Research Roundup

Hiding telomerase from chromatin

Telomerase helps cancerous cells survive by extending telomeres at the end of chromosomes. According to new results from Judy Wong, Leonard Kusdra, and Kathleen Collins (University of California, Berkeley, CA), cancer cells recruit additional telomerase by setting it free from its subnuclear storage depot.

Telomerase is activated upon association of two subunits, telomerase reverse transcriptase (TERT) and telomerase RNA, into a ribonucleoprotein (RNP) complex. Collins’ group tracked the active form in normal and cancerous cells by expressing GFP-labeled TERT in limiting amounts that would assemble rapidly with the RNP. This technique revealed that telomerase differed mainly in its location. “A normal cell hides telomerase, by tying it to the nucleolus,” says Collins. In these cells, telomerase was concentrated in the nucleolus during S phase, when its activity is required to maintain chromosome ends. In contrast, transformed cells released all of their telomerase from the nucleoli, regardless of cell cycle phase.

The proteins that control telomerase localization are not yet known, but the ability of transformed cells to bypass this regulation may give them a twofold advantage. First, telomerase would be more effective on an established telomere because more of it is released from nucleolar stores. Additionally, continuous release of telomerase may support the high genomic instability of cancerous cells: adding telomeres to broken chromosome ends might allow normal segregation of rearranged chromosomes that might otherwise arrest the cell cycle.

Reference: Wong, J.M.Y., et al. 2002. Nat. Cell Biol. 4:731–736.

Promiscuous Ras turns on the wrong partner

A cancerous form of Ras is dangerous because it intrudes on pathways where it is normally unwelcome, according to results from David Prober and Bruce Edgar (Fred Hutchinson Cancer Research Center, Seattle, WA).

The small GTPase Ras is stimulated by epidermal growth factor receptors in flies and vertebrates. Activated Ras initiates multiple cellular responses, including cell growth and differentiation. The importance of downstream effectors such as PI3K and Myc for each response has not been firmly determined, in part because their involvement varies depending on the cell culture system used.

Prober and Edgar put some of this controversy to rest by examining how Ras can control cell growth in vivo. In the developing fly wing, both Myc and PI3K were up-regulated in clones of cells expressing an activated form of Ras, which increases cell size and growth rates. Although this form of Ras increased both Myc and PI3K, these pathways were activated independently of each other.

The activated Ras is one commonly found in mammalian tumors. But in normal cells, although wild-type Ras was required for Myc signaling, it had no effect on PI3K activity. Thus, says Edgar, “oncogenic Ras seems to short circuit endogenous signals,” by impinging on the PI3K pathway. The combined effects of Myc (which turns on transcription of translational machinery) and PI3K (which may increase nutrient import into cells) make oncogenic Ras a superpotent variant for increasing growth.

Reference: Prober, D.A., and B.A. Edgar. 2002. Genes Dev. 16:2286–2299.

Semaphorins—not just for axons

An axon guidance factor can work with growth factor receptors to trigger invasive growth, according to a recent article by Silvia Giordano, Paolo Comoglio, and colleagues (Institute for Cancer Research, University of Torino, Torino, Italy).

The guidance cues are semaphorins, soluble and cell surface molecules that have homology to Met, a scatter factor (SF) receptor tyrosine kinase. Met and semaphorins also share homology with the extracellular domain of semaphorin receptors, known as plexins. Because plexins and semaphorins are expressed outside the nervous system, Giordano et al. examined what function they might control in other tissues.

They found that ligand stimulation of a plexin in epithelial cells caused invasive growth, including scattering and anchorage-independent growth. Met is the only kinase known to trigger invasive growth and, as expected, without Met, this plexin-stimulated growth was blocked. Epithelial cells seem primed for crosstalk between the two receptors, as Met and plexin were in a preformed complex, mediated by their conserved domains. SF and semaphorins in combination produced a stronger response than either alone. “These two modalities of activation can cooperate for certain biological responses but not for others, and this could be a way to fine tune responses such as invasion, without interfering with growth,” says Giordano.

Reference: Giordano, S., et al. 2002. Nat. Cell Biol. 4:720–724.