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Commentary

Advances in Liver Physiology and Metabolic Homeostasis

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DESCRIPTION

The liver is one of the most metabolically active organs in the human body, serving as the central regulator of carbohydrate, lipid, protein and micronutrient metabolism. Beyond its well recognized roles in detoxification and bile production, the liver functions as a dynamic metabolic hub that maintains systemic homeostasis by integrating hormonal, nutritional and neural signals. Recent advances in liver physiology have significantly expanded our understanding of hepatic function, revealing complex molecular networks that govern metabolic adaptation in both health and disease. These discoveries are reshaping the prevention, diagnosis and treatment of metabolic disorders that continue to rise worldwide. One of the most important developments in liver physiology has been the recognition of the liver as an active endocrine organ. Hepatocytes synthesize and secrete numerous signaling molecules, collectively known as hepatokines, which influence metabolism in distant organs including skeletal muscle, adipose tissue, the pancreas, and the brain. Molecules such as Fibroblast Growth Factor 21 (FGF21), angiopoietin like proteins and fetuin. A participate in regulating glucose utilization, lipid oxidation, insulin sensitivity, and energy expenditure. The identification of these liver derived factors has shifted the traditional view of hepatic physiology from a passive metabolic processor to an active coordinator of whole body metabolic homeostasis.

The regulation of glucose metabolism remains one of the liver's most essential physiological functions. During fasting, the liver maintains blood glucose concentrations through glycogenolysis and gluconeogenesis, ensuring a continuous energy supply to glucose dependent tissues. Following food intake, hepatic glucose uptake and glycogen synthesis help restore energy reserves while preventing excessive hyperglycemia. These tightly regulated processes depend on coordinated interactions between insulin, glucagon, cortisol and numerous intracellular signaling pathways. Disruptions in hepatic glucose regulation contribute directly to insulin resistance and the development of type 2 diabetes mellitus, making this area a major focus of current metabolic research. Advances in lipid metabolism have also transformed our understanding of liver physiology. The liver orchestrates fatty acid synthesis, cholesterol metabolism, lipoprotein production and fatty acid oxidation. However, excessive caloric intake and sedentary lifestyles have contributed to a global increase in Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD), previously known as non-alcoholic fatty liver disease. Researchers now recognize that hepatic fat accumulation is not merely a consequence of obesity but also an important driver of systemic metabolic dysfunction. Lipotoxicity, oxidative stress, mitochondrial dysfunction and chronic inflammation collectively impair hepatic function and accelerate disease progression toward fibrosis, cirrhosis and hepatocellular carcinoma.

Mitochondrial physiology has emerged as another critical area of investigation. Hepatic mitochondria generate the majority of cellular through oxidative phosphorylation while regulating fatty acid oxidation, reactive oxygen species production and apoptosis. Impaired mitochondrial function contributes to metabolic imbalance and chronic liver disease by reducing energy efficiency and promoting oxidative injury. Recent studies have identified mitochondrial quality control mechanisms, including mitophagy and mitochondrial biogenesis, as promising therapeutic targets capable of restoring metabolic homeostasis and preventing liver injury. Growing attention has also been directed toward the liver gut axis. The liver continuously receives nutrients, microbial metabolites, bile acids and inflammatory mediators through the portal circulation, creating an intimate relationship between hepatic physiology and the intestinal microbiome. Alterations in gut microbial composition influence bile acid metabolism, immune activation and hepatic lipid accumulation, thereby contributing to insulin resistance and chronic liver disease. Modulation of the gut microbiota through dietary interventions, probiotics, prebiotics and microbiome based therapies represents an exciting frontier in metabolic medicine.

Technological innovations are accelerating discoveries in hepatic physiology. Single-cell transcriptomics, spatial omics, metabolomics, and advanced imaging technologies now enable researchers to examine liver architecture and cellular interactions with unprecedented precision.

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