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APC: More than a beta (catenin) blocker

Tumor suppressor could stop cancer through its effect on actin cytoskeleton.

The adenomatous polyposis coli (APC) protein serves as the colon's guardian, keeping tumors at bay. Okada et al. (1) reveal a new function for the protein: helping to renovate the cytoskeleton by triggering actin assembly. The result suggests a second way that mutations in APC could lead to cancer.

A faulty APC gene occurs in more than 80% of colon cancers and is one of the early "gateway" mutations leading to abnormal growth. Researchers probing APC's anti-cancer powers have focused on how it curbs the activity of β-catenin, a key link in the Wnt pathway that manages cell division and differentiation (2). But APC also helps shape the cytoskeleton. The protein latches onto and stabilizes growing microtubule ends (3, 4) and connects to actin filaments (5). "There have been more and more clues in the literature that the loss of APC's cytoskeletal effects may contribute to cancer," says senior author Bruce Goode. Still unknown, however, was how APC alters the actin cytoskeleton.

To find out, Okada et al. experimented with a C-terminal fragment of APC that interacts with microtubules and actin. This pruned protein triggered actin polymerization in vivo and in vitro, the team showed.

The researchers then compared APC's methods to those of other actin nucleators that spur filaments to grow. The Arp2/3 complex, for instance, almost tricks actin into polymerizing because it resembles the fast-growing barbed end of a filament. By contrast, researchers think that formins such as mDia1 take a more passive approach, stepping in to stabilize short actin chains that form spontaneously. A third category, which includes Spire and Cobl, plays matchmaker, gathering actin monomers that unite into a polymer seed. Okada et al. found that APC dimerizes and then works like the Spire-containing group, corralling up to four actin monomers into a complex that seeds further elongation.

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But that discovery raised another question. Cells deploy proteins that rein in actin extension. For example, profilin latches onto actin monomers and curbs spontaneous nucleation. And capping protein seals the barbed ends of actin filaments, preventing them from elongating and thus limiting their growth. APC can assemble actin filaments even if profilin is around. But how does it overcome capping protein?

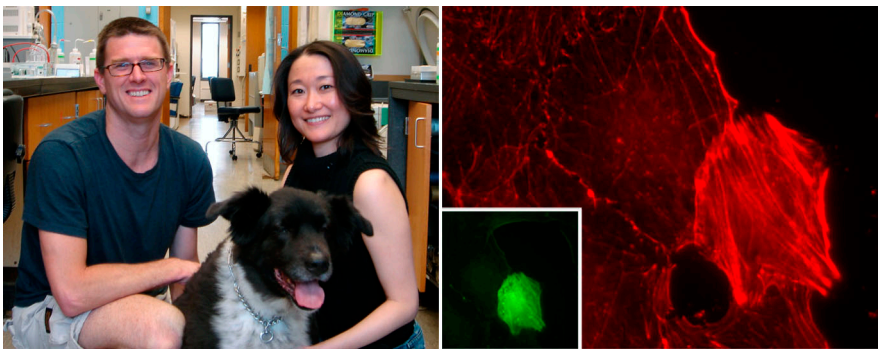
The answer is that APC gets help, collaborating with formins that deter capping protein. Okada et al. found that when capping protein and profilin are present, APC or mDia1 alone is a weak nucleator. But combining the two boosts actin assembly nearly fourfold.

APC is the seventh actin nucleator that researchers have identified. "The cellular functions of actin are so pervasive," Goode says. "It's involved in dozens of critical processes, so it makes sense that cells have a large number of factors that promote actin assembly." So far, APC is the only nucleator with direct links to cancer. Goode says that it's plausible that APC mutations could foment tumors not just through their effects on Wnt signaling, but also through their impact on the cytoskeleton. Cancer-causing mutations typically lop off the protein's actin-binding section.

Colon epithelial cells are born deep in crypts in the intestinal lining, and as they mature they differentiate, migrate into position, and give up their ability to divide. These choreographed changes involve precise rearrangements of the cytoskeleton and, if disrupted, could lead a cell down the path to cancer. By creating mice with a version of APC that can't nucleate actin, the researchers hope to nail down whether this mechanism contributes to tumor formation.

Because APC directly lengthens microtubules and actin, the protein could serve as an intermediary between the two cytoskeletons. So another question to investigate, the researchers say, is APC's role in situations where microtubules and actin remodel in concert, such as cell protrusion and migration.

Focal Point



A team led by Bruce Goode (left) and Kyoko Okada (shown here with lab dog Sasha) discovered that the tumor suppressor APC can trigger actin polymerization. This image of a layer of cells highlights the actin structures that formed in one cell after an injection of an APC fragment. The inset reveals that the GFP-tagged fragment latched onto actin.

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