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 resemble 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.


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.


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.

SynCAM and sidekick synchronize synapse synthesis

Learning, memory, forgetting—these are functions of synapses, the connections between nerve cells. Although studies of nerve cell differentiation, migration, and axonal pathfinding have put neurons in the right neighborhood, considerable work is needed to understand the smaller scale problems of choosing an axon partner and forming a synapse.

Synapse formation requires SynCAM, according to Thomas Biederer, Thomas Südhof, and colleagues (University of Texas Southwestern Medical Center, Dallas, TX), who found that SynCAM mediated cell adhesion and initiated synapse differentiation. Expression of SynCAM in nonneuronal cells both induced neighboring neurons to form functional presynaptic terminals and, if glutamate receptors were added to the mix, induced postsynaptic terminals and, if glutamate receptors were added to the mix, induced postsynaptic differentiation. According to Biederer, the widely expressed SynCAM is one of four closely related proteins that may initiate synapse formation throughout the central nervous system.

With SynCAM so widely expressed at many synapses, the brain needs an additional method to order neurons into an organized pattern. This process of synaptic partner choice is addressed by Masahito Yamagata, Joshua Weiner, and Joshua Sanes (Washington University, Saint Louis, MO). They chose retinal ganglion cells (RGCs) to study synaptic specificity because axons of RGCs restrict themselves to specific layers within neuronal tissue, forming easily identifiable parallel lines of synapses.

They then looked for proteins that marked one RGC subset as different from another and found two adhesion proteins, sidekick (sdk)-1 and sdk-2. Sdks were concentrated at synapses and mediated adhesion only with other cells expressing the same sdk. Each sdk was found in nonoverlapping sets of cells, and ectopic expression redirected RGC axons toward inappropriate layers. Not every synaptic layer contained a sdk isoform, indicating that other proteins also mediate specificity. Both SynCAM and sdks are transmembrane immunoglobulin domain proteins with intracellular PDZ protein-binding motifs. Determining which PDZ domain proteins interact with SynCAM or sdk will be one next step toward determining the mechanics of synapse assembly.


Stand up and take hold

Integrin is being examined inside and out. Olga Vinogradova, Edward Plow, Jun Qin, and colleagues (The Cleveland Clinic Foundation, Cleveland, OH) have focused on its intracellular portion, and Junichi Takagi, Timothy Springer, and colleagues (Harvard Medical School, Boston, MA) have examined extracellular domains. Their combined efforts reveal a jackknife-like opening of the stimulated protein.

Changes in integrin structure in response to cellular signals regulate its binding to extracellular matrix (ECM) proteins like fibrinogen during processes such as platelet aggregation. Integrin is composed of α and β subunits, each of which is a transmembrane protein with a short cytoplasmic tail and several large extracellular domains. The binding sites for extracellular ligands lie far from the transmembrane domain, so how an intracellular signal is transmitted through so many extracellular domains has been difficult to determine.

The Cleveland Clinic group examined how the cytoplasmic tails respond to internal signals. Their studies revealed that the α and β tails of inactive integrin interact at a region adjacent to the plasma membrane. Activation of integrin, either by known constitutive mutations or by binding of the cytoskeletal protein talin, disrupted the cytoplasmic interaction and allowed the extracellular portion to bind fibrinogen.

The extracellular structural consequences of cytoplasmic uncoupling was then examined by the Harvard group. Their electron micrographs of linked soluble extracellular α and β domains confirmed a previous crystal structure of integrin in a condensed shape, like a “V” that points back toward the cell. A cell surface version held in this bent conformation by a disulfide bond did not bind fibrinogen unless the disulfide was broken. Based on the EM of the soluble protein, disrupting a membrane-proximal link between integrins causes the integrin to extend upwards like an opening switchblade. The extended form places the ligand-binding domain atop the dimer, where it is more accessible to physiological substrates. Thus, says Takagi, “we show that extension is at least partly responsible for making integrin high affinity.” However, two extended forms were found, which differed in the angle of the ligand-binding region. Takagi is now examining how these two conformers affect ligand binding.


Integrin affinity for extracellular ligands increases when it opens from a bent (left) to an extended (right) shape.