THE BIG IDEAS

Genes vs. Metabolism
Confusion + The oncogenic paradox.

Energy Metabolism
As the root cause of cancer.

Mitochondria
Suppressing tumor growth.

Accumulation
Of mitochondrial damage.

Two Key Things
Lower glucose. Raise ketones.

Conclusions
Are pretty compelling.

Cancer as a Metabolic Disease - Journal Article

Open Access Journal Article from Nutrition & Metabolism

BY THOMAS N. SEYFRIED AND LAURA M. SHELTON · NUTRITION & METABOLISM
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> "Emerging evidence indicates that impaired cellular energy metabolism is the defining characteristic of nearly all cancers regardless of cellular or tissue origin. In contrast to normal cells, which derive most of their usable energy from oxidative phosphorylation, most cancer cells become heavily dependent on substrate level phosphorylation to meet energy demands. Evidence is reviewed supporting a general hypothesis that genomic instability and essentially all hallmarks of cancer, including aerobic glycolysis (Warburg effect), can be linked to impaired mitochondrial function and energy metabolism. A view of cancer as primarily a metabolic disease will impact approaches to cancer management and prevention."
>
> ~ Thomas N. Seyfried and Laura M. Shelton from *Cancer as a Metabolic Disease*

This is our fourth Note specifically related to cancer I created after my brother's diagnosis. The first three: *Anticancer* by David Servan-Schreiber, *Tripping over the Truth* by Travis Christofferson and *The Metabolic Approach to Cancer* by Nasha Winters.

This is actually a Note on an open access article from the scientific journal *Nutrition and Metabolism*. I have Thomas Seyfried's book (also called *Cancer as a Metabolic Disease*) but I decided to start with the 22-page journal article (7 pages of which are references) rather than the book because the book is a 400+ page textbook-like beast and I figured this would be a great place for us to start. :)

I plan to cover the book as well but wanted to share Notes on the journal article first because the 15 pages here are, as Nasha Winters says, "A must read!" I completely agree.

Thomas Seyfried is the leading research scientist making the case for the metabolic approach to cancer (vs. as we've discussed, and will discuss more in this Note, a genetic approach). He and Laura Shelton brilliantly and lucidly unpack the case for cancer as a metabolic disease. Bonus: Your brain gets a nice workout as every word is chosen wisely for peer-reviewable hardiness.

Get the article in the journal *Nutrition & Metabolism* here. (It's free.) And, if you or your family are dealing with cancer, I HIGHLY recommend you print it out. Read it. Share it with your team. (And, get a copy of Seyfried's book here.)

My printout of the of the article is almost entirely underlined and circled and marked all up. The article is incredibly coherent and packed with wisdom. I'm excited to break it down and share it in a way that's easy to grasp and practical so let's jump straight in!

> "Numerous studies show that tumor mitochondria are structurally and functionally abnormal and incapable of generating normal levels of energy."
>
> ~ Thomas Seyfried and Laura Shelton

CONFUSION AND "THE ONCOGENIC PARADOX"

"Cancer is a complex disease involving numerous tempo-spatial changes in cell physiology, which ultimately lead to malignant tumors. Abnormal cell growth (neoplasia) is the biological endpoint of the disease. Tumor cell invasion of surrounding tissues and distant organs is the primary cause of morbidity and mortality for most cancer patients. The biological process by which normal cells are transformed into malignant cancer cells has been the subject of a large

" It is interesting in this regard that carcinogenesis, whether arising from viral infection or from chemical agent, produces similar impairment in respiratory enzyme activity and mitochondrial function"

~ Thomas Seyfried and Laura Shelton

research effort in the biomedical sciences for many decades. Despite this research effort, cures or long-term management strategies for metastatic cancer are as challenging today as they were 40 years ago when President Richard Nixon declared a war on cancer [1,2].

Confusion surrounds the origin of cancer. Contradictions and paradoxes have plagued the field [3-6]. Without a clear idea on cancer origins, it becomes difficult to formulate a clear strategy for effective management. Although very specific processes underlie malignant transformation, a large number of unspecific influences can initiate the disease including radiation, chemicals, viruses, inflammation, etc. Indeed, it appears that prolonged exposure to almost any provocative agent in the environment can potentially cause cancer [7,8]. That a very specific process could be initiated in very unspecific ways was considered "the oncogenic paradox" by Szent-Gyorgyi [8]. This paradox has remained largely unresolved [7]."

