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Review

The many pathways driving liver inflammation in MASH

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SUMMARY

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent chronic liver disease worldwide, affecting one-third of the global population. Most patients exhibit simple steatosis, whereas up to 20% develop metabolic dysfunction-associated steatohepatitis (MASH), potentially culminating in liver cirrhosis and hepatocellular carcinoma. Diverse parallel mechanisms contribute to the development of MASH, which are fueled by hepatic lipotoxicity, intestinal dysbiosis, and pro-inflammatory diets shaping innate and adaptive immune responses. Moreover, adipose tissue is driving systemic inflammation in obesity, contributing to the inflammatory burden in obesity-related MASH. Polygenetic and multiomic risk scores identify distinct types of MASLD with dominant aggressive liver disease or extrahepatic cardiometabolic disease. Here, we review the complexity of multiple parallel inflammatory hits in MASH and delineate that most current MASH drugs exert pleiotropic metabolic and anti-inflammatory properties. These new therapies will change the clinical management of this disease in the near future.

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) has evolved in recent years as the most common liver disease globally.[1–4] Although this disease presents in up to 80% of people as hepatic steatosis without further progression of liver disease, a substantial subgroup of patients develops metabolic dysfunction-associated steatohepatitis (MASH).[5] Consequently, chronic liver inflammation promotes the development of advanced liver fibrosis, liver cirrhosis, and hepatocellular carcinoma (HCC).[6] Historically, MASLD has been regarded as a disease of the liver, whereas research from the past two decades culminated in the perception that MASLD/MASH is part of the systemic metabolic disorders, together with type 2 diabetes (T2D), cardiovascular, heart, and kidney diseases.[7] This is clinically supported by evidence that people with MASLD primarily die from cardiovascular disease (CVD) and extrahepatic cancers, besides liver-related mortality.[8] Notably, the recently introduced MASLD classification includes overlap with alcoholic liver disease (ALD), i.e., MetALD, which will not be discussed herein.[9–11]

Together with the amount of lipids in the liver, inflammation is a major contributor to liver fibrosis and disease progression.[6] Several factors have been identified in the past years contributing to inflammation in MASH, including various lipid species, the gut microbiota, dietary components, and genetic factors, as discussed in this article. Lipotoxicity, in this context, is defined by hepatic accumulation of triglycerides (TGs), free cholesterol, saturated fatty acids, and sphingolipids and drives sterile inflammation and cell death.[12] Sterile inflammation, which occurs in all tissues in the absence of pathogens, has been a major concept in understanding MASH and other liver diseases.[13] However, recent evidence demonstrating a perturbed gut microbiota and even the presence of intrahepatic bacterial DNA has challenged the notion that MASH is solely driven by sterile inflammation.[14] Chronic unresolved liver inflammation, as observed in MASH, may promote an insufficient healing process accompanied by fibrosis with deleterious consequences.[15] Noninvasive parameters, such as assessment of circulating cytokines, C-reactive protein (CRP), or ferritin, have been extensively studied but still do not allow for defining the inflammatory burden of an inflamed liver.[16–18] Liver fibrosis, which is often the net result of inflammation, can be reliably assessed by non-invasive clinical tests, including elastography, that correlate well with histological criteria.[19–22] Beyond the liver, chronic low-grade inflammation is observed in many metabolic disorders, including MASLD, and likely contributes to major extrahepatic complications of MASLD, namely CVD and extrahepatic cancer.[23–25] In this review, we will discuss how diverse

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mechanisms evoke liver inflammation from steatosis to MASH and activate innate and adaptive immunity, potentially resulting in substantial hepatic organ damage and extrahepatic complications.

LIPOTOXICITY: A PROTOTYPIC PATHWAY DRIVING LIVER INFLAMMATION

Lipotoxicity has emerged as a crucial factor that contributes to inflammation in MASLD.[12,26] Sedentary lifestyle and overconsumption of saturated fatty acids, glucose, and fructose, major substrates for lipogenesis, have fueled the global MASLD epidemic.[1,3,27] Several components contribute to hepatic steatosis, such as (1) an increased influx of lipids but especially free fatty acids (FFAs) mainly derived from food, the visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT) with increased lipolysis in the AT especially in case of insulin resistance, which is commonly observed in MASLD; (2) an increase in *de novo* intrahepatic lipogenesis (DNL); (3) a decrease in fatty acid oxidation within the liver; and (4) decreased export of lipids through very-low-density lipoproteins (VLDLs). It remains unclear what blood lipid profile preferentially associates with MASLD and its subsets, whereas the intrahepatic composition of various lipids probably reflects the most important aspect in MASLD susceptibility.

TGs

Dietary FFAs fuel intrahepatic TG accumulation via hepatocellular long-chain fatty acids bound to coenzyme A (CoA).[12] TGs, dominant intrahepatic lipid species, have been erroneously regarded as inert bystanders not causing liver inflammation.[28] Diacylglycerol-O-acyltransferase 2 (DGAT2) is the key rate-limiting enzyme catalyzing the synthesis of TG by linking diacylglycerol to acyl-CoA. Inhibition of DGAT2 using a specific inhibitor decreased SREBP-1 and fatty acid synthesis and lowered hepatic TG in an MASLD model.[29] This inhibitory effect on DGAT2 enhanced phosphatidylethanolamine (PE) levels in the endoplasmic reticulum (ER), shifting diacylglycerol (DAG) into phospholipid synthesis, thereby improving hepatic steatosis.[29] Preclinical and clinical studies using antisense oligonucleotides targeting DGAT2 demonstrated reduction of hepatic TG levels and improved hepatic steatosis and oxidative gene expression.[30–32] Preclinical studies showed that this therapeutic approach might improve insulin sensitivity in experimental models.[33] Acetyl-CoA carboxylase (ACC) inhibitors cause an increase in serum TG levels, although they show efficacy in the reduction of hepatic TGs, and this might be overcome by the parallel use of a small-molecule DGAT2 inhibitor.[34]

ATP-citrate lyase (ACLY) regulates DNL by generating ACC, and pharmacological inhibition of ACLY improves MASH and fibrosis in a mouse model.[35] In addition, inhibition of ACLY also enhances tumor immunity and suppresses liver cancer in a mouse model of MASH-HCC.[36] Counteracting intestinal TG absorption by inhibiting monoacylglycerol acyltransferase (MGAT2) was effective in reducing MASH in mice and in non-human primates and reduced weight in a phase 1 study of healthy volunteers with obesity.[37] A body of evidence, including data from human genetics described later, demonstrates that TGs are not “simple inert” but rather deleterious lipids in MASLD.

Free cholesterol

High cholesterol carried by low-density lipoproteins (LDLs) is a major risk factor for CVD and atherosclerosis, promoting vessel inflammation.[38,39] Cholesterol might also have the potential to affect MASLD and promote liver inflammation.[40] Mitochondrial free cholesterol sensitized mice toward TNF- and Fas-induced steatohepatitis in dietary and genetic MASLD models by depletion of mitochondrial glutathione.[41] Hepatic cholesterol synthesis and HMG CoA reductase are increased in MASLD and correlate with disease severity and LDL-cholesterol levels.[42] A high-cholesterol diet used in a mouse model over 14 months induced MASH and HCC.[43] Liver disease with hepatic steatosis, inflammation, and increased cell proliferation was transferable via fecal microbiota transplantation (FMT) to germ-free mice, and the cholesterol-lowering drug atorvastatin corrected the associated gut dysbiosis and prevented liver inflammation and HCC.[43] Whereas it is currently believed that hepatocyte cholesterol accumulation is a potential culprit for MASLD, a recent study also reported that lysosomal cholesterol in macrophages causes MASH and liver fibrosis.[44] A new mechanism has been recently identified by which EH-domain-binding protein 1 (EHBP1), a gene identified by GWAS, acts as a regulator of cholesterol biosynthesis and reduces hepatic cholesterol accumulation via promoting sortilin-mediated PCSK9 release.[45] Mechanistically, EHBP1 decreased LDLR, hepatic cholesterol uptake, and TAZ and improved preclinical MASLD models of liver inflammation.[45] Increased hepatocyte cholesterol upregulates TAZ, a transcriptional regulator promoting hepatic fibrosis,[46] and this pathway also promotes HCC proliferation.[47]

Statin treatment is associated with lower liver lipids, inflammation, and fibrosis, as examined by liver biopsy,[48] and with decreased liver stiffness progression and reduced liver-related complications.[49] The beneficial effect of statin treatment on the liver is likely mediated by a direct inhibition of *SREBP1c*, a master regulator of TG synthesis.[50] In a large cohort of people with familial hypercholesterolemia, treatment with statin/ezetimibe or PCSK9 inhibitors improved MASLD.[51] Although large randomized controlled trials using cholesterol-lowering drugs are still not available with regard to MASH evaluation, indirect evidence supports that these drugs might be beneficial in people with MASLD, with the added value of reducing CVD risk.

