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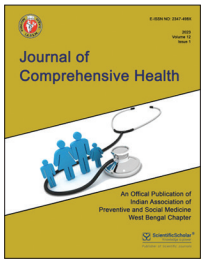

Review Article

Non-alcoholic Steatohepatitis and Hepatocellular Carcinoma are Influenced by Oxidative Stress, Inflammation, and Apoptosis via Activating the AMPK-Caspase Axis and JAK/STAT Pathway

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ABSTRACT

The progression of non-alcoholic fatty liver disease (NAFLD) to hepatocellular carcinoma (HCC) and non-alcoholic steatohepatitis (NASH) is looked at in this article. It highlights how inflammation, oxidative stress, apoptosis, and fat accumulation all contribute to this development. Mouse models and patient data are used in the study to explore these pathways. NASH development is linked to the adenosine monophosphate-activated protein kinase (AMPK)-caspase 6 axis, where fibrosis is correlated with caspase 3 and 6 activation. There are preventive benefits against NASH when caspase 3 and 6 are inhibited. Reduction of inflammation and oxidative stress can result in reduced fibrosis and steatosis, which are important contributors to the pathogenesis of NASH. In NASH, the immune system is also essential for managing the inflammatory milieu. The transformation of NAFLD-NASH-HCC is attributed in part to lipid buildup, apoptosis, oxidative stress, inflammation, and the immune system, according to the research. The importance of oxidized phospholipids and the Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathway in the development of HCC and the progression of NASH are also covered. The results offer significant perspectives on possible therapeutic targets, including the JAK/STAT pathway and the AMPK-caspase axis.

Keywords: Hepatocytes, Oxidative stress, Inflammation, Apoptosis, Non-alcoholic fatty liver disease-non-alcoholic steatohepatitis-hepatocellular carcinoma, Adenosine monophosphate-activated protein kinase-caspase axis, Janus kinase/signal transducers and activators of transcription

INTRODUCTION WITH OBJECTIVES

The development of non-alcoholic fatty liver disease (NAFLD) and it's more severe form, non-alcoholic steatohepatitis (NASH), is influenced by lipid metabolism and inflammation. Lipid buildup in NASH causes liver damage and programmed cell death.[1-3] Research indicates that NASH patients have elevated levels of inflammation and cell death in contrast to individuals with uncomplicated steatosis. One kind of cell death called necroptosis is assumed to be crucial for the development of NASH. Fibrosis formation is correlated with higher activation of caspase 6, a particular mechanism implicated in cell death in NASH.[4] NASH is also a result of inflammation, with tumor necrosis factor (TNF) signaling mitigating liver damage and hepatocyte death.[5] Hepatocyte damage and mortality are impacted by oxidative stress, which is brought on by an imbalance in the generation of intracellular reactive oxygen species (iROS) and intracellular antioxidant molecules.[3,6] It has been

discovered that the progression from basic steatosis to NASH is accelerated by nuclear factor erythroid 2-related factor (NRF 2), a master regulator of antioxidant response.[7] NAFLD is associated with the Janus kinase/signal transducers and activators of the transcription (JAK/STAT) signaling pathway and P38 mitogen-activated protein kinase (P38 MAPK).[8] One possible treatment strategy to lessen fat buildup is to alter these pathways. In NASH, the immune system plays a role in regulating inflammation since pro-inflammatory substances lead to the death of hepatocytes under stress. Targeting oxidized phospholipids has been tried to delay the evolution of NASH since they are a factor in oxidative stress. In general, hepatocellular death, inflammation, and fibrosis in NASH are caused by the interplay of lipid metabolism, inflammation, oxidative stress, and immune cell activity. Comprehending these pathways is essential to formulating efficacious therapy approaches for the advancement of NAFLD-NASH-HCC.

THE DEVELOPMENT OF NASH AND HEPATOCELLULAR INJURY: THE ROLE OF LIPIDS

Lipids play an important role in hepatocellular injury by increasing the chances of hepatocellular programmed cell death. As NASH occurs when hepatic leukocytes (e.g., macrophages) locally release proinflammatory cytokines, steatosis induced by long-term feeding of a high-fat diet (HFD) may sensitize hepatocytes to cytokine-induced cell death in a murine model.[9,10] On the contrary, it has been shown that NASH patients experience more apoptosis and inflammation in comparison to simple steatosis patients.[11] It can be hypothesized that necro apoptosis may also play a pivotal role in the pathogenesis of NASH.[12] It is also evidenced that apoptosis of the liver can also encourage the development of NASH in murine models. In contrast, eliminating Ikbkg in hepatocytes prevents nuclear factor-B signaling's pro survival impact, which causes stochastic hepatocyte cell death and liver damage in Hep∆*Ikbkg* mice fed a conventional chow diet, which eventually causes steatosis, NASH, and thereby hepatocellular carcinoma (HCC), this depicts how NAFLD develops naturally.[13]

ADDRESSING THE FUNCTION OF HEPATOCYTE SUSCEPTIBILITY, THE ADENOSINE MONOPHOSPHATE-ACTIVATED PROTEIN KINASE (AMPK)-CASPASE AXIS, AND IMMUNE ORGANS IN THE PATHOPHYSIOLOGY OF NASH

