Gastroenterology 2018;■:1–21

Bioactive Lipid Species and Metabolic Pathways in Progression and Resolution of Nonalcoholic Steatohepatitis

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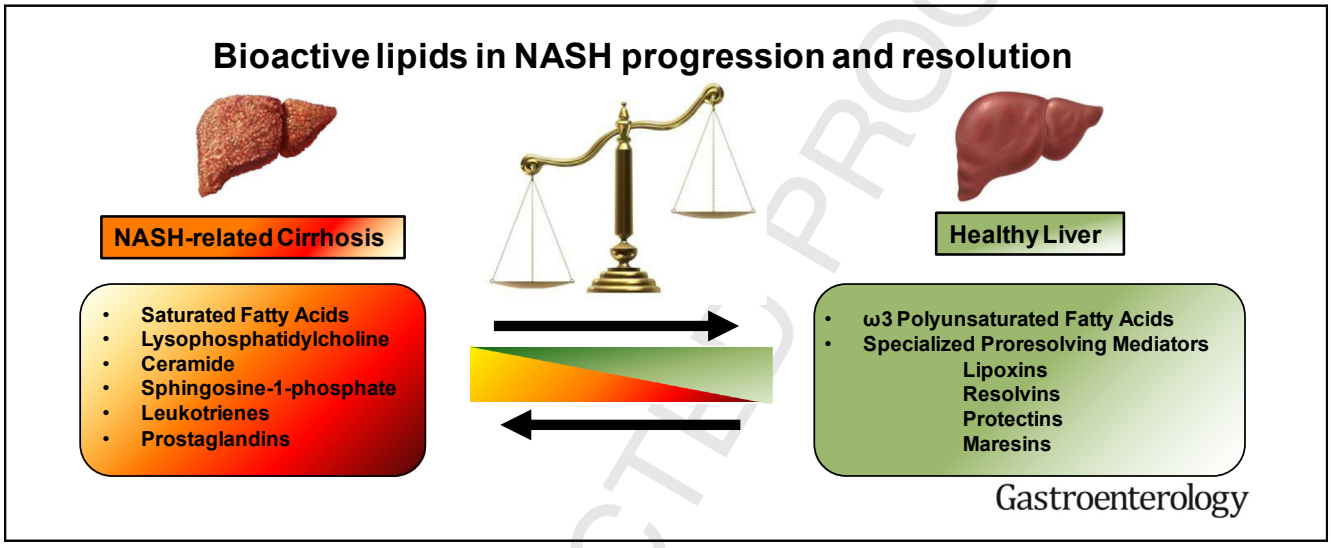

The prevalence of nonalcoholic steatohepatitis (NASH) is increasing worldwide, yet there are no effective treatments. A decade has passed since the initial lipidomics analyses of liver tissues from patients with nonalcoholic fatty liver disease. We have learned that liver cells from patients with NASH have an abnormal lipid composition and that the accumulation of lipids leads to organelle dysfunction, cell injury and death, and chronic inflammation, called lipotoxicity. We review the lipid species and metabolic pathways that contribute to the pathogenesis of NASH and potential therapeutic targets, including enzymes involved in fatty acid and triglyceride synthesis, bioactive sphingolipids and polyunsaturated-derived eicosanoids, and specialized pro-resolving lipid mediators. We discuss the concept that NASH is a disease that can resolve and the roles of lipid molecules in the resolution of inflammation and regression of fibrosis.

Keywords: Nonalcoholic Fatty Liver Disease; Triglycerides; Fatty Acids; Therapy.

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the world and an emerging risk factor for liver-related complications, including cirrhosis and hepatocellular carcinoma.[1] NAFLD encompasses a histologic spectrum ranging from simple steatosis (nonalcoholic fatty liver [NAFL]) to nonalcoholic steatohepatitis (NASH),[1] with variable degrees of fibrosis, with the latter having the potential to progress to cirrhosis.[2]

The liver-related burden of NASH is increasing and NASH is projected to be the leading indication for liver

Abbreviations used in this paper: AA, arachidonic acid; ACC, acetyl–coenzyme A carboxylase; ASMase, acid sphingomyelinase; CeS, ceramide synthase; CoA, coenzyme A; COX, cyclo-oxygenase; DES, dihydro-ceramide desaturase; DGAT, diacylglycerol acyltransferase; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ER, endoplasmic reticulum; EV, extracellular vesicle; FA, fatty acid; FADS, fatty acid desaturase; FFA, free fatty acid; FXR, farnesoid X receptor; HFD, high fat diet; HSC, hepatic stellate cell; IL, interleukin; JNK, c-Jun N-terminal kinase; LDL, low-density lipoprotein; LOX, lipoxygenase; LPC, lysophosphatidylcholine; LT, leukotriene; LX, lipoxin; LXR, liver X receptor; MOMP, mitochondrial outer membrane permeabilization; MUFA, monounsaturated fatty acid; NAFL, nonalcoholic fatty liver; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NF-κB, nuclear factor-κB; PC, phosphatidylcholine; PG, prostaglandin; PLA2, phospholipase A2; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acid; RCT, randomized controlled trial; ROS, reactive oxygen species; Rv, resolvin; S1P, sphingosine-1-phosphate; S1PR, sphingosine-1-phosphate receptor; SCD-1, stearoyl coenzyme A desaturase-1; SFA, saturated fatty acid; SMase, sphingomyelinase; SphK, sphingosine kinase; SPM, specialized pro-resolving mediators; SREBP, sterol regulatory element-binding protein; TG, triglyceride; TGF, transforming growth factor; TNF, tumor necrosis factor; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; TRAIL-2, tumor necrosis factor-related apoptosis-inducing ligand receptor 2; TX, thromboxane; VLCFA, very-long acyl-chain fatty acid.

