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REVIEW

Innate immune regulatory networks in hepatic lipid metabolism

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Abstract
Hepatic lipid metabolism is closely associated with certain diseases, such as obesity, diabetes, fatty liver, and hepatic fibrosis. Hepatic steatosis results from systemic metabolic dysfunction that occurs via multiple processes. The initial process has been characterized as hepatic lipid accumulation that may be caused by increased liver lipid uptake and de novo lipogenesis or decreased lipid oxidation and lipid export; subsequently, multiple additional factors that trigger inflammation and insulin resistance (IR) aggravate the progression of hepatic steatosis. Emerging evidence indicates that inflammation stands at the crossroads of innate immunity and lipid metabolism and links the initial metabolic stress and subsequent metabolic events in lipid metabolism. Therefore, in this review, we summarize the regulatory role of innate immune signaling molecules in maintaining lipid metabolic homeostasis; these revelations can guide the development of potential therapies for nonalcoholic fatty liver disease (NAFLD).

Keywords Innate immunity · Inflammation · Lipid metabolism · Insulin resistance · NAFLD

Introduction

Ectopic lipid metabolism leads to multiple liver diseases, ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma (HCC). There is a worldwide pandemic of nonalcoholic fatty liver disease (NAFLD), which occurs in parallel with epidemics of obesity, type 2 diabetes (T2D), and metabolic syndrome (MetS) [1]. Patients with NAFLD have high risks of premature cardiovascular- and/or liver-related death [2]. At present, around the world, 23–29% of individuals in the general population are affected by NAFLD. This proportion is even higher among individuals with T2D (60–70%) and individuals who are morbidly obese (75–92%) than in the general population [3]. Currently, lifestyle

modification via improving nutrition and exercise is the main treatment for NAFLD [4, 5]. Unfortunately, there have been still no FDA-approved effective therapies for NAFLD so far. Therefore, advanced insights into the pathophysiology of NAFLD have provided potential new therapeutic options.

Accumulating evidence suggests that the liver is not only a metabolic organ but also an innate immune organ. Many types of innate (Kuffer cells, dendritic cells, natural killer cells, and innate lymphoid cells) and adaptive (T cells and B cells) immune cells are enriched within the liver and function for liver physiology and pathology [6]. In addition to nonspecific host defense against invading pathogens, innate immune cell-derived innate immune activation also plays prominent role in driving hepatic metabolic disturbance in NAFLD. In metabolic disorders, the continuing production of metabolites constitutively activate innate immune signaling, leading to excessive inflammatory cytokine release, thereby further promoting hepatic steatosis and even developed to fibrosis [7]. Considering such important driving force of innate immune signaling in NAFLD progression, in-depth recognition of its role in NALFD development is urgently required.

Hepatic lipid metabolism

There has been an extensive viewpoint that NAFLD may result from the accumulation of toxic lipid species (e.g.,

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diacylglycerols, ceramides, and lysophosphatidyl choline species), which are produced from the surplus metabolic energy substrates (e.g., carbohydrates and fatty acids) due to the inadequately metabolic capacity of liver [8]. Hepatic lipid metabolism is closely interrelated with hepatic glucose metabolism, both of which have strong effects on the pathogenesis of liver diseases [9]. Two main processes determine the flux of lipid in the liver, the production of lipid species (cholesterol and fatty acids), and breakdown of them via fatty acid oxidation. Fatty acids from lipolysis of triglyceride in adipose tissue flow to the liver and subsequently be oxidized to production of acetyl-coenzyme A (CoA), which serves as the substrates of gluconeogenesis. In contrast, fatty acids also can be synthesized from glucose by

de novo lipogenesis. Glucose from gluconeogenesis and an individual's diet is metabolized via glycolysis into pyruvic acid, which is then reduced to CoA and used as material for triglyceride synthesis [10] (Fig. 1). The metabolic fate of fatty acids is determined either by mitochondrial β-oxidation or esterification to form triglyceride, which is generally considered as a protective response to a supply of fatty acids exceeding the liver's metabolic capacity [11]. However, if the transport rates of triglyceride as very low-density lipoprotein (VLDL) are lower than the synthesis rates of triglyceride, an excess of triglyceride accumulates to form lipid droplets in hepatocytes and causes metabolic abnormalities (e.g., endoplasmic reticulum (ER) stress and mitochondrion dysfunction), which are usually
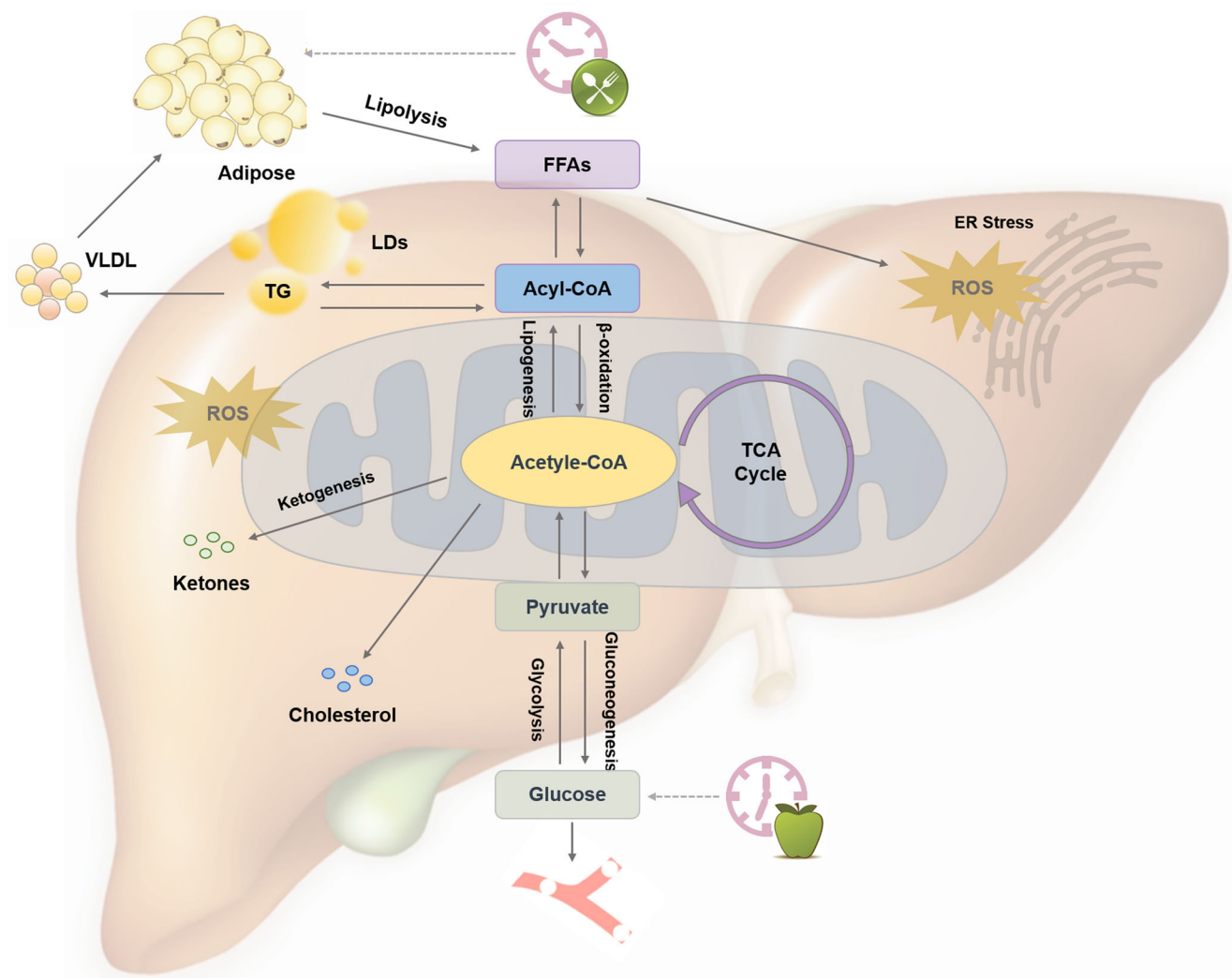

