

New 'Achilles' heel' in breast cancer: tumor cell mitochondria

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Researchers at the Kimmel Cancer Center at Jefferson have identified cancer cell mitochondria as the unsuspecting powerhouse and "Achilles' heel" of tumor growth, opening up the door for new therapeutic targets in breast cancer and other tumor types.

Reporting in the online Dec. 1 issue of *Cell Cycle*, Michael P. Lisanti, M.D., Ph.D., Professor and Chair of [Stem Cell Biology](#) & Regenerative Medicine at Thomas Jefferson University, and colleagues provide the first in vivo evidence that breast cancer cells perform enhanced [mitochondrial](#) oxidative phosphorylation (OXPHOS) to produce high amounts of energy.

"We and others have now shown that cancer is a 'parasitic disease' that steals energy from the host -- your body," Dr. Lisanti said, "but this is the first time we've shown in human breast tissue that cancer cell mitochondria are calling the shots and could ultimately be manipulated in our favor."

Mitochondria are the energy-producing powerplants in normal cells. However, cancer cells have amplified this energy-producing mechanism, with at least five times as much energy-producing capacity, compared with normal cells. Simply put, mitochondria are the powerhouse of cancer cells and they fuel [tumor growth](#) and metastasis.

The research presented in the study further supports the idea that blocking this activity with a mitochondrial inhibitor -- for instance, an off-patent generic drug used to treat diabetes known as Metformin -- can reverse tumor growth and chemotherapy resistance. This new concept could radically change how we treat cancer patients, and stimulate new metabolic strategies for cancer prevention and therapy.

Investigating the Powerhouse

Whether cancer cells have functional mitochondria

has been a hotly debated topic for the past 85 years. It was argued that cancer cells don't use mitochondria, but instead use glycolysis exclusively; this is known as the Warburg Effect. But researchers at the Jefferson's KCC have shown that this inefficient method of producing energy actually takes place in the surrounding host stromal cells, rather than in epithelial cancer cells. This process then provides abundant mitochondrial fuel for cancer cells. They've coined this the "Reverse Warburg Effect," the opposite or reverse of the existing paradigm.

To study mitochondria's role directly, the researchers, including co-author and collaborator Federica Sotgia, Assistant Professor in the Department of Cancer Biology, looked at mitochondrial function using COX activity staining in human breast cancer samples. Previously, this simple stain was only applied to muscle tissue, a mitochondrial-rich tissue.

Researchers found that human breast cancer epithelial cells showed amplified levels of mitochondrial activity. In contrast, adjacent stromal tissues showed little or no mitochondrial oxidative capacity, consistent with the new paradigm. These findings were further validated using a computer-based informatics approach with gene profiles from over 2,000 human [breast cancer](#) samples.

It is now clear that cancer cell mitochondria play a key role in "parasitic" energy transfer between normal fibroblasts and cancer cells, fueling tumor growth and metastasis.

"We have presented new evidence that cancer cell mitochondria are at the heart of tumor cell growth and metastasis," Dr. Lisanti said. "Metabolically, the drug Metformin prevents cancer cells from using their mitochondria, induces glycolysis and lactate production, and shifts cancer cells toward the conventional 'Warburg Effect'. This effectively starves the cancer cells to death".

Personalized Treatment

Although COX mitochondrial activity staining had never been applied to cancer tissues, it could now be used routinely to distinguish cancer cells from normal cells, and to establish negative margins during cancer surgery. And this is a very cost-effective test, since it has been used routinely for muscle-tissue for over 50 years, but not for cancer diagnosis.

What's more, it appears that upregulation of mitochondrial activity is a common feature of human breast [cancer cells](#), and is associated with both estrogen receptor positive (ER+) and negative (ER-) disease. Outcome analysis indicated that this mitochondrial gene signature is also associated with an increased risk of tumor cell metastasis, particularly in ER-negative (ER-) patients.

"Mitochondria are the 'Achilles' heel' of tumor cells," Dr. Lisanti said. "And we believe that targeting mitochondrial metabolism has broad implications for both cancer diagnostics and therapeutics, and could be exploited in the pursuit of personalized [cancer](#) medicine."

Provided by Thomas Jefferson University

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