

Apoptosis and non-alcoholic fatty liver diseases

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Abstract

The number of patients with nonalcoholic fatty liver diseases (NAFLD) including nonalcoholic steatohepatitis (NASH), has been increasing. NASH causes cirrhosis and hepatocellular carcinoma (HCC) and is one of the most serious health problems in the world. The mechanism through which NASH progresses is still largely unknown. Activation of caspases, Bcl-2 family proteins, and c-Jun N-terminal kinase-induced hepatocyte apoptosis plays a role in the activation of NAFLD/NASH. Apoptotic hepatocytes stimulate immune cells and hepatic stellate cells toward the progression of fibrosis in the liver through the production of inflammasomes and cytokines. Abnormalities in glucose and lipid metabolism as well as microbiota accelerate these processes. The production of reactive oxygen species, oxidative stress, and endoplasmic reticulum stress is also involved. Cell death, including apoptosis, seems very important in the progression of NAFLD and NASH. Recently, inhibitors of apoptosis have been developed as drugs for the treatment of NASH and may prevent cirrhosis and HCC. Increased hepatocyte apoptosis may distinguish NASH from

NAFLD, and the improvement of apoptosis could play a role in controlling the development of NASH. In this review, the association between apoptosis and NAFLD/NASH are discussed. This review could provide their knowledge, which plays a role in seeing the patients with NAFLD/NASH in daily clinical practice.

Key words: Apoptosis; Autophagy; c-Jun N-terminal kinase; Nonalcoholic fatty liver diseases; Nonalcoholic steatohepatitis

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Core tip: Nonalcoholic fatty liver diseases (NAFLD), including nonalcoholic steatohepatitis (NASH), are one of the most serious health issues. We searched articles written in English and listed on PubMed for the role of apoptosis in NASH. There are close association between apoptosis and NAFLD/NASH. Several inhibitors of apoptosis have been suggested as potential treatments for NASH, and some are now being tested in clinical trials. Therefore, we should focus on the role of apoptosis in the progression of NAFLD/NASH.

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INTRODUCTION

The term nonalcoholic fatty liver disease (NAFLD) includes nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). The mechanism by which NASH progresses is still largely unknown. Liver biopsy is an important procedure for the diagnosis of NASH, with a typical case of NASH having hepatocellular steatosis and ballooning, mixed acute and chronic lobular inflammation, and zone 3 perisinusoidal and pericellular fibrosis^[1]. These findings have also been observed in the liver of patients with alcoholic steatohepatitis. NAFLD cirrhosis and NAFLD-hepatocellular carcinoma (HCC) are the second leading cause of liver transplants in the USA^[2]. Accordingly, there is increasing evidence that HCC can develop in the NASH^[2].

In the liver of patients with alcoholic hepatitis, infiltrating polymorphonuclear leukocytes and apoptotic bodies derived from hepatocytes are observed^[3]. A combination of environmental factors, host genetics, and gut microbiota can lead to an excess accumulation of fat in the hepatocytes, which can result in lipotoxicity and trigger hepatocyte cell death, liver inflammation, fibrosis, and pathological angiogenesis, resulting in NASH, cirrhosis, and HCC^[4]. In this topical review, we will discuss apoptosis, which is involved in the

development of NASH.

APOPTOSIS AND THE ACTIVATION OF CASPASES IN THE PROGRESSION OF NASH

Feldstein *et al.*^[5] observed that terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL)-positive hepatocytes were significantly increased in the livers of NASH patients, compared to those from patients with alcoholic hepatitis or simple steatosis. Caspases have apoptotic functions as well as non-apoptotic functions. During apoptosis, the caspase cascade shapes the immunogenic properties of apoptosis^[6]. Feldstein *et al.*^[5] found that active caspases 3 and 7 as well as the strong expression of Fas receptors in NASH specimens were strongly correlated with hepatocyte apoptosis and the progression of NASH. Caspase 3 activation and hepatocyte apoptosis are prominent features of different experimental models of NAFLD as well as human NAFLD and have been shown to be correlated with disease severity^[5].

