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REVIEW ARTICLE

The relevance of acid sphingomyelinase as a potential target for therapeutic intervention in hepatic disorders: current scenario and anticipated trends

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Abstract

Acid sphingomyelinase (ASMase) serves as one of the most remarkable enzymes in sphingolipid biology. ASMase facilitates the hydrolysis of sphingomyelin, yielding ceramide and phosphorylcholine via the phospholipase C signal transduction pathway. Owing to its prominent intervention in apoptosis, ASMase, and its product ceramide is now at the bleeding edge of lipid research due to the coalesced efforts of several research institutions over the past 40 years. ASMase-catalyzed ceramide synthesis profoundly alters the physiological properties of membrane structure in response to a broad range of stimulations, orchestrating signaling cascades for endoplasmic reticulum stress, autophagy, and lysosomal membrane permeabilization, which influences the development of hepatic disorders, such as steatohepatitis, hepatic fibrosis, drug-induced liver injury, and hepatocellular carcinoma. As a result, the potential to modulate the ASMase action with appropriate pharmaceutical antagonists has sparked a lot of curiosity. This article emphasizes the fundamental mechanisms of the systems that govern ASMase aberrations in various hepatic pathologies. Furthermore, we present an insight into the potential therapeutic agents used to mitigate ASMase irregularities and the paramountcy of such inhibitors in drug repurposing.

Keywords Acid sphingomyelinase · Liver disorders · Hepatocellular carcinoma · Autophagy · Ceramide · Therapeutic targets

Abbreviations

AFLD	Alcoholic fatty liver disease
ALK-SMASE	Alkaline sphingomyelinase
ALT	Alanine aminotransferase
APAP	*N*-Acetyl-para-aminophenol
ASH	Alcoholic steatohepatitis
ASMase	Acid sphingomyelinase
CERS	Ceramide synthases
CERT	Ceramide transfer protein
DCA	Deoxycholic acid
DILI	Drug-induced liver injury
ER	Endoplasmic reticulum
EVS	Extra cellular vesicles
FIASMA	Functional inhibitors of acid sphingomyelinase
HSCS	Hepatic stellate cells
I/R	Ishemia–reperfusion
JNK	Jun N-terminal kinase
KDA	Kilo Dalton
LMP	Lysosomal membrane permeabilization
SL	Sphingolipid
SM	Sphingomyelin
SMASES	Sphingomyrelinase
SMPD1	Sphingomyelin phosphodiesterase 1
TNF	Tumor necrosis factor
Zn	Zinc

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Key points
Acid sphingomyelinase (ASMase) occupies a prominent position in the sphingolipid catabolism.
ASMase and its product ceramide exhibit pleiotropic signaling capabilities.
ASMase/ceramide axis is implicated in a plethora of hepatic disorders.
A wide range of molecules are recognized to impede the action of ASMase.
A better comprehension of the biological mechanisms influencing ASMase action can lead to therapeutic breakthroughs in hepatology.

Introduction

Sphingolipids (SLs) are very complex molecules with hundreds of distinct configurations in the three main structural sections: the headgroup, the sphingoid long-chain base, and the fatty acid (Futerman 2021). The synthesis of SLs commences in the endoplasmic reticulum (ER) and extends into the Golgi body, with successive synthetic steps disseminated along the several subcompartments of the secretory pathway (Parashuraman and D'Angelo 2019). Previously, it was assumed that the first step in SL biosynthesis happened by condensing palmitoyl-CoA with a serine molecule using the enzyme serine palmitoyl transferase (SPT). Moreover, several acyl-CoAs are now known to be SPT substrates, and amino acids, alanine and glycine, can serve as replacement substrates. This discovery played a significant role in elucidating how SLs are implicated in human disorders. For example, hereditary sensory neuropathy type 1 (HSN1), an autosomal genetic anomaly resulting from mutations in the SPT gene that affects the selectivity of SPT, allows it to utilize alanine instead of serine. This research emphasized how advances in SL biology have revolutionized our comprehension of human pathologies (Futerman 2021).

Ceramide (Cer) is the model sphingolipid that has dominated biomedical research in recent years. It is well documented for its dual functions as a secondary lipid messenger that controls a variety of cellular signal transduction pathways and as a significant facet of membrane bi-layer structure. It has been discovered to have a crucial role in apoptosis, senescence, cell stress, cell differentiation, and metabolism, rendering it a vital factor in human diseases (Coll et al. 2007). The Cer structure includes the sphingosine backbone, which is amide-bonded to a fatty acyl group. Ceramide synthases (CerS), a group of enzymes with an affinity for specific fatty acids, produce a varied family of ceramides with unique biological features based on the length of the attached fatty acid (Coll et al. 2007).

Acid sphingomyelinase (ASMase) is well known as an intermediate signaling enzyme in cell death pathways and metabolic liver disorders. It is a well-studied lysosomal enzyme with an ideal pH of 5 and has the principal function of degrading sphingomyelin to generate Cer. When isolated from urine, it was found to be a 72-kDa monomeric glycoprotein with a 61-kDa polypeptide core (Peters et al. 2021).

ASMase can be found practically in every cell type, although it is most abundant in the endolysosomal compartment. It can, however, translocate to the plasma membrane (PM), most likely at the outer leaflet, under certain conditions (Romiti et al. 2000). In addition to its proven involvement in apoptosis, new data suggest that ASMase has a role in autophagy, ER stress, liver fibrosis, and lysosomal membrane permeabilization (LMP), which are all capable of influencing liver complications (Insausti-Urkia et al. 2020). The lipid content of lysosomal membranes can alter as a consequence of SM disintegration driven by ASMase action. It has been reported that tumor necrosis factor (TNF-α)-induced apoptosis in the liver is mediated by ASMase action (Hajduch et al. 2021). While ASMase is widely recognized for its involvement in apoptosis, it also modulates the lysosomal cathepsins, which are crucial for hepatic stellate cell (HSCs) proliferation, differentiation, and hepatic fibrosis (Han and Kaplowitz 2015).

In this review, we discuss the molecular mechanisms by which ASMases drive the incidence and advancement of liver disorders. We also explore the prospective therapeutic interventions targeting ASMase action for the management of hepatic disorders.

Sphingomyelin

In mammalian cells, sphingomyelin (SM) is the most prevalent sphingolipid, occurring primarily in the PM and lipoproteins, mainly low-density lipoproteins (LDLs). Cer is less prevalent than SM. As a result, even tiny changes in SM concentrations can significantly impact Cer abundance (Régnier et al. 2019). The liver plays a crucial role in lipid metabolism. Up to 5% of freshly produced SLs are secreted in the form of very-low-density lipoprotein (VLDL) by hepatocytes, making them a significant source of SLs. Hepatic adipose tissues contain seven-to-eight times more SM than subcutaneous and intra-abdominal adipose tissues (Zeidan and Hannun 2010).

Sphingomyelin structure comprises a base sphingosine which is connected to various additional groups, as indicated in Fig. 1. An amide bond links a fatty acid to an amine. Phosphate is connected to choline by a phosphate ester bond. A variety of acyl chains may be found in SM, including 16:0, 18:0, 22:0, 24:0, and 24:1; nevertheless, 16:0 is the most frequent SM species observed in mammalian tissues (Calhoun and Shipley 1979). The formation of lipid rafts inside the PM is known to be promoted by the action of SM between cholesterol and glycosphingolipid. Almost 70% of the total cellular SM is found in these rafts (Simons and Ikonen 1997). A significant change in the SM content of the lipid rafts on the cell PM contributes to the development of insulin resistance, fatty liver disease, obesity, and inflammation (Chakraborty and Jiang 2013). The enzyme neutral sphingomyelinase (NSMase) catalyzes the hydrolysis of SM in plasma membranes, whereas acid sphingomyelinase (ASMase) catalyzes the hydrolysis of SM in endosome and lysosome membranes (Knapp et al. 2005).

Sphingomyelinases

The sphingomyelinases (SMases) are a class of enzymes that initiate SM disintegration with various biochemical attributes, producing Cer and phosphocholine. The SMases are split into three sub-classes based on pH and their subcellular location: ASMase, NSMase, and alkaline sphingomyelinase (Alk-SMase). NSMase and ASMase are found throughout the body and are responsible for Cer production in specific intracellular compartments, primarily the PM and lysosomes. ASMase catalyzes the production of Cer by utilizing SM via endosomes, but it can also be secreted as secretory ASMase (S-SMase) via Golgi trafficking (Canals et al. 2011).

