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. β1- and β2-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.

These findings distinguish IPC migration patterns from those of conventional DCs, which migrate into the lymph node from peripheral tissues through afferent lymphatics. The authors suggest that IPCs might use the same receptors to gain access to other inflamed tissues such as the skin. If so, interfering with the function of these receptors might be therapeutic in the treatment of autoimmune disorders, such as psoriasis and systemic lupus erythematosus, in which IPCs accumulate in the skin and contribute to disease pathogenesis.

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. β-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 vaccine against highly mutable proteins such as the HIV envelope protein.

In their study, Torosantucci and colleagues used laminarin, a well-characterized β-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-β-glucan antibodies and were protected against otherwise lethal challenge with C. albicans and A. fumigatus. Immune serum and a β-glucan specific monoclonal antibody also protected naive mice when transferred intravenously. In vitro, anti-β-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.