Mitochondrial Rescue - Turning cancer cells off

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Professor Otto Warburg of the Max Planck Institute won a Nobel prize for his discoveries of how the human body uses sugars in health and in disease. In his seminal work 'On the Origin of Cancer Cells" published in 1956 he described the "irreversible" damage to respiration as a metabolic process in malignant cells, resulting in a shift to anaerobic glycolysis. Observing well oxygenated cancer cells with abnormally high glycolysis and lactate production suggested to him that defects in mitochondrial ("grana") functions are at the heart of the transformation of normal cells to malignant cells (Warburg 1956).

The "Grana" of Warburg are today called *mitchondria*. Of note is the fact that mitochondrial DNA comes from your mother's egg, and contains no DNA from your father, whereas the nuclear DNA is a mix from both parents. The most important consequence of mitochondria incurring compromised oxidative capacity is loss of programmed cell death , or the apoptosis "off-switch" for old or mutated cells. This is a process that allows a cell to shut down and be recycled after 50 doublings, or earlier if the nuclear DNA becomes mutated and damaged. It prevents making two bad cells from an old or damaged cell. The cell membranes turn inside out, the cell is recycled, and a local stem cell wakes up out of dormancy to make a fresh new cell with the counter reset to zero. As we lose the ability to weed out bad cells, the potential for mutations that lead to cancer increase.

Cancer cells with mitochondrial failure become very hard to kill, and will continue to accrue mutations which make the cancer more invasive, hypermetabolic, and adaptable to metastatic environments. It is the restoration of this apoptotic switch by the oxidative stress of chemotherapy and radiation which make these the most widely applied and generally successful therapies for most cancers, which otherwise have quite different biology.

Warburg's hypothesis is often misinterpreted to support the idea that oxygen is cytotoxic to cancer, and cancer cannot arise in a high-oxygen environment. It is also taken to imply that cancers originate only in an acid-environment, and that alkalizing is an effective cytoxic therapy for cancer. These myths have failed to unlock the potential for targeting mitochondria to cure cancer suggested by this seminal work (Wenzel 2004).

Mitochondria of tumour cells lose their ability to perform oxidative phosphorylation. Cellular energy metabolism shifts to anaerobic glycolysis.

Early on in the growth of a tumor, at about 2 mm in diameter, oxygen depletion begins to occur in the center of these cell clusters. Oxygen doesn't freely diffuse this far into tissues, and the hyper-metabolic nature of cancer cells depletes what is there at an abnormal rate. The hypoxic cells send out distress signals, summoning immune and regulatory cells to reestablish blood inflow by neo-angiogenesis. A chronic inflammation repair process is created, but unable to fix the genetic problems of the transformed cells, it becomes "the wound that will not heal". Growth factors and other immune cell products support continued tumor growth, and any immune-cell going into attack

mode against cancer cells are shut off by cytokines such as transforming growth factor TGF-B1. The immune system is now working for the cancer. They can even cannabilize fibroblasts and other cells to give spare parts to the suffering cancer cells.

The new blood vessels in tumors do not remodel into efficient capillary beds, as is expected in normal tissue repair. As cancerous tumors mature, leakiness of the blood vessels creates a build-up of fluid pressure. Oncotic pressure eventually crushes the vessels, creating pockets of severely low oxygen, called hypoxia. If the oxygen tension falls to zero, called anoxia, like any human cell, the cancer cells will die. Sub-lethal hypoxia can cause mitochondria membranes to become hyper- polarized, and oxidative metabolism shuts off. The cancer cell adapts by starting to process sugars into energy without oxygen, through the whole of the cell cytoplasm. This *anaerobic glycolysis* creates lactic acid as a waste product, and at this point the cancers become highly acidic.
This fermentation of sugars, very similar to how yeast generate energy, is not very efficient at creating ATP. This may on the surface appear to create a disadvantage for the cancer cell, but in fact it creates an abundance of building blocks for proteins, fatty acids and nucleic acids desperately needed by the cancer cells to maintain their overly-rapid growth rate (Bui 2006).

Most of the anabolic processes required for accelerated growth rate are accomplished by increased glycolysis. Anaerobic glycolysis is supported by replenishing TCA cycle intermediates, such as acetyl-CoA and citrate, a process called *anaplerosis* (DeBerardinis 2008, Kroemer 2008, Ramos-Montoya 2006). Anaplerosis sustains TCA cycle function by either converting pyruvate to oxaloacetate or by breaking down glutamine into alpha-ketoglutarate by glutaminolysis (DeBerardinis 2007).