Caspase 3 is known to cleave several cellular substrates including cytokeratin-18 (CK-18), which is the major intermediate fragment protein in the liver^[7]. Caspase 3 generated CK-18 fragments are an independent predictor of NASH in patients with suspected NAFLD^[7,8]. Traffic-related air pollution has been shown to be associated with CK-18, a marker of hepatocellular apoptosis, in an overweight and obese pediatric population^[9]. Mallory-Denk bodies (MDBs) are characteristic of both alcoholic and NASH and discriminate between the relatively benign simple steatosis and the more aggressive NASH. It has been shown that in genetically susceptible mice overexpressing CK-8, consumption of a high-fat diet (HFD) triggered hepatocellular injury, ballooning, apoptosis, inflammation, and MDB development^[10].

Inhibition of hepatic apoptosis by pharmacological pan-caspase inhibitor VX-166 may reduce the development of fibrosis in mice with NASH^[11,12]. Increases in active caspase 2, active caspase 3, and apoptosis were observed in the livers of patients with NASH^[13]. Ballooned hepatocytes in NASH downregulate caspase 9, a pivotal caspase that executes the mitochondrial apoptosis pathway^[14]. In rodents, a lack of caspase 8 expression in hepatocytes was shown to reduce the methionine-choline-deficient (MCD)-dependent increases in apoptosis, decreased the expression of pro-inflammatory cytokines, and reduced hepatic infiltration^[15]. Caspase 8 may thus be critical for the pathogenesis of NASH.

Caspase 2 is an initiator caspase in lipid-induced cytotoxicity (lipoapoptosis), which plays a role in the pathogenesis of NASH^[16]. Caspase 2 plays a role in lipid-induced hepatocyte apoptosis and is related to the production of apoptosis-associated fibrogenic factors^[17]. Additionally, liver free coenzyme A content was shown to be reduced in mice with NASH. Decreased hepatic free coenzyme A content was associated with increased

caspace 2 activity and correlated with more severe liver cell apoptosis, inflammation, and fibrosis^[18].

It has been reported that Fas, Fas ligand (FasL), and caspase 8 mRNA activation are important contributing factors to NAFLD^[19]. Another study showed that children with NASH had significantly higher levels of soluble Fas and soluble FasL than those in the "not NASH" group^[20]. Fas apoptosis inhibitory molecule (FAIM), a ubiquitously expressed antiapoptotic protein, functions as a mediator of Akt signaling^[21]. Loss of FAIM leads to spontaneous obesity and hepatic steatosis^[21].

Hepatic cell apoptosis is associated with miR-34a/Sirtuin 1 (SIRT1)/p53 signaling in NASH^[22]. p53 and its transcriptional target, miR34a, have been shown to be involved in the pathogenesis of fatty liver. The p53 inhibitor, pifithrin- α -p-nitro, was shown to attenuate steatosis, associated oxidative stress, and apoptosis in murine models of NAFLD^[23]. The DNA damage checkpoint protein Ataxia telangiectasia mutated pathway plays a role in the response to hepatic fat accumulation and promotes hepatocellular apoptosis and fibrosis in mice models of NAFLD^[24]. Massive hepatic progenitor cell expansion, especially in children with NASH, is associated with the degree of liver injury, hepatocyte apoptosis, and cell-cycle arrest^[25].

Increased vimentin fragment levels are known to indicate the existence of substantial hepatocellular apoptosis in the progression of NASH^[26]. Levels of the augments of liver regeneration (ALR) protein were lower in liver tissues from patients with advanced alcoholic liver disease and nonalcoholic steatohepatitis than in liver tissues from controls^[27]. Levels of steatosis and apoptosis were reduced in mice with a liver-specific deletion of ALR^[27]. Impairment of the formation of a newly discovered ubiquitin ligase complex called linear ubiquitin chain assembly complex, has been shown to result in insufficient NF- κ B activation and may thus be one of the molecular mechanisms underlying the enhanced apoptotic response of hepatocytes in NASH mouse models^[28].

IgM-free apoptosis inhibitor of macrophage serum levels appear to be a sensitive diagnostic marker for NASH-HCC^[29]. Activation of apoptosis signal-regulating kinase 1 (ASK1) in hepatocytes is a key step in the progression of nonalcoholic steatohepatitis^[30]. Additionally, tumor necrosis factor alpha-induced protein 3 directly interacts with and deubiquitinates ASK1 in hepatocytes^[30].