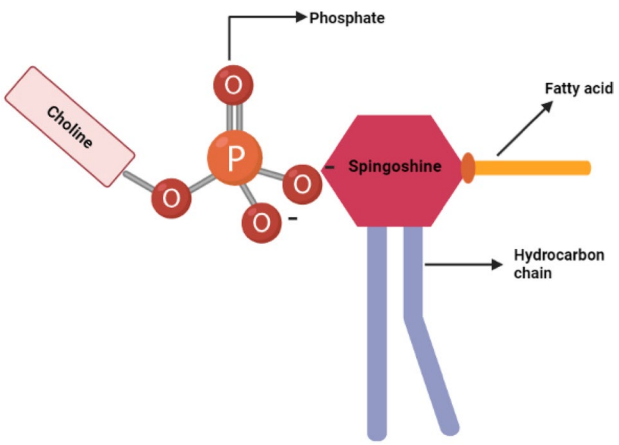


Fig. 1 The fundamental constituents of sphingomyelin

On a molecular level, SMases are phosphodiester bond hydrolases, and their peak activity is pH-dependent (Insausti-Urkia et al. 2020). The secretory ASMase as well as the lysosomal ASMase require different amounts of Zn^{2+} ions for optimal function. Both forms are derived from an inactive form that is proteolytically processed at the C terminal to produce endosomal/lysosomal ASMase and secretory ASMase. The ASMase counterpart, which is 65 kDa, is highly vulnerable to inhibitors like desipramine/imipramine, unlike its proASMase form (Jenkins et al. 2011).

The acid sphingomyelinase/ceramide axis

Cer is a well-studied sphingolipid, owing to its growing importance as a secondary messenger which influences a wide range of cellular metabolic functions. It is found in all complex SLs and has a role in a number of physiological processes, including regulating membrane permeability(Grassmé et al. 2003), cell differentiation, proliferation, death (Obeid et al. 1993), stress signaling (Teichgräber et al. 2008), and inflammation (Hebbar et al. 2015). It is the basic unit of SLs and is made up of a sphingoid long-chain base that has been N-acylated with a fatty acid. Cer is produced in the endoplasmic reticulum (ER) and subsequently transferred to the Golgi apparatus by a protein called ceramide transfer protein (CERT), where it acts as a substrate for sphingomyelin (SM) production (Hannun and Obeid 2002). Cer, under the influence of ASMase, can be utilized to generate Cer-rich membrane platforms, which can trigger apoptosis, growth inhibition, and other cellular responses (Yu et al. 2000). It was initially identified as a pro-apoptotic facilitator and may be converted into a range of metabolites, including sphingosine 1-phosphate, which has antiapoptotic tendencies and was first revealed in cancer research (Coll et al. 2007).

Cer is prevalent through cellular membranes, and its production is mediated by a variety of pathways, including (a) the de novo synthesis from L-serine and palmitoyl-CoA facilitated by the activity of serine palmitoyl transferase (SPT) and Cer synthases (CERS); (b) the degradation of membrane SM by sphingomyelinases (SMases), the most prominent of which are ASMase (Fig. 2) and NSMase; (c) Cer is processed by ceramidase to sphingosine, which can then be regenerated via the salvage route upon acylation (Yang et al. 2016). Activated de novo synthesis/sphingomyelinase stimulation produces long-lasting or temporary ceramides that affect the physiologic effects of stress, death receptors, and chemotherapy. Cer works by targeting internal organelles, including mitochondria, lysosomes, and the endoplasmic reticulum, to link external inputs to cell responses (ER) (Coll et al. 2007).

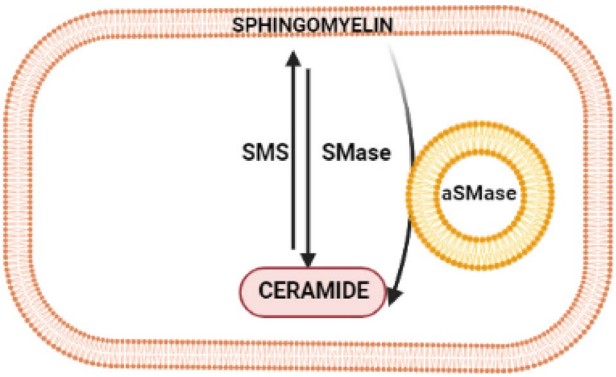


Fig. 2 The Sphingomyelinase pathway depicting the generation of ceramide from sphingomyelin upon the action of sphingomyelinases in the cell membrane. The acronyms for sphingomyelinase, acid sphingomyelinase, and sphingomyelin synthase are SMase, ASMase, and SMS, respectively

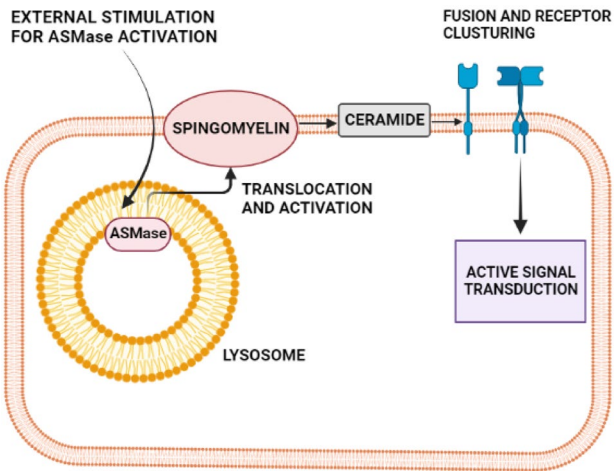


Fig. 3 An illustration of the synthesis of ASMase and ASMase/ceramide signal transduction. ASMase is found in the lysosomes and is electrostatically bound to the inner lysosomal membrane. The enzyme shifts from the lysosome to the extracellular leaflet of the cell membrane in response to events that trigger the ASMase. Activated ASMase generates ceramide from sphingomyelin. This leads to the formation of ceramide-enriched domains, and the aggregation of particular receptors' expedites and intensifies signaling pathways

ASMase is present in almost all cell types; however, it is most common in the endolysosomal compartment. Furthermore, under some circumstances, it can translocate to the PM, likely at the outer leaflet (Kho et al. 2022). The ASMase gene, abbreviated as SMPD1 (Sphingomyelin phosphodiesterase 1) in humans and Smpd1 in mice, is 5–6 kb long, comprising six exons, and is located on chromosome 11 at p15.1–p15.4 region (Dastani et al. 2007). The SMPD1 gene codes for two types of ASMases (endosomal and lysosomal ASMases). ASMase is widely recognized for its role as an intermediary signaling protein in cell death cascades and metabolic liver disorders. In vitro, ASMases function best at a pH of around 4.5 and 5.0. The enzyme was therefore believed to be primarily lysosomal. The endosomal/lysosomal ASMase hydrolyzes lysosomal SM supplied by lipoproteins. Recent research characterizing the crystal structure of mammalian ASMase revealed an N-terminal saposin domain and a catalytic domain that assumes a calcineurin-like structure with two Zn^{2+} ions (Insausti-Urkia et al. 2020). The relevance of this enzyme for cellular function was initially discovered in Niemann-Pick disease types A and B, which are hereditary disorders brought on by excessive SM agglomeration in a variety of organs.

ASMase generates Cer, which impacts a number of signal transduction pathways involved in metabolism, calcium homeostasis, autophagy, and lysosomal upkeep. As a consequence, ASMase is a vital molecule responsible for a variety of cellular activities. In human platelets, the enzymatic activity of ASMase may be detected. During thrombin-induced platelet aggregation, the platelet ASMase is released in a dosage-dependent manner. Furthermore, ASMase secretion is followed by a considerable drop in intracellular platelet ASMase activity of about 40%. Acute release of ASMase by thrombin-activated platelets can lead to a rapid surge in ASMase extracellular concentrations (Romiti et al. 2000).

Regulation of the ASMase/ceramide signal transduction

In a wide range of cell types, ASMase is stimulated by a plethora of cellular stimulations that are facilitated by both receptor and non-receptor-based mechanisms. The diversity of ASMase stimulators is more significant than any other enzyme implicated in sphingolipid metabolism. It comprises the triggering of death receptors such as CD95, TNF-α, and TRAIL receptors (Stephan et al. 2017). It has been established that exposure to UV-C radiation also provokes the stimulation and translocation of ASMase, resulting in the accumulation of Cer in raft microdomains contributing to the regulation of C-Jun N-terminal kinase (JNK) signal transduction (Charruyer et al. 2005). Viral and bacterial infection has also been implicated in the activation of ASMase signal transduction.

