A morphogen must be both off and on for hairs to grow, according to Kobielak et al. on page 609. Their studies of bald mice reveal that bone morphogenetic protein (BMP) controls the switch from dividing to differentiating hair cells by working at the right time and place. Hair cells arise from a pool of epithelial precursors that first proliferate and then differentiate to form the hair channel and the hair itself. Proliferation signals originate from a set of mesenchymal cells called the dermal papillae (DP) at the base of the hair follicle. Further up the follicle, differentiation is a response to Wnt signaling, which works through stabilized β-catenin and Lef1 to turn on genes such as hair keratins. Now, Kobielak et al. find that the later differentiation depends on both the absence of BMP signaling during proliferation, which allows a buildup of Lef-1, and the presence of BMP signaling later on, which is somehow permissive for Wnt signaling once that pool of Lef-1 has accumulated.

Kobielak et al. tease out these functions by knocking out the BMP receptor 1A in the embryonic skin epithelium. The resulting hairless mice reveal that BMP signaling must first be off, and then on, for hairs to form. At the base of the mutant hair follicle, Lef1 was expressed in progenitor cells as expected. But these proliferating cells never differentiated. Although Lef1 was present further up the hair shaft, β-catenin was not stabilized and differentiation genes were not activated. The precise cause of the block is not known, but BMP signaling might activate Wnt receptors or inactivate the β-catenin degradation machinery.

The authors propose that BMPs control the timing of responses to Lef1 in the hair shaft. Progenitor cells have BMP receptors, but they are turned off by the BMP inhibitor Noggin secreted by the nearby DP. They therefore maintain an undifferentiated state while accumulating Lef1. As the proliferating cells move away from the source of Noggin, BMP receptors are activated, thus promoting Wnt signaling and differentiation.

Breast cells pull on their surroundings to sense whether to proliferate or differentiate, according to Wozniak et al. on page 583. This matrix-sensing pathway may explain why carcinoma risk is increased in women with fibrous breast tissue.

Differentiation of breast epithelial cells into tubules occurs in vitro if the cells are cultured in a 3D collagen matrix floating in medium. If the same matrix is made more rigid by attachment to a surface, tubulogenesis is disrupted, indicating that breast cells sense the flexibility of their surroundings. Wozniak et al. now find that the small GTPase Rho and its effector, ROCK, are essential for the cells to pull against the matrix and to respond to the resistance encountered.

The breast epithelial cells attach to their collagenous matrix via integrin receptors, which regulate Rho/ROCK-mediated actin–myosin contractility. The authors show that if the cells are able to contract their matrix, as in the floating 3D gels, Rho is down-regulated and the focal adhesion protein FAK is scattered throughout the cell. As expected, these cells differentiate into tubules—a process that may require matrix flexibility to work efficiently. In contrast, if the matrix is made too rigid for cells to contract (e.g., by increasing collagen levels in the floating gels), Rho activity remains high and FAK is found at matrix adhesion sites—a sign of strengthened contact points.

When FAK is at adhesions, the cells proliferate rather than form tubules, indicating that strengthened matrix contacts send a mitotic signal, although its exact identity is unknown. A pathological increase in matrix deposition, as found in dense breast tissue and in fibroids, and the resulting increased rigidity are thus expected to cause abnormal proliferation that might promote breast cancer. The authors are currently using a mouse model with dense collagen breast tissue to test this theory.