



Fat Starves Cancer

by Dr. Kelly J. Gibas



WHO IS OTTO?

After billions of dollars trying to map the human genome with hopes of unlocking the 'mystery' behind cancerous mutations, oncology is coming back full circle to cancer as a metabolic disease. President Nixon declared war on cancer over 40 years ago. Since 1981, the mutation theory of cancer has been solidly in place and guiding research, yet despite the enormous amounts of money, time, and energy that have been poured into cancer research, we continue to lose the war against this killer disease. 1500 Americans die every day from cancer. The latest push by the NCI was called the Cancer Genome Atlas Project. Its mission: "To systematically explore the entire spectrum of genomic changes involved in more than 20 types of human cancer." The goal of this ambitious (and expensive) project was to once and for all, find and sequence all of the genetic mutations responsible for cancer. But so far, the search for causative mutations has remained elusive – in fact, to date, the data suggests that mutations are not involved in ways previously assumed. *One sentence that is worth repeating can sum up the sequencing data from the Cancer Genome Atlas Project – 'No mutation has yet to be identified that is reliably diagnostic of any type of cancer.'* So, the field of cancer research is slowly returning to the discoveries of a 1924 Nobel Prize winning German biochemist, Otto Warburg. Warburg is perhaps the great granddaddy of the metabolic theory of cancer with his brilliant discovery of "aerobic glycolysis." As he so eloquently discovered...cancer cells, even in the presence of adequate oxygen, love to ferment sugar in the cytoplasm of the cell. *Cancer cells are sugar addicts!*

CANCER'S SWEET TOOTH

Cancer has a sweet tooth; in fact, researchers, like Dr. Thomas Seyfried of Harvard Medical School and author of *Cancer As a Metabolic Disease*, say cancer cells actually revert to a primitive form of cell life, which ferments glucose...like a fungus...instead of respiring with oxygen in the mitochondria like normal cells. And cancer cells have a *voracious* appetite for sugar; glucose burned with oxygen in the mitochondria will produce 36 molecules of energy in the form of ATP. Glucose fermented in the cytoplasm without oxygen only produces 2 molecules of ATP with *loads of lactate waste left behind*. This requires the cancer cell to digest 18x as much glucose to yield the same energy as a normal cell... *yes, cancer has an appetite for sugar*; but, the story doesn't stop there. The pile of lactate left behind by the cancer's fermentation is not wasted. In fact, the liver recycles the waste and converts it into *new sugar!* The lactic acid, through the process of gluconeogenesis, is converted to more glucose to feed the sweet tooth of the cancer. In addition, some of this new sugar produced through the lactic acid cycle is shunted into cellular growth (PPP shunt) where new RNA and DNA are assembled into 'daughter cells'...leading to the cancer's growth and proliferation.



This “reserve” system of *fermentation-lactate-gluconeogenesis-new sugar* was designed as an energy backup system for anaerobic states of hypoxia (low oxygen) such as high intensity exercise where the muscle’s demand for fuel exceeds the availability of oxygen. In this situation, the production of new sugar by the liver is adaptive and the cycle of respiration is quickly reset once the oxygen levels are restored. However, cancer is a different story... there’s no shortage of oxygen. Although aerobic glycolysis and anaerobic glycolysis are similar, lactic acid is produced in both situations, aerobic glycolysis arises in tumor cells from damaged respiration whereas anaerobic glycolysis arises in normal cells from the absence of oxygen. Oxygen will reduce anaerobic glycolysis and lactic acid production in most normal cells (Pasteur effect), the continued production of lactic acid in the presence of oxygen can represent an abnormal Pasteur effect. *This is the situation in most tumor cells. As Warburg discovered, aerobic glycolysis, arising from damaged respiration, is the single most common phenotype found in all cancer.*

THE RETROGRADE SIGNAL

What is causing a cancer cell to permanently revert to this primitive, ancient form of fermenting? Seyfried, and others aligned with the metabolic theory, say an SOS signal is being sent from the cell’s mitochondria to the nucleus; it’s a “retrograde” *signal of distress*, which turns on ancient pathways of cellular preservation. *This archaic pathway of survival reverts the cell away from respiration with oxygen and over to sugar fermentation.* In addition, the retrograde signal has a cascading effect within the cell’s nucleus... it triggers an overexpression of the mTOR enzyme pathway for growth/proliferation and represses the AMPK pathway responsible for many of the functions of programmed cell death and the maintenance of cell polarity.

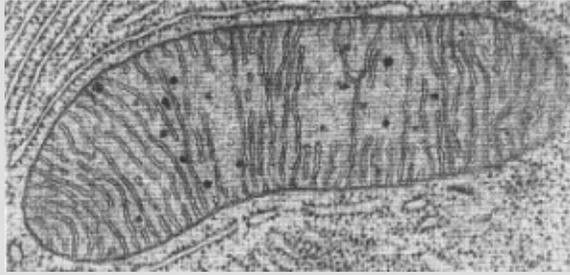
Long story short...the retrograde signal is a survival mechanism, which turns on uncontrolled growth and turns off apoptosis (selective death) of pre-cancerous cells. Hence, in the metabolic theory, cancer is acquired *epigenetically* rather than *genetically*. So...*what is flipping the retrograde switch?* To explore the answer, we must examine the mitochondria of the cell to find some convincing clues.