Cer, which is generated when ASMase is activated, influences a number of signal transduction pathways (Fig. 3) and has been shown to mediate hepatocellular injury during ischemia/reperfusion (I/R) liver damage. Following I/R, genetic or pharmacological blocking of the ASMase/Cer pathway by imipramine preserved the liver from cellular damage. It lowered blood ALT (alanine aminotransferase) levels, which is a clinical indicator of liver diseases. The same study revealed that pentoxifylline, a TNF-α blocking medication, decreased ASMase activation, showing that TNF-α and ASMase activation play a crucial role during I/R-induced liver damage (Llacuna et al. 2006). According

to another study, in an in vivo model of TNF-α-induced fatal hepatitis, *S*-adenosyl-l-methionine (SAM) reduction prompted the stimulation of caspases 8 and 3, leading to liver damage and mice mortality. In contrast, ASMase−/− animals had low hepatic SAM deficiency, caspase activation, and liver injury (Marí et al. 2004).

ASMase plays a significant role in bile salt-induced liver injury. In primary hepatocytes of rats, the cellular stress was induced by the bile salt deoxycholic acid (DCA). At physiological dosages, DCA-activated ASMase and Cer elevation was detected as early as 2 min after DCA administration, and it peaked at 10 min. In contrast to that, ASMase-deficient hepatocytes were protected from this response. Hepatocytes lacking FAS receptor (FAS-R) and ASMase were insensitive to DCA-induced JNK signal transduction upregulation (Gupta et al. 2004).

By reducing the pH of endosomes carrying ASMase from 6.0 to 5.6, the hydrophobic bile salts can activate the ASMase/Cer pathway. The endosome acidification response to bile salt treatment is maintained by increasing cytosolic chloride, which is known as an activator of the H^+ATPase pump. These findings unequivocally demonstrate that ASMase plays a critical role in the liver damage associated with cholestatic diseases (Becker et al. 2007). Using cell culture and animal models, Lang et al. discovered that ASMase/Cer signal transduction is responsible for liver failure and anemia in Wilson's disease. Since the ASMase/Cer pathway is linked to a number of hepatic ailments and anomalous signal transduction pathways, blocking this axis may be effective in alleviating liver diseases (Brewer 2007; Lang et al. 2007) (Fig. 4).

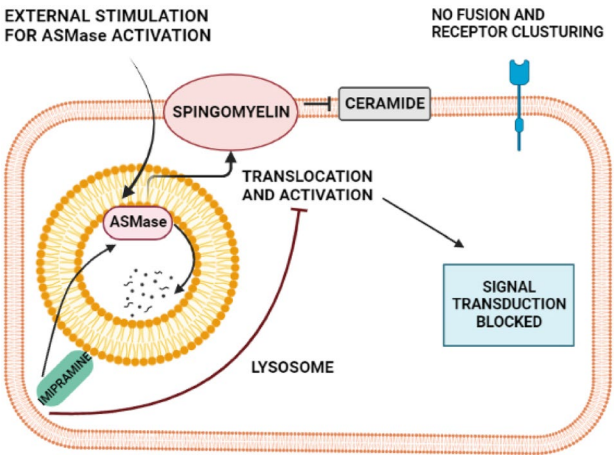


Fig. 4 An illustration of the functional inhibition of ASMase and ASMase/ceramide signal transduction. ASMase is degraded in the lysosomes by the action of functional inhibitors of acid sphingomyelinase (FIASMA), such as imipramine. Thus, the complete signal transduction is disrupted by imipramine treatment therapy, since ASMase-activating stimuli can no longer enable the enzyme to translocate to the plasma membrane

The function of ASMase in autophagy

Under stressful conditions, autophagy is a key process that enables the lysosomes to degrade cytosolic content, leading to constitutive recycling and energy generation. Autophagy can be classified into three types: macroautophagy, microautophagy, and chaperone-mediated autophagy. Macroautophagy has been the subject of the most extensive research. Bacteria, defected organelles, misfolded peptides, and other specialized substances are sequestered by cytosolic double-membrane projections called autophagosomes (Perrotta et al. 2015). An essential aspect of the autophagic process is its dynamic control, which is dependent on a highly organized execution to carry out autophagy. In the beginning, autophagy was characterized as a form of cell death distinct from apoptosis and necrosis (Schweichel and Merker 1973). A comprehensive understanding of autophagic cell death is still not that clear, and once it is, it will undoubtedly put a spotlight on aspects of physiology and pathophysiology that are still ambiguous. An excellent illustration of this is provided by recent studies on the role of ASMase in autophagy.

Even though ASMase is an essential enzyme that regulates the production and disintegration of Cer, less information is available about the specific character of ASMase in autophagic processes, and its commitment to the autophagy system has thus far gone nearly unnoticed. As far as we are cognizant, Smith and Schuchman's (2008) analysis offered potential evidence of its involvement in autophagy (Smith and Schuchman 2008). According to their discovery, the gamma-ray illumination involving a recombinant ASMase boosted the number of acid vesicles and autophagosomes in skin cancer cells. ASMase, as well as Cer, were later demonstrated to be activated by amino acid scarcity in HL-60 cell lines, and ASMase downregulation considerably reduced the development of autophagosomes brought on by amino acid scarcity (Taniguchi et al. 2012). Such findings suggest that ASMase may enhance the generation of autophagosomes brought on by various stress factors.

In nerve cells as well as fibroblasts, it was demonstrated that the ASMase from lysosomal origin firmly stimulated the lipidated LC3 and p62 concentrations, enhancing its activity and leading to the deformity of autophagic flux (Lee et al. 2014). Consequently, lysosomal ASMase may function as a suppressor instead of an activator of autophagic proteolysis (Lee et al. 2014). Additionally, it has been discovered that ASMase is positively associated with improved autophagolysosome development, suggesting that a lack of ASMase results in improper autophagic flux, which in turn causes the flawed destabilization of autophagosomes (Li et al. 2014). Studies conducted in vitro on a variety of cell lines

repeatedly demonstrated that some potent ASMase antagonists, such as siramesine and clomipramine, have an antagonistic influence on the autophagic flux, which increases the development of autophagosomes. It's captivating to analyze that ASMase action was found to be inhibited by chloroquine, a potent repressor of autophagic flux (Petersen et al. 2013).

The impact of impaired ASMase activity in the pathophysiological mechanisms of numerous severe disorders has recently been revealed, and it appears that in the majority of these scenarios, the pathogenic influence of the imbalanced ASMase activity may actually be caused by the impairment of the ASMase-autophagy axis. (Table 1). Autophagic disruption promotes the advancement of several hepatic anomalies, such as alcoholic and non-alcoholic steatohepatitis, wherein autophagy distortions foster steatotic and fibrogenic pathways (Czaja et al. 2013). As a consequence, the existing information points to ASMase as a highly compelling therapeutic target for autophagy-related ailments.

Potential functions of ASMase in liver anomalies

The liver plays a prominent role in lipoprotein biosynthesis and regulation. Apart from producing SM, it is also entailed in SM hydrolysis and ASMase expression. Since liver ASMase activity is greater than that of most other organs, ASMases are vital in maintaining liver metabolism and Cer balance. Mutations in SMases, especially ASMases, cause significant alterations in normal liver function and SM buildup, as observed in numerous liver anomalies such as Niemann Picks type A/B diseases (NPA/NPB). Hepatomegaly, a clinical manifestation of liver failure frequently observed in Niemann–Pick patients, is brought on by a decline in ASMase activity (Zeidan and Hannun 2010).

The activation of the ASMase/Cer pathway is linked to the development of a variety of liver disorders (Zeidan and Hannun 2010). The buildup of deformed proteins in the endoplasmic reticulum (ER) causes ER stress. ASMase has been shown to cause ER stress by increasing Cer synthesis and altering Ca^{2+} signaling (Fernandez et al. 2013). Consequently, ASMase is linked to a plethora of liver pathologies (Table 2), which are mentioned as follows.

Alcoholic and non-alcoholic steatohepatitis (ASH/NASH)

NASH and ASH are the advanced phases of metabolic associated fatty liver disease (MAFLD) and alcoholic fatty liver disease (AFLD). However, the factors that lead to the development of simple hepatic steatosis into NASH or ASH are difficult to ascertain. First and foremost, because of their intimate ties to the global epidemics of diabetes and obesity, they are becoming more and more critical public health challenges and are anticipated to have a significant impact on healthcare in the years ahead (Mitra et al. 2020; Scaglioni et al. 2011).