FFAs

The FFAs oleic and linoleic acid activate inflammatory pathways such as nuclear factor kappa B (NF-κB).[52] They activate expression of various adhesion molecules such as vascular adhesion molecule-1 (VCAM-1) in human endothelial cells,[53] similar to palmitate, which increases hepatic VCAM-1 expression in mice.[54] Inflammasomes are multiprotein complexes with important functions in the processing of proinflammatory cytokines. The inflammasome pyrin-domain-containing protein 3 (NLRP3) results in the release of active IL-1 beta (IL-1β), which plays a fundamental role in metabolic disorders and metabolic inflammation as observed in MASLD.[55,56] Various FFAs, such as palmitate, activate NLRP3 in diverse cell types, and ablation of Nlrp3 in mice prevents obesity-induced inflammasome activity and enhances insulin signaling.[57,58] FFAs are not only diet derived but also substantially released by AT during insulin resistance, which

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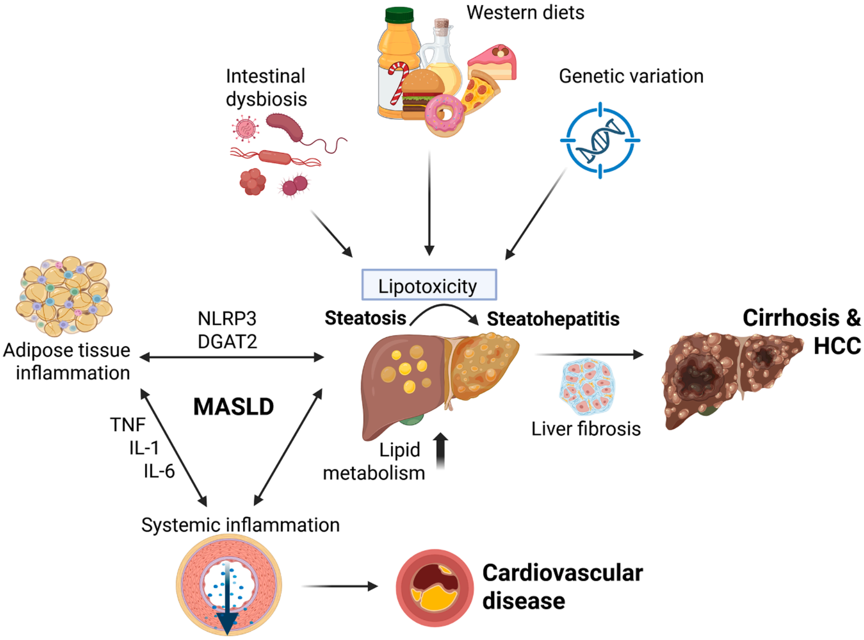

Figure 1. The concept of MASLD and its complications
Various environmental and genetic factors determine the metabolic stress in metabolically active organs such as the liver and AT. Metabolic stress converges on lipotoxicity and a large repertoire of cellular mechanisms eliciting danger signaling (e.g., the inflammasomes, unfolded protein response, oxidative stress) in hepatocytes and the hepatic innate immune system. Danger signaling evokes an acute or chronic inflammatory response leading to steatohepatitis, which promotes liver fibrosis and eventually cirrhosis with hepatocellular carcinoma. Systemic inflammation associated with metabolic diseases also promotes extrahepatic complications such as cardiovascular disease (e.g., atherosclerotic myocardial infarction) and solid cancers.

is frequently observed in MASLD.[59] SAT is larger than the VAT, and SAT releases the majority of FFAs in insulin resistance, and release of FFAs is associated with increased hepatic macrophage activity.[12,60]

Sphingolipid metabolism

Sphingolipid metabolism reflects another lipotoxic pathway. Sphingolipids are synthesized via sphingomyelin synthases (SMSs), also generating ceramide. Hepatic overexpression of ceramidase prevented hepatic steatosis and hepatic/AT insulin resistance after an HFD—an effect also observed when this enzyme was overexpressed in AT.[61] Induction of ceramidase in the AT substantially improved hepatic steatosis even more potently when overexpressing this enzyme in the liver, indicating an important role for AT lipid pathways in MASLD.[61] Whereas some studies have shown that a high-fat and high-cholesterol diet (HFHCD) upregulates hepatic Sms1 in mice and hepatic levels are increased in MASH patients,[62] disruption of intestinal hypoxia-inducible factor (HIF2α) decreased hepatic steatosis by lowering intestine and serum ceramide levels.[63] Ceramide might also be affected by gut bacteria, as the *Ruminococcus torques*-derived bacterial metabolite 2-hydroxy-4-methylpentanoic acid suppressed the HIF-2α-ceramide axis in a murine MASLD model, thereby improving liver inflammation and fibrosis.[64] Specific targeting of acid ceramidase reduced liver fibrosis in an MASLD model via inhibition of YAP/TAZ, raising the possibility that ceramide could also play a role in MASLD-related fibrosis.[65] Sphingomyelin phosphodiesterase (SMPD3) drives MASH via sphingomyelin hydrolysis and ceramide upregulation.[66] Ablation of this enzyme improved experimental MASH, and mechanistically, this process was SIRT-1 dependent.[66] Ceramides are well-studied lipotoxic lipids in patients with MASH exhibiting increased circulating concentrations and increased hepatic content that directly correlates with hepatic insulin resistance.[12,67]

Other pathways fueling MASLD

Numerous other factors contribute to the perturbation of hepatic lipid homeostasis. DNL is also considerably increased in MASLD.[26,68] Inflammatory signals such as TNF also lead to hepatic steatosis in experimental models.[69] Whereas dietary carbohydrates and lipids are well described as carbon sources for hepatic fatty acid synthase, dietary protein reflects an additional important factor for DNL.[70] Hepatic transcriptome analysis revealed increased arachidonate 12 lipoxygenase expression in human MASH and in various animal MASH models, thereby directly targeting ACC1, which was shown to be beneficial in an experimental mouse model.[71] Important MASLD genetic factors such as the PNPLA3 I148M variant show hepatic mitochondrial dysfunction and especially a reduced DNL favoring ketogenesis[72] (see also section lipid-droplet biology orchestrates sterile inflammation). Various other factors contribute to lipid abnormalities and lipotoxicity, such as macrophage scavenger receptor 1,[73] adipose TG lipase,[74] IL-22,[75] coagulation factor VII,[76] PPAR and farnesoid X receptor (FXR) signaling,[77,78] and the metabolite itaconate.[79] In summary, lipotoxicity has appeared as a crucial and major pathway promoting liver inflammation; however, the final proof for its relevance in MASH awaits controlled clinical trials investigating the efficacy and safety of targeting specific molecular hubs (Figure 1; Box 1).

THE GUT MICROBIOME AND GUT-LIVER AXIS FUELING LIVER INFLAMMATION

Intestinal barrier in MASLD

The gut microbiota controls intestinal permeability, and alterations in its composition are associated with impaired intestinal permeability.[80] Human MASLD is associated with an impaired intestinal barrier and gut permeability correlated with the histological degree of hepatic steatosis.[81] Bacteria-derived ethanolamine might constitute a metabolite involved in this pathway, as ethanolamine accumulation was observed in obesity-related disorders involving *miR-101a-3p* destabilizing occludin 1 (*Zo1*).[82] Importantly, *Lactobacillus rhamnosus*

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Box 1. Key points

- Abdominal obesity is a hallmark of most MASLD patients.
- Multiple parallel hits contribute to the development of MASH, including lipotoxicity, gut dysbiosis, proinflammatory diets, and host genetics.
- Inflammatory diets containing fat, glucose, and fructose are major drivers of the MASLD pandemic.
- Lipotoxicity of diverse lipid species, such as triglycerides, free cholesterol, free fatty acids, or sphingolipids, drives sterile hepatic inflammation.
- Gut dysbiosis characterizes stages of MASLD and promotes liver inflammation and fibrosis via diverse mechanisms.
- Genetic variation affects lipid metabolism and hepatic immune responses in MASLD.
- Cumulative intrahepatic and extrahepatic (systemic) inflammation contributes to complications of MASH, such as liver cirrhosis, hepatocellular carcinoma, cardiovascular diseases, and extrahepatic cancers.
- MASH therapies are rapidly emerging in clinical trials targeting thyroid hormone signaling and hormonal pathways of the gut-liver axis, exerting pleiotropic and anti-inflammatory mechanisms.
- Inflammation is a key driver of this disease, and effective future therapies might have to target metabolic and inflammatory pathways.
- Assessment of inflammation, i.e., MASH in humans, is still challenging as it might appear intermittently during the clinical course and could be missed by liver biopsy. Future non-invasive strategies assessing the liver's inflammatory burden are eagerly awaited.

