Controlling RAGE

The liver has a finite capacity for regeneration. In mice, removal of 70% of the liver (partial resection) is tolerated but 85% removal (massive resection) is often fatal. Cataldegirmen et al. show on page 473 that blocking RAGE (receptor for advanced glycation end products) allows massively resected mice to survive and regain liver function.

Previous studies in mice suggested that recovery after partial resection requires an inflammatory stimulus—possibly provided by bacterial endotoxins, which are continuously filtered by the liver. This triggers activation of NF-κB in liver cells and production of the proregenerative cytokines TNF and interleukin 6 (IL-6), which are essential for hepatocyte proliferation.

RAGE signaling is known to enhance chronic inflammation. The authors previously found that RAGE also promotes regeneration of injured nerves, which like liver regeneration requires inflammation.

Cataldegirmen et al. now show that inflammation is also a good thing in the massively resected liver, but it is nevertheless suppressed by RAGE. The expression of RAGE was up-regulated on liver dendritic cells (DCs) after massive but not partial resection. RAGE signaling antagonized NF-κB activation in liver cells and decreased the production of TNF and IL-6. Blocking RAGE signaling, or expressing a mutant RAGE on DCs only, reversed the inhibition of inflammation and promoted liver regeneration.

The mechanism behind the unusual anti-inflammatory action of RAGE is not yet clear. Whatever the mechanism, the authors think that RAGE inhibition may be an effective way to enhance liver regeneration in humans. JEM

MIC1 and MIC3: partners in invasion

Adhesive proteins that are discharged from the parasite Toxoplasma gondii and grab onto target cells are needed for infection, according to a study on page 453. Cerede et al. removed two proteins from T. gondii and with it stripped the parasite of its virulence in mice.

Microneme proteins MIC1 and MIC3 are soluble members of a family of parasitic adhesion proteins that are secreted from the parasite, based on an unknown trigger, and bind to the surface of host cells. These proteins are thought to facilitate binding of the parasite to host cells, but their contribution to virulence remains largely unexplored.

Deletion of both MIC1 and MIC3, Cerede et al. now show, prevents parasites from invading host cells and establishing infection in mice. Reexpression of either protein in the deficient parasite strain restored virulence. Mice exposed to the deficient strain of T. gondii were protected from later infection with wild-type parasites, suggesting that removal of MIC1 and MIC3 did not affect immunogenicity.

T. gondii can be transmitted to humans by ingestion of infected meat or cat feces–contaminated food and is a risk for pregnant women as it can cause congenital infections in the developing fetus. The authors suggest that this deficient strain could be used as a veterinary immunization, thereby preventing animal infections and limiting human exposure. JEM

DOKing TLR4 signals

Two adaptor proteins prevent cells from overreacting to bacterial lipopolysaccharide (LPS), report Shinohara et al. on page 333. Dok-1 and Dok-2 dampen intracellular signals from the LPS receptor, Toll-like receptor 4 (TLR4), which may help explain how cells mount a potent response to invading bacteria without also triggering destructive inflammatory responses.

Dok-1 and Dok-2 are adaptor proteins found in hematopoietic cells that are activated by tyrosine kinases in response to antigen and cytokine receptor signals. Once activated, they suppress intracellular signals by inhibiting the GTPase Ras, thereby keeping cellular activation and multiplication under control. The importance of this control is evident in mice lacking both proteins, which have been shown to develop leukemia.

Shinohara et al. now provide evidence that these proteins also inhibit LPS-induced TLR4 signals. Dok-1 and Dok-2 are tyrosine phosphorylated within 1 minute of LPS treatment, and cells lacking either protein displayed enhanced Erk activation in response to LPS. Mice lacking these proteins died from an unchecked production of the inflammatory cytokine TNF, a cause of endotoxic shock, when given a normally sublethal dose of LPS.

This is the first standby pathway described for TLR4 inhibition in macrophages; all other macrophage TLR4 regulators are inducible, suggesting that Dok-1 and Dok-2 may be primarily responsible for controlling the rapid process of primary endotoxic shock in these cells. JEM
**LSP1**: gatekeeper of the endothelium

Endothelial cells use an actin-binding protein to retract and allow neutrophils to crawl out of blood vessels, according to a new study by Liu et al. (page 409).

Neutrophils must traverse the endothelial cell barrier to migrate out of blood vessels into inflamed or injured tissue. Transendothelial migration, once thought to be controlled primarily by the neutrophil, is now known to be a two-way street that requires active participation by both cell types. Endothelial cells respond to neutrophil adhesion by increasing their intracellular calcium levels and rearranging proteins that maintain the tight junctions between neighboring cells. The rearrangement of junctional proteins in endothelial cells ultimately causes them to retract from one another and allows the neutrophils to pass, although the signaling pathways involved are not completely understood.

Leukocyte-specific protein 1 (LSP1) is an intracellular actin-binding protein that is expressed in many white blood cells, including neutrophils. LSP1 is a downstream target of kinases that are essential for neutrophil motility and chemotaxis, but the function of LSP1 in neutrophil transmigration remains unclear, as studies using LSP1-deficient mice have produced conflicting results.

Liu et al. now show that LSP1 expression is required for neutrophils to traverse the vascular endothelial cell barrier in muscle, as fewer cells were able to cross the endothelium in LSP1-deficient mice. Surprisingly, however, the neutrophils themselves did not need LSP1. Neutrophils lacking LSP1 migrated across wild-type endothelium with the ease of wild-type neutrophils. Wild-type neutrophils, by contrast, could not squeeze through LSP1-deficient endothelial cells.

LSP1-deficient mice are resistant to histamine-induced blood vessel leakage which is caused by endothelial cell retraction, suggesting that LSP1 is an indispensable component of the retraction machinery. Exactly how LSP1 links cell surface signals to the cytoskeletal changes that allow retraction remains to be determined. JEM

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**Cancer-causing motifs**

A conserved activation motif identified in the envelope (Env) protein of murine mammary tumor virus (MMTV) can drive transformation of mammary epithelial cells, according to Katz et al. on page 431. The ability of this motif to transform cells single-handedly suggests that viral infection may be an important and previously unrecognized trigger for breast cancer.

The motif in question is the immunoreceptor tyrosine kinase–activating motif (ITAM). These conserved motifs are usually found in immune cells and, when phosphorylated, serve as docking sites for the assembly of proteins that signal the activation and differentiation of the cell. They have also been found in proteins from some oncogenic viruses such as Epstein Barr virus and Kaposi’s sarcoma virus, but what role these motifs play in the transformation process has remained unexplored.

Katz and colleagues now uncover an ITAM motif in the Env protein of MMTV and show that expression of Env in mammary epithelial cells transforms them. The ITAM motif was the key to transformation, as replacement of the conserved tyrosine residues in the motif or inhibition of the kinases that phosphorylate these residues stripped the Env protein of its oncogenic potential.

This study puts the spotlight on a potential new mechanism for MMTV-induced epithelial cell transformation, which has largely been attributed to positional effects—integration of proviral DNA into locations that trigger the expression of cancer-causing host genes. An intriguing wrinkle to this study is the presence of sequences highly homologous to MMTV envelope protein—with intact ITAM motifs—in the DNA of as many as 40% of human breast tumors, although a human homologue of MMTV has yet to be found. JEM