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Editorial Board Member of World Journal of Gastroenterology, Hasan Ozen, MD, Professor, Department of Pediatrics, Division of Gastroenterology, Hepatology and Nutrition, Hacettepe University School of Medicine, Ankara 06100, Türkiye. haozen@hacettepe.edu.tr

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Understanding the molecular crossroads in acute liver failure: A pathway to new therapies

Chun-Yao Cheng, Wen-Rui Hao, Tzu-Hurng Cheng

Abstract

In this editorial we comment on the article published in a recent issue of the World Journal of Gastroenterology. Acute liver failure (ALF) is a critical condition characterized by rapid hepatocellular injury and organ dysfunction, and it often necessitates liver transplant to ensure patient survival. Recent research has elucidated the involvement of distinct cell death pathways, namely ferroptosis and pyroptosis, in the pathogenesis of ALF. Ferroptosis is driven by iron-dependent lipid peroxidation, whereas pyroptosis is an inflammatory form of cell death; both pathways contribute to hepatocyte death and exacerbate tissue damage. This comprehensive review explores the interplay between ferroptosis and pyroptosis in ALF, highlighting the role of key regulators such as silent information regulator sirtuin 1. Insights from clinical and preclinical studies provide valuable perspectives on the dysregulation of cell death pathways in ALF and the therapeutic potential of targeting these pathways. Collaboration across multiple disciplines is essential for translating the experimental insights into effective treatments for this life-threatening condition.

Key Words: Silent information regulator sirtuin 1; Ferroptosis; Pyroptosis; P53/glutathione peroxidase 4/gasdermin D; Acute liver failure
Core Tip: Understanding the interplay between ferroptosis and pyroptosis is crucial for delineating the complex pathophysiology of acute liver failure (ALF). Targeting key regulators of these cell death pathways, particularly silent information regulator sirtuin 1, holds promise for the development of novel therapeutic strategies for mitigating hepatocyte injury and improving clinical outcomes in patients with ALF. Multidisciplinary collaborations that integrate basic science, translational research, and clinical trials should be conducted to accelerate the translation of the experimental findings into effective treatments for this life-threatening condition.

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INTRODUCTION

Acute liver failure (ALF) poses a major clinical challenge because of its rapid onset and high mortality rate. Characterized by extensive hepatocellular injury leading to organ dysfunction, ALF has various etiologies, including drug toxicity, viral hepatitis, and metabolic disorders. Despite advancements in medical care, liver transplant remains the primary therapeutic option, which indicates the urgent need to further clarify the underlying pathophysiology of ALF and develop novel treatment strategies. In a study by Zhou et al[1] that was published in the World Journal of Gastroenterology, the intricate molecular mechanisms underlying ALF progression were elucidated, shedding light on potential novel therapeutic targets. The study focused on the interplay between two distinct modes of cell death, namely ferroptosis and pyroptosis, and on their upstream regulatory pathways, particularly those involving silent information regulator sirtuin 1 (SIRT1)[1].

SIRT1 IN ALF

Zhou et al[1] investigated the involvement of ferroptosis and pyroptosis in ALF by using clinical samples and animal models. They observed the dysregulation of key proteins involved in these pathways — such as GPX4, SLC7A11, p53, and GSDMD — in liver tissues from patients with ALF. Furthermore, in mouse models where ALF was induced by lipopolysaccharide and D-galactosamine, they demonstrated that inhibiting ferroptosis and pyroptosis attenuated liver injury and improved the survival rate. Central to their findings was the role of SIRT1, a protein deacetylase that is involved in multiple cellular processes, including metabolism, stress response, and inflammation. Zhou et al[1] demonstrated that SIRT1 activation protected against ALF by inhibiting the p53/GPX4/GSDMD signaling pathway, thereby suppressing both ferroptosis and pyroptosis. Conversely, inhibition of SIRT1 exacerbated liver injury, highlighting the therapeutic potential of SIRT1 in ALF. These findings have significant clinical implications, suggesting that the targeting of ferroptosis and pyroptosis pathways through methods such as SIRT1 modulation might lead to new therapeutic strategies for ALF. However, several questions must be addressed, such as the precise mechanisms linking SIRT1 to ferroptosis and pyroptosis and the potential side effects of pharmacological interventions targeting the related pathway.

HALLMARK OF ALF

ALF is a severe manifestation of liver injury, often resulting from factors such as drug toxicity, viral infections, or metabolic disorders. The hallmark of ALF is the rapid and heavy loss of hepatocytes, leading to impaired liver function and systemic complications. For example, Chen et al[2] demonstrated the mitigative effects of boswellic acid on acetaminophen-induced hepatic injury, suggesting the potential of natural compounds in ameliorating liver damage[2]. Despite advancements in medical care, the mortality rate associated with ALF remains unacceptably high[3]. As mentioned, the study by Zhou et al[1] explored the molecular intricacies of ALF and focused on two pathways of cell death, namely ferroptosis and pyroptosis. Ferroptosis is characterized by iron-dependent lipid peroxidation and mitochondrial dysfunction, whereas pyroptosis is a proinflammatory form of cell death; both pathways have gained attention for their roles in various pathological conditions, including liver diseases[4,5].
**CONCLUSION**

In summary, the intricate interplay between ferroptosis and pyroptosis underscores the multifaceted nature of cell death pathways in ALF. Targeting the key regulators of these pathways, particularly SIRT1, holds promise for the development of novel therapeutic strategies for mitigating hepatocyte injury and improving clinical outcomes in patients with ALF. Further research is warranted to clarify the mechanistic complexities of cell death pathways and confirm their therapeutic potential in clinical settings. Collaboration across multiple disciplines is essential for translating experimental insights into effective treatments for this life-threatening condition.

**FOOTNOTES**

Author contributions: Cheng CY and Hao WR contributed equally; Cheng CY wrote the paper; Hao WH and Cheng TH revised the paper; All authors have read and approve the final manuscript.

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Country of origin: Taiwan

ORCID number: Tzu-Hurng Cheng 0000-0002-9155-4169.

S-Editor: Li L
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