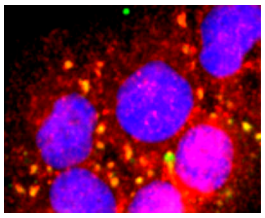
In This Issue

Text by Ben Short
bshort@rockefeller.edu

Plakophilin 1 is found in translation



PKP1 (red) colocalizes with eIF4A1 (green) in large RNA-protein particles called stress granules.

A cell adhesion protein has a second job in stimulating mRNA translation, report Wolf et al.

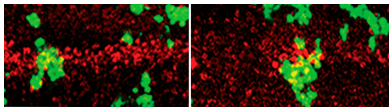
Plakophilin 1 (PKP1) is an essential component of desmosomes and a member of the armadillo adhesion protein family. Other armadillo proteins, like β-catenin and p120^{ctn}, have additional functions outside of holding cells together: β-catenin is a transcription factor as well as a constituent of adherens junctions, for example. Wolf et al. performed a yeast two-hybrid screen using PKP1 as bait, to see if the desmosomal protein was also capable of moonlighting.

The researchers found that PKP1 binds an ATPase called eIF4A1, a subunit of a cytoplasmic translation initiation complex that recruits ribosomes to the 5′ end of mRNAs. PKP1 overexpression promoted eIF4A1's association with its fellow initiating factors and boosted the translation of mRNAs that depend on this complex. In vitro, PKP1 stimulated eIF4A1's enzymatic activity, which is used to unwind mRNAs and make them accessible to ribosomes. PKP1 isn't essential for translation, but its depletion resulted in small, slowly proliferating cells.

PKP1's ability to stimulate translation may explain why the protein is overexpressed in a number of tumors, says senior author Mechthild Hatzfeld. But cell context is important because PKP1 downregulation can also promote tumorigenesis by reducing cell adhesion. The researchers now want to investigate this dual effect, and determine how the different cellular pools of PKP1 are regulated.

Wolf, A., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.200908135.

p53 strands cell cycle on archipelago



Cyclin E (red) is reduced in *Drosophila* cells lacking a component of the mitochondrial electron transport chain (right).

The tumor suppressor p53 spurs the destruction of a critical cell cycle regulator to prevent cells from proliferating during an energy shortage, say Mandal et al.

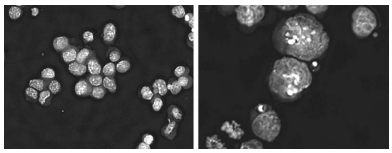
Cell division uses up a lot of energy, so cells ensure they have enough resources to complete the job before committing to it. *Drosophila* cells with a mutation in their mitochondrial electron transport chain generate less ATP, and stop their DNA from replicating by activating a stress response that eliminates cyclin E, a cell cycle regulator that would otherwise push the cells into S phase. The pathway involves p53, but how this protein lowers cyclin E levels is unknown.

Mandal et al. found that p53 stimulates cyclin E's degradation by increasing the transcription of a protein called archipelago. Archipelago recruits cyclin E to an E3 ubiquitin ligase called SCF, which ubiquitinates the cyclin and targets it to the proteasome. Reducing archipelago levels in *Drosophila* with dysfunctional mitochondria restored cyclin E expression and allowed cells to reenter S phase, despite their low ATP levels. The researchers showed that archipelago is a direct transcriptional target of p53, driving cyclin E's destruction and cell cycle arrest during unfavorable metabolic conditions.

p53 can initiate cell death in response to stresses such as DNA damage but it doesn't induce proapoptotic genes following disruption of the electron transport chain. This suggests that p53 has thresholds of stress activation, says lead author Sudip Mandal, which would allow cells to resume proliferation if metabolic conditions improve.

Mandal, S., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.200912024.

Unpacking condensins' function in ES cells



The nuclei of ES cells lacking Smc2 (right) are large and misshapen.

Fazzio and Panning reveal that chromatin regulatory proteins common to all eukaryotic cells can have additional, unique functions in embryonic stem (ES) cells.

The study follows on from an RNAi screen in which the authors identified 62 chromatin structural and regulatory factors that were essential for ES cell survival. Two of these proteins were Smc2 and Smc4, which together form the catalytic heart of the condensin complexes that promote chromosome condensation in mitosis and meiosis. Because somatic cells lacking condensins continue to proliferate with relatively minor mitotic defects, Fazzio and Panning wondered why ES cells died in the absence of Smc2 or Smc4.

ES cells lacking the condensin subunits accrued massive amounts of DNA damage and apoptosed in a p53-dependent manner. It isn't clear why ES cells are so sensitive to the loss of condensins, but it may be connected to two other phenotypes seen in ES, but not somatic, cells. After Smc2 or Smc4 knockdown, mitotic ES cells arrested in metaphase and interphase ES cell nuclei were enlarged and misshapen.

This suggests that condensins promote mitotic progression and maintain interphase chromatin compaction in ES cells—functions that they don't have in somatic cells. In fact, 47 of the 62 genes identified in the original screen can be depleted in differentiated cells without affecting viability, indicating that the chromatin of ES cells is fundamentally different from somatic cell chromatin. Author Barbara Panning says that, if cancer progenitor cells are similarly reliant on particular chromatin regulators, it may be possible to target them therapeutically without harming their healthy, differentiated neighbors.

Fazzio, T.G., and B. Panning. 2010. *J. Cell Biol.* doi:10.1083/jcb.200908026.