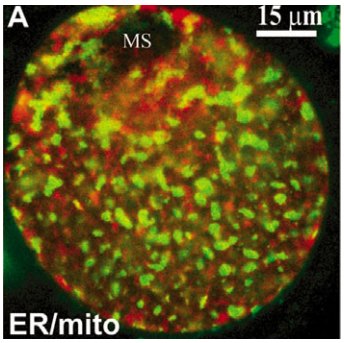
Mitochondrial disease: replacing defective maternal mitochondria



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Mutations in mitochondrial DNA (mtDNA) contribute to several prevalent disorders such as neurodegenerative disease, diabetes and cancer. Mitochondrial disorders are inherited maternally, since all of the mitochondria in an embryo are derived originally from the egg. Therapy for most mitochondrial disease is limited to mitigating disease symptoms and slowing progression. Tachibana et al. present a technique to transfer mitochondria-free nuclear DNA from one egg into a denucleated egg in rhesus macaque monkeys. After fertilization, the eggs develop into healthy offspring with mtDNA and nuclear DNA from unique female origins. DNA tests confirmed the absence of mtDNA from the female nuclear donor. These results demonstrate a potential method for bypassing the normal mechanisms of mitochondrial inheritance.

Tachibana, M., Sparman, M., Sritanaudomchai, H., Ma, H., Clepper, L., Woodward, J., Li, Y., Ramsey, C., Kolotushkina, O. and Mitalipov, S. (2009). Mitochondrial gene replacement in primate offspring and embryonic stem cells. *Nature* **461**, 367-372.

Neurodegeneration: ironing out the mechanism of Friedreich's ataxia

Friedreich's ataxia (FA) is a progressive genetic disorder of the nervous system that is characterized by incoordination and cardiac degeneration. It results from the expression of a non-functional frataxin protein, which normally helps to maintain appropriate iron levels within mitochondria. The mutant protein causes cytosolic iron deficiency and mitochondrial iron overloading by methods that are not understood. Huang et al. used a conditional knockout mouse model, where frataxin was specifically deleted in only the heart and skeletal muscle, to investigate the role of frataxin in iron localization and metabolism in these tissues. Without frataxin, the expression of the iron import protein transferrin receptor 1 (TfR1) increases along with heme catabolism by heme oxygenase 1. Iron storage in cytosolic ferritin decreases and the accumulating free iron is transported into mitochondria through the transport protein mitoferrin 2 (Mfrn2), which is also upregulated in the absence of frataxin. This demonstrates a possible mechanism for the mitochondrial iron loading that underlies the pathology of Friedreich's ataxia.

Huang, M. L., Becker, E. M., Whitnall, M., Rahmanto, Y. S., Ponka, P. and Richardson, D. R. (2009). Elucidation of the mechanism of mitochondrial iron loading in Friedreich's ataxia by analysis of a mouse mutant. *Proc. Natl. Acad. Sci. USA* **22**, 16381-16386.

Aging: *C. elegans* uses TCER-1 to prolong life

Starvation can extend the life span of *C. elegans* by more than threefold. The severe caloric restriction stimulates a nuclear receptor, NHR-49, and causes apoptosis of all germ cells, which is a necessary step for prolonged life. Ghazi et al. show that removing germ cells from *C. elegans* increases the expression of the transcription elongation factor TCER-1. TCER-1 activates the transcription factor DAF-16/FOXO, which is known to increase longevity in the worm. Although loss of germ cells is typically required to extend life span, overexpression of TCER-1 in worms that still contain normal germ cells is sufficient to increase their longevity. This indicates that TCER-1 is at least part of the signal that causes increased life span after germ cell destruction in *C. elegans*.

Ghazi, A., Henis-Korenblit, S. and Kenyon, C. (2009). A transcription elongation factor that links signals from the reproductive system to lifespan extension in *Caenorhabditis elegans*. *PloS Genet.* **5**, e1000639.

Cancer: Polycomb complex is a tumor suppressor in Drosophila

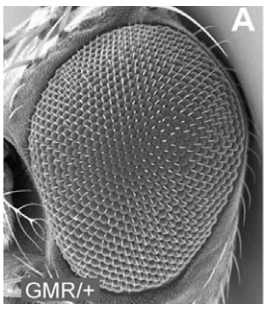

Image reproduced from Whitworth et al. (2008). *Dis. Model. Mech.* **1**, 168-174.

Polycomb group (PcG) proteins remodel chromatin and regulate the binding of transcription factors to promoter sites in DNA. In many cases, PcG proteins maintain stem cell-like characteristics in cells and may thus promote cancer. Classen et al. now report that a PcG complex called Polycomb repressive complex 1 (PRC1) suppresses tumor formation in the Drosophila imaginal disc. Mutations to the PcG proteins cause cell hyperproliferation and, consequently, abnormal tissue architecture. This phenotype depends upon activation of JAK-STAT, a pathway that responds to environmental cues to regulate cell proliferation, differentiation and death. The authors show that PRC1 usually represses the expression of Unpaired family ligands, which activate the JAK-STAT pathway. Thus, PRC1 inhibits imaginal disc growth and acts as a tumor suppressor by inducing epigenetic modifications in the fly.

Classen, A. K., Bunker, B. D., Harvey, K. F., Vaccari, T. and Bilder, D. (2009). A tumor suppressor activity of Drosophila Polycomb genes mediated by JAK-STAT signaling. *Nat. Genet.* **41**, 1150-1155.