HL-200 had the highest activity in metabolizing ethanolamine, and when used in mice as a probiotic, it was able to restore ethanolamine-related gut permeability and intestinal inflammation.[82] Bile acids are critical for maintaining the intestinal barrier, and especially secondary bile acids, mainly regulated by the gut microbiota, exert important effects on the intestinal barrier.[83–85]

Intestinal dysbiosis: A key feature of MASLD/MASH

The gut microbiota is of major importance for gastrointestinal health and disease and for many disorders beyond the gastrointestinal tract. It is composed predominantly of bacteria, but viruses, fungi, and archaea also reside in this complex ecosystem.[86] Many microbial functions are crucial for the host, for example, the control of the intestinal barrier. Commensal gut microbes contribute to hepatic steatosis in *ob/ob* mice, which in turn can be improved by probiotics.[69] Metagenomic studies in MASLD revealed that advanced fibrosis is especially associated with intestinal dysbiosis with increased abundance of Proteobacteria and *Escherichia coli* and decreased abundance of *Ruminococcus obeum* or *Eubacterium rectale*.[87] In a large European MASLD cohort, including primarily people with hepatic steatosis, *R. obeum* and *E. rectale* and various Firmicutes such as Lachnospiraceae were depleted.[88] Phenylacetic acid, a microbial product of aromatic amino acid metabolism, was increased in people with MASLD and caused hepatic steatosis in a mouse model. Importantly, in this study, an increase in microbial-associated functional pathways related to endotoxin and immune responses was observed.[88] In another MASLD study, patients with non-cirrhotic MASH were characterized by 12 MASH-associated bacterial species, including *E. coli*, *Streptococcus parasanguinis*, and *S. salivarius*, while certain fecal bile acids were also decreased in MASH compared with healthy controls.[89] People with MASLD and MASH have a distinct intestinal microbiome if overweight or lean (accounting for 10% of the MASLD population), suggesting that dysbiosis could be important in both MASLD phenotypes.[90] Bacteria such as *Eubacterium hallii*, *Blautia obeum*, *Eggerthela lenta*, *Clostridium bolteae*, *Intestinibacter bartlettii*, and *Roseburia intestinalis* were negatively associated with the severity of MASLD.[90] New bacterial strains isolated from children with MASLD have been recently characterized as *Enterococcus sp.* B6, *Streptococcus sp.* R61, *Escherichia sp.* Y64, and *Klebsiella sp.* Y129; all four exhibited lipogenic effects *in vitro*.[91] Stage of liver disease is highly relevant, as in patients with MASH cirrhosis, the microbial landscape changes with frequent fecal detection of oral microbes.[92,93] Dietary factors have a major impact on the gut microbiota.[94] A 4-month administration of resistant starch, digested in the large intestine, to people with MASLD not only influenced gut microbiota composition but also significantly decreased body weight and intrahepatic TG content. This effect was partly mediated by changes in the gut microbiota and especially a reduction in intestinal *Bacteroides stercoris* concentrations in mice, while monocolonization of this bacterium worsened liver inflammation.[95]

Mechanisms linking gut microbes to liver inflammation

Gut microbes and their metabolites might exert key functions in the gut-liver axis in either a protective or detrimental manner. The best investigated pathway driving inflammation in the liver and potentially beyond reflects the pathogen-associated molecular pattern (PAMP) endotoxin, a prototypic inducer of proinflammatory cytokines and inflammation. Its presence in the liver at various stages of MASLD is well documented.[96,97] Endotoxin can also be frequently detected in the circulation in MASH, and both endotoxin and lipopolysaccharide-binding protein serum levels correlate with the degree of liver fibrosis.[98] Considering the importance of an impaired intestinal barrier and the presence of intrahepatic endotoxin, it is not surprising that the body has developed counteracting mechanisms to limit the body's exposure to PAMPs. Indeed, intestine-derived high-density lipoprotein 3 (HDL_3) as an early defense mechanism inactivates endotoxin in the portal tract, thereby preventing activation of inflammatory cascades in the liver.[99] A recent study provided additional insights into how a liver might be protected from PAMPs and inflammation.[100] In healthy conditions, immunosuppressive macrophages located in periportal vein zones release

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high levels of IL-10 and express Marco, a scavenger receptor that restrains PAMPs and damage-associated molecular patterns (DAMPs). Importantly, the presence of this type of macrophage was dependent on the gut microbiota and especially Odoribacteraceae via production of the secondary bile acid isoallolithocholic acid (isoalloLCA). Importantly, human MASH was associated with a decrease in these immunosuppressive macrophages.[100] Pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) or nucleotide-binding oligomerization domain (NOD)-like receptors, are crucial for the interaction of the immune system with intestinal bacteria. Tlr4-deficient mice are protected from fructose-induced liver disease.[101] Inflammasome deficiency (Nlrp3/6) altered the gut microbiome, resulting in portal influx of TLR4 and TLR9, exacerbating liver inflammation in an MASLD mouse model.[102] Intestinal bacteria-derived PAMPs, such as various TLRs, will reach the liver and potentially contribute to liver inflammation in MASLD, especially if the intestinal barrier is impaired.

Besides PAMPs and PRRs, other metabolites might contribute to inflammation, such as ethanol produced by intestinal bacteria. Several intestinal bacteria can produce ethanol. High-alcohol-producing fecal concentrations of *Klebsiella pneumoniae* exist in MASLD patients, MASH patients exhibited higher blood alcohol concentrations, and stool transfer from MASH patients caused MASLD in mice.[103] In another clinical study, MASH patients showed the highest alcohol concentrations in the portal vein, and specifically, Lactobacillaceae were correlated with ethanol production.[104] Therefore, ethanol, with its proinflammatory properties, might also contribute to liver inflammation in MASLD.

Numerous preclinical and clinical studies investigated pre-, pro-, or synbiotics, antimicrobials, bacteriophages, or FMT in MASLD and observed beneficial effects.[105] Many challenges remain in this specific field, as consistency across many clinical studies is lacking, and long-term microbiome-targeting strategies, as needed for such a disease, are not yet available. In summary, evidence is now increasing that gut dysbiosis and affected metabolites are relevant features of various stages of MASLD, including MASH (Figure 1).[106]

ACTIVATION OF INNATE AND ADAPTIVE IMMUNITY: A COMMON PATHWAY OF VARIOUS TRIGGERS

Innate immunity

Whereas many different “hits,” such as lipotoxicity, gut dysbiosis, diet, and genetics, trigger inflammation, all these stressors finally activate innate and adaptive immunity in MASH. PRRs are expressed outside and within the liver, especially on myeloid cells, such as monocytes, macrophages, or dendritic cells, but equally on endothelial or epithelial cells. They are activated by various stressors such as lipids, microbes, and dietary components, causing IL-1β, TNF, and IL-6 production, among many others. Increased expression of proinflammatory cytokines is a hallmark of MASH, and they act either locally or even systemically, depending on the degree of various stimuli.[107] Substantial intrahepatic production of these cytokines triggers an acute-phase reaction, causing the systemic release of various proteins that are detectable in the circulation of people with MASH, such as CRP or ferritin.[17,18] Increased expression of proinflammatory cytokines in the liver results in diverse cellular infiltration, which is further aggravated by chemokine production, again mainly under the control of proinflammatory cytokines, further worsening infiltration with immune cells, including neutrophils. TNF, a crucial cytokine in inflammatory processes, is highly expressed in MASH livers, and its neutralization in mouse models attenuated the disease process.[69,108] IL-1β behaves equally, is highly expressed in MASH livers, and both IL-1$\alpha^{-/-}$ and IL-1$\beta^{-/-}$ mice are protected from hepatic steatosis and liver inflammation.[109–111] Besides inflammatory cytokines, inflammasomes (mediating IL-1β production) constitute another major pathway of innate immunity in MASLD. Mice deficient in NLRP3 are protected from obesity-related inflammation, AT inflammation (ATI), and MASLD.[112] An oral NLRP3 inhibitor used in mice mitigates hepatic steatosis in HFD-induced MASLD.[113] Another important aspect is whether inflammatory pathways differ in early versus later stages of MASLD, as in early stages, lipid-driven inflammation might dominate, whereas in later disease stages, when the intestinal barrier further deteriorates and portal hypertension appears, microbe-driven inflammation might become more relevant.[80] Besides cytokines or inflammasomes, many other components of innate immunity are activated in MASLD, especially hepatic macrophages.[114,115] Other important players are further contributing to MASH, such as mitochondrial dysfunction, oxidative stress, insulin resistance, or ER stress.[6,15,116–118]

Adaptive immunity

Adaptive immunity may be equally important in MASH.[14,114] MASH is associated with dominantly intrahepatic Th1 cells, accompanied by increased IFNγ production,[119] and accumulation of Th17 cells promotes evolution of MASH.[120] Severity of MASH in mice has been correlated with the intrahepatic presence of antigen-presenting cells, such as dendritic cells.[121] Natural killer T (NKT) cells, although considered innate-like and potentially reflecting a cell type of relevance in both innate and adaptive immunity, recognize lipid antigens and are increased in patients with MASH.[122] Liver resident CXCR6^{+}CD8^{+} cells cause liver damage in MASLD mouse models after metabolic activation of the purinergic type 2 receptor P2RX7, proposing a concept of T cell exhaustion or auto-aggression in this disease.[123] In this study, MASH patients exhibited a similar transcriptional signature, and IL-15 was an involved cytokine. Adaptive immunity might be of special importance in MASH-associated HCC. Both in humans and in MASLD mouse models, CD4^{+} T cells are depleted, and this was correlated with increased hepatic HCC development.[124] Another study showed progressive accumulation of exhausted, unconventionally activated CD8^{+}PD1^{+} T cells in mice and human MASH-associated HCC.[125] It is currently unclear how innate and adaptive immunity interact in this disease, and whether adaptive immunity is important in the majority of patients with MASH who exhibit liver inflammation. Several other cytokines detected in MASH livers, besides the classical proinflammatory cytokines such as IL-15 or the IL-1 family cytokine IL-33, are able to activate both innate and adaptive immune processes.[126]

LIPOTOXICITY-MICROBIOTA-IMMUNE CROSSTALK

Multiple interactions exist between lipids and the gut microbiota, in particular affecting via bile acid metabolism, liver

