Research Roundup

Bugs to the rescue

Bugs that live in our gut are not only not harmful but provide signals that maintain gut tissue integrity, according to Seth Rakoff-Nahoum, Ruslan Medzhitov, and colleagues (Yale University, New Haven, CT).

The benefits of commensal, or non-pathogenic gut bacteria, are well known. For example, these bacteria digest tricky carbohydrates and supply certain micronutrients. But inappropriately enthusiastic responses to the bacteria are characteristic of inflammatory bowel diseases (IBD) such as Crohn’s disease. So Medzhitov suspected that mice less able to respond to bacterial products might end up better off.

Instead, mice deficient for Toll-like receptor (TLR) responses to bacterial products such as lipopolysaccharide (LPS) were more susceptible than wild-type mice to a colon-damaging chemical. The increased damage and death was not the result of bacterial invasion, as lymphocyte infiltration was low, and epithelial damage and bleeding remained high when the same mice had antibiotics added to their regimen. Furthermore, wild-type mice died from chemical-induced damage when treated with antibiotics that completely eliminated commensal bugs.

Low doses of LPS or another TLR ligand rescued intestinal damage in the antibiotic-treated wild-type mice, apparently by inducing protective cytokines and heat shock proteins. Such a regimen might be contemplated for the damaged digestive tracts of chemotherapy patients, who are given high doses of prophylactic antibiotics to back up their weakened immune systems.

In contrast to earlier conclusions by IBD researchers, Medzhitov says it is now clear that “the recognition of commensals is not just an unwanted side effect.” The body may use the influx of commensals into an intestinal wound as an indicator of damage. In internal organs lacking commensals, there appear to be endogenous ligands that signal similarly, and indeed Medzhitov has preliminary evidence that some of these also induce the TLR system. Whether a tissue repair system evolved to take on an immune defense duty, or vice versa, is now open to debate.

Reference: Rakoff-Nahoum, S., et al. 2004. Cell. 118:229–241.

Protein-only prions

When Stanley Prusiner proposed the protein-only hypothesis of prion infectivity, he envisioned a simple experiment. Make the protein in vitro, and infect the mouse. Now, Giuseppe Legname, Prusiner (University of California, San Francisco, CA), and colleagues have done just that, albeit with a lack of potency that has left some people in doubt.

The problem is that the most potent material—brain extract—is a mess. A misfolded version of the endogenous PrP protein emerged decades ago as the putative infectious agent. But in infected brains it is clumped in an insoluble amyloid form that is difficult to purify and impossible to crystallize. Thus, the exact nature of the most infectious form is a mystery. “The only measurable thing we have right now is the amount of β-sheet,” says Legname. “We do not know the actual structure.”

His approach was to start with the recombinant version of a truncated form, known to be predisposed to forming amyloid, and select conditions that favored β-sheet content. This preparation was injected into the brains of mice overexpressing a similarly truncated protein. Between 380 and 660 d later, the mice showed disease symptoms, which could be serially transferred to other mice.

Some researchers believe that the test system is poised to become infectious, and the injection may be just one of many neurotoxic stresses that would eventually get it going (Couzin, 2004). Legname does acknowledge that “you may well need accessory factors in vivo”—factors that would only be transferred from brain extract not recombinant material. And even the most infectious conformation may be lost once the protein is injected into a host.

But Legname reminds the doubters that “yeast prion systems have established that the protein-only hypothesis is right,” although of course they lack the brain pathology of mammals. He remains confident that the “hundreds of different conditions” that the team is testing to increase infectivity will bring down the presymptomatic time and eventually allow disease initiation by recombinant protein in wild-type mice.

References: Couzin, J. 2004. Science. 305:589; Legname, G., et al. 2004. Science. 305:673–676.