ASMase is utilized as a potential new target for ASH and NASH treatments, owing to its role in inducing Cer synthesis leading to hepatic apoptosis and hepatic fibrosis. In the individuals suffering from NASH, ASMase expression and activity were shown to be elevated in liver and blood samples. ASMase promotes the stress-mediated response and initiates hepatocellular apoptosis in reaction to the TNF-α and Fas-induced severe clinical liver damage (Insausti-Urkia et al. 2020). It has been thoroughly researched that ASMase, which yields Cer by hydrolyzing SM, facilitates TNF-α/Fas-induced hepatocellular cell death and stimulates hepatic fibrogenesis (Garcia-Ruiz et al. 2015). Substantial studies have revealed that ASMase influences vital processes that lead to metabolic derangement, fibrosis, and lipotoxicity, including ER stress, autophagy, and lysosomal membrane permeabilization (LMP), contributing to ASH and NASH (Garcia-Ruiz et al. 2015) (Fig. 5).

ASMase stimulation in steatohepatitis can be triggered by a variety of pathways. As an enzyme, it mediates stress regulation and cell death and is triggered by TNF-α, ROS,

Table 1 Association of ASMase expression and autophagic flux in several anomalies

Pathology	Regulation of ASMase	Autophagic flux	Implications	References
Steatohepatitis	↑	↑	Steatosis	Fucho et al. (2014)
Niemann–Pick disease type A	↓	↓	Cell death	Gabandé-Rodríguez et al. (2014)
Alzheimer's disease	↑	↓	Cell death	Lee et al. (2014)
Atherosclerosis	↓	↓	Atherogenesis	Petersen et al. (2013)
Macular degeneration	↑	↓	Tubulin acetylation	Toops et al. (2015)
Endothelial cells	↓	↑	Contributes to pathology	Justice et al. (2018)
Coronary atherosclerosis	↓	↓	Contributes to pathology	Li et al. (2014)
Melanoma	↑	↓	Induction of mTOR pathway	Cervia et al. (2016)

Table 2 The function of ASMase in different liver pathologies

Liver disorder	Protein involved	Mechanism	Reference
NASH/ASH	ASMase	ER stress, autophagy, and LMP	Garcia-Ruiz et al. (2015)
Ischemia–reperfusion (IR) liver injury	ASMase	ASMase inhibition reduces ceramide generation leading to the attenuation of ALT, caspase 3 activation, and the release of cytochrome C	Llacuna et al. (2006)
Hepatolenticular degeneration	ASMase	Cu^{+2} triggers the programmed cell death in liver cells via the ASMase activation and the accumulation of ceramide	Lang et al. (2007)
Hepatocellular carcinoma	ASMase	Recombinant human ASMase works synergistically with sorafenib to reduce tumor volume in HCC animal models	Savić et al. (2013)
Drug-induced liver injury	ASMase	ASMase protects against acetaminophen-induced liver injury by influencing mitochondrial turnover, improving mitophagy, and the removal of defective organelles that cause APAP-mediated liver injury	Insausti-Urkia et al. (2020)
Viral hepatitis	ASMase	A considerable elevation of serum acid sphingomyelinase is driven on by non-alcoholic fatty liver disease and chronic hepatitis C virus infection	Grammatikos et al. (2014)
Niemann-Pick disease	ASMase	Acid sphingomyelinase insufficiency in type B Niemann–Pick disorder induces lysosomal sphingomyelin storage, mostly affecting the lungs, liver, and spleen	Garnacho et al. (2017)

ASMase acid spingomyelinase, *NASH* non-alcoholic steatohepatitis, *ASH* alcoholic steatohepatitis, *ER* endoplasmic reticulum, *LMP* lysosomal membrane permeabilization, *ALT* alanine aminotransferase

and oxidative stress, all of which are crucial elements in steatohepatitis. It has been demonstrated that animals lacking ASMase were immune to alcohol-induced liver ER stress and hepatic steatosis. This ER stress resistance was alcohol-specific, since in vivo tunicamycin administration caused ER stress in ASMase non-functional animals, leading to hepatic steatosis (Fernandez et al. 2013). Alcohol-induced ER stress resistance was devoid of hyperhomocysteinemia in ASMase knockout mice, and amitriptyline was shown to prevent wild-type mice from alcohol-induced hepatic steatosis, lipopolysaccharide-mediated liver injury, and ER stress (Fernandez et al. 2013). Finally, the researchers examined ASMase mRNA levels in liver samples from people with symptomatic alcoholic hepatitis and normal individuals, and it was reported that ASMase mRNA levels in patients were two-to-three times higher than in healthy controls. Overall, it was revealed that ASMase plays a significant role in human alcohol-induced hepatic injury (Fernandez et al. 2013).

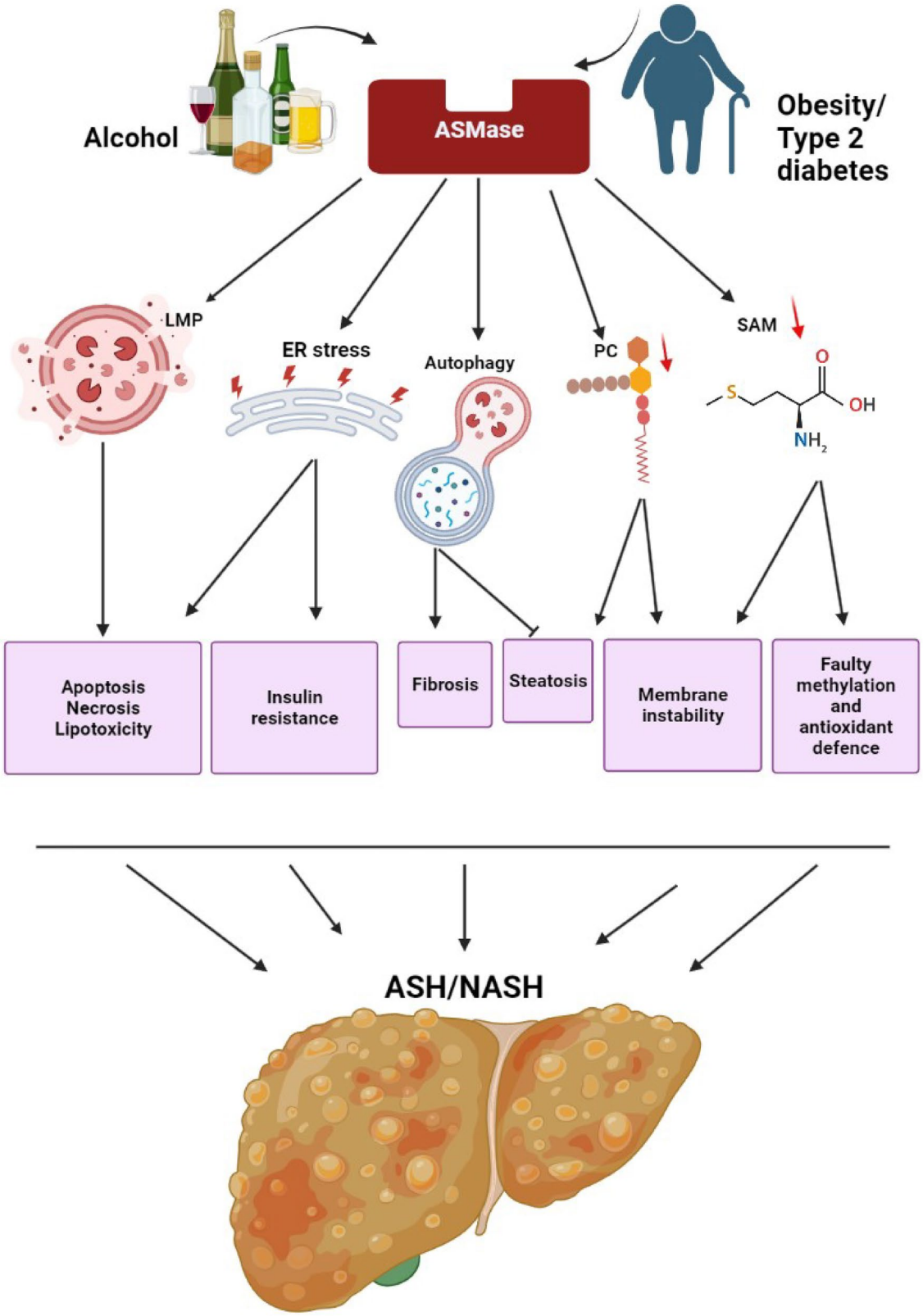
Additionally, recent findings link ASMase activity to alterations in *S*-adenosyl-L-methionine (SAM) and phosphatidylcholine (PC) balance, indicating that inhibiting ASMase and improving PC and methionine metabolism may be an effective way to treat ASH/NASH (Alarcón-Vila et al. 2023).

