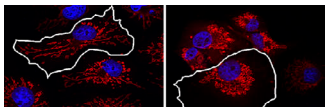
In This Issue

Text by Ben Short
bshort@rockefeller.edu

A new CLUH to mitochondrial biogenesis



Compared with mitochondria (red) in control cells (left), mitochondria in cells lacking CLUH (right) appear fragmented and clustered. DNA is shown in blue.

A cytosolic protein promotes mitochondrial biogenesis by binding to mRNAs encoding mitochondrial proteins, Gao et al. reveal.

CLUH is the mammalian homologue of a family of proteins that, in yeast, flies, and other organisms, regulates the morphology and distribution of mitochondria. How the proteins carry out this function, and whether CLUH plays a similar role in mammalian cells, is unknown.

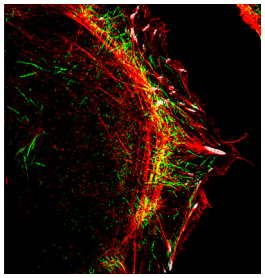
Gao et al. found that CLUH mainly localized to the cytosol of mammalian cells, but small fractions of the protein appeared to associate with mitochondria and newly synthesized microtubules. In the absence of CLUH, mitochondria fragmented and clustered on one side of the nucleus, instead of forming a tubular network dispersed throughout the cell.

To learn more about CLUH's function, the researchers looked for genes whose expression pattern in various cell types and conditions matched the expression of *CLUH*. Many of these coregulated genes encoded mitochondrial proteins, but others encoded proteins involved in RNA processing and translation. Gao et al. therefore wondered whether CLUH might regulate the synthesis of nuclear-encoded mitochondrial proteins. Indeed, the researchers found that CLUH bound to hundreds of mRNAs encoding mitochondrially targeted proteins, and the levels of several of these proteins were reduced in cells lacking CLUH.

Senior author Elena Rugarli thinks that CLUH might ensure that mitochondrial proteins are translated near to mitochondria so that they can be quickly imported into the organelle. She now wants to investigate whether CLUH regulates the stability, transport, or translation of its target mRNAs.

Gao, J., et al. 2014. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201403129.

Septins provide a link to epithelial migration



Super-resolution imaging shows that septin filaments (green) localize to the interface of the radial stress fibers and transverse arcs formed by F-actin (red). Focal adhesions are labeled white.

Septin filaments crosslink actin stress fibers to promote focal adhesion maturation and cell migration, Dolat et al. reveal.

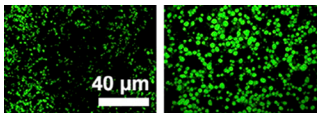
During normal development and tumor metastasis, epithelial cells undergo an epithelial-to-mesenchymal transition (EMT) that loosens their contacts with neighboring cells and enhances cell motility. At the front of migrating mesenchymal cells, radial actin stress fibers transduce force from contractile actin filaments (known as transverse arcs) at the top of the cell to the focal adhesions that attach the cell to the underlying extracellular matrix, promoting adhesion maturation and cell motility. Dolat et al. investigated the potential role of another cytoskeletal element, the filaments formed by the septin family of GTPases, which are often overexpressed in renal cell carcinomas.

The researchers found that septin filaments interweave with transverse arcs and radial actin stress fibers at the front of migrating kidney epithelial cells. Knocking down septins disrupted the actin network's organization and inhibited the maturation of focal adhesions. This phenotype could be rescued by overexpressing the actin-bundling protein α-actinin, suggesting that septin filaments serve to cross-link actin stress fibers. Indeed, Dolat et al. found that septin 9 could bundle actin filaments in vitro.

Septin 9 was up-regulated in kidney cells undergoing EMT. Overexpressing this septin enhanced cell migration, whereas knocking down septic 9 impeded cell motility. Senior author Elias Spiliotis now wants to determine how septins cross-link actin filaments and to investigate what governs their localization and assembly in the leading edge of migrating epithelia.

Dolat, L., et al. 2014. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201405050.

Acinus cleavage cuts down on autophagy



Larval fat bodies expressing cleavage-resistant Acinus (right) contain more autophagosomes (green) than control fat bodies (left).

Nandi et al. describe how a caspase and a kinase combine to regulate the levels of a protein that stimulates autophagy.

During autophagy, double-membraned autophagosomes engulf cytoplasmic material and deliver it to lysosomes for degradation. This process is drastically up-regulated in starving cells that need to recycle basic nutrients in order to survive. But even well-fed cells use low levels of autophagy to rid themselves of unwanted components such as misfolded proteins or damaged organelles. Autophagy is blocked in the absence of a protein called Acinus and hyperactivated in flies overexpressing this protein. How Acinus levels are regulated in vivo is unclear, however, although it is known that the mammalian protein is a substrate for the protease caspase-3 and the kinase AKT.

Nandi et al. discovered that, in flies, Acinus is cleaved by the caspase Dcp-1. Mutating the cleavage site or knocking out Dcp-1 increased Acinus protein levels and enhanced autophagy even in well-fed flies. Acinus cleavage was inhibited by AKT-mediated phosphorylation. Mutating the AKT phosphorylation sites to phosphomimetic aspartate residues stabilized Acinus and increased the levels of autophagy in fly tissues.

Flies expressing cleavage-resistant forms of Acinus lived longer than wild-type animals, probably due to the protective effects of enhanced autophagy. Indeed, expression of non-cleavable Acinus mutants partially protected flies from the neurodegeneration induced by aggregation-prone Huntingtin protein. Senior author Helmut Krämer now wants to investigate how Acinus stimulates autophagy, as the protein's biochemical function is currently unclear.

Nandi, N., et al. 2014. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201404028.