Cancer: A Metabolic Disease with Metabolic Solutions

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Provocative Question

Is cancer a nuclear genetic disease or a mitochondrial metabolic disease?
Current Dogma:
Cancer is a Genetic Disease

Cancer cells carry the oncogenic and tumor suppressor mutations that define cancer as a “Genetic Disease”.

Hallmarks of Cancer: The Next Generation

Douglas Hanahan¹,²,* and Robert A. Weinberg³,*

Cell 144, March 4, 2011
Evidence that challenges the somatic mutation theory of cancer
Role of the mitochondria in the origin of tumors

1. Normal Cell
   - Normal Cells
2. Tumor Cell
   - Tumor Cells
3. Normal Cytoplasm + Tumor Nucleus
   - Normal Cells
4. Tumor Cytoplasm + Normal Nucleus
   - Tumor Cells/Death

Seyfried, Cancer as a Metabolic Disease, 2012 John Wiley Press; Seyfried et al., 2014, Carcinogenesis
If somatic mutations are not the origin of cancer, then how do cancer cells arise?
Warburg Theory of Cancer

1. Cancer arises from damage to cellular respiration.

2. Energy through fermentation gradually compensates for insufficient respiration.

3. Cancer cells continue to ferment lactate in the presence of oxygen (Warburg effect).

4. Enhanced fermentation is the signature metabolic malady of all cancer cells.
Cellular Energy Metabolism

Glucose

- Glycolysis: Glucose → 2 Pyruvate
- Electron shuttle across membrane
- 2 NADH

Krebs Cycle

- 2 NADH
- 6 NADH
- 2 FADH₂

Glutamine

- Electron transport chain and oxidative phosphorylation

Cytosol

- +2 ATP
- 5.5% by substrate level phosphorylation

Mitochondrion

- +2 ATP
- 5.5% by substrate level phosphorylation
- +36 ATP
- 89% by OxPhos
Mitochondrial Morphology

Normal Mitochondria

GBM Mitochondria

cristolysis

Arismendi-Morillo Int J Biochem Cell Biol 41, 2062-68, 2009
Cancer as a Mitochondrial Metabolic Disease

Oncogenic Paradox

- RAS oncogene
- Rare Mutations
- Viruses
- Inflammation
- Hypoxia
- Radiation
- Carcinogens
- Age

ROS

The Warburg Effect + Mitochondrial Fermentation

Tumor Suppressor Genes, Oncogenes

Nucleus

HIF-1α

Genome Instability

VEGF

RTG Activation

RTG Activation

Cancer Hallmarks

Default State
1. Self-sufficiency in growth signals
2. Insensitivity to anti-growth signals
3. Limitless replicative potential
4. Sustained Angiogenesis
5. Evasion of Apoptosis
6. Metastasis

Macrophage fusion hybrid

SLP

OxPhos

% of ATP production

-56 kJ

Progression (Time)

Reversible

Irreversible

Seyfried, *Cancer as a Metabolic Disease*, 2012 John Wiley Press; Seyfried et al., 2014, *Carcinogenesis*
If most cancers express the Warburg effect as the result of impaired respiration, then what therapies might be effective for managing tumors?
One strategy is to reduce levels of fermentable fuels while elevating levels non-fermentable fuels.
Calorie Restriction (CR): A Metabolic Cancer Intervention

- Involves a total dietary restriction
- Differs from starvation
- Maintains minerals and nutrients
- Enhances mitochondrial biogenesis & OxPhos
- CR in mice mimics water-only therapeutic fasting in humans
Biomarkers for Calorie Restriction

1. Reduced Blood Glucose

2. Elevated Blood Ketone Bodies

\( \beta \)-Hydroxybutyrate (\( \beta \)-OHB) → Acetoacetate → Acetone

- Elevated Blood Ketone Bodies
Calorie restriction reduces intracerebral growth of the CT-2A astrocytoma

AL  CR

40% CR initiated 3 days post-inoculation
Plasma glucose predicts ketone body levels and CT-2A tumor growth

Anti-Tumor Effects of Calorie Restriction

1. **Anti-angiogenic**
   
   Mukherjee et al., Clin. Cancer Res., 2004

2. **Anti-inflammatory**
   
   Mulrooney et al., PLOS One, 2011

3. **Pro-apoptotic**
   
   Mukherjee et al., Brit. J. Cancer 2002
Can a restricted ketogenic diet manage brain cancer in mice?
## Composition (%) of the standard diet (SD) and the ketogenic diet (KD)