Fig. 1 Sources and fates of fatty acids in liver. Acetyl-CoA is the central intermediate product in the conversion between hepatic glucose and lipid. Blood glucose is derived from diet, hepatic glycogenolysis, and gluconeogenesis processes. During fasting, the liver is in hepatic glucose output state required to maintain blood glucose homeostasis. FFAs from adipose tissue lipolysis are converted into glucose through β-oxidation and the TCA cycle processes in mitochondria. During feeding, the liver is in hepatic glucose uptake state. Glucose from an individual's diet is converted into lipid via glycolysis and pyruvate cycling in mitochondria.

FFAs from lipolysis or hepatic glucose conversion are esterified into triglycerides (TG), which can be either stored in LDs or packaged into very low density lipoproteins (VLDL) to shuttle lipid to other tissues including adipose tissue. Excessive FFAs in the liver cause ER stress and production of ROS. The excess acetyl-CoA from the hepatic glucose and lipid metabolism can be used to produce ketone bodies for an additional energy shuttle between the liver and other organs and cholesterol for cell membrane and plasma lipoprotein construction

coupled with inflammatory cytokine release, microphage infiltration, fibrogenesis, and insulin resistance (IR) [12] (Fig. 2). Fatty acid metabolism is highly influenced by blood glucose. During hypoglycemia, fatty acids from lipolysis are metabolized through β-oxidation and TCA cycle to produce glucose maintaining the blood glucose homeostasis, while hyperglycemia causes insulin resistance. Insulin resistance in adipose tissue dysregulates lipolysis, leading to aberrant release of fatty acids, that further aggravates impaired insulin signaling throughout the body.

Innate immune-derived inflammation mediates subsequent metabolic events in lipid metabolism

The innate immune system, as the first line of defense against pathogen invasion, recruits immune cells, including macrophages, neutrophils, dendritic cells (DCs), and natural killer (NK) cells, to invaded sites for pathogen recognition and the initiation of a rapid but generic response [13–15]. Extracellular pathogens or endogenous injury signaling are first recognized by pattern recognition receptors (PRRs) on cell membranes or endosome membranes; adaptor kinase complexes are then recruited to PRRs to transduct signals to downstream MAPK

signal cascades, eventually resulting in the activation of ERK/JNK/p38MAPK/NF-κB signals and leading to the transcription of proinflammatory cytokine genes and type I/II IFNs [16, 17] (Fig. 3). The pathogens induced acute immune inflammation activates the JAK-STAT pathway or other immune receptor-triggered pathways for regulating the activation, differentiation, and/or function of immune cells to defend against antigen invasion. However, the metabolite (e.g., glucose and FAs) driven chronic metabolic inflammation regulates IR-mediated lipid metabolism directly via suppression of the insulin signaling pathway (Fig. 3).

