Researcher targets mechanism that allows cancer to spread

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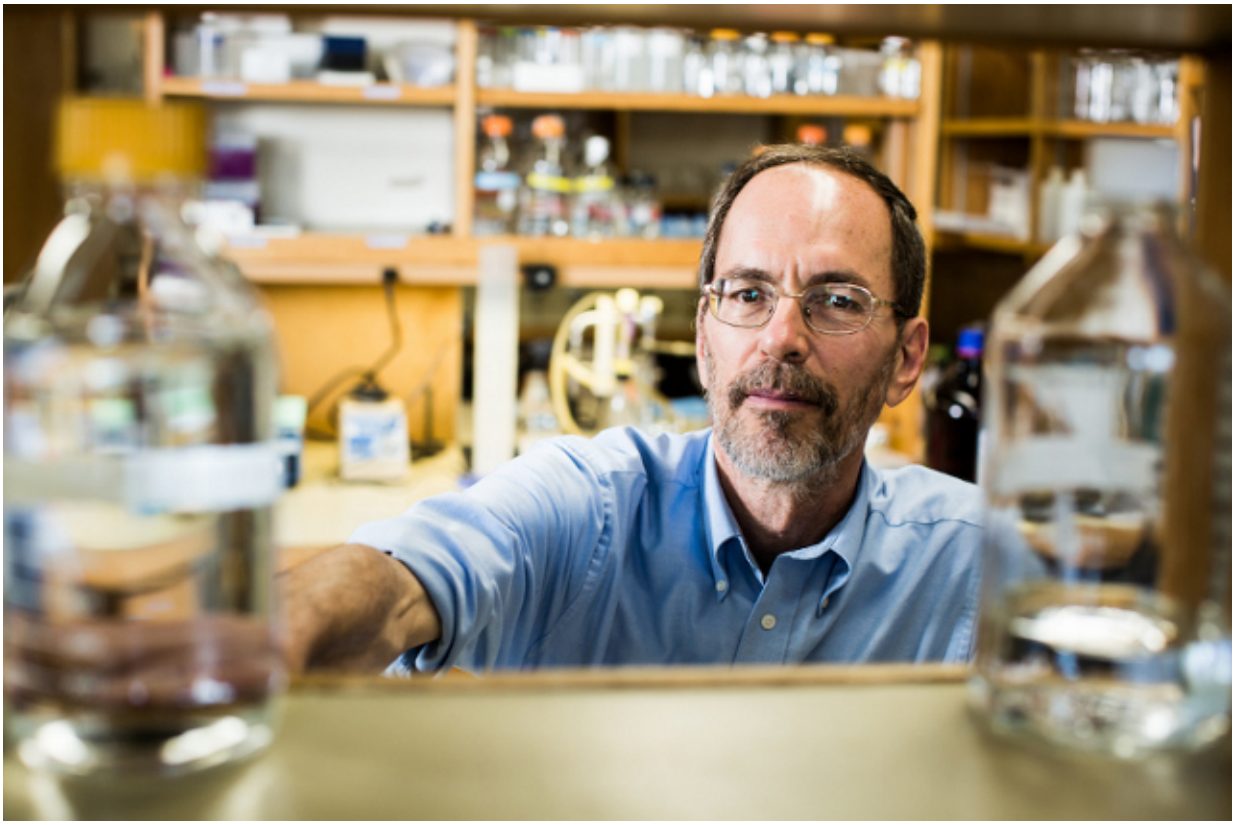

"Understanding the basic processes that cells use to grow and survive gives you the foundation to develop therapies when those processes go wrong," Michael Forgac says. Credit: Jake Belcher

The majority of women who die from breast cancer don't die from the primary malignancy. They die when the aggressive cancer metastasizes,

spreading rapidly throughout the body and forming new tumors in the bone, lungs and brain.

"Unfortunately, there are not any therapeutics out there that address metastasis," says Tufts cell biologist Michael Forgac. "It's a huge unmet clinical need."

Chemotherapy and radiation, the typical cancer treatments, "are really brutal techniques from a living organism's perspective," says Forgac, professor and vice chair of the Department of Developmental, Molecular and Chemical Biology at Tufts School of Medicine. Although these therapies destroy cancer cells, they often inflict collateral damage on the rest of the body, mowing down healthy cells alongside cancerous ones.

