“Reversed” Krebs Cycle Can Feed Tumors

Cancer cells with mitochondrial mutations can ramp up the withdrawal of various intermediates from the Krebs cycle

An unusual metabolic pathway, found only in the mitochondria of some tumors, might provide a target for cancer-fighting drugs. The pathway, identified by researchers at the University of Texas (UT) Southwestern Medical Center, involves the effective reversal of the citric acid cycle, also known as the Krebs cycle.

Contrary to conventional wisdom, the mitochondria of most cancer cells function normally. Instead of primarily producing energy (as in normal cells), certain cancer cells ramp up the withdrawal of various intermediates from the Krebs cycle to churn out macromolecular precursors essential for rapid cell growth.

Ralph DeBerardinis, MD, PhD, assistant professor of pediatrics at UT Southwestern, and colleagues at Northwestern University and the National Cancer Institute set out to study how these precursors were made in a subset of cancer cells that have mutations preventing them from using the normal oxidative pathway of the Krebs cycle.

In a study published in *Nature*, the team analyzed human osteosarcoma cells with genetically modified mitochondrial DNA and with patient renal cell carcinoma cells that had a naturally occurring mitochondrial mutation. The scientists found that these cells use the enzyme isocitrate dehydrogenase in a reductive carboxylation to generate the citrate they need to produce acetyl-coenzyme A for lipid synthesis as well as other Krebs cycle metabolites and related macromolecular precursors.

“It’s not really a reverse cycle,” says DeBerardinis. “But it’s as if each of these enzymes is working in reverse of what we see in the textbook.”

Because the reductive carboxylation pathway does not exist in cells with normal mitochondria, DeBerardinis says, it could lead to a cancer cell-specific therapy. But, he cautions, the pathway doesn’t exist in every cancer cell, and scientists don’t yet know how to shut it down.

Two other research teams found the same changes in macromolecular synthesis while studying metabolism in hypoxic cancer cells. DeBerardinis notes that most solid tumors contain a subset of hypoxic cells, making it likely that many tumors take advantage of them.

One team, which published its results in the same issue of *Nature*, consisted of researchers from Massachusetts Institute of Technology, the University of Coimbra in Portugal, Massachusetts General Hospital, and Dana-Farber Cancer Institute. The second team, based at Memorial Sloan-Kettering Cancer Center and the University of Pennsylvania, reported its work in *PNAS*. 
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