**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 re-arranging 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