CAMs Are Stopping Cancer in Its Metastatic Tracks

A counterintuitive idea is making the rounds in cancer research: Stickiness promotes mobility. Proteins that help cells stick together, called cellular adhesion molecules (CAMs), may be a driving force in metastasis, and they seem to be present in almost every cancer tested. The good news is that blocking CAMs seems to slow the spread of cancer.

In fact, using antibodies to interfere with CAMs is promising enough to warrant a clinical trial, according to Peter Altevogt, Ph.D., at the German Cancer Research Center in Heidelberg, where a phase I trial is planned. “Since the situation with tumor patients is so disastrous, it’s exciting,” he said. “Antibody-based therapy bears a lot of hope and expectation.”

But researchers are also trying to understand the underlying biology—what the CAMs do on the surface in the first place, whether they transfer biochemical signals from the surface to the cell’s interior, and whether tackling them with antibodies is likely to cause a chain reaction that leads to cellular suicide.

“There’s not a huge amount of information out there,” said Anthony Montgomery, Ph.D., a cell biologist at the University of California, San Diego. “But it’s gaining more momentum.”

Adhesion molecules keep cells together; the CAMs sit on cell surfaces and stick to each other. Other proteins, such as e- and n-cadherin, anchor cells to the matrices to form tissues. But unlike the cadherins, which form strong links, CAMs are generally like the glue on sticky notes—not overly adhesive but sticky enough to get the job done. They can be found on cells that normally stay in one place, such as epithelial cells, or cells that float through the bloodstream, such as those of the immune system.

A key feature of CAMs is that their presence on cancer cells indicates a worse prognosis. But why? So far, CAM research has revealed only a few scattered details about their role in cancer malignancy. “The story is much more complicated than it was several years ago,” said Avri Ben-Ze’ev, Ph.D., a cancer biologist at Weizmann Institute of Science in Tel Aviv, Israel. For example, there appear to be no hard-and-fast rules indicating which molecules will be found associated with which cancers.

L1 Antibodies

Most CAMs are related structurally to immunoglobulins (Igs), the family of proteins into which antibodies fall. One of the newest and most promising CAMs is L1, which has a long history in neuronal development. Since 1983, neuroscientists have been learning how it aids young neurons to get where they need to be. Scientists found the protein on the surface of brain tumors in 1986 and on melanoma in 1989. The list has been growing since.

Now L1 is finding itself in the cancer therapy spotlight. In January, Altevogt’s team reported that injecting antibodies to human L1 into mice carrying human ovarian tumors could reduce the tumor load by 60%. “This recent paper is very important,” said Montgomery, who was not involved with the work.

In the experiment, the team seeded tumors with human cultured ovarian cancer cells in nude mice, animals without immune systems that serve as incubators for human cancers. After letting the cancer cells grow for 2 days within the abdominal cavity, the team injected L1 antibodies twice weekly into the cavity. After 38 days, the mice that didn’t receive therapy were at death’s door, but the treated animals were still alive and had far smaller tumors and smaller amounts of ascites, the cells that collect in the abdominal cavity as cancers grow.

“We’re mimicking the situation when cancer patients have residual disease,” said Altevogt. Even though surgeons remove as much of the cancer as possible, there are always some cancer cells left. And the presence of L1 on cancer cells increases the chances that the patients will die within 1–6 years. Altevogt hopes to start clinical safety trials of L1 antibodies within about a year.

He is also pursuing L1 as a diagnostic tool. The protein stretches across the cell’s membrane and the part that sticks out gets cut off, creating fragments that can be detected in blood. “We hope to develop it into a marker for cancer,” he said.

Producing L1 in cultured tumor cells increases their invasive properties and motility, said Montgomery. It works in some cells by activating a procancer set of genes called the mitogen-activated protein kinase pathway, which turns on many genes previously identified to promote metastases. But which ones get turned on depends on the cell type.

“That says there’s multiple mechanisms; some could be important in some tumors and not others,” he said.

In 2005 Ben-Ze’ev’s group found that L1 existed only in cells at the invasive front of colon cancers but not in the tumor mass. The invasive front also loses e-cadherin, which normally anchors the cells.

