

Public release date: 18-Sep-2006

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Contact: Christine Leon
leon.christine@mayo.edu
904-953-2299
Mayo Clinic, Jacksonville

Two-faced protein can stop metastasis or promote it, researchers say

A protein known to be a key component of the glue that holds cells together also is involved in breaking them apart and promoting their movement when tumors begin to spread to other parts of the body, researchers at Mayo Clinic have found.

The study, published in the Sept. 18 online issue of the Journal of Cell Biology, helps illuminate the very first steps involved in metastasis, the spread of cancer that makes the disease difficult to treat, and suggests that a future designer drug might be able to block the beginning of this dangerous process, or stop it once it starts.

"Our data show that this one protein, p120 catenin, is a key player in both suppressing invasion and promoting it," says the study's senior author, Panos Anastasiadis, Ph.D., a Mayo Clinic cancer researcher. "This is very exciting, because the findings open up a whole new field of discovery for novel therapeutics that should be applicable to most types of tumors."

Their laboratory study looks at how p120 catenin interacts with different cadherin cell adhesion proteins in cancer cells. Cadherin proteins go through a cell membrane, and on the outside, they act like Velcro, sticking to other cadherin proteins on adjacent cells. On the inside of the cell membrane, cadherins bind, chain-like, to catenins, and catenins, in turn, regulate a cell's shape and function.

The best understood cadherin is E-cadherin, which provides tight connections between epithelial cells, forming a strong barrier-like layer covering the inside of organs and body cavities and the outside skin of humans. "E-cadherin holds a human's cells and tissues together," Anastasiadis says.

The other cadherins featured in this study belong to a group that collectively is called "mesenchymal" cadherins, which provide a looser bond between the cells that sparsely populate the connective tissue. "Collagen usually provides the strength to the connective tissue, so tight cell-cell adhesion is not that important," he says.

Sometimes, such as during human development or wound repair, epithelial cells need to travel to other areas, and to do this, they undergo a process known as "epithelial-mesenchymal transition" (EMT). The cell reduces its production of E-cadherin proteins and increases expression of mesenchymal cadherins, thus effectively loosening the anchors that keep the cell bound to its neighbors.

Cancer, unfortunately, has adopted this strategy in order to spread, Anastasiadis says. "When the function of E-cadherin is lost in a cell, it can break free from its neighbors and travel to settle elsewhere," he says. "This means that E-cadherin normally helps suppress invasion."

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But researchers have noted that the p120 catenin protein seems mysteriously two-faced: while it normally strengthens cell-cell bonding, in some cases it can also negatively affect cell adhesion. They also have found that over production of p120 increases a cell's ability to move. But the significance of these observations had eluded scientists.

In this study, Masahiro Yanagisawa, M.D., Ph.D., a research fellow in Anastasiadis' laboratory, and Anastasiadis provide an answer as to why p120 acts this way, which helps explain how the EMT shift between E-cadherin and mesenchymal cadherins allows cancer cells to break away from tissue and spread.

They found that p120 "prefers" to bind to E-cadherin, rather than to mesenchymal cadherins. So in normal epithelial cells p120 always associates with the more abundant E-cadherins. But when E-cadherin production is lost during the progression of cancer, p120 catenins begin binding to mesenchymal cadherins. And when that happens, the researchers found that p120 unexpectedly switches on a cascade of events that promote cell movement.

"We show that E-cadherin suppresses invasion, at least in part, by binding to p120 protein in the cell," Anastasiadis says. "If E-cadherin is missing, p120 is free to bind to mesenchymal cadherins, setting off a process that leads to metastasis."

Thus, p120 acts as a "rheostat" that promotes either stability when associated with E-cadherin or motility when it interacts with mesenchymal cadherins, he says.

The investigators say that further research is needed to see if p120 functions the same way in living tissue as it does in laboratory cell culture, and they add that other "pathways" are likely involved in the transition to metastasis. But if the results continue to hold up, "it might be therapeutically possible to selectively shut down the pro-invasive function of p120 on mesenchymal cadherins while keeping the pro-adhesion function of p120 in normal epithelial cells.

"We have provided a better understanding of the processes involved in the initiation of tumor spread, and it is this process that we all seek to shut down," Anastasiadis says.

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Anastasiadis and Yanagisawa co-authored the study, which was funded by the National Institutes of Health and the Florida Department of Health.

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