BAF goes nuclear

Barrier-to-autointegration factor (BAF) was first described as a cellular activity that prevents retroviral DNA from undergoing suicidal autointegration, but its function in uninfected cells remained obscure. Segura-Totten et al. (page 475) have now performed a detailed biochemical characterization of BAF. The work defines critical functional motifs of this DNA-bridging protein, and suggests that BAF is essential for chromatin decondensation and nuclear envelope assembly and growth.

Previous work had shown that BAF binds to DNA and to proteins containing a LEM domain, a structure that defines a family of nuclear membrane proteins.

Two channels, one program

The biophysical and structural characteristics of chloride ion channels have been studied extensively, but little is known about the molecular regulation and signaling pathways associated with these highly conserved proteins. Rutledge et al. (page 435) analyzed the activation of the CLH-3 chloride ion channel in C. elegans during meiotic cell cycle progression and in response to oocyte swelling. The work demonstrates the utility of the worm system in studying these channels, and suggests that CLH-3 and its putative mammalian orthologue, CIC-2, respond to similar regulatory inputs to carry out similar physiological functions.

The authors found that during oocyte maturation, or in response to oocyte swelling, CLH-3 is activated by serine/threonine dephosphorylation. RNAi inhibition demonstrates that the dephosphorylation is mediated by CeGLC-7α and CeGLC-7β, phosphatases that help to regulate meiotic and mitotic cell cycles in worms. Rat CIC-2 heterologously expressed in mammalian cells is also activated by serine/threonine dephosphorylation, suggesting that the two channels share a common regulatory mechanism, despite their wide evolutionary separation. Rutledge et al. suggest that both channels may depolarize membranes to transduce signals between cell types, such as worm oocytes and the surrounding contractile sheath cells, that are coupled by gap junctions.

A new path for endostatin

The ability of endostatin to inhibit angiogenesis has produced sensational headlines, but efforts to understand how this collagen fragment actually works have drawn considerably less fanfare. On page 529, Hanai et al. now demonstrate that endostatin acts through a novel pathway to inhibit Wnt signaling, suggesting that the effects of endostatin on tumors may be more complex than previously thought.

Using Xenopus embryonic development as a model system, the authors found that high concentrations of endostatin produced developmental abnormalities characteristic of Wnt signaling defects, a notion that was confirmed in cultured mammalian cells. Endostatin seems to act through a novel pathway to target β-catenin, a mediator of Wnt signaling, for proteasomal degradation. A downstream transcriptional activator that acts independently of β-catenin rescues cells from two of the effects of endostatin: cell cycle arrest and inhibition of endothelial cell migration.

The new work raises the possibility that endostatin may have direct antitumor effects, mediated by the inhibition of Wnt signaling, in addition to its antiangiogenic activity. The results also implicate Wnt and β-catenin in the regulation of endothelial cell migration and cell cycle progression, suggesting that downstream effectors of this pathway might be promising targets for future cancer therapies.