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physiology, and MASLD. Bile acids regulate lipid and glucose homeostasis in the liver and exert immunomodulatory signaling effects affecting inflammation and immunity.[85] An altered microbiota composition, as observed in MASLD, impairs bile acid diversity. Secondary bile acids, produced by gut microbial metabolism of cholesterol, such as hyodeoxycholic acid, improved experimental MASLD by inhibiting FXR and upregulating hepatic CYP7B1.[84] *Bacteroides uniformis* strains are potent producers of 3-succinylated cholic acid via a specific β-lactamase.[83] Via such a pathway, this bile acid alleviated MASH and also upregulated intestinal *Akkermansia muciniphila* growth.[83] Multiple other interactions exist between lipids and microbiota, as the gut microbiota, for example, also regulates the synthesis of sphingolipids such as ceramide.[127,128] Gut *Bacteroides*-derived sphingolipids localize to host epithelial tissue and the portal vein, affecting hepatic ceramide production.[127] Bacterial sphingolipids from *Bacteroides thetaiotaomicron* are able to recover excess hepatic lipid accumulation in a mouse model of hepatic steatosis.[128] Moreover, *Turicibacter* is decreased in human obesity, and an HFD reduces *Turicibacter* colonization in mice.[129] Interestingly, *Turicibacter* suppresses host ceramides, and *Turicibacter*-derived lipids prevent obesity. Interaction between lipids, microbiota, and immunity is also illustrated by various microbial-related metabolites such as isoalloLCA and 2-hydroxy-4-methylpentanoic acid. Odoribacteraceae are effective producers of isoalloLCA,[130] and isoalloLCA suppresses T_H17 cell differentiation by inhibiting retinoic acid receptor-related orphan nuclear receptor-γt.[131] Time-restricted feeding improves MASLD and results in intestinal enrichment of *Ruminococcus torques*, while this bacterium suppresses the intestinal HIF-2α-ceramide pathway via synthesis of 2-hydroxy-4-methylpentanoic acid.[64] Key interactions exist among lipids, the microbiota, and various immune cells, thereby contributing to metabolic disorders such as MASLD.[132–134] Lipids act as metabolic regulators of T_H17 cells and macrophages,[135] and the gut microbiota shapes immunity through broad metabolite production. All these studies and many others illustrate multiple interactions between drivers of MASH, such as lipids, the gut microbiota, and immunity, and highlight the potential for bile acid interventions.

PROINFLAMMATORY DIETS: A SOURCE FOR MASLD/MASH

Various dietary components affect inflammation across organ systems and cause or contribute to chronic diseases.[136] Overwhelming evidence demonstrates that a healthy lifestyle prevents CVD, various cancers, T2D, and MASLD. Diet may have detrimental proinflammatory effects and/or anti-inflammatory health-promoting effects.[137] Whereas many mechanisms might explain detrimental or beneficial effects of diet, it is important to acknowledge that diet is a major determinant of gut microbiota composition over life.[94,138]

Lipids

Many proinflammatory aspects discussed in the section lipotoxicity: a prototypic pathway driving liver inflammation, such as activation of the inflammasome by FFAs, also refer to dietary lipids. The proinflammatory effects of an HFD have been well studied preclinically and in humans. An HFD in healthy volunteers administered for 1 month causes endotoxemia and immune activation.[139] These data suggest that an HFD consumed frequently could contribute to low-grade inflammation. Detection of circulating endotoxin supports an accompanying impaired intestinal epithelial barrier by fat consumption in humans, although so far mainly demonstrated preclinically.[140,141] A prolonged HFD induced intestinal inflammation with increased cytokine synthesis and was reversed experimentally by IL-22.[142] Consumption of saturated milk-derived fatty acids caused colitis, promoted the production of taurine-conjugated bile acids, and resulted in the overgrowth of the pathobiont *Bilophila wadsworthia* in IL-10$^{-/-}$ mice.[143] Such a concept, i.e., propagation of a pathobiont by a diet that promotes disease, is intriguing but has so far not been proven for human liver diseases.

Saccharide consumption

The obesity and MASLD pandemics are also driven by overconsumption of saccharides and carbohydrates. Various mechanistic studies have demonstrated detrimental proinflammatory effects of various monosaccharides. Commensal-specific Th17 cells protected a mouse model against metabolic syndrome by regulating lipid absorption, nicely illustrating the interaction between the diet, immunity, and gut microbiota.[144] High dietary sucrose content depleted Th17 cells, and mechanistically, sugar and ILC3 supported outgrowth of *Faecalibaculum rodentium*, thereby displacing Th17-favoring commensals.[144] The fructose pandemic reflects a major culprit in the global explosion of MASLD in the past two decades. It is not only a potent energy source but is also able to drive specific liver pathologies, including MASH.[145] Fructose, as opposed to glucose, feeds directly into hepatic lipogenesis, escaping insulin-mediated regulation, and excessive fructose triggers barrier dysfunction and the release of TLR agonists from commensals, driving liver inflammation and endotoxemia.[146] Excessive fructose consumption is another example, not only driving lipotoxicity and liver inflammation but also affecting the gut microbiota by promoting proinflammatory strains, such as Proteobacteria and *E. coli*.[147] Fructose-induced hepatic lipogenesis also involves microbiota-derived acetate.[148] Hepatic ER stress driven by excessive fructose intake activates IRE1 and induces expression of the PIDDosome subunits caspase-2, RAIDD, and PIDD1, along with INSIG2, an inhibitor of SCAP-dependent SREBP activation, thereby favoring the transition from simple steatosis to steatohepatitis.[149] The gluconeogenic enzyme fructose-1,6-bisphosphatase 1 (FBP1) controls HCC development in MASH.[150] Overall, excess sugar consumption may contribute substantially to the proinflammatory effects of diet.

Dietary/microbe-regulated proinflammatory metabolites

Gut microbes convert certain nutrients, such as choline or carnitine, into trimethylamine (TMA), which is metabolized in the liver by flavin monooxygenases to TMA *N*-oxide (TMAO).[151] *In vitro*, TMAO enhances platelet responsiveness and thrombosis formation.[152] Whereas evidence is increasing that TMAO levels correlate with CVD,[153] an important role in MASLD is understudied.[154] Phenylacetic acid (see above) is another microbial product

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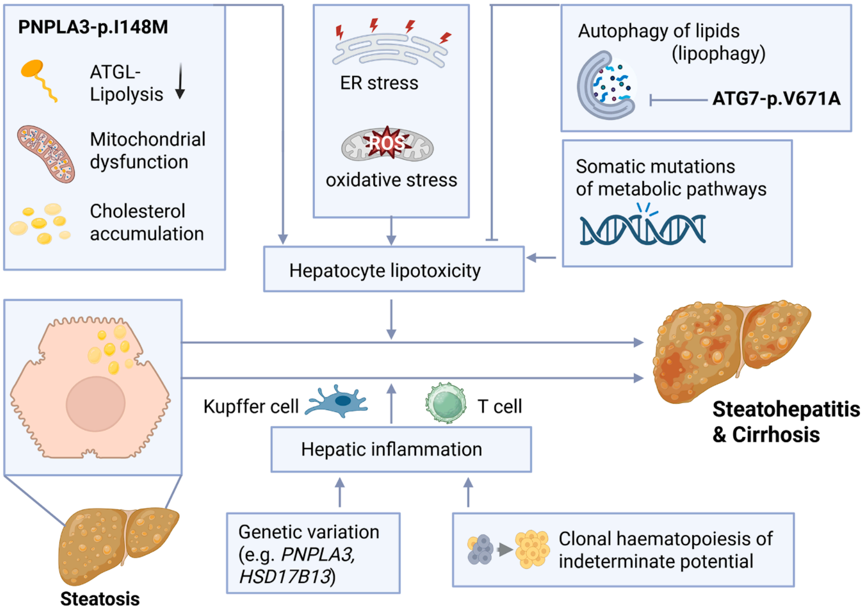

Figure 2. Mechanisms involved in MASLD progression
Host genetics affect hepatocyte lipid metabolism and inflammatory responses of innate and adaptive immunity in MASLD. For example, PNPLA3 variation (I148M) impairs lipolysis and promotes mitochondrial dysfunction and cholesterol accumulation in hepatocytes. Related metabolic stress signaling at the ER and in mitochondria promotes lipogenesis and, consequently, lipotoxicity, thereby promoting steatosis. Somatic mutations further contribute to metabolic perturbation in MASLD. In turn, hepatocyte autophagy of lipids (lipophagy) counteracts lipotoxicity and protects against hepatic inflammation. Innate and adaptive immunity contribute to hepatic inflammation, which is shaped by host genetic variation, clonal hematopoiesis of indeterminate potential, and many other factors. Collectively, complex pleiotropic mechanisms contribute to the progression of liver steatosis to steatohepatitis and cirrhosis.

driving hepatic steatosis.[88] Microbial-derived imidazole propionate, a microbial histidine-derived metabolite, is highly present in the portal vein of people with T2D and affects insulin resistance, although it has so far not been studied in MASH.[155] In a murine model, imidazole propionate causes atherosclerosis, the major complication of human MASLD, interacting with imidazoline-1 receptor, thereby acting proinflammatory, and its serum levels were associated with atherosclerosis in two independent human cohorts.[156]

HOST GENETICS AS A DETERMINANT OF MASLD PROGRESSION

In the past decade, human genetics has revealed that disrupting lipid homeostasis in the hepatocyte determines TG accumulation, which ignites inflammation. However, it is still not clear why some livers tolerate large neutral TG loads, whereas others become inflamed and scarred. Below, we discuss inflammation from common germline variants through rare coding changes, somatic selection, and systemic modifiers (Figure 2).

