ATHEROSESCLEROSIS NEEDS SHC

Liu et al. find that an adaptor protein called Shc orchestrates the response of endothelial cells to stress caused by turbulent blood flow.

In endothelial cells, alterations in blood flow are sensed by cell–cell junctions and cell–matrix adhesions, which can trigger inflammation and the formation of atherosclerotic plaques. The adaptor protein Shc, which is expressed in the endothelium, regulates responses to mechanical forces at the cell surface, leading the authors to explore its involvement in endothelial inflammation.

They now find that Shc becomes phosphorylated (and activated) primarily in areas of turbulent blood flow. Active Shc was found both at cell–cell junctions, in a complex with VE-cadherin and VEGFR2, and at cell–matrix adhesions where it associated with integrins in a cadherin-dependent manner. But Shc’s arrival at adhesions was delayed for 30 minutes after the onset of shear stress, suggesting that signaling from cell–cell contacts may occur first and control the cell’s interactions with the matrix.

Knockdown of Shc expression with siRNA suppressed signals from both cell–cell junctions and adhesions. As the latter signals activate the pro-inflammatory transcription factor NF-κB, the lack of Shc blocked the expression of two NF-κB–dependent atherosclerotic genes that encode the leukocyte-specific adhesion molecules VCAM-1 and ICAM-1. Endothelial cells were therefore unable to bind monocytes—the cells that trigger plaque formation when they ingest fat.

The intriguing delay between the appearance of phosphorylated Shc at cell–cell junctions and matrix adhesion sites is still unexplained: “We don’t know whether there are two pools of Shc, or whether it translocates from cell–cell junctions to adhesions,” says Tzima.

Liu, Y., et al. 2008. J. Cell Biol. doi:10.1083/jcb.200709176.

SUMO KEEPS LAMIN A IN PLACE

A posttranslational defect in nuclear envelope protein lamin A causes it to clump and distort the shape of the nucleus, say Zhang and Sarge.

Lamin A forms a structural network that lines the inner surface of the nuclear envelope. Mutations in lamin A cause a large number of diseases, such as muscular dystrophy and cardiomyopathy. Now, Zhang and Sarge show that two cardiomyopathy-causing mutations prevent post-translational modification of lamin A by SUMO (small ubiquitin-like modifier), which leads to its aberrant localization both in cell models and diseased human tissue.

The authors focused on the effects of SUMO on lamin A, as a recent yeast two-hybrid screen indicated that lamin A binds a sumoylating enzyme. They found that the disease-causing mutations within lamin A occurred at residues near its sumoylation site, which prevented SUMO addition.

To understand how defective sumoylation affects lamin A functions, the authors then examined its localization. In mouse cardiomyocytes, wild-type lamin A was distributed continuously around the nuclear periphery, but mutated lamin A was clumped irregularly. Lamin A was similarly aggregated in skin fibroblasts from a patient with mutation-induced cardiomyopathy, and the nucleus was irregularly shaped. In both cell types, mutant lamin A was associated with decreased cell viability.

Altered nuclear shape can disrupt many nuclear processes, including gene expression and DNA replication. It is still unclear how these changes, triggered by the absence of SUMO, contribute to disease pathogenesis.

Zhang, Y.-Q., and K.D. Sarge. 2008. J. Cell Biol. doi:10.1083/jcb.200712124.

PEGGING MITOCHONDRIAL POSITION

Mitochondria need microtubule-binding proteins for proper positioning, say Chiron et al.

Mitochondria rely on microtubules to move around the cell and for distribution into daughter cells. Many cell types use microtubule-bound motors to move mitochondria. Yeast cells instead depend on microtubule growth to do the job, but how mitochondria are lashed onto the growing microtubules was unknown.

In normal yeast cells, mitochondria are evenly distributed throughout the cell. In a screen of temperature-sensitive yeast mutants, the authors discovered one in which mitochondria aggregated at the ends of the cell, a phenomenon that also occurs when microtubules depolymerize. The mutant gene that caused this phenotype was peg1, which encodes a homologue of the mammalian microtubule