Those are the opening two paragraphs to our journal article.

As we've discussed, we've spent a LOT of money trying to figure cancer out. Since Nixon declared "war on cancer" two days before Christmas in 1971, we've spent $100 billion researching cancer and we currently spend over $100 billion every year on cancer medications. And, yet, we haven't made a whole lot of progress since the war on cancer began.

I ask again: How is that possible?

Well, that leads us back to a discussion regarding the ORIGINS of cancer.

Is it genetic? This is what everyone in the traditional paradigm thinks (and have been thinking for the last 45+ years).

Or... Is the cause metabolic? That, of course, is the alternative view presented by Seyfried and Shelton.

And... Why should we care? Well, quite simply, if you (or your loved ones) are dealing with cancer, your lives depend on it. The theory of the origins of cancer determine the therapeutic approach. If you're starting with the wrong theory regarding the origins of cancer, your approach won't be too well-informed and therefore too effective, eh?

Hence, $100 billion + $100 billion = 0 improvement.

Which leads us to the goal of the paper.

ENERGY METABOLISM

"Our goal is to revisit the argument of tumor cell origin and to provide a general hypothesis that genomic mutability and essentially all hallmarks of cancer, including the Warburg effect, can be linked to impaired respiration and energy metabolism. In brief, damage to cellular respiration precedes and underlies the genome instability that accompanies tumor development. Once established, genome instability contributes to further respiratory impairment, genome mutability, and tumor progression. In other words, effects become causes. This hypothesis is based on evidence that nuclear genome integrity is largely dependent on mitochondrial energy homeostasis and that all cells require a constant level of usable energy to maintain viability. While Warburg recognized the centrality of impaired respiration in the origin of cancer, he did not link this phenomenon to what are now recognized as the hallmarks of cancer. We review evidence that make these linkages and expand Warburg's ideas on how impaired energy metabolism can be exploited for tumor management and prevention."

The central theme of the paper is to establish the METABOLIC origin of cancer—establishing the fact this THIS is the primary *cause* of cancer, and that all the genetic mutations (and other hallmarks of cancer) are the downstream *effects* of metabolic dysfunction.

This is how you solve the riddle of the oncogenic paradox.

"Viewed collectively, the bulk of the experimental evidence indicates that mitochondria structure and function is abnormal in cancer cells. Hence, mitochondrial dysfunction will cause cancer cells to rely more heavily than non-cancer cells on substrate level phosphorylation [aka fermentation of sugar] for energy production in order to maintain membrane pump function and cell viability."

~ Thomas Seyfried and Laura Shelton

Cancer can be initiated by such a wide range of triggers (from viruses and radiation to inflammation and chemicals) because those things all damage cellular respiration. Once the metabolism is disrupted, things get weird.

(This is also why Nasha Winters says: *"The genetic mutations considered by conventional medicine as the root causes of cancer are, in fact, modifiable by epigenetic factors. Indeed, it is well established that genetics is the cause of only 5-10 percent of cancers and most of these genes encode proteins that impact mitochondrial respiration. It is mitochondrial damage that causes cancer, not the genes. If the inherited cancer gene does not damage mitochondria, cancer will not occur."*)

Check out the journal article for a compelling overview of the linkages between energy metabolism and all the hallmarks of cancer (like uncontrolled growth, evasion of programmed cell death, and tissue invasion and metastasis).

Again, why does this matter? (I'm well aware of the fact that I'm repeating myself.)

Because, when we identify the origins of cancer as METABOLIC in nature (rather than genetic), we focus our therapeutic protocols on getting our energy metabolism back in order.

Might not sound like a big deal, but it is.

