrity of the stomach lining, thus contributing to the development of H. pylori–induced gastric disease. JEM