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Researchers identify dangerous 'two-faced' protein crucial to breast cancer spread and growth

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Two critical properties of cancer cells are their ability to divide without restraint and to spread away from the primary tumor to establish new tumor sites. Now, researchers from the Mayo Clinic campus in Florida have found a protein they say acts as a deadly master switch, both freeing cancer cells from a tumor while ramping up new growth.

This is potentially good news, say the researchers, who published their study in the Nov.17 issue of the *Journal of Cell Biology*. If this protein — known as p120 catenin — is that powerful, it may be possible to turn the tables on cancer by designing an agent that would suppress it.

"We believe p120 could be an excellent target for therapy," says the study's lead investigator, Panos Anastasiadis, Ph.D., a Mayo Clinic cancer researcher. "Most cancer therapies target cancer growth, but miss migrating cancer cells that eventually re-establish the tumor, often at distant sites. Our best hope for long-term cancer therapy is to target both cancer cell growth and tumor spread, or metastasis.

"An anti-p120 agent could provide a much-needed double whammy — stop cancer spread and shut down growth at the same time."

Dr. Anastasiadis adds that while the discovery was made in breast cancer cells, it has relevance to a number of cancers, including those of the lung, kidneys, and skin, in which p120 plays a role. "These findings have

significant implications for our understanding of tumor biology and for improving cancer treatment," he says.

This study expands upon a body of research at the Mayo Clinic campus that is uniquely devoted to understanding, and then halting, cancer metastasis. Dr. Anastasiadis and his collaborators, including study co-author Edith Perez, M.D., a Mayo Clinic oncologist in the Breast Cancer Program, had earlier discovered that p120 activity is necessary if cancer is to spread. But they did not know about its role in growth promotion until this latest work.

P120 acts in cells by regulating the function of proteins called cadherins. Cadherins are membrane proteins that help cells stick to each other to form a tissue. On the outside of a cell's membrane, they act like Velcro, fusing to other cadherin proteins on adjacent cells. On the inside, they latch on to a chainwork of catenins, which are proteins that regulate a cell's shape and function. The best understood of the cadherins is E-cadherin, which binds all epithelial cells to each other, forming layers that cover the inside of organs and body cavities, and the outside skin of humans. In short, E-cadherin holds a human's cells and tissues together, Dr. Anastasiadis says.

P120 normally binds onto E-cadherin, strengthening cell-cell bonding. But in some cases it detaches from E-cadherin, which allows the cell to lose its adhesive grip to adjacent cells and switch on a program that promotes cell movement. The loss of E-cadherin expression during a process known as epithelial-mesenchymal transition (EMT) is one mechanism of activating p120's pro-migratory function, the researchers say. EMT is necessary during human development, or during wound healing in adults. But it is a process that is hijacked by tumors to allow cancer cells to migrate and colonize other organs. "When E-cadherin production is lost during the progression of cancer, p120 catenin induces invasion and metastasis," Dr. Anastasiadis says.

In this study, the researchers discovered that not only does p120 promote metastasis when it is not bound to E-cadherin, it also turns on growth-promoting genes and proteins. In laboratory and animal experiments, they found that "free" p120 makes cancer very aggressive, able to grow in conditions that other cancer cells can't. They specifically found that p120 activates a family of molecules that includes Ras and Rho, which promote cell growth and movement.

"What is really interesting here is that p120 is acting like a tumor suppressor when it is bound to E-cadherin, and like a tumor promoter when it isn't," Dr. Anastasiadis says.

The researchers believe these findings could help explain why in some solid tumors, such as breast, lung, kidney, and melanoma, loss of E-cadherin is associated with a more aggressive, less treatable prognosis. "We think that when E-cadherin is lost, p120 is now free to turn on growth promotion pathways that can overtake the benefits of targeted chemotherapeutics," he says.

"So in breast cancer that is HER2-positive, anti-HER2 therapies such as Herceptin will not function well if p120 has turned on alternate growth mechanisms," Dr. Anastasiadis says. "A similar effect would also be expected in EGFR-positive lung cancer and anti-EGFR treatment." Both HER2 and EGFR are growth-promotion proteins.

A potential solution would be to design an agent that targets the tumor-promoting function of p120 that is not bound to E-cadherin, he says. "This won't be easy, but based on our current understanding of p120 function we believe it is possible," says Dr. Anastasiadis.

Source: Mayo Clinic