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Review

# Lysophospholipid Metabolism and Signalling in Non-Alcoholic Fatty Liver Disease

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## Abstract

Non-alcoholic liver disease (NAFLD) constitutes a global health pandemic. It is estimated that about 25% of the world's population suffers from NAFLD. In the long-term, a subgroup of the patients can develop inflammation and fibrosis. The end result in some cases is cirrhosis and even liver-related death. The epidemiology and natural history of NAFLD lead to extreme financial costs.

To date, there is no approved treatment for NAFLD. Lipotoxicity has been proposed to be one of the main regulators of the implicated molecular pathomechanisms. Research has been focused on the role of cholesterol, free fatty acids and ceramides. Nevertheless, lysophospholipids, such as sphingosine 1-phosphate (S1P), lysophosphatidylcholine (LPC), lysophosphatidic acid (LPA), lysophosphatidylinositol (LPI), lysophosphatidylethanolamine (LPE) have emerged as potential contributors to NAFLD/NASH. Finally, the metabolism of other lysophospholipids, such as lysophosphatidylserine (LPSer), lysophosphatidylglycerol (LPG), and lysocardiolipin (LCL), has come to light in the context of NAFLD. In this review, we try to summarize the current knowledge regarding the potential of lysophospholipid signalling and metabolism as therapeutic targets and biomarkers in NAFLD and/or NASH.

## Keywords

non-alcoholic fatty liver disease, lysophosphatidylcholine, lysophosphatidic acid, lysophospholipids, sphingosine 1-phosphate

## INTRODUCTION

The diagnosis of non-alcoholic fatty liver disease (NAFLD) is based upon evidence of hepatic steatosis, either by imaging or by histology after the exclusion of other secondary causes of hepatic fat accumulation such as significant alcohol consumption, use of steatogenic medication and hereditary, autoimmune or viral hepatic disorders. NAFLD is histologically further categorized into non-alcoholic fatty liver (NAFL) defined as the presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes, and non-alcoholic steatohepatitis (NASH) defined as the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis.[1] Advanced fibrosis occurs in a subgroup of patients with NASH, leading to cirrhosis and possibly to the development of hepatocellular carcinoma.[2]

NAFLD constitutes a global health pandemic affecting about 25% of the world's population, with the metabolic syndrome being the major risk factor. In addition, a subgroup of NAFLD patients suffers from steatohepatitis (NASH) and/or advanced fibrosis.[2]

The therapeutics of NAFLD has extremely high financial costs. In the context of growing clinical and quality-of-life burden of NAFLD, the economic burden of this important liver disease for the United States and Europe is likely to increase.[3]

From a pathophysiological point of view, a two-hit hypothesis, based on appearance of steatosis (first hit), followed by a second hit leading to inflammation, hepatocyte damage, and fibrosis, was initially proposed. Recent studies suggest that NASH is the result of numerous conditions acting in parallel, including genetic predisposition, abnormal lipid metabolism, oxidative stress, lipotoxicity, mitochondrial dysfunction, altered production of cytokines and adipokines, gut dysbiosis and endoplasmic reticulum stress.[4]

Recently, lipotoxicity has been proposed to be one of the main regulators of the implicated molecular pathophysiological mechanisms. Research has focused on the role of cholesterol[5], free fatty acids[6] and ceramides[7]. Nevertheless, lysophospholipids, such as sphingosine 1-phosphate (S1P), lysophosphatidylcholine (LPC), lysophosphatidic acid (LPA), lysophosphatidylinositol (LPI), and lysophosphatidylethanolamine (LPE) have also emerged as potential contributors to NAFLD/NASH **(Fig. 1)**. However, there is a need to analyze and highlight the current literature regarding the role of lysophospholipids in NAFLD in order to shed light on the therapeutic potential hidden in their metabolic and signalling pathways. In the present review, our aim was to summarize the current knowledge on dysregulated lipid homeostasis in NAFLD and examine the cellular mechanisms of hepatic lipotoxicity and its contribution to the ongoing liver injury in this disease. For this purpose we conducted a detailed search in PubMed combining each of the following keywords: "sphingosine 1-phosphate", "lysophosphatidylcholine", "lysophosphatidic acid", "lysophosphatidylserine", lysophosphatidylethanolamine", "lysophosphatidylinositol", "lysophosphatidylglycerol", "lysocardiolipin", "lysophosphatidylthreonine", with each of the keywords: "non-alcoholic fatty liver disease", "non-alcoholic steatohepatitis", "NAFLD", "NASH", "metabolic fatty liver disease", "insulin resistance", and "hepatic fibrosis". For the selection of the papers, we required that the role of at least one of these lysophospholipids be examined in the context of NAFLD, NASH, hepatic fibrosis or insulin resistance. This revealed 45 papers.

