The Insights of Nonalcoholic Steatohepatitis

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Abstract

Nonalcoholic steatohepatitis (NASH) is a form of fatty liver disease where benign hepatic steatosis leads to chronic inflammation in the steatotic liver of a patient without any history of alcohol abuse. NASH is a necro-inflammatory response that ensues when hepatocytes are injured by lipids (lipotoxicity). NASH is strongly associated with obesity and the metabolic syndrome, conditions that cause lipid accumulation in hepatocytes (hepatic steatosis). NASH is characterized by the presence of steatosis (the accumulation of fat in 5% or more of hepatocytes), hepatocellular ballooning, and inflammation. In NASH, lipotoxic hepatocytes result in the production of factors that promote wound healing as an attempt to replace dying hepatocytes. The presence of chronic and/or aberrant inflammation can lead to scar tissue deposition and the development of fibrosis and hepatocellular carcinoma Although clinical trials show promising results, there is actually no pharmacological agent approved to treat NASH. The rapidly increasing prevalence of this disease and of its aggressive form NASH will require novel therapeutic approaches based on a profound understanding of its pathogenesis to halt disease progression to advanced fibrosis or cirrhosis and cancer.This review emphases on our understanding of the epidemiology and pathogenesis of nonalcoholic steatohepatitis, which reinforces practice guidelines and drug development for this life-threatening liver disease.

Keywords: steatosis, lipotoxicity, fatty liver, hepatocytes

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Introduction

Nonalcoholic steatohepatitis is strongly associated with overweight or obesity and the metabolic syndrome. A recent analysis of studies involving more than 8.5 million persons from 22 countries showed that more than 80% of patients with nonalcoholic steatohepatitis are overweight or obese, 72% have dyslipidemia, and 44% have received a diagnosis of type 2 diabetes mellitus (Benedict and Zhang,2017). A major concern for individuals withNASH is the likelihood of their progression to end-stage liver diseases that may eventually require transplantation. NASH is projected to become the leading cause of liver-related morbidityand mortality superseding hepatitis C virus.Oxidative stress is considered as a key pro-inflammatory mediator of NASH. Oxidative stress in hepatocytes can result fromfat overload which is directly associated with an elevated level ofcirculating free fatty acids

(Calzadillaand Adams,2016). The concentration of circulating free fatty acids is low in a normal condition which is increasedin metabolic syndrome. Influx of elevated level of circulatingfree fatty acids into hepatocytes results in an increased fatty acidoxidation in mitochondrial and extra-mitochondrial sites leadingto over-production of reactive oxygen species (ROS). Excessgeneration of ROS creates an imbalance in relation to antioxidant defense mechanisms, which in turn leads to oxidative stressand mitochondrial dysfunction. Mitochondrial dysfunction eventually leads to apoptosis of hepatocytes and thereby, exacerbatethe pro-inflammatory events of NASH (Angulo et al.,2007).

Pathogenesis

Nonalcoholic fatty liver disease comprises nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH), which each progress differently (Ekstedt et al.,2006). NAFL rarely results in cirrhosis or liver cancer, whereas patients with NASH are at risk for these outcomes. The rate of hepatocyte death is greater in NASH than in NAFLD-the key factor that differentiates NASH from NAFL4. The toxic effects of specific lipids on hepatocytes (hepatic lipotoxicity) could cause hepatocyte death in patients with NASH5. However, the risk for lipotoxicity differs according to the type of lipid that accumulates, and is modified by factors that can exacerbate or defend against their effects (Satapathyand Sanyal,2015; Dixon et al.,2001).

Steatosis, the accumulation of fat in hepatocytes, is present in NAFL and NASH. Steatosis occurs whenever the import or synthesis of fat exceeds fat export or degradation. Triglyceride (triacylglycerol) is the most conspicuous type of fat in fatty livers. So, the extent of triglyceride accumulation has been the basis for grading the severity of steatosis in NAFLD. Triglycerides per se are not hepatotoxic, so steatosis grade or severity do not predict hepatic injury, inflammation, or fibrosis (Ray K, 2013; Powell et al.,1990). On the other hand, some of the other types of lipids that accumulate in fatty livers (e.g. fatty acids, diacylglycerol, oxysterols, cholesterol, and phospholipids) can injure hepatocytes. The realization that lipotoxocity is caused by lipids other than triglyceride has spurred development of strategies to prevent or treat NASH by blocking hepatic accumulation of lipotoxic lipids. Lipotoxicity therefore initiates NASH development and is a new therapeutic target (Caldwell et al.,1999).

