

How One Protein Helps Cancer Both Spread and Grow

Hutch scientists discover single molecule's 'intricate regulation' of two key aspects of metastasis

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Though a tumor may seem to be a mess of overgrown cells, it cannot spread through the body and spark new tumors without coordinating two different processes: moving cells to a new area, and then increasing their number. In [work](#) published today in *Developmental Cell*, scientists at Fred Hutchinson Cancer Research Center have identified a protein called endophilin A3 that, unexpectedly, can help tumors balance these competing needs.

“When we think about cancers that metastasize, one of the basic principles of what these cells are able to do is they can move really fast to places they shouldn’t go, and then they grow at rates they shouldn’t be growing,” said first author Raj Poudel, PhD, a postdoctoral fellow jointly mentored by Jihong Bai, PhD, and Robert Eisenman, PhD, the study’s senior authors.

“What this study does is find something that can affect both those processes, but with very intricate regulation ... So that’s the exciting part, it drives both of the aspects of what we consider physical metastasis.”

EndoA3 may play a role in cancer

Poudel’s work on the protein, called EndoA3 for short, creates an unexpected synergy between Bai and Eisenman’s areas of expertise. Bai studies neurons and Eisenman studies molecular networks on which tumors rely. It turns out that while endophilin proteins are normally found in neurons, EndoA3 is highly — and unusually — expressed in some cancers, such as colon cancer.

Neurons use EndoA3 and related molecules to perform a process called endocytosis, through which they pick up outside molecules by using a section of their membrane to package them and draw them inside the cell. Endocytosis is not restricted to neurons, and other studies have linked endocytosis to cancer. Poudel found that colon tumors often express high levels of EndoA3, though it’s not usually found in colon tissue. This prompted him to look at whether EndoA3 could be supporting tumor growth by enhancing endocytosis.

Working with two University of Washington undergraduate students, Allen Su and Thuong Ho, Poudel manipulated tumor cell lines to express high levels of EndoA3. They saw that EndoA3 did

indeed increase endocytosis in these cells. It also increased their growth rate and, unexpectedly, their ability to move across petri dishes. Cancer cells that seed new tumors in new areas need both of these capabilities.

EndoA3's new function inside the cell

Cells rely on an internal skeleton, or cytoskeleton, of long molecular fibers to create their shape. They change shape by quickly putting together and taking apart these fibers, made up of a protein called actin. And they move by building actin fibers in arm- and finger-like projections they can use to crawl.

When Poudel and his team forced cells to overexpress EndoA3, they saw that they made these projections faster, extending and retracting them more quickly than cells without EndoA3. But how was a protein involved in endocytosis involved in rearranging the cytoskeleton?

EndoA3, the researchers found, performs two different roles, each dependent on its physical location within the cell. Poudel discovered that much of EndoA3 is situated inside the cell, in an area known as the cytoplasm. At the cell membrane, EndoA3 aids endocytosis and tumor growth. But in the cytoplasm, it binds a protein that regulates actin rearrangement. Through this protein, called TIAM1 (short for tumor-cell lymphoma invasion and metastasis 1), EndoA3 directs the formation of the membrane projections that cells use to move.

Many of the EndoA3 mutations seen in colon cancer cause it to shift more into the cytoplasm and increase cellular movement, the scientists showed.

“We found that we can make it more cytoplasmic and make the elements of migration go up, and we can make it more membrane-bound and the elements of endocytosis go up,” Poudel said.

The key to EndoA3's effects appears to be balance, say the researchers.

Bai likened the competing nature of EndoA3's two tasks to work-life balance: “If you are spending more time here [at work] you can do less at home. But if you're spending more time at home, you can do less here.”

If more EndoA3 is sitting on the membrane, directing endocytosis and proliferation, there will be less EndoA3 in the cytoplasm to promote the cytoskeletal reorganization needed for the cell to migrate — and vice versa. Whether the balance will shift toward cell migration or proliferation will depend on what kind of signals the cell is receiving from its environment, and the constellation of mutations the cancer cell and EndoA3 have accumulated.

Much cancer research has focused on the molecular pathways that tumor cells use to turn genes on and off, Eisenman said.

“Here's a mechanism that can go right around that,” he noted. Though alterations in how the EndoA3 gene is turned on could certainly alter its effects, “the signaling could be in the cytoplasm to a very large extent.”

Cells don't move randomly; instead, their movement is guided by triggers from their environment. "Now there is a molecular link that we can study more, to see, can this link be generating coordination between extracellular signals and the way the cell moves?" Bai said.

Future directions

Many interesting questions, both basic and translational, remain to be explored, the scientists said.

First of all, it's not clear how EndoA3-regulated endocytosis links up with proliferation and tumor growth. Nor is it clear exactly what role EndoA3 plays in the life cycle of a tumor. While they know EndoA3 can support proliferation and metastasis, the team would also like to know whether it can actually drive, rather than merely enhance, cancer development and progression.

"Is it involved in initiation [of cancer], is it involved in progression, is it involved in only the metastatic response?" Eisenman asked.

It remains to be seen how many other tumors beyond colon cancer rely on EndoA3 in the same way.

And because EndoA3 is not expressed in many healthy tissues, "targeting that could be a particular way to regulate certain cancer tissue development without general impact on other systems," Bai speculated.

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