Traffic jam suppresses immunity

Organ rejection in transplant patients can be prevented using the drug FTY720, but the drug’s mechanism of action has been unknown. Now, Suzanne Mandala, Hugh Rosen, and colleagues (Merck Research Laboratories, Rahway, NJ) show that it acts by retaining lymphocytes in lymph nodes, preventing their circulation through the bloodstream.

B and T lymphocytes are either retained in lymph nodes in order to contact antigens and antigen-presenting cells or sent back out into the bloodstream for circulation. Circulating lymphocytes may enter tissues, where they mediate protective activities or cause tissue damage. Most immunosuppressive drugs work by inhibiting lymphocyte function: they either kill the cells directly, inhibit their production, or block signals downstream of antigen recognition. But FTY720 works in a novel manner.

Rosen’s group found that a phosphate ester metabolite of FTY720 mimics the natural lipid sphingosine-1-phosphate (S1P) and binds several forms of S1P receptors. Activation of the receptors causes the sequestration of lymphocytes at nodes and a corresponding decrease in circulating lymphocytes. “This is the first indication that S1P and its receptors regulate lymphocyte trafficking and that, if manipulated pharmacologically, [they] can give rise to immunosuppression,” says Rosen. Unlike S1P, the side effects of which include low blood pressure, FTY720 is better tolerated in clinical use. The reasons behind this distinction are yet unclear, but may involve the failure of FTY720 to bind all S1P receptors.

Reference: Mandala, S., et al. 2002. Science. 10.1126/science.1070238

Proteases commit microbicidal

White blood cells use proteases to kill their targets, according to new results from Emer Reeves, Hiu Lu, Anthony Segal (University College, London, England), and colleagues. The findings contradict previously accepted notions that reactive oxygen species (ROSs) are the killing agents. ROSs like superoxide are produced by NADPH oxidase activity when white blood cells, primarily neutrophils, phagocyte pathogens. For decades it has been thought that high concentrations of the toxic ROSs resulting from this respiratory burst are directly responsible for killing microorganisms. But the new results prove otherwise.

Segal’s group showed that mice deficient in protease activity have increased sensitivity to microbes. Additionally, purified neutrophils from the protease-deficient mice are impaired in their antimicrobial activity in vitro. “Our results are conclusive,” says Segal. “By taking out the proteases, we do not interfere with the respiratory burst, but do interfere with killing.”

The proteases are activated through increases in both pH and hypertonicity in the phagocytic vacuoles. These changes arise when NADPH oxidase activity drives electrons into the vacuole. To compensate for the charge transfer across the membrane, K+ also enters. The resulting hypertonic conditions release the cationic proteases from their bound state on an anionic proteoglycan matrix. K+ entry also results in alkaline conditions that stimulate protease activity. The proteases are then free to bind to and digest the target microbes.

Reference: Reeves, E., et al. 2002. Nature. 416:291–297.

Learning by palmitoylation

Learning is probably driven by use-dependent changes in synaptic strength. Now, Alaa El-Husseini, David Bredt (University of California at San Francisco, San Francisco, CA), and colleagues have identified regulated protein palmitoylation as one means to control the strength of synapse responses.

Synaptic activity is controlled by AMPA channels, which respond to the neurotransmitter glutamate by letting in Na+ until the neuron fires. Ca2+ influx through NMDA receptors (also activated by glutamate) alters synaptic responses by influencing the number of AMPA receptors clustered at the synapse.

It now appears that protein palmitoylation is key to this modulation. The localization of AMPA receptors is controlled by the PDZ domain protein PSD-95, which also clusters at synapses and binds to the AMPA-trafficking protein stargazin. The clustering of PSD-95 is known to require its palmitoylation. Now, Bredt and colleagues demonstrate that increased glutamate receptor activity accelerates depalmitoylation of PSD-95 and that depalmitoylation causes endocytosis and dispersion of both PSD-95 and AMPA receptors, leading to depression of synaptic strength.

“This defines a mechanism for activity-dependent changes in AMPA receptor numbers and defines protein palmitoylation as a new signaling mechanism at synapses,” says Bredt. The enzymes that add and remove PSD-95 palmitoyl groups have not been identified, but Bredt speculates that they will be Ca2+ regulated, as Ca2+ entry into the cell (e.g., through NMDA receptors) is required for AMPA dispersion.

Reference: El-Husseini, A., et al. 2002. Cell. 108:849–863.
From migration to circulation

A pathway required for blood vessel development in vertebrates also functions in flies, according to new results from Nam Cho, Mark Krasnow (Stanford University, Stanford, CA), and colleagues. The results imply that cell migration, not angiogenesis, may have been the original function of the vascular endothelial growth factor receptor (VEGFR) tyrosine kinase family and its ligands.

The active migration of blood cells, or hemocytes, occurs during fly embryogenesis when the heart has not yet begun pumping. Fly blood does not travel through a closed circulatory system, but Cho found that flies have homologues of the VEGF pathway, which is required for vertebrate blood vessel development. This suggests that the proteins have a more ancient function.

That function appears to be the migration of blood cells during embryogenesis, according to the new study. Cho and colleagues found that, in flies lacking VEGFR, blood cells differentiate, but do not migrate normally and aggregate in the anterior of the embryo. Inactivation of all three homologues of the VEGF ligand resulted in the same cell migration defect. Ectopic expression of a VEGF ligand caused misrouting of blood cells, suggesting that it may act as a chemoattractant to assure that the hemocytes travel along pathways where phagocytosis of apoptotic cells is required.

Blood cell chemoattractant activity has also been demonstrated in vitro for a vertebrate VEGF, but has largely been ignored. “While most of the press for VEGF involves its role in angiogenesis... it may have originally evolved for blood cell functions,” says Cho. However, it is not known whether the vertebrate homologues still serve similar functions in blood cells. The simple genetics of the fly system should facilitate the identification of signaling molecules downstream of VEGF, which may aid in the discovery of therapeutic agents for blocking angiogenesis during tumor growth or increasing vascular growth after injuries such as heart attack.

Reference: Cho, N., et al. 2002. Cell. 108:865–876.