

Energy Boost: The Warburg Effect Returns in a New Theory of Cancer

In 1930, German biochemist Otto Warburg, M.D., proposed that cancer was caused by altered metabolism—deranged energy processing—in the cell. Warburg, winner of a Nobel Prize in 1931, is now considered by many to be the greatest biochemist of the first half of the 20th century. His cancer theory, though, mostly fell on deaf ears. Altered metabolism “may be a symptom of [cancer], but not the primary cause,” wrote fellow biochemist and Nobelist Hans Krebs, M.D., Ph.D., echoing the majority viewpoint. Warburg went to his grave in 1970 insisting he was right, but for 30 years his cancer theory appeared to be buried along with its originator.

Now Warburg’s theory is enjoying a resurrection. Two prominent cancer biologists contend that a shift in energy production from oxidative phosphorylation to glycolysis—the so-called “Warburg effect”—is a fundamental property of cancer cells, not just a byproduct of the cell’s transformation into cancer. “We think it’s a requirement of transformation,” said University of Pennsylvania cancer biologist Craig Thompson, M.D. “You can’t become fully transformed until you’ve had this shift.” If Thompson is right, the implication is enormous: a whole new area of vulnerability for cancer cells, one that promises novel targeted treatments. “Can we exploit any of this for therapeutic reasons?” asked Chi Dang, M.D., Ph.D., a cell biologist at Johns Hopkins University Medical School in Baltimore who is doing similar work. “The answer is going to be yes.”

But there is hardly consensus on that viewpoint. Cancer biologist Robert Weinberg, Ph.D., of the Whitehead Institute at the Massachusetts Institute of Technology in Cambridge, is one prominent skeptic. “To date, the weight of evidence indicates that the shift to ‘aerobic glycolysis’ is an epiphenomenon of cell transformation rather than a

causally important process,” he wrote in an e-mail. Weinberg, though, concedes that Thompson “may have some new evidence [for] a causal role.”

Power Supply

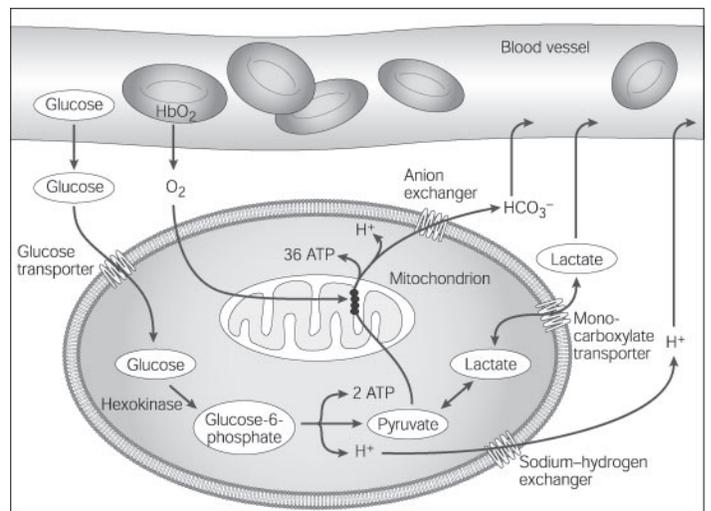
More than 60 years have passed since biochemists detailed the two main ways to generate energy, in the form of adenosine triphosphate (ATP), in normal cells: oxidative phosphorylation in mitochondria and glycolysis in the cytoplasm. All cells use both pathways but rely overwhelmingly on oxidative phosphorylation, switching to glycolysis at times of oxygen deprivation. (Marathon runners and other endurance athletes benefit from this shift.) Warburg showed that many tumors relied on glycolysis even in the presence of oxygen—the Warburg effect. “He made the fundamental observation that holds up today,” said Thompson. But the true reasons for it, Thompson added, eluded Warburg.

Warburg thought cancer was caused by defects in oxidative phosphorylation, or “respiration,” in the mitochondria, forcing the cell to revert to a more “primitive” form of energy generation—glycolysis. In his view, this switch caused such cells to become undifferentiated and cancerous. But evidence for defective respiration in cancer cells has been scant. Thompson’s model, on the other hand, links the Warburg effect not to mitochondrial defects but to

mutations in signaling pathways that govern glucose uptake into cells.

Those mutations “deregulate nutrient uptake, and that [deregulation] is a primary and driving force in cellular transformation,” Thompson said. “Once cells are autonomous for their ability to take up nutrients, they’re no longer dependent on [the] extracellular environment ... and that explains all the shift to glycolysis.” Such transformed cells take up glucose continuously, generating energy in the cell—energy used to drive cell division and growth.

Glycolysis produces only two ATP molecules per glucose molecule, compared with 38 for complete oxidation. But for a cancer cell, “It’s actually highly efficient, if the thing to do is produce ATP as fast as you want to supply growth and proliferation,” Thompson said. “If you want to get ATP quickly, you do that by increasing the glycolytic rate.” And oxidative phosphorylation, Thompson added, doesn’t shut down completely.



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Blood delivers glucose and oxygen to cells. Glucose is ultimately converted to pyruvate, generating two ATP per glucose. In the presence of oxygen, pyruvate is oxidized to HCO₃⁻, generating 36 additional ATP per glucose. In the absence of oxygen, pyruvate is reduced to lactate, which is exported from the cell. Aerobic glycolysis was first described by Otto Warburg almost 7 decades ago. (Source: Nat Rev Cancer 2004;4:891-9.)