Thus, the activation of caspases and other molecules that are involved in apoptosis are frequently observed in the livers of NASH patients and may be related to the progression of NAFLD and NASH.

BCL-2 FAMILY MEMBERS AND MITOCHONDRIA IN THE PROGRESSION OF NASH

Liver injury in NASH patients is associated with apoptosis

and NF- κ B activation even though anti-apoptotic B-cell lymphoma 2 (Bcl-2) is strongly expressed^[31,32]. These changes are caspase-dependent. They are also associated with mitochondrial membrane depolarization and the release of cytochrome c, which activate the mitochondrial apoptosis pathways including activation of the proteins Bcl-2-associated X (Bax) and Bcl-2-interacting mediator of cell death (Bim)^[33]. The upregulation of Bax and Bcl-2 expression may also be play an important role in apoptosis in NAFLD^[19], although it has been reported that NASH patients had significantly lower levels of anti-apoptotic protein Bcl-2^[34]. The degree of apoptosis was inversely correlated with the level of Bcl-2^[34].

Activation of endoplasmic reticulum (ER) stress-associated c-Jun N-terminal kinase (JNK) promotes apoptosis by modifying the expression and function of pro-apoptotic members of the Bcl-2 family such as Bcl-2 homology 3 (BH3) only protein Bim and p53-upregulated modulator of apoptosis (PUMA)^[35]. PUMA promotes the activation of Bax and thus mitochondrial outer membrane permeabilization, which leads to the relocation of these pro-apoptotic mediators into cytosol^[35]. Cazanave *et al*^[36] reported that miR-296-5p levels were inversely related to the BH3-only protein PUMA mRNA levels in human liver specimens, and that miR-296-5p regulates PUMA expression during hepatic lipoapoptosis.

Transglutaminase 2 (TG2), which is induced in the nuclei of ethanol-treated hepatocytes, crosslinks and inactivates the transcription factor, SpI, which results in hepatic apoptosis^[37]. In NASH patients, nuclear TG2 and crosslinked SpI formation were elevated. Additionally, activation of apoptosis inducing factor and a release of cytochrome c were observed^[37]. Hypoxia, oxidative stress, and lipoapoptosis could all influence the expression of mitochondrial-encoded NADH dehydrogenase (MT-ND3) in hepatocytes and MT-ND3 may play a role in the progression of hepatic steatosis^[38]. Hepatocyte-specific c-Met deletion in hepatocytes was shown to trigger NASH progression. Increased apoptosis was a prominent feature in c-Met Δ (hepa) livers^[39]. Intermittent high glucose levels under lipotoxicity could contribute to the development of NAFLD by increasing oxidative stress and hepatocyte apoptosis via changes in mitochondrial permeability and subsequent mitochondrial dysfunction^[40].

Bid promotes liver fibrosis coupled with a reduction of inflammation in experimental NASH models. In these models, hepatocyte apoptosis triggered hepatic stellate cell activation as well as liver fibrosis^[41]. Increased expression of hepatocellular carcinoma down-regulated mitochondrial carrier protein (HDMCP) was identified in NASH animal models and HFFA-72h cultured L02 cells. The miR-146-HDMCP-downstream effector pathway is involved in NASH^[42]. Collectively, previous studies have demonstrated that apoptosis resulting from mitochondrial injury is associated with the progression of NAFLD and NASH.

ACTIVATION OF JNK AND APOPTOSIS IN NASH

Monounsaturated and saturated fatty acids have been shown to induce cellular steatosis, apoptosis, and JNK activation in hepatocytes^[33]. Steatotic hepatocytes from a murine NAFLD model were sensitive to TNF- α -induced apoptosis via the ASK1-JNK signaling pathway^[43]. Free fatty acids (FFA)-induced ER stress is associated with JNK activation, which has been well documented in human steatosis^[35]. Mixed lineage kinase 3 (MLK) 3 is one of the mitogen-activated protein kinases (MAP3K) that mediate JNK activation in the liver. MLK3 is involved in human NASH through JNK activation^[44].

