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New studies explain how cancer cells 'eat us alive'

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Four key studies now propose a new theory about how cancer cells grow and survive, allowing researchers to design better diagnostics and therapies to target high-risk cancer patients. These studies were conducted by a large team of researchers at Thomas Jefferson University's Kimmel Cancer Center.

This new idea also explains why so many cancer patients say that "their cancer is eating them alive" - an accurate observation that has never been understood, the researchers say.

These four new studies, co-published in the September issue of the journal *Cell Cycle*, provide evidence that tumor growth and metastasis is directly "fueled" by normal supporting cells.

These supporting cells are called fibroblasts, and they produce the stroma (connective tissue) that surrounds tumor cells. As the cancer progresses, increasing numbers of these stromal cells eat themselves to provide recycled nutrients to tumor cells - leading to dramatic weight loss in patients.

They also found that without recycled nutrients provided by fibroblasts, tumor cells are more fragile and die. Based on this breakthrough, the researchers propose that available drugs (now on the market), which sever the "parasitic" connection between tumor cells and fibroblasts, may be effective therapeutics.

“We think we have finally figured out how cancer really works - and this reverses 85 years of dogma, upon which current cancer research and therapy is based,” says the study’s senior investigator, Michael P. Lisanti, M.D., Ph.D., Chairman of Jefferson’s Department of Stem Cell Biology & Regenerative Medicine.

The prevailing theory, known as the Warburg Effect, developed by German researcher Otto Warburg in 1924 (for which he won a Nobel prize), says that tumor cells change their metabolism in order to fuel their own growth. As evidence, Warburg pointed to a lack of mitochondria, which are tiny “power plants,” in laboratory cancer cells, saying these cells have found another way to produce the energy they need.

Richard Pestell, MB, BS, MD, Ph.D, FRACP, director of the Kimmel Cancer Center and co-author on these studies notes, “These studies suggest that the absence of mitochondria in laboratory cancer cells may reflect in part that cultured cells have had to adjust to life outside of their original environment, without their stromal partner.” Drs. Lisanti, Pestell and colleagues found this out by performing a simple experiment in which they mixed cancer cells and fibroblasts together, and then searched for mitochondria. The found the fibroblasts didn’t have any mitochondria, and that the cancer cells had all the mitochondria.

“The Warburg Effect is happening, but it is happening to fibroblasts, not to cancer cells. Fibroblasts have no mitochondria because they are eating them to provide energy to cancer cells, and cancer cells have a ton of mitochondria because they need these power plants to process all the recycled nutrients given to them by fibroblasts, which then helps them grow and spread,” Dr. Lisanti says.

They have dubbed this finding “The Reverse Warburg Effect.”

“It’s amazing,” Dr. Lisanti says. “Much of what we know about cancer is backwards because cancer researchers used isolated tumor cells for most cancer studies. Now, when we put cancer cells back in their stromal environment, we see how cancer cells critically depend on fibroblasts for their survival.”

Tumor cells do this by employing oxidative stress as a weapon. Then, oxidative stress in fibroblasts “tricks” these stromal cells into eating themselves to feed cancer cells, the researchers say. This process of “self-eating” or “self-cannibalism” is called autophagy.

During periods of starvation, normal cells undergo autophagy. This metabolic re-programming allows cells to recycle nutrients by continually eating themselves, including their mitochondria. This permits starving cells to recycle nutrients and to survive under hostile conditions.

Now, Dr. Lisanti and colleagues have figured out how cancer cells take advantage of this recycling process. To satisfy their large appetite, hungry cancer cells induce oxidative stress in the fibroblasts and this stress forces the stromal cells to eat themselves, which provides recycled nutrients or “food” to fuel survival of nearby cancer cells.

“It’s that simple. Cancer cells are eating us alive by stealing nutrients from normal cells using oxidative stress, and by employing those recycled nutrients to support their own growth. Stem cells are then recruited from the bone marrow to produce fresh fibroblasts, to continually fuel cancer cell growth,” Dr. Lisanti says. “For years, cancer patients have said they felt as though the cancer in their body was eating them alive. These patients were right. Essentially, the cancer knows how to induce oxidative stress and turns a local wasting process into a whole-body phenomenon.”

