Cancer as a Mitochondrial Metabolic Disease: Implications for Novel Therapeutics

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Over 1,600 people die each day from cancer in the US according to recent data from the American Cancer Society (Siegel et al., 2018). Brain cancer has now replaced blood cancer as the leading cause of cancer death in children. The failure to manage cancer has been due in large part to the dogmatic belief that cancer is a constellation of genetic diseases, (https://medlineplus.gov/magazine/issues/winter13/articles/winter13pg2-3.html).
Accumulating evidence, however, indicates that cancer is primarily a mitochondrial metabolic disease involving disturbances in energy production through respiration and fermentation (Seyfried et al., 2014). The disturbances in tumor cell energy metabolism are linked to abnormalities in the structure and function of mitochondria that disrupt ATP synthesis through oxidative phosphorylation (OXPhos) (Seyfried, 2015; Seyfried & Shelton, 2010). Consequently, all cancer can be considered a single disease with a common pathophysiological mechanism involving dysfunction of mitochondrial OxPhos.

The gene mutations observed in various cancers and all other recognized cancer hallmarks are considered downstream effects, and not causes, of the initial disturbance of cellular energy metabolism (Seyfried, 2012; Seyfried et al., 2014). Cancer growth and progression can be best managed following a whole-body transition from fermentable metabolites, primarily glucose and glutamine, to respiratory metabolites, primarily ketone bodies (Seyfried et al., 2017).

Normal cells transition to ketone bodies for energy under low glucose conditions. Ketone body metabolism thus protects the brain against hypoglycemia. Tumor cells, on the other hand, cannot effectively use ketone bodies for energy due to their dysfunction in OxPhos. Therapeutic fasting and calorie restricted ketogenic diets lower cancer-provoking glucose and insulin-like growth factor (IGF-1) levels, while elevating ketone bodies (Marsh et al., 2008; Mukherjee et al., 2004; Mukherjee et al., 2002). The metabolic transition from glucose to ketone bodies reduces tumor angiogenesis and inflammation while enhancing tumor cell apoptosis.

The Press-Pulse therapeutic paradigm used with the Glucose/Ketone Index will facilitate the non-toxic management and prevention of cancer (Meidenbauer et al., 2015; Seyfried et al., 2017). As each individual is a unique metabolic entity, personalization of metabolic therapy as a broad-based cancer treatment and prevention strategy will require fine-tuning to match the therapy to an individual's unique physiology. The efficacy of metabolic therapy for management of malignant cancer is seen in preclinical models and in humans with various cancers (Elsakka et al., 2018; Iyikesici et al., 2017; Seyfried et al., 2014; Seyfried et al., 2017; Shelton et al., 2010; Toth & Clemens, 2016).

It is anticipated that metabolic therapies targeting glucose and glutamine while increasing therapeutic ketosis will significantly improve quality of life and overall survival for most cancer patients.

References

Elsakka, A.M.A., Bary, M.A., Abdelzaher, E., Elnaggar, M., Kalamian, M., Mukherjee, P. & Seyfried, T.N. (2018). Management of Glioblastoma Multiforme in a Patient Treated With Ketogenic Metabolic Therapy and Modified Standard of Care: A 24-Month Follow-Up. *Front Nutr*, **5,** 20.

Iyikesici, M.S., Slocum, A.K., Slocum, A., Berkarda, F.B., Kalamian, M. & Seyfried, T.N. (2017). Efficacy of Metabolically Supported Chemotherapy Combined with Ketogenic Diet, Hyperthermia, and Hyperbaric Oxygen Therapy for Stage IV Triple-Negative Breast Cancer. *Cureus*, **9,** e1445.

Marsh, J., Mukherjee, P. & Seyfried, T.N. (2008). Akt-dependent proapoptotic effects of dietary restriction on late-stage management of a phosphatase and tensin homologue/tuberous sclerosis complex 2-deficient mouse astrocytoma. *Clin Cancer Res*, **14,** 7751-62.

Meidenbauer, J.J., Mukherjee, P. & Seyfried, T.N. (2015). The glucose ketone index calculator: a simple tool to monitor therapeutic efficacy for metabolic management of brain cancer. *Nutr Metab (Lond)*, **12,** 12.

Mukherjee, P., Abate, L.E. & Seyfried, T.N. (2004). Antiangiogenic and proapoptotic effects of dietary restriction on experimental mouse and human brain tumors. *Clin Cancer Res*, **10,** 5622-9.

Mukherjee, P., El-Abbadi, M.M., Kasperzyk, J.L., Ranes, M.K. & Seyfried, T.N. (2002). Dietary restriction reduces angiogenesis and growth in an orthotopic mouse brain tumour model. *Br J Cancer*, **86,** 1615-21.

Seyfried, T.N. (2012). *Cancer as a Metabolic Disease: On the Origin, Management, and Prevention of Cancer*. John Wiley & Sons: Hoboken.

Seyfried, T.N. (2015). Cancer as a mitochondrial metabolic disease. *Front Cell Dev Biol*, **3,** 43.

Seyfried, T.N., Flores, R.E., Poff, A.M. & D'Agostino, D.P. (2014). Cancer as a metabolic disease: implications for novel therapeutics. *Carcinogenesis*, **35,** 515-27.

Seyfried, T.N. & Shelton, L.M. (2010). Cancer as a metabolic disease. *Nutr Metab (Lond)*, **7,** 7.

Seyfried, T.N., Yu, G., Maroon, J.C. & D'Agostino, D.P. (2017). Press-pulse: a novel therapeutic strategy for the metabolic management of cancer. *Nutr Metab (Lond)*, **14,** 19.

Shelton, L.M., Huysentruyt, L.C. & Seyfried, T.N. (2010). Glutamine targeting inhibits systemic metastasis in the VM-M3 murine tumor model. *Inter. J. Cancer.* , **127,** 2478-85.

Siegel, R.L., Miller, K.D. & Jemal, A. (2018). Cancer statistics, 2018. *CA Cancer J Clin*, **68,** 7-30.

Toth, C. & Clemens, Z. (2016). Halted Progression of Soft Palate Cancer in a Patient Treated with the Paleolithic Ketogenic Diet Alone: A 20-months Follow-up. *American Journal of Medical Case Reports*, **4,** 288-292.