There has to be a better way, says Forgac, who's working to develop therapies that target cancer cells directly and leave healthy tissue untouched. Once researchers can solve that puzzle, he says, it may be possible to shrink tumors and prevent them from spreading without taking a hefty toll on a patient's body.

In his laboratory at the Sackler School, Forgac is focusing on tiny molecular structures called V-ATPases. They're miniature proton pumps that reside in a cancer cell's outer membrane and regulate pH levels inside malignant cells—a trait that's essential for their survival. As the diseased cells grow, he says, they generate unusual amounts of acid inside them. V-ATPases act like the water pump in your basement during a heavy rain, pumping out extra acid (instead of water) before it begins to kill off the cell.

By using drugs that stop those pumps from working, Forgac says, researchers can trap acid inside cancer cells, making it harder for the cells to survive and invade new tissues—at least that's what has occurred in cancer cells cultured in a dish.

There's a big catch, however, when it comes to cells in a living human.

Cancer cells aren't the only ones that rely on V-ATPases—in fact, nearly every cell in our body uses them to some degree. Inside the lysosome, a cell's "stomach," V-ATPases play a major role in helping break down proteins for energy. Shutting down these cellular pumps indiscriminately would not only kill off cancer cells, but would also kill nearly every other cell in the body.

"When we think about trying to target [V-ATPases] for a cancer therapy, we need to figure out how to do that in a selective way," says Forgac. "It's quite clear that if you inhibit all the V-ATPases in your body, you die."

Picking a Target

The trick to targeting just the V-ATPases that show up in cancer cells lies in a tiny detail within the structure of a V-ATPase, Forgac says.

With the exception of a few specialized cells in the body, V-ATPases are mostly found deep inside a cell. In aggressive cancer cells, however, the pumps tend to migrate to the cells' outer membrane, since that's a better location for venting off excess acid. So how do they get there?

Zoom in on a V-ATPase pump, and you'll see 12 different proteins woven together into a complex molecular machine. Most of them are identical from one pump to another, but in cancer cells, a particular part gets made at higher levels. Cancer cells make more of one piece of the V-ATPase called a3. Forgac says this piece acts as a sort of "address" for the V-ATPase, directing it toward the exterior of the cell.

"We've explored V-ATPases in a number of breast cancer cell lines, and what we found is that generally, the more invasive the breast cancer cell

line is, the more a3 is expressed," he says. If it's possible to develop drugs that target only V-ATPase pumps that have an a3 piece inside, he adds, it might be possible to home in on cancer cells while leaving other tissues intact.

"This is pretty exciting," says Phil Hinds, professor and chair of the Department of Developmental, Molecular and Chemical Biology at Tufts. "The fact that a3-containing V-ATPases might be targeted by new drug candidates is the culmination of years of basic research on Michael's part."

That goal is still a long way off, he notes, but a basic understanding of how a3 is over-expressed and how it directs the pumps to the cell surface is essential before any drug can be created.

Forgac is starting to probe the connection between a3 and cancer. Instead of just examining cancer cells in isolation, he will study how a3 affects the spread of malignancies in lab mice.

Using a DNA editing technique called CRISPR, students in his lab will delete the gene responsible for a3 in cancer cells. They'll then inject those edited cancer cells into healthy mice and track how long they take to metastasize. If the edited cancers spread more slowly than their unedited peers, Forgac says, it could mean that a3 does indeed play a major role in letting cancers move throughout the body.

"This is setting the stage for the next step," he says. "If it turns out that our hypothesis is true—that disrupting or knocking down a3 reduces metastasis and tumor growth—then we can start to work on developing safe, effective therapeutics."

Some of Forgac's work is being supported by a $100,000 grant from the Breast Cancer Alliance, a nonprofit based in Connecticut that funds

research on the disease.

"We know Dr. Forgac is the leader of this particular research, with strong preliminary data supporting him," says the organization's executive director, Yonni Wattenmaker.

Granted, it will be a while before Forgac's work leads to any new breast cancer treatments. At the moment, he's mostly doing fundamental research, probing the ways that these tiny cellular mechanisms actually function. He feels strongly, however, that this sort of basic understanding is the bedrock of any future progress in medicine.

"You can't fix a broken watch until you know how the watch works," he says. "In medicine, it's the same thing. Understanding the basic processes that cells use to grow and survive gives you the foundation to develop therapies when those processes go wrong."

Provided by Tufts University