The metabolites in lipid metabolism serve as a physiological burden to the metabolic system. The physiological response to the metabolites includes ER stress, dysfunctional unfolded protein response (UPR), apoptosis, inflammation, and enhanced injury [18–20]. Recent studies in mice have revealed that hepatocyte inflammatory response may be a key link between the initial metabolic stress (e.g., ER stress and UPR response) and subsequent metabolic events (e.g., fibrogenesis and IR) in NASH [21]. The inflammatory signaling derived from stressed or injured hepatocytes and activated macrophages (Kupffer cells in the liver) promotes activation of resident hepatic stellate cells into myofibroblasts to produce excessive extracellular matrix proteins, accumulation of that pushes the occurrence of fibrogenesis [22]. In addition,
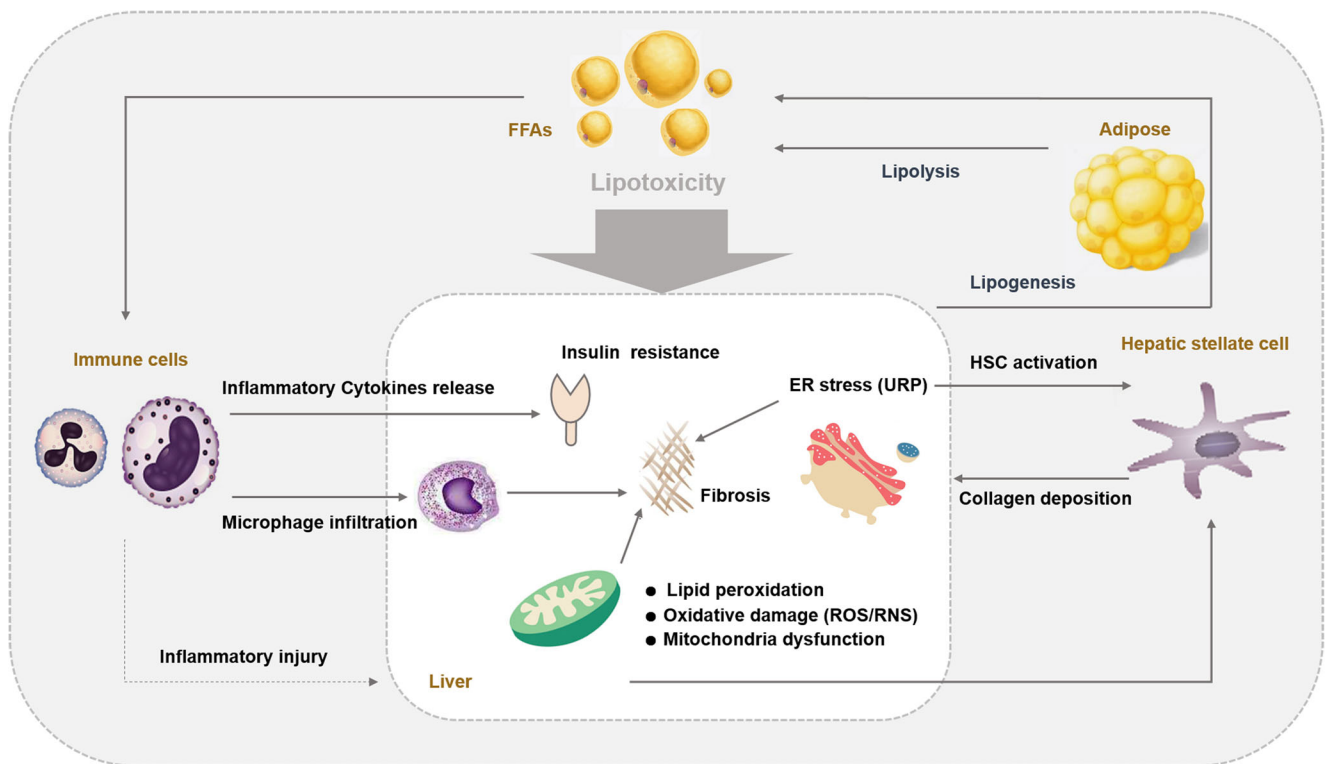

Fig. 2 Multiple pathophysiological processes are involved in the progression of NAFLD and NASH. FFA delivery to liver from the adipose or synthesis in liver leads to hepatic lipotoxicity, which triggers inflammatory cytokine release, microphage activation and infiltration, collagen deposition, ER stress, mitochondrion dysfunction, and hepatic stellate cell (HSC) activation, jointly causing hepatic inflammatory injury, insulin resistance, and fibrosis
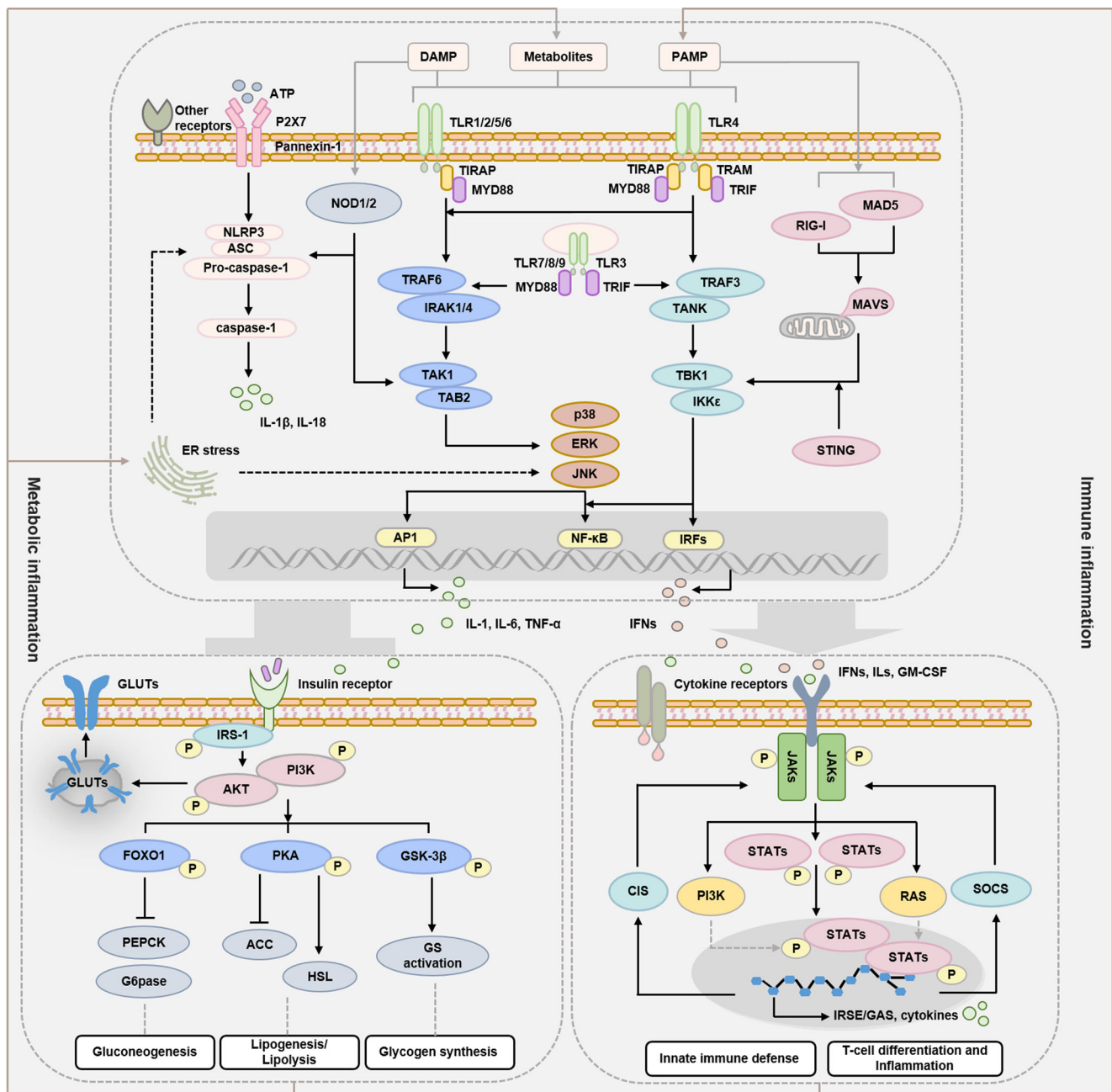
inflammatory cytokines and phosphorylation of mitogen acti-vated protein kinase (MAPK) in the process of inflammatory activation significantly impair post-receptor insulin signaling [23]. Thus, inflammatory response along with metabolic events drive the pathogenesis of NASH.

