**Research Roundup**

**Swelling with tumors**

The association of inflammation with tumors was first noted nearly 2,000 years ago by Galen. Today, chronic inflammation caused by intestinal diseases such as colitis is known to be a major contributing factor to the onset of colon cancer. In a new report by Florian Greten, Michael Karin (University of California, San Diego, CA), and colleagues, NF-κB, an inflammation-inducing transcription factor, is shown to promote intestinal tumors via two pathways in two cell types.

Colon cancers depend on interactions between the intestinal epithelial cells that form the tumors and white blood cells, which trigger inflammation. The authors show that a mouse model of colitis-associated colon cancer is severely reduced if NF-κB is inhibited in either cell type by deleting its activating kinase, IKKβ.

If NF-κB was inhibited in the white blood cell lineage, epithelial tumors were less numerous and smaller because white blood cells could not induce inflammation. Proliferation of the epithelial cells was limited, probably because the dormant mutant white blood cells did not secrete growth factors.

If NF-κB activity was blocked in intestinal epithelial cells, fewer tumors formed. The scarcity of tumors was due to increased apoptosis of the epithelial cells. NF-κB, possibly to help keep the intestinal epithelium intact, activates transcription of the anti-apoptotic protein Bcl-XL. Since Bcl-XL was not induced in the absence of IKKβ, DNA damage surveillance mechanisms were able to kill premalignant intestinal cells.

Drugs that target IKKβ are in preclinical testing. Past studies suggest they may have unwanted effects. “One red flag is skin cancer,” says Karin. “In keratinocytes, if you knock out IKKβ, you get more skin cancer. But this [increase] requires inflammation. A drug doesn’t only affect one cell type.” So a drug that also causes the loss of NF-κB activity in blood cells may override the skin cancer risk.

**Reference:** Greten, F.R., et al. 2004. *Cell. 118*:285–296.

**Shh is out on a limb**

Cells in the developing limb escape a positive feedback loop by growing a nonresponsive barrier of cells. This timing mechanism that limits both limb size and digit number is described by Paul Scherz, Clifford Tabin (Harvard Medical School, Boston, MA), and colleagues.

The number of fingers that grow on a hand is set by the Shh morphogen. Shh is made by cells in a zone at the posterior—posterior axis by telling neighboring cells to make another morphogen, called Gremlin. Gremlin instructs the tip of the bud to express Fgf, which promotes limb outgrowth and Shh expression.

Escape from this loop in chicks depends on a newly discovered property of Shh-producing cells. Neither they nor their descendants make Gremlin. The cause of this inability is unknown, but high levels of Shh may induce some inherited protein or chromatin alteration that represses Gremlin.

As the cells that once made Shh divide and expand anteriorly out of the Shh zone, a barrier is formed. “Eventually, Gremlin cells are beyond the point where they can reach [Shh],” says Scherz, “so Gremlin is down-regulated.” If this barrier is cut away before the loop terminates, and the two borders stitched together, the limb fills in this space with Shh descendents and grows normally. Different limb sizes might be achieved by changing the size of the barrier cells, the rate of their division, or the distance of Shh transport.

Brian Harfe (University of Florida, Gainesville, FL), Scherz, Tabin, and colleagues also show that both Shh concentration and exposure time control digit development. Using fate mapping experiments in mice, the group shows that the two most posterior digits and part of the middle digit are made of former Shh-expressing cells.

These fingers were thus differentiated from each other despite exposure to the maximum concentration of Shh. But the more posterior the finger, the longer its exposure time. “There has to be some kind of counting mechanism,” says Scherz, “that builds up in cells based on longer exposure,” such as a transcription factor or phosphorylated protein, whose levels control digit morphology.

**References:** Scherz, P.J., et al. 2004. *Science. 305*:396–399.

Harfe, B.D., et al. 2004. *Cell. doi:10.1016/S0092-8674(04)00712-3.*