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2018.06.031

transplantation by 2020 as a consequence of increased disease prevalence and the lack of effective treatment.[3]

Lipotoxicity, defined as an abnormal cellular lipid composition leading to toxic lipid accumulation, organelle dysfunction, cell injury, and chronic inflammation, is the hallmark of NASH.[2,4]

Our understanding of the main lipid species and pathways involved in lipotoxicity in NASH has substantially advanced in the past decade owing to progress in lipidomics, a subcategory of metabolomics that uses analytical chemistry techniques such as mass spectrometry and chromatography to identify and quantify the diverse lipid species contained in biological samples.[2] The analysis of data derived from liver and blood samples of patients across the entire NAFLD spectrum has generated specific lipid signatures that are associated with different liver disease stages[5–11] (Table 1). The interpretation of these signatures has disclosed novel metabolic pathways underlying liver disease progression or resolution, paving the way to new therapeutic approaches, and allowed the identification of noninvasive diagnostic biomarkers of NASH and of fibrosis, which currently can be most reliably identified by invasive liver biopsy.[1]

Lipidomics studies have shown that, although most hepatic lipids in NAFLD accumulate in the form of triglycerides (TGs), TGs are an inert form of lipid storage and protect against lipotoxicity, which is rather determined by the accumulation of toxic intermediates in TG synthesis, including saturated fatty acids (SFAs) and free cholesterol, or complex lipids, including glycerophospholipids and sphingolipids, and/or by a deficiency in lipid species that are essential for cellular integrity, including phospholipids, ω-3 polyunsaturated fatty acids (PUFAs), or PUFA-derived specialized pro-resolving mediators (SPMs).[10,11]

We reviewed recent advances regarding lipid species involved in NASH progression and resolution and discussed mechanistic insights and potential therapeutic targets.[11] We focused on different types of free fatty acids (FFAs), phospholipids, sphingolipids, and PUFA-derived eicosanoids and SPMs. The role of cholesterol accumulation in the pathogenesis of NASH has been reviewed elsewhere.[12]

Role of SFAs in the Pathogenesis and Progression of NASH

In NAFLD, as in other insulin-resistant states, hepatic exposure to circulating FFAs is increased because of unrestricted lipolysis of adipose tissue TGs; in addition, hepatic uptake of circulating FFAs, which involves a tetrameric plasma membrane protein complex that is composed of plasma membrane fatty acid (FA)-binding protein, caveolin-1, FA translocase (CD36), and calcium-independent membrane phospholipase A2β, is upregulated.[13] These 2 factors explain why in NAFLD nearly 60% of hepatic FFAs derive from lipolysis of adipose tissue TG, and the remaining hepatic FFAs originate from de novo lipogenesis (25%) and dietary TGs (15%).[14] In addition to quantity, the type of FFA is altered in NAFLD, with a substantial accumulation of the SFAs palmitate acid (C16:0) and stearate acid (C18:0) relative to monounsaturated fatty acids (MUFAs) and PUFAs (chemical structures reported in Supplementary Figure 1*A–C*). The extent of the accumulation of these SFAs in the steatotic liver parallels liver disease severity[8–10] and, consistently, these SFAs possess substantial lipotoxicity through various mechanisms. SFAs can bind and activate hepatocyte plasma membrane receptors, including death receptor tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) receptor 2 (TRAIL-R2) and damage-associated molecular pattern receptors, such as Toll-like receptor-4.[2,15]

The TRAIL-2 signaling pathway triggers caspase 8 proteolytic autoactivation, which results in direct or indirect (through Bcl-2 protein family-mediated mitochondrial outer membrane permeabilization [MOMP])

Table 1. Main Lipidomics Studies in Patients With NAFLD

Study	Population	Biological sample	Technique	Findings in NASH vs NAFL
Puri et al 2007[5]	Non-cirrhotic NASH (n = 9), NAFL (n = 9), control (n = 9)	Liver	TLC	↓PC; ↑lysoPC; ↓DHA, EPA, AA; ↑ω-6–to–ω-3 PUFA ratio; ↑FC
Puri et al 2009[6]	Non-cirrhotic NASH (n = 50), NAFL (n = 25), control (n = 50)	Plasma	TLC	↓DHA-to-DPA ratio; ↓MUFAs; ↓plasmalogens; ↑5-, 8-, 11-, 15-HETE
Gorden et al 2015[7]	Cirrhosis (n = 20), NASH (n = 20), NAFL (n = 17), control (n = 31)	Plasma	LC-MS	↓lysoPE; ↑PE; ↑Cer, DH-Cer and DH-deoxyCer; ↓Sph
Zhou et al 2016[8]	NASH (n = 69), NAFL (n = 117), non-NASH (n = 249), non-NAFL (n = 132)	Plasma	UPLC-MS	↑SFA (14:0, 16:0, 18:0); ↑MUFA (44:1, 54:1); ↓sphingomyelin; ↓lysoPC
Chiappini et al 2017[10]	NASH (n = 15), NAFL (n = 39), control (n = 7)	Liver	LC-MS	↑SFA (14:0, 16:0, 18:0); ↑MUFA (16:1, 18:1); ↑ω-6–to–ω-3 PUFA ratio; ↑Cer (C16, C18); ↓phospholipids (PC, PE, PI, PS); ↑sphingomyelin

Cer, ceramide; DH, dihydro; DPA, docosapentaenoic acid; FC, free cholesterol; HETE, hydroxyeicosatetraenoic acid; LC, liquid chromatography; lysoPC, lysophosphatidylcholine; MS, mass spectrometry; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PS, phosphatidylserine; Sph, sphingosine; TLC, thin-layer chromatography; UPLC, ultra-performance liquid chromatography.