Multiple TLR pathway-mediated and inflammasome-mediated inflammatory responses participate in regulation of lipid metabolism. A number of serine kinases, cytokines, and molecular pathways involved in innate immune networks can induce the phosphorylation of serine residues on IRS-1 and then weaken insulin signaling transduction, thereby play an important role in the development of IR in lipid metabolism.

The JNK/ERK/p38MAPK pathways phosphorylate FOXO1 to enhance the development of IR and alter lipid metabolism [24, 25]. TNF-α induces the activity of the PKC, SOCS1/3, ERK, JNK, and IKKβ/NF-κB pathways to increase serine phosphorylation of IRS-1. IL-6 activates the JAK-STAT sig-naling pathway and increases SOCS3 production to reduce the expression of glucose transporter 4 (GLUT4) and IRS-1. MCP-1 regulates IR via the phosphorylation of ERK1/2 and p38MAPK to degrade IRS-1 [26] (Fig. 4). In addition, TNFα and other inflammatory cytokines lead to the induction of ER stress, afterwards downregulating the BCAA/TCA pathway to attenuate lipogenesis in visceral adipose depots.

Fig. 3 Innate immune-derived immune and metabolic inflammation, respectively, impinges on immune defense and IR. TLR signaling pathways include the MyD88-dependent pathway and the TRIF-dependent pathway. MyD88-dependent pathway: TLR1, TLR2, TLR4, TLR5, TLR6, TLR7, TLR8, and TLR9 initiate signaling by binding to MyD88 and IRAKs and recruiting TRAF6, TAK1, and TAB2, thereby activating p38MAPK, ERK, and JNK; this activation results in AP1 and NF-κB nuclear translocation and the initiation of gene transcription associated with innate immune responses and inflammation. TRIF-dependent pathway: TLR4 and TLR3 recruit TRIF to activate TBK1/IKKε via TRAF3 and TANK, which results in NF-κB nuclear translocation and the activation of IRF-induced inflammatory cytokines. RLR signaling pathway: pathogen association molecular pattern (PAMP) is recognized by RLRs (MDA5 and RIG-I), which are constitutively expressed in the cytoplasm and initiate MAVS-dependent signaling, leading to activation of IRFs and NF-κB and the subsequent production of type I/II IFNs and inflammatory cytokines. NLR signaling pathway: damage-associated molecular pattern (DAMP) triggers NOD1/2 to activate NLRP3/ASC/caspase-1 inflammasome pathway to produce IL-1β and IL-18. P2X7 receptor and pannexin-1 channel: activation of the pannexin channel through binding of ATP to P2X7 receptor leads to activation of NLRP3/ASC/caspase-1 inflammasome pathway and release of IL-1β and IL-18. JAK-STAT pathway: IFNs and cytokines bind to the corresponding receptors and activate JAK kinase, which selectively phosphorylates STATs. Phosphorylated STATs then translocate to the nucleus to regulate the transcription of target genes. Insulin signaling pathway: insulin stimulates insulin receptor to recruit and phosphorylate IRS-1, which subsequently phosphorylates and activates PI3K and AKT, resulting in inhibition of FOXO1 nuclear translocation and activation of PKA and SGK-3β, finally promoting lipolysis and glycogen synthesis, and inhibiting lipogenesis and gluconeogenesis. The release of inflammatory cytokines and activation of p38MAPK, ERK, JNK, and NF-κB pathways in innate immune networks interfere with insulin signaling pathway. Conversely, the inflammatory cytokines bind to specific receptors to activate JAK-STAT pathway. The metabolites from glucose and lipid metabolism and the PAMP from innate immune defense return to trigger innate immune regulatory networks

A variety of innate immune molecules are involved in hepatic lipid metabolism

PRRs participate in regulation of lipid metabolism

Intracellular or surface-expressed PRRs have been revealed to be relevant participants in NAFLD/NASH because of their central roles in recognizing cell damage and pathogen invasion [27]. Mammals have several distinct classes of PRRs, including TLRs, NOD-like receptors (NLRs), RIG-1-like receptors (RLRs), AIM2-like receptors (ALRs), C-type lectin receptors (CLRs), and other nonspecific sensors [28]. The activation of PRR systems, particularly TLR signaling pathways, is a critical response in liver disease.