Another trick that L1 uses is to shed a protein fragment, which can transform other cells into cancer rogues. Altevogt said when the piece is chopped off, what’s left of L1 signals the cell to invade and migrate. Ben-Ze’ev speculates that the shed L1 fragments are chopped off by enzymes in the surrounding tissue, not in the cancer cells. Then the fragments mobilize other cells to the cancer’s cause.

“They lay down tracks. They are building a railroad and moving around on it,” he said. In December 2005, Ben-Ze’ev’s group showed that another IgCAM called NrCAM, found in pancreatic, renal, and colon cancers, can also shed a cell-transforming fragment.

Another IgCAM that appears to be an Achilles’ heel for cancer cells is NCAM. This molecule is found in cancers of the gallbladder, head and neck,
and skin. Oncologist Masakatsu Fukuda, D.D.S., of Meikai University School of Dentistry in Sakado, Japan, has found that antibodies to NCAM stimulate cultured salivary gland tumor cells to commit suicide.

**The Back Story**

The burgeoning interest in the Ig-like CAMs seems so far to parallel that of an epithelial CAM (EpCAM). Interest in EpCAM arose back in the 1980s when researchers were developing monoclonal antibody technologies against cancers. “The hope was that these monoclonal antibodies would be magic bullets,” said William Gillanders, M.D., of Washington University in St. Louis.

Identified in 1986, EpCAM is a small surface protein on many types of cancer cells that stimulates the immune system with more gusto than other cell surface proteins, earning a spotlight as well as almost two dozen aliases. Although antibodies to EpCAM slowed the growth of colon tumors in lab animals, human phase III trials in the mid-1990s failed to improve survival of colorectal cancer patients.

But in those studies, no one tested the cancers to determine if the cells had donned EpCAM in the first place, said Gillanders, and that doomed the trials. Nor were the antibodies “humanized”—produced in such a way as to prevent people’s immune systems from attacking them. More recent studies, though small, have addressed these issues and have been more successful. For example, a humanized monoclonal antibody to EpCAM, called ING-1, can prevent the growth of or kill some cultured cancer cells. In 2004, researchers presented a phase I trial in which they tagged ING-1 with radioactivity and gave it to three cancer patients whose tumors had large amounts of EpCAM. Images of these volunteers revealed that ING-1 converged near their cancers—and highlighted metastases as well.

Now scientists are learning how EpCAM increases metastases. Engineering cultured cells with extra EpCAM showed that EpCAM appears to loosen a cell’s grip by weakening the strength of cadherin’s hold. Two years ago, cell biologists showed that EpCAM itself makes cells cancerous and invasive. In 2004, a team led by Oliver Gires, Ph.D., at Ludwig-Maximilians University of Munich, Germany, produced EpCAM in cultured epithelial cells that don’t normally make the protein. They found that the cells grew three times faster when making the adhesion protein. Also, turning on production of EpCAM turned on c-myc, a gene whose mutant version is found in many cancers, as well as a protein involved in cell division.

Gillanders’ group did just the opposite to EpCAM. They blocked the protein’s production in cultured breast cancer cells, which cut the rate of cell growth by 30%–80% in four different cell lines. Also, the cells could barely move, losing more than 90% of their migratory and invasive abilities.

But how EpCAM works has yet to be puzzled out. According to Ben-Ze’ev, “there’s no direct link between EpCAM and the nucleus,” where the procancer genes reside. Gillanders agreed. “There’s no evidence to date that if you bind EpCAM [with antibodies], you get any functional impact,” he said. The best evidence that it’s involved in biochemical signaling within the cell, he said, is that the protein collects with other proteins into “signaling pods” on the cell surface.

Piecing together which CAMs are important to which cancers is key to using the molecules as therapeutic targets. “As we become more savvy with which cancers is key to using the molecules as therapeutic targets. As we become more savvy with which patients are expressing these proteins and who should be treated with the antibodies, then that should improve the efficacy,” said Gillanders.

—Mary Beckman