<table>
<thead>
<tr>
<th>Components</th>
<th>Standard Diet (SD)</th>
<th>Ketogenic Diet (KD)</th>
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</thead>
<tbody>
<tr>
<td>Carbohydrate</td>
<td>62</td>
<td>3</td>
</tr>
<tr>
<td>Fat</td>
<td>6</td>
<td>72</td>
</tr>
<tr>
<td>Protein</td>
<td>27</td>
<td>15</td>
</tr>
<tr>
<td>Energy (Kcal/gr)</td>
<td>4.4</td>
<td>7.2</td>
</tr>
<tr>
<td>F/ (P + C)</td>
<td>0.07</td>
<td>4</td>
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</tbody>
</table>

* The ketogenic diet should always be consumed in restricted amounts!
The KD-R Reduces Intracerebral Growth of Mouse and Human Brain Tumors

Mouse Brain Tumor Growth

<table>
<thead>
<tr>
<th></th>
<th>SD-UR</th>
<th>KD-UR</th>
<th>KD-R</th>
</tr>
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<tbody>
<tr>
<td>CT-2A</td>
<td></td>
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Human Brain Tumor Growth

<table>
<thead>
<tr>
<th></th>
<th>SD-UR</th>
<th>KD-UR</th>
<th>KD-R</th>
</tr>
</thead>
<tbody>
<tr>
<td>U87-MG</td>
<td></td>
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</table>

n = 11-14 mice/group

Zhou et al., Nut & Met, 2007

* P < 0.01
Influence of the KD-R on Plasma Glucose and \( \beta \)-OHB Levels in CT-2A Tumor-Bearing Mice

Blood Glucose

Blood \( \beta \)-OHB

n = 11-14 mice/group

Zhou et al., Nut & Met, 2007

* P < 0.01
Metabolic management of cancer following changes in plasma glucose & ketones
Clinical Question

Can the KD-R be effective for the metabolic management of malignant brain cancer in patients?
The results showed that a ketogenic diet, which reduced blood glucose and elevated blood ketones, could provide long-term management in two children with recurrent inoperable brain tumors.
Patient: Female 65 yrs old, 64 kg (141 lbs)

12/5/08: Progressive memory loss, chronic headaches, nausea
GBM is Responsive to Metabolic Therapy

Figure 1 MRI contrast enhanced images of a large multi-centric mass involving the right hemisphere pole. (A) Temporal pole, (B) frontal operculum, insular lobe, posterior putamen, (C) frontal operculum, head of caudate nucleus. Note the presence of peripheral edema (arrows).

Figure 4 Brain MRI taken a few days after ending the standard radiotherapy plus concomitant temozolomide therapy together with KD-CR protocol. No clear evidence of tumor tissue or associated edema was seen. Arrow indicates porencephaly.

Figure 3 Levels of circulating glucose (black line) and urinary ketones (red line) in the patient during the period from January 8 to February 7, 2009. The values are within normal physiological ranges for people who maintain low calorie dieting [46].
Influence of a natural ketogenic diet on blood glucose and ketone levels in an adult patient with a diffuse, infiltrative brainstem glioma

Data is represented as mean ± 95% CI.
The glucose ketone index calculator: a simple tool to monitor therapeutic efficacy for metabolic management of brain cancer

Joshua J Meidenbauer, Purna Mukherjee and Thomas N Seyfried*

Glucose (mmol)/Ketone (mmol) = GKI

Therapeutic efficacy is considered best with index values approaching 1.0 or below
Influence of a natural ketogenic diet alone on the G/K Index in an adult patient with a diffuse, infiltrative brainstem glioma

Data is represented as mean ± 95% CI

n = 5-24 for Jun-12 – Sep-12
n = 28-32 for Oct-12 – Feb-14
The Press-Pulse Paradigm: A Novel Therapeutic Strategy for the Metabolic Management of Cancer

1. Cyclic Energy Stress Targets Mutated Tumor Cells:
   a. Calorie restricted ketogenic diet.
   b. Calorie restricted raw vegan diet.
   c. Hyperbaric oxygen therapy.
   d. Non-toxic drugs.
Press-Pulse therapy using the KD-R with the glycolysis inhibitor 2-DG for managing CT-2A astrocytoma

Dose: 25 mg/kg BW  n = 3-6/group

Marsh et al., Nutrition & Met
Press-Pulse therapy using the KD with hyperbaric oxygen for managing systemic metastatic cancer in VM mice

Influence of a restricted ketogenic diet on brain metastases of the VM-M3 tumor cells:

Akgoc et al. (unpublished)
Influence of raw KD-R on mast cell tumor in a dog

July 2013

September 2013

April 2014

January 2015
Ketone Strong: Emerging evidence for a therapeutic role of ketone bodies in neurological and neurodegenerative diseases

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Conclusions

1. Cancer is a type of mitochondrial metabolic disease.

2. The GKI can be used to monitor success of metabolic therapy for cancer management.

3. The “Press-Pulse” paradigm can serve as a non-toxic therapeutic approach to cancer management.
TRIPPING OVER THE TRUTH

The Metabolic Theory of Cancer

Travis Christofferson
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