



GUEST EDITORIAL

The Cellular, Molecular, and Pathologic Consequences of Stress on the Liver



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It has been well documented that stress responses have detrimental effects on liver tissue. Stress and stress-responsive factors disrupt liver homeostasis and activate cellular and pathophysiological mechanisms.¹ This, in turn, exacerbates both acute and chronic hepatic pathologic conditions.² Although significant advances have been made in our understanding of these mechanisms, critical gaps remain in defining the crosstalk between these pathways. Consequently, therapeutic targeting of stress responses remains challenging in the context of liver diseases. This special theme issue is a collection of reviews that highlight the different types and mechanisms of stress and stress responses that contribute to liver disease and how effective management of these interconnected pathways may uncover novel treatment options.

Stress response pathways, such as the unfolded protein response (UPR), the integrated stress response, and the oxidative stress response, play central roles in cellular adaptation of pathologic states and enable restoration of tissue homeostasis. The review by Hanquier et al³ describes the role of UPR and integrated stress response in liver fibrogenesis mediated by activated hepatic stellate cells. Multiple stress-responsive mechanisms converge to regulate UPR and integrated stress response. Therefore, it is critical to understand the regulatory elements that impact fibrogenesis. This review highlights the importance of therapeutic targeting of activated hepatic stellate cells and associated stress response mechanisms to alleviate liver injury and limit fibrosis. Increasing evidence links endoplasmic reticulum stress with progression of liver cancers.

Luna-Marco et al⁴ provide a comprehensive review on the role of UPR on hepatocellular cancer pathogenesis. The review underlines the important role of various metabolic pathways and illustrates how disruption of metabolism

correlates with increased endoplasmic reticulum stress and hepatocellular cancer progression. Jackson et al⁵ discuss the cellular and molecular mechanisms regulating endoplasmic reticulum stress and the UPR in the progression of various liver diseases through promoting cell damage, inflammation, and death. In addition, the review also brings to light the multiple pharmacologic and biological interventions that target the UPR. Other forms of stress, including oxidative stress, also influence chronic liver disease. Banerjee et al⁶ provide a detailed perspective on how oxidative stress, induced by reactive oxygen species, affects a myriad of liver diseases. The review outlines the sources of reactive oxygen species in the liver and consequences of oxidative stress on alterations in the liver vasculature and progression of liver pathologies.

Alcoholic liver disease in itself is associated with activation of several stress response pathways that contribute to its progression. One such pathway is autophagy, a process well established to be important in liver

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disease, but not well understood. The review by Qian and Ding⁷ provides insights into the important roles of the autophagic protein p62, which accumulates as a result of impaired autophagic response. Significant progress has been made in mechanisms modulating autophagy and liver diseases in recent years. This review emphasizes the regulatory role of p62 in protein quality control, formation and degradation of stress granules, and accumulation of hepatic inclusion bodies that impact progression of alcoholic liver disease. Iron loading is also implicated in alcoholic liver disease progression. Ali et al⁸ provide a detailed overview of the role of iron loading in exacerbation of alcohol-induced liver injury. The multiple cellular and molecular mechanisms underlying alcohol-induced iron loading in the liver are described, as well as how elevated iron levels in patients with alcoholic liver disease promote liver fibrosis and aggravate disease pathogenesis.

Cholestatic liver diseases are another area where stress responses have been an important area of study. Hrnčir et al⁹ underline how intrahepatic bile ducts respond to stress and injury, and they provide a comprehensive overview on the signaling mechanisms and tissue- and cellular-level responses by the biliary epithelial cells across a large spectrum of cholangiopathies. This study also identifies potential critical overlapping mechanisms exhibited by the biliary epithelial cells in response to stress that might pave the way for common therapeutic targeting of specific cellular responses. Cholestatic liver diseases are also influenced by hormones, such as estrogen. Ismail et al¹⁰ discuss how physiological stress can directly impact estrogen levels and influence progression of cholestatic diseases. The review provides an overview of the key aspects of sexual dimorphism on estrogen signaling and how understanding the multifaceted roles of estrogen can enable development of therapeutic strategies to combat chronic cholestatic diseases.

Finally, an important, but understudied, aspect of liver diseases is the contribution of the gut microbiota. The review by Pant et al¹¹ focuses on the role of butyrate, a gut microbiota-derived short-chain fatty acid, in liver disease and metabolic regulation. The blood draining from the gut to the liver directly exposes the liver to a large amount of gut microbiota-derived metabolites. Understanding the

contribution of butyrate to metabolism may be helpful in the prevention of liver diseases. The article provides an overview of the beneficial therapeutic as well as the adverse outcomes of the clinical use of butyrate in multiple hepatic pathologies.

In summary, this thematic collection of reviews provides a comprehensive understanding of basic and clinical research correlating hepatic tissue injury to stress. It details the novel cellular mechanisms and proposed therapeutic intervention strategies that are currently employed to uncover multiple facets of hepatic injury and tissue response to stress.

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