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.

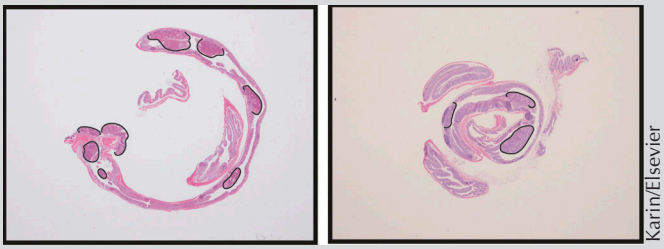
Colon cancers depend on interactions between the intestinal epithelial cells that form the tumors and white blood cells, which trigger inflammation. The authors show that a mouse model of colitis-associated colon cancer is severely reduced if NF-κB is inhibited in either cell type by deleting its activating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



Karin/Elsevier

Fewer intestinal tumors (outlined) form if NF-κB is inactive in epithelial cells (right).

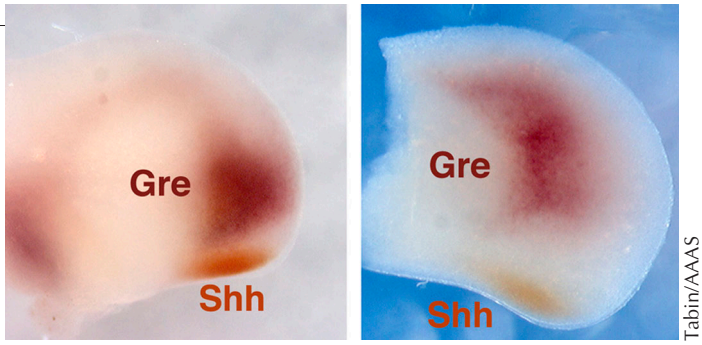
Shh is out on a limb

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 of the limb bud and sets the anterior–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 descendents 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.



Tabin/AAAS

Descendents of cells expressing Shh (orange) expand (right) to form a barrier blocking further Gremlin induction and limb outgrowth.

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/S0092867404007123.

TEXT BY NICOLE LEBRASSEUR
LEBRASN@ROCKEFELLER.EDU

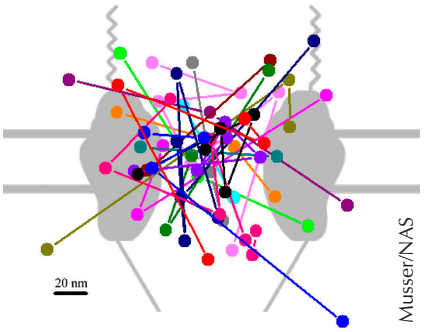
Ping pong in the pore

Proteins traversing the nuclear pore complex (NPC) bounce back and forth within the central pore until they are finally expelled, according to Weidong Yang, Jeff Gelles, and Siegfried Musser (Texas A&M University System Health Science Center, College Station, TX).

The group imaged single import complexes (ICs)—importin(s) and cargo—interacting with NPCs. Trajectories of the ICs within the pore indicate rapid, random movement forward and backward.

One transport model proposes an affinity gradient across the pore between ICs and pore components, but the back and forth movements do not support this model. Rather, the data suggest that molecules move randomly within the pore and exit either side. "If the IC enters the pore and reexits the same side," says Musser, "no net energy went in, so you've lost nothing. But if the IC gets out the other side, it can be dissociated by RanGTP, and you've [achieved] transport."

The distribution of the time an IC resides within a pore suggests there is only one rate-limiting step during import. When RanGTP was depleted, ICs lingered longer in the pore, so RanGTP-mediated dissociation is probably this limiting step. Since dissociation is expected to occur on the nucleoplasmic side, the IC may need to land close enough to the pore's edge to encounter RanGTP and exit. ■

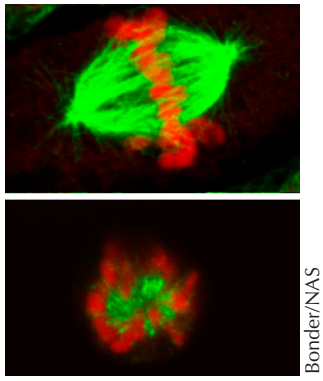


ICs move randomly within the central nuclear pore.

Reference: Yang, W., et al. 2004. *Proc. Natl. Acad. Sci. USA.* doi:10.1073/pnas.0403675101.

Division at right angles

A misoriented mitotic spindle may be a short cut to metastasis, based on results from Jurii Vasiliev (Moscow State University, Russia), Edward Bonder (Rutgers University, Newark, NJ), and colleagues.



A spindle turned perpendicular (bottom) to the surface leaves only one daughter on the matrix.

Cells in an epithelial layer normally divide perpendicular to their surface; each daughter cell thus remains in contact with the matrix and surrounding cells. The new results show that cells with too much RhoA activity, as found in several cancer cell lines, lost the spindle orientation needed for this perpendicular division. Many of the cells thus made a spindle that left only one daughter on the matrix.

The other cell, atop its matrix-bound sister, lacked the spread phenotype of matrix-attached cells. Due to inadequate cell–cell adhesions, these rounded cells occasionally detached from the epithelium, floated off in the medium, and settled at new sites.

Cells with overactive RhoA were more contracted and had altered actin networks suggestive of hyperactive myosin II. Blocking myosin II activity reversed the RhoA effects. Bonder now wonders, "does myosin II activity alter the movement of the formed spindle relative to the cell itself, or is the process of forming the spindle aberrant from the very start?"

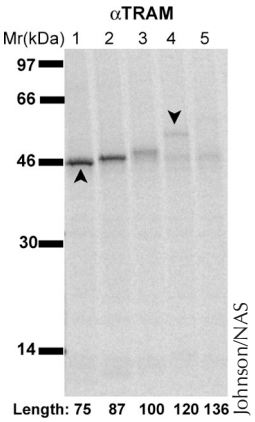
The results suggest that cancerous cells may not have to acquire the ability to migrate to metastasize. "[Unregulated] cell division would lead not only to increased tumor mass," says Bonder, "but could also be squirting out cells." Circulatory flow could then sweep off some of these cells and deposit them elsewhere. ■

Reference: Vasiliev, J.M., et al. 2004. *Proc. Natl. Acad. Sci. USA.* doi:10.1073/pnas.0404723101.

Getting to the inner circle

Contiguity between the ER and the nuclear envelope means nuclear membrane proteins have a direct shot to their target. In fact, inner nuclear membrane (INM) proteins were thought to need only to diffuse to the nucleus, pass through the nuclear pore, and then be retained by nuclear-localized binding partners. But new results suggest a more active process.

Suraj Saksena, Arthur Johnson, and colleagues (Texas A&M University, College Station, TX) now show that INM-bound proteins are sorted as they enter the ER through the translocon. They find that transmembrane sequences of both viral and mammalian INM proteins cross-link to Sec61α and TRAM, which are fundamental translocon proteins. Association with TRAM continues even though the growing peptide is long enough to release the transmembrane segment into the bilayer.



Lasting proximity to TRAM indicates active sorting to the INM.

Only two native non-INM proteins have been found to be adjacent to TRAM. "This sent us a signal that TRAM might act as a recognition component," says Johnson. "This goes along with my belief that the cell doesn't let anything happen randomly."

After leaving the translocon, the viral INM proteins were handed off to other viral proteins that are known to be needed for INM targeting. Now, the authors are seeking the endogenous nontranslocon components that take care of this job. ■

Reference: Saksena, S., et al. 2004. *Proc. Natl. Acad. Sci. USA.* doi:10.1073/pnas.0404934101.