Here's how they put it: "Is it genomic instability or is it impaired energy metabolism that is primarily responsible for the origin of cancer? This is more than an academic question, as the answer will impact approaches to cancer management and prevention. Metabolic studies in a variety of human cancers previously showed that loss of mitochondrial function preceded the appearance of malignancy and aerobic glycolysis [90]. However, the general view over the last 50 years has been that gene mutations and chromosomal abnormalities underlie most aspects of tumor initiation and progression including the Warburg effect and impaired respiratory function. The gene theory of cancer would argue that mitochondrial dysfunction is an effect rather than a cause of cancer, whereas the metabolic impairment theory would argue the reverse. If gene mutations are the primary cause of cancer then the disease can be considered etiologically complicated requiring multiple solutions for management and prevention. This comes from findings that the numbers and types of mutations differ markedly among and within different types of tumors. If, on the other hand, impaired energy metabolism is primarily responsible for cancer, then most cancers can be considered a type of metabolic disease requiring fewer and less complicated solutions."

P.S. Seyfried provides the scientific framework for understanding the metabolic ORIGINS of cancer. Nasha Winters provides a comprehensive handbook (*The Metabolic Approach to Cancer*) on how to approach your therapy given the metabolic origins.

MITOCHONDRIAL SUPPRESSION OF TUMORIGENICITY

"In other words, the well-documented tumor-associated abnormalities in oncogenes, tumor suppressor genes, and chromosomal imbalances can arise as a consequence of the progressive impairment of mitochondrial function."

~ Thomas Seyfried and Laura Shelton

"While the mutator phenotype of cancer can be linked to impaired mitochondrial function, normal mitochondrial function can also suppress tumorigenesis. It is well documented that tumorigenicity can be suppressed when cytoplasm from enucleated normal cells is fused with tumor cells to form cybrids, suggesting that normal mitochondria can suppress the tumorigenic phenotype [156-158]. Singh and co-workers provided additional evidence for the role of mitochondria in the suppression of tumorigenicity by showing that exogenous transfer of wild type mitochondria to cells with depleted mitochondria (rho^{o} cells) could reverse the altered expression of the APE1 multifunctional protein and the tumorigenic phenotype [113]. On the other hand, introduction of mitochondrial mutations can reverse the anti-tumorigenic effect of normal mitochondria in cybrids [159]. It is also well documented that nuclei from cancer cells can be reprogrammed to form normal tissues when transplanted into normal cytoplasm despite the continued presence of the tumor-associated genomic defects in the cells of the derived

tissues [160-162]. These findings indicate that nuclear gene mutations alone cannot account for the origin of cancer and further highlight the dynamic role of mitochondria in the epigenetic regulation of carcinogenesis."

That's some fascinating stuff. We talked about similar studies in Travis Christofferson's *Tripping over the Truth* where Travis describes studies done on "recon" cells. See those Notes for more.

Short story: Take a cancerous nucleus. Drop it into an otherwise healthy cell—replacing the healthy nucleus with the cancerous nucleus. What happens? If you believe in the gene theory, you'd expect the cell to become cancerous. But it doesn't.

Now, take a cancerous cytoplasm. Drop it into an otherwise healthy cell—keeping the nucleus healthy. What happens? If you believe in the gene theory, nothing should happen. Yet... That's not what happens. With cancerous cytoplasm, the cell tends to become cancerous.

Whether we're talking about "recons" or "cybrids," that's a win for the metabolic theory.

ACCUMULATION OF MITOCHONDRIAL DAMAGE

" While numerous genetic abnormalities have been described in most human cancers, no specific mutation is reliably diagnostic for any specific type of tumor. On the other hand, few if any tumors are known, which express normal respiration."

~ Thomas Seyfried and Laura Shelton

"Considered collectively, these observations suggest that the bulk of the genetic abnormalities found in cancer cells, ranging from point mutations to gross chromosomal rearrangements, can arise following damage to the structure and function of mitochondria.

Impairment of mitochondrial function can occur following prolonged injury or irritation to tissues including disruption of morphogenetic fields [123,151]. This tumorigenic process could be initiated in the cells of any tissue capable of producing mitochondrial stress signaling following repetitive sub-lethal respiratory damage over prolonged periods. The accumulation of mitochondrial damage over time is what ultimately leads to malignant tumor formation. Acquired abnormalities in mitochondrial function would produce a type of vicious cycle where impaired mitochondrial energy production initiates genome instability and mutability, which then accelerates mitochondrial dysfunction and energy impairment and so on in a cumulative way. An increased dependency on substrate level phosphorylation for survival would follow each round of metabolic and genetic damage thus initiating uncontrolled cell growth and eventual formation of a malignant neoplasm. In other words, the well-documented tumor-associated abnormalities in oncogenes, tumor suppressor genes, and chromosomal imbalances can arise as a consequence of the progressive impairment of mitochondrial function."

