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Варша Гопакумар Наир
Ассистент кафедры патологической анатомии
Самаркандский государственный медицинский университет

РАСКРЫТИЕ МЕХАНИЗМОВ КЛЕТОЧНОЙ ГИБЕЛИ ПРИ ВОСПАЛЕНИИ ПЕЧЕНИ

Резюме

Воспаление в печени играет двойственную роль: при контролируемом течении оно может быть защитным, способствуя восстановлению тканей и поддержанию гомеостаза, однако при чрезмерной активации приводит к массивной гибели гепатоцитов и усугублению заболеваний печени. Как резидентные, так и рекрутированные иммунные клетки вносят вклад в гибель гепатоцитов за счёт высвобождения воспалительных медиаторов, включая цитокины, хемокины, активные формы кислорода и липидные медиаторы. Гибель гепатоцитов, в свою очередь, стимулирует врождённые иммунные ответы через высвобождение DAMP-молекул (молекул, ассоциированных с повреждением), формируя порочный круг воспаления и повреждения тканей. Понимание клеточных и молекулярных механизмов, лежащих в основе этих процессов, имеет решающее значение для разработки терапевтических подходов, направленных на снижение повреждения печени и предотвращение прогрессирования к фиброзу и раку.

Ключевые слова:
воспаление печени, гибель гепатоцитов, апоптоз, некроз, иммунно-опосредованное повреждение печени, молекулы, ассоциированные с повреждением (DAMPs), клетки Купфера, фиброз печени, воспалительные сигнальные пути.

Varsha Gopakumar Nair
Assistant, Department of Pathological Anatomy
Samarkand State Medical University

UNRAVELING THE MECHANISMS OF CELL DEATH IN LIVER INFLAMMATION

Resume

Inflammation in the liver exhibits a dual role: it can be protective when controlled, promoting tissue repair and homeostasis, but harmful when excessive, leading to massive hepatocyte loss and worsening liver diseases. Both resident and recruited immune cells contribute to hepatocyte death through the release of inflammatory mediators, which include cytokines, chemokines, reactive oxygen species, and lipid messengers. Hepatocyte death further stimulates innate immune responses via DAMPs, establishing a vicious cycle of inflammation and tissue damage. Understanding the cellular and molecular mechanisms that drive this process is crucial for developing therapies to mitigate liver injury and prevent progression to fibrosis and cancer.

Keywords: Hepatic inflammation, hepatocyte death, apoptosis, necrosis, immune-mediated liver injury, damage-associated molecular patterns (DAMPs), kupffer cells, liver fibrosis, inflammatory signaling pathways.

Abstract

Liver inflammation can play either protective or harmful roles depending on its intensity and duration. Mild, self-limiting inflammatory responses have been shown to support hepatocyte survival, facilitate tissue repair, and restore liver homeostasis. In contrast, excessive or persistent inflammation can trigger widespread hepatocyte death, aggravating various liver disorders, including ischemia-reperfusion injury, metabolic diseases such as obesity, diabetes, and non-alcoholic fatty liver disease, alcoholic hepatitis, xenobiotic-induced toxicity, and infections. These conditions may lead to irreversible liver damage, fibrosis, or even cancer. Both liver-resident cells (e.g., Kupffer cells, hepatic stellate cells, sinusoidal endothelial cells) and infiltrating immune cells (e.g., monocytes, macrophages, dendritic cells, natural killer cells) release pro-inflammatory mediators, including cytokines, chemokines, lipid signaling molecules, and reactive oxygen species, promoting hepatocyte apoptosis or necrosis.

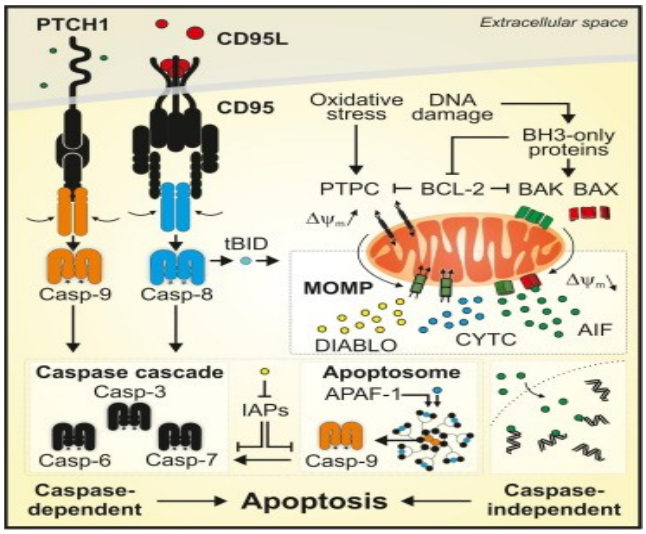
Introduction

Liver inflammation exhibits a dual nature, being either protective or harmful depending on its intensity and duration. Mild, self-limiting inflammatory responses support hepatocyte survival, promote tissue repair, and help restore liver homeostasis. Conversely, excessive or chronic inflammation can trigger widespread hepatocyte death, aggravating a variety of hepatic conditions, including ischemia-reperfusion (IR) injury, metabolic disorders such as obesity, diabetes, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), alcoholic hepatitis, xenobiotic toxicity, and infections. These processes are often associated with irreversible liver damage, fibrosis, and even carcinogenesis.

Both liver-resident cells, such as Kupffer cells, hepatic stellate cells, and sinusoidal endothelial cells, and immune cells recruited to the liver under stress—including monocytes, macrophages, dendritic cells, and natural killer cells—release a variety of pro-inflammatory mediators. These include cytokines, chemokines, lipid signaling molecules, and reactive oxygen species, which can directly induce hepatocyte apoptosis or necrosis. Dying hepatocytes release damage-associated molecular patterns (DAMPs) that activate innate immune responses, creating a self-amplifying cycle of inflammation and cell death [6].

