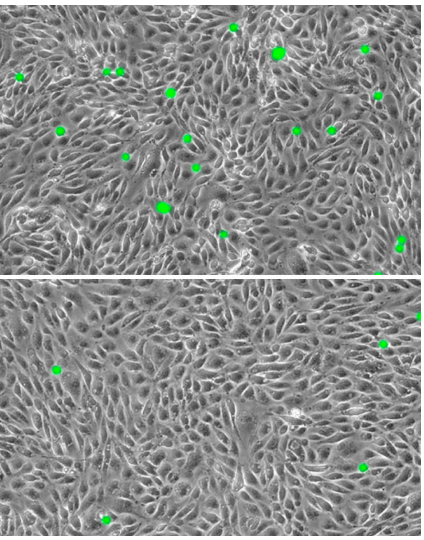
In This Issue



Knockdown of Shc (bottom) prevents adhesion of monocytes (green) to endothelial cells.

ATHEROSCLEROSIS 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.

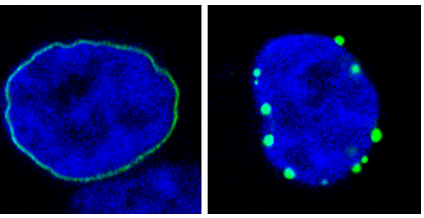
In endothelial cells, alterations in blood flow are sensed by cell–cell junctions and cell–matrix adhesions, which can trigger inflammation and the formation of atherosclerotic plaques. The adaptor protein Shc, which is expressed in the endothelium, regulates responses to mechanical forces at the cell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



Lamin A (green) preserves nuclear shape when it is SUMOylated, but aggregates and distorts the nucleus (blue) when it is SUMO deficient (right).

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.

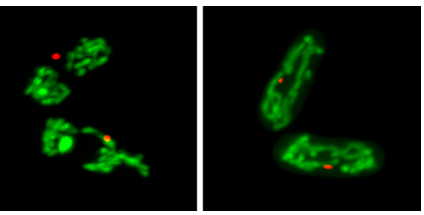
Lamin A forms a structural network that lines the inner surface of the nuclear envelope. Mutations in lamin A cause a large number of diseases, such as muscular dystrophy and cardiomyopathy. Now, Zhang and Sarge show that two cardiomyopathy-causing mutations prevent post-translational modification of 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 sumolyation 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.



Mitochondria (green) in Peg1 mutants aggregate (left), whereas wild-type mitochondria are more spread out (right).

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

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plus end–binding protein CLASP.

Mitochondrial aggregation could not be recapitulated by mutants of either the motor protein dynein or other plus end–binding proteins. The Peg1 mutation did not affect the cytoskeleton, and the changes were independent of the cell cycle, suggesting the aggregation was not due to other changes in microtubules.

Peg1 was found to be a mitochondrial peripheral membrane protein. As CLASP links membranes to microtubules in mammalian cells, Chiron proposes a similar function for Peg1 in yeast, and suggests that it hitches mitochondria to microtubules.

Chiron, S., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200712147.

NUCLEOPHOSMIN MUTATION IS DOUBLE TROUBLE

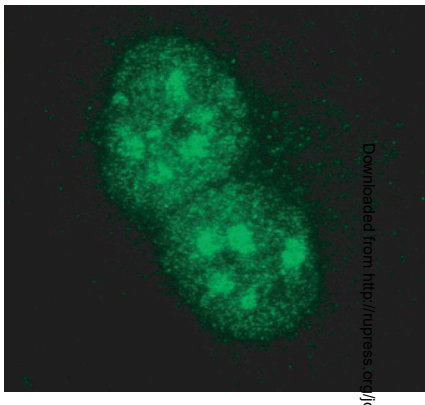
Bonetti et al. find that mutations in a nucleolar chaperone destroy a tumor suppressor and simultaneously activate an oncogene.

Mutations in the nucleolar chaperone nucleophosmin (NPM) are a major cause of acute myelogenous leukemia. One way NPM mutations cause cancer is by failing to sequester the tumor suppressor Arf in the nucleolus, thus allowing its degradation in the cytoplasm. Bonetti and colleagues now show that mutant NPM has the same effect on another protein called Fbw7-γ, which suppresses the oncogenic protein c-Myc.

Fbw7-γ ubiquitinates c-Myc and promotes its degradation, thus lowering the levels of this powerful transcription factor. In cells lacking functional NPM, the authors showed that Fbw7-γ partially relocalized to the cytoplasm and was degraded. As a consequence, the half-life of c-Myc doubled in NPM mutant-bearing cells, and the total amount of c-Myc rose. Cytoplasmic Fbw7-γ could not prevent c-Myc from promoting tumors in culture. This loss of Fbw7-γ regulation of c-Myc could be mitigated by blocking nuclear export.

Mutant NPM still bound to Fbw7-γ, but was unable to retain it in the nucleolus. The authors think that the chaperone activity of normal NPM ensures proper folding of its binding partners and helps prevent their degradation by retaining them in the nucleolus.

Bonetti, P., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200711040.



Nucleophosmin saves the tumor suppressor Fbw7-γ (green) from cytoplasmic destruction by sequestering it in the nucleolus.

ACTIN AND MYOSIN IN THE MITOTIC SPINDLE

Cables of actin stretch from pole to pole of the mitotic spindle, and, with myosin, help control spindle length and shape, according to Woolner et al.

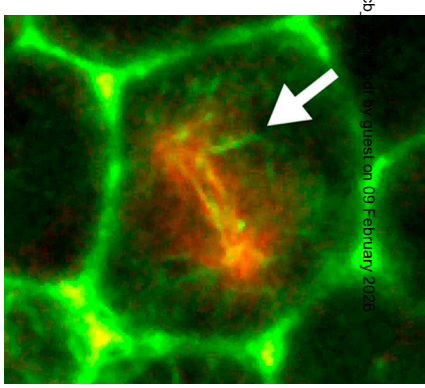
Microtubules and their motors are indispensible for mitotic spindle formation, but whether actin filaments and actin-based myosin motors are also part of the spindle apparatus is a controversial issue. Mitotic spindles interact with cortical actin, which is thought to anchor them. One protein that might be mediating this interaction is Myo10, an unconventional myosin that can bind both actin and microtubules. Because Myo10 is important for meiotic spindle formation, the authors sought to define its function in mitotic spindles.

They now find that knockdown of Myo10 leads to longer spindles, and fragmented star-shaped spindle poles. In the absence of Myo10, spindle rotation movements were slow and smooth rather than quick and jerky. The normally spasmodic spindle movement suggests that Myo10 anchors the spindle by forming brief, transient links with cortical actin.

Rescue experiments indicated that Myo10 has both actin-dependent and -independent functions during mitosis. Spindle pole fragmentation was rescued by Myo10 that lacked the actin-binding head domain. However, the long-spindle defect required the actin-binding region, or could be suppressed by disrupting actin, suggesting that actin helps elongate the spindle, whereas Myo10 shortens it.

As Myo10's actin-binding domain was required for normal spindle length, the authors sought actin in the spindle. Live cell imaging showed dynamic actin cables within mitotic spindles, oriented longitudinally and rotating along with the spindle as a whole, "as if the cables helped determine the direction of spindle motion," says Woolner. The mechanism for coordination of actin and Myo10 is still unclear, but the authors envision Myo10 "walking along the actin, holding the poles at a fixed point."

Woolner, S., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200804062.



Actin cables (green) surround the spindle (red) as it assembles.