FGF gets in your bones

Integrated differentiation of bone precursors gets shut down, say Mansukhani et al. on page 1065, if there is too much FGF receptor (FGFR) activity.

Bones form through the maturation of osteoblasts. This process is disrupted in the skulls of patients with activating mutations in FGFR1 and FGFR2. The new evidence suggests that FGF counteracts differentiation by blocking Wnt. Microarray analysis revealed that, although Wnt-regulated genes are normally turned on in maturing osteoblasts, their activation is dampened in the overactive FGFR mutant osteoblasts.

A major mediator of the FGF-induced Wnt down-regulation seems to be the Sox2 transcription factor. Normally associated with neurons or embryonic stem cells, Sox2 is now shown to be strongly expressed in osteoblasts when FGF signaling is high. Sox2 was associated with β-catenin in osteoblasts and blocked Wnt signaling, possibly by competing with other β-catenin partners, such as TCF/LEF transcriptional coactivators.

Wnt signals are used in multiple differentiation pathways, including several that are not blocked by FGF. Perhaps Sox2 is permanently silenced in the unaffected cell types. It will now be important to examine FGF and Sox2 regulation in normal and pathological skull development. Sox2 was found at osteogenic fronts in mice crania, where FGFR2 activity is known to be high, and may act as a brake on osteoblast differentiation. Harmonious bone formation, like other developmental processes, probably results from the interplay between positive and negative signals. JCB

Binding a bent integrin

A bent integrin still has room for its ligand, according to Adair et al. on page 1109. Integrin activation by internal signals may therefore not depend on the protein assuming a more extended conformation.

To prevent unregulated adhesion, most integrins are expressed in an inactive form. EM and crystal structures showed that the extracellular domain of the integrin αVβ3 without its ligand can assume a bent conformation. 2D EM reconstructions of the same domain in the presence of a small peptide suggested that the bound form, in contrast, was extended. These results supported a switchblade model, in which the binding of cytoplasmic signals initiates the movement of several intra- and extracellular domains that opens and activates the integrin by exposing its ligand-binding site.

But Adair et al. suggest that such large-scale changes may not be necessary. The authors generated 3D EM reconstructions using a larger, physiological ligand (in this case, a piece of fibronectin). Particles to be analyzed were also selected automatically to minimize bias.

The 3D maps showed that most of the fibronectin-bound integrin complexes were in a bent conformation. The maps with and without the ligand looked generally similar. But in the ligand’s presence, additional densities consistent with the size of two fibronectin domains were found at the ligand-binding sites.

If, as the findings indicate, no large-scale opening is needed to make room for ligand, then the mechanism of activation by intracellular signals should be revisited. For instance, a slight sideways movement of a membrane-proximal extracellular domain of the β-subunit away from the ligand-binding site may be sufficient. This model involves much smaller conformational changes than does the switchblade model.

It is possible that the switchblade movement has quite a different function. For example, it may be part of the conformational changes induced by ligand binding that culminate in intracellular responses. JCB