In This Issue

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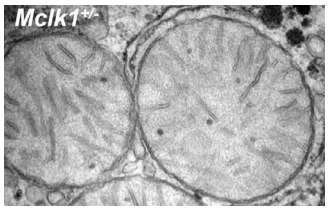
The mystery of the (not) missing coenzyme



Mitochondria from a *Mclk1*$^{+/-}$ mouse appear normal, but their respiratory function is impaired due a decrease in inner membrane UQ levels.

Lapointe et al. reveal that the partial depletion of a mitochondrial enzyme inhibits respiration by altering the distribution of the coenzyme ubiquinone (UQ).

The mitochondrial hydroxylase MCLK1 helps to synthesize UQ (also known as coenzyme Q), which transfers electrons along the respiratory chain of the mitochondrial inner membrane and also serves as an antioxidant there and in other cellular membranes. Though *Mclk1*-null mice die during embryogenesis, mice with a single copy of the *Mclk1* gene live longer than wild-type animals, possibly because their metabolism is altered by a reduction in mitochondrial respiration. Yet UQ levels appear to be unchanged in *Mclk1* heterozygotes, leaving it unclear why these animals have dysfunctional mitochondria.

Lapointe et al. found that, although the total amount of UQ was the same in mitochondria from *Mclk1*$^{+/-}$ and wild-type mice, the coenzyme's distribution was altered in MCLK1-deficient animals so that UQ levels were higher than normal in the outer mitochondrial membrane and lower than normal in the inner membrane. Supplementing *Mclk1*$^{+/-}$ mice with extra dietary UQ restored inner membrane UQ levels and rescued electron transport.

Mice heterozygous for Coq3, another enzyme involved in UQ synthesis, showed no changes in the level or distribution of UQ or any alteration in mitochondrial function or lifespan. This suggests that MCLK1 is a limiting factor for UQ synthesis and that decreased inner membrane levels of the coenzyme compromise respiration and promote longevity. The paradoxical increase in outer membrane UQ in *Mclk1*$^{+/-}$ mice could be due to delayed turnover of the antioxidant molecule as a protective response against the oxidative stress caused by impaired respiratory chain function.

Lapointe, J., et al. 2012. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201203090.

Sec and Tat share the workload

Keller et al. describe how two transport pathways cooperate to insert a bacterial protein into the cell membrane.

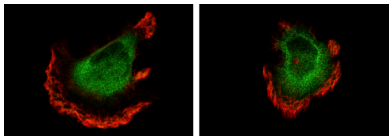
Bacteria and chloroplasts have two different systems that translocate proteins across or into membranes. The Sec pathway transports unfolded proteins through the SecYEG membrane channel, whereas the twin-arginine transport (Tat) machinery translocates proteins such as the Rieske redox protein, whose C-terminal iron-sulphur domain must be carefully folded in the cytosol before being transported across the membrane. The Rieske proteins of *Streptomyces coelicolor* and other actinobacteria, however, contain three transmembrane domains (TMDs) instead of one and have N termini that lack the twin-arginine motif usually recognized by the Tat machinery. How these bacteria insert their Rieske proteins into membranes is therefore unclear.

Keller et al. identified an internal twin-arginine motif next to the third TMD of the *S. coelicolor* Rieske protein Sco2149. Mutating these arginines, or deleting the Tat machinery, blocked membrane integration of the third TMD of a Sco2149-based reporter expressed in *E. coli*. The first two TMDs were still inserted successfully, however. Keller et al. found that these TMDs were translocated by the SecYEG channel and an associated protein called YidC.

The Sec and Tat pathways of *E. coli* therefore cooperate to integrate Sco2149 correctly into the cell membrane. The authors now want to check that Sco2149 is processed similarly in *S. coelicolor* and to investigate how transport is switched between the Sec and Tat machineries after the Rieske protein's first two TMDs have been translocated. The researchers suspect that collaboration between the Sec and Tat systems may be more widespread, especially if internal twin-arginine motifs can be found in other bacterial membrane proteins.

Keller, R., et al. 2012. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201204149.

Tiam1 increases turnover



A control cell stained for actin (red) spreads out and polarizes on fibronectin (left), whereas a cell lacking Tiam1 remains compact and largely unpolarized (right).

The guanine nucleotide exchange factor Tiam1 promotes cell migration by regulating the turnover of cell–matrix adhesions, Wang et al. reveal.

Migrating cells polarize to form a protrusive front and a retracting tail. The Rac GTPase helps establish and maintain this polarity by stimulating membrane protrusion and promoting the rapid turnover of integrin-based adhesions at the cell's leading edge. Integrins activate Rac in response to cell adhesion, but how they do this is unclear. Wang et al. found that Tiam1, a Rac activator required for polarized cell migration, binds to talin, an adaptor protein that connects integrins to signaling molecules and the actin cytoskeleton.

Tiam1 colocalized with talin at adhesions, particularly at the cell front, but was displaced when talin was depleted by RNAi. Cells lacking either talin or Tiam1 showed decreased Rac activation in response to integrin adhesion, delaying cell spreading and polarization. And adhesion turnover was slower at the leading edge, thus inhibiting cell migration. Talin-deficient cells could be rescued by the re-expression of wild-type talin but not of talin mutants unable to bind or recruit Tiam1 to adhesions.

Tiam1's localization to adhesions was also regulated by the PAR polarity complex, which binds to Tiam1 through PAR3 and phosphorylates it via atypical protein kinase C (aPKC). Depleting PAR3 or inhibiting aPKC prevented adhesion-induced Rac activation and cell spreading. The researchers speculate that the phosphorylation of Tiam1 by aPKC promotes the exchange factor's association with talin, allowing integrin-based adhesions to stimulate Rac and promote polarized cell migration.

Wang, S., et al. 2012. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201202041.