Lipid-droplet biology orchestrates sterile inflammation

The strongest steatotic liver disease risk allele in all ancestries, PNPLA3 p.I148M, exemplifies the “lipotoxic” paradigm. The mutant protein accumulates on lipid droplets, sterically blocking ATGL-mediated lipolysis and impairing the export of mono- and polyunsaturated fatty acids (PUFAs).[157] *In vivo* tracer studies show lower DNL with a biochemical signature of redox stress that may prime Kupffer and hepatic stellate cells (HSCs) for cytokine release and collagen deposition.[72] A knockin mouse for p.I148M fed an MASH-inducing diet and treated with a *PNPLA3* antisense oligonucleotide shows lower production of *Mcp1*, a cytokine involved in macrophage recruitment, indicating a role of Pnpla3 p.I148M in inducing inflammation.[158] Two phase-1 clinical trials prove that ablation of *PNPLA3* reduces liver fat content and may quench liver inflammation.[159,160] Larger and longer studies are underway to assess the clinical benefits of these approaches.

TM6SF2 p.E167K augments steatosis through VLDL retention and at the same time protects against CVD.[161,162] Carriers of this loss-of-function variant have lower circulating ApoB-containing lipoprotein particles because TM6SF2 has a role in intracellular stabilization of ApoB.[162,163]

MBOAT7 rs641738 increases hepatocyte lipid content by interfering with phosphatidyl-inositol metabolism and fueling TG synthesis by generating its precursors.[164] Interestingly, MBOAT7 deficiency in macrophages alters membrane phospholipid composition with a redistribution of arachidonic acid toward proinflammatory eicosanoids, providing an example of the interaction between lipid species and inflammation.[165]

In contrast, MARC1 p.A165T results in a loss of function due to higher proteasomal degradation.[166] This loss of function reduces oxidative stress by promoting mitochondrial β-oxidation,[167] emphasizing that lowering liver lipid content contributes to quenching inflammation.

In contrast to the lipotoxic variants that dominate SLD genetics, the rs72613567 in *HSD17B13* protects against steatohepatitis, advanced fibrosis, and HCC without affecting liver neutral lipid content. This variant reshapes hepatic phospholipid composition and dampens inflammation by reducing the IL-6 pathway.[168] Mediation analyses suggest that the protective effect of this variant is mediated by reducing the severity of portal inflammation.[169] Human hepatocyte targeted-siRNA trials confirmed that therapeutic inactivation of *HSD17B13* lowers ALT without changes in liver TG content, uncoupling liver TG content from inflammation.[170]

Autophagy and the inflammatory checkpoint

Rare loss-of-function variants in core autophagy genes, especially the ATG7 p.V671A, shift the balance from steatosis toward MASH and HCC.[171] Carriers show no changes in liver-fat

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content, yet transcriptomics reveal intensified TNF-mediated inflammation.[171] Mechanistically, defective *ATG7* reduces lipophagy, preventing safe lipid-droplet disposal,[172] and mitophagy, allowing ROS-leaking mitochondria to accumulate and perpetuate inflammation.[171] The observation that thyroid-hormone analogs restore selective autophagy[173] and reverse MASH fibrosis in clinical trials[174] suggests autophagy as a pharmacologic anti-inflammatory lever.

Somatic adaptation to gluco-lipotoxic stress

Whole-liver deep sequencing of explanted cirrhotic tissue uncovered a pattern of convergent clonal selection for loss-of-function mutations in *GPAM* (a protein resident in the outer mitochondrial membrane) and in *FOXO1* (a pivotal protein for insulin-mediated energy homeostasis).[175,176] Although germline *GPAM* loss protects against MASLD, hepatocytes acquire somatic *GPAM* hits only after fibrosis is established in an adaptive attempt to mitigate lipotoxicity. Similarly, *FOXO1-S22W* somatic mutations lock the transcription factor in its fasting-mimicking conformation, sustaining gluconeogenic efflux from the hepatocyte. Such parallel evolution suggests that chronic stress creates a Darwinian niche in which hepatocytes with metabolic reprogramming compete with their neighbors (Box 1).

LIVER CROSSTALK WITH EXTRAHEPATIC TISSUES CONTRIBUTES TO THE INFLAMMATORY BURDEN IN MASH

Adipose tissue

AT inflammation has emerged as of major importance in obesity and related disorders such as MASLD.[177] The AT contains a plethora of inflammatory mediators and immune cells and constitutes a major organ of inflammation in obesity and related disorders.[178,179] TNF is increased in human obesity and decreases substantially after weight loss.[180] VAT contains three times more IL-6 compared with SAT.[181] Importantly, whole-body AT mass may contribute up to 35% of the body's circulating IL-6 source, proposing a key contribution for an inflamed AT to systemic low-grade inflammation.[182] Visceral fat mass associates directly with the degree of liver inflammation in MASH.[183] Weight loss after bariatric surgery is potently anti-inflammatory, as it almost eliminates TNF, IL-1β, and IL-6 expression in SAT and the liver,[184] and extensive weight loss furthermore decreases serum IL-6 levels, correlating directly with an improvement in insulin resistance,[185] while myeloid cells produce 90% of proinflammatory cytokines in the AT.[186]

Janus kinase 1 (JNK1) drives the expression of AT-derived IL-6, which regulates hepatic insulin signaling and worsens hepatic insulin resistance in a preclinical model.[187] *In vitro* and *in vivo* studies targeting adipocyte-specific adenosine A2AR by a specific agonist massively decreased VAT inflammation and reduced subsequent hepatic and cardiac dysfunction after an HFD.[188] The adipokine neuregulin-4 (Nrg4) is induced in the AT via exercise and knockdown of adipose Nrg4, as well as hepatic deletion of its receptor, negatively affecting MASLD via a cGAS-STING pathway.[189] AT macrophage-derived small extracellular vesicles drive liver fibrosis in a murine MASH model via release of the microRNA (miR)-155 and miR-34a, supporting a role for a proinflammatory AT-liver axis.[190] In addition, several clinical reports have addressed the important role of the AT in MASLD. VAT and SAT exhibit increased expression of inflammatory genes in MASH, and an inflammatory signature of five AT genes predicted liver disease severity.[191] In the FLINT trial (assessing obeticholic acid against MASH), participants with more pronounced reduction of deep SAT and potentially VAT exhibited a higher rate of histological improvements, including lobular inflammation.[192] Using single-cell analysis, multiple AT macrophage populations were characterized in VAT of MASH patients, while AT macrophage dysfunction was associated with loss of AT vascular integrity and degree of liver disease.[193] Despite the descriptive nature of these clinical reports, they support a relevant AT-liver axis in MASLD. Besides classical cytokines, key adipokines such as adiponectin or leptin are also of major relevance in the AT-liver axis in MASLD.[179,194] Many AT-derived factors, from various lipids to cytokines, may therefore affect distant organs and contribute to systemic and hepatic pathologies.

Liver inflammation and hepatic outcomes

In MASLD, the fibrosis stage is related to liver outcomes, including decompensation, HCC, and liver-specific mortality.[195,196] Whether inflammation-independent liver fibrosis exists cannot be answered currently, as many diverse mechanisms are involved in fibrosis development,[19] in which fibrogenic myofibroblasts are considered of critical importance.[197] These cells interact with various parenchymal and non-parenchymal liver cells and either receive inflammatory signals or produce them and secrete substantial other factors, including chemokines or also inhibitors of matrix degradation.[15] With respect to inflammation, especially transforming growth factor β (TGFβ) or platelet-derived growth factor (PDGF), reflect key players who are released mainly by myeloid cells and endothelial cells, commonly under the control of proinflammatory cytokines, DAMPs, PAMPs, or toxic lipids.[15] Overwhelming evidence has been generated over the years in MASLD models (and others) showing that proinflammatory cytokines (e.g., IL-1β, TNF, or IL-17) and inflammasomes (e.g., NLRP3), mainly via NF-κB activation, crucially regulate liver fibrosis and activate HSCs.[198–201] IL-11 reflects another recent example causing lipotoxicity, inflammation, and liver fibrosis in murine MASH and even extending health- and lifespan in mammals.[202,203] These preclinical studies warrant clinical research to be translated to human MASLD.

When liver disease progresses, fibrosis may emerge, leading to advanced fibrosis, liver cirrhosis, and finally HCC.[204,205] In some studies, MASLD now appeared a leading cause of HCC.[206] Indeed, preclinical evidence is supportive that inflammatory cytokines such as IL-6 are involved in this process. Obesity-driven HCC development depends on IL-6 and TNF, as shown in dietary and genetic MASLD models involving NF-kB activation.[207] The IL-6-related transcription factors signal transducer and activator of transcription 1 and 3 (STAT1, STAT3) also regulate obesity-related MASH and HCC.[208] Liver cancer progenitor cells progress toward HCC in an IL-6-dependent manner.[209] Overall evidence is substantial that inflammation-driven fibrogenesis leads to all known detrimental liver outcomes, including cirrhosis and HCC.