The interplay of p-JNK with mitochondrial Sab (Sh3bp5) leads to impaired respiration, production of reactive oxygen species (ROS), sustained JNK activation, apoptosis in condition of lipotoxicity, and ultimately contributes to the pathogenesis of NASH^[45]. Dramatically reduced expression of cellular repressor of E1A-stimulated genes (CREG) and hyperactivated JNK1 signaling has been observed in the livers of NAFLD patients^[46]. CREG is a robust suppressor of hepatic steatosis and metabolic disorders through its direct interaction with ASK1 and the subsequent inactivation of ASK1-JNK1 signaling^[46]. Thus, JNK signaling pathways play an important role in the apoptosis of NAFLD and NASH.

APOPTOSIS, AND IMMUNE CELLS AND HEPATIC STELLATE CELLS

The complement cascade to clear apoptotic cells and promote liver regeneration is also involved in the progression of NAFLD and NASH^[47]. Distant major histocompatibility complex class I-related chains A and B (MIC A/B) have been identified as ligands for the NK cell receptor G2D (NKG2D) in humans. Compared to controls, patients with NASH displayed increases in NKG2D and MIC A/B mRNA, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-death receptor 5 (DR5), CD95/Fas mRNA, and hepatocyte apoptosis^[48]. These increases suggest that MIC A/B levels also affect the progression of NASH. TRAIL-producing natural killer (NK) cells actively promote a pro-inflammatory environment in the early stages of fatty liver disease, which suggests that this cell compartment may contribute to the progression of NASH^[49].

Proliferation of hepatic macrophages, and the subsequent production of pro-inflammatory cytokines, initiate inflammatory cascades, orchestrate the activities of transcription factors involved in lipid metabolism/translocation, and modulate programmed cell death^[50]. The macrophage activation marker-soluble CD163 was independently associated with the apoptosis marker CK-18 in Australian and Italian NAFLD patients^[51]. Furthermore, down-modulation of NF- κ B1 stimulates the progression of NASH in mice by promoting natural

killer T (NKT)-cell-mediated responses^[52]. Macrophage scavenger receptors), which play a role in the activation of signal transduction pathways that regulate inflammation, apoptotic cell clearance, chemoattraction and angiogenesis, are involved in both the early and advanced stages of NASH^[53].

Wobser *et al.*^[54] has demonstrated that human hepatic stellate cells (HSCs) that were incubated with conditioned medium (CM) from steatotic hepatocytes and had fibrogenic activation and were resistant to apoptosis, which is important in the progression of fibrosis in chronic liver diseases^[54]. Myeloperoxidase (MPO), a highly oxidative enzyme secreted by leukocytes, contributes to the activation of HSCs and is a part of a proapoptotic and profibrotic pathway of progression in NASH^[55]. Thus, in patients with NAFLD and NASH, apoptotic hepatocytes stimulate immune cells and HSCs, which contributes to the progression of fibrosis in the liver.

PRO-INFLAMMATORY CYTOKINES AND CHEMOKINES

Feeding tumor necrosis factor (TNF) receptors 1 and 2 double-knock out mice (TNFRDKO mice) with an MCD-diet for 8 weeks attenuated liver steatosis and fibrosis and also suppressed hepatic induction of TNF- α , vascular cell adhesion molecule 1, and intracellular adhesion molecule 1, compared to wild-type control mice^[6]. These results suggest that blocking the signaling of TNF receptors 1 and 2 is a promising therapeutic target for patients with NASH^[56]. The TNF receptor 1-signaling pathway plays a role in aggravating a state of "simple steatosis" towards a phenotype with "NASH"^[57]. Cyclooxygenase (COX)-2 may promote hepatocellular apoptosis by interacting with TNF- α and IL6 in rats with NASH^[58]. COX-2 is highly expressed in NASH.

