In This Issue

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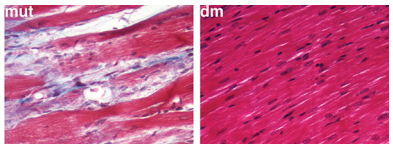
Balanced mitochondria behave better



Heart tissue is damaged in mice lacking *Mff* (left) but appears normal in mice that are also missing *Mfn1* (right).

Chen et al. find that evening out mitochondrial fusion and fission allows the organelles to regain their normal function.

Mutations in genes that control mitochondrial fusion or fission are responsible for various diseases, including dominant optic atrophy. In all of these diseases, either fusion or fission is defective, and one potential therapeutic approach is to restore the balance between the two opposing processes.

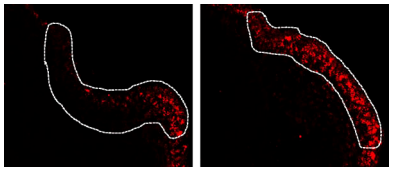
To test whether this approach is feasible, Chen et al. engineered mice to lack *Mff*, a gene that spurs mitochondrial fission. Although the mice had defects in many of their organs, the most severe abnormalities were in the heart. The animals developed dilated cardiomyopathy, in which the heart enlarges and its walls thin. The condition typically killed the rodents when they were around 13 weeks old. Loss of *Mff* also caused metabolic defects in the animals. ATP levels fell by 50%, and the main respiratory complexes were sluggish.

The researchers then asked if reducing mitochondrial fusion could correct these problems. They found that mice that are deficient in *Mff* and the fusion-promoting gene *Mfn1* had normal hearts and lifespans. In fact, the rodents' mitochondria were more efficient than those of healthy mice, sustaining a higher level of oxygen consumption. The animals missing both genes weren't normal, however. The male animals were sterile because of a defect in the testes.

Although fusion and fission were reduced in the animals lacking *Mff* and *Mfn1*, the two processes were in equilibrium, enabling mitochondria to work normally. Thus drugs that restore the balance between fusion and fission could be beneficial for diseases such as dominant optic atrophy.

Chen, H., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201507035

KDM4B doesn't leave a mark



The H3K9me3 mark (red) is normally rare in otic ectoderm (left), but its levels increase after loss of KDM4B (right).

The histone demethylase KDM4B orchestrates an early step in the development of the inner ear, Uribe et al. show.

The inner ear starts out as a slab of ectoderm, the otic placode, that buckles and bends into a spherical structure known as the otic vesicle. At the same time the otic placode is forming, early embryos produce KDM4B, which switches on genes by removing the H3K9me3 epigenetic mark.

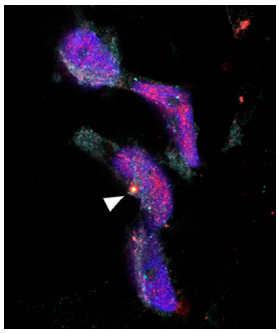
Uribe et al. found that KDM4B was expressed in the otic placode of early chick embryos, coincident with a decline in H3K9me3 levels in the placode. Otic vesicles in KDM4B-deficient embryos were deformed, and expression of four transcription factors that control inner ear development declined. As the otic placode invaginates, cells change shape and position. Loss of KDM4B altered the distribution and polarity of proteins, such as E-cadherin and actin, that control cell shape and adhesion to other cells.

Uribe et al. next tried to identify KDM4B's targets. They discovered that the enzyme binds to and activates the gene encoding the transcription factor DLX3, which had previously been implicated in inner ear development. Adding DLX3 to embryos that lacked KDM4B in their otic ectoderm restored normal otic vesicle formation.

The results indicate that KDM4B promotes invagination of the otic placode by relieving repression of DLX3. The next steps are to determine which genes DLX3 switches on and what controls expression of KDM4B.

Uribe, R.A., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201503071

TDP-43 crosses the divide



Exogenous TDP-43 (green) can be absorbed by cells, allowing it to assemble with endogenous TDP-43 (red) to form a cytoplasmic granule (arrowhead).

A protein implicated in amyotrophic lateral sclerosis (ALS) travels between neurons, Feiler et al. show.

The protein TDP-43 may promote the pathology of ALS, in which deterioration of motor neurons leads to paralysis and death. Clumps of the protein accumulate in the motor neurons of patients, and mutations in its gene cause inherited forms of ALS. In individual patients, the illness starts in one location, such as a hand, and then spreads to adjacent body regions. Some evidence suggests that TDP-43 travels between neurons and thus might carry the disease in a prion-like manner, but researchers haven't confirmed that the protein makes these journeys.

Researchers have debated whether "infectious" proteins like TDP-43 move between neuronal cell bodies or across synapses. Feiler et al. showed that, in culture, TDP-43 travels from the cell body of one motor neuron to the cell body of another. Cells released the proteins inside microvesicles and exosomes, which other cells took up. Using a microfluidic culture system, the team also found that TDP-43 crosses synapses and that this transmission occurs in both directions.

When a cell absorbed TDP-43, the protein interacted with endogenous TDP-43 and seeded the formation of protein clusters. Lysates from postmortem brains of ALS patients also spurred aggregation. The findings indicate that TDP-43 jumps between neurons and therefore might "transmit" the propensity for protein clustering from one cell to another. This behavior could explain why the disease appears to spread in patients.

Feiler, M.S., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201504057