The critical shift between glycolysis and oxidative phosphorylation is controlled by the relative activities of two enzymes, pyruvate dehydrogenase (PDH) and lactate dehydrogenase (LDH), that determine the catabolic fate of pyruvate . Hypoxia inducible factor (HIF) can induce LDH activity while inhibiting PDH activity by stimulating its inhibitor PDK1 (Kim 2006, Wigfield 2008). Hypoxia results in hydrogen peroxide (H2O2) and nitric oxide (NO) generation, which in turn results in hydroxyl radicals and super oxides. Jurasunas postulated that this scenario results in depletion of the potent antioxidant manganese-super oxide dismutase MnSOD, which destroys the respiratory chain in hypoxic mitochondria (Jurasunas 2006).

As free radicals of oxygen accumulate there is an excessive uptake of lactate and pyruvate in the hypoxic mithochondria. This raises the mitochondrial membrane potential Delta -Psi-m ($\Delta\Psi m$). Cancer cells thereby have hyperpolarized mitochondrial membranes compared to normal cells, preventing them from throwing the apoptotic off-switch no matter how old or mutated they become. Hexokinase II is highly expressed in cancer cells, induced by alterations to the Ras-P13-Akt signal transduction pathway. Hexokinase binds to mitochondrial porin, suppressing the calcium channels and the potassium channel K+v1.5 (Lemasters 2006, Wallace 2005).

Lactate dehydrogenase is upregulated in tumors, favouring cancer growth via VEGF and HIF-1α, increased angiogenesis, and metastasis via direct enhancement of cellular motility (Gottfried 2006, Koukourakis 2005, Koukourakis 2006, Kulawiec 2009, Ordys 2010, Pelicano 2006, Ralph 2010, Seth

2011, Walenta 2004, Walenta 2000). Hypoxia also increases Survivin. A build-up of the electron transport molecule NADH inactivates the vital tumor suppressor gene PTEN. This activates Akt protein kinase B survival pathway, resulting in immortalization of the cancer cell.

Strategies that successfully allow mitochondria in tumour cells to once again perform oxidative phosphorylation have proven to be potent anti tumour agents.

In 2007 Bonnet, Michelakis and group at the University of Alberta tested an old drug dichloroacetate or DCA on breast cancer infested rats, and made an astonishing discovery. Based on a hypothesis that inhibiting a mitochondrial enzyme pyruvate dehydrogenase kinase or PDK might repolarize mitochondrial membranes and spark up respiration in cancer cells, they found evidence DCA might do the job, and it did indeed reverse what Warburg deemed irreversible (Bonnet 2007).

An important line in the abstract states "DCA induces apoptosis, decreases proliferation and inhibits tumor growth, without apparent toxicity." This may well apply to the rats in this study, but clear evidence of neurotoxicity and other risks to humans existed before this trial. In fact, human studies on DCA for diabetic acidosis had shown this drug was far from safe. DCA had long been listed as an environmental toxin and carcinogen by the USA Environmental Protection Agency. Release of DCA into the environment was a crime (Backshear 1975, Felitsyn 2007, Kaufmann 2006, Schaefer 2006). This impression of safety was compounded by an article that soon followed in the journal *New Scientist* claiming this drug was safe, and effective for most cancers (Coghlan 2007).

In the Globe& Mail June 2, 2007, Mikelakis warned of "severe nerve damage. People may lose their ability to walk, or speak." from impurities in DCA bought from sources such as the internet. Others reported nausea, drowsiness and peripheral neuropathy in DCA users.

There is no question DCA can reduce human tumors. DCA activates private dehydrogenase kinase, triggering an influx of acetyl-CoA into mitochondria. This drives more NADH into complex I. Superoxides that form are converted into hydrogen peroxide by manganese- super oxide dismutase. The H2O2 inhibits proton (H+) efflux, reducing mitochondrial membrane potential $\Delta\psi m$. This opens the mitochondrial transition pore (MTP), inhibiting calcium ion entry via voltage-dependent channels. Reduced intra-mitochondrial calcium (Ca++) suppresses a tonic activation of nuclear factor of activated T lymphocytes (NFAT). NFAT1 is a nuclear transcription activator similar in action to activator protein 1 (AP-1) and nuclear factor kappa B (NFκB). This reduces Kv1.5 expression, increasing potassium ion K+ efflux, reducing inhibition of caspases, and finally triggering cancer cell apoptosis.

An interesting side-note is the fact that DCA converts into *glyoxalate,* an old remedy once promoted for cancer (Biswas 1997, Herbert 1979, Ray 1997). Victor Herbert quotes the leading DCA researcher Dr. Stacpoole, as saying " the efficacy and safety of chronic dichloroacetate administration is unknown" (Stacpoole 1998).

I saw the toxicity of DCA on the nervous system for cancer patients who tried this experimental approach. I have seen cases completely disabled by the drug. Because the DCA was off- patent, it took Michelakis many months to fund a human trial. Two of my patients went to Edmonton and were enrolled, but returned to Victoria in about 2 weeks with severe neuropathy. As a result of this experience, the investigators wisely reduced the dose to 1/3 that level, and restricted its application to CNS tumors. The result was brain tumor responses with "acceptable toxicity" (Michelkakis 2010).