CELLULAR POWER PLANT

Oxidative energy production takes place in a cellular organelle called the mitochondria. The mitochondria are known as the cellular “power plants.”

A healthy cell produces 89% of its energy using oxygen, and only 11% through non-oxidative metabolism (non-oxidative metabolism is also known as “fermentation”). Oxidative energy production is far more efficient than fermentation. Almost 20 times more energy is released when glucose is completely oxidized, as opposed to when it is fermented.

Mitochondria, like the nucleus, have a double membrane. The outer membrane is fairly smooth. But the inner membrane is highly convoluted, forming folds called cristae. The cristae greatly increase the inner membrane's surface area. *It is on these cristae that food (glucose or fatty acids) combines with oxygen to produce ATP – the primary energy source for the cell.*



Healthy Mitochondria. Note the abundant looping structures inside the mitochondria (cristae), this is where all energy is produced through oxidative pathways.

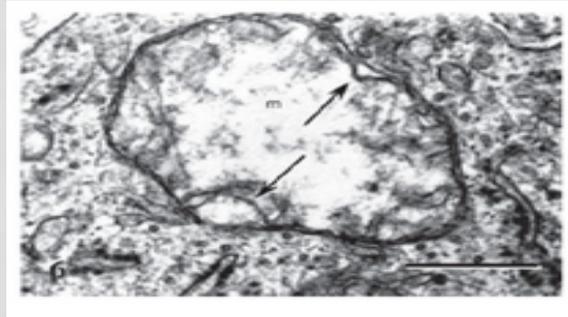


Image of a mitochondria from a cancer cell. Note the almost complete absence of cristae.

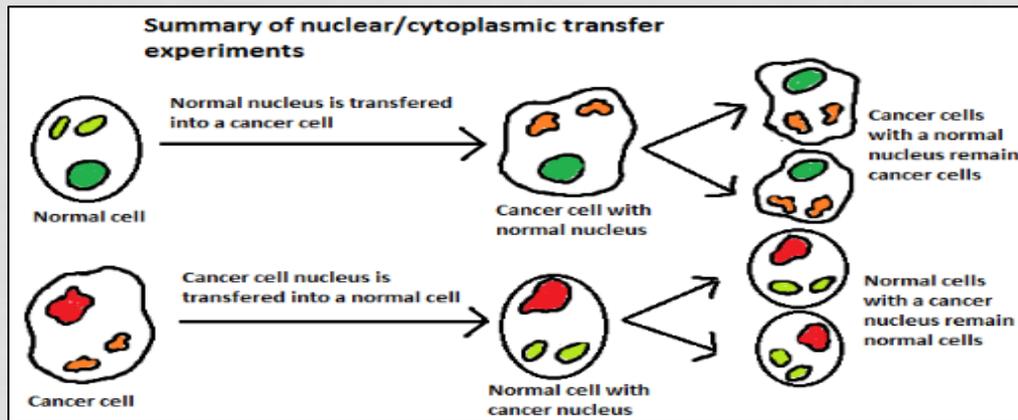
It is well established that once a cell has an impaired ability to produce energy through oxidative pathways, the genomic instability (increased potential for DNA mutations to occur), that accompanies tumor development, inevitably follows. *However, as Seyfried argues, the genomic instability of the cell appears to be a secondary consequence, or an epiphenomenon, to the true cause of the cancer, metabolic dysfunction.* Once the mitochondria acquire a threshold degree of damage, and the cell reverts to fermentation to obtain energy, cancer has begun.

Emerging evidence reveals that all of the hallmarks of cancer can be explained by mitochondrial damage followed by a shift to non-oxidative energy metabolism. *Once the oxidative energy generating capacity of the cell is impaired, the cell undergoes a dramatic transformation; important oncogenes (cancer causing genes) are switched on (retrograde signaling), initiating the uncontrolled proliferation that is the hallmark of the disease.*

LEARNING FROM THE HYBRID

In fact decades ago, brilliant studies of cytoplasmic transfer proved that it was in fact the mitochondria of the cell, not the nucleus (DNA) that initiated cancerous growth.





A diagram summarizing a series of experiments conclusively determining that it is the mitochondria, and not nuclear DNA, that causes cancer. A transplanted cancerous nucleus ***did not*** initiate cancer in a healthy cell.