## Sphingosine-1-phosphate

Sphingosine is released from ceramide through the action of sphingomyelinase. Then, 1-sphingosine phosphate (S1P) is formed by the phosphorylation of sphingosine by the remaining kinase located in the cytoplasm and the endoplasmic reticulum of various cell types. S1P can be dephosphorylated by sphingosine phosphatase, and, in addition,

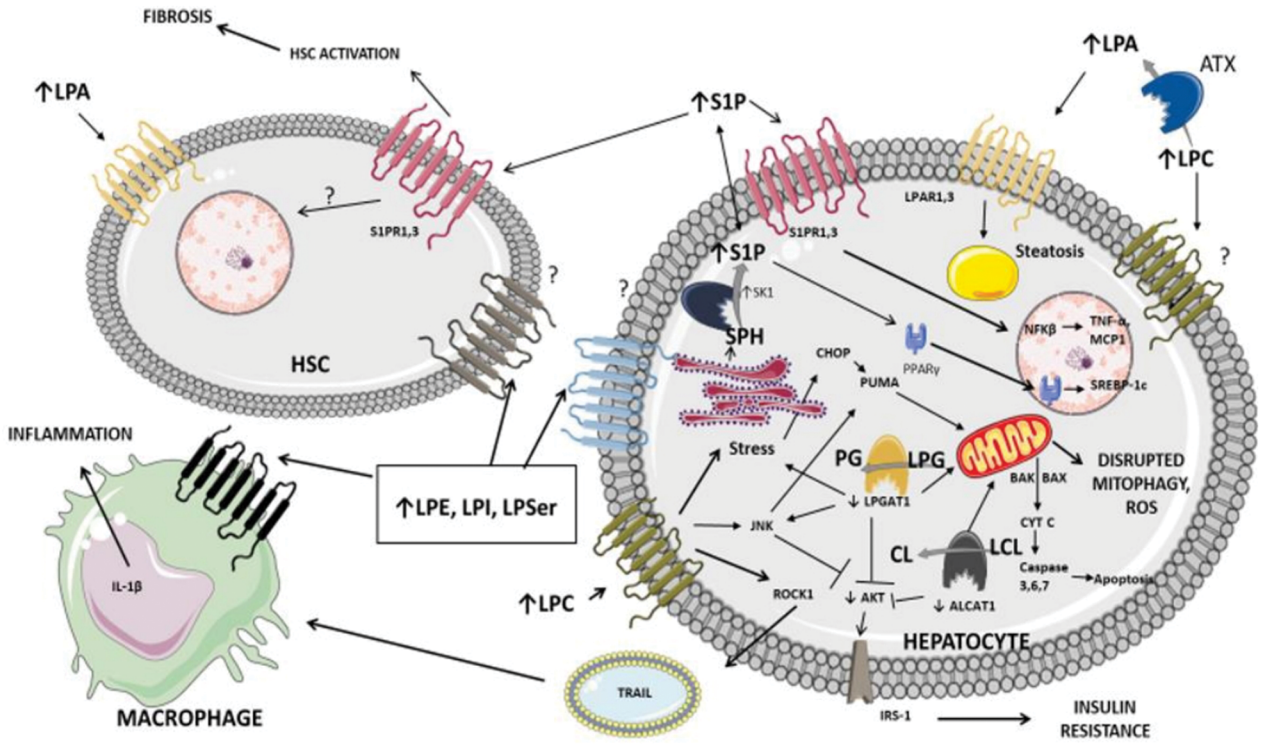


**Figure 1.** Lysophospholipid signalling in the pathogenesis of NAFLD. ATX: autotaxin; CHOP: C/EBP homologous protein; CL: cardiolipin; JNK: c-jun N-terminal kinase; MCP1: monocyte chemoattractant protein 1; LPA: lysophosphatidic acid; LPC: lysophosphatidylcholine; LCL: lysocardiolipin; LPE: lysophosphatidylethanolamine; LPG: lysophosphatidylglycerol; LPI: lysophosphatidylinositol; LPSer: lysophosphatidylserine; NFkB: nuclear factor kB; PG: phosphatidylglycerol; PPARγ: peroxisome proliferator-activated receptor γ; PUMA: P53 upregulated modulator of apoptosis; ROCK1: Rho associated protein kinase 1; SREBP-1c: sterol regulatory element protein 1c; S1PR1: sphingosine 1-phosphate receptor 1; S1PR3: sphingosine 1-phosphate receptor 3; S1P: sphingosine 1-phosphate; TNF-α: tumor necrosis factor α. This figure was created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License; https://smart.servier.com.

the action of S1P lyase degrades it irreversibly. S1P binds to sphingosine 1-phosphate receptors (S1PR)- 1,2,3,4,5, which mobilize G proteins. The binding of S1P to its receptors can lead to the activation of multiple signalling pathways.[8]

S1P is increased in experimental animals with NASH. Synthesis of S1P in hepatocytes is induced by palmitate-induced endoplasmic reticulum stress. S1P, after being secreted to the extracellular milieu, binds to its receptor S1PR1, resulting in its activation. This leads to the activation of NFKβ and the expression of pro-inflammatory cytokines, such as tumor necrosis factor α (TNF-α) and monocyte chemoattractant protein 1 (MCP1). Experimental animals deficient in sphingosine kinase did not develop NASH. At the same time, the siRNA-mediated targeted knock down of S1P1 prevented the expression of TNF-α and MCP-1 in HEPG2 cells.