Hepatic fibrosis

A prevalent and challenging clinical issue globally, hepatic fibrosis is the wound-healing reaction of the liver to its persistent damage. Numerous variables and aetiologies, such as viral exposure, cholestasis, ASH, and NASH, can cause advanced liver problems, which are commonly manifested by liver fibrosis. The percentage of individuals at threat for fibrosis and progressive liver damage is growing substantially (Erickson 2009).

The stimulation of ASMase is significant and selective when HSCs are activated in vitro. During HSC activation, ASMase activity rises in tandem with cathepsin-B and cathepsin-D expression. HSC transdifferentiation into myofibroblasts requires both cathepsins. Their suppression reduced HSC proliferation and smooth muscle expression (Hajduch et al. 2021). The profibrogenic phenotype of HSCs is diminished by the pharmacological inhibition or silencing of ASMase. This indicates that ASMase is involved in HSC transdifferentiation. The pathogenic condition created by total ASMase loss may be eliminated with shallow levels of ASMase activity, revealing the paradoxical function of ASMase in pathophysiology (Moles et al. 2010).

ASMase expression and Cer levels were found to be elevated in a bile duct ligation-induced mice model (Li et al. 2020). Additionally, transgenic mice with bone marrow cells that are ASM−/− produced more TNF-α and IL-1 following the ligation. According to the research, Cer and ASMase are crucial for Kupffer cells to operate appropriately in decreasing inflammation, promoting hepatocyte longevity, restoration, and guarding against liver fibrosis (Li et al. 2020). In comparison, a different study demonstrates that in bile duct-ligated animals, concurrent suppression of IL-6 and



ASMase dramatically diminishes hepatocyte death, cytokine production, and hepatic fibrosis (Hubel et al. 2017). Additionally, current research indicates that inhibiting ASMase has a preventive role on hepatic function. HSC activation promotes hepatic fibrosis in long-term sepsis survivors. It has been documented that medication with desipramine

◂**Fig. 5** Demonstration of the involvement of ASMase in the advancement of NASH/ASH: the stimulation of ASMase due to alcohol or other mechanisms results in the induction of lysosomal membrane permeabilization (LMP), ER stress, and autophagy, all of which have a role in the progression of NASH/ASH and promote I/R, lipogenesis, fibrosis, and steatosis. Additionally, *S*-adenosyl-L-methionine (SAM) and phosphatidylcholine (PC) are down-regulated by ASMase activation, inducing liver steatosis, injury, inflammation, and fibrosis, which are the hallmarks of ASH/NASH

reduces the release of the cytokines IL-1 and MCP1 to restore liver function and fibrosis (Li et al. 2020). The complex roles played by Cer, the use of distinct cells, or varied animal models in separate studies could all contribute to the contentious effect of ASMase on liver fibrosis.

Drug-induced liver injury (DILI)

Hepatocellular degeneration induced by a toxic dose of medications or xenobiotics is a major cause of liver failure. Because acetaminophen (APAP) is one of the most regularly used pain medicines worldwide, it is the standard drug-induced liver injury paradigm. APAP is a dose-dependent hepatic toxin and a leading cause of liver failure (Lee 2004). The dangerous electrophile *N*-acetyl-*p*-benzo-quinoenimine (NAPQI) generated by APAP metabolism is detoxified by conjugating with the reduced form of glutathione. Prolonged APAP intake or a depleted liver GSH supply promotes NAPQI interaction with mitochondrial protein thiols, resulting in mitochondrial dysfunction and the release of generated ROS and oxidative stress. Additional ROS production, ATP deprivation, and hepatocellular death are caused by excessive mitochondrial ROS production, which enhances mitochondrial JNK trafficking and intensifies the triggering of mitochondrial permeability transition pore opening (Hanawa et al. 2008).

As previously mentioned, lysosomal architecture and dynamics are deeply impacted by the deposition of SM and other lipids driven by ASMase insufficiency. Due to the faulty integration of mitochondria-containing autophagosomes with lysosomes mediated by ASMase insufficiency, lysosomal cholesterol buildup lowers mitophagy and makes individuals more vulnerable to the liver-damaging effects of APAP. ASMase protects APAP by influencing mitochondrial turnover and the removal of defective organelles that cause APAP-mediated liver injury as a consequence of maintaining SM/cholesterol balance (Baulies et al. 2015).

Hepatocellular carcinoma (HCC)

The most frequent kind of liver cancer is hepatocellular carcinoma (HCC), which accounts for 85% of all primary liver malignancies. It is a highly aggressive tumor with a dismal prognosis and a low survival rate. The histology of HCC varies greatly depending on the site of origin, making it difficult to identify with a single biomarker (Mir et al. 2022). It is a genetically distinct neoplasm in which the number of intricate signal transduction pathways induces increased proliferation and angiogenesis (Mir et al. 2021). HCC is the most advanced stage of chronic liver disease. Unfortunately, current treatment is inefficient and limited, and advanced HCC develops drug resistance, requiring early identification for survival. Cer levels are much lower in HCC tissues due to the enhancement of mechanisms that promote its degradation; hence, boosting Cer levels specifically within the tumor might be a viable therapy approach (Insausti-Urkia et al. 2020).

It has also been suggested that SLs and SMases contribute to HCC pathogenesis via their interconnections with the mTOR pathway and autophagy, both of which are significant in HCC pathogenesis. The mTORC2 signal transduction pathway has been implicated in inducing liver carcinogenesis by activating lipid synthesis and denovo fatty acid synthesis, which promotes steatosis and tumor growth. Further, increased lipogenesis was linked to increased mTORC2 activity, and blocking sphingolipid synthesis decreased tumor progression, indicating a connection between steatosis and tumor production and, therefore, hepatosteatosis acts as a driver of HCC progression (Xu et al. 2019). Despite substantial research, many tumors, including HCC, have strategies that lead to chemoresistance development. After sorafenib therapy, Cer-influencing enzymes, mostly glucosylceramide synthase (GCS), are more expressed in liver cancer cells like HepG2 and Hep3B, decreasing Cer-promoting apoptotic activation and showing resistance to sorafenib treatment. GCS knockdown rendered liver cancer cells more susceptible to sorafenib, which is consistent with their results (Stefanovic et al. 2016).

It has been identified that recombinant human acid sphingomyelinase (rhASM) in combination with sorafenib considerably reduced tumor volume, elevated tumor necrosis, and curtailed tumor blood vessel integrity in HCC. In this scenario, there was no evidence of persistent liver damage or weight loss after recombinant human ASMase (rhASM) administration (Savić et al. 2013).

Ischemia–reperfusion (I/R) liver injury

When performing hepatic surgeries, partial or mostly entire blockage of hepatic blood flow is frequently required. This disruption of blood circulation is known as "warm ischemia," and when the organ is revascularized, and molecular oxygen is restored, the organ experiences a phenomenon known as "reperfusion injury," which worsens organ function. Hepatic ischemia/reperfusion (I/R) damage is a dangerous complication that causes considerable hepatocellular loss and inhibits liver function. It may occur in a number of

clinical settings, including liver surgery and transplantation. Following an ischemia phase in which the oxygen supply and nutrients are restricted, I/R is triggered by the repair of blood circulation. Oxidative stress and inflammation are the principal causes of cellular damage caused by I/R. In the liver, signaling lipid intermediates, such as SLs and Cers, have been identified as essential players in stress response and cell death (Unal et al. 2017).

NSMase, in addition to ASMase, has been linked to I/R damage. Furthermore, NSMase inhibition does not lower ER stress. It reduces apoptotic stimulation during I/R injury, suggesting that NSMase plays a crucial role in I/R liver injury (Llacuna et al. 2006). It has been reported that hepatocellular death results from the production of Cer during I/R, since JNK signal transduction is activated, and this is followed by the translocation of Bcl-2-like protein 11 (BimL) protein to the mitochondria. ASMase stimulation, JNK activation, and mitochondrial-dependent hepatocellular apoptosis were all inhibited by the administration of the drugs, such as pentoxifylline and imipramine (Llacuna et al. 2006) (Fig. 6).

