# Tumor suppressor acts as oncogene in some cancers, say researchers

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Researchers at Mayo Clinic in Florida have found that a molecule long believed to be a beneficial tumor suppressor — and thus a potential cancer drug target — appears to act as an oncogene in some lethal brain tumors.

The protein, epithelial cadherin (E-cadherin), is known for its ability to keep cancer cells glued together, preventing them from breaking away and metastasizing. But, based on their findings, published online in *PLoS ONE,* the scientists suggest E-cadherin can also function as an oncogene in some cancers. An oncogene helps push cancer development and growth.

They say the findings could explain recent, puzzling observations about E-cadherin expression in breast cancer, for example. While loss of E-cadherin is generally considered a harbinger of metastasis, researchers have also found that most breast cancer that has spread retains E-cadherin expression. Ovarian tumors also have been paradoxically found to produce more and more E-cadherin as they grow.

"This surprising finding should compel us all to shift our thinking about E-cadherin," says the study's lead investigator, cancer biologist Panos Z. Anastasiadis, Ph.D. "Up to now, we have all thought that if a tumor loses E-cadherin function, that represents a movement toward metastasis. That makes sense because 50 percent of cancers don't express E-cadherin and they are linked to a worse prognosis.

"But now it appears that E-cadherin expression in a tumor could be responsible for cells growing out of control if the protein is not functioning as it should be."

Dr. Anastasiadis focuses his research on the biological factors involved in cancer metastasis. In this study, he and a research team, which included scientists from Mayo Clinic's campuses in Florida and Minnesota, examined protein expression in glioblastoma cancer cells. Glioblastoma is the most common, as well as the most dangerous, brain cancer.

"Our interest is to understand the pathways that induce glioblastoma to be so invasive," he says. "The problem with this cancer is that the tumors can be very aggressive, and single cancer cells can spread all over the brain."

Among other proteins, the researchers looked at cadherins, of which about 20 are expressed in the brain — more than in any other organ. These are transmembrane proteins that play critical roles in determining how cells bind to each other in a tissue. The researchers expected to find significant amounts of neural cadherin (N-cadherin) in the tumors, but not E-cadherin, which is expressed in epithelial rather that normal brain tissue.

In epithelial tissue, loss of E-cadherin usually represents a switch in cell behavior known as epithelial-mesenchymal transition (EMT). In EMT, cells that had been tightly bound to each other loosen up, due to loss of E-cadherin, and other proteins — including other members of the cadherin superfamily — then promote migration of individual cells away from a cancer cluster. Drugs are being developed that target this EMT switch, says Dr. Anastasiadis.

Given these facts, the researchers say that what they found surprised

them. While N-cadherin was expressed in most human brain tumor cell lines — and N-cadherin is potentially oncogenic — some also expressed E-cadherin. They also found those cells that expressed E-cadherin acted more aggressively than brain cancer that did not express the protein. The researchers then validated their findings in animal studies. Finally, they performed an experiment in which they removed E-cadherin expression from glioblastoma cells and found these cells had a reduced ability to move, and grew at a much slower pace.

"E-cadherin expressed in these glioblastomas did not function to keep cells stuck together. Instead, they promoted tumor growth and migration," Dr. Anastasiadis says. "This is the complete opposite of what we have known about E-cadherin. For some reason, in these brain cells, E-cadherin expression is linked to aggressive cell behavior and poor prognosis."

The findings suggest "cadherins, as a whole class of proteins, need to be studied in more detail," he says. "E-cadherin expressed in glioblastoma functioned like an oncogene and it could be doing the same in many breast, ovarian, and other tumors found elsewhere in the body.

"Understanding what causes the switch in E-cadherin function from a tumor suppressor to an oncogene, and how to block it, will be critical," concludes Dr. Anastasiadis. "But the bottom line is that we cannot view E-cadherin simply as a tumor suppressor anymore."

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