Does there exist a less toxic alternative for activating oxidative phosphorylation in mitochondria of tumour cells?

In 2007 I recognized the potential of this approach, awakening mitochondrial apoptosis switching through inhibition of PDK, but also saw the clinical limitations of the DCA drug. I began a search for a less harmful PDK inhibitor. I was able to find evidence that R+ alpha lipoid acid and thiamine (vitamin B-1) could do this (McKinney 2008). As we have come to expect with all natural and non-toxic approaches to cancer, single agents are rarely very potent. John Boik's excellent texts have pointed out the need to find synergistic groupings of botanicals and nutraceuticals, if we expect to create significant impact on advanced cancers (Boik 1996, Boik 2001). I can say that the clinical application of my original mitochondrial rescue plan has produced responses in cancers, including rather difficult ones such as sarcoma and lung cancer. It is certainly in need of further refinement. I do not presently see it being useful in lymphomas and leukemias. These are the natural medicines I propose for mitochondrial rescue of cancer cells, to reverse the Warburg Effect:

R+ alpha lipoic acid is a potent natural PDK inhibitor (Hagen 1999, Hagen 2002, Korotchina 2004, Li 2009, Liu 2002, Moungjaroen 2006, Simbula 2007, Wenzel 2005a, Zeigler 1999). It is used intravenously and orally for cancer, and has the added benefit of treating neuropathy.

The only other natural compound which is known to be a direct inhibitor of PDK is thiamine , or vitamin B1. Because it is fat soluble and thought to integrate better into mitochondrial membranes, we favor clinical use of benfotaimine (Babaei-Jadidi 2003, Comin-Anduix 2001, Parkhomenko 1987).

Some believe L-carnitine is key to mitochondrial restoration (Cruciani 2006, Hoang 2007, Wenzel 2005b), but it is not a PDK inhibitor, and will generate enough free radicals of oxygen to damage mitochondria further, unless accompanied by sufficient fat soluble antioxidants such as R+ ALA. In fact, the two supplements have an excellent synergy and should be given together (McCarty 2009, McMackin 2007). My clinical preference is prescription of acetyl-L-carnitine, which is fat soluble.

Co-enzyme Q-10 is widely recognized as a fat-soluble antioxidant that is clinically useful for mitochondrial disorders (Beal 1994, Berbel- Garcia 2004, Matthews 1998, Perumal 2005a, Rodriguez 2007). However, it can inhibit opening of the mitochondrial transition pore, which could counteract the DCA effect (Li 2005). My clinical experience suggests grapeseed extract is a better choice (Hu 2006).

B-vitamins are involved in energy metabolism as co-factors for many important enzymes. A B-complex seems a reasonable support for mitochondria dysfunction (Perumal 2005a, Perumal 2005b).

Indole-3-carbinol has been a most useful cancer therapy as a STAT-3 transcription factor inhibitor, and for its anti-estrogen effects. It has a potent effect on upregulation of bax in mitochondria, causing membrane depolarization and activation of apoptotic caspases (Rahman 2000, Rahman 2003).

Quercitin can increase or decrease mitochondrial membrane potential Delta Psim ($\Delta\psi m$) depending on concentration, inducing apoptosis (Kellner 2004, Kothan 2004, Yang 2006, Zhang 2005). This versatile anti-cancer agent interferes with glycolysis via reduced generation of glycolytic substrates adenosine diphosphate and inorganic phosphate (Suolinna 1975).

Gamma tocopherol is a dietary form of vitamin E that can stabilize mitochondrial membranes. It can be washed out of membranes by intake of excess alpha-tocopherol supplements. Always use the "mixed tocopherols" containing the gamma form, never just the "natural source" d-alpha tocopherol (Mahabir 2008).

Fish oils are an excellent omega 3 oil for mitochondrial membrane health, reducing mitochondria calcium levels (Hansford 1999).

Other adjuncts for mitochondrial regeneration include intense aerobic exercise (Lanza 2010), calorie restricted diets (Spindler 2010), and the diabetic drug Metformin (Suwa 2006)

SUMMARY OF MITOCHONDRIAL RESCUE PROTOCOL

- **R+ alpha lipoic acid – 300 mg tid**
- **Thiamine or benfotaimine – 80 to160 mg bid, and the full B-complex bid**
- **Acetyl-L-carnitine – 500 to 1,000 mg tid**
- **Grapeseed extract – 200 to 500 mg bid**
- **Indole-3-carbinol – 200 mg tid**
- **Quercitin – 1,000 mg bid to tid**
- **Gamma tocopherol - 40 to 80 mg, in 400 to 800 IU mixed tocopherols.**
- **A diet with ample omega 3 marine oils, olive oil, lemongrass, berries, pomegranate, grapes, apples, cabbage family vegetables, chili peppers, onions, garlic, and whole grains.**
- **Regular intense aerobic activity at least 3 times weekly, best 45 minutes daily.**

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