Lipoapoptotic supernatants stimulated monocyte migration to a similar magnitude as monocyte chemoattractant protein, CCL2 (MCP-1)^[59]. The release of pannexin1-dependent pathophysiological eATP in lipoapoptosis can stimulate the migration of human monocytes in NASH^[59]. In cultured Kupffer cells, cholesterol induced the expression of chemotactic and inflammatory cytokines (CCL2 and CXCL2, and IL1 β , TNF and oncostatin M, respectively) and rendered hepatocytes more susceptible to apoptosis^[60]. Lipids, which stimulate DR5, have been shown to induce the release of hepatocyte extracellular vesicles, which contain TRAILS. Lipids also induced the expression of IL1 β and IL6 messenger RNAs in bone marrow-derived macrophages in mice^[61]. The C-X-C motif chemokine 10 (CXCL10), which is known to be a pro-inflammation chemokine, was recently shown to play a pivotal role in the pathogenesis of NASH. By binding to its specific receptor CXCR3, CXCL10 recruits activated CXCR3+ T lymphocytes and macrophages to the parenchyma and promotes inflammation, apoptosis, and fibrosis^[62].

The dsRNA receptor Nod-like receptor X1 and NLRP3

inflammasomes may be important in the development of NASH^[63]. The function of receptor interacting protein kinase-3 (RIP3)-dependent “necroptosis” in NASH and NASH-induced fibrosis is currently unknown^[64]. RIP3-dependent necroptosis controls NASH-induced liver fibrosis^[64]. The absence of RIP3, a key mediator of necroptosis, exacerbates HFD-induced liver injury. This exacerbation is associated with increased inflammation and hepatocyte apoptosis as well as early fibrotic responses. These findings indicate that shifts in the mode of hepatocellular death can influence disease progression. Therefore, they may have therapeutic implications because manipulation of hepatocyte cell death pathways is currently considered to be a target for treatment of nonalcoholic fatty liver disease^[65]. Thus, inflammasomes and cytokines induce apoptosis and respond to hepatocyte apoptosis in NAFLD and NASH.

OXIDATIVE STRESS

It has also been reported that oxidized phosphatidylcholine is localized in apoptotic hepatocytes in the livers of patients with the steatotic disorders, which indicates that oxidized phosphatidylcholine is formed in oxidatively damaged hepatocytes^[66]. Transforming growth factor β (TGF β) may regulate p53/p66Shc signaling in both the progression of human NASH and ROS levels and apoptosis^[67]. NAFLD patients with reticuloendothelial system (RES) iron have increased TUNEL staining and cellular oxidative stress^[68]. RES iron has been shown to be associated with NASH as well as more-severe histologic features^[68].

TGF β signaling activates Smad- and TGF β -activated kinase 1-dependent signaling and plays a role in regulating cell survival, proliferation, fibrosis, and tumorigenesis. In hepatocytes, TGF β signaling contributes to hepatocyte death and lipid accumulation through Smad signaling and ROS production, leading to the development of NASH^[69]. NOX isoforms, including NOX1, NOX2 and NOX4, and NOX-derived ROS have all been implicated in regulating HSC activation and hepatocyte apoptosis. Both HSC activation and hepatocyte apoptosis are essential steps for the initiation of liver fibrosis and its progression^[70]. Mainstream cigarette smoke has been shown to be associated with the degree of oxidative stress and hepatocellular apoptosis in NASH mice^[71].

Oxidative stress is central to the pathogenesis of NASH. ROS are characterized by oxidative stress. ROS are generated in several cellular sites and their production is influenced by multi-organ interactions. For fatty liver diseases, mitochondrial dysfunction is the main source of ROS and is closely related to endoplasmic reticulum stress. Both are caused by lipotoxicity and together these three factors form a cycle of progressive organelle damage that results in sterile inflammation and apoptosis^[72].

ER STRESS

FFAs can increase ER stress, leading to nuclear NF- κ B activation and TG2 induction through the pancreatic ER kinase (PERK)-dependent pathways^[37,73]. CCAAT/enhancer-binding protein homologous protein (CHOP) deficiency has been found to attenuate apoptosis, inflammation, fibrosis, and tumorigenesis in mice who are exposed to fat-loading conditions. This finding indicates CHOP promotes hepatocarcinogenesis in NASH^[74]. The overexpression of hypoxia-inducible factor 1 α (HIF-1 α) has also been shown to blunt upregulation of the ER stress markers, CHOP and chaperone immunoglobulin heavy chain binding protein (GRP78/Bip), while knocking down HIF-1 α increases the level of CHOP. These findings indicate that hepatocyte lipotoxicity is associated with decreased HIF-1 α expression^[75].

