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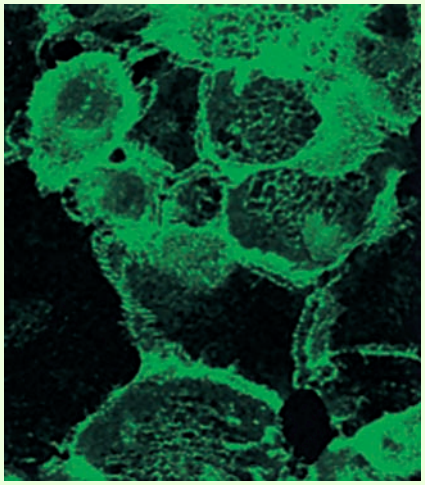
In This Issue

Sticking together a signal

Calautti et al. have taken a collection of proteins that affect cell adhesion in keratinocytes and linked them into a pathway (page 137). The result is a simple sequence from Rho through to the phosphorylation of catenins associated with adherens junctions. But there are hints that reality may be more complex, with more side-branches and collaborations.

During differentiation of keratinocytes these skin cells strengthen their attachment to one another, and both Fyn kinase and Rho are activated. The ultimate effect of activating Rho—phosphorylation of catenins—requires Fyn. Calautti et al. link Rho and Fyn into the same pathway by showing that both activation of Rho and the interaction of Rho with the PRK2 kinase are sufficient and, in the case of Rho, required to turn on Fyn. PRK2, a Rho effector, increases Fyn activity after being added to a Fyn immunoprecipitate, although this effect may be indirect. Thus the pathway leads through Rho, PRK2, and Fyn, leading, finally, to catenin tyrosine phosphorylation and establishment of cell–cell adhesion.



Activated Rho recruits p120^{ctn} to cell–cell adhesions.

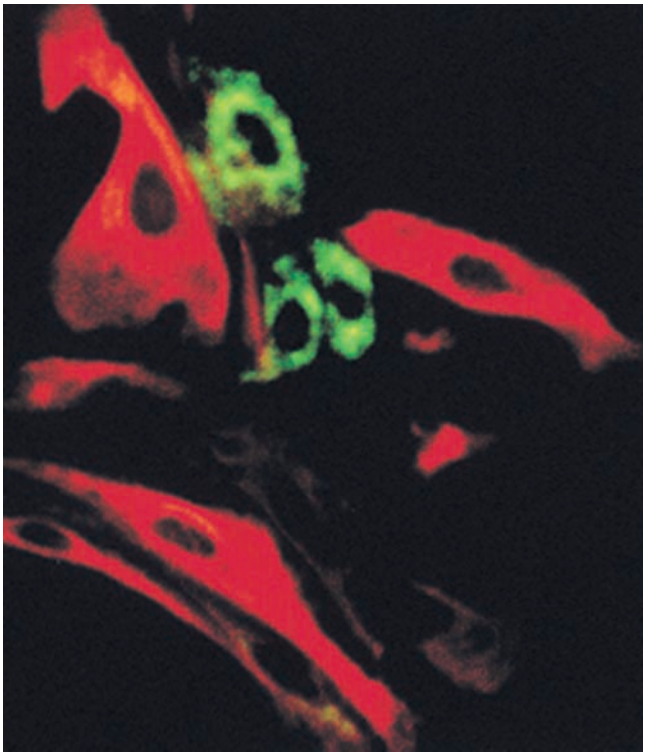
The same research group has previously shown that a PRK2 relative called PKC-η is activated during keratinocyte differentiation and can phosphorylate Fyn. But this does not appear to result in catenin phosphorylation. Calautti et al. suggest that PRK2–Fyn may take care of catenins, while in another part of the cell PKC-η–Fyn may induce other aspects of terminal differentiation, such as a halt in cell division. In fact, two pools of Fyn exist in the keratinocytes, one of which is found in association with E-cadherin at cell–cell borders, and the other in the cytoplasm. Additional complications may arise in the PRK2–Fyn pathway, where other Rho-effector proteins may be needed to reinforce and sustain the signal responsible for Fyn activation. ■

Let's make liver

Detoxification is what livers do best, and regenerating after toxic insults is what livers do second best. All that proliferative capacity suggests that liver stem cells might be a very different and more prevalent beast than stem cells from other organs. But, on page 173, Suzuki et al. report that the fetal mouse liver, just like the adult bone marrow, has as its founder a relatively rare and undifferentiated cell type.

Suzuki et al. have attempted to isolate liver stem cells before, but their isolation strategy fell short of allowing clonal analysis. Now they add one additional selection marker (cMet, the receptor for hepatocyte growth factor) and use cell sorting to achieve a 560-fold enrichment for hepatic colony-forming units in culture (H-CFU-Cs). These single cells do not express markers for either hepatocytes or cholangiocytes (the cells that form bile ducts), and are capable of self-renewal both in vitro (single cells can be replated to yield more undifferentiated cells) and in vivo (recently divided cells have the undifferentiated phenotype). Signs of differentiation arise, however, with longer times in culture.

