Mitochondrial Dysfunction, Neurodegenerative Diseases and Malignancy October 18, 2017

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INTRODUCTION: Mitochondrial dysfunction is associated with memory loss and dementia, Parkinson's disease and ALS (Amyotrophic Lateral Sclerosis or Louis Gehrig's disease) as well as with developing cancer and diabetes. Adequate energy is important for all processes of life. Entropy is the lowest energy state or the state of most disorder (like most children's bedrooms). Keeping a complex system (like our body) in a healthy state takes adequate chemical energy. This chemical energy (ATP) is produced by oxidative phosphorylation in the mitochondria (more on this later).

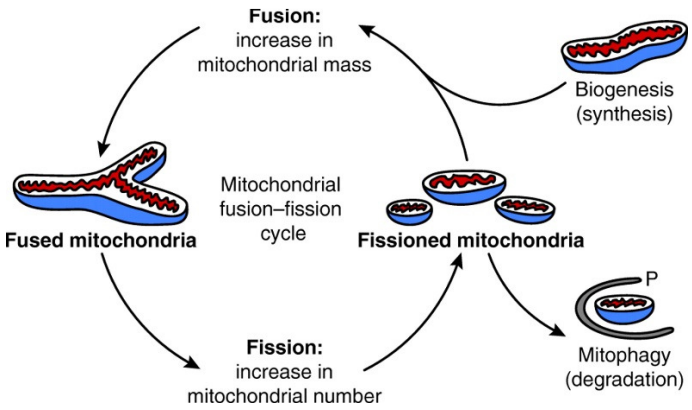
There are two things we can do to keep our mitochondria healthy, triggering the mitochondrial life cycle of fusion, fission and recycling of mitochondrial components into new mitochondria (see diagram below):

1. Exercise increases healthy oxidative stress through interval exercise (but avoid Vitamin C, which appears to block this healthy form of oxidative stress)
2. Calorie restriction:
    a. Starvation (not a ready option for most of us, particularly not for people with cancer) promotes ketosis
    b. Intermittent fasting (14 hours, 20 hours, 24 hours or more) promotes ketosis
    c. Ketogenic diet- low carbohydrate diets mimic fasting and promotes ketosis
    d. Metformin- mimics the fasting metabolism

Why do this? For a possible reduction of subsequent disease, maybe? But giving what I love most; pasta, bread, potatoes and rice, not to mention apples, oranges and bananas, etc? Not sure about that.
But more importantly, do this for an immediate improvement in our mental functioning and sense of wellbeing- now. A clearer mind may be worth it.
How to do this? www.ruled.me is a reasonable resource, which has a 30-day plan with grocery lists, recipes, meal plans and instructions on intermittent fasting. Simply stated, do a little fasting and:
Do Eat: Eggs, Leafy greens, Above ground vegetables, High fat dairy (organic heavy cream and butter), Natural oils and fats (olive oil, avocado oil, coconut oil, fish oil, grapeseed oil), Fish/Poultry/Meats, Nuts and seeds.
Do Not Eat: Bread, Pasta, Rice, Potatoes, Sugar, Honey, Sweet fruits (e.g. Apples, oranges, bananas, melons, raisins, etc.)

BACKGROUND: The following are the telegraphic high-level facts you need to move forward. The subsequent sections will fill in some of the blanks. Please see summary below for more information.

1. Mitochondria are the powerhouse of the cell. They also control apoptosis (programmed cell death of weak or abnormal cells- a good thing).
    a. Diagram of fission/fusion/recycling of mitochondria. Stimulating the lifecycle of the mitochondria promotes the production of new mitochondria, that fuse with mid-life mitochondria to renew their function, as well as promotes the recycling the older mitochondria to the lysosomes (mitophagy) to degrade them to provide the building blocks for the new mitochondria.



2. Cancer may be primarily a disorder of mitochondrial energy production (leading to increased oxidative stress) followed by somatic genetic mutations and increases in oncogene signaling (see Seifried 2015, attached)