MiR-615-3p regulates lipoapoptosis by inhibiting CHOP and may be associated with the pathogenesis of NASH^[76]. After exposure to saturated FFA, CHOP has been shown to induce hepatocyte cell apoptosis and inflammatory responses by activating NF- κ B through a pathway involving the expression of IL1 receptor associated kinase 2. This activation results in the direct secretion of the cytokines IL8 and TNF α from hepatocytes^[77]. Glucagon-like peptide-1 was found to protect against NAFLD by inactivating the ER stress-associated apoptosis pathway^[78].

Loss of the unfolded protein response of regulator X-box binding protein 1 enhances injury in both *in vivo* and *in vitro* models of fatty liver injury^[79]. Hepatocytes in a lipotoxic state ultimately undergo apoptosis through the upregulation of proteins involved in various pathways including PERK, CHOP, JNK, BIM, PUMA, and eventually, caspases^[80].

AUTOPHAGY

Expression of microtubule associated protein 1 light chain 3 α (LC3)-II, a hallmark of autophagic flux, was found to be markedly increased in liver specimens from patients with NASH. JNK1 promotes palmitic acid-induced lipoapoptosis, whereas JNK2 activates pro-survival autophagy and inhibits palmitic acid lipotoxicity^[81]. Palmitate may induce autophagy by activating the PKC α pathway in hepatocytes. Autophagy plays a protective role in palmitate-induced apoptosis in hepatocytes^[82]. Tumor protein p53 binding protein 2 (ASPP2) is a pro-apoptotic member of the p53 binding protein family that inhibits autophagy^[83]. Xie *et al.*^[83] reported that ASPP2 may participate in the lipid metabolism of non-alcoholic steatohepatitis. Mitochondrial uncoupling protein 2 (UCP2) also plays a role in the development of NASH^[84]. Increasing UCP2 expression in hepatoma cells may contribute to cell autophagy and may inhibit apoptosis as result of fatty acid injury^[84]. Cellular degradation of Kelch-like ECH-associated protein 1 through the progress of sequestrosome (SQSTM)1/p62-dependent autophagy

activates JNK, upregulates expression of Bim and PUMA, and contributes to hepatocyte apoptosis induced by saturated FFAs^[85]. Parkin-mediated mitophagy may mitigate hepatocyte apoptosis, improve mitochondrial quality, and suppress steatosis (lipid accumulation) in animal models of alcoholic fatty liver disease^[86]. In rats treated with ethanol-enhanced hepatic mitophagy was associated with Parkin mitochondrial translocation, which was triggered by oxidative mitochondrial DNA damage^[86]. Rubicon is overexpressed and plays a pathogenic role in NAFLD by accelerating hepatocellular lipoapoptosis and lipid accumulation and inhibiting autophagy^[87]. Sirtuin 3 (SIRT3) is a nicotinamide adenine dinucleotide-dependent deacetylase that is primarily located inside the mitochondria^[88]. SIRT3 negatively regulates autophagy, thereby enhancing the susceptibility of hepatocytes to SFA-induced cytotoxicity^[88].

Thus, ROS production, oxidative stress, and ER stress are all known to induce apoptosis. Autophagy modifies the progression of NAFLD and NASH and may have a protective role in hepatocyte apoptosis.

GLUCOSE METABOLISM AND APOPTOSIS

Hepatic insulin signaling is impaired in NASH patients, where downregulation of insulin-sensitive targets is associated with increased apoptosis and fibrogenesis^[89]. Hyperinsulinemia has been shown to alter nuclear transcriptional regulators of cholesterol homeostasis. This leads hepatic accumulation of free cholesterol, hepatic injury, and apoptosis in NASH patients^[90].

Fibroblast growth factor (FGF)-21 is highly expressed in the liver and regulates glucose and lipid metabolism in rodents. Concentration of FGF-21 were found to be significantly and independently correlated with hepatic fat content and markers of hepatic apoptosis in obese youth^[91]. Another study found that FGF-21 mRNA expression in the human liver increased with steatosis grade and that its serum level is significantly elevated in adult NAFLD patients^[92].

