Cancer cells accelerate aging and inflammation in the body to drive tumor growth

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Researchers at the Kimmel Cancer Center at Jefferson have shed new light on the longstanding conundrum about what makes a tumor grow-and how to make it stop. Interestingly, cancer cells accelerate the aging of nearby connective tissue cells to cause inflammation, which ultimately provides "fuel" for the tumor to grow and even metastasize.

This revealing symbiotic process, which is similar to how muscle and brain cells communicate with the body, could prove useful for developing new drugs to prevent and treat cancers. In this simple model, our bodies provide nourishment for the cancer cells, via chronic inflammation.

"People think that inflammation drives cancer, but they never understood the mechanism," said Professor and Chair of Stem Cell Biology & Regenerative Medicine at Jefferson Medical College of Thomas Jefferson University and a member of the Kimmel Cancer Center. "What we found is that cancer cells are accelerating aging and inflammation, which is making high-energy nutrients to feed cancer cells."

In normal aging, DNA is damaged and the body begins to deteriorate because of oxidative stress. "We are all slowly rusting, like the Tin-man in the Wizard of Oz," Dr. Lisanti said. "And there is a very similar process going on in the tumor's local environment." Interestingly, cancer cells induce "oxidative stress," the rusting process, in normal connective tissue, in order to extract vital nutrients.

Dr. Lisanti and his team previously discovered that cancer cells induce this type of stress response (autophagy) in nearby cells, to feed themselves and grow. However, the mechanism by which the cancer cells induce this stress and, more importantly, the relationship between the connective tissue and how this "energy" is transferred was unclear.

"Nobody fully understands the link between aging and cancer," said Dr. Lisanti, who used pre-clinical models, as well as tumors from breast cancer patients, to study these mechanisms. "What we see now is that as you age, your whole body becomes more sensitive to this parasitic cancer mechanism, and the cancer cells selectively accelerate the aging process via inflammation in the connective tissue."

This helps explain why cancers exist in people of all ages, but susceptibility increases as you age. If aggressive enough, cancer cells can induce accelerated aging in the tumor, regardless of age, to speed up the process.

The researchers' findings were published online June 1st in the journal *Cell Cycle* in three separate papers.

One paper analyzes the gene profiles of the laser-captured connective tissue, associated with lethal tumors, in human breast cancer patients. In this paper, lethal cancers show the same gene expression pattern associated with normal aging, as well as Alzheimer's disease. In fact, these aging and Alzheimer's disease signatures can identify which breast cancer patients will undergo metastasis. The researchers find that oxidative stress is a common "driver" for both dementia and cancer cell spreading.

In another study, the researchers explain that cancer cells initiate a "lactate shuttle" to move lactate-the "food"-from the connective tissue to the cancer cells. There's a transporter that is "spilling" lactate from the connective tissue and a transporter that then "gobbles" it up in the cancer cells."

The implication is that the fibroblasts in the connective tissue are feeding cancer cells directly via pumps, called MCT1 and MCT4, or mono-carboxylate transporters. The researchers see that lactate is like "candy" for cancer cells. And cancer cells are addicted to this supply of "candy."

"We've essentially shown for the first time that there is lactate shuttle in human tumors," said Dr. Lisanti. "It was first discovered nearly 100 years ago in muscles, 15 years ago in the brain, and now we've shown this shuttle also exists in human tumors."

It's all the same mechanism, where one cell type literally "feeds" the other. The cancer cells are the "Queen Bees," and the connective tissue cells are the "Worker Bees." In this analogy, the "Queen Bees" use aging and inflammation as the signal to tell the "Worker Bees" to make more food.

Researchers also identified MCT4 as a biomarker for oxidative stress in cancer-associated fibroblasts, and inhibiting it could be a powerful new anti-cancer therapy.

"If lethal cancer is a disease of "accelerated aging" in the tumor's connective tissue, then cancer patients may benefit from therapy with strong antioxidants and anti-inflammatory drugs," said Dr. Lisanti. "Antioxidant therapy will "cut off the fuel supply" for cancer cells." Antioxidants also have a natural anti-inflammatory action.

Provided by Thomas Jefferson University

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