Latent TGFβ: a molecular sensor
Transforming growth factor β (TGFβ) is an important cytokine that regulates cell growth, apoptosis and inflammation. It is secreted as part of a latent complex containing mature TGFβ, its cleaved propeptide and latent-TGFβ-binding protein (LTBP). This complex is stored in the extracellular matrix (ECM), releasing TGF-β in response to changes in the ECM. On p. 217, Justin Annes and co-workers present a novel hypothesis in which the latent TGF-β complex is viewed as a molecular sensor. Within this sensor, the propeptide functions as a ‘detector’ that senses perturbations in the ECM by interacting with TGFβ activators such as integrins and thrombospondin and responds by releasing the ‘effector’, mature TGFβ. LTBP acts as the ‘localizer’ of the sensor, binding covalently to the ECM. The new model is consistent with the phenotypes of individuals in whom latent TGFβ processing or assembly is defective and explains several puzzling aspects of TGFβ biology. For example, the fact that TGFβ1, TGFβ2 and TGFβ3 have similar properties and expression patterns but isoform-specific effects in vivo can now be accounted for by differences in how their detectors respond.

Assembling the hemidesmosome
Hemidesmosomes are rivet-like complexes that anchor epithelial cells to the extracellular matrix (ECM), physically linking it to the cell’s cytoskeleton. They contain at least five proteins: integrin α6β4, which is central to the complex and binds to laminin 5 in the ECM; plectin, a plakin that connects the complex to keratin intermediate filaments; bullous pemphigoid antigen 230 (BP230), another plakin; BP180; and CD151. Arnoud Sonnenberg and co-workers have examined how these components fit together, combining exhaustive two-hybrid analysis with assessment of the ability of point mutants to complement genetic deficiencies in keratinocytes (see p. 387). This has allowed them to map pairwise interactions between the integrin, plectin, BP180 and BP230. The studies also reveal a hierarchical assembly mechanism of unanticipated complexity. For example, although BP230 can interact with both α6β4 and BP180, plectin is required for incorporation of BP180, and recruitment of BP230 occurs only if BP180 is present. These findings allow the authors to propose an assembly model in which the integrin first interacts with plectin, which unfolds its cytoplasmic domain, and BP180 and BP230 are then recruited sequentially.

DAXX: apoptotic or anti-apoptotic?
DAXX is an essential, highly conserved protein that is associated with PML nuclear bodies and might function as a transcriptional repressor. Knockout work seems to indicate that it has an anti-apoptotic role; however, a variety of overexpression studies in cultured cells suggest that the protein instead promotes apoptosis. So which is it? Jennifer Michaelson and Philip Leder have settled this question by using RNA interference to knock down DAXX synthesis in the very cell lines used in the overexpression experiments (see p. 345). They demonstrate that apoptosis is increased in DAXX-depleted cells and that transfection of the anti-apoptotic protein Bcl-2 can rescue this phenotype. These findings indicate that DAXX does indeed protect cells from apoptosis, casting significant doubt on the overexpression work. The authors do, however, observe derepression of transcription in the DAXX-depleted cells, confirming that the protein functions as a repressor. Interestingly, they also identify the transcription factors NF-kB and E2F1 as novel DAXX targets. Since both are implicated in control of apoptosis, inhibition of NF-kB- and E2F1-dependent transcription could underlie the anti-apoptotic activity of DAXX.