Deleting keratins to find one

By knocking out the two known keratin 6 (K6) genes in mice, Wojcik et al. (page 619) have discovered a third murine K6 gene, and simultaneously created a promising model system for studying keratin function in more detail.

In an effort to study the function of K6, the authors generated a mouse line lacking both K6a and K6b, and found that plaques develop on the tongues of these mice and cause the majority to die of starvation within two weeks of birth. Surprisingly, and in contrast to a previously described mouse K6a/b knockout line, ~25% of the mice survive to adulthood and grow normal hair and nails. Further analysis uncovered a previously undescribed murine K6 gene, an ortholog of the K6hf gene from human hair follicles, which the authors have named MK6hf.

While the presence of MK6hf helps explain why the knockout mice develop normal hair and nails, some mysteries remain. MK6hf is not expressed in oral epithelia, and all of the mice exhibit ultrastructural abnormalities in their tongues, so it is unclear why some survive to adulthood while others die. Wojcik and colleagues are now performing backcrosses to search for unknown genetic modifiers involved in epithelial integrity. The results also suggest that inducible K6 expression may be less important in wound healing than was previously believed, since the knockout mice heal wounds normally.

ARNO gets things moving

Stationary cells sometimes undergo a dramatic morphological change and begin to migrate, a transition that is essential for processes like wound healing, development, and tumor metastasis. Beginning on page 599, Santy and Casanova provide important new mechanistic insights into this transition, and also describe a novel assay that should be useful in future studies of the ARF family of GTPases.

Because of the importance of ARF proteins in modulating actin assembly, Santy and Casanova reasoned that ARNO, a guanine nucleotide exchange factor for ARFs, might control changes in the actin cytoskeleton. They found that when ARNO is expressed in MDCK cells, many of the cells change dramatically, forming fan-shaped lamellipodia and becoming migratory. A novel pull-down assay, in which an immobilized ARF-binding protein is used to isolate ARFs, shows that ARNO expression selectively activates ARF6 in the MDCK cells. In turn, ARNO-induced activation of ARF6 causes increased activation of both Rac1 and phospholipase D in the cells, apparently by independent pathways that function together to induce cell migration.

The work is the first demonstration of Rac activation through an ARF-mediated pathway, and localization experiments suggest a model in which ARF6 activates Rac through a GIT/Pkl-paxillin-PIX complex. Intriguingly, ARNO expression only causes migration in MDCK cells that have a free edge exposed at the outside of a cell cluster or wound. The authors suggest that the free edge creates a novel membrane and cytoskeletal environment where ARNO can be recruited to induce migration.

The hidden power of platelets

Platelets get no respect. Traditionally, these anucleate cells have been acknowledged as critical mediators of blood clotting, but they were considered metabolically challenged drones, incapable of signal-dependent gene expression. Now, Lindemann et al. (page 485) demonstrate that platelets are not only able to translate preformed mRNAs in response to environmental signals, they may also provide an important link between the coagulation and inflammatory cascades via regulated production of an inflammatory cytokine.

Using an arrayed cDNA library, the authors identified a variety of mRNAs present in resting platelets, including one encoding the interleukin-1β (IL-1β) precursor. Activation of the platelets as in clot formation triggers IL-1β production; the IL-1β then induces adhesiveness of endothelial cells for neutrophils, an inflammatory reaction. The platelet-produced IL-1β accumulates over a period of several hours, indicating that platelets can exert long-term influence over an inflammatory response. Previous work had shown that activated platelets could synthesize new proteins, but the new study is the first demonstration that the cells can inducibly produce physiologically relevant levels of cytokines.

The results suggest that platelets may be more important in mediating pathological responses than was previously recognized. Myocardial infarction, for example, begins with platelet deposition near a ruptured atherosclerotic plaque, followed by leukocyte infiltration. If the synthesis of IL-1β by the platelets is facilitating leukocyte accumulation, this signal might be a good therapeutic target.