Blockade of TLR2 signaling prevents high-fat diet (HFD)-induced IR in mice [29]. Hepatocyte TLR4-deficient mice exhibit improved glucose tolerance, decreased inflammation, enhanced insulin sensitivity, and ameliorated hepatic steatosis in the context of a HFD challenge [30]. Another study has revealed that TLR4 deficiency enhances the expression of fatty acid oxidases, including ACOX, CPT-1, MTPa, MTBb, PBE, and 3-ketoacyl-CoA thiolase, and presents lower triglyceride

accumulation, which indicates that TLR4 plays an important role in the onset of steatosis [31]. TLR5-deficient mice are susceptible to spontaneous gut inflammation and exhibit elevated neutral lipid level [32]. Dietary short-chain fatty acids (SCFAs) increase liver de novo lipogenesis, further aggravating metabolic syndrome in TLR5-deficient mice [33]. Although increased expression and activity of peripheral and hepatocytic TLR6 in morbidly obese NAFLD/NASH patients has been investigated, the capability of TLR6 regulating NAFLD progression has been unclear [34]. TLR9-deficient mice on a CDAA diet show less steatosis, inflammation, and liver fibrosis than wild-type (wt) mice on the same diet; in addition, the CDAA diet-induced IR and weight gain are suppressed by TLR9-deficiecy [35]. Mitochondrial DNA that serves as a TLR9 ligand drives NASH in mice and patients, whereas blockade of TLR9 reverses NASH [36, 37].

NLRP3 forms a subcellular multiprotein complex that consists of NLRP3, the adaptor protein ASC, and the protease caspase-1. Activation of the inflammasome results in activation of caspase-1 and the proinflammatory cytokines IL-1β and IL-18 and subsequently mediates cell death [38]. NLRP3 inflammasome activation is implicated in the progression of NAFLD from NAFL to NASH. NLRP3(−/−) mice are protected from hepatomegaly, liver injury, and activated macrophage infiltration induced by long-term CDAA feeding [39]. Treatment with the NLRP3 selective inhibitor MCC950 normalizes the expression of hepatic caspase-1, IL-1β, MCP-1, and IL-6 and lowers ALT/AST, which were shown to be increased in vehicle-treated foz/foz mice [40]. The NLRP3 and NLRP6 inflammasomes also negatively regulate NAFLD/NASH progression by modulating the interaction between gut microbiota and the host [41].

Adaptor proteins also regulate hepatic lipid metabolism

TLR4 signaling transduction primarily depends on MyD88 and TRIF adaptor proteins [42]. TRIF(−/−) mice exhibit increased CXCL1 and CCL3 expression and neutrophil and macrophage infiltration, which promotes liver inflammation and injury [43]. Hepatocyte-specific MyD88 deletion predisposes mice to glucose intolerance, inflammation, and hepatic IR, independent of body weight and adiposity [44]. In a study, global deletion of MyD88 drive HFD-fed mice weight gain, proinflammatory CD11c + AT machrophages increase and glucose homeotasis impairment [45]. In addition, genetic deletion of MyD88 in hepatocytes changes the gut microbiota composition and metabolomes of mice in ways that resemble diet-induced obesity [46].

TRAFs are important adaptor proteins in immunity, inflammation, and cell death. The depletion of TRAF1 leads to inhibition of NF-κB activity and reversion of the palmitic acid (PA)-induced attenuation of AKT and GSK-3β phosphorylation. The accumulation of LDs in hepatocytes and the
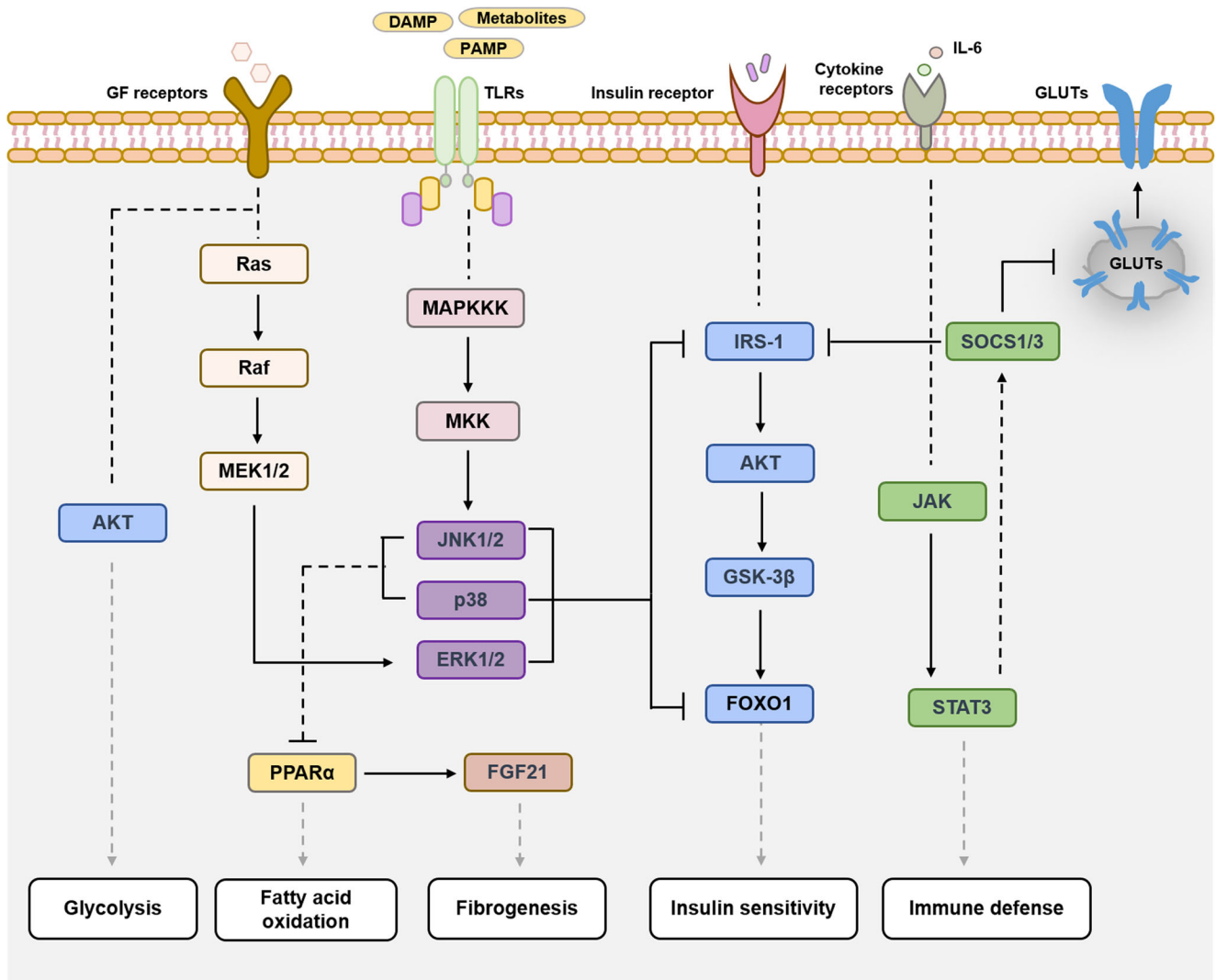
Fig. 4 MAPK signaling molecules push forward IR and fibrogenesis. JNK and p38MAPK activation suppresses PPARα and FGF21, leading to fatty acid oxidation abrogation and fibrosis promotion. The JNK/ERK/p38MAPK pathways phosphorylate IRS-1 or FOXO1 to enhance the development of IR. Activation of JAK-STAT signaling pathway and increase of SOCS3 production reduce the expression of glucose transporter 4 (GLUT4) and IRS-1 to drive IR progression