3. Cancer cells have adapted to avoid apoptosis (programmed cell death), which is partially accomplished through further depression of mitochondrial function (Schwartz 2017)
    a. Oncogenes and oncoviruses code for proteins that suppress and or/harm mitochondria
    b. Cancer cells suppress mitochondrial function and survival
        i. Cancer cells depend on fermentation to produce ATP (energy) rather than oxidative phosphorylation (OxPhos, better known as the Krebs cycle via the mitochondria) to create ATP. Fermentation does not require oxygen but does require glucose (sugar)
        ii. This fermentation process only creates 2 ATP per glucose molecule, as opposed to the 32 ATP per glucose molecule that the mitochondria create through OxPhos.
        iii. Therefore, the PET scans for cancers light up, because PET scans measure the marked increase in glucose uptake required by rapidly proliferating cancer cells.
4. So why would cancer cells choose such an inefficient system for energy production?
    a. By-products of fermentation are lactic acid, which is toxic to normal cells and the immune system, and NADH, which neutralizes the superoxide radicals or reactive oxygen species [ROS, oxidative stress] that the remaining mitochondria produce. This protects cancer cells from oxidative stress.
    b. Fermentation also supports the pentose phosphate shunt that produces lipids and nucleic acids for cellular proliferation (the building blocks for growing more cancer cells)
    c. Lactic acid and the low oxygen state of the tumor micro-environment is toxic to normal cells and the immune cells
        i. but this is survivable by the more primitive cancer cells and particularly their stem cells, which are the most primitive forms that promote the regrowth of tumors and development of resistance to cancer chemotherapy. These cancer stem cells regrow following chemotherapy and have often become resistant to the previous chemotherapy
5. Survival of the fittest?
    a. So why do cancer cells survive and grow while normal cells die in the cancer microenvironment? Isn't this the opposite of Darwin's theory? Well, the human body is an incredibly complex organism that requires large amounts of energy to keep it healthy and to eliminate the unhealthy components (apoptosis- programed cell death). Mitochondria control much of this process. So why do cancer cells eventually take over? Because they can survive in very toxic environments because of their de-differentiation into using more primitive cell functions (like fermentation). But if you limit fermentation and increase oxidative phosphorylation, the cancer cells will move either toward death due to increased oxidative stress from the remaining mitochondria or differentiate back toward normalcy/health. Starvation, fasting and ketosis will deprive the cancer of adequate sugar thereby reducing fermentation and the production of NADH, while the ketones increase mitochondrial function and protect normal cells from oxidative stress.
    b. Immune function in the tumor microenvironment is also important in the survival or killing of cancer. In the tumor microenvironment the following conditions are found (Lussier 2016)
        i. Increased T-regulatory cells (T-regs) that mediate immunosuppression by suppressing the Th1 pathway (the Th1 pathway protects us from cancer) through IL-10 and other immunosuppressive cytokines as well as through direct cell-to-cell contact with CD8+ cytotoxic effector T-cells
        ii. Increases in other immune inhibitory checkpoints
    c. The ketogenic diet appears to reverse some of these findings with decreases in T-regs and T-reg function while there are increases in CD4+ helper T-cells and reduced IL-10 production by T-regs in response to tumor antigens and improvement in Th1 pathway function.
        i. There is increased NK-cell function as well. These cells are the natural killer cells that are part of the innate immune system that if first to recognize non-self/invaders such as viruses, fungi and bacterial as well as abnormal cells including cancerous cells.

6. To prevent, control or eliminate cancer we need to:
    a. Increase mitochondrial function
        i. Increased ROS in cancer cells increase stress and susceptibility to treatment
        ii. Increase energy via OxPhos to allow the differentiation of cancer cells back to normal cellular function or to move the cancer cells toward apoptosis
    b. Decrease fuel/glucose for cancer cells
        i. Decreased energy production because cancers primarily use glucose as fuel, as opposed to all normal tissues that can use glucose and/or ketone bodies (acetoacetate and beta hydroxybutyrate from fasting or the ketogenic diet)
        ii. Decreases NADH production (NADH neutralizes oxidative stress), which leads to increased oxidative stress in the cancer cells making them more susceptible to chemotherapy and radiation therapy and apoptosis
        iii. Decreases lactic acid production (lactic acid inhibits the normal cells and immune cells), which allows the immune system to be more active in attacking the tumor
        iv. All of this increases the sensitivity of the cancer cells to chemotherapy, radiation therapy and immune function
7. How do we do this?
    a. Intermittent fasting (for 14-20 hours per day a few days per week; more on this later), which produces ketone bodies (fuel for normal cells) and reduces available glucose and glutamine (fuel for cancer cells) while fasting
    b. Ketogenic diet, which also produces ketone bodies and reduces available glucose and glutamine. But avoid too much protein, some of which can be converted into sugar for cancer cells
    c. Exercise that produces sweat (needs to be interval exercise with oxidative stress that turns on mitochondria)
    d. A few nutritional supplements
        i. Alpha lipoic acid (see Schwartz 2017)
        ii. N-Acetyl cysteine (glutathione precursor, that reduces oxidative stress within the mitochondria)
        iii. Metformin (see O'Flanagan 2017)
        iv. Avoid large doses of Vitamin C (1,000 mg) or E (400 IU) (you want to increase oxidative stress in cancer cells). Vitamin C blocks signals for mitochondrial growth (like exercise) so if you take vitamin C 1,000 mg prior to exercise you will block the training effect
    e. Avoid excess calories/nutrition (which inhibit mitochondrial growth, division and recycling)
        i. Particularly sugar and starches, including the sweet fruits like apples, oranges and bananas) as eating these foods raise glucose and insulin/IGF1 levels (more on this later)
        ii. If the mitochondria sense excess food resources, they slow their lifecycle (fission/fusion/recycling) and thereby get old and feeble (not a good thing).
        iii. Much of the difference between the young and old populations is the number and health of our mitochondria (and Jedi warriors had elevated numbers and quality of mitochondria, hence their enhanced abilities ☺)
    f. You want to decrease inflammation, increase blood flow and increase oxygenation
        i. Avoid gluten (allergenic protein in grains), casein (allergenic protein in cow's milk), lectins (allergenic proteins in Nightshade vegetables-tomatoes, eggplant, peppers, potatoes) that can cause inflammation in susceptible people
        ii. Practice meditation, deep breathing, exercise (reduce cortisol, epinephrine, hyperglycemia and hyperinsulinemia)
8. What are the other benefits of this approach?
    a. The ketogenic diet can clear brain fog (decreased memory and ability to focus)
        i. Improves dementia, Parkinson's disease, ALS, ADHD, depression, seizures (Gano 2014)
    b. Optimize waist circumference

