Signaling from strange places

The tumor suppressor p53 can act as a transcription factor, but only a few p53-activated genes have been found, and the biochemical basis of p53-mediated apoptosis has been especially difficult to probe. Now, Bourdon et al. describe the discovery and characterization of a novel p53-inducible proapoptotic gene (page 235).

By comparing gene expression in normal and p53-knockout mice exposed to ionizing radiation, the authors identified Scotin, a novel gene that is directly trans-activated when p53 binds to a specific site in its promoter. Mouse Scotin and its human homologue appear to induce apoptosis in a caspase-dependent manner. Scotin has the structure of a type I transmembrane receptor, but is located in the endoplasmic reticulum and the nuclear membrane, not in the Golgi apparatus, mitochondria, or plasma membrane. The authors are now trying to determine whether this localization pattern is required for Scotin activity, and whether the protein can promote apoptosis in response to endoplasmic reticulum stress as well as DNA damage.

The chromosomal location of the human Scotin gene, 3p21.3, is also tantalizing, as this region is rearranged or deleted in a wide range of human tumor types. Bourdon et al. found a dominant-negative phenotype in Scotin mutants, indicating that a mutation in a single allele of the gene could be sufficient to block the apoptotic activity of the protein. In preliminary studies focusing on breast cancer, researchers have already found mutations in Scotin in tumors from several patients, suggesting that Scotin may be a clinically important new tumor suppressor gene.

Watching Ca\(^{2+}\) waves break

Most models of intracellular Ca\(^{2+}\) signaling invoke calcium-induced calcium release (CICR), a positive feedback mechanism that amplifies small elevations in cytoplasmic Ca\(^{2+}\) to produce complex signals. But what determines the pattern of signaling, and how does a cell avoid triggering Ca\(^{2+}\) release in the wrong place? Ashby et al., reporting on page 283, addressed these questions with a powerful new technique and arrived at some surprising conclusions.

Using spatially restricted uncaging of caged Ca\(^{2+}\), the authors were able to boost cytosolic Ca\(^{2+}\) concentrations in specific regions within pancreatic acinar cells. These cells ordinarily produce polarized Ca\(^{2+}\) waves after stimulation with an agonist. When caged Ca\(^{2+}\) is uncaged in the apical region of the cells, a CICR wave spreads from the apical region toward the basal membrane. In contrast, uncaging Ca\(^{2+}\) in the basal region does not produce a CICR wave at all. CICR is usually associated with ryanodine receptors, which are found in both the apical and basal regions of these cells. However, Ashby et al. found that inhibitors of either ryanodine receptors or IP3 receptors block the induced waves, indicating that CICR requires cooperation between both types of Ca\(^{2+}\) release channels. As IP3 receptors are restricted to the apical region, a CICR wave can only be induced there. Ca\(^{2+}\) uncaging did not stimulate IP3 production, so participation of the IP3 receptors in CICR wave generation does not require elevation of the IP3 concentration.

Although CICR waves could not be initiated in the basal region, waves that originate in the apical region can travel through the basal region. One possibility is that Ca\(^{2+}\) channels may be closely spaced along “gunpowder trails” in the basal region, allowing a signal that originated elsewhere to propagate along a route with a high density of Ca\(^{2+}\)-sensitive and Ca\(^{2+}\)-releasing sites. Such a system would help determine the pattern of Ca\(^{2+}\) signaling while preventing Ca\(^{2+}\) release in the wrong part of the cell.