Title: Microbial Bile Acid, 3-oxo-LCA, inhibits colorectal cancer progression

Authors: F. Sun, X. Dong, T. Fu

Link: https://www.abstractsonline.com/pp8/#!/20272/presentation/6345

Citation:

Funding:

Scientific Abstract:

Colorectal cancer (CRC) affects a significant number of individuals each year, ranking as a leading cause of cancer-related deaths in the U.S. Bile acids (BAs), natural compounds crucial for digesting dietary fats, not only influence the gut microbiota but are also involved in gut health through their interaction with the Farnesoid X Receptor (FXR). Recent findings have highlighted certain microbiota-generated BAs like 3-oxo-lithocholic acid (LCA) and IsoLCA, modulate host immunity, hinder the expansion of intestinal pathogens, and potentially anti-aging. Despite the advancements in identifying the gut microbes behind these BAs, their precise impact on intestinal cells (IECs) and their role in disease progression are largely unexplored. Our pilot investigation unveiled 3oxoLCA as an FXR agonist, restoring FXR signaling in both cancer cells and APCmin/+ mice (a classic CRC mice model). As a result, 3-oxo-LCA inhibits the growth of both human and mouse CRC cells, such as MC38, CT26 and HCT116. Additionally, 3-oxo-LCA also restrained the intestinal stem cells (ISCs)' proliferation in organoids from both wild-type and APCmin/+ mice, and patient-derived CRC organoids (PDCOs). Remarkably, treatment with 3-oxo-LCA decreased BAs levels, improved gut barrier function, reduced tumor load, and inhibited tumor progression in APCmin/+ mice. Furthermore, 3-oxo-LCA significantly suppressed tumor growth in cancer cell-derived xenograft model mice. Crucially, the 3-oxo-LCA-FXR interaction transcriptionally regulated key apoptotic genes, encouraging cancer cell death. These discoveries highlight the therapeutic promise of incorporating 3-oxo-LCA into strategies for treating CRC.

Title: Microbioal bile acid, 7-oxo-dca, promotes intestinal tumorigensis

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Funding: This work is funded by University of Wisconsin–Madison startup grants (AAI3795, AAI3894), UWCCC startup support (AAI5122), UW fall competition support from Wisconsin Alumni Research Foundation (AAL8735), Badger Challenge award (AAM7958), PhRMA foundation Faculty Starter Grant (AAN1771), American Cancer Society Coaches vs. Cancer Bo Ryan-Jay Holliday Families Fund Research Scholar Grant (RSG-23-1150338-01), Margaret Q. Landenberger Research Foundation (AAM7699), and NIH 1R37CA288447-01 to TF.

Scientific Abstract:

Background: Colorectal cancer (CRC) affects over 100,000 patients annually and is the third leading cause of cancer-related deaths in the US. Bile acids (BAs), cholesterol-derived surfactants that emulsify dietary lipids to facilitate absorption, are critical mediators of gut physiology and metabolism, partly through affecting their natural receptors, Farnesoid X Receptor (FXR)'s activity. BAs dysregulation is a convergent point of genetic and dietary risk factors of CRC4. Recently, a couple of gut microbiome-derived BAs, such as 7-oxo-deoxycholic acid (7-oxo-DCA), have been identified in liver diseases. While the gut microbes responsible for generating 7-oxo-DCA have been identified, yet the impacts of 7-oxo-DCA on intestinal epithelial cells remain largely elusive.

Methods & Results: Here we discovered that 7-oxo-DCA elevated in both the serum and cecum samples of genetically mutated APCmin+/- mice, either on a normal chow diet (ND, adenoma model) or on a High-fat diet (HFD, adenocarcinomas model). Moreover, we found that 7-oxo-DCA facilitates human normal and cancer cell lines, HIEC6 and HCT116 cells' growth and migration. Further, 7-oxo-DCA promotes intestinal stem cells' proliferation in intestinal organoids generated from WT and APCmin+/- mice. In addition, our in vivo administration of 7-oxo-DCA in APCmin+/- mice displayed increased total BAs amount, higher gut permeability, and more tumor loads. Mechanistically, we revealed that 7-oxo-DCA is an antagonistic BA of FXR and downregulated FXR signaling in vitro and in vivo.

Conclusion: In summary, we uncover the novel role of a microbial BA, 7-oxo-DCA, and its role in promoting intestinal tumorigenesis. The modulation of the BA-FXR axis in the tumor initiation and progression will hasten the development of novel diagnostic and therapeutic tools for CRC.

Written Lay Abstract:

Over 100,000 people are diagnosed with colorectal cancer each year, and over 50,000 people die from colorectal cancer each year. The lining of the intestine needs bile acids to help move and absorb nutrients from our diet. When bile acids are not working normally, we can develop colorectal cancer. This scientist team studied two gut microbes (molecules) made by bile acids, called 7-oxo-DCA and 3-oxo-LCA.

The bile acid 7-oxo-DCA is related to liver disease, but we do not know if it affects colorectal cancer. The scientists took blood and intestine samples from mice with colorectal cancer. The 7-oxo-DCA was higher in these mice with colorectal cancer. The scientists also found that 7-oxo-DCA increases cell growth in both normal and cancer human cells. The bile acid 7-oxo-DCA also supported growth of mice's intestine stem cells. In the mice given 7-oxo-DCA, the intestines absorbed more water, nutrients, and molecules, and had more tumors. 7-oxo-DCA made regulation of bile acids and metabolism in the gut less likely.

Another bile acid called 3-oxo-LCA is responsible for immunity, stopping the spread of disease in the gut, and may even protect against aging. However, we do not know how this bile acid affects colorectal cancer. The scientists in this study found that 3-oxo-LCA increases regulation of bile acids and metabolism in the guts of mice and in human cancer cells. This means that 3-oxo-LCA lowers growth of colorectal cancer cells in mice and humans. Treating mice with colorectal cancer with 3-oxo-LCA lowered bile acids, improved their gut function, and lowered their number of tumors. 3-oxo-LCA also encouraged cancer cell death, which is important for stopping cancer.

This research tells us that the bile acid 7-oxo-DCA may be related to colorectal cancer, and that the bile acid 3-oxo-LCA may be useful in treatment of colorectal cancer. Altogether, this research helps us understand how colorectal cancer happens and how to better treat it.

Visual Lay Abstract: