Recruiting interferon producers

On page 687, Diacovo and colleagues describe how natural interferon-producing cells (IPCs) make their way from the bloodstream into the peripheral lymph nodes (PLNs), where they help fight pathogens.

IPCs, also called plasmacytoid dendritic cells (DCs), are the major producers of type I interferons and respond to virus infection using intracellular Toll-like receptors that bind viral RNA or DNA. During infection, IPCs accumulate in secondary lymphoid tissue where they boost the antiviral function of other cells, including natural killer cells and DCs, but how they gain entry into the lymph nodes had been a mystery until now.

Using intravital microscopy, which enables real-time viewing of cellular movement in vivo, Diacovo and colleagues showed how inflammation drives IPC migration into PLNs. The important players in this process were adhesion molecules called selectins. L-selectin expressed on the surface of blood-borne IPCs and E-selectin expressed on specialized endothelial venules in the PLNs promoted IPC attachment to and rolling along the vessel endothelium during inflammation. $\beta_1$- and $\beta_2$-integrins expressed on the cell surface then allowed IPCs to establish a firm foothold on the vessel wall. Finally, the chemokine receptor CCR5 was shown to be necessary for the IPCs to squeeze through the endothelial cells lining the vessel wall into the PLNs.

Fungus-fighting vaccine

On page 597, Torosantucci and colleagues describe a novel vaccine with the potential to confer protection against multiple fungal pathogens. In mice, the vaccine induced protective immunity against Candida albicans and Aspergillus fumigatus, both common fungal pathogens that prey on immunocompromised individuals.

Effective antifungal therapy can be hampered by drug toxicity and acquired resistance. A therapeutic or prophylactic vaccine might circumvent these problems, but none are commercially available. $\beta$-glucan, a polysaccharide component of all pathogenic fungal cell walls, is an attractive antigenic target for vaccine development as it is critical for survival and is not expected to readily mutate in response to immune pressure—a common problem for vaccination against highly mutable proteins such as the HIV envelope protein.

In their study, Torosantucci and colleagues used laminarin, a well-characterized $\beta$-glucan from the brown alga Laminaria digita, as a source of immunizing antigen. Laminarin's weak immunogenicity was overcome by hooking it up to the highly immunogenic diphtheria toxin, a protein carrier commonly used in human vaccines.

Mice and rats immunized with this vaccine developed anti-$\beta$-glucan antibodies and were protected against otherwise lethal challenge with C. albicans and A. fumigatus. Immune serum and a $\beta$-glucan specific monoclonal antibody also protected naive mice when transferred intravenously. In vitro, anti-$\beta$-glucan antibodies bound preferentially to C. albicans hyphae and inhibited fungal growth in the absence of cells, suggesting that protection was antibody mediated rather than cell mediated. Thus the vaccine might protect individuals with defects in the phagocytic cells that normally attack fungal invaders.

"This is the first time that a single vaccine formulation has been effective against such diverse pathogens as Candida and Aspergillus," says senior author, Antonio Cassone. The authors now plan to test this vaccine in humans. They also plan to test it against certain bacteria and protozoa known to express glucan or glucan-like molecules.
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 Ca$^{2+}$ release–activated Ca$^{2+}$ (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*