[9] Subsequently, another experimental study of NAFLD, showed that sphingosine kinase 1 deficiency or siRNA-mediated knock down of S1P2 and S1P3 receptors protected animals from the development of steatosis. Mechanistically, S1P induces hepatic steatosis through activation of AKT/mTOR and subsequent expression of peroxisome proliferator-activated protein γ (PPARγ).[10]

It has also been found that induction of non-alcoholic liver disease by palmitate and subsequent S1P release into the extracellular space by hepatocyte activates the S1PR2 of hepatocytes inducing insulin resistance[11], and the S1PR3 of hepatic stellate cells (HSCs) inducing fibrosis[12]. In fact, S1P inhibits the proliferation of hepatocytes[13], while also promoting the activation and differentiation of hepatic stellate cells (HSCs) to myofibroblasts, as well as their contraction, collagen production, migration, and their proliferation[14]. The role of S1P in steatohepatitis is highlighted by the fact that administration of the S1P antagonist, FTY720, to experimental animals led to NASH treatment.[15]

Finally, in the nucleus, S1P binds to and inhibits HDAC, thus inducing activation of transcription of various genes, such as genes whose protein products are nuclear (cytoplasmic) receptors like PPRAγ, but also lipid metabolism enzymes.[16]

## Lysophosphatidylcholine

Han et al.[17] found that patients with non-alcoholic steatohepatitis have increased lysophosphatidylcholine and the administration of lysophosphatidylcholine to experimental animals models leads to liver inflammation. Administration of palmitic acid to hepatocytes increased LPC content, an effect associated with c-jun N-terminal kinase (JNK)-induced apoptosis. In fact, inhibitors of phospholipase A2 (PLA2) or the Gai subunit inhibited liver cell apoptosis, indicating LPC action is mediated through a membrane receptor. The same pathway is probably involved in fatty acid-induced insulin resistance.[18] Furthermore, another study shows that LPC can lead to liver cell apoptosis through ER stress-induced activation of C/EBP homologous protein and P-53 upregulated modulator of apoptosis.[19]