c. Eliminate Type 2 diabetes (and improves Type 1 diabetes)
    i. Diabetes promotes tumor growth through both the elevated blood sugar as fuel, as well as insulin and insulin-like growth factor 1 (IGF-1) that can increase tumor growth by an additional 20-40% in animal studies
d. Decreased side-effects of chemotherapy and radiation therapy by protecting normal cells from oxidative stress as they continue to have adequate mitochondria energy and reduced ROS
    i. Decreased GI side-effects of nausea and anorexia
    ii. Decreased or the lack of bone marrow suppression and low blood counts
    iii. Decreased neuropathy and possibly less "chemo-brain" and possibly the reversal of these with the combination of ketosis and alpha lipoic acid (a supplement that reverses neuropathy)

SUMMARY

1. Cancers primarily use sugar as fuel.
    a. Cancer cells have severe limitation of mitochondrial energy production and depend on fermentation of sugar as fuel. This is due to several reasons (eg. oncogenes, oncogenic viruses, mitochondrial DNA gene deletions due to ROS) leading to suppression of mitochondrial function and survival.
    b. This dependence on fermentation in cancer cells leads to the production of increased level of lactic acid in the tumor microenvironment, leading to increased toxicity to normal cells and increased invasiveness and metastases.
    c. Cancer cells have cell surface receptors (GLUT1 and GLUT3) that avidly take up glucose, even in a low glucose environment, to the detriment of surrounding normal tissues in the absence of ketone bodies.
    d. As fermentation does not require oxygen, this adaptation helps cancer cells grow even in the low oxygen states that occur in the center of rapidly proliferation cancers.
2. You can starve your cancer cells.
    a. Normal cells can use fat (ketone bodies- acetoacetic acid and beta-hydroxybutyrate) as fuel; this includes all normal cells including the brain and muscles. When you are fasting and/or in ketosis, you markedly reduce the available sugar for cancer growth but your normal cells have adequate energy and less oxidative stress because burning ketones produces less ROS.
3. Fasting and/or ketosis stresses the cancer cells because they cannot use ketone bodies as fuel; they develop increased levels of reactive oxidative species (ROS; oxidative radicals that damage tissues) but have inadequate energy or NADH to reduce the ROS, leading to increased injury, genetic mutations and susceptibility to chemotherapy and radiation therapy and eventually cell death.
4. In summary, the tumor microenvironment is hostile to healthy cells in the presence of glucose and without ketone bodies. Fasting and/or ketosis allows healthy tissues to stay healthy and puts the nutritional and oxidative stress in the cancer cells. This state reduces insulin and IGF-1, which also reduces proliferation of cancer cells.

Next Steps

What if we could avoid most cancers, rid ourselves of diabetes, and postpone neurodegenerative diseases, would we do it?

