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Biography

Feng He, is the Director of the Center for Cancer Research at the School of Integrated Medicine, Shanghai University of Traditional Chinese Medicine. His research focuses on the role of stress responses in regulating immune and metabolic homeostasis in gastrointestinal cancers and metabolic diseases, including fatty liver disease, He has published over 40 SCI-indexed papers in prestigious journals such as Cancer Cell, Journal of Hepatology, PNAS, Pharmacological Research, and Journal of Biological Chemistry. His work includes 9 highly cited papers and 2 hot papers, with more than 7,000 citations worldwide, Professor He has been recognized among the Stanford/Elsevier World's Top 2% Scientists. He has reviewed over 400 manuscripts for more than 70 international journals and serves as an Associate Editor or Editorial Board Member for journals including BMC Biology, eGastroenterology, and MedMat.

Role of Conjugated-Bile Acids (C-BAs) in hypernutrition-associated liver metastasis of colorectal carcinoma

Abstract:

Hypernutrition and hyperlipidemia are well-established risk factors for colorectal carcinoma (CRC) progression and metastasis. However, beyond conventional lipids such as triglycerides and cholesterol, the mechanisms linking hypernutrition to CRC liver metastasis—the most frequent site of distant spread—remain poorly understood. Here, using a mouse cecum orthotopic CRC model combined with high fat diet (HFD) feeding, along with in vitro endothelia cell assays, we showed that elevated circulating blood lipids, particularly primary conjugated-BAs (C-BAs), induced by excessive dietary fat intake, promoted CRC metastasis to liver. This effect is associated with disruption of both intestinal epithelial barrier (IEB) and gut vascular barrier (GVB). HFD-induced hypernutrition disrupts bile acid homeostasis, leading to increased bile acid levels in the serum, colon, and ileum. Notably, four primary C-BAs were significantly elevated: taurocholic acid (TCA), taurochenodeoxycholic acid (TCDCA), glycocholic acid (GCA), and glycochenodeoxycholic acid (GCDCA). Administration of individual BAs recapitulated the pro-metastatic effects of HFD in vivo. Mechanistically, these C-BAs impaired FXR-mediated feedback regulation of bile acid metabolism and activated oxidative stress and Ca^{2+}–MLCK signaling, resulting in GVB disruption. This was accompanied by decreased expression of tight junction (TJ) proteins, Claudin, Occluding, and ZO-1, but increased VEGFA and PV-1 expression, resulting in the increased intestinal permeability and enhanced liver metastasis of CRC. Importantly, the FXR agonist obeticholic acid restored FXR signaling, reduced intestinal permeability, and attenuated HFD-driven CRC liver metastasis. Our findings uncover a mechanistic link between dietary hypernutrition and GVB dysfunction mediated by conjugated bile acids, highlighting FXR as a potential therapeutic target for preventing hypernutrition-associated CRC metastasis.