Pathophysiology of Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis

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KEYWORDS

• Nonalcoholic fatty liver disease (NAFLD) • Nonalcoholic steatohepatitis (NASH)
• Inflammation • Fibrosis • Genetic factors

KEY POINTS

- Hepatic steatosis is a consequence of impaired lipid metabolism in the liver. Major contributing factors are hepatic insulin resistance and increased influx of free fatty acids in the liver.
- Impaired adipose tissue function, dysbiosis of the gut microbiome, and recently identified genetic factors influence the development of nonalcoholic fatty liver disease.
- Although fatty liver progresses to nonalcoholic steatohepatitis (NASH) in a significant proportion of patients, the underlying mechanisms are not completely elucidated.
- Inflammation in the liver is triggered by the production of proinflammatory cytokines and chemokines by adipocytes, hepatic macrophages, and lipid-laden hepatocytes, which promote activation of stellate cells, the key cell type responsible for fibrogenesis in the liver.
- NASH is a common liver disease that is associated with progression to hepatocellular carcinoma and cirrhosis; therefore, there is an urgent need to discover drug targets and develop effective therapies.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a major public health concern because of its increased prevalence worldwide and potentially severe sequelae.[1] NAFLD is a hepatic manifestation of metabolic syndrome and a risk factor for type 2 diabetes mellitus, dyslipidemia, and hypertension.[1] NAFLD encompasses a broad spectrum

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of liver disorders, ranging from simple steatosis to the more severe form, nonalcoholic steatohepatitis (NASH), that may progress to cirrhosis or hepatocellular carcinoma.[1] The hallmark of NAFLD is triglyceride (TG) accumulation in the cytoplasm of hepatocytes. This arises from an imbalance between lipid acquisition (ie, fatty acid uptake and de novo lipogenesis [DNL]) and removal (ie, mitochondrial fatty acid oxidation [FAO] and export as a component of very low-density lipoprotein [VLDL] particles).[2]

NASH, the more severe form of the disease, is characterized by steatosis, hepatic inflammation, and hepatocellular ballooning and may include varying degrees of fibrosis.[3] The understanding of the pathophysiology of NASH has evolved substantially from the original 2-hit hypothesis wherein a first hit, such as insulin resistance (IR), resulted in hepatic steatosis, and a subsequent second hit, such as oxidative stress, was required to develop NASH.[4] It is now apparent that the 2-hit hypothesis is not sufficient to describe the multiple pathways that may be interrelated and contribute to NASH. Thus, a multihit model has been proposed more recently for the pathophysiology of NASH, with multiple parallel hits occurring to cause NASH.[5]

The purpose of this article is to present an overall review of the most recent pathophysiologic concepts related to NAFLD and NASH.

PATHOPHYSIOLOGY OF NONALCOHOLIC FATTY LIVER DISEASE

Adipose Tissue Dysfunction and Increased Free Fatty Acid Flux to the Liver

Adipose tissue is the systemic site for storage of energy in the form of TGs.[6] Furthermore, it is an important endocrine organ involved in the secretion of hormones, cytokines, and chemokines, called adipokines.[7] Obesity as a result of overnutrition and/or underexertion commonly results in adipose tissue dysfunction.[6] Adipose tissue dysfunction has been thought to play a pivotal role in the development of metabolic disorders, such as IR and NAFLD (**Fig. 1**).[8] In an obese state, excess free fatty acids (FFAs) can enter the liver through the portal circulation. Increased levels of hepatic FFAs induce increased lipid synthesis and gluconeogenesis.[9] Studies from both animal models and human subjects have shown that increased levels of circulating FFAs can also lead to peripheral IR.[9,10] In addition, FFAs can contribute to

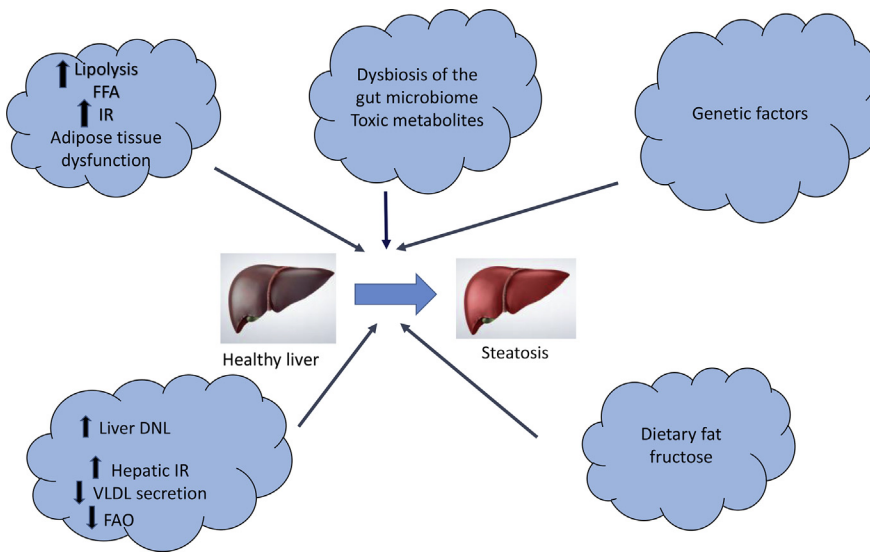

Fig. 1. Factors influencing nonalcoholic fatty liver (NAFL).