expression of two key gluconeogenesis enzymes, PEPCK and G6Pase, produce a similar tendency, indicating that TRAF1 knockdown blocks the effect of PA on the suppression of glucose uptake [47]. TRAF1 promotes hepatic steatosis by enhancing the activation of apoptosis signal-regulating kinase 1 (ASK1)-mediated JNK/p38MAPK cascades; thus, TRAF1 functions as a positive regulator of IR, inflammation, and hepatic steatosis [48]. TRAF3 also functions as a regulator of hepatic lipid metabolism. TRAF3 deletion enhances the ability of insulin to stimulate the phosphorylation of AKT in hepatocytes, whereas TRAF3 overexpression suppresses insulin signaling. Glucose increases the level of TRAF3 in hepatocytes, which in turn elevates hepatic glucose production to promote hyperglycemia [49]. Specific deletion of TRAF3 in mice myeloid cell significantly attenuates either genetic ob/ or HFD-induced IR, hepatic steatosis, glucose intolerance, hyperglycemia and hyperinsulinemia [50]. The CD40-TRAF2/3/5 signaling pathway in MHCII(+) cells protects against adipose tissue inflammation and metabolic complications associated with obesity [51], whereas the CD40-TRAF6 interaction aggravates adipose tissue inflammation and metabolic complications [51]. TRAF5 overexpression significantly improves NASH-like phenotypes in HFD-fed mice and retards NAFLD progression in ob/ob mice [52].

The MAPK family plays important roles in hepatic lipid metabolism

The MAPK family consists of serine and threonine protein kinases that modulate physiological and pathophysiological

cell responses, including the ERK1/2, p38MAPK, JNK, and ERK5 signaling pathways. These proteins uniformly play their regulatory roles via the classical MAPKKK-MAPKK-MAPK signaling pathway. Extracellular stimuli phosphorylate various MAPK family members and activate different subtypes of MAPK signal transduction pathways, particularly the ERK1/2, p38MAPK, and JNK signaling pathways, eventually leading to IR, hepatic lipid metabolism abnormalities, and even the development of NAFLD [53, 54].

Research has demonstrated that TAK1, a member of the MAP3K family in innate immune signal transduction, serves as an important regulator of energy homeostasis and involves in the development of metabolic syndrome. TAK1-deficiency greatly decreases the expression of lipid uptake-, synthesis- and storage-related genes (e.g., Cidea and CD36) in mice livers; however, restoration of TAK1 expression produces the opposite effects [55]. In the liver, TAK1-mediated autophagy prevents excessive lipid accumulation by targeting mammalian target of rapamycin complex 1 (mTORC1) [56]. Hepatocyte-specific deletion of TAK1 aggravates hepatosteatosis by suppressing the peroxisome proliferator-activated receptor-alpha (PPARα) target genes and β-oxidation [57]. TAK1 regulates cholesterol and fatty acid biosynthesis by binding to and inhibiting mature forms of SREBPs to maintain lipid homeostasis [58].

Another MAP3K kinase, ASK1 (which is also known as MAP3K5), has been proposed as a novel and effective target for NASH therapies [59]. In a comparison between ASK1-deficient and wt mice, ASK1 deficiency significantly decreased hepatic steatosis in HFD-fed mice [60]. Cellular repressors of E1A-stimulated genes (CREGs) directly interact with ASK1 and inhibit its phosphorylation, thereby blocking the downstream MKK4/7-JNK1 signaling pathway and leading to significantly ameliorated obesity, IR, and hepatic steatosis [61]. DKK3 negatively regulates hepatic IR, inflammation and steatosis; this function depends on DKK3 binding to ASK1 and thereby inhibits activation of the downstream JNK/p38MAPK pathways [62]. Conversely, TRAF1 promotes the activation of ASK1-mediated JNK/p38MAPK cascades and thus enhances hepatic steatosis [48].

JNK is one of the most investigated MAPK signal transducers in obesity and IR. Hepatic JNK signaling activation coincides with the development of steatohepatitis in MCD diet-fed mice. Mice deficient in JNK exhibit decreased inflammation, triglyceride accumulation and lipid peroxidation compared with those in wt and JNK2(-/-) mice [63]. Relative to wt mice, mice injected with the JNK inhibitor XG-102 show significantly lower levels of serum ALT, AST, TC, TG, HOMA-IR, and TNF-α but higher protein expression of p-c-Jun and cleaved caspase-3 [64]. Treatment with the JNK inhibitor SP600125 relieves NAFLD in HFD-fed rats, a finding supported by decreased expression of autophagy-associated genes (Atg3 and Atg5) and microtubule-associated protein 1A/B (MAP1A/B) and phosphorylation of IRS-1 and protein kinase B (PKB) [65].

