Elucidating the Potential Use of Ketogenic Diets in Cancer Management

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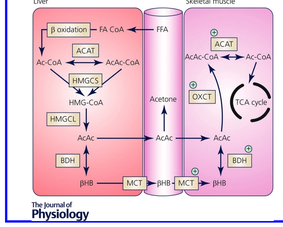
INTRODUCTION

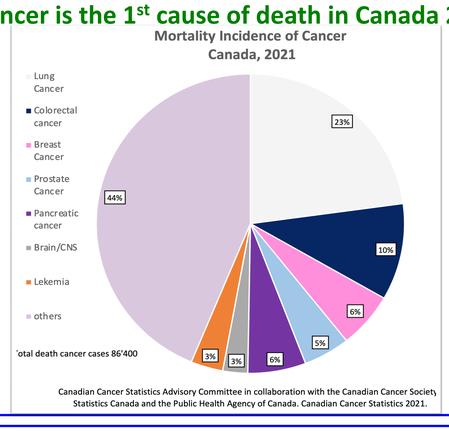
Ketogenic Diet (KD) is a dietary pattern that conveys consuming high fat, very low carbs & sufficient protein contents. KD was 1st pioneered in the 1920s as a therapeutic diet by Dr. Russell Wilder who was serving as the Head of Diabetic Care at Mayo Clinic. KDs have been used since 1920 as therapeutics diets for children exhibiting drug-resistant epilepsy. The beneficial results of KDs were associated with high levels of ketone bodies in patients' blood samples[10]. Ketone Bodies (KB) are mainly synthesised in the liver from oxidation of fatty acids during fasting starvation, where they make up a major fuel source of the brain[5]. Cancer is currently the leading cause of death in Canada. Numerous studies have shown that cancer cells exhibit abnormal metabolic changes and are highly dependent on glucose uptake[4]. As KDs are high-fat and very-low in carbohydrate content, they can create a metabolic environment harmful to the growth of cancerous tissue by decreasing glucose availability[9]. This dietary approach is relatively cost effective and safe, has been shown to exhibit anticancer effects[10]. Conversely, cancerous tissue may also utilize ketones for energy metabolism to support their growth requirements. As such, our goal was to evaluate ketone metabolism in various cancer cell lines, to better understand which types of cancer may be susceptible to KDs as a therapeutic strategy.



- **BDH1**/ 3-hydroxybutyrate dehydrogenase
- **OXCT1**/succinyl-CoA:3-ketoacid CoA transferase (SCOT) (rate limiting step)
- **ACAT**/ Ac-CoA acetyltransferase

Metabolism of ketone bodies
Figure adapted from (Evans M et al, 2017)[6]

Cancer is the 1st cause of death in Canada 2021

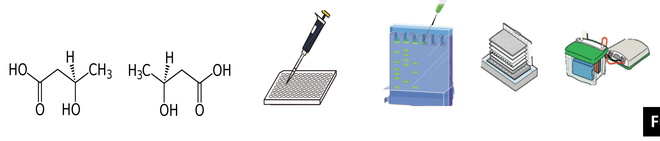


HYPOTHESIS

Our working hypothesis is that cell lines of different cancer types will express succinyl-CoA:3-ketoacid CoA transferase (SCOT) enzyme indicating they are capable of oxidizing ketone bodies for energy. We also hypothesise that increased delivery of β-hydroxybutyrate (βOHB), the most abundant circulating ketone, will influence rates of cancer cell proliferation and survival.

METHODS & EXPERIMENTAL DESIGN

We will expose a variety of cancer cell lines (HCT116 , MC38, CMT93 cells – CRC; H1299 cells – lung cancer) to increasing concentrations of βOHB (0.1-2.0 mM) in under serum starvation.



Ketone Bodies Treatment (β-hydroxybutyrate)

Add βOHB to cancer cells

Study cells' protein expression using Western Blot

Future Assays

CCK8 Proliferation Assay

Transwell Migration Assay

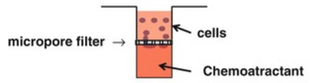


Diagram adopted from Hieda M. et al, 2015 Histone Modifications Associated with Cancer Cell Migration & Invasion

Lung Cancer is 1st cause of death among cancer cases in Canada,2021

Lung cancer are often classified as either small and non-small cell cancer (NSCC) which makes up nearly 80% of cases, originate in glandular cells of the outer layer of lungs. Although smoking is considered important risk factor, literature has shown great effects of diet and supplementations on the prognosis[2].

Lung Cancer Cell Line

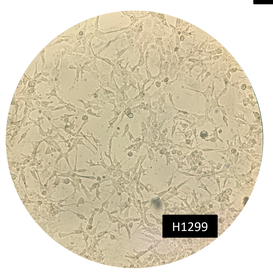
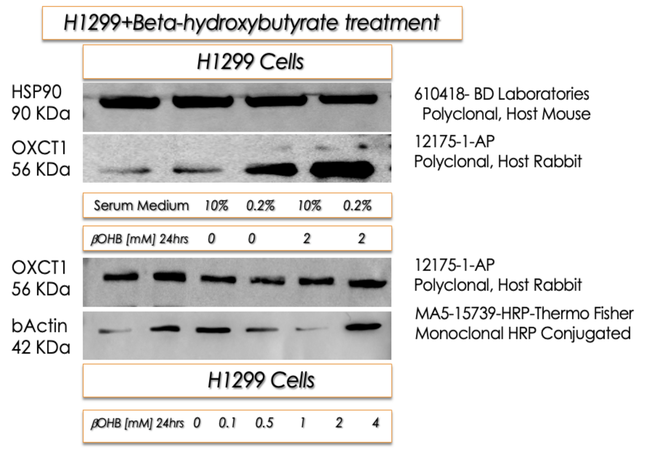