LPC is actively involved in additional NASH pathogenetic mechanisms. It seems that through Ras-homologue-associated, coiled-coil containing protein kinase 1 (ROCK1) leads to the production of extracellular vesicles, which are rich in the apoptotic molecule TRAIL, inducing activation of macrophages.[20] Interestingly, increases in LPC in the context of NAFLD/NASH could possibly be caused by decreases in the activity of LPC acyltransferase 3.[21] In a follow-up study, reversion of NAFLD was associated with lower LPC/PC (phosphatidylcholine) ratio, while NAFLD persistence was associated with increase in the LPC/LPE ratio.[22] This study implies that LPC could partially underline the effect of low PC content and PC/PE ratio. Indeed, PC has been found to be reduced in patients with NAFLD and NASH in comparison with healthy controls.[23] Decreased PC/PE ratio has been found in the liver, erythrocytes, and plasma of patients with NAFLD and NASH in relation to healthy individuals.[24,25] In experimental studies using animal models, lower PC/PE ratio determines the development of hepatic steatosis and inflammation.[26,27] These effects could be attributed to the role of the PC/PE ratio in regulating the induction of endoplasmic reticulum stress[28], and the role of PC in the synthesis of liver triacylglycerols by activating sterol regulated element-binding protein (SREBP-1)[29].

## Lysophosphatidic acid

Lysophosphatidic acid is a bioactive lipid. It acts by binding to heterotrimeric G protein-coupled receptors. To date, five LPA receptors, LPA1-5, have been identified. Depending on the receptor activated, different G proteins are mobilized, and therefore different signalling pathways are activated. The result at the cellular level may be cell survival, proliferation, motility, etc.[30] It appears that the axis of autotaxin (an enzyme with lysophospholipase D activity, converting LPC to LPA) and lysophosphatidic acid is involved in the pathogenesis of NAFLD. In particular, serum LPA levels were found to be associated with the degree of hepatic fibrosis and hepatic steatosis.[31,32] In addition, LPA caused in vitro proliferation of hepatocytes and hepatic stellate cells.[33] Furthermore, in an experimental model of hepatic fibrosis, autotaxin expression was found to be induced by hepatocytes, resulting in an increase in LPA, which acts on HSCs and activates them. Inhibition of this pathway prevents hepatic fibrosis, while genetic deletion of hepatocellular ATX prevents lipid disorder and hepatocellular carcinoma.[34]

## Lysophosphatidylethanolamine (LPE)

NAFLD resolution was associated with a decrease in plasma LPE to PE ratio and lower phospholipase A2 with PE to LPE conversion activity.[22] On the other hand, the levels of LPE in the plasma of NASH patients were reported to be significantly higher than those of the healthy controls.[35] However, others found contradictory results.[36]

## Lysophosphatidylinositol (LPI)

LPI exerts its functions through binding to its receptor GPR55.[37] MBOAT7 encodes for an acyltransferase of LPI. rs641738 variant of MBOAT7 is associated with liver injury and fibrosis in patients with NAFLD[38], while rs626283 variant is associated with presence of NAFLD and insulin resistance[39]. LPI plasma levels were found increased in patients with NAFLD and chronic hepatitis B compared to healthy controls.[40] However, the exact mechanisms for the contribution of LPI to NAFLD have not been explored.

## Lysophosphatidylserine (LPSer)

The levels of LPSer and its potential in NAFLD have not been studied so far. Nevertheless, Uranbileg et al.[41] found increased activity levels of PSer-Phospholipase A1.

## Lysophosphatidylglycerol

Zhang et al.[42] studied the role of LPG acyltransferase (LPGAT1) which converts LPG to PG in the molecular pathogenesis of NAFLD and NASH. They showed that in an experimental animal model of NASH, LPGAT1 deficiency leads to I) hepatic steatosis through upregulation of SREBP-1c, ACC, FAS1, II) hepatic fibrosis through upregulation of collagen I and II, and III) hepatic insulin resistance through inhibition of AKT and GSK3 signalling by disrupting mitochondria-associated membranes, IV) decrease in mitophagy, V) increase in ER stress response, VI) increase in and susceptibility to oxidative stress, and VII) mitochondrial disruption. These results show that decreases in LPG is a potential disruptor of many important cellular functions. However, the exact physical intervention of LPG within these effects remains to be studied. The effect of LPGAT1 deficiency could be explained by changes in cardiolipin remodelling.[42] In addition, LPGAT1 has been found to display monoacylglycerol acyltransferase activity, a function related to hepatic steatosis.[43]

