Weill Cornell Medicine

Restricting Dietary Sugars Improves the Treatment of Colorectal and Small Intestine Cancers

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Background & Unmet Need

- Colorectal cancer (CRC) is the third most common type of cancer in the world
- A high fructose diet is connected to cancer and obesity, the two largest causes of mortality
- The mechanism of why high-fructose corn syrup (HFCS) leads to worse cancer outcomes was previously unknown
- HFCS is converted to a carcinogen, fructose 1-phosphate (F1P), by ketohexokinase (KHK)
- F1P is structurally similar to fructose 1,6-bisphosphate (FBP), an inhibitor of PKM2 gene, and promotes hypoxia
- **Unmet Need:** Improved understanding of the impact of dietary sugars on cancer, to inform dietary recommendations and targeted therapies

Technology Overview

- **The Technology:** Method to reduce or eliminate sugar from diet or administer a treatment targeting the fructose-uptake pathway to inhibit or reduce onset of colon and intestinal cancers
- **The Discovery:** Specific molecules in the fructose-uptake pathway are upregulated in high-fat diets and promote tumor growth and incidence
- **PoC Data:** In mice models, HFCS enhances tumor growth by promoting hypoxic cell survival, as evidenced by the presence of longer intestinal cell villi (Fig. 1)
- Small molecules that target upregulated proteins in the fructose-uptake pathway (HPK, GLUT5, P3K, PKM2) prevent cancerous phenotypes, including longer villi length in intestinal cells and prolonged cell survival that increase adiposity in mice (Fig. 2)
- Making dietary changes to reduce fructose levels or pharmacologically targeting the fructose-uptake pathway may thus improve treatment outcomes

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Patents:
US Application Filed

Publications:
Taylor et al. *Nature*. 2021.

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Technology Applications

- Restriction of dietary sugars (e.g., sucrose, fructose) may reduce the risk of oncogenesis in patients at high risk of developing colorectal cancer
- Special meal kits for cancer patients with reduced amounts of the identified sugars and proteins
- Administering inhibitors of GLUT5, KHK, FASN, PI3, or PKM2 activator to reverse cancer progression in individuals with high-sugar diets

Technology Advantages

- Dietary changes can be implemented immediately and are a low-cost option
- Drug candidates already exist for several genes in fructose-uptake pathway: PHGDH, GLUT5, KHK, FASN, PI3 kinase

Supporting Data / Figures

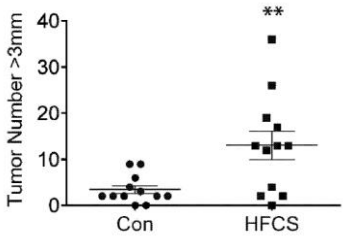

Figure 1: Mice fed with a HFCS diet have higher incidence of tumors ($p < 0.01$).

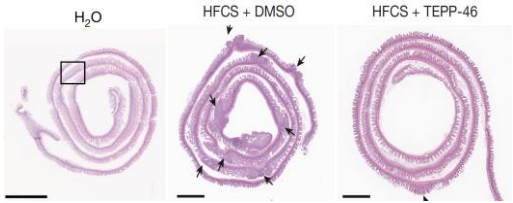

Figure 2: From left to right: normal intestine, untreated HFCS-fed mice, HFCS-fed mice treated with TEPP-46 (a PKM2 activator). Untreated HFCS-fed mice exhibit elongated villi and thus increased nutrient absorption and adiposity, encouraging tumor growth. Treatment with TEPP-46 abolishes the observed phenotype in HFCS-fed mice.

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