Let's shine a spotlight on this: *"The accumulation of mitochondrial damage over time is what ultimately leads to malignant tumor formation."*

Recognizing the origin of cancer as the repeated damage to mitochondria, we step back and treat, as Nasha Winters says, the TERRAIN rather than just focus on the tumor.

She says: *"Comprehending the complexities of the individuals' biological terrain is akin to a gardener understanding the ideal conditions for growing vegetables. A successful gardener knows that it takes more than a piece of land and a packet of seeds to grow a bountiful harvest. It requires knowledge of soil biochemistry, the planting requirements of all the various types of seeds, proper balance of nutrients, fertilizing agents, and the right amount of water and sunlight. It also requires insight into how pests, insects, weeds, molds, and fungi impact the soil or plants. The ten terrain elements we've identified are like systems within that garden. Regulating a healthy human biological terrain is similar to raising a healthy, thriving garden. When the body is fed a diet that provides adequate amounts of macro- and micronutrients, vitamins, and minerals; is exposed to a variety of microbes; and has adequate amounts of exercise, sleep, fresh water, sunlight, love, and attention; then the body, like a healthy garden, will flourish. Conversely, if it is fed antinutrients and chemicals, receives insufficient sunshine, and endures too much stress, it will wither.*

" Considered collectively, these findings indicate that the integrity of the nuclear genome is dependent to a large extent on the functionality and energy production of the mitochondria."

~ Thomas Seyfried and Laura Shelton

So the key is this: Since cancer consists of cells gone awry in response to toxic diets and environments, we must optimize the body's healing mechanisms instead of waging war on them. We need to treat the terrain, not the tumor. We must build the body up instead of attacking it. Our strategy works: The only side effect of the metabolic approach is feeling better. Much better. In fact, for over a decade, Dr. Nasha has seen hundreds of Stage IV cancer patients who have lived far beyond their 'expiration date' because they have followed this model. As we will explain, each terrain element is optimized using the oldest form of medicine: food. It sounds simple, yet in the modern world of medicine, it's about as radical and 'unfounded' as it can be."

Now for the core part of Seyfried and Shelton's therapeutic intervention:

LOWER GLUCOSE + RAISE KETONES

"If cancer is primarily a disease of energy metabolism as reviewed here, then rational approaches to cancer management can be found in therapies that specifically target energy metabolism. ...

Besides lowering circulating glucose levels, dietary energy restriction elevates circulating levels of fatty acids and ketone bodies (b-hydroxybutyrate and acetoacetate) [266,269,270]. Fats and especially ketone bodies can replace glucose as a primary metabolic fuel under calorie restriction. This is a conserved physiological adaptation that evolved to spare protein during periods of starvation [271,272]. Many tumors, however, have abnormalities in the genes and enzymes needed to metabolize ketone bodies for energy [273-275]. A transition from carbohydrate to ketones for energy is a simple way to target energy metabolism in glycolysis-dependent tumor cells while enhancing the metabolic efficiency of normal cells [276,277] ...

These findings highlight the different responses to energy stress between the metabolically incompetent tumor cells and competent normal cells. Consequently, a shift in energy metabolism from glucose to ketone bodies protects respiratory competent normal cells while targeting the genetically defective and respiratory challenged tumor cells, which depend more heavily on glycolysis than normal cells for survival [10,278,279]."

As we've discussed, and as Seyfried and Shelton painstakingly document, cancer cells preferentially create energy via the fermentation of sugar. (That's the essential aspect of their damaged metabolism.)

" In essence, dietary energy restriction and ketone body metabolism delays entropy. As cancer is a disease of accelerated entropy, dietary energy restriction targets the very essence of the disease."

~ Thomas Seyfried and Laura Shelton

This is known as the Warburg Effect. And, it's why PET scans—which show hot spots of glucose metabolism—are used to detect metastasis. (It's also the essence of our UPS driver's wisdom: "Cancer loves sugar!")