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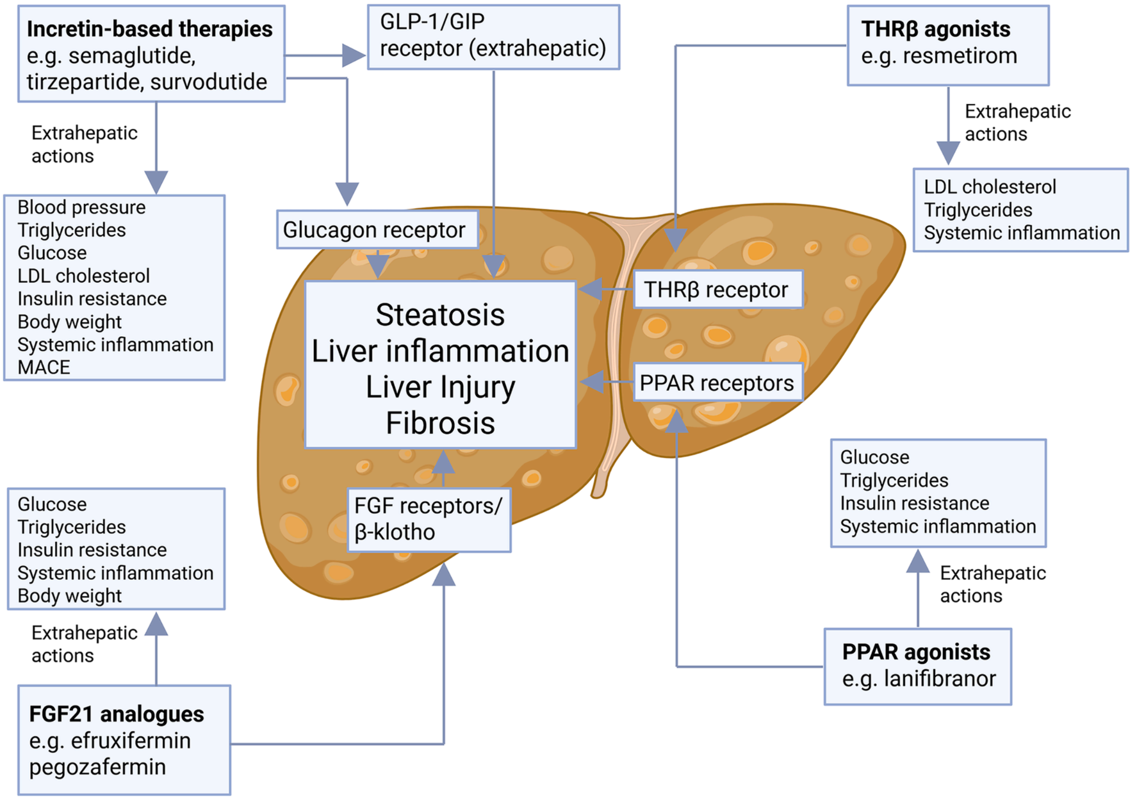

Figure 3. Emerging therapies tackling MASLD

Diverse pharmacologic therapies are emerging in phase II and phase III clinical trials to treat metabolic liver disease and specifically to reverse steatosis, liver inflammation, injury, and fibrosis. These therapies have direct actions on the liver through specific receptors that control hepatic metabolism and inflammation; however, these therapies also have extrahepatic effects on systemic metabolism and inflammation. Notably, GLP-1Rs and GIP receptors are arguably not expressed in the human liver, suggesting that the beneficial effects of these drugs on the liver are indirect. Collectively, recent and ongoing clinical trials will substantially improve the treatment of MASLD in the future while also conveying beneficial systemic effects in patients with cardiometabolic co-morbidities, e.g., a reduction in major adverse cardiovascular events (MACEs).

Extrahepatic outcomes

CVDs

Extrahepatic complications are the leading factors in MASLD-related mortality,[23–25] and metabolic inflammation, i.e., low-grade inflammation or metaflammation,[210] might play a key role. This type of chronic smoldering inflammation is observed in many metabolic disorders, including T2D, obesity, MASLD, and atherosclerosis.[38] Levels of high-sensitivity C-reactive protein (hsCRP) correlate with cardiovascular and malignancy-related mortality in MASLD.[211] The landmark CANTOS study neutralizing IL-1β demonstrated a reduction in hsCRP levels and improved clinical outcomes, such as myocardial infarction and stroke, proving the importance of metabolic inflammation in atherosclerosis.[212] There might also exist a cardiac-hepatic inflammatory axis, as myocardial infarction preclinically and in a clinical study worsened progression of MASLD, potentially mediated via increased circulating Ly6C^{hi} monocytes migrating to the liver and cardiac periostin.[213] The importance of assessing the clinical implications of CVD in MASLD is now emerging.[214,215] Cholesterol-independent inflammation is increasingly recognized in atherosclerosis, suggesting that, in addition to cholesterol, other factors contribute to vessel inflammation, e.g., microbial components or diet.[156,216]

Extrahepatic cancers

Chronic inflammation and cancer are highly intertwined by many mechanisms.[217] A key role for obesity as a cancer driver is also substantiated by bariatric surgery studies, in which death rates from CVD and cancer decreased.[218,219] MASLD is associated with a higher rate of extrahepatic cancers, especially gastrointestinal cancers, breast cancer, and gynecological cancers, affecting survival.[8,220,221] MASLD shows, independent of obesity, a 2-fold higher rate of extrahepatic cancers.[222] When assessing data from the National Health and Nutrition Examination Survey (NHANES) cohorts, MASLD patients with higher systemic inflammatory burden had a substantially higher rate of cancers and all-cause mortality independent of BMI, age, or race, suggesting an important role for systemic inflammation.[223] A key role for inflammation in cancer development also came from the CANTOS study, in which canakinumab treatment significantly reduced incident lung cancer.[224] In conclusion, evidence is accumulating that chronic systemic inflammation contributes to cancer development.

TREATMENT OPPORTUNITIES IN MASH

In this section, we will review therapies for MASH-related fibrosis that are in phase 3 clinical development, including resmetirom,

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semaglutide, survodutide, tirzepatide, lanifibranor, efruxifermin, and pegozafermin (Figure 3). These therapies mostly act pleiotropically and also exert anti-inflammatory effects, as regulatory requirements for effective therapies request resolution of MASH and improvement of fibrosis.[225] Importantly, these medical therapies are combined with lifestyle intervention, i.e., physical exercise with recommendations for a healthy diet—cornerstones of MASLD treatment. We refer the reader to other reviews that provide a much more in-depth assessment of current and emerging therapeutic drug development in MASH-related fibrosis.[226,227]

Thyroid hormone receptor beta agonist

There are several thyroid hormone receptor beta (THR-β) agonists in clinical development for MASH-related fibrosis. Resmetirom, an oral, liver-directed, once-daily THR-β agonist, is FDA approved under subpart H for conditional use in patients with MASH with moderate to advanced fibrosis without cirrhosis. A 52-week treatment with 100 or 80 mg resmetirom was better than placebo for improving fibrosis and MASH resolution.[174] Further studies are underway to assess predictors of response to resmetirom and when to stop resmetirom and when to consider adding other therapies or switching therapies in MASH-related fibrosis.

Incretin-based therapies

Semaglutide is a glucagon-like-peptide-1 receptor agonist (GLP-1RA) that is clinically approved for the management of T2D and/or obesity and has been studied in patients with biopsy-proven MASH with stage 2–3 fibrosis.[228] In a recently published phase 3 trial, a 72-week treatment with 2.4 mg weekly subcutaneous injections of semaglutide was better than placebo in improving fibrosis and MASH resolution.[229] Importantly, hepatocytes and HSC do not express GLP-1 or GIP receptors,[230] such that semaglutide indirectly acts on the liver, for example, by weight loss and blockade of FFA trafficking to hepatocytes. The effect of GLP-1 analogs may be lower in those with the PNPLA3 genotype.[228]

Survodutide, a dual GLP-1 and glucagon-receptor agonist, leads to activation of both GLP-1Rs and glucagon receptors, which is associated with weight loss; increased energy expenditure; greater liver fat reduction due to direct action of glucagon on the hepatocytes, inducing gluconeogenesis; and improved insulin resistance with continued use due to GLP-1 agonism.[231] Glucagon receptors are widely expressed on hepatocytes. Most dual agonists lead to greater liver fat reduction when compared with GLP-1 agonists alone.[232] In a recent phase 2b trial, a 48-week treatment with survodutide was better than placebo in improving fibrosis and MASH resolution.[233] Survodutide has now moved on to a phase 3 trial to examine its efficacy in improving long-term clinical outcomes.

Tirzepatide, a dual GLP-1 and gastric inhibitory polypeptide (GIP) agonist, is clinically approved for the treatment of T2D mellitus and obesity and is currently being investigated for MASH-related fibrosis. The dual mechanism of action of tirzepatide leads to greater weight loss than seen with semaglutide alone. In a recent phase 2b trial, a 52-week treatment with tirzepatide was better than placebo in improving fibrosis and MASH resolution.[234]

Retatrutide is a triple agonist including the glucose-dependent insulinotropic polypeptide, GLP-1, and glucagon receptors, all combined in one formulation. In phase 2b trials in obesity, retatrutide has been shown to provide weight loss of up to 24%, which is significantly greater than what is seen by either semaglutide or tirzepatide alone. In a substudy, a 24-week treatment with retatrutide led to normalization of liver fat content by MRI-PDFF in very high percentages.[235]

Further studies are underway to better understand the mechanistic pathways underlying improvements in liver fibrosis and MASH resolution by various incretin-based therapies. One key issue that is not yet fully understood is the muscle loss associated with weight loss seen with GLP-1 agonists and whether dual or triple agonists have a differential profile in the relative amounts of muscle versus AT weight loss. Sarcopenia is a major risk factor in patients with cirrhosis and may increase the risk of decompensation; hence, careful assessment and monitoring are needed among those with established cirrhosis and use of these agents.