The glycolytic shift is one way to explain why positron emission tomography (PET) is so good at picking out malignant and fast-growing tumors and metastases. The test uses a radiolabeled glucose analogue to track glucose uptake by tumors.

Activation of the Akt kinase pathway is, in Thompson's view, the main driver of the Warburg effect. In experiments reported in the June 1 issue of *Cancer Research*, Thompson found that activated Akt stimulated aerobic glucose metabolism in glioblastoma cell lines and that the cells then died when glucose was withdrawn. Akt activation "makes the cell independent of the normal signal transduction that controls its biology," Thompson said. "We believe that's a fundamental shift in the way we should be thinking about cancer."

Such a shift has yet to take place. Most cancer researchers believe that Akt acts mainly on cell growth, proliferation, and angiogenesis, not glucose metabolism. "When we first started proposing this, quite honestly I think most people just thought we were off the deep end," Thompson said. But the advantages of deregulated glycolysis to a cancer cell, he says, are obvious. "If you put more fuel in, things will work more efficiently," Thompson explained. "The deregulation of the Akt pathway [is] simply upregulating your ability to take up nutrients, to conserve amino acids and lipids ... to fuel cell growth."

Thompson's views are iconoclastic, but he's not the only prominent scientist to place metabolism at the center of carcinogenesis. Dang, now vice dean for research at Johns Hopkins, showed in 1997 that the *myc* oncogene can turn on glycolysis—a surprising finding, since most scientists assumed that cell metabolism is self-regulating. Dang now says that a shift to glycolysis in most cancers is "a necessary component for tumorigenesis. Any component of a very complex network is not going to be sufficient, but certainly it's necessary."

To claim that the glycolytic shift leads to cancer remains, for now, scientific heresy. To gain general acceptance of their theory, Thompson and Dang must first show that the Warburg effect is not

just a response to the tumor's environment. Specifically, they must demon-



Dr. Craig Thompson

strate that it's not just a way for the cell to adapt to the hypoxia—shortage of oxygen—typically found in the tumor core. "There's a camp out there that says, 'Ah, this is all reactive,'" Dang said. "That is, it's all response to hypoxia."

Hypoxia became a major field of cancer research when Johns Hopkins molecular biologist Gregg Semenza, M.D., Ph.D., first identified hypoxia-inducible factor 1 (HIF-1) in 1991. Semenza and others later showed that HIF-1 regulates a multiplicity of genes, including all of the glycolytic enzymes. HIF-1 (and glycolysis) can be induced not only by hypoxia, Semenza has shown, but also by defects in the Akt pathway even under aerobic conditions. The cancer cell, Semenza speculates, anticipates hypoxia. Hardwiring HIF-1 this way, he says, is "a mechanism to ensure that the tissue will receive adequate oxygenation during ... periods of growth."

The challenge HIF-1 poses for the Thompson and Dang models is that its activation is tied to hypoxia. So HIF-1-induced glycolysis is a reactive process, and does not "cause" the cancer. Hypoxia does induce a glycolytic shift by means of HIF-1, agrees Thompson. But HIF-1, he insists, "is not the primary cause of the high rate of glucose uptake in tumors." Ongoing experiments, he suggests, will confirm that the glycolytic shift in cancer happens independent of hypoxia. That's crucial to make the case for causation.

Dang, for his part, says that unpublished experiments from his group show that *myc* can drive glycolysis in the absence of HIF-1. Semenza himself is noncommittal on this key question, but he finds Dang's data convincing. "Clearly the regulation of the glycolytic enzymes and glucose transporters is not exclusively through HIF-1," he said.

Thompson's model, Semenza added, is "a really important one for looking at potential ways to target cancer cells."

Into the Clinic

Biotechnology companies, more than basic researchers, have enthusiastically embraced the new view of glycolysis. "We think upregulation of glycolytic activity is an essential feature of cancers as they progress," said Robin Kral, vice president of Reata Discovery, a Dallas biotechnology company. In September, Reata licensed compounds called asymmetric bisimidazoacridones that appear to block Akt. Reata is also working on inhibitors of the proton pump v -ATPase, which acts to deacidify the cytosol in cancer cells.

Threshold Pharmaceuticals, a South San Francisco biotech company, has coined the term "metabolic targeting" to give cachet to the new treatment strategy. Evidence linking the Warburg effect to oncogenes "is very solid," said Threshold president George Tidmarsh, M.D., Ph.D. "We know, down to exquisite molecular detail, how cancer cells regulate glycolysis." Threshold's leading compound, glufosfamide, just entered phase III testing in pancreatic cancer. Threshold has another metabolic agent, 2-deoxy-D-glucose—the same molecule that, in radiolabeled form, is used in PET imaging—in phase I studies. (It works by replacing glucose and shutting down glycolysis.) A third agent, TH-070, which blocks a key glycolytic enzyme, is in a phase II study in benign prostatic hypertrophy.

To these companies, the question of whether glycolysis is a cause of cancer or a byproduct is a minor concern. Either way, they see the Warburg effect as vital for the cancer cell's survival and growth. But validation of the controversial Thompson and Dang models could represent a fundamental change in the view of cancer. "Is it the whole story?" Thompson asked. "No. There are other genes that control growth [and] control DNA mutation rates. They are equally important ... but I think this is another big stool on which the transformation process sits."

—Ken Garber