Hepatocytes are capable of robust replication, which enables regeneration of lost parenchyma—a property that underpins the clinical success of split-liver transplantation, where a single donor organ can sustain two recipients [4]. However, chronic inflammation coupled with continuous regenerative stimuli increases the risk of hepatocellular carcinoma [5]. Dysregulated inflammatory responses have been linked to nearly all forms of hepatotoxic stress, including IR injury, excessive alcohol consumption, exposure to xenobiotics or heavy metals such as Cu^{2+} and Hg^{2+}, infections, and systemic metabolic disorders such as NAFLD, NASH, obesity, diabetes, and metabolic syndrome [6].

Mitochondrial dysfunction is a common feature across most hepatic disorders and can either directly drive massive hepatocyte death or sensitize cells to otherwise mild stressors, such as hypoxia or nutrient deprivation [7,8]. Structural and functional mitochondrial abnormalities have been observed in IR injury, NASH, sepsis, and Wilson's disease [8–10].



Both extrinsic and intrinsic apoptosis, as well as regulated necrosis, contribute to hepatocyte death in response to various hepatotoxic insults, including viral and bacterial infections [2], metabolic disorders [3], alcohol overconsumption [4], and xenobiotic toxicity [5] (Fig. 1 and Supplementary Discussion).
Key members of the tumor necrosis factor (TNF) superfamily—including TNFα, CD95L (FASL), and TNF-related apoptosis-inducing ligand (TRAIL, TNFSF10)

—are among the most well-characterized triggers of hepatocyte death. TNFα is produced in large amounts by hematopoietic cells exposed to live bacteria or lipopolysaccharide (LPS) in vivo, contributing to fatal shock syndromes that prominently involve the liver [6]. Notably, both the severe hepatotoxicity and systemic lethality of TNFα are markedly reduced in Ripk3$^{-/-}$ mice, indicating a significant role for regulated necrosis, challenging the notion that this model is purely apoptotic.10

Materials and Methods

This review is based on a comprehensive analysis of the current literature addressing liver inflammation, hepatocyte death, and the underlying cellular and molecular mechanisms. Peer-reviewed articles were identified through systematic searches of major scientific databases, including PubMed, Scopus, and Web of Science. Searches were conducted using combinations of relevant keywords such as liver inflammation, hepatocyte death, apoptosis, regulated necrosis, mitochondrial dysfunction, TNF signaling, ischemia-reperfusion injury, NAFLD, NASH, and hepatic carcinogenesis.

Original research articles, reviews, and meta-analyses published in English were considered, with particular emphasis on studies providing mechanistic insights into inflammatory signaling pathways and cell death regulation in the liver. Preference was given to well-established experimental models, translational studies, and clinically relevant findings. Reference lists of selected articles were also manually screened to identify additional relevant publications. The collected literature was critically evaluated and synthesized to provide an integrated overview of current knowledge and emerging concepts in the field.

Discussion

Chronic liver inflammation represents a critical driver of hepatocyte loss and disease progression across a wide spectrum of hepatic disorders. While transient and controlled inflammatory responses are essential for tissue repair and maintenance of liver homeostasis, sustained or dysregulated inflammation promotes excessive hepatocyte death, ultimately compromising liver function. The data reviewed herein highlight the complex interplay between immune-mediated signaling, mitochondrial dysfunction, and cell death pathways in shaping liver pathology.

A central theme emerging from recent studies is the pivotal role of mitochondria as integrators of metabolic stress, inflammatory cues, and death signals. Mitochondrial dysfunction not only directly contributes to hepatocyte apoptosis and regulated necrosis but also sensitizes liver cells to secondary stressors such as hypoxia, nutrient deprivation, and toxic insults. These effects are particularly

relevant in metabolic liver diseases, where altered lipid and glucose metabolism impose chronic stress on hepatocellular mitochondria.

Inflammatory mediators produced by liver-resident immune cells and recruited circulating leukocytes—including cytokines, chemokines, lipid messengers, and reactive oxygen species—serve as major initiators of hepatocyte death. Among these, TNF superfamily members play a prominent role by activating both apoptotic and necroptotic signaling cascades. Importantly, growing evidence indicates that regulated necrosis significantly contributes to liver injury in conditions previously thought to be dominated by apoptosis alone, reshaping our understanding of inflammatory hepatotoxicity.

The reciprocal relationship between hepatocyte death and inflammation further amplifies tissue damage. Dying hepatocytes release damage-associated molecular patterns (DAMPs) that activate innate immune receptors, perpetuating inflammatory signaling and establishing a self-reinforcing cycle of cell death and immune activation. Over time, this vicious loop not only drives parenchymal loss but also promotes fibrogenesis and increases the risk of hepatocellular carcinoma, particularly in the context of chronic liver disease.

From a therapeutic perspective, these insights underscore the potential value of strategies aimed at simultaneously limiting inflammation and preserving hepatocyte viability. Targeting key inflammatory mediators, modulating mitochondrial function, or selectively inhibiting specific cell death pathways may offer effective means to halt disease progression. Given the redundancy and complexity of inflammatory and death signaling networks, combination therapies that integrate hepatoprotective and anti-inflammatory approaches are likely to be most effective.

In conclusion

The prevalence of liver diseases continues to rise in developed countries, driven by lifestyle factors such as high-calorie diets, poor nutritional balance, sedentary behavior, and excessive use of hepatotoxic medications, alongside increased life expectancy. Considering the central involvement of hepatocyte death and inflammation in the development of most liver disorders, a promising therapeutic approach may be the application of hepatoprotective and anti-inflammatory strategies, either individually or in combination.

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