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Contents

Monthly Volume 16 Number 7 July 27, 2024

EDITORIAL

ORIGINAL ARTICLE

Retrospective Cohort Study

Retrospective Study

Prospective Study

Basic Study

LETTER TO THE EDITOR

World Journal of Hepatology

Monthly Volume 16 Number 7 July 27, 2024

Contents

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LETTER TO THE EDITOR

Acute liver failure: A clinically severe syndrome characterized by intricate mechanisms

Ran An, Jing-Lin Wang

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Abstract

Acute liver failure presents as a clinical syndrome characterized by swift deterioration and significant mortality rates. Its underlying mechanisms are intricate, involving intricate interplays between various cells. Given the current scarcity of treatment options, there's a pressing need to diligently uncover the disease's core mechanisms and administer targeted therapies accordingly.

Key Words: Acute liver failure; Hepatocyte; Macrophage; Necroptosis; Pyroptosis; Ferroptosis

Core Tip: Acute Liver Failure (ALF) is a clinical syndrome characterized by a complex pathogenesis and a high mortality rate. The core mechanism that triggers ALF has been shown to be the imbalance of the immune microenvironment. The functions of the immune system during liver injury are diverse, encompassing both the early clearance of damaging substances and later tissue repair. However, achieving a smooth transition between these functions and avoiding the aggravation of liver injury caused by excessive activation or suppression of the immune system is a current research hotspot.

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TO THE EDITOR

Acute liver failure (ALF) can be caused by various factors, including medications, viral infections, physical injury, and autoimmune reactions. We have reviewed the fascinating study of Li *et al*[1], in which they suggest that hepatocyte pyroptosis leads to monocyte infiltration in the liver, ultimately resulting in the development of ALF.

This study intriguingly revealed that hepatocytes undergoing pyroptosis exhibit high expression of monocyte chemotactic protein 1 (MCP1), which then promotes the recruitment of macrophages and ultimately leads to ALF. The current understanding is that programmed cell death, encompassing pyroptosis, ferroptosis, and necroptosis, is the main mechanism of hepatocyte injury in ALF. Damage-associated molecular patterns (DAMPs) released from injured cells activate the innate immune system, leading to the recruitment of circulating immune cells[2,3]. However, the aforementioned article suggests that MCP1, crucial for macrophage recruitment, is also produced by pyroptotic hepatocytes. This finding provides a basis for targeting therapeutic interventions towards reducing hepatocyte pyroptosis or modulating the MCP1-CC chemokine receptor type 2 axis to address ALF.

However, the study does possess certain limitations due to the presence of multiple pathways of hepatocyte death in ALF. For instance, acetaminophen induces ferroptosis in hepatocytes by increasing growth arrest specific 1 levels[4]. Additionally, the combination of HBV X protein and D-galactosamine can produce similar effects by inhibiting the expression of solute carrier family 7 member 11[5]. Concanavalin A triggers the release of various inflammatory factors by activating T lymphocytes, consequently leading to hepatocytes necroptosis[6]. Ultimately, the release of DAMPs activates the immune system within the liver, resulting in corresponding outcomes. Therefore, focusing solely on pyroptosis to reduce macrophage recruitment may offer limited effectiveness.

As the largest immune organ, the liver is rich in Kupffer cells (KCs), natural killer cells, natural killer T cells, and numerous other innate immune cells, all of which are essential for handling different pathogenic substances circulating in the body[7]. Indeed, the prevailing consensus, as emphasized in aforementioned study, is that macrophage recruitment worsens liver injury[8]. This is due to the significant infiltration of inflammatory cells in early stages of the disease, aimed at clearing necrotic substances, which can result in the excessive release of inflammatory factors and the subsequent death of more cells. It is important to note that this outcome is not only solely due to macrophages but also involves other innate immune cells as well as subsequent adaptive immunity. For instance, neutrophils can even induce hepatocyte injury through the formation of extracellular traps[9]. Therefore, in addition to investigating the role of macrophage recruitment by pyroptotic hepatocytes in causing tissue damage, it is imperative to delve deeper into the specific mechanisms underlying macrophage function in the liver.

In vivo, about 90% of macrophages are located within the liver, primarily comprising resident KCs along with macrophages derived from monocytes or peritoneum[10]. In instances of liver injury, there is a significant increase in the number of macrophages within the liver, either through their own proliferation or recruitment from other sites. Under various stimuli, these macrophages can assume different functional states, a phenomenon often referred to as polarization effects. In the later phases of disease, macrophages transition into an M2 phenomenon, actively participating in the process of liver damage restoration[10]. Consequently, indiscriminately reducing macrophage infiltration could potentially impede subsequent liver regeneration. At the same time, it is suggested that researchers should also explore whether macrophages undergo pyroptosis or other forms of cell death. Studies indicates that the release of interleukin-1β and interleukin-18 from pyroptotic macrophages is heightened, exacerbating inflammatory damage to liver cells. Simultaneously, the release of DAMPs can directly intensify hepatocyte injury[11,12]. In summary, we suggest that future research on macrophages during liver injury should concentrate on interventions to revert their proinflammatory state early on and evaluate the influence of their survival on liver injury outcomes. This approach may provide valuable insights into potential therapeutic strategies for managing liver damage and promoting tissue regeneration.

In summary, the functions and survival status of macrophages undergo dynamic changes during the liver injury process. When focusing on ALF, it is important to consider the role of macrophages in inducing monocyte recruitment, as well as their ability to clear necrotic tissue and promote repair. Future research on ALF treatment should prioritize improving the immune microenvironment in the liver, correcting the excessive pro-inflammatory actions of macrophages, and promoting their transition to a tissue repair functional state.

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