Briefly, under conditions of chronic energy surplus, adipose tissue produces adipo-cytokines that prevent adipocytes from assimilating fatty acids and promote release of fatty acids from adipose depots. This results in increased delivery of fatty acids to the liver and fuels hepatocyte triglyceride synthesis. The ability of triglyceride synthesis to compensate for increased hepatic fatty acid exposure appears to determine whether or not lipotoxicity results (Poonawala et al.,2000;Teli et al.,1995). For example, studies of

mouse models of NASH showed that inhibiting liver triglyceride synthesis increased hepatic accumulation of free fatty acids and the severity of liver injury and fibrosis, despite reducing steatosis. Other studies extended the evidence that fatty acids (rather than triglyceride) are hepatotoxic, demonstrating that lipotoxicity is affected by the specific types of fatty acid that accumulate. Lipids can cause toxicity by diverse mechanisms. For example, lipotoxicity can result from lipid metabolism (MarraandLotersztajn, 2013). Mitochondrial and peroxisomal fatty acid oxidation generate reactive oxygen species that may be immediately toxic or that eventually deplete antioxidant reserves, rendering hepatocytes more vulnerable to other factors that generate oxidative stress. Accumulation of fatty acids within mitochondria could also dissipate the proton-motive force that typically occurs during mitochondrial respiration (Rm et al., 2014; Luoet al.,2012). This makes mitochondria more vulnerable to other insults that collapse the mitochondrial membrane potential, such as tumor necrosis factor alpha (TNF) and could lead to release of mitochondrial factors that promote apoptosis. Extreme depolarization of mitochondrial membranes causes complete cessation of mitochondrial electron transport and ATP synthesis, resulting in cellular necrosis. Because damaged mitochondria cannot metabolize fatty acids efficiently, fatty acids accumulate (Suiter et al.,2018; Jung and Choi, 2014). In addition to its directly cytotoxic effects, fatty acid accumulation exacerbates insulin resistance and hyperinsulinemia, which leads to further hepatic lipid accumulation, and promotes inflammatory and fibrogenic responses, as well mitogenic responses that could be carcinogenic (Masarone et al.,2018).

Another mechanism for lipotoxicity involves changes in cell signaling. For example, fatty acids interact with or modify other molecules, including transcription factors (hepatocyte nuclear factor-alpha) and innate immune receptors (toll-like receptors), leading to overall changes in signaling pathways that regulate metabolism and stress responses (Lefebvre et al.,2016). Other types of lipids (oxysterols, diacylglycerol, cholesterol, and phospholipids) are also involved in signaling mechanisms that control cell metabolism. Aberrant accumulation of these molecules therefore disrupts hepatocyte metabolic homeostasis and compromises cell viability. Lipotoxicity induces several different types of cellular stress, including ER stress and impaired autophagy. In addition, it promotes a sterile inflammatory response that can potentiate liver cell injury and death.

Drugs in development for the treatment of NASH

Several pharmacological therapies have been evaluated in recent clinical trials for the treatment of NASH. These efforts have targeted the processes involved in the pathogenesis and progression of NASH, including metabolic stress, inflammation, and fibrosis (CENTAUR,2019).

ASK1 inhibitor

Selonsertib is a small-molecule inhibitor of apoptosis signal-regulating kinase 1 (ASK1), which regulates signaling for hepatic inflammation and fibrosis in settings of oxidative stress. Selonsertib has been investigated in combination with simtuzumab, a humanized monoclonal lysyl oxidase-like antibody that inhibits cross-linking of collagen in pathologic stroma (AURORA, 2019).

Dual CCR2/CCR5 antagonist

Cenicriviroc (CVC) is a dual C-C chemokine receptor type 2 and 5 (CCR2/CCR5) antagonist with nanomolar potency against both receptors. These receptors mediate the interactions that influence liver inflammation and fibrosis, therefore giving CVC an anti-inflammatory and antifibrotic effect (Friedman et al.,2018).

FXR agonist

Obeticholic acid (OCA) is a selective agonist of the farnesoid X receptor (FXR), a bile acid nuclear receptor. FXR is highly expressed in the liver and helps regulate lipid metabolism and inflammation—key underlying pathways that drive NASH and NASH-related fibrosis. OCA is currently approved by the FDA for the treatment of primary biliary cholangitis and is being studied for NASH and other indications (selonsertib,2016).

PPAR alpha-delta dual agonist

Elafibranor is a peroxisome proliferator-activator receptor (PPAR) alpha-delta dual agonist. PPAR alpha agonists are involved in fatty-acid oxidation, whereas PPAR delta agonists have an anti-inflammatory effect (selonsertib,2016).

THR beta-agonist

MGL-3196 is a small-molecule, liver-directed thyroid hormone receptor (THR) beta-agonist. The high selectivity for the beta-receptor subtype, the predominant isoform in the liver, aims to reduce the effects of extrahepatic thyroid receptor activation (via the alpha-receptor), such as increased respiration and cardiac tissue hypertrophy (Ratziu et al.,2016).

Conclusion

Nonalcoholic steatohepatitis, a type of liver damage that is strongly associated with visceral adiposity and the metabolic syndrome, has become a major cause of cirrhosis and liver cancer. The prevalence of nonalcoholic steatohepatitis in the United States approaches that of type 2 diabetes, and annual medical costs directly attributable to nonalcoholic fatty liver disease already exceed $100 billion, much of which is attributable to nonalcoholic steatohepatitis, underscoring the importance of developing interventions to prevent and treat this disease. A number of inherited and environmental factors increase the risk of nonalcoholic steatohepatitis and influence its progression. The pathogenic mechanisms are being unraveled; metabolic stress, inflammation, and fibrosis have been identified as key processes. Pharmacologic agents that target these mechanisms are being investigated in clinical trials.

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