A recent study suggested that there is an indirect relation between the hepatosplenic axis in the development of NAFLD and immune disturbances.[3,14-16] Further studies are needed to escalate the role of immune organs in the development of NAFLD-NASH-HCC through disturbing redox equilibrium and immune homeostasis in clinical trials. Furthermore, a hallmark of the major urinary protein (MUP)-urokinase-type plasminogen activator (uPA) mouse model is increased hepatocyte susceptibility to cell death. MUP-uPA mice already exhibit increased hepatocyte death compared to wild-type mice. In addition to increasing hepatocyte death and precipitating NASH, HFD feeding of MUP-uPA mice leads to more NASH development.[17] NASH was also found to be associated with hepatocyte apoptosis when AMPK was deleted in hepatocytes. In a diet-induced model of NASH, the deletion of AMPK led to the death and acceleration of fibrosis in hepatocytes; the activation of caspase six by AMPK limits the death of hepatocytes during NASH.[4] Therefore, it can be stated that the AMPK-caspase 6 axis plays a pivotal role in the pathogenesis of NASH. However, the activation of caspase six is increased in various mouse models of NASH and correlates with the development of fibrosis in NASH patients. A broad-spectrum caspase inhibitor protects against NASH in mice that are induced by diet through caspase six inhibition.[4,18,19] A crucial role of inflammation in NASH is the reduction of hepatocyte death and liver injury caused by TNF-induced signaling, which ultimately leads to reduced steatosis and fibrosis in the liver.[5] Furthermore, a recent study stated that the activation of caspase 3 in a flavor-enhancing high-lipid diet-fed rat model also developed NAFLD-mediated cell death by lowering mitochondrial transmembrane potential. It can further lead to NASH. On the contrary, the inhibition of caspases by exogenous antioxidants blunted this anomalous situation.[2,3,14,20] Therefore, HFD-induced stress and hepatocellular apoptosis are significant components of the pathogenesis of NASH via targeting the AMPK-caspase axis. Furthermore, the liver environment during NASH also stimulates oxidative stress in both mouse models and patients.[21,22]

NEW ROUTES AND MEDICINAL OBJECTIVES IN NAFLD

Moreover, Nfe2l2 knockout mice have an accelerated transition from simple steatosis to NASH in response to diet-induced NASH induced by NRF2, a master regulator of antioxidant response.[7] Moreover, Hep∆*Ikbkg* mice are more prone to oxidative stress, and antioxidants mitigate the progression to NASH.[13] During NASH, oxidative stress causes hepatic protein tyrosine phosphatases to be oxidized and inactivated, like protein tyrosine phosphatase non-receptor type (PTPN) 2; as a result of PTPTN2 deletion in hepatocytes, uncontrolled signals are generated through STAT1 and STAT3, accelerating steatosis progression to NASH and HCC progression from NASH.[23] In addition, a major factor in the development of NAFLD is the JAK-STAT signaling pathway. P38γ, one of the P38 MAPKs, controls the JAK/STAT pathway in NAFLD. It has been demonstrated that in mouse hepatocytes exposed to free fatty acids,

inhibition of P38γ suppresses lipid formation. These results imply that by modifying the JAK/STAT cascade, targeting P38γ may be a viable therapeutic approach for decreasing lipid accumulation in NAFLD.[8]

THE DEVELOPMENT OF NASH AND HCC IS ASSOCIATED WITH OXIDATIVE STRESS, INFLAMMATION, AND LIPOGENESIS

NASH, fibrosis, and HCC development are independently promoted by oxidative stress. Hepatocytes are more susceptible to cytokine-induced cell death when mitochondrial oxidative stress occurs due to hepatic accumulation of free cholesterol.[24] There is a crucial role for the immune system in controlling the inflammatory environment in NASH; emphatically, proinflammatory factors such as TNF, produced by immunocytes, cause lipid-loaded, stressed hepatocytes to die, and these liver cells are then susceptible to cell death by cytokines.[25] In addition, the oxidized phospholipids produced during NASH are also non-enzymatic products of oxidant-mediated lipid peroxidation, whereas they produce iROS and cause mitochondrial damage. In addition, a diet-induced mouse model of NASH-HCC shows a reduction in oxidative stress, inflammatory response, fibrosis, liver cell death, and progression of NASH-to-HCC when oxidized phospholipids were neutralized by antibodies.[6] It has been shown that neutralizing oxidized phospholipids on NASH progression have beneficial effects. Thus, oxidative stress, inflammation, and lipid loading all interact during NASH to incite hepatocellular death, which results in hepatocellular derangements, inflammation, and fibrosis of liver tissue. NASH onset and severity are modulated by the immune cell-rich environment in the liver due to inflammation's role in these processes. Proinflammatory factors such as ATP or extracellular vesicles and endothelial cells released by hepatocytes also provoke inflammation, and chemokines such as TNF, interleukin(IL)-6, and chemokine (C-C motif) ligand (CCL) 2.[26-29] Even though non-immune cell types (e.g., hepatocytes and endothelial cells) can also influence hepatic inflammation in different mechanisms, the article mainly warned about the cross-talk between the apoptosis of hepatocytes to contribute to NAFLD and NASH to develop HCC.

CONCLUSION

This study highlights the significance of lipid accumulation, apoptosis, oxidative stress, and inflammation in the development of NASH and HCC. The findings suggest that hepatocellular apoptosis, mediated by various factors such as the AMPK-caspase axis, plays a pivotal role in NASH pathogenesis. Inhibition of caspase shows protective effects against NASH. Oxidative stress and inflammation further contribute to NASH progression, while antioxidants can mitigate its development. The immune cell-rich environment in the liver modulates NASH onset and severity through inflammatory processes. Moreover, the neutralization of oxidized phospholipids shows beneficial effects in reducing oxidative stress, inflammation, and fibrosis, thereby preventing NASH-to-HCC progression. Overall, the cross-talk between hepatocyte apoptosis, lipid accumulation, oxidative stress, and inflammation plays a crucial role in the development of NAFLD, NASH, and HCC. These findings provide insights into potential therapeutic targets and interventions to prevent and treat NAFLD-mediated NASH and its associated complications through targeting the AMPK-caspase axis and JAK/STAT pathway.

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Ethical approval

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Declaration of patient consent

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There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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