In This Issue

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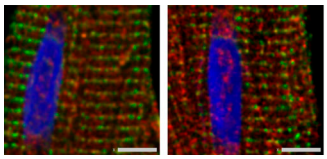
Why a microRNA's absence makes the heart grow larger



Hypertrophic cardiomyocytes (right) show increased levels of IP_3RII protein (red) compared with control cells (left).

Drawnel et al. describe how a calcium channel and a microRNA regulate each other to promote pathological remodeling of heart muscle.

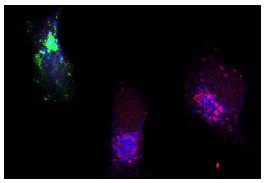
In response to stresses such as infarction, aging, or hypertension, cardiac muscle cells grow to provide the heart with extra capacity, but this hypertrophy often results in cell death and heart failure. The inositol triphosphate receptor II (IP_3RII) calcium channel is up-regulated in hypertrophic cardiac muscle. The calcium it releases from sarcoplasmic and perinuclear stores provokes cardiac arrhythmias and induces changes in gene transcription that promote cardiomyocyte growth and remodeling. How IP_3RII levels are regulated is unknown, however.

Drawnel et al. found that IP_3RII's expression was normally restricted by miR-133a, a microRNA whose levels decrease during hypertrophy to permit cardiac remodeling. Blocking the interaction between miR-133a and IP_3RII mRNA increased the channel's expression and induced hypertrophy in cardiomyocytes. The researchers then investigated what triggers miR-133a's down-regulation during hypertrophy and found that the calcium released through IP_3RII itself was required to switch off miR-133a transcription. Blocking IP_3-induced calcium release prevented miR-133a's repression in response to hypertrophic stimuli, thereby inhibiting IP_3RII up-regulation.

IP_3RII therefore initiates a positive feedback loop to promote its own expression and drive cardiac hypertrophy. The authors now want to investigate how calcium signaling represses miR-133a; their initial results suggest that calcium release converts the transcription factor SRF into an inhibitor of miR-133a expression.

Drawnel, F.M., et al. 2012. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201111095.

A SIMPLE explanation for Charcot-Marie-Tooth disease



In the absence of SIMPLE (green), the EGF receptor and its ligand (red) accumulate in early endosomes (blue).

Lee et al. reveal how a protein linked to the peripheral neuropathy Charcot-Marie-Tooth disease (CMT) regulates the endosomal trafficking and activity of signaling receptors.

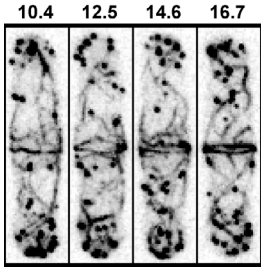
CMT type 1C is an autosomal dominant form of the disease caused by mutations in an early endosomal protein called SIMPLE. SIMPLE's function is unknown, though the protein interacts with Tsg101, a component of the endosomal ESCRT-I complex that sorts proteins for delivery to late endosomes and lysosomes. Lee et al. found that SIMPLE also associated with STAM1 and Hrs, which together form the ESCRT-0 complex that promotes the initial step of endosomal sorting.

All three of these ESCRT proteins were recruited less efficiently to endosomes in the absence of SIMPLE, thereby inhibiting endosome-to-lysosome transport. EGF usually induces the degradation of its receptor, ErbB1, by stimulating the receptor's internalization and delivery to lysosomes. But ErbB1 was trapped in the early endosomes of HeLa cells lacking SIMPLE, prolonging the receptor's signaling activity to downstream MAP kinases. CMT-linked SIMPLE mutants were unable to restore ErbB1 trafficking and even acted as dominant negatives to impair ESCRT localization and endosomal sorting in the presence of wild-type SIMPLE.

Schwann cells, which normally form the myelin sheath around peripheral nerves, are progressively lost in CMT type 1C patients. Lee et al. found that degradation and inactivation of the neuregulin receptors ErbB2 and ErbB3 were delayed in Schwann cells expressing SIMPLE mutants. Lee et al. now want to generate transgenic mice to test whether prolonged activity of this signaling pathway causes the demyelination associated with CMT type 1C.

Lee, S.M., et al. 2012. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201204137.

Global sourcing for ring construction



In this time-lapse series, actin filaments form throughout a mitotic fission yeast and assemble into the medial cytokinetic ring.

The fission yeast cytokinetic ring is formed from actin filaments nucleated throughout the cell, Huang et al. reveal.

Most eukaryotic cells generate a contractile actomyosin ring to separate their daughter cells at the end of mitosis. How actin filaments assemble into the ring is incompletely understood, however, mainly because it is difficult to label all the actin-based structures in a living cell without compromising actin function. In fission yeast, the cytokinetic ring is largely thought to assemble from actin filaments nucleated by the formin Cdc12p at punctate "nodes" around the cell equator. However, using an improved actin-binding probe called lifeact, Huang et al. found that Cdc12p nucleated actin filaments all around the cortex of mitotic fission yeast and that many of these filaments moved to the cell equator and incorporated into the cytokinetic ring.

Fission yeast ring assembly proceeds via two different pathways, relying on either the anillin protein Mid1p or the membrane-binding F-BAR protein Cdc15p. Cdc12p still formed actin filaments in the absence of these two proteins, indicating that these assembly pathways act downstream of actin nucleation. Huang et al. found that two myosin motor proteins—Myo2p and Myo51p—helped move nonmedial actin cables toward the cell equator so that they could join up with filaments nucleated from medial nodes.

Senior author Mohan Balasubramanian says that several animal cell types also appear to build their cytokinetic rings from actin filaments nucleated throughout the cell. He now wants to investigate how the myosin motors move actin filaments toward the cell equator.

Huang, J., et al. 2012. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201209044.