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Commentary

Oxidative Stress and Genotoxicity Induced by Secondary Bile Acids: Mechanisms in Colorectal Neoplasia

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ABOUT THE STUDY

Bile acids are critical molecules in the human body that play an essential role in the digestion and absorption of dietary lipids. They are produced in the liver from cholesterol and released into the bile before entering in the intestinal lumen, where they function as solvents to break down and absorb lipids. Bile acids are now known as key signaling molecules that modulate a variety of physiological and pathological processes. The primary role of bile acids within the gastrointestinal system is to maintain lipid homeostasis, which is achieved by their amphipathic nature, allowing them to interact with both hydrophobic lipids and the aqueous environment of the intestine. However, an imbalance in bile acid production, secretion, or reabsorption can lead to profound disruptions in gastrointestinal health. These disruptions can appear in various ways, from functional bowel disorders to inflammatory conditions and malignancies. These illnesses are mostly caused by abnormal bile acid metabolism and altered bile acid signaling, which suggests that they are important mediators in the pathophysiology of the gastrointestinal tract.

The enterhepatic circulation of bile acids ensures their efficient recycling, as the majority of bile acids secreted into the intestine are reabsorbed in the ileum and returned to the liver. Disruption of this cycle can lead to malabsorption of fats and fat-soluble vitamins, contributing to symptoms such as steatorrhea and malnutrition. Furthermore, excessive exposure of the intestinal mucosa to bile acids due to impaired reabsorption can result in mucosal injury and increased intestinal permeability. These changes create a permissive environment for inflammation, microbial dysbiosis, and further pathological sequelae. Bile acids also function as signaling molecules through their interaction with nuclear and membrane receptors, such as the Farnesoid X Receptor (FXR) and the Takeda G Protein-Coupled Receptor 5 (TGR5). Activation of these receptors regulates a range of processes, including lipid and glucose metabolism, gut motility, and inflammation. Dysregulation of bile acid receptor signaling has been implicated in the pathogenesis of several gastrointestinal disorders. For instance, reduced FXR activity is associated with increased intestinal inflammation and dysbiosis, contributing to conditions such as Inflammatory Bowel Disease (IBD). Similarly, altered TGR5 signaling can impact bile acid-induced secretion and motility, leading to motility disorders and functional bowel conditions like Irritable Bowel Syndrome (IBS).

The interaction between bile acids and the gut microbiota further emphasizes their role in gastrointestinal health and disease. The gut microbiota actively participates in bile acid metabolism, converting primary bile acids into secondary bile acids through deconjugation and dehydroxylation. These secondary bile acids have distinct biological activities and can exert toxic effects on the intestinal epithelium if present in excessive concentrations. Dysbiosis, characterized by an imbalance in gut microbial composition, can disrupt this delicate interplay, resulting in altered bile acid breakdown that contribute to the development and progression of gastrointestinal disorders. Bile acids can influence microbial composition and function, creating a bidirectional relationship that is important for maintaining intestinal homeostasis. In addition to their roles in metabolic and inflammatory pathways, bile acids are potent modulators of the intestinal barrier. They influence the expression and distribution of closed junction proteins, which regulate the permeability of the intestinal epithelium. Disruption of the intestinal barrier due to bile acid imbalance can lead to increased translocation of luminal antigens and pathogens, causing immune responses and exacerbating inflammation. This mechanism is particularly relevant in conditions such as IBD and Small Intestinal Bacterial Overgrowth (SIBO), where barrier dysfunction is one of the features.

The role of bile acids in gastrointestinal disorders extends to their impact on motility and secretion. Bile acids stimulate water and electrolyte secretion in the intestine, which is important for maintaining the fluidity of intestinal contents and facilitating digestion and absorption. However, excessive secretion driven by bile acid malabsorption or overproduction can result in diarrhea, as seen in Bile Acid Diarrhea (BAD). Conversely, reduced bile acid production or secretion may contribute to

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constipation by impairing the normal stimulatory effects on gut motility and secretion. Chronic exposure to high levels of bile acids in the colon has been implicated in the development of colorectal cancer. Secondary bile acids, such as deoxycholic acid and lithocholic acid, can exert genotoxic and cytotoxic effects, promoting DNA damage, oxidative stress, and inflammation. These effects contribute to the initiation and progression of colorectal neoplasia, emphasizing the complex role of bile acids as both physiological mediators and pathological agents.