Intrahepatic expression of dipeptidyl peptidase-4 (DPP4) and circulating DPP4 (cDPP4) levels and its enzymatic activity are all increased in NAFLD^[93]. Circulating DPP4 activity correlates with measures of hepatocyte apoptosis and fibrosis in NAFLD in patients with type 2 diabetes mellitus and/or obesity^[93]. Senescence marker protein-30 is involved in both glucose metabolism disorder and NAFLD^[94].

TRAIL receptor signaling was also found to be involved in the pathogenesis of NASH in mice with a genetic deletion of the TRAIL receptor^[95]. Furthermore, patients with NASH had significantly reduced plasma TRAIL concentrations compared to controls, patients with simple steatosis, or obese individuals^[96]. TRAIL protects against insulin resistance, NAFLD, and vascular inflammation. Increasing TRAIL levels may be an attractive therapeutic strategy for reducing symptoms

of diabetes as well as liver and vascular injuries, which are commonly observed in individuals with NAFLD^[96].

LIPID METABOLISM AND APOPTOSIS

The serine/threonine kinases, glycogen synthase kinase GSK-3 α and GSK-3 β , can participate in pro-apoptotic signaling during FFA-induced lipoapoptosis^[35]. More specifically, saturated fatty acids strongly induce hepatocyte apoptosis^[97]. Saturated fatty acids up-regulate the inflammasome in hepatocytes and lead to sensitization to LPS-induced inflammasome activation and inflammatory injury^[98,99]. Saturated fatty acids also induce hepatocyte apoptosis and the activation of caspase 8, which triggers the release of dangerous molecules^[98].

Resistance to lipoapoptosis is, in part, due to an autocrine hedgehog signaling pathway^[14]. Farnesoid X receptor is a member of the nuclear receptor superfamily that plays a crucial role in bile acid, cholesterol, lipid, and glucose metabolism as well as apoptosis^[100]. It is also involved in the pathogenesis of NASH. The cellular inhibitor of apoptosis proteins 1 and 2 (cIAP-1 and cIAP-2) are potent inhibitors of death receptor-mediated apoptosis. Proteasomal degradation of cIAPs by FFA contributes to hepatocyte lipoapoptosis^[101]. Palmitate-induced lipoapoptosis is dependent on calcium-stimulated mitochondrial activation, which induces oxidative stress and hepatic cell lipotoxicity^[102].

Free cholesterol accumulates in NASH patients but not in simple steatosis. Mitochondrial free cholesterol deposition causes hepatocyte apoptosis and necrosis by activating JNK1^[103]. High-mobility-group-box 1 and toll-like receptor 4 are both involved in this activation mechanism^[103]. Cholesterol markedly promoted the apoptosis of steatosis HepG2 cells *in vitro*, likely through the up-regulation of expression of Bax and caspase 3^[104]. Palmitate activation by fatty acid transport protein 4 triggers hepatocellular apoptosis via altered phospholipid composition and steatosis by acylation into complex lipids^[105]. These complex lipids are involved in the development of NAFLD^[105]. E2F transcription factors are known regulators of the cell cycle, proliferation, apoptosis, and differentiation. E2F1 regulates lipid synthesis and glycolysis and thus contributes to the development of NAFLD^[106].

Androgen-dependent proapoptotic polycystic ovarian syndrome (PCOS) may directly contribute to NAFLD progression in PCOS patients^[107]. A recent study gave a complementary fast food (FF) diet to a NASH mouse model, thus mimicking features of the metabolic syndrome. The study found that miR-21 levels increased in both the liver and muscle and expression of peroxisome proliferator-activated receptor α , a key miR-21 target, was decreased^[108]. In a typical model of NASH-associated liver damage, miR-21 ablation results in a progressive decrease in steatosis, inflammation and lipoapoptosis, with a subsequent impairment of fibrosis^[108].