PPAR agonists

Lanifibranor, an oral pan-peroxisome proliferator-activated receptor (P-PAR) agonist, is being developed for the treatment of MASH-related fibrosis. In a recent phase 2b trial, a 24-week treatment with either 1,200 or 800 mg lanifibranor was better than placebo in improving both MASH resolution and fibrosis.[236] Phase 3 trials are underway to assess its long-term efficacy in improving liver-related morbidity and mortality.

Fibroblast growth factor (FGF)-21 analogs

FGF-21 is a pleiotropic hormone primarily produced by the liver that regulates energy homeostasis and lipid and glucose metabolism.[237] It is released during starvation and is associated with fat oxidation in the liver and improves insulin sensitivity in the liver. FGF-21 not only has peripheral action in the liver but also has central action primarily in the hippocampus and may have an important role in crosstalk between the adipocyte-liver-brain axis.[238] Recent data suggest that FGF-21 agonism may be beneficial not only in improving metabolic dysfunction in the liver but also in craving due to alcohol and carbohydrate preference. These data have ignited new research across the spectrum of steatotic liver disease, ranging from MASLD and MASH to metALD and ALD.[238–240]

Efruxifermin, a bivalently Fc-FGF-21 analog, is being developed for treatment of MASH-related fibrosis and cirrhosis. In a phase 2b trial among patients with MASH with stage 2 or 3 fibrosis, a 24-week treatment with efruxifermin was better than placebo in improving fibrosis and MASH-related inflammation.[241] A phase 2b trial among patients with cirrhosis due to MASH randomized them to either efruxifermin or placebo over 96 weeks. Efruxifermin, either at 28 or 50 mg once weekly, was better than placebo in improving fibrosis over 96 weeks of treatment.[242]

Pegozafermin, a long-acting glycol-pegylated form of FGF-21 analog, is in clinical development for MASH-related fibrosis, cirrhosis, and severe hypertriglyceridemia. In a recent phase 2b trial, a 24-week treatment with pegozafermin was better than placebo in improving fibrosis and causing MASH resolution.[243] Phase 3 trials are underway to examine long-term clinical

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Table 1. Anti-inflammatory activities of resmetirom, GLP-1RAs, PPAR agonists, and FGF-21 analogs

Drug	Primary target	Suppression of NF-κB and proinflammatory cytokines (TNF, IL-1, IL-6)	Induction of IL-10/adiponectin (anti-inflammatory pathways)	Decrease in circulating hsCRP (human studies)	MASH resolution + fibrosis improvement (human studies)
Resmetirom	THR-β	+	+	?	+
GLP-1RAs (e.g., semaglutide)	GLP-1R	+	+	+	+
PPAR agonists (lanifibranor)	nuclear PPAR receptors	+	+	+	+
FGF-21 analogs	FGFR1c + β-klotho	+	+	?	+

hsCRP, high-sensitivity C-reactive protein; FGF, fibroblast growth factor; FGFR1c, fibroblast growth factor receptor 1; GLP-1R, glucagon-like peptide-1 receptor; GLP-1RA, glucagon-like peptide receptor agonist; NF-κB, nuclear factor kappa B; THR-β, thyroid hormone receptor beta.

benefits of efruxifermin and pegozafermin in improving liver-related morbidity and mortality. There are several other FGF-21 analogs (such as efimosfermin) that are also in clinical development with promising results and likely to advance to larger phase 2b/3 trials in the future.[244]

HOW CURRENT THERAPIES FOR MASH AFFECT INFLAMMATION

It is commonly accepted that approved and currently investigated drugs for MASH act in a pleiotropic manner, affecting diverse metabolic pathways and also exerting anti-inflammatory effects. As discussed in this article, inflammatory pathways are of crucial importance in this disease. Although classical anti-inflammatory drugs used in many immune-mediated disorders, such as anti-cytokine drugs, might not be suitable candidates for MASH treatment, an effective MASH treatment is supposed to target primarily metabolic pathways besides acting anti-inflammatorily. Indeed, as outlined here, several MASH drugs effectively target inflammation (Table 1).

Resmetirom acts through its selective agonism of THR-β in hepatocytes, resulting in various downstream effects relevant to MASH. It inhibits activation of STAT3 and NF-κB pathways, thereby reducing macrophage infiltration and production of proinflammatory cytokines in murine MASH livers.[245] These activities were dependent on regulator of G protein signaling 5 (RGS5), which is downregulated in murine MASH and upregulated by resmetirom.[245] Resmetirom may suppress inflammation by mirroring TRH-β-mediated restoration of autophagy,[173] and indeed, in a phase 2 trial, this drug lowered serum levels of cytokeratin-18 fragments and, importantly, increased serum levels of the anti-inflammatory adipokine adiponectin.[246] Resmetirom directly improves mitochondrial function in the liver by activating β-oxidation, which is likely to be beneficial in individuals with MASH-related fibrosis regardless of PNPLA3 genotype.[247] Via such mechanisms, resmetirom reduces hepatic steatosis, which reflects a key driver of inflammation and fibrosis in MASH.

Incretin-based therapies such as semaglutide reduce systemic and tissue inflammation through various mechanisms, also independent of weight loss.[248] Multiple GLP-1RAs reduce serum hsCRP levels, an acute phase reactant produced by hepatocytes under the control of the pro-inflammatory cytokines TNF, IL-1, and IL-6.[248,249] Even a single dose of exenatide or semaglutide suppressed endotoxin-induced TNF in mice.[250] GLP-1RAs suppress NF-κB, JNK, and the NLRP3 inflammasome, which results in decreased expression and production of proinflammatory cytokines.[251] In accordance with a strong anti-inflammatory impact, GLP-1RAs such as exendin-4 promote the synthesis of the anti-inflammatory cytokine IL-10[252] and adiponectin.[179,253] Agonism of GLP-1R also affects macrophage biology and promotes the induction of M2 polarization commonly associated with protective and anti-inflammatory activities.[254] Suppression of systemic TNF by GLP-1R agonism also involves α1-adrenergic, δ-opioid, and κ-opioid receptor signaling in the central nervous system.[255] In endothelial cells, GLP-1RAs activate AMPK and reduce, by various mechanisms, expression of inflammatory adhesion molecules such as VCAM-1 or E-selectin monocyte activation, and thereby attenuate vascular inflammation.[256] Semaglutide also suppresses ATI in preclinical models.[257] Numerous preclinical experimental models have convincingly demonstrated anti-inflammatory activities of GLP-1RAs.[248] Importantly, a recent study demonstrated not only that semaglutide improved inflammation and fibrosis in murine MASLD models but also observed via aptamer-based proteomic analyses of serum samples from patients being treated with this drug that 72 proteins were significantly correlated with MASH resolution.[258] Most of these 72 proteins were related to metabolism, inflammation, and fibrosis, highlighting the importance of these pathways in this disease.[258] Collectively, GLP-1RAs and potentially other incretins (not discussed here) act as immunometabolic modulators affecting both metabolic and many inflammatory pathways relevant to various metabolic disorders, including MASH.

Lanifibranor interacts with various metabolic, inflammatory, and fibrogenic pathways in preclinical MASH models.[259] This drug attenuated hepatic inflammatory infiltration and proinflammatory cytokine activation in preclinical MASH models[260] and positively affected cardiometabolic health in MASH patients and increased circulating adiponectin concentrations.[261]

FGF-21 analogs also exert several anti-inflammatory activities. They potently suppress gluco-lipotoxicity and inflammatory processes.[262] FGF-21 and its analogs suppress NF-κB, decrease synthesis of proinflammatory cytokines, and induce IL-10.[263] Anti-inflammatory effects of FGF-21 have been

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observed in various tissues, including the liver and preclinical models of MASH.[264] FGF-21 analogs efficiently suppress hepatic and ATI, and these effects are β-klotho dependent and include suppression of oxidative stress and modulation of the inflammatory response.[265] Collectively, it may be assumed that anti-inflammatory activities are crucial for most clinically beneficial MASH drugs and therefore reflect an important feature of their pleiotropic nature (Box 1).

