Researchers unlock key to personalized cancer medicine using tumor metabolism

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Identifying gene mutations in cancer patients to predict clinical outcome has been the cornerstone of cancer research for nearly three decades, but now researchers at the Kimmel Cancer Center at Jefferson have invented a new approach that instead links cancer cell metabolism with poor clinical outcome. This approach can now be applied to virtually any type of human cancer cell.

The researchers demonstrate that recurrence, metastasis, and poor clinical outcome in breast cancer patients can be identified by simply gene profiling cancer cells that are using ketones and lactate as a food supply.

These findings are reported in the April 15th online issue of *Cell Cycle.* The investigators are calling this new approach to personalized cancer medicine "Metabolo-Genomics."

High-energy metabolites have long been suspected to "fuel" aggressive tumor cell behavior. The researchers used this premise to generate a gene expression signature from genetically identical cancer cells, but one cell group was fed a diet of high-energy metabolites. These lactate- and ketone-induced "gene signatures" then predicted recurrence, metastasis, and poor survival.

So, it appears that what cancer cells are eating determines clinical outcome, not necessarily new gene mutations.

Michael P. Lisanti, M.D., Ph.D., 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 at Jefferson, together with other researchers, found that treatment of human breast cancer cells with high-energy metabolites increases the expression of genes associated with normal stem cells, including genes upregulated in embryonic and neural stem cells.

What's more, lactate and ketones were found to promote the growth of normal stem cells, which has critical applications for stem cell transplantation and for a host of different human diseases. It appears that these metabolites increase "stemness" in cancer cells, which drives poorer outcomes.

"Tumors that are using the body's own nutrients (lactate and ketones) as "fuel" have a poorer outcome for patient survival, a behavior that now can be used to predict if a patient is at a high-risk for recurrence or metastasis," Dr. Lisanti said. "This is getting to the heart of personalized cancer medicine. Now, we have identified a panel of biomarkers that directly links cancer metabolism with targeted cancer therapy."

These findings suggest, according to the authors, that high-risk cancer patients (those whose cancer cells use high-energy metabolites) can be treated with new therapeutics that target oxidative mitochondrial metabolism, such as the antioxidant metformin, a drug that is also used to treat diabetes.

"Knowing the gene signatures of patients whose cancer cells are "eating" these metabolites (lactate and ketones) for fuel is a pivotal piece of new information that we can use to diagnose and treat cancer patients," said Martinez-Outschoorn, M.D., of the department of Medical Oncology at Thomas Jefferson University, and the lead author of the paper. "It's not just that we know those patients will have poor survival; we know that

those patients are using mitochondrial metabolism, which is the type of energy metabolism that we should be targeting with new anti-cancer drugs."

The researchers propose that this new approach to diagnosis and subsequent treatment be called "Metabolo-Genomics" since it incorporates both cell metabolism and gene transcriptional profiling. This strategy could now be used to direct which patients receive a particular "tailored" anti-metabolic therapy.

Genetic markers, like expression of the mutationally activated HER2 gene, provide biomarkers that can be used to identify breast cancer patients at high-risk for recurrence or metastasis, and to modify their subsequent treatment with targeted therapies (i.e., herceptin, a drug used in aggressive breast cancers). But with "Metabolo-Genomics," it is now about using "global" cancer cell metabolism for these predictions.

"Just by feeding cancer cells a particular energy-rich diet, it changes their character, without introducing mutations or altering their genetic profile," Dr. Lisanti said. "We've only fed them high energy nutrients that help them to use their mitochondria, and this changes their transcriptional profile. It's a new biomarker for "lethal" cancers that we can now treat with the right drugs, such as the anti-oxidant metformin."

Dr. Lisanti and his colleagues believe that tumor metabolism is the new big picture for understanding how cancers undergo recurrence and metastasis.

Provided by Thomas Jefferson University

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