Table 1 Inhibitors of apoptosis for nonalcoholic steatohepatitis

Drug and reagents	Targets	Mechanism of action	Ref.
Triacin C	Intracellular long-chain acyl-CoA synthetases (ACSL)	Triacylglycerol (TAG) accumulation into lipid droplets	[112]
Ezetimibe	AMPK phosphorylation	TFEB-mediated activation of autophagy and NLRP3 inflammasome inhibition	[113]
Baicalin	Inhibition of NF-κB	NF-κB anti-inflammation signaling pathways	[114]
Granulocyte colony stimulating factor (G-CSF)	PI3K/ Akt	Activation of PI3K and Akt pathway	[115]
Elafibranor (GFT505)	PPAR α/δ	Agonist of PPAR α/δ receptors	[116]
Isoquercitrin	Dipeptidyl peptidase-IV(DPP-IV)	Activation of glucagonlike peptide-1 (GLP-1)	[117]
Activated carbon N-acetylcysteine (ACNAC) microcapsules	Telomerase	Improved telomerase activity	[118]
3-Acetyl-oleanolic acid (3Ac-OA)	Glucose transporter type 2 (GLUT-2), low-density lipoprotein receptor (LDLR)	AMPK-related pathways	[119]
Meretrix oligopeptides (MMO)	NF-κB	NF-κB anti-inflammation signaling pathways	[120]
Seladelpar (MBX-8025)	Proliferator-activated receptor- delta (PPAR- δ)	Selective PPAR- δ agonist	[121]
Resveratrol	Sirt1	Antioxidant	[122]
TBE-31	NF-E2 p45-related factor 2 (Nrf2)	Regulation of intracellular redox homeostasis	[124]

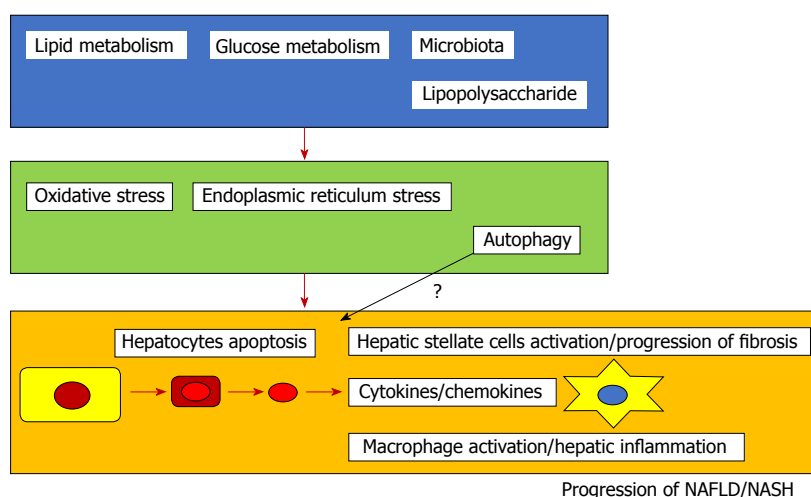


Figure 1 Disease progression of nonalcoholic fatty liver diseases and nonalcoholic steatohepatitis. The exact role of autophagy in nonalcoholic fatty liver diseases/nonalcoholic steatohepatitis remains unclear. NAFLD: Nonalcoholic fatty liver diseases; NASH: Nonalcoholic steatohepatitis.

MICROBIOTA AND APOPTOSIS

Intestinal endotoxin [lipopolysaccharide (LPS)] augments liver injury in MCD mice^[109]. In a recent study, a group of male C57BL/6 mice were fed with a MCD diet for 17 days, injected with LPS intraperitoneally, and sacrificed 6 h after LPS injection. The study found that LPS upregulated TNF- α production, which induce hepatocyte apoptosis^[110]. Palmitate and lysophosphatidylcholine (LPC) induced upregulation of the p53-upregulated modulator of apoptosis and cell-surface expression of the death receptor TNF-related apoptosis-inducing ligand receptor 2^[111]. In part, microbiota may be involved in the progression of NAFLD and NASH through hepatocyte apoptosis.

CONCLUSION

Cell death, including apoptosis, seems important in the

progression of NAFLD and NASH (Figure 1). Recently, several inhibitors of apoptosis have been suggested as potential treatments for NASH (Table 1)^[112-124]. Clinical trials for the treatment of NASH are currently being conducted^[125] and some are targeting apoptosis in NASH patients. Increased hepatocyte apoptosis may distinguish NASH from NAFLD^[126]. Repair responses may play an important role in controlling the disease severities of NASH^[126]. We reviewed published articles related to this topic and discussed the importance of apoptosis in NAFLD and NASH.

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