Feng He

Shanghai University of Traditional Chinese Medicine
China

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

Abstract:

Hypernutrition and hyperlipidemia are established risk factors for colorectal carcinoma (CRC) progression and metastasis. However, beyond conventional lipids like triglycerides and cholesterol, the mechanisms linking hypernutrition to CRC liver metastasis, which is the most frequent site of distant metastasis, remain poorly understood. Here, by using mouse cecum orthotopic CRC model and high fat diet (HFD) feeding, as well as in vitro endothelia cell culturing, we showed that the increased blood lipids, specifically primary conjugated-BAs (C-BAs), induced by excessive dietary fat uptake, promotes CRC metastasis to liver, accompanied with disruption of intestinal epithelial barrier (IEB) and gut vascular barrier (GVB). HFD-induced hypernutrition and hyperlipidemia dysregulated bile acid metabolism, resulting in increased BA concentrations in 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 adverse effects of HFD feeding in vivo. Mechanistically, these C-BAs induced escape of FXR feedback to sense BA metabolism and activated oxidative stress/Ca2+-MLCK signaling to impair gut vascular barrier (GVB), accompanied with decreased expression of tight junction (TJ) proteins, Claudin, Occluding, and ZO-1, but increased VEGFA and PV-1 expression, resulting in the aggravated intestinal leakage and liver metastasis of CRC. TCDCA and GCDCA showed worse outcomes in the GVB disruption. The FXR agonist obeticholic acid rescued C-BAs-induced FXR signaling inhibition, reduced intestinal permeability, and attenuated HFD-driven CRC liver metastasis. Our findings establish a mechanistic link between dietary hypernutrition and GVB impairment, contributing to heightened liver metastasis of CRC, and support FXR as a promising therapeutic target for hypernutrition-associated CRC metastasis.

Biography

Feng He has completed his PhD from University of Oklahoma and postdoctoral studies from University of California, San Diego, School of Medicine. He is the director of the Center for Cancer Research, School of Integrated Medicine at Shanghai University of Traditional Chinese Medicine, China. He has published more than 35 papers in reputed journals, such as Cancer Cell, Journal of Hepatology, PNAS, Pharmacological Research, and Journal Biological Chemistry. Dr. He has been selected as one of the Stanford/Elsevier World's Top 2% Scientists and has been serving as an editorial board member of several repute journals.