Perspective

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Challenges and opportunities in nonalcoholic steatohepatitis

https://doi.org/10.1515/mr-2022-0024
Received July 29, 2022; accepted August 21, 2022;
published online September 13, 2022

Abstract: Nonalcoholic steatohepatitis (NASH) has emerged as the leading cause of chronic liver disease worldwide and is rapidly increasing in prevalence due to the obesity epidemic. There are currently no Food and Drug Administration (FDA) approved drugs to treat NASH, and therefore a critical need exists for novel therapies that can halt or reverse the progression to hepatic fibrosis, cirrhosis, and hepatocellular carcinoma. Clinical trials to date using single drugs to treat NASH have shown disappointing efficacy. Combination therapies to attack different targets underlying disease pathogenesis of NASH are being explored as a strategy currently. Novel RNA therapies are also being developed to target previously "undruggable" targets and are close to the maturity necessary to be viable therapeutic approaches for the treatment of NASH and fibrosis. Identifying circulating biomarkers of fibrosis could serve as a valuable, non-invasive diagnostic tool to guide clinical practice. Despite progress in translational and clinical research, one of the major reasons for the absence of effective therapeutics is our incomplete understanding of the pathophysiology that underlies the progression from steatosis to NASH and its most deadly consequence-fibrosis. Multi-omics platforms will help to drive effective precision medicine development in NASH and hepatology.

Keywords: hepatic stellate cells; liver fibrosis; nonalcoholic steatohepatitis.

The epidemic of obesity has resulted in hundreds of millions of people worldwide developing fatty liver (steatosis). While steatosis is a relatively benign condition, approximately 20%–30% of these subjects will develop liver inflammation, dysfunctional fibrosis, and hepatocyte death, a severe condition known as nonalcoholic steatohepatitis (NASH, also known as Metabolic dysfunction-associated steatohepatitis [MASH]). The overall prevalence of NASH has been estimated to be 5%–20% of the population with up to 35 million people potentially affected globally [1]. NASH can progress to cirrhotic liver disease and is the leading cause of liver failure. Further, NASH is now also the fastest growing cause of liver cancer globally due to the reduction of Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) induced liver cancer, thus changing the global epidemiology of liver cancer [2]. Therefore, NASH is predicted to become the leading cause of liver transplantation in the United States by 2025 [3]. The cost of treatment increases with disease severity or when patients have complications or comorbidities. In many countries, NASH has been associated with a significant economic and societal burden due to increased healthcare resource utilization, as well as high direct medical and non-medical costs [3].

Due to the high prevalence and clinical importance of NASH, the study of NASH has refocused from the characterization of the clinical phenotype through the presence and extent of fibrosis to a detailed phenotypic characterization of accompanying comorbidities, genetic polymorphisms, and environmental factors that contribute to disease progression. Despite current efforts, many gaps still remain in our understanding of its pathophysiology, leading to a lack of mechanism-based therapeutic targets and treatment options. NASH most likely develops as a result of multiple hits, including older age, physical inactivity, obesity, insulin resistance (diabetes), hypertension, hyperlipidemia (high cholesterol, high triglycerides) and other insults that promote inflammation, fibrosis, and hepatocyte death in the liver [4]. However, the molecular mechanisms corresponding to these pathogenic processes and their integration are poorly understood. In particular, there is a great need to elucidate the mechanisms leading to hepatic fibrosis, which is the leading determinant of long-term mortality in patients with NASH. Extensive data indicates that activated hepatic stellate cells constitute the primary source of extracellular matrix (ECM)—producing cells and are the critical effectors in NASH fibrogenesis [5]. Although some factors have been proposed to activate hepatic stellate cells in NASH, the work in this area is far

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from complete and has not yet resulted in effective therapeutics to delays or reverses NASH progression.

In the absence of approved pharmacological therapies for NASH, most large biopharmaceutical companies are currently developing novel therapeutics for the treatment of NASH. These companies collaborate with private research and academic institutes to conduct clinical trials. The large number of NASH clinical trials can be divided into four major categories (Figure 1): (1) Metabolic targets that reduce insulin resistance, inhibit core enzymes of *de novo* lipogenesis, or improve mitochondrial fatty acid β-oxidation; (2) Inflammation targets that block inflammatory cell infiltration or repress inflammatory pathways, prevent endoplasmic reticulum (ER) stress-induced oxidative damage, or inhibit hepatocyte cell death; (3) Gut-liver axis targets that modulate enterohepatic circulation of bile acids, or modify the gut microbiome; and (4) Anti-fibrotic targets that directly target hepatic stellate cells, reduce collagen deposition, or improve fibrolysis in the liver [6]. According to the Food and Drug Administration (FDA), emerging therapies for NASH cirrhosis would have to demonstrate either reversal of fibrosis with an associated reduction in portal hypertension or at least delay the progression with an eventual decrease in liver-related outcomes. For non-cirrhotic NASH, it is expected that reversal of fibrosis by one stage or resolution of NASH with no worsening in fibrosis will need to be accompanied by overall survival benefits. Clinical trials to date using single drugs in NASH have shown disappointing efficacy, especially in fibrosis. Because multiple pathways drive NASH progression, targeting only a single pathway or molecule may not be sufficient. This has provoked efforts to try combination therapies that attack different targets underlying disease pathogenesis. Although most of the pipelines are based on traditional small molecule drugs and antibody drugs, the approval of siRNA drugs and the success of mRNA vaccines has pushed RNA therapies closer to being viable therapeutic approaches that are able to target previously "undruggable" targets [7, 8].

