Research Roundup

Inducing Sprouty degradation

Receptor tyrosine kinases are often regulated by negative feedback loops that limit their signaling duration. But cells then need to get out of that loop so that they can respond once again. One way to balance the scales is a "signal-dependent degradation of a negative regulator," according to Dafna Bar-Sagi.

The inducible degradation of the protein hSpry2, a human homologue of the negative regulator Sprouty, is the subject of two recent articles. In the fly, Sprouty is an antagonist of fibroblast and epidermal growth factor (FGF and EGF) signaling, whereas the human version inhibits only FGF signaling. Now, Amy Hall, Natalia Jura, Bar-Sagi, and colleagues (State University of New York, Stony Brook, NY) and Chanan Rubin, Yosef Yarden, and colleagues (Weizmann Institute, Rehovot, Israel) show that when EGF activates its receptor, it also triggers degradation of hSpry2.

Both groups demonstrated that EGF induced the phosphorylation of hSpry2—a modification that increased hSpry2's association with the ubiquitin ligase c-Cbl. Although ubiquitinated hSpry2 was then degraded by the proteasome, the transient EGF-induced recruitment of c-Cbl to hSpry2 prevented the ubiquitin ligase from associating with the EGF receptor (EGFR). Thus, hSpry2 delayed c-Cbl-mediated degradation of EGFR.

As hSpry inhibits FGF signaling, this pathway also got a boost from the interaction of hSpry2 and c-Cbl. Bar-Sagi's group found that growth factor–induced degradation of hSpry2 limited its duration as an inhibitor of FGF signaling and allowed cells to respond once again to FGF stimulation. Interference with the degradation of hSpry2 resulted in sustained inhibition of FGF signaling.

Although both stories highlight the inducible c-Cbl–regulated degradation of hSpry2, it is not clear how hSpry2 inhibits FGFR before hSpry2 is degraded, or why this activity is lost from the EGFR cascade in human cells.

References: Rubin, C., et al. 2003. *Curr. Biol.* 13:297–307. Hall, A., et al. 2003. *Curr. Biol.* 13:308–314.

Nucleoli come undone

The nucleolus is essential for ribosome synthesis, cell cycle control, and telomerase sequestration. This complex of rDNA, RNA, and proteins disassembles around ovulation and later reassembles during early embryogenesis. Somatic nuclei transplanted into eggs during nuclear cloning also undergo nucleolar disassembly and reassembly—processes that may contribute to the low efficiency of nuclear transplantation cloning. Now, Koichi Gonda, Nobuaki Kikyo, and colleagues (University of Minnesota, Minneapolis, MN) find that, despite their complexity, nucleoli need only a small RNA-binding protein to make them fall apart.

Gonda et al. purified two proteins from frog egg cytoplasm, FRGY2a and FRGY2b, that have nucleolar disassembly activity. Recombinant versions of either protein dispersed nucleolar proteins and RNA, leaving only small nucleolar remnants. FRGY2a/b may release proteins bound to RNA within the nucleoli through nonspecific competition, as regions imparting nonselective charge interactions with RNA were necessary for disassembly. Alternatively, they may target specific RNAs or RNA-protein particles, such as preribosomes. The latter argument is supported by the fact that mammalian nucleoli were not disassembled in frog eggs, although FRGY homologues have been identified in mouse and human cells.

The findings offer a simple biochemical method for studying nuclear remodeling during cloning as well as nucleolar assembly in general. The identification of RNAs or proteins that interact with FRGY2a/b should point to components necessary to maintain nucleoli. Nucleoli harbor certain cancer- and aging-related proteins, including p53-binding proteins and telomerase. “If we can understand how these proteins are localized or released by certain stimuli, we may be able to modify their localization for therapeutic applications,” says Kikyo.

Reference: Gonda, K., et al. 2003. *Nat. Cell Biol.* 10.1038/nclb039.