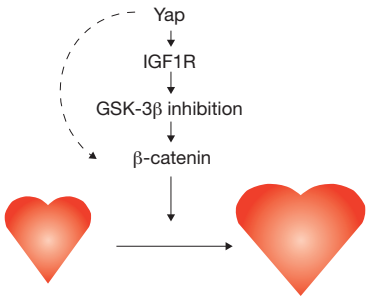
RESEARCH HIGHLIGHTS

Hair follicles run by clockwork

In mammals, epidermal stem cells located in the bulge region of the hair follicle undergo cycles of activation and dormancy to ensure hair renewal. However, not all these stem cells respond to activation at the same time, and the reason behind this heterogeneity has been unclear.

Aznar-Benitah and colleagues (10.1038/nature10649) now show that the circadian rhythm machinery modulates gene expression in the bulge to prime a subpopulation of cells for activation. They observed that a circadian reporter is heterogeneously expressed in the bulge stem cells. Cells with high circadian activity expressed higher levels of genes involved in stem cell proliferation and hair growth, whereas cells with low activity exhibited a dormant expression profile. The authors showed that Bmal1, a master regulator of clock activity, directly modulates the rhythmic expression of genes linked to activation. Its deletion reduced stem cell proliferation in the bulge, whereas loss of a negative clock regulator had the reverse effect. Bmal1 knockout animals displayed signs of premature ageing with defects in hair renewal, but were less prone to Ras-mediated skin tumorigenesis. Remarkably, epidermal stem cells of the interfollicular epidermis, which are constantly cycling, were unaffected by Bmal1 loss. It will be interesting to see if other adult stem cells with cyclic activity are also under circadian control. NLB

Yap makes the heart grow



Cardiomyocyte proliferation is crucial for embryonic heart development, yet the signalling pathways that regulate proliferation are incompletely defined. Olson and colleagues now reveal a central role for the Hippo pathway protein Yap in this process (*Sci. Signal.* **4,** ra70; 2011).

Targeted deletion of Yap in mouse cardiac progenitor cells decreased their proliferation and resulted in embryonic lethality. In contrast, overexpressing constitutively active Yap in the heart increased the number of cardiomyocytes. Further analysis of these transgenic hearts revealed upregulation of insulin-like growth factor 1 receptor (IGF-1R) and β-catenin levels, with associated induction of their downstream targets. This raises the possibility that Yap-mediated cardiomyocyte proliferation requires the IGF and β-catenin signalling pathways. Knockdown of IGF-1R and β-catenin abolished the Yap-dependent increase in cardiomyocyte cell division.

The authors went on to show that the transcriptional activity of Yap is required for upregulating β-catenin signalling. Intriguingly, Yap also induced phosphorylation and inhibition of GSK3β, which should further increase β-catenin accumulation. Constitutively active Yap stimulated the IGF signalling pathway in the absence of IGF, whereas inhibiting IGF signalling limited the Yap-dependent increase in β-catenin activity. Together, these results suggest that Yap regulates the IGF and β-catenin signalling pathways to promote embryonic heart growth. EJC

Mapping the mitochondria

The intricate structure of mitochondrial membranes supports efficient ATP synthesis through oxidative phosphorylation. Weissman, Nunnari and colleagues construct a quantitative genetic interaction map of yeast mitochondria, called the MITO-MAP, that reveals insights into the organization of this organelle (*J. Cell Biol.* **195,** 323-340; 2011).

The MITO-MAP was constructed by analysing pair-wise genetic interactions between 1,482 yeast genes. Importantly, although many previously unappreciated interactions were identified in this study, the data set was consistent with other published small-scale interaction networks in yeast. With the MITO-MAP as a guide, the authors uncovered a six-member protein complex termed MitOS (Fcj1, Aim5, Aim13, Aim37, Mos1 and Mos2) that links the mitochondrial outer and inner membranes. Subsequent microscopy revealed that MitOS components assemble into heterogenous structures on the inner membrane.

Deleting members of MitOS induced defects in mitochondrial inner-membrane structure and cristae junctions. The authors identified genetic interactions between MitOS and ATP synthase, and propose that ATP synthase is necessary for MitOS-dependent regulation of inner mitochondrial membrane structure. Future studies will help resolve the precise function of MitOS in inner membrane organisation, but the MITO-MAP remains a rich resource for understanding mitochondrial structure and function. EJC

Autophagy clears dad's mitochondria

In most eukaryotes, sperm mitochondria are not inherited, despite entering the ooplasm after fertilization. Miyuki and Ken Sato now show that in *Caenorhabditis elegans* the disappearance of paternal mitochondria can be attributed to autophagy triggered by fertilization (10.1126/science.1210333).

Using dye to track mitochondria, the authors confirmed that paternal mitochondria are lost by the 16-cell stage. Expression of a green fluorescent protein (GFP)-labelled version of the authophagy protein LGG-1 (the worm LC3/Atg8 homologue) showed that autophagosomes form around the paternal pronuclear DNA after fertilization and colocalize specifically with paternal mitochondria in the early embryo. Moreover, inhibition of autophagy caused retention of paternal mitochondria, and impaired hatching and embryonic survival. Mutants deficient in lysosomal function also failed to clear paternal mitochondria, demonstrating the involvement of lysosome-dependent degradation. The authors observed that the sperm-derived mitochondria appear defective, and speculate that their selective targeting may prevent the spread of damaged mitochondria. The fertilization-triggered clearance of paternal mitochondria is likely to mediate the maternal inheritance of mitochondrial DNA, and as autophagy is also known to be upregulated in mice following fertilization, this mechanism may be conserved in mammals. CKR

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