Despite the increasing prevalence of NASH globally, the disease remains underdiagnosed [9]. NASH diagnoses are complex due to non-specific symptoms such as fatigue and upper abdominal pain. Although non-invasive diagnostic methods are ideal and under intensive study, liver biopsy remains the gold standard for diagnosing and assessing the progression of NASH and liver fibrosis. However, the biopsy itself faces unprecedented challenges for patient enrollment and safety. Furthermore, the interpretation of the biopsy requires a high level of expertise and training. Hence, experienced physicians are needed to perform the biopsy and interpret the findings. In many cases, NASH is not identified until advanced liver damage has already occurred [10]. Detecting fibrosis in the population with fatty liver is essential to predict liver-related outcomes and inform treatment decisions. A circulating signature of fibrosis could serve as a valuable, non-invasive diagnostic tool, it could also be useful for monitoring the progress of NASH treatment and as a useful endpoint for clinical trials. In addition, a diagnostic test could be applied as a complement to a therapeutic drug to determine its applicability to a specific patient, either for treatment eligibility or treatment response. Complementary diagnostics help to guide clinical practices, particularly to determine eligibility or optimize therapy through early identification of responder status. Current efforts are being made to discover new biomarkers focused on the known hallmarks in the progression of the disease, namely, hepatocyte death or apoptosis, oxidative stress, inflammation, and fibrosis [11]. Given the complex pathophysiology of NASH, a single marker may not indicate the liver status and satisfy the clinical requirement. In order to develop a comprehensive marker system involving multiple cell types, including hepatocytes, macrophages, and hepatic stellate cells, as well as related secretome studies are essential to solve this problem. Two biomarker consortiums, the Non-Invasive Biomarkers of Metabolic Liver Disease (NIMBLE) project and the Liver Investigation-Testing Marker Utility in Steatohepatitis (LITMUS) project, from the USA and Europe, aim to address these issues by validating and qualifying biomarkers for the testing of nonalcoholic fatty liver diseases [6].

In basic and translational research studies, there is an imperative to clarify the cellular and molecular mechanisms

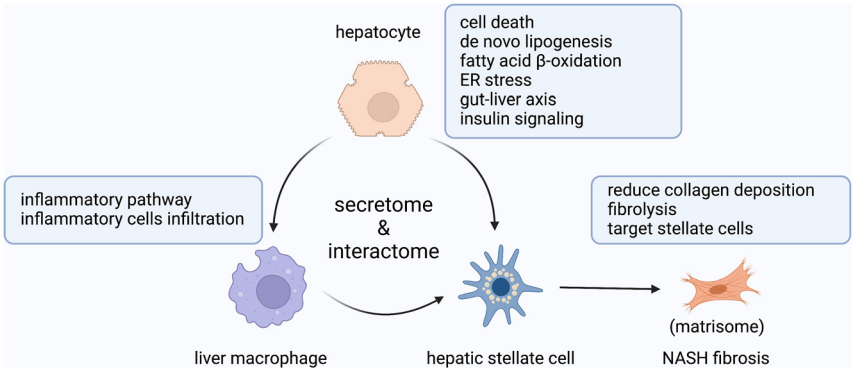

Figure 1: Scheme of current therapeutic targets and future study strategy in NASH fibrosis. The current drug targets are listed in the box. Hepatocytes, liver macrophages (Kupffer and infiltrated macrophages), and hepatic stellate cells communicate through secretome and interactome, contributing to NASH fibrosis in which heterogenicity could be further investigated by matrisome. NASH, nonalcoholic steatohepatitis; ER, endoplasmic reticulum.

of fibrosis regression in order to refine effective anti-fibrotic drugs for NASH. Although hepatocyte injury is a key driver of NASH, multiple other cell lineages within the hepatic fibrotic niche play significant roles in inflammation, mesenchymal cell activation, extracellular matrix accumulation, as well as fibrosis resolution [5]. Furthermore, a better understanding of collagen and other ECM dynamics in different stages of fibrotic liver disease, understanding the heterogeneity of hepatic stellate cells, and understanding the mechanisms of fibrogenesis are fundamental to uncovering suitable therapeutic targets [12]. In addition, the constituents of the cellular interactome, and how the various subpopulations, such as hepatocytes, ductular cells, Kupffer cells, bone marrow-derived macrophages, other immune cells, endothelial cells and mesenchymal cells, interact with hepatic stellate cells to drive fibrogenesis is an area of active research [13]. New technology platforms including single-cell and single-nuclei RNA-sequencing, transcriptome-epigenome sequencing, spatial transcriptomics, secretome, ligand-receptor interactome analysis, high throughput Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) perturbed phenotype analysis, and matrisome analysis will clarify our understanding of how cells interact with each other, and respond to either a healthy or pathological liver microenvironment (Figure 1) [14]. Deploying these types of technologies will help to drive the development of effective precision medicine in hepatology.

Acknowledgments: I thank Dr. David Ngai (Columbia University) for the manuscript editing. The Figure was created with BioRender.com.
Research funding: None declared.
Author contributions: The author has accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: Author states no conflict of interest.
Ethical approval: Not applicable.

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