Investigating a Ketogenic Diet as a Potential Adjunctive Therapy for Colon Cancer Treatment

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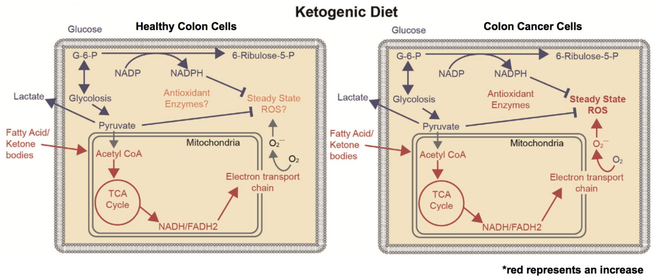
Introduction:

- Colon cancer represents one of the greatest public health challenges today. Colon cancer is the second leading cause of cancer-related deaths in the US that affect both men and women (2019).
- An adjunctive treatment that assists the standard cancer treatment could increase the number of positive patient outcomes. The ketogenic diet, a high-fat and low-carbohydrate diet, has been of special interest to the medical community recently. Normally, the body uses carbohydrates as its primary source of energy; however, through the mostly exclusive consumption of fat, the ketogenic diet forces the body to alter its typical method of energy production (2014). This alteration in energy production is well-received by healthy cells, but causes problems to cancer cells.
- These difficulties arise from the major metabolic differences between cancer cells and healthy cells:
  - Increased mitochondrial DNA mutations, leading to a dysfunctional electron transport chain that produces reactive oxygen species (2014)
  - Increased dependence of anaerobic glycolysis, termed the Warburg Effect (2009)
  - Increased NADPH production in order to neutralize the increased levels of ROS produced in the mitochondria (2009)

Goals:

- Investigate the effects a ketogenic diet has on colon cancer cells, specifically cell proliferation and metabolic reprogramming.
- Help establish a nutritional adjunctive therapy in the treatment of colon cancer.

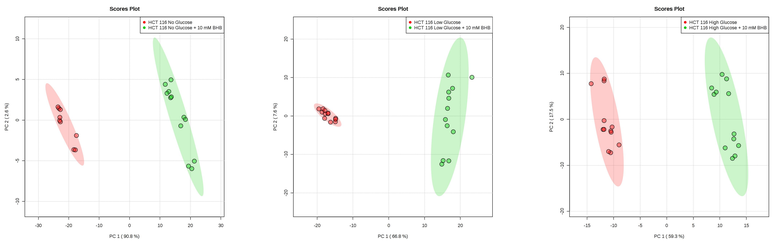


Sources:

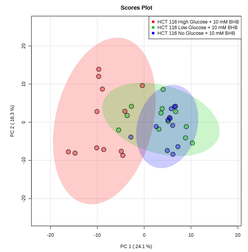
Allen, B. G., S. K. Bhatia, et al. (2014). "Ketogenic diets as an adjuvant cancer therapy: history and potential mechanism." Redox Biol 2: 963-970.
United States Cancer Statistics: Colorectal Cancer Statistics. 1999-2019 Cancer Incidence and Mortality Data. from https://www.cdc.gov/cancer/colorectal/statistics/.
Vander Heiden, M. G., L. C. Cantley, et al. (2009). "Understanding the Warburg effect: the metabolic requirements of cell proliferation." Science 324(5930): 1029-1033.

Major Findings:

Major Finding #1: Ketone body treatment (green) induces metabolic reprogramming in colon cancer cells cultured in all glucose concentrations.



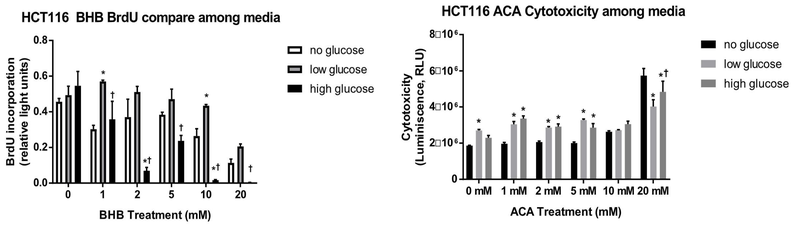
Major Finding #2: Ketone body treatment induced similar metabolic reprogramming in all glucose (no (0 g/L), low (1 g/L) and high (4.5 g/L)) concentrations.



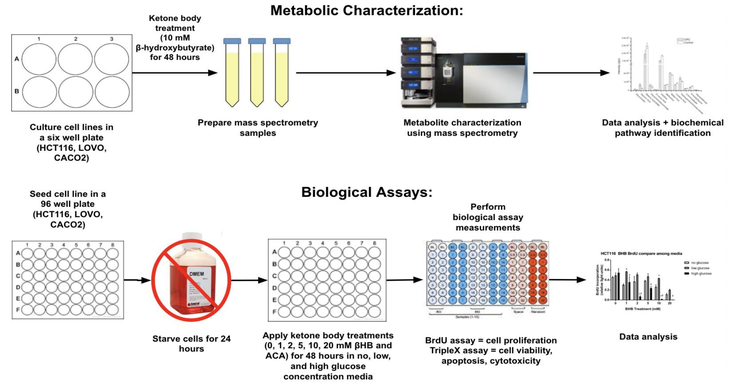
Major Finding #3: Metabolic pathway comparison between control and ketone body-treated cancer cells (HCT116) at each glucose concentration show significant differences between major energy metabolic pathways.

	No Glucose	Low Glucose	High Glucose
Glycolysis/Gluconeogenesis	7.12E-08	7.75E-02	8.14E-11
TCA Cycle	1.47E-13	1.07E-10	2.18E-18
Pyruvate Metabolism	1.99E-12	0.104	1.15E-18
Pentose Phosphate Pathway	1.85E-05	0.427	6.77E-12

Major Finding #4: As ketone body (βHB and ACA) treatment concentration increased, cellular growth slowed and cellular toxicity increased.



Methods:



Conclusions:

- Inducing the equivalent of a ketogenic diet on in vitro colon cancer cell line (HCT 116) caused metabolic reprogramming.
- The metabolic reprogramming caused a lower rate of survival, via less cell growth and increased cytotoxicity, in the colon cancer cell line (HCT 116).
- Overall, a laboratory equivalent of a ketogenic diet caused the colon cancer cell line (HCT 116) to have negative differential growth.

Future Goals:

- Perform similar experiments on a healthy colon epithetical cell line (CCD) for comparison.
- Quantify the damage induced by a ketogenic diet on more colon cancer cell lines by measuring reactive oxygen species and cell apoptosis.
- Test the expression of enzymes present in the metabolic pathway to determine the magnitude of the effect a ketogenic diet can have on cancer cell growth.
- Further investigate the alterations in major energy pathways, identifying metabolites with therapeutic potential.
- Identify and target key differences between healthy and cancerous metabolism as possible therapeutic interventions.