In This Issue

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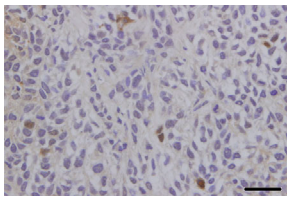
mTORC2 tips the balance in cell survival



Inhibition of mTORC2 provokes apoptosis (brown cells) in a human breast cancer cell line by releasing suppression of *miR-9-Y3p*.

Zou et al. demonstrate that mTORC2 acts as a rheostat to regulate cell survival versus apoptosis.

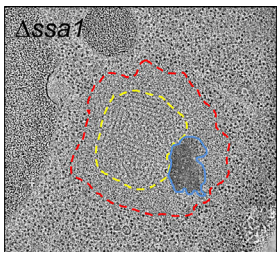
The protein kinase mammalian target of rapamycin (mTOR) is present in two distinct multiprotein complexes, mTORC1 and mTORC2, that regulate metabolism, cell proliferation, and survival. Cells are known to leverage microRNAs to regulate expression of proteins both up- and downstream of mTORC1. However, the functions and regulation of mTORC2 are less well studied.

To learn more about mTORC2 signaling, Zou et al. sought to identify its miRNA targets. miRNA expression profiling after mTORC2 inhibition in human breast cancer cells showed that mTORC2 specifically down-regulated expression of *miR-9-3p*, a miRNA that provokes apoptosis by impairing expression of the transcription factor E2F1. mTORC2 prevented *miR-9-3p* expression by reducing stability of the transcription factor c-Myc. No prior studies had shown that mTORC2 can regulate c-Myc directly, but Zou et al. found that mTORC2 reduced c-Myc's stability by inhibiting its dephosphorylation by the phosphatase PP2A. First author Zhipeng Zou aims to investigate this new pathway in more depth.

Ultimately, high mTORC2 activity promoted cell survival via E2F1, whereas low mTORC2 activity caused apoptosis—explaining why mTORC2 inhibition blocks cancer cell growth. Senior author Xiaochun Bai points out that E2F1 mediates survival of cancer cells exposed to genotoxic drugs. The researchers therefore want to test whether mTORC2 inhibitors synergize with these drugs to promote cancer cell apoptosis.

Zou, Z., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201411128

Chaperones caught partying with prions



A nonfibrous shell (red boundary) and other misfolded proteins (blue) accumulate around an amyloid array (yellow) in yeast lacking the Hsp70 protein Ssa1.

O'Driscoll et al. reveal how Hsp70 chaperones and their cofactors affect the deposition of amyloid aggregates in yeast.

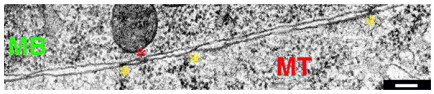
Prions are misfolded proteins that convert other prion proteins to the misfolded, amyloid state, causing them to aggregate into fibrils. Yeast cells sequester prion fibrils into compact aggregates, a process assisted by the chaperone Hsp70 and its cochaperone Hsp40. In cooperation with Hsp70, the protein remodeling factors Hsp110 and Hsp104 fragment amyloid fibrils and promote prion formation and propagation.

O'Driscoll et al. investigated how the Hsp70 system interacts with amyloid aggregates using a fluorescently tagged version of the yeast prion [*PSI*+] that, when overexpressed, forms a highly ordered cytoplasmic array of amyloid fibrils. Correlative fluorescence and electron tomography showed that, whereas Hsp70 and Hsp40 are present throughout these aggregates, Hsp104 is present around their outer surface, and Hsp110 is not concentrated there. However, when individual Hsp70 isoforms were deleted, Hsp110 was also recruited to the surface layer, and electron microscopy revealed that this layer contained a nonfibrous form of the prion.

The authors speculate that the actions of Hsp104 and Hsp110 result in formation of the nonfibrillar shell by dissolving existing amyloid fibrils from the outside in. Consistent with this, overexpression of either Hsp104 or Hsp110 disrupted fibril structure and packing. On the other hand, Hsp110-deficient cells had longer amyloid fibrils, suggesting that Hsp110 regulates fibril length. Senior author Helen Saibil is interested to see whether, and how, these interactions might occur in other types of amyloid aggregates.

O'Driscoll, J., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201505104

Growing up and growing pores in myoblast fusion



During *Drosophila* flight muscle formation, myoblasts (MB) flatten against myotubes (MT), then form many direct contacts (yellow stars) that evolve into fusion pores (red star).

Dhanyasi et al. describe how myoblasts form muscle syncytia in *Drosophila* flight muscles.

Development of mammalian skeletal muscle involves fusion of myoblasts with myotubes to form multinucleate muscle fibers. Myoblast fusion also takes place during *Drosophila* embryogenesis and during development of the adult flight muscles. Although flight muscle development generally shares more features with mammalian skeletal muscle development than does embryonic myogenesis, it remains less well studied.

Dhanyasi et al. used electron microscopy to get a good view of developing flight muscles, preparing their samples with a technique that maximizes cell membrane preservation. Knockdown of adhesion molecules or mediators of actin polymerization known to be important for myoblast fusion revealed that cell adhesion molecules facilitated an initial association between the myoblast and myotube. Then, polymerization of branched actin filaments in the myoblast flattened it against the myotube, bringing their membranes into close apposition. Finally, the membranes of the two cells directly contacted each other at several spots, culminating in the formation and expansion of multiple fusion pores. Senior author Eyal Schejter says that future studies will explore the role of actin in pore formation in greater detail.

Interestingly, fusion pores have also been implicated in embryonic myoblast fusion, although recent studies have suggested that the process instead involves the formation of fingerlike projections from the myoblast surface into the myotube. Dhanyasi et al. found such projections were rare in fusing flight muscles. This may reflect stage-specific differences, says Schejter, or may also be relevant to the embryonic fusion mechanism.

Dhanyasi, N., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201503005