1. The evidence is accumulating the way to do this is with intermittent fasting (14-20 hours) and/or the ketogenic diet (eg. Paleo diet or the Mediterranean Hunter-Gatherer diet).
    a. Starves cancer cells, most of which require sugar as fuel
    b. Stabilizes the brain and increases focus by increasing mitochondrial number and function (as well as reducing seizures and neurodegenerative diseases), not to mention reducing insulin resistance and hyperglycemia (both stimulants of cancer)
    c. Associated with weight loss and improvement in diabetes, fatty liver, etc.
2. We are still closely related to our ancestors from sub-Saharan Africa (the original Eve, according to mitochondrial gene studies)
    a. The diet of our ancestors in sub-Saharan Africa was 60-70% fat (mostly from nuts and seeds, more in winter), 15% protein, and the balance from green leafy vegetables, some berries and a few roots.

b. Our ancestors began about 6 million years ago. Humans in our current form (homo sapiens) have existed for approximately 200,000 years, while our current structure of civilization has been for 6,000 years. Our dependence on grains such as wheat and rice are therefore a relatively recent event. This is not an adequate period for us to adjust genetically to marked change in our choices of food. Grains do allow us to gather in large communities but may have also increased the opportunity for diseases such as diabetes, heart disease and cancer.
c. There is good evidence that a diet without grains or simple carbohydrates can markedly improve glycemic control in patients with diabetes. Evidence is accumulating that it may also be helpful in the prevention and treatment of neurologic disorders and possibly malignancies.

3. Survival of the tribe depends on the survival of the most productive individuals who require the least resources
    a. Those individuals most physically active develop less disease including diabetes, heart disease and cancer. These would be those individuals who were performing more of the hunting and gathering.
        i. Exercise turns on the immune system to increase surveillance and elimination of cancer
        ii. Exercise is associated with less diabetes and heart disease
    b. Those individuals that consume less food develop less disease, as is being discussed in this manuscript
    c. The summary is, our future is determined less by our genetic make-up (our ability to procreate/reproduce) and more by what and how much we contribute to our community
4. How do we implement this?
    a. There are many sources of information on this but there have been no randomized controlled trials of one particular approach until now. Many trials are ongoing.
    b. One website that may be helpful is www.ruled.me. He discusses the diet and has a 30-day plan that includes intermittent fasting in weeks 3 and 4.
    c. I am asking my patients who have been successful controlling their malignancies (metastatic colon cancer and Glioblastoma multiforme with recurrence) with the ketogenic diet for more ideas for what to eat and how they manage their diet around their chemotherapy session.

Ketogenic diet recommendations (simple version; eat usual foods but follow these rules)
Do Eat: Eggs, Leafy greens, Above ground vegetables, High fat dairy (organic heavy cream and butter), Natural oils and fats (olive oil, avocado oil, coconut oil, fish oil, grapeseed oil), Fish/Poultry/Meats, Nuts and seeds.
Do Not Eat: Bread, Pasta, Rice, Potatoes, Sugar, Honey, Fruits (e.g. Apples, oranges, bananas, melons, raisins, etc.)

The Staying Healthy Handout (summary of Dr. Steeles approach)

Staying Healthy Handout 20170831.pd

The Warrior Diet (summary of intermittent fasting)

THE WARRIOR DIET 20170831.docx

Reversal of Neurodegenerative Disorders

Reversal of neurodegeneration 2(

Additional Reading


Seyfried Press-pulse Cancer 2017.pdf

1. Seyfried et al. Nutrition & Metabolism (2017) 14:19

Discusses the implementation of theory of cancer management into practice


Schwartz 2017 Warburg effect and C

2. http://dx.doi.org/10.1016/j.semcancer.2017.01.005

Discusses fermentation and approaches to improving mitochondrial function, including alpha lipoic acid


O'Flannagan 2017 CR KD Cancer.pdf

3. O'Flanagan et al. BMC Medicine (2017) 15:106

Discusses calorie restriction, intermittent fasting, ketogenic diet and metformin


Allen 2014 Ketosis and cancer.pdf

4. RedoxBiology2(2014)963–970

Mitochondrial oxidative stress and malignancy


Lucier 2016 KD and NK cell funtion.pdf

5. Lussier et al. BMC Cancer (2016) 16:310

Ketogenic diet as an adjuvant to increase Th-1 immune surveillance of malignancies


Seyfried Cancer Mito 2015.pdf

6. *Seyfried TN (2015) Cancer as a mitochondrial metabolic disease. Front. Cell Dev. Biol. 3:43.*

Cancer as primarily a mitochondrial energy disorder followed by somatic genetic abnormalities.


Iyikesici 2017 MSCT in breast cancer.pdf

7. İyikesici M, 2017 Efficacy of Metabolically Supported Chemotherapy

Example a case report of a patient with breast cancer treated with KD and other interventions. Also references case series of pancreatic cancer and a case of rectal cancer


Gano 2014 KD Mito and neurologic diseas

8. Ketogenic diets, mitochondria, and neurological diseases. J. Lipid Res. 2014. 55: 2211–2228.