Feeding stimulates JNK and p38α/βMAPK activation concomitant with downregulation of PPARα and the fibroblast growth factor 21 (FGF21), and ablation of hepatic JNK abrogates this phenomenon and induces fibrosis [23] (Fig. 4).

Mounting evidence has demonstrated that p38MAPK pushes forward the gluconeogenesis. Suppression of hepatic p38MAPK signaling attenuates insulin resistance [66]. In obesity, hepatic p38MAPK promotes the phosphorylation and nuclear tranlocation of the spliced form of X-box binding protein 1 (Xbp1s) so as to reduce the ER stress to maintain euglycemia [67]. Kujiraoka et al. demonstrated that hepatic ERK2 deficiency impairs glucose metabolism and promotes insulin resistance [68]. In addition, ERK1 knockout enhances lipogenesis and triglyceride accumulation, whereas weakens fatty acid oxidation in the development of hepatic steatosis [69].

Transcription factors implicated in innate immunity mediate hepatic lipid metabolism

The interferon regulatory factors (IRFs), as important immune factors, not only perform innate immune function but also exhibit immune-independent function under hepatic pathological conditions (e.g., liver injury and/or metabolic dysfunction) [70, 71]. As mentioned above, TRIF deficiency worsens hepatic steatosis induced by a HFD. This aggravated steatosis in TRIF(−/−) mice is attributable to the direct binding of IRF3 to the stearoyl-CoA desaturase 1 (SCD1) promoter [1, 72]. Global knockout of IRF3 significantly promotes HFD-induced hepatic IR and steatosis; in contrast, overexpression of IRF3 preserves glucose and lipid homeostasis by blocking IKKβ signaling transduction [73]. Interestingly, another study has suggested the opposing view that IRF3 deficiency improves adipose inflammation and insulin sensitivity, which enhances the browning of subcutaneous fat and increases adipose expression of GLUT4 [74]. Research has indicated that IRF7 and IRF9, which have been characterized as major transcription factors in IFN responses, play protective roles against metabolic disorders. IRF7-knockout (KO) mice fed a HFD diet show not only improved insulin sensitivity and glucose and lipid homeostasis but also ameliorated diet-induced hepatic steatosis. Additionally, IRF7 KO decreases macrophage infiltration to protect multiple organs from local and systemic inflammation [75]. Opposite phenotypes are observed for IRF9. IRF9 KO mice fed a HFD diet exhibit higher inflammation, lower insulin sensitivity, and more severe hepatic steatosis, whereas reexpression of IRF9 ameliorates these phenotypes. Importantly, PPARα is the target gene of IRF9, as evidenced by the fact that introduction of PPARα into IRF9 KO mice rescues insulin sensitivity and attenuates hepatic steatosis and inflammation [76].

In summary, most molecules in innate immune networks have a strong impact on liver inflammation, IR, lipid peroxidation, and even hepatic steatosis. The overexpression or knockout of certain genes alleviates or aggravates the development of

NAFLD. Thus, an emergent topic for discussion is NAFLD therapies that target innate immune regulatory networks.

Innate immune molecules might be promising targets for metabolic disease therapies

During lipid overload in the liver, the development of hepatic steatosis is determined by types of lipid accumulation and methods of fat consumption. The overaccumulation of lipids causes lipotoxicity, which induces the release of stress signals to trigger the activation of sterile inflammatory pathways; over time, this phenomenon leads to chronic injury and fibrosis [77]. However, importantly, metabolic inflammation is mainly mediated by innate immune signaling pathways. Therefore,

our group has been performing a great deal of research to demonstrate that innate immune networks are important in regulating hepatic lipid metabolism and would likely be attractive targets for NAFLD/NASH therapies.

The binding of FFAs and endotoxins to TLR4 enhances the activation of downstream IKK-NF-κB and MAPK signaling pathways, which are important for controlling inflammation, IR, and glucose metabolism [78]. We have demonstrated that transmembrane BAX inhibitor motif-containing 1 (TMBIM1) promotes the lysosomal degradation of TLR4 in cooperation with endosomal sorting complex required for transport (ESCRT), thereby facilitating the formation of multivesicular bodies (MVBs) that ultimately protect against NAFLD in mice and monkeys [79] (Fig. 5). Due to the critical role of TLR4 degradation in TMBIM1-ameliorated NASH, we propose that TLR4 is an attractive target for NASH therapy.
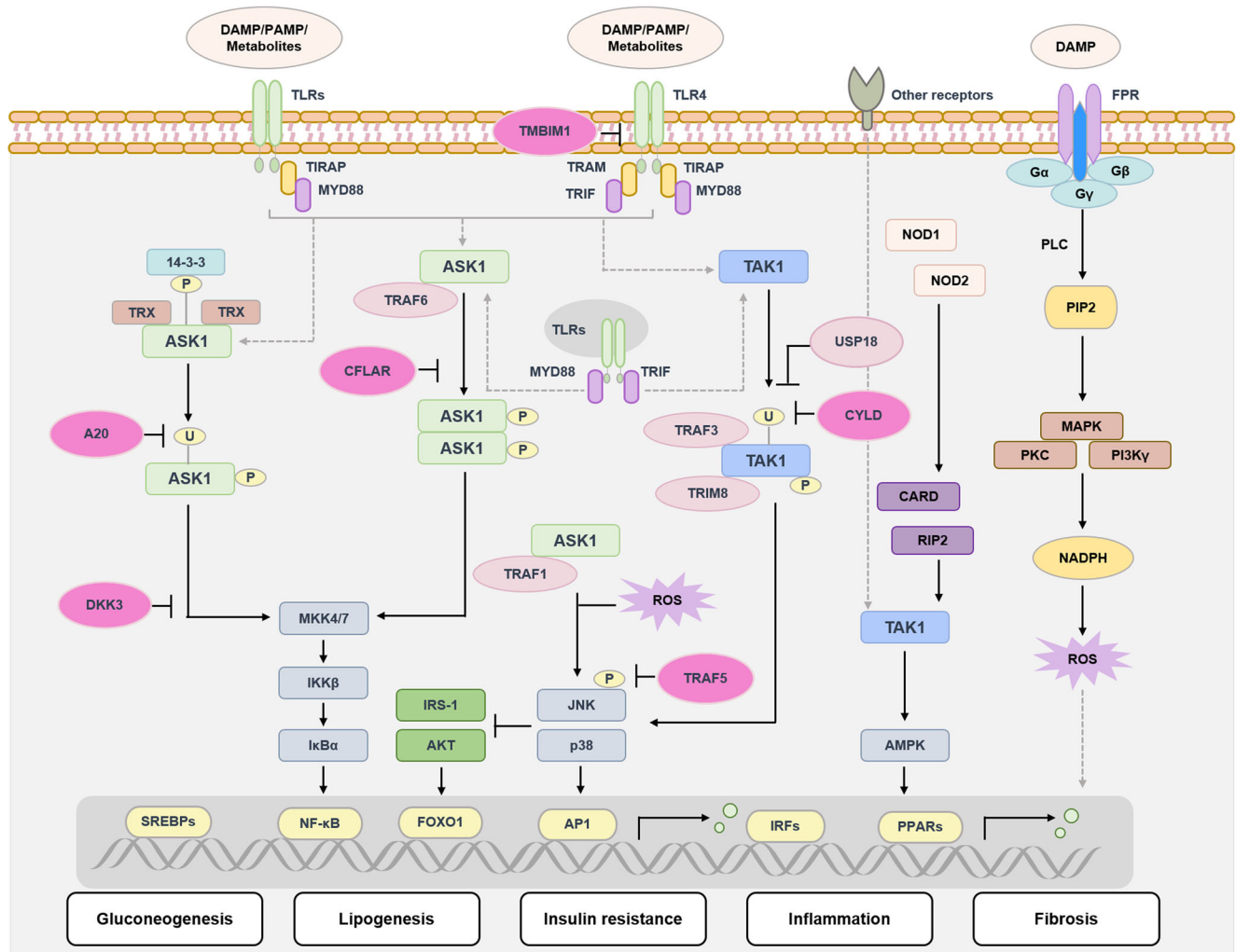

