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Perspective

The Role of Bile Acids in Cholestasis and Fibrosis: Mechanisms of Liver-Gut Axis Dysregulation

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ABOUT THE STUDY

Bile acids play a pivotal role in the regulation of various Gastro Intestinal (GI) functions, influencing both normal and pathological processes within the digestive system. These molecules, primarily synthesized in the liver from cholesterol, are important for the emulsification and absorption of dietary fats and fat-soluble vitamins in the small intestine. Their dynamic interaction with different cellular and molecular pathways impacts gut motility, microbiota composition, and the immune response, making them important in the development and progression of a wide range of GI disorders. The precise mechanisms through which bile acids exert their effects on GI health are complex, involving signaling pathways, nuclear receptors, transporters, and enzymes that are distributed throughout the GI tract. One of the fundamental roles of bile acids is their ability to facilitate the digestion and absorption of lipids. Upon secretion into the duodenum, bile acids emulsify fats, breaking them into smaller droplets that are more easily digested by pancreatic enzymes. This process is important for the absorption of long-chain fatty acids and fat-soluble vitamins like vitamins A, D, E, and K. Disruptions in bile acid metabolism or secretion can lead to malabsorption of these nutrients, which in turn may contribute to various GI disorders such as malnutrition, diarrhea, and steatorrhea.

However, bile acids are not only involved in digestion but also act as signaling molecules that regulate several aspects of GI function. They interact with nuclear receptors, particularly the Farnesoid X Receptor (FXR) and the Pregnane X Receptor (PXR), which is present in the liver, intestines, and other tissues of the GI tract. Activation of these receptors by bile acids regulates the expression of a variety of genes involved in bile acid synthesis, transport, and metabolism. This regulatory feedback loop is critical for maintaining bile acid homeostasis and ensuring the optimal functioning of the digestive system. In situations where bile acid levels are dysregulated, such as in certain liver diseases, this feedback mechanism can be disrupted, leading to pathologic bile acid accumulation or deficiency, both of which contribute to GI dysfunction.

The interaction of bile acids with the gut microbiota is another key aspect of their role in GI health. The gut microbiome is a complex community of microorganisms that play a central role in nutrient metabolism, immune modulation, and barrier function. Bile acids are known to influence the composition and diversity of the gut microbiota, and conversely, the microbiota can modify bile acid composition by converting primary bile acids into secondary bile acids. For example, alterations in the microbiota, such as in conditions like Inflammatory Bowel Disease (IBD) or Irritable Bowel Syndrome (IBS), can lead to changes in bile acid profiles, which may exacerbate symptoms or contribute to disease progression. Moreover, the presence of certain bile acids in the colon can affect microbial growth, influencing both local and systemic immune responses. Bile acids also play a critical role in regulating gut motility. Through their action on specific receptors, such as the bile acid receptor Takeda G protein-coupled receptor 5 (TGR5), bile acids can modulate smooth muscle contractions in the intestines, influencing the movement of contents through the GI tract. This can have profound effects on the clinical presentation of GI disorders, including conditions characterized by abnormal motility, such as IBS or functional dyspepsia. In addition, bile acid-induced motility changes can contribute to symptoms such as diarrhea or constipation, which are commonly observed in GI disorders like Bile Acid Malabsorption (BAM). BAM is a condition where the normal reabsorption of bile acids in the ileum is impaired, resulting in excessive bile acids in the colon, which leads to fluid secretion, diarrhea, and discomfort.

The role of bile acids in inflammation and immune response is another area of increasing interest. Bile acids have been shown to modulate the immune system both locally in the GI tract and systemically. By activating receptors like FXR and TGR5, bile acids can regulate the production of pro-inflammatory cytokines, chemokines, and antimicrobial peptides, which help maintain the balance between host defense and tolerance to commensal microorganisms. In disorders such as IBD, which includes Crohn's disease and ulcerative colitis, bile acid-induced changes in the immune response may contribute to the chronic inflammation seen in these conditions. Additionally, dysregulated bile acid signaling can lead to an exaggerated

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immune response, promoting the development of colitis or exacerbating disease progression. Bile acids also have direct effects on the intestinal epithelial cells, influencing intestinal barrier function and permeability. The integrity of the intestinal barrier is important for maintaining gut homeostasis and preventing the translocation of pathogens and toxins from the gut lumen into the bloodstream. Bile acids, through their action on various signaling pathways, help preserve tight junctions between epithelial cells, which are need for maintaining barrier integrity. In conditions like bile acid reflux or cholestasis, where there is an accumulation of bile acids in the liver or intestines, the barrier function can be compromised, leading to intestinal inflammation, increased permeability, and a higher risk of infections.