Co-author Ubaldo Martinez-Outschoorn, M.D., a medical oncologist at

Jefferson says “Patients have been telling us that cancer is eating them alive for years: Now we know they were right!” One of his cancer patients recently said, “Doc, I can’t eat enough food to maintain my weight. No matter how much I eat, I feel tired, and I am always losing weight.”

“Now that we understand the mechanism, this reverses our thinking about cancer metabolism and about how to stop this stress and starve the cancer cells,” he says.

In one of the published studies, Dr. Lisanti shows that using anti-oxidants can prevent oxidative stress in the fibroblasts, thus cutting off the fuel supply to cancer cells, starving them. “We are now performing drug screening assays to discover new anti-oxidants and other molecules like this,” he says.

The researchers have additionally identified two key metabolites - ketones and lactate - produced by the co-opted fibroblasts that provide high-energy food to the cancer cells. This finding also explains a mystery and provides a warning.

The mystery concerns why people with diabetes are much more likely to develop cancer than non-diabetics. The reason, Dr. Lisanti says, is that diabetic patients produce elevated levels of ketones, and he now shows that ketones fuel cancer cell growth.
The warning comes from the common use of lactate, a type of sugar, in cancer patients. Surgeons often give their cancer patients an intravenous solution of lactate before, during, and after surgery, Dr. Lisanti says. “But we see that cancer cells are using energy-rich fuels, such as lactate, to increase their numbers of mitochondria to power cancer cell growth, survival, and metastasis, so surgeons may want to re-consider or stop this practice.”

The findings have led the researchers to question the value of research using isolated laboratory cancer cells - the basis of most cancer research - and the anticancer drugs that result from it.

For example, genetic mutations have long been thought to be the root cause of cancer, but Dr. Lisanti's group observed that these alterations might be the consequence of the tumor cell's interactions with the normal stroma. Oxidative stress induced by cancer cells in fibroblasts feeds back upon cancer cells, amplifying the production of reactive oxygen species (ROS). They believe that ROS is then used by cancer cells to mutate their own genes to promote survival.

"These ROS molecules cause DNA damage in the cancer cells, resulting in genomic instability - random mutations and DNA breakage, as well as abnormal chromosome numbers. This instability helps cancer cells evolve into a more aggressive form," Dr. Lisanti says.

"So, we see three consequences resulting from activating oxidative stress in normal stromal cells," he says. "First, it forces stromal cells to make food for cancer cells. Second, this abundance of food protects the cancer cells against death. Finally, oxidative stress modifies cancer cell DNA, causing mutations and allowing them to evolve into a more aggressive form."

Additionally, the researchers say their new theory of stromal metabolic re-programming suggests that cancer cells do not need blood vessels to feed them, which explains why some angiogensis inhibitors (drugs that shut down blood vessel growth) have not worked - and, in fact, may be dangerous.

"If an aggressive cancer cell can use oxidative stress to extract nutrients from normal stromal cells, it can go anywhere without the need for a blood supply. This may be how cancer cells spread all over the body,"

Dr. Lisanti says. “Furthermore, angiogenesis inhibitors induce hypoxia, which is low oxygen, in the stroma. This is exactly the condition that drives nutrient recycling via autophagy. So angiogenesis inhibitors may help provide food or recycled nutrients to feed cancer cells. This explains why angiogenesis inhibitors have been very disappointing in clinical trials, as they may be having just the opposite effect, promoting cancer cell growth and metastasis.”

These new findings also have clear implications for cancer diagnosis, the researchers say. Many of the molecules that Dr. Lisanti’s group identified could be used as diagnostics to identify high-risk cancer patients or to monitor the success of their anti-cancer therapy.

Among them is caveolin-1 (Cav-1), which is produced by fibroblasts. Dr. Lisanti had shown earlier that loss of Cav-1 predicts poor prognosis in breast cancer patients, and is linked to early tumor recurrence, metastasis, and drug resistance. He now understands why, as breast cancer patients with absent stromal Cav-1 are feeding their cancer cells via recycled nutrients. That explains why a loss of stromal Cav-1 is such a good biomarker for identifying high-risk patients.

“The idea that a cancer cell’s local environment is important for tumor growth is now well-accepted by the cancer research community,” Dr. Lisanti says. “Now we show why this notion is correct.”

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