Even more extensive differentiation can be seen in vivo, with transplanted H-CFU-Cs growing to form functional parts of liver, bile duct, pancreas and intestine. Thus, Suzuki et al. may have discovered an endodermal stem cell, or at least a liver stem cell with impressive abilities to transdifferentiate if placed in the right environment. This flexibility may be paired with the superior proliferative capabilities of differentiated hepatocytes during the process of liver regeneration. ■



Progenitor cells express either liver (green) or bile duct (red) markers.

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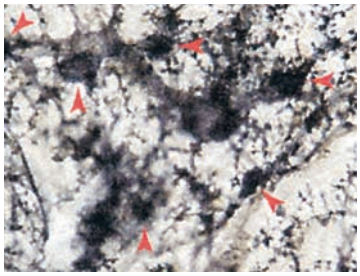
To Rb or not to Rb

Caution and more experiments are in order, say Jiang and Zacksenhaus (page 185), for drug companies hoping to activate the Rb pathway with anticancer compounds. The authors have found that expression of a constitutively active version of the tumor suppressor Rb can result in the counterintuitive outcome of more tumor formation.



Active Rb causes nodule formation.

Initially, expression of activated Rb in transgenic mice does suppress cell proliferation somewhat. But Jiang and Zacksenhaus suggest that this growth suppression may also positively select for cells with transforming mutations. Usually most cells with such mutations would be eliminated by apoptosis. But Rb is known to suppress apoptosis, and this appears to occur in the transgenic mice. In mammary tissue, where the tumors are eventually seen, apoptosis during involution is reduced by 44%.

This failure in apoptosis may give rise to the focal hyperplastic nodules that the authors see in approximately one third of the transgenic animals. The large tumors that finally arise are fewer in number than these nodules, and no longer express the activated Rb transgene, suggesting that extinction of Rb expression may be at least one of the steps leading to final transformation.

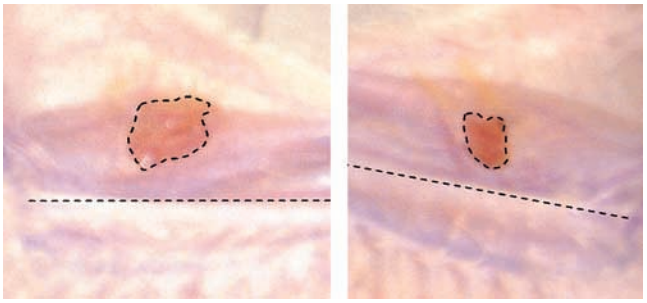
Mammary tissue may be particularly susceptible to such a tumor-formation pathway because a large proportion of the epithelium turns over during each estrous cycle, as the tissue is prepared for a potential pregnancy and then restored to its former state. Similar problems may arise in human tissues that remodel extensively, such as breast, ovary, and endometrium. Zacksenhaus suggests, therefore, that antiproliferative drugs should be paired with proapoptotic drugs in new combinatorial drug trials. ■

Squeezing for healing

A chicken chemokine can help heal wounds by inducing fibroblasts to become myofibroblasts, according to results reported by Feugate et al. on page 161. The contractile myofibroblasts help close the wound by pulling together the necessary cells and matrix.

Chemokines are better known for their activities in the immune system, but increased production of chicken chemotactic and angiogenic factor (cCAF) has also been observed during wound healing. Now Feugate et al. report that cCAF reduces fibroblast proliferation by 25%, not by increasing cell death, but by inducing differentiation of fibroblasts into myofibroblasts. The differentiated cells make α-smooth muscle actin (α-SMA), and have an increased ability to contract a collagen gel.

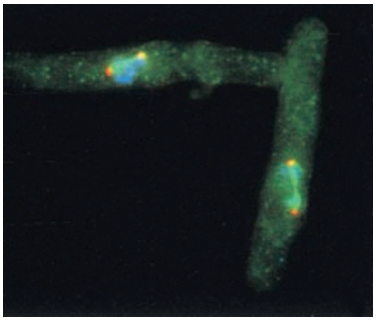
Regular application of cCAF to a chicken wound accelerates the early stages of wound healing by almost two days. The authors suggest that a peptide mimetic might accelerate wound healing in humans, whereas a cCAF antagonist might reduce the scar-inducing numbers of myofibroblasts in conditions such as scleroderma. ■



Wounds treated with cCAF (right) heal faster.

Polo meets the APC

Polo kinases have been linked to activation of the anaphase promoting complex (APC) during mitosis, but the importance of this effect has been debated. Now, May et al. study this problem using polo-like kinase Plo1 from fission yeast (page 23). They show that Plo1-mediated activation is essential—a metaphase arrest results when Plo1 can no longer bind avidly to the Cdc23 subunit of the APC.



Mitotic arrest results when APC and Plo1 cannot interact.

The authors came to this conclusion after identifying mutants that were dependent on high Plo1 expression for their survival. One of the mutants made a Cdc23 protein that interacted poorly with Plo1, a deficit that May et al. suggest is overcome by excess Plo1. Following up on this clue, May et al. mapped the Plo1–Cdc23 interaction to the noncatalytic domain of Plo1 and the TPR domain of Cdc23.

The APC subunit or residues that act as the Plo1 target remain unknown. In tracking down this target, May et al. plan to continue their analysis of the APC at the level of individual subunits or residues rather than as a whole complex. ■