Fig. 5 The most potential drug targets and prototypes for NAFLD therapies. DAMP, PAMP, or metabolites activate TLRs and others (e.g., formyl peptide receptor (FPR) pathway) signaling pathways, leading to activation of p38MAPK, JNK, NF-κB, and AMPK pathways, which blocks insulin signaling and leads to dysfunction of insulin-mediated glucose and lipid metabolism. ASK1 and TAK1, which mainly mediate metabolite-induced TLR signal transduction, may be the most potential targets for NAFLD therapies. More importantly, by targeting ASK1 or TAK1, some molecules, such as CFLAR, A20, CYLD, DKK3, and TMBIM1, are proposed as promising drug prototypes for NAFLD therapies

However, TLR4 is also crucial for initializing the innate immune response, and the complete deletion of TLR4 may disrupt immunity. Therefore, we believe that maintaining the dynamic balance of TLR4 at an appropriate level rather than severely blocking TLR4 function would be beneficial for NASH therapy.

Research on ACSP8 and FADD-like apoptosis regulator (CFLAR; also known as c-FLIP) has provided strong support for our theory. We have demonstrated that CFLAR attenuates NASH by disrupting ASK1 N-terminal dimerization and autophosphorylation and the subsequent suppression of JNK1 activity [80] (Fig. 5). Similarly, the deubiquitinase tumor necrosis factor alpha-induced protein 3 (TNFAIP3) ameliorates NAFLD and NASH by markedly removing K63, K29, and K11 linkage of ASK1 and inactivation of ASK1-p38-JNK1/2 signaling [81] (Fig. 5). Thus, we propose that with respect to the targeting of ASK1, certain molecules, such as CFLAR and TNFAIP3, are likely to be potential leading molecular targets for NAFLD/NASH treatment.

In addition, ubiquitin-specific protease 18 (USP18) and deubiquitinase cylindromatosis (CYLD), members of the deubiquitinating enzyme family, negatively regulate NAFLD progression by interacting with and deubiquitinating TAK1, leading to the inhibition of TAK1 activation and the subsequent suppression of downstream JNK, p38, and NF-κB signaling pathways [82, 83] (Fig. 5). In contrast, tripartite motif 8 (TRIM8), an E3 ligase, robustly enhances steatohepatitis by binding to TAK1 to promote its phosphorylation and the activation of JNK/p38MAPK/NF-κB signaling [84] (Fig. 5). Another study has shown that the binding of hepatocyte TRAF3 to TAK1 in response to a HFD-induced TAK1 ubiquitination and subsequent autophosphorylation, followed by enhanced activation of downstream IKKβ-NF-κB and MKK-JNK-IRS-1[307] signaling cascades, as well as disruption of AKT-GSK-3β/FOXO1 signaling [85] (Fig. 5). Therefore, we believe that TAK1 is responsible for functional homeostasis in the liver. Furthermore, the viable option of maintaining TAK1 expression at an appropriate level rather than completely ablating TAK1 may be helpful for protecting the liver against steatosis.

Conclusions

In conclusion, lipid production and lipid breakdown demonstrate that lipid species positively and negatively regulate inflammation, which in turn significantly alters lipid metabolism in the liver, adipose tissue, and macrophages under conditions involving infection or a HFD. This interconnected network maintains lipid metabolism homeostasis. Both basic and clinical studies have established that innate immune activation directly triggers and amplifies hepatic inflammation and affects the development of hepatic fibrosis in NAFLD/NASH.

Given the dearth of effective treatments currently available for these conditions, we must continue to elucidate the mechanisms and pathogenesis underlying the progression of NAFLD, because such knowledge will be important for designing therapeutic interventions. In accordance with this objective, our team has been devoted to identifying key immune molecules, such as TLR4, TAK1, and ASK1, that play important roles in hepatic lipid metabolism and potential drug prototypes (e.g., CFLAR, TMBIM1, TNFAIP3, and CYLD) that target these immune molecules (Fig. 5); this research will provide significant contributions to improving NAFLD therapies.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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