Figure adapted from Cancer Treatments Centers of America

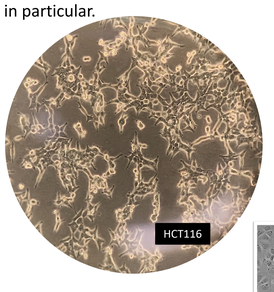
H1299 cell line, Passage number 3, 72hrs incubation in RPMI growth medium, 10%Serum, 1% streptomycin at 37°C&5% CO_2.
(Image taken via light microscope, SA/Ussher lab)

Results
Lung cancer cells' expression of SCOT increases in response to elevated βOHB concentrations



Colorectal Cancer is 2nd cause of death among cancer cases in Canada, 2021

Current treatment lines are insufficient and in constant need for new strategies. Unhealthy dietary habits are associated with higher risk of CRC, high sugar consumption in particular.



HCT116 cell line, Passage Number 8, 24 hr incubation in DMEM growth medium high glucose, 10% Serum, 1% Streptomycin at 37°C&5% CO_2.
(Image taken via light microscope, SA/Ussher lab)

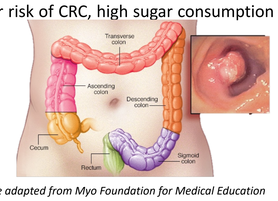
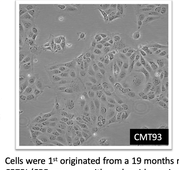
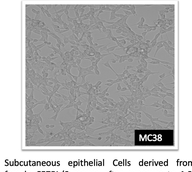


Figure adapted from Myo Foundation for Medical Education

CRC Cell Lines

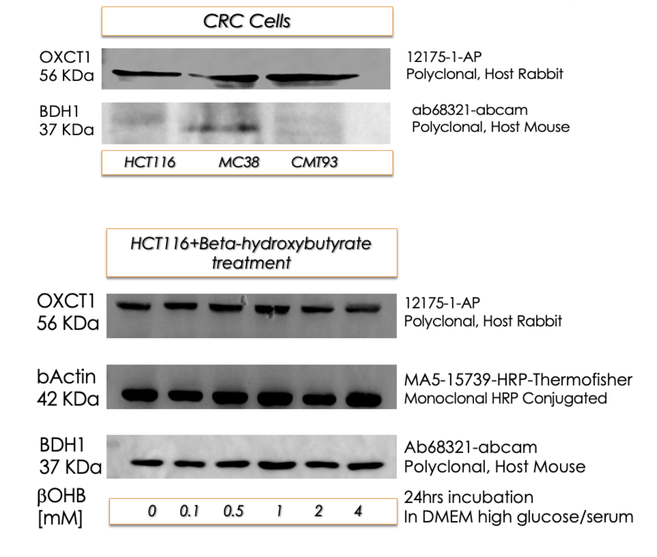


Cells were 1st originated from a 19 months male C57BL/CRF mouse with polypoid carcinoma. Tumor was induced by exposing the mouse model to IP injections of methyl azoxymethanol acetate (MAM). CMT93 presents epithelial morphology and can be good model to study colorectal cancer[12].



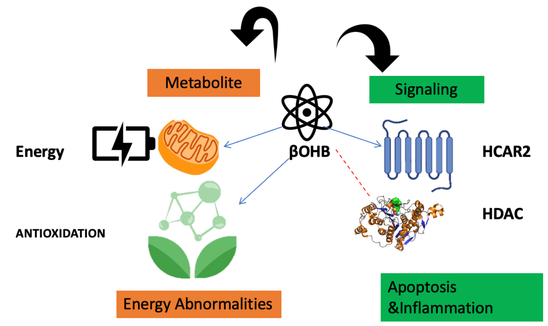
Subcutaneous epithelial Cells derived from female C57BL/6 mouse after exposure to 1,2-dimethylhydrazine dihydrochloride (DMH). Cells shown high tendency to metastasise. MC38 is considered best model to study cancer immunotherapy and evaluation of efficacy of Immune checkpoint inhibitors such as PD[11].

Colorectal cancer cells do express SCOT enzyme



FUTURE DIRECTIONS

BOHB has a potential anticancer effect as both a metabolite and a signaling molecule. Future aims of this project to study the effects of βOHB treatments on proliferation and migration of cancer [cells][1,3,7].



- *HCAR2; G-protein-coupled hydroxycarboxylic acid receptor [1]*
- *HDAC; histone deacetylases (HDACs) where some inhibitors are current anticancer agents such as Vorinostat& Romidepsin[1]*

SUMMARY & CONCLUSIONS

The preliminary results suggests that both lung cancers and CRCs utilize ketones. Future studies aimed at assessing how ketone metabolism impacts cancer growth/survival will help elucidate the potential use of a KD in the management of these specific cancers.

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