Trashing *Salmonella*

Macrophages use nitric oxide (NO) to gain the upper hand against *Salmonella* infection, according to a study on page 625. McCollister and colleagues show that NO released by macrophages foils *Salmonella’s* attempts to avoid degradation in lysosomes.

*Salmonella* is an enteric pathogen that infects macrophages and causes illnesses ranging from mild gastroenteritis to potentially fatal systemic disease. Once inside macrophages, *Salmonella* avoid the cells’ antimicrobial defenses using a specialized protein secretion system. This system, known as the *Salmonella* pathogenicity island 2 (SPI2) type III secretion system, injects proteins from the bacteria-containing phagosome into the cytosol of the infected cell. These proteins disrupt normal vesicular trafficking and prevent the fusion of the phagosome with the degradative lysosomes where the bacteria would be digested. *Salmonella with a defective SPI2 system survive poorly in macrophages and are unable to cause systemic disease.

Previous studies have shown that interferon (IFN)-γ–induced activation of macrophages is essential for effective defense against *Salmonella* infections. McCollister and colleagues now show that IFN-γ helps outsmart the bacteria by inducing the sustained production of NO by macrophages. Macrophage–produced NO inhibited transcription of the sensor kinase that controls the SPI2 system. Without the SPI2 system in place, the *Salmonella*-containing phagosomes were free to fuse with lysosomes and the bacteria were destroyed. *JEM*

**T cell CRAC dependence**

Calcium transport is critical for the activation of transcription pathways that drive T cell proliferation and function. On page 651, Feske and colleagues show that Ca²⁺ release–activated Ca²⁺ (CRAC) channels in the plasma membrane are the major, if not only, pathway for T cell receptor–activated calcium influx in T cells. The mechanism of activation and identity of these CRAC channels continues to elude researchers.

The authors analyzed channels in T cells from patients with a form of severe congenital immunodeficiency (SCID) that is characterized by impaired T cell activation and a near total lack of calcium influx. Using electrophysiological techniques, they showed that the lack of calcium influx was due to a complete failure of CRAC channel opening, and not a consequence of dysregulated intracellular calcium stores or aberrant expression of other suspected ion channels. The authors believe that the CRAC channels are present in the patients’ T cells but that their activation is somehow impaired.

The specificity and severity of the defect in T cells from the SCID patients provide a powerful tool to pinpoint the identity of the CRAC channel and determine its mode of activation. The authors are now using positional cloning approaches and genetic complementation to try to isolate the underlying molecular components. *JEM*

**Fas gets protective**

A deadly receptor reveals a benevolent side in a study on page 575. Landau and colleagues show that the cell death–inducing receptor Fas is required for protection against neurodegeneration in a mouse model of Parkinson’s disease (PD).

The Fas receptor (Fas), best known for its apoptotic role in the immune system, is widely expressed in nonimmune tissues, including the central nervous system. In the brains of patients with PD, the expression of both Fas and Fas ligand (FasL) is reduced, whereas the expression of soluble Fas is elevated. Soluble Fas is a decoy receptor that impairs Fas signaling by competing for free ligand. Apoptosis has been implicated in PD neurodegeneration, but this occurs independently of caspase-8, an upstream activator in Fas–mediated apoptosis, suggesting that Fas may not be the predominant death inducer in PD.

Using mice with Fas/FasL mutations, the authors showed that decreased Fas expression increased susceptibility to a PD–causing neurotoxin. Neuronal cell loss was markedly increased in Fas–deficient mice, and these mice developed severe PD symptoms within days of toxin exposure. In contrast, two strains of mice that express Fas but have mutations in the Fas death domain, a region responsible for apoptotic signaling, were resistant to PD.

Fas defects might also underlie PD in humans, as circulating T cells from patients with PD failed to up-regulate Fas expression in response to mitogenic stimulation. Although the Fas–induced signals that protect the brain have yet to be identified, these findings suggest that, in this model of PD, Fas–induced neuroprotection trumps Fas–induced cell death. *JEM*