Niemann–Pick A/B (NPA/B)

Niemann–Pick Disorder (NPD) is a hereditary lysosomal storage disease with faulty lipid metabolism caused by genetic abnormalities and leads to irregular accumulation of fatty molecules in numerous tissues throughout the body,

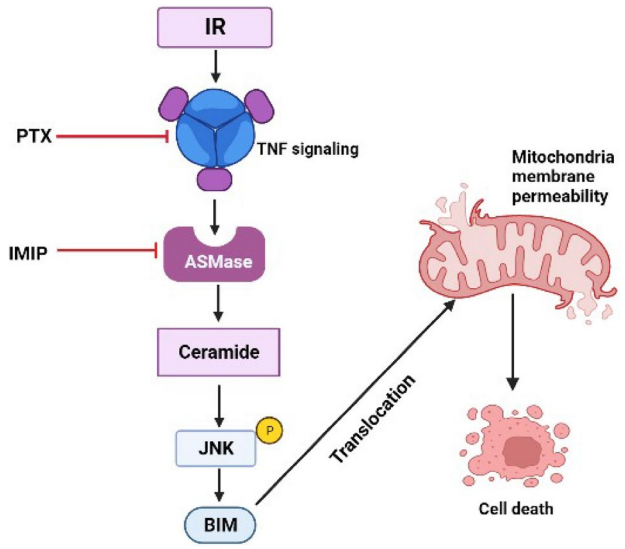


Fig. 6 The involvement of ASMase in the mechanism of cell death induced by ischemia–reperfusion injury(I/R): ceramide production following I/R affects mitochondria via JNK signal transduction and consequent BimL localization to mitochondria, results in hepatocellular apoptosis. Treatment with inhibitors like pentoxifylline (PTX) or imipramine (IMIP) inhibited ASMase action, JNK stimulation, and mitochondrial-dependent hepatocellular death

causing harm in the afflicted areas. The primary cause of this illness is the lack of lysosomal ASMase (Patiño-Escobar et al. 2019). Niemann-Pick disease has been classified into four categories based on its origin and symptoms: type A, type B, type C1, and type C2. Whenever the SMPD1 gene is defective, it produces faulty L-ASMase, causing type A and B NP disorders. Mutations in the NPCI and NPC2 proteins/genes lead to type-C1 and type-C2 NPD, influencing lipid transport. Type A NPD most usually manifests itself in newborns of around three months of age with an enlarged liver and spleen, as well as extensive lung damage that leads to lung illnesses and, ultimately, respiratory failure. A cherry red patch in the eye is another sign of type-A NPD. Children that have type-A NPD, on the other hand, will not live beyond childhood (Chang et al. 2005). Due to a deficiency in the NPC1 protein or potentially a different gene product, NPC cells in the type II variant of Niemann–Pick disease are unable to release lipoprotein-derived free cholesterol from the lysosomal compartment, and despite the existence of a normal ASMase gene in NPC fibroblasts, ASMase activity is suppressed by up to 80%. This implies that ASMase activity is down-regulated or inhibited by the increased lysosomal cholesterol content of NPC cells. (Reagan et al. 2000).

The use of genomic and bioinformatics techniques uncovered Niemann–Pick C1-Like 1 (NPC1L1) Protein. This protein is a homolog of Niemann–Pick C1 (NPC1). When compared to NPC1, NPC1L1's amino acid sequences are 51% similar and 42% identical (Jia et al. 2011). Long-standing research has demonstrated that higher dietary cholesterol encourages animal hepatocytes to accumulate triglycerides as well as cholesterol. Decreased intestinal absorption of cholesterol may thereby lessen hepatic triglyceride buildup. In accordance with this, silencing of NPC1L1 has been observed to hinder the progression of fatty liver in mice fed with a diet high in cholesterol and bile acids. Ezetimibe is a potent suppressor of cholesterol metabolism that is frequently used to manage hyperlipidemia, and NPC1L1 is its primary target on the molecular scale. Apart from lowering blood cholesterol, research suggests that NPC1L1 insufficiency or ezetimibe therapy also protects diet-induced hepatic steatosis and obesity (Jia et al. 2011). The prevention of hepatic steatosis by ezetimibe therapy or NPC1L1 depletion has also been explained by a number of other factors, notably increased C-Jun N-terminal kinase (JNK) activation, lowered ER stress, and diminished ROS production (Nomura et al. 2009). The prevention of fatty liver disease by ezetimibe therapy or NPC1L1 silencing is illustrated in Fig. 7.

Hepatosplenomegaly is common in NPD type B individuals and can be drastic in the occurrence or absence of symptoms related to liver dysfunction. Bone marrow transplant (BMT) has been performed on numerous ASMase-deficient NPD patients. Although the consequences of the

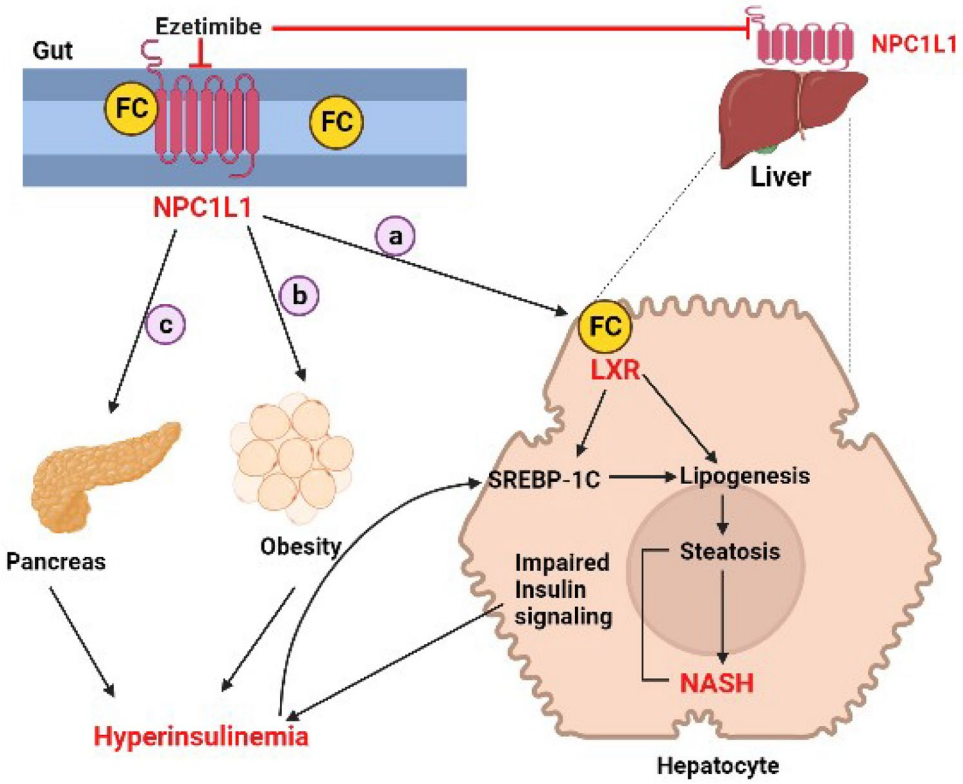


Fig. 7 Mechanism proposed for NPC1L1 impairment or ezetimibe therapy to alleviate MAFLD: **a** downregulation of NPC1L1 reduces intestinal absorption and enhances the biliary output of free cholesterol (FC). As a result, NPC1L1 may assist in preventing hepatic steatosis by minimizing hepatic cholesterol levels and the cholesterol-dependent stimulation of the liver X receptor (LXR), a nuclear receptor that facilitates hepatic lipid synthesis. Minimal lipid deposition in the liver as a function of NPC1L1 suppression may optimize liver insulin signal transduction by restricting hepatic lipid contents, ER stress, and/or the release of inflammatory mediators and ROS. Such scenarios prevent the advancement of simple steatosis to NASH, diet-induced insulin sensitivity, and the establishment of hyperinsulinemia, a disorder that encourages hepatic lipid synthesis through a mechanism that involves a membrane-bound transcription factor SREBP-1c. **b** For inexplicable reasons, diet-induced adiposity is averted by NPC1L1 suppression, which may also safeguard the liver from pathological changes by improving overall insulin sensitivity. **c** Downregulation of NPC1L1 significantly lowers blood insulin levels. It is not apparent if this decrease is simply due to improved insulin sensitivity. The suppression of NPC1L1 may directly affect the secretion of insulin from beta cells, impeding the liver from going through insulin-driven lipid synthesis

transplant surgery may be catastrophic, there has been a reported sharp decrease in liver and spleen enlargement following BMT. Apart from BMT, other therapies include enzyme replacement therapy (ERT). ERT is now being considered a therapeutic option for ASMase insufficiency. For ASMase insufficiency, rhASM has been synthesized in Chinese hamster ovary cells and has undergone rigorous characterization to assess ERT for this disorder. Following that, young animal models received an injection of this recombinant enzyme through their tail veins (Schuchman and Desnick 2017). Although ERT is anticipated to be imparted for individuals with ASMase deficiency in the coming years. Scientific investigations should emphasize obtaining extensive enzyme administration to the brain as well as creating replacements for enzyme infusions, such as gene therapy and small molecule methods. These strategies should be made more accessible by the recently discovered crystal structure of ASMase and the creation of novel, secure gene therapy vectors.

