Research Roundup

Coming undone at the seams

Cells come unglued and transition to a more motile phenotype with the help of an E3 ligase, according to new results from Walter Birchmeier and colleagues (Max-Delbrück-Center for Molecular Medicine, Berlin, Germany).

Birchmeier’s study focused on cadherins, adhesion molecules that act as anchors via a catenin link to the actin cytoskeleton. During embryogenesis and carcinoma progression, disruption of cadherin-mediated adhesion between epithelial cells helps them make the transition to a more mobile, mesenchymal phenotype. This transition involves endocytosis of cadherin and catenin molecules following phosphorylation by tyrosine kinases such as Src or c-Met.

In the new study, Birchmeier identified a cadherin-binding protein, Hakai, that promotes endocytosis of the cadherin complex, leading to disruption of cell adhesion. Hakai binds to E-cadherin, the prototypical member of the cadherin family, in a phosphorylation-dependent manner. It also competes with other adhesion molecules, such as p120ctn, for E-cadherin binding.

Birchmeier says that “Hakai smelled of degradation,” as it has sequence similarity to c-Cbl, an E3 ligase that ubiquitinates phosphorylated tyrosine kinase receptors and prompts their internalization and degradation. Hakai, which is Japanese for destruction, increases ubiquitination of the E-cadherin complex, particularly when E-cadherin is phosphorylated by Src or in response to growth factors.

Disruption of cell adhesion by Hakai causes cell scattering, similar to that observed during the transition to a mesenchymal phenotype. Birchmeier now plans to test whether Hakai’s motility-promoting properties are used by tumor cells to trigger invasion and metastasis.

Reference: Fujita, Y., et al., 2002. Nat. Cell Biol. 10.1038/ncb738.

Anticancer lubrication

A new mouse model for the study of cancer reveals that mucus lubrication in the intestine is vital for preventing tumor formation.

Unregulated expression of Muc2, the most abundant mucin in the gastrointestinal lining, is often found in human tumors. Furthermore, the goblet cells that synthesize and secrete mucins are often depleted in intestinal mucosal structures that progress to tumors. These findings led Anna Velcich (Albert Einstein Cancer Center/Montefiore Medical Center, Bronx, NY) and colleagues to examine the effects of Muc2 during the early steps of tumorigenesis.

Mice lacking Muc2 had an increased ratio of proliferating to apoptotic epithelial cells, resulting in altered maturation and increased migration of epithelial cells in the intestine. They were also more likely to develop intestinal, colon, and rectal tumors. The mice are the first good model for studying rectal tumors, which are common in humans.

The exact pathway from lack of mucin to cancer is not known. c-Myc overexpression was present, but the nuclear accumulation of β-catenin and the overt inflammatory response present in other mouse models were not found in the Muc2 mutants. Velcich speculates that Muc2 may shield cells from noxious molecules in the lumen content, such as bile acids, that may trigger cell proliferation.

Reference: Velcich, A., et al. 2002. Science. 295:1726–1729.

A trip to the ER

Dephosphorylation of activated receptor tyrosine kinases (RTKs) involves a trip to the surface of the ER, according to new results from Benjamin Neel (Beth Israel-Deaconess Medical Center, Boston, MA), Philippe Bastiaens (EMBL, Heidelberg, Germany), and colleagues.

The new results demonstrate that the protein tyrosine phosphatase PTP1B dephosphorylates RTKs at distinct locations on the cytoplasmic face of the ER. Although it was shown that the ER-localized PTP1B interacts with and can dephosphorylate several growth factor receptors, Neel says it was generally thought that dephosphorylation at this location was simply reversing gratuitous autophosphorylation during RTK synthesis in the ER.

The groups demonstrated, however, that upon growth factor activation, two RTKs, EGFR and PDGFR, move from the plasma membrane and pass by the ER. A high percentage of these internalized RTKs interacted with PTP1B. The authors used FRET to visualize this interaction in cells by engineering a PTP1B mutant that traps its RTK substrate.

The distinct locations of kinase activation by phosphorylation (at the plasma membrane) and dephosphorylation by PTP1B (at the ER) may provide a necessary time delay between turning on and off signaling receptors, thus regulating the lifespan of an active RTK signal. Dephosphorylation could deactivate receptors before they are either sent back to the plasma membrane or to degradative lysosomes.

Reference: Haj, F., et al. 2002. Science. 295:1708–1711.