Integrins make a choice

Signaling researchers have only a few factors with which to explain a whole lot of biology. On page 407, Goel et al. describe how two integrin variants channel the actions of a single factor, insulin-like growth factor (IGF), into two distinct pathways that induce either adhesion or proliferation.

The β1A integrin variant was known to be associated with proliferation and the β1C variant to inhibit it. IGF and its receptors had also been found to enhance adhesion through β1 integrins.

Goel et al. find that, in cells with β1A integrin, IGF binding to its receptor induces formation of a ternary complex of integrin, IGF receptor and the downstream signaling protein IRS-1. The resultant boost in cell proliferation is, however, prevented by expression of the β1C integrin. A short insertion in the cytoplasmic tail of β1C brings in the Gab1 and Shp2 proteins, with the Shp2 phosphatase removing the phosphates that would otherwise have led to IRS-1 recruitment and signaling.

The result is synergistic activation of adhesion by the IGF receptor and β1C integrin. It is not yet clear which molecular output the IGF receptor is bringing to the adhesion equation. But removal of β1C with a ribozyme prevents IGF-stimulated adhesion, and β1C addition to prostate tumor cells before their injection into host animals significantly reduces the size of the resultant tumors.

Freedom from substrate

Most cells undergo a form of apoptosis called anoikis when they are grown in suspension. Janes and Watt report on page 419 that squamous cell carcinomas (SCCs) avoid this fate by expressing an alternative integrin called αvβ6. The pathway may be appropriated from cells that require a temporary reprieve from substrate-dependent growth during differentiation or tissue repair.

The αvβ6 integrin is known to favor tumor formation by increasing cell invasion and proliferation and inhibiting matrix assembly, but the new study is the first to demonstrate its ability to confer a survival advantage. The authors introduced αv into an α6-null cell line and showed that suspended transfectants died because their αvβ6 acted via caspase 8 to suppress activation of an Akt survival signal. Addition of both αv and β6, however, resulted in formation of αvβ6, which supported Akt activation and survival.

Squamous epithelial cells start off attached to a basement membrane, but when they detach and move upwards into suprabasal layers, the Akt survival signal may give them sufficient time to respond to differentiation cues. The expression of αvβ6, as occurs in repairing and proliferating tissues, may extend this survival benefit under special conditions. Normally, αvβ6’s reprieve is temporary, but tumors appear to switch on αvβ6 more robustly and thus make the condition of substrate-independent growth permanent.

Rho in podosomes

Berdeaux, Díaz, and colleagues report that active Rho (Rho[GTP]) is localized to podosomes in oncogenically transformed cells (page 317). These matrix-digesting, actin-rich, short-lived protrusions help osteoclasts to eat bone and migratory and cancer cells to chew their way through matrix. Their function in Src-transformed cells is now found to rely on Rho activity.

Rho is known to promote the formation of focal adhesions and actin stress fibers, so the disappearance of stress fibers after transformation with oncogenic Src was presumed to reflect down-regulation of Rho. But Berdeaux et al. report that levels of Rho[GTP] are not decreased in Src-transformed cells. Instead, focal adhesions and stress fibers may be lost because Src induces a block in signaling downstream of Rho and a loss in cell–matrix adhesion.

Active Rho is, however, found in Src-induced podosomes. Inhibition of Rho disrupted localization of several proteins to podosomes, and almost completely abolished the secretion of matrix-digesting enzymes. Thus, Rho is necessary to form not only focal adhesions and stress fibers in normal cells but also the more dynamic and transient podosomes characteristic of transformed and tumor cells. The relevant Rho effectors are not known, but Rho may work by recruiting active Src to podosomes or by reorganizing the actin core in these structures. Several of the many signaling proteins in podosomes may, in turn, regulate the localization and activation of Rho.