Viral hepatitis

Viral hepatitis B (HBV), like viral hepatitis C, is a primary type of chronic liver disease characterized by severe inflammation and hepatic damage, which may progress to cirrhosis, hepatic failure, and liver cancer. The relationship between SMases and viral hepatitis is currently unclear; however, it seems to be connected with the generation of extracellular vesicles (EVs) influenced by the sphingolipid mechanisms. EVs are bi-layer particles that contain proteins, lipids, and nucleic acids, among other substances. Several physiological processes have been found to be impacted by their activity,

such as signaling complexes in intercellular communication. SLs, especially ceramides, may govern the formation of EVs due to their effects on the structural and functional properties of lipid membranes (De Toro et al. 2015). Ceramides may induce membrane bilayers to generate domains and lateral phase separation, as well as promote negative curvature and membrane invagination. Furthermore, it has been shown that ASMase activity is essential for lipid phases. The structural regions of scaffold proteins, which have been associated with death-receptor-related liver diseases in lysosomes, are modulated by ASMase. In viral hepatitis, EVs play a unique role, because they may contain viral particles, enabling the virus to propagate to neighboring cells. It was recently reported that ceramide-induced extracellular vesicles act as a DNA carrier for HBV and can disseminate to naive hepatocytes (Sanada et al. 2016). Thus ASMase/ceramide axis can be an important target for preventing EV-associated HBV infection.

Hepatolenticular degeneration

Hepatolenticular degeneration, also referred to as Wilson's disease, is an inherited syndrome resulting from changes in the ATP7B protein, which is a copper-transporting ATPase in the liver. As a consequence of the malfunction, Cu^{2+} builds in the liver and other tissues of the body. The inhibition of ASMase in animals with Wilson's disease significantly retarded the onset of illness and prevented these animals from developing fibrosis and hepatic failure. This unveiled a causal link between ASMase and the progression of Wilson's disease. Moreover, these findings point to ASMase as a potential target for the therapy of Wilson disease, which was previously unknown. The amounts of free Cu^{2+} (1–3 mM) required to activate ASMase, release Cer, and trigger apoptosis in hepatic cells and erythrocytes are identical to those reported in the blood plasma of patients suffering from Wilson disease. This extends to the clinical importance of findings, suggesting that Cer may have a role in Wilson's disease or even other types of Cu^{2+} poisoning (Lang et al. 2007).

Cu^{2+} activates the endogenous CD95–CD95-ligand system, causing apoptosis in hepatocytes, whereas CD95 deficiency protects hepatocytes against Cu^{2+}-induced apoptosis. Apoptosis induction in hepatocytes requires activation of ASMase and production of Cer in both in vitro and in vivo; therefore, Cu^{2+} could at least partially produce Cer in hepatocytes via the CD95–CD95-ligand pathway. In this instance, Cu^{2+} may trigger CD95, which would then drive the activity of ASMase and initiate the release of Cer to induce cell death. Nevertheless, in the blood, Cu^{2+} causes phosphatidylserine exposure and erythrocyte mortality via leukocyte-secreted ASMase, indicating that Cer may potentially be implicated in CD95-independent mechanisms leading to hepatocyte and erythrocyte death following cellular Cu2 + treatment (Lang et al. 2007).

Liver dysfunction attributed to sepsis

Chronic sepsis patients may experience fibrosis and liver damage**.** ASMase, which is also an essential enzyme of liver programmed cell death and HSCs stimulation, has been associated with the enhancement of acute liver injury along with protracted fibrogenesis (Quillin et al. 2015). Pharmaceutical suppression of ASMase positively impacted oxidative stress, hepatobiliary activity, macrophage intrusion, and HSCs' stimulation, as well as total survival during both the acute and the post-acute stages. ASMase suppression improved liver function in the acute phase, and the restriction of HSC stimulation averted the progression of sepsis-associated liver fibrosis in the post-acute stage (Chung et al. 2017). Throughout this scenario, the instability of hepatic biotransformation capability involving the cytochrome P450 (CYP) system is a significant stressor in host defense (Chung and Claus 2021). In animal models, the downregulation of ASMase seems to substantially impact the function of many liver CYP enzymes in both the acute and post-sepsis phases (Chung et al. 2018). Mice receiving amitriptyline treatment displayed enhanced viability and had been shielded from excessive cytokine production and pulmonary edema in rodent models of peritonitis and endotoxemia. Enhanced IL-10 concentration and less immune cell encumbrance at the infection site are indicators of anti-inflammatory effects following amitriptyline treatment (Xia et al. 2019).

A definite correlation has been analyzed between ASMase action comorbidities and unflattering outcomes in all studies involving patients with severe infection, sepsis, and multiple organ dysfunction. However, blocking ASMase action can halt the abrasive effects of excessive immune reaction. The fact that a wide range of medications exhibits ASMase inhibitory effects brings us to the juncture where we can further discuss the alleged positive impacts of ASMase suppression in routine medical care.

Inhibitors of ASMase activity

Due to their distinct physicochemical characteristics, a wide range of ionic amphipathic molecules are recognized to impede the action of ASMase through lysosomotropism. This phenomenon was initially documented by Albouz et al. (1981). Interplay with ASMase membrane-embedding N-terminal saposin motif resulted in the enzyme separation from the internal lysosomal membrane and subsequent degradation. As a consequence of the considerable reduction in sphingolytic action, such molecules are referred to

Table 3 The functional inhibitors of acid sphingomyelinase (FIASMA)

Inhibitor class	Therapeutic agents	References
Anti-depressants	Imipramine	Hoertel et al. (2021)
	Duloxetine	Villoutreix et al. (2021)
	Escitalopram	Chen et al. (2020)
	Fluoxetine	
	Fluvoxamine	
	Amitriptyline	
	Citalopram	
	Clomipramine	
	Desipramine	
	Lofepramine	
	Maprotiline	
	Mirtazapine	
	Nortriptyline	
	Paroxetine	
	Protriptyline	
	Sertraline	
	Trimipramine	
	Venlafaxine	
Anti-histamines	Loratadine	Villoutreix et al. (2021)
	Promethazine	Weston et al. (2020)
	Astemizole	Wang et al. (2021)
	Clemastine	Chen et al. (2021)
	Cyproheptadine desloratadine	Hou et al. (2021)
	Hydroxyzine	Reznikov et al. (2021)
Anti-psychotics	Chlorpromazine chlorprothixene	Plaze et al. (2021)
	Fluphenazine	Chen et al. (2021)
	Flupenthixol	Villoutreix et al. (2021)
	Perphenazine	Yang et al. (2020)
	Pimozide	Vatansever et al. (2021)
	Promazine	Weston et al. (2020)
	Thioridazine	Udrea et al. (2020)
	Trifluoperazine triflupromazine	
Calcium channel blockers	Amlodipine	Xiao et al. (2020)
	Bepridil	Vatansever et al. (2021)
	Fendiline	Cho et al. (2015)
	Mibefradil	Hinkovska-Galcheva et al. (2021)
	Perhexiline	Kato et al. (2007)
Antiarrhythmics	Amiodarone	Chen et al. (2021)
	Aprindine	Hoertel et al. (2021)
Anti-diarrheal	Loperamide	Jeon et al. (2020)
Anti-estrogen	Tamoxifen	Imamura et al. (2021)
	Clomiphene	Xiong et al. (2021)
Anti-spasmodic	Alverine	Hinkovska-Galcheva et al. (2021)
	Camylofin	Kornhuber et al. (2008)
	Dicycloverine	
	Mebeverine	
Anti-tussives	Dextromethorphan	Kornhuber et al. (2010)
	Cloperastine	Hoertel et al. (2021)
Vasodialators	Dilazep	Kornhuber and Gulbins 2021)
	Suloctidil	
Mucolytics	Ambroxol	Kornhuber and Gulbins 2021)
Beta-blockers	Carvedilol	Kornhuber et al. (2011)
Natural products	Conessine	Kornhuber and Gulbins 2021)
	Solasodine	
	Tomatidine	

as functional inhibitors of ASMase (FIASMA) (Table 3). Notable features of these medications include their human licensure for medical usage, low toxicity, and wide applications for a variety of therapeutic reasons, such as the management of intensive care individuals. Thus ASMase antagonists show potential for a variety of new therapeutic interventions, including apoptosis and other deleterious consequences observed in various disease conditions. An extensive list of FIASMA encompasses imipramine, fluoxetine, paroxetine, terfenadine, and others.