## Lysocardiolipin (LCL)

Lysocardiolipin metabolism has been studied extensively in a study by Wang et al.[44] In that study, they showed that lysocardiolipin acyltransferase 1 (ALCAT1), which is responsible for an aberrant cardiolipin remodeling, controls several molecular pathomechanisms of NAFLD. In experimental animal models, they showed that ALCAT1 expression is increased and is implicated in I) hepatic steatosis through upregulation of SREBP-1c, ACC, FAS1, II) hepatic fibrosis through upregulation of collagen I and II, III) hepatic insulin resistance through inhibition of AKT and GSK3 signalling, IV) decrease in mitophagy, V) decreased autophagosome biogenesis, VI) increase in and susceptibility to oxidative stress, and VII) mitochondrial disruption.

It is obvious that both ALCAT1 and LPGAT1 converge on the same molecular mechanisms. Hence, it could be convincing that the metabolism of LPG and LCL controls NAFLD pathogenesis through cardiolipin remodelling; cardiolipin, due to its unique chemical composition, is implicated in oxidative phosphorylation[45], mitochondrial shape and permeability[46,47], apoptosis[47], autophagosome formation[48] and, finally, mitophagy[49].

## Future directions

The aforementioned studies imply that lysophospholipids contribute to the development of hepatic steatosis, inflammation, fibrosis and insulin resistance, but there are certainly various limitations. In particular, substantial experimental works with knock-down animals and other interventions targeting the synthesis and/or action of sphingosine 1-phosphate indicate that there could exist a therapeutic potential for NAFLD. However, the translation of these findings in the clinical settings remains to be elucidated. Furthermore, preliminary studies regarding the role of LPC, LPA, LPE, LPI, LPG, and LPSer imply their potential in NAFLD. Since these lipids have important signalling ability[50,51], we propose that their role in the context of NAFLD merits further investigation, and could unveil novel therapeutic targets. However, interventions targeting the synthesis and the action of these lipids in experimental models of NAFLD, and measurements of the levels of these lipids in larger groups of NAFLD patients, would provide more insight regarding their active role in the disease pathogenesis and their therapeutic potential.

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# Competing interests

The authors have declared that no competing interests exist.

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# Метаболизм лизофосфолипидов и передача сигналов при неалкогольной жировой болезни печени

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## Резюме

Неалкогольная жировая болезнь печени (НАЖБП) представляет собой глобальную пандемию в области здравоохранения. Подсчитано, что НАЖПБ страдает 25% населения мира. В долгосрочной перспективе у части пациентов может развиться воспаление и фиброз. Конечным результатом в некоторых случаях является цирроз печени и даже смерть. Эпидемиология и анамнез НАЖБП приводят к чрезмерным финансовым затратам.

В настоящее время не существует одобренного лечения НАЖБП. Считается, что липотоксичность является одним из основных регуляторов задействованных молекулярных путей. Исследования сосредоточены на роли холестерина, свободных жирных кислот и церамидов. Однако лизофосфолипиды, такие как сфингозин-1-фосфат (S1P), лизофосфатидилхолин (LPC), лизофосфатидная кислота (LPA), лизофосфатидилинозитол (LPI), лизофосфатидилэтаноламин (LPE), считаются потенциальными факторами риска возникновения НАЖБП/ НАСГ. В заключение можно сказать, что метаболизм других лизофосфолипидов, таких как лизофосфатидилсерин (LPSer), лизофосфатидилглицерин (LPG) и лизокардиолипин (LCL), связан с НАЖБП. В этом обзоре мы пытаемся систематизировать текущую информацию о потенциале передачи сигналов и метаболизма лизофосфолипидов в качестве терапевтических мишеней и биомаркеров при НАЖБП и/или НАСГ.

## Ключевые слова

неалкогольная жировая болезнь печени, лизофосфатидилхолин, лизофосфатидная кислота, лизофосфолипиды, сфингозин-1-фосфат