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

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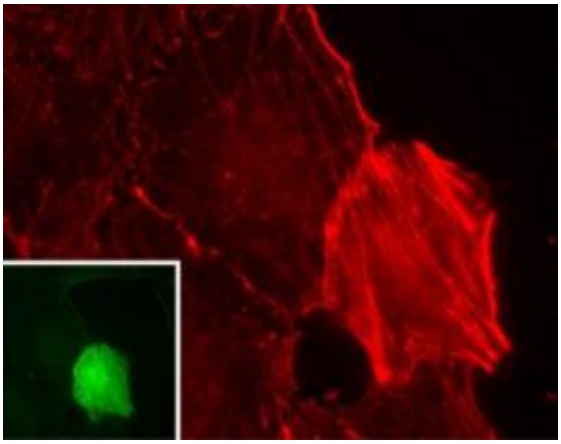

A new study in the *Journal of Cell Biology* suggests that APC mutations could promote tumors not just through their effects on Wnt signaling, but also through their impact on the cytoskeleton. This image of a layer of cells highlights the actin structures that formed in one cell after an injection of an APC fragment. The inset reveals that the GFP-tagged fragment latched onto actin. Credit: Okada, K., et al 2010. J. Cell Biol. doi:10.1083/jcb.201001016.

The APC protein serves as the colon's guardian, keeping tumors at bay. Now researchers 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. The study appears online on June 21 in the *Journal of Cell Biology*.

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 beta-catenin, a key link in the Wnt pathway that manages cell division and differentiation. But APC also helps shape the cytoskeleton. The protein latches onto and stabilizes growing microtubule ends and connects to actin filaments, though it was unclear exactly how APC affects actin dynamics.

A team of researchers led by Bruce Goode at Brandeis University found that APC plays matchmaker, corralling actin monomers into a complex that seeds further elongation. 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. The team found that when capping protein and profilin are present, APC or the formin 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, because cancer-causing mutations typically lop off the protein's actin-binding section.

More information: Okada, K., et al 2010. J. Cell Biol. doi:10.1083/jcb.201001016