Perspective
Volume 09:02, 2024

Journal of Molecular Histology & Medical Physiology

ISSN: 2684-494X

Open Access

Hepatic Lipotoxicity and Liver Damage in NASH are mitigated by Targeting Extracellular RNA

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Introduction

Hepatic lipotoxicity, a condition characterized by the accumulation of lipids in liver cells, has emerged as a critical factor in the pathogenesis of Non-Alcoholic Steatohepatitis (NASH). NASH is a progressive form of Non-Alcoholic Fatty Liver Disease (NAFLD) that can lead to liver fibrosis, cirrhosis, and eventually hepatocellular carcinoma. While the exact mechanisms underlying NASH progression are complex and multifactorial, recent research has highlighted the role of extracellular RNA (exRNA) in mediating hepatic lipotoxicity and liver damage. This article explores the relationship between hepatic lipotoxicity, exRNA, and NASH progression, focusing on how targeting exRNA can mitigate liver damage and offer potential therapeutic interventions [1].

Non-Alcoholic Fatty Liver Disease (NAFLD) encompasses a spectrum of liver disorders ranging from simple steatosis (accumulation of fat in the liver) to more severe conditions such as Non-Alcoholic Steatohepatitis (NASH), liver fibrosis, cirrhosis, and Hepatocellular Carcinoma (HCC). NASH is characterized by hepatic inflammation, hepatocyte injury, and fibrosis, representing a significant public health concern due to its rising prevalence and potential for progressive liver damage. The pathogenesis of NASH is multifactorial, involving a complex interplay of genetic, metabolic, and environmental factors. Central to the development of NASH is hepatic lipotoxicity, which refers to the toxic effects of excessive lipid accumulation in liver cells. Lipotoxicity arises from imbalances in lipid metabolism, leading to the accumulation of Free Fatty Acids (FFAs), triglycerides, and other lipid intermediates within hepatocytes [2].

Description

The lipid molecules can disrupt cellular functions, promote oxidative stress, induce Endoplasmic Reticulum (ER) stress, and trigger inflammatory responses, ultimately contributing to hepatocyte injury and liver damage. The intricate mechanisms linking lipid accumulation to liver injury involve various molecular pathways, including but not limited to lipogenesis, lipolysis, mitochondrial dysfunction, and inflammasome activation. Extracellular RNA (exRNA) encompasses a diverse group of RNA molecules, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), that are released into the extracellular space from various cell types, including hepatocytes. These exRNAs can act as signaling molecules, modulating cellular processes in both physiological and pathological conditions. In the context of hepatic lipotoxicity and NASH, emerging evidence suggests that exRNAs play a crucial role in mediating lipid-induced cellular damage and inflammation within the liver [3].

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Received: 20 February 2024, Manuscript No. jmhmp-24-133028; **Editor Assigned**: 22 February 2024, PreQC No. P-133028; **Reviewed**: 05 March 2024, QC No. Q-133028; **Revised**: 11 March 2024, Manuscript No. R-133028; **Published**: 18 March 2024, DOI: 10.37421/2684-494X.2024.9.119

Certain exRNAs, such as miRNAs, can modulate lipid metabolism by targeting key genes involved in lipogenesis, lipid droplet formation, and lipid transport. Dysregulation of these miRNAs in response to lipid overload can disrupt lipid homeostasis and exacerbate hepatic lipotoxicity. ExRNAs can function as extracellular signaling molecules, activating inflammatory pathways in hepatic cells and promoting the release of pro-inflammatory cytokines. This inflammatory response contributes to the progression of liver damage and fibrosis in NASH. Hepatic lipotoxicity induces cellular stress responses, including ER stress and oxidative stress. ExRNAs have been implicated in modulating these stress pathways, either exacerbating stress-induced damage or promoting cellular adaptation and survival [4].

ExRNAs can facilitate intercellular communication between different cell types within the liver microenvironment. By transmitting molecular signals, exRNAs can influence the crosstalk between hepatocytes, immune cells, stellate cells, and endothelial cells, thereby shaping the overall inflammatory and fibrotic response in NASH. AntagomiRs are synthetic RNA molecules designed to specifically bind and inhibit miRNAs involved in lipid metabolism or inflammatory signaling. Similarly, ASOs can target other exRNAs, such as lncRNAs or circRNAs, to attenuate their pathological effects. These nucleotide-based therapies can effectively reduce the levels of pro-inflammatory and pro-fibrotic exRNAs, thereby alleviating liver damage in NASH. Exosomes, small extracellular vesicles containing exRNAs, have gained attention as potential carriers for targeted drug delivery. Engineered exosomes can be loaded with therapeutic RNAs or small molecules designed to modulate exRNA functions [5].

Conclusion

Small molecule inhibitors that target upstream regulators of exRNA biogenesis or release pathways represent another avenue for therapeutic intervention. These inhibitors can modulate exRNA production, secretion, or uptake by target cells, thereby altering the overall exRNA signaling landscape in the liver and ameliorating NASH-related pathologies.

Hepatic lipotoxicity and liver damage in NASH are complex processes influenced by a myriad of factors, including dysregulated lipid metabolism, inflammatory signaling, and intercellular communication mediated by exRNAs. Targeting exRNA pathways represents a promising approach to mitigate NASH progression and alleviate liver damage. Strategies such as antagomiRs, exosome-based therapies, RNA interference, and small molecule inhibitors offer innovative ways to modulate exRNA functions and restore hepatic homeostasis. Continued research into the molecular mechanisms underlying exRNA-mediated lipotoxicity will further enhance our understanding of NASH pathogenesis and pave the way for novel therapeutic interventions aimed at improving patient outcomes.

Acknowledgement

None.

Conflict of Interest

None.

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How to cite this article: Schmidt, Benjamin. "Hepatic Lipotoxicity and Liver Damage in NASH are mitigated by Targeting Extracellular RNA." *J Mol Hist Med Phys* 9 (2024): 119.