Pulling on a cytokine

The extracellular matrix (ECM) acts as a storage facility for tons of factors waiting to do business in the cell. Annes et al. (page 723) show that the ECM anchoring of one factor, the cytokine TGF-β, is essential for its activation. The anchoring may give cells something to pull against, with the pulling mediating the activation.

Most TGF-β is secreted as a complex containing TGF-β, a TGF-β-pro-domain, and a protein called the latent TGF-β binding protein (LTBP). By the time the complex is extracellular, the TGF-β-pro-domain has been cleaved from TGF-β but remains non-covalently bound to TGF-β and covalently linked (via disulfides) to LTBP. The pro-domain stops TGF-β from signaling, but the complex can be activated in the presence of cells expressing the integrin α6β1.

The mechanism of TGF-β activation remained a mystery. The authors first established that TGF-β plus its TGF-β-pro-domain could not be activated by α6β1 in the absence of LTBP. Furthermore, LTBP’s known binding to the pro-domain was not enough. A second domain of LTBP, called the hinge domain, was also needed for activation. This is the same domain required for LTBP binding to ECM, and its function could be replaced by another anchoring mechanism: surface-coated antibodies targeted against an unrelated LTBP epitope.

Thus, the function of LTBP may be in part to anchor latent TGF-β in the ECM. But for activation, the authors speculate that this anchoring also gives the cell something to pull against. Only when integrin-mediated pulling meets resistance (because the integrin on the cell binds to TGF-β, and the TGF-β binds to the ECM-anchored LTBP) would the pro-domain be released. Activation would fail if any link was broken: if the cell was expressing an integrin that does not bind to TGF-β; the LTBP isoform did not bind to the ECM; or a protease separated the TGF-β-binding and ECM-binding domains of LTBP. All these variations would limit the activation of this extremely potent cytokine.

Mineralized mice

Lot’s wife turned into a pillar of salt because she looked back at Sodom and Gomorrah; but most people are saved from being turned into one big pile of minerals by mineralization inhibitors. Murshed et al. (page 625) now show that these inhibitors act locally and selectively despite circulating systemically. A better understanding of how this works could suggest ways to tackle the ectopic mineralization seen during arthritis.

Mineralization is necessary in bone, but must be prevented in soft tissues—such as artery walls and cartilage—that have an extensive, mineralization-prone extracellular matrix (ECM). It is unclear how this distinction is made by inhibitors that are made locally but also circulate systemically.

Murshed et al. investigated this process by expressing a known mineralization inhibitor, Matrix gla protein (MGP), in various mouse tissues. MGP could act locally when expressed locally: expression in arterial walls inhibited the ectopic mineralization normally seen there in mice lacking MGP; and expression in bone-generating osteoblasts reduced bone mineralization in wild-type mice. But MGP expressed in liver, so that it reached high levels in the bloodstream, did not have such effects. Although the resulting serum could inhibit osteoblast mineralization in vitro, there was no effect on either ectopic arterial wall mineralization or normal bone mineralization.

The authors confirmed that the mineral-binding gla (γ-carboxylated glutamic acid) residues of MGP are necessary for its inhibitor activity; the bone protein osteocalcin has similar gla residues but was found not to be a mineralization inhibitor. But the mechanism that keeps MGP action local remains to be determined.