Seyfried and Shelton tell us (in precise science-speak) that we need to switch from using glucose as our primary fuel to ketones. We'll talk about it more in our Notes on Miriam Kalamian's *Keto for Cancer* but this is EXACTLY what we're doing with my brother: lowering glucose while raising ketones.

(In fact, Miriam is my brother's day-to-day nutritional consultant. Seyfried wrote the foreword to her book. She has us regularly (as in throughout the day) measuring glucose and ketone levels as a core part of our metabolic approach.)

Here's the good news: Cancer has an Achilles heel. It burns through sugar at an alarming rate but, when you cut off that supply line, you are able to exploit its metabolic inflexibility. The cancer cells are so damaged that, basically, they can ONLY use glucose for fuel whereas healthy cells are metabolically flexible and can use either glucose or ketones. More on that soon.

Note: My brother got a PET scan yesterday. We'll learn more about the results this week. Again, PET scans show hot spots of glucose metabolism. One of the metaphors we've used to describe our approach is to "flip the switches OFF!" Make it all go dark by lowering glucose and raising

" Part of this tissue damage will involve injury to the mitochondria in the affected cells. The prevention of inflammation and damage to the tissue microenvironment will go far in reducing the incidence of most cancers. Hence, simply reducing exposure to cancer risk factors, which produce chronic inflammation and mitochondrial damage, will reduce the incidence of at least 80% of all cancers. In principle, there are few chronic diseases more easily preventable than cancer."

~ Thomas Seyfried and Laura Shelton

ketones. Longer chat but on that note, I'm THRILLED that Rick's glucose went from 145+ (diabetic) the day he was admitted to the hospital to 93 (normal) in a little over 5 weeks with no medications, etc. (And, it's even lower now.)

CONCLUSIONS

"Evidence is reviewed supporting a general hypothesis that cancer is primarily a disease of energy metabolism. All of the major hallmarks of the disease can be linked to impaired mitochondrial function. In order to maintain viability, tumor cells gradually transition to substrate level phosphorylation using glucose and glutamine as energy substrates. While cancer causing germline mutations are rare, the abundance of somatic genomic abnormalities found in the majority of cancers can arise as a secondary consequence of mitochondrial dysfunction. Once established, somatic genomic instability can contribute to further mitochondrial defects and to the metabolic inflexibility of the tumor cells. Systemic metastasis is the predicted outcome following protracted mitochondrial damage to cells of myeloid origin. Tumor cells of myeloid origin would naturally embody the capacity to exit and enter tissues. Two major conclusions emerge from the hypothesis; first that many cancers can regress if energy intake is restricted and, second, that many cancers can be prevented if energy intake is restricted. Consequently, energy restricted diets combined with drugs targeting glucose and glutamine can provide a rational strategy for the longer-term management and prevention of most cancers."

Those are the last words of the journal article. More than anything, I hope I inspired you to go get the article, print it out, find a quiet place to work out your brain, and gain a deeper understanding about the metabolic origins and therapies of cancer.

Let's live on the long tail and change the conversation on cancer. Love to you and your family!

Brian Johnson,
Chief Philosopher

If you liked this Note, you'll probably like…

- The Metabolic Approach to Cancer
- Tripping over the Truth
- Anticancer
- The Telomere Effect
- The Keto Reset Diet
- Fat for Fuel

About the Authors of "Cancer as a Metabolic Disease"

THOMAS N. SEYFRIED WITH LAURA M. SHELTON

Dr. Seyfried published a groundbreaking treatise entitled, *Cancer as a Metabolic Disease: On the Origin, Management, and Prevention of Cancer* (Wiley, 1st ed., 2012). The treatise provides extensive information showing that cancer can be best defined as a mitochondrial metabolic disease rather than as a genetic disease. This new concept has implications for the development of new non-toxic cancer therapies including the ketogenic diet. Experts in the cancer research field have praised this comprehensive study as one of science's hottest topics.

Laura M. Shelton, Ph.D. is a trained biochemist with a background in cancer metabolism, who has extended her knowledge into the more general area of metabolic disorders to include diabetes and inborn errors of metabolism.

About the Author of This Note

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Brian Johnson loves helping people optimize their lives so they can actualize their potential as he studies, embodies and teaches the fundamentals of optimal living—integrating ancient wisdom + modern science + practical tools. Learn more and optimize your life at optimize.me.