In brief, the experiments consisted of transferring the nucleus (where the DNA resides) of a cancer cell into a healthy cell that has had its nucleus removed. The newly created hybrid cell had the genetic material of a cancer cell, with all of its defects, but now had the healthy mitochondria of a normal cell. Intuitively, if the origin of cancer was indeed mutations to DNA, the newly created hybrid cells, that still retained all of the mutations within the nucleus, should be tumorigenic. But they were not! They were perfectly healthy! These experiments were carefully executed, with strict controls, and were found to be very reproducible. Experiments like these provide irrefutable evidence – ultimately proving that DNA mutations are not driving cancerous growth; it's the mitochondria.

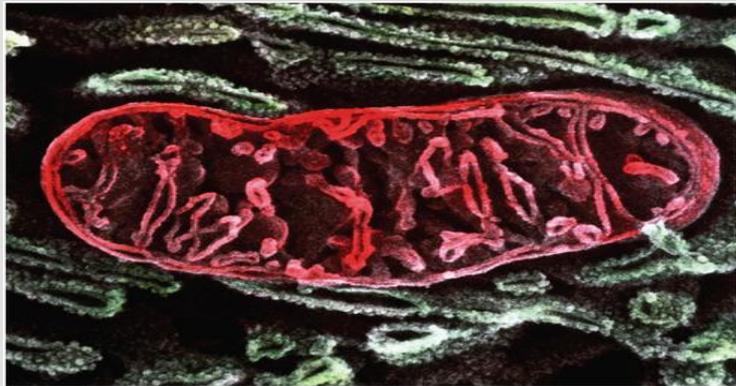
THE KREB'S CYCLE

All cells must produce energy to survive. Hans A. Krebs first elucidated the process of cells converting food into energy, the Citric Acid Cycle (Krebs Cycle), in 1937. Krebs proposed a specific metabolic pathway within the cells to account for the oxidation of the basic components of food – carbohydrates, protein and fats – for energy. The Krebs' cycle takes place inside the mitochondria or the 'power plant' of cells and provides the energy required for the organism to function.

Mitochondria are found in all cells in the human body, with the exception of mature red blood cells. The primary function of these tiny organelles (each cell contains between 500 and 2,000 mitochondria) is to convert energy found in nutrients and store the energy in the form of adenosine triphosphate (ATP). ATP is the universal energy-yielding molecule used by enzymes to perform a wide range of cellular functions. Humans cannot survive, even for a second, without a constant supply of ATP.

In order to carry out energy conversion, mitochondria require oxygen. The purpose of the respiratory and circulatory systems is to deliver oxygen to the tissues for use by mitochondria, and to eliminate carbon dioxide. *The consumption of oxygen by mitochondria is called cellular respiration.*





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NUTRITION AND HEALTHY MITOCHONDRIA

Mitochondria are the organelles in all cells that breakdown nutrients and produce energy for the body's myriad of functions. *Nutrition plays a critical role in the process of mitochondriogenesis (creation of new mitochondria); and, poor nutrition with resulting insulin resistance can subsequently lead to serious health problems.* For example, with impaired metabolism such as insulin resistance, pre-diabetes or diabetes, less glucose is able to get into the cell's mitochondria to produce energy -- that's why many diabetics get tired easily and remain fatigued throughout the day, wanting to take a nap or go to sleep... *a consequence of impaired mitochondrial functioning.* Hence, diabetics/pre-diabetics will rely heavily on the liver's production/recycling of glucose (Cori Cycle) as their impaired metabolism prevents fat burning in the fasted state, which leads to inflammation and lipo-toxicity (inability to oxidize fatty acids) causing more insult to mitochondrial membranes. Likewise, diabetics have smaller mitochondria and fewer of them. And, the children of diabetics, even if not diabetic, have fewer and smaller mitochondria. Furthermore, studies suggest a strong genetic predisposition toward mitochondrial defects and its occurrence in the 'pre-diabetic' state. Studies in humans showed similar down-regulation of metabolic and mitochondrial pathways in obesity and insulin resistance. *Making diabetes/obesity/insulin resistance known and recognized risk factors for cancer.*

The most powerful and proven ways to increase the number and the health of mitochondria (biogenesis) in the body is long-term calorie restriction (fasting), the use of fatty acids for fuel (ketosis/beta-oxidation) and exhaustive physical activity (HIIT). Does this sound familiar?

WHAT ABOUT BOB?

So, what's the benefit of a BOB diet... *Sugar is the Achilles heel of cancer!* Cancer cells have damaged mitochondria with an absence of cristae, the looping structures inside of the mitochondria that produce energy through oxidation; the damaged cristae forces glucose to ferment in the cytoplasm of the cell. As we flux our diets away from sugar (carbs) and over to fats/protein, we bypass the loop of glycolysis and *literally prevent aerobic glycolysis*; fatty acids enter the cell using a separate fuel transporter. Fat metabolizes directly in the mitochondria. In fact, Seyfried in his book *Cancer as a Metabolic Disease* boldly encourages sugar restriction for cancer prevention... *"The pre-cancerous cells that we all have in our bodies undergo programmed cell death from: two-48 hour fasts or 7 days of a ketogenic diet per calendar year."*

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