A high throughput analysis targeting direct ASMase antagonists yielded no leads (Mintzer et al. 2005). Since the crystallographic structure of this enzyme is not yet recognized, it is challenging to establish therapeutic agents that can logically inhibit ASMase by engaging directly with the enzyme (Gorelik et al. 2016). As a result, there are apparently very few instances of antagonists interfering specifically with ASMase. To treat ASMase-related disorders, ASMase antagonists are needed. Zoledronic acid, which is therapeutically used to prevent osteoporosis, is one of many biphosphonates that are effective and specific antagonists of ASMase. Contrary to functional antagonists, direct inhibition does not require significant lysosomal drug levels to block ASMase action.

Weak organic bases have been acknowledged to have the ability to decrease ASMase action since the early days (Kornhuber et al. 2010). One such example is desipramine, which has been recognized as an inhibitor of ASMase activity (Hurwitz et al. 1994). According to some studies, ASMase is shielded from proteolytic disintegration, because it is linked to the intra-lysosomal membranes. The ASMase separates from the inner membrane as a consequence of desipramine action and similar medications. Thus, it undergoes photolytic degradation (Hurwitz et al. 1994) (Fig. 4). Weak bases do not directly block the ASMase action but rather hinder it functionally. The FIASMAs encompass a plethora of drugs comprising dextromethorphan, fluoxetine, maprotiline, nortriptyline, orphenadrine, sertraline, triflupromazine, etc. The majority of them are FDA-approved recognized bioactive substances that are anticipated to be mildly detrimental and possibly readily accessible for therapeutic usage (Table 3). A molecule needs to have the right absorption, distribution, metabolism, and excretion (ADME) qualities to be a successful pharmaceutical in addition to being potent against a receptor. The majority of the currently offered FIASMAs have favorable ADME characteristics. All of these medications have oral bioavailability, and several of them penetrate the blood–brain barrier. As a result, several FIASMAs have the potential to be employed in the treatment or avoidance of central nervous system disorders.

There are noticeable differences between the FIASMAs in the cell uptake dynamics. In cell culture environments, based on the logP- and pKa-values, FIASMAs penetrate the cells and lysosomes between minutes to hours. The FIASMAs listed above have a quick lysosomal pickup rate and a substantial lysosomal accumulation. Benztropine, desipramine, fluoxetine, maprotiline, paroxetine, and protriptyline have a lysosome: extracellular ratio of less than 100:1(Kornhuber et al. 2010). The unique physicochemical features of FIASMAs, notably mild basicity and substantial lipophilicity, result in significant tissue adherence, as indicated by the great apparent quantity of distribution of these medicines in human beings (Kornhuber et al. 2010). There is presently no substitute for FIASMAs when attempting to suppress ASMase activity in human subjects. The creation and safety assessment of certain direct ASMase antagonists will yet take several years. Only then will it be feasible to assess and evaluate the relative benefits of direct and functional ASMase inhibitors against one another.

Drug repurposing of ASMase antagonists

It is becoming more and more appealing and expedient to repurpose the existing medications to address either widespread or unusual disorders owing to the utilization of pharmaceuticals with well-known pharmacokinetics and safety characteristics, which may result in reduced total development expenditures and quicker production as they have already received legal oversight (Pushpakom et al. 2018). Given the extensive pool of potent therapeutics, it is especially crucial in the context of ASMase as the fundamental mechanisms of adequate suppression are well established (Kölzer et al. 2004). Furthermore, as explained in this study, there have been optimistic outcomes through preliminary and clinical research, as well as some additional findings depicting the positive influence of ASMase inhibition in a plethora of disorders.

Studies in the past have described the efficacy of amitriptyline in a variety of critical disorders, including malignancy, infections, and metabolic and neurodegenerative diseases, all of which are classified as ASMase-related ailments (Beckmann et al. 2014). Microbial transmission is also aided by the ASMase-ceramide system. Rhinovirus stimulates ASMase, prompting Cer to be synthesized and the development of Cer-enriched membrane regions, which serve as virus gateways. It has been demonstrated that ASMase antagonists prevent viral infection, as amitriptyline and imipramine effectively prevent rhinovirus infection (Kornhuber and Gulbins 2021). According to research, amitriptyline is a contender that merits further investigation for the treatment of infectious disorders and excessive host immune response. However, negative consequences of a missing residual activity, as demonstrated by phagocytosis incapacity and increased bacterial load, were also detected

(Chung and Claus 2021). Furthermore, there is a definite correlation between ASMase function and the degree of sepsis, including adverse consequences (Chung et al. 2018).

It is quite intriguing that the routinely used anti-depressants fluoxetine effectively prevented SARS-CoV-2 infiltration and spread in the cell culture environment without inducing undesirable side effects. According to experimental studies, SARS-CoV-2 triggers the ASMase-Cer complex, leading to the development of membrane domains that are high in ceramides. These membrane domains concentrate ACE2, the SARS-CoV-2 cell receptor, and make it easier for the virus to enter cells and infect them (Carpinteiro et al. 2020). Research conducted in vitro revealed that many FIASMA drugs, notably fluoxetine and amitriptyline, blocked ASMase action and the generation of membrane domains rich in Cer, which impeded the infection of cell lines with SARS-CoV-2 (Carpinteiro et al. 2020). Furthermore, substantial antiviral action against two influenza A virus strains was demonstrated, and this effect was also monitored when amiodarone and imipramine, two FIASMAs, were used as therapeutic agents (Schloer et al. 2020).

It has been observed that ASMase regulators, notably ionic amphipathic medications such as anti-depressants and antiarrhythmic medications, diminish ASMase activity by displacing ASMase from the lysosomal membrane, resulting in low membrane potential inducing cell death. Furthermore, siramesine and clomipramine significantly restricted autophagic flow by neutralizing lysosomal pH (Al-Bari 2022). The changing behavior of ASMase in malignant cells may encompass a wide variety of intricate mechanisms, such as complex signal transduction pathways, programmed cell death, and immune clearance. Furthermore, its role as an inhibitory or driving factor is still controversial. Currently, awareness regarding ASMase and its modulators is insufficient. Moreover, there are still a number of mysteries related to ASMase action in a plethora of disorders, including liver anomalies which makes space for more investigations.

Conclusions and future perspectives

It is evident that ASMase has a twofold purpose: it performs a critical housekeeping activity within practically all cellular lysosomes and late endosomes, contributing to membrane turnover. At the cell surface, ASMase plays a significant role in the remodeling of microdomain formations and the induction of apoptotic signals. The rearrangement of Cer-rich microdomains has an impact on a variety of cellular processes, including calcium metabolism, microbial invasion, and autophagy. These findings point to a potential role for ASMase antagonists in the management of a number of prevalent disorders, such as sepsis, acute lung damage, ischemia, depression, and liver-related ailments. Particularly pertinent is the involvement of ASMases in NASH and the emergence of HCC from it, which has advanced to become the most significant chronic liver disease worldwide and is predicted to intensify soon due to its close association with type 2 diabetes and obesity.

The therapy of common liver pathologies may thus benefit from understanding the triggering pathways and identifying the metabolites implicated in ASMase signal transduction. Even though a new crop of ASMase antagonists is being investigated, tricyclic anti-depressants, which are already available in clinics, have been demonstrated to antagonize ASMase effectively. Amitriptyline has been found to influence ASMase as evidence of concept in pre-clinical animal models of both ASH and NASH. Combination therapy with such therapeutic agents may be an essential tool for navigating the complex network of signal transduction pathways implicated in liver anomalies. The utilization of ASMase as an anti-oncogenic target in hepatocellular carcinoma should also be further explored because of its rapid involvement in the Cer generation. To prevent an adverse reaction, the exposure period and dosage for ASMase antagonists must be carefully selected. The development of selective and reversible ASMase inhibitors as possible therapies for liver disorders would need more investigation and has a great prospect.

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Conflict of interest The authors declare no conflicts of interest.

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