CONCLUSIONS AND FUTURE DIRECTIONS

Inflammation plays a crucial role in most liver diseases, and evidence is now accumulating that both innate and adaptive immune pathways contribute to intrahepatic and extrahepatic features of this disease. It is accepted that MASLD is not an isolated liver disease but a complex syndrome promoted by environmental cues such as diet and related microbial perturbation. Despite recent advances, it remains unclear why approximately 20% of the MASLD population develops MASH, identification of additional genetic factors might also be of importance, and the definition of preclinical mouse models suitable for such investigations might help in the future.[266,267]

Future research directions must address unresolved issues in MASLD. Initial studies have now demonstrated that polygenic risk scores and multiomic analysis might enable identification of different disease subtypes with more aggressive liver disease or more dominant extrahepatic disease manifestation.[268] The recent advent of single-cell/spatial technologies will allow deciphering of the heterogeneity of the liver immune microenvironment and also further definition of subtype disease classification.[269–271] The contribution of the gut microbiota and related metabolites at various stages will need many more robust clinical studies, potentially enabling us to prove the relevance of certain metabolites, as demonstrated for imidazole propionate in atherosclerosis.[156] It is also important to elucidate in the future causal interactions between lipotoxicity and the gut microbiota validated through respective clinical trials, as recently shown for THR-β agonists.[272]

An effective future therapy for MASH should not only be able to decrease or eliminate causative stressors, such as proinflammatory lipids, but ideally might also exert pleiotropic anti-inflammatory actions to limit the systemic inflammatory burden. Various currently investigated drugs, such as GLP-1RAs, have demonstrated such pleiotropic anti-inflammatory activities.[258,273] Furthermore, besides effective new drugs, adaptation of lifestyle with a healthy diet and exercise acts potently anti-inflammatory.[136,274] However, targeted dietary interventions specific to MASLD are understudied yet essential for long-term management; for instance, a Mediterranean diet appears favorable, especially with regard to CVD. Based on the importance of inflammation and subsequent fibrosis for the outcome of MASH, it is also obvious that, besides targeting inflammatory/fibrotic pathways, efficient targeting of disease-causing metabolic pathways seems most crucial for the management of MASH.[225,275] The field is now advancing rapidly, and an improved understanding of underlying disease mechanisms might lead to new therapies and better management of this global pandemic disorder.

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REFERENCES

1. Israelsen, M., Francque, S., Tsochatzis, E.A., and Krag, A. (2024). Steatotic liver disease. Lancet *404*, 1761–1778. https://doi.org/10.1016/S0140-6736(24)01811-7.
2. Tilg, H., Petta, S., Stefan, N., and Targher, G. (2026). Metabolic dysfunction-associated steatotic liver disease in adults: a review. JAMA *335*, 163–174. https://doi.org/10.1001/jama.2025.19615.
3. Huang, D.Q., Wong, V.W.S., Rinella, M.E., Boursier, J., Lazarus, J.V., Yki-Järvinen, H., and Loomba, R. (2025). Metabolic dysfunction-associated steatotic liver disease in adults. Nat. Rev. Dis. Primers *11*, 14. https://doi.org/10.1038/s41572-025-00599-1.
4. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO) (2024). EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J. Hepatol. *81*, 492–542. https://doi.org/10.1016/j.jhep.2024.04.031.
5. Singh, S., Allen, A.M., Wang, Z., Prokop, L.J., Murad, M.H., and Loomba, R. (2015). Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin. Gastroenterol. Hepatol. *13*, 643–654.e1. https://doi.org/10.1016/j.cgh.2014.04.014.
6. Loomba, R., Friedman, S.L., and Shulman, G.I. (2021). Mechanisms and disease consequences of nonalcoholic fatty liver disease. Cell *184*, 2537–2564. https://doi.org/10.1016/j.cell.2021.04.015.
7. Romeo, S., Vidal-Puig, A., Husain, M., Ahima, R., Arca, M., Bhatt, D.L., Diehl, A.M., Fontana, L., Foo, R., Frühbeck, G., et al. (2025). Clinical staging to guide management of metabolic disorders and their sequelae: a European Atherosclerosis Society consensus statement. Eur. Heart J. *46*, 3685–3713. https://doi.org/10.1093/eurheartj/ehaf314.
8. Targher, G., Byrne, C.D., and Tilg, H. (2024). MASLD: a systemic metabolic disorder with cardiovascular and malignant complications. Gut *73*, 691–702. https://doi.org/10.1136/gutjnl-2023-330595.
9. Rinella, M.E., Lazarus, J.V., Ratziu, V., Francque, S.M., Sanyal, A.J., Kanwal, F., Romero, D., Abdelmalek, M.F., Anstee, Q.M., Arab, J.P., et al. (2023). A multisociety Delphi consensus statement on new fatty liver disease nomenclature. J. Hepatol. *79*, 1542–1556. https://doi.org/10.1016/j.jhep.2023.06.003.

Please cite this article in press as: Tilg et al., The many pathways driving liver inflammation in MASH, Cell Metabolism (2026), https://doi.org/10.1016/j.cmet.2026.02.018

10. Arab, J.P., Díaz, L.A., Rehm, J., Im, G., Arrese, M., Kamath, P.S., Lucey, M.R., Mellinger, J., Thiele, M., Thursz, M., et al. (2025). Metabolic dysfunction and alcohol-related liver disease (MetALD): Position statement by an expert panel on alcohol-related liver disease. J. Hepatol. *82*, 744–756. https://doi.org/10.1016/j.jhep.2024.11.028.
11. Diaz, L.A., Ajmera, V., Arab, J.P., Huang, D.Q., Hsu, C., Lee, B.P., Louvet, A., Thiele, M., Tavaglione, F., Tincopa, M., et al. (2025). An expert consensus Delphi panel in metabolic dysfunction- and alcohol-associated liver disease: opportunities and challenges in clinical practice. Clin. Gastroenterol. Hepatol. *24*, 633–645.e4. https://doi.org/10.1016/j.cgh.2025.02.017.
12. Carli, F., Della Pepa, G., Sabatini, S., Vidal Puig, A., and Gastaldelli, A. (2024). Lipid metabolism in MASLD and MASH: From mechanism to the clinic. JHEP Rep 6. JHEP Rep. *6*, 101185. https://doi.org/10.1016/j.jhepr.2024.101185.
13. Kubes, P., and Mehal, W.Z. (2012). Sterile inflammation in the liver. Gastroenterology *143*, 1158–1172. https://doi.org/10.1053/j.gastro.2012.09.008.
14. Tilg, H., Adolph, T.E., Dudek, M., and Knolle, P. (2021). Non-alcoholic fatty liver disease: the interplay between metabolism, microbes and immunity. Nat. Metab. *3*, 1596–1607. https://doi.org/10.1038/s42255-021-00501-9.
15. Horn, P., and Tacke, F. (2024). Metabolic reprogramming in liver fibrosis. Cell Metab. *36*, 1439–1455. https://doi.org/10.1016/j.cmet.2024.05.003.
16. Zimmermann, E., Anty, R., Tordjman, J., Verrijken, A., Gual, P., Tran, A., Iannelli, A., Gugenheim, J., Bedossa, P., Francque, S., et al. (2011). C-reactive protein levels in relation to various features of non-alcoholic fatty liver disease among obese patients. J. Hepatol. *55*, 660–665. https://doi.org/10.1016/j.jhep.2010.12.017.
17. Pihlajamäki, J., Kuulasmaa, T., Kaminska, D., Simonen, M., Kärjä, V., Grönlund, S., Käkelä, P., Pääkkönen, M., Kainulainen, S., Punnonen, K., et al. (2012). Serum interleukin 1 receptor antagonist as an independent marker of non-alcoholic steatohepatitis in humans. J. Hepatol. *56*, 663–670. https://doi.org/10.1016/j.jhep.2011.10.005.
18. Armandi, A., Sanavia, T., Younes, R., Caviglia, G.P., Rosso, C., Govaere, O., Liguori, A., Francione, P., Gallego-Duràn, R., Ampuero, J., et al. (2024). Serum ferritin levels can predict long-term outcomes in patients with metabolic dysfunction-associated steatotic liver disease. Gut *73*, 825–834. https://doi.org/10.1136/gutjnl-2023-330815.
19. Schwabe, R.F., Tabas, I., and Pajvani, U.B. (2020). Mechanisms of fibrosis development in nonalcoholic steatohepatitis. Gastroenterology *158*, 1913–1928. https://doi.org/10.1053/j.gastro.2019.11.311.
20. Peiseler, M., Schwabe, R., Hampe, J., Kubes, P., Heikenwälder, M., and Tacke, F. (2022). Immune mechanisms linking metabolic injury to inflammation and fibrosis in fatty liver disease - novel insights into cellular communication circuits. J. Hepatol. *77*, 1136–1160. https://doi.org/10.1016/j.jhep.2022.06.012.
21. Calès, P., Canivet, C.M., Costentin, C., Lannes, A., Oberti, F., Fouchard, I., Hunault, G., de Lédinghen, V., and Boursier, J. (2025). A new generation of non-invasive tests of liver fibrosis with improved accuracy in MASLD. J. Hepatol. *82*, 794–804. https://doi.org/10.1016/j.jhep.2024.11.049.
22. Jayakumar, S., Middleton, M.S., Lawitz, E.J., Mantry, P.S., Caldwell, S.H., Arnold, H., Mae Diehl, A., Ghalib, R., Elkhashab, M., Abdelmalek, M.F., et al. (2019). Longitudinal correlations between MRE, MRI-PDFF, and liver histology in patients with non-alcoholic steatohepatitis: Analysis of data from a phase II trial of selonsertib. J. Hepatol. *70*, 133–141. https://doi.org/10.1016/j.jhep.2018.09.024.
23. Ekstedt, M., Franzén, L.E., Mathiesen, U.L., Thorelius, L., Holmqvist, M., Bodemar, G., and Kechagias, S. (2006). Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology *44*, 865–873. https://doi.org/10.1002/hep.21327.
24. Libby, P., Ridker, P.M., and Hansson, G.K.; Leducq; Transatlantic Network; Atherothrombosis (2009). Inflammation in atherosclerosis: from pathophysiology to practice. J. Am. Coll. Cardiol. *54*, 2129–2138. https://doi.org/10.1016/j.jacc.2009.09.009.
25. Dulai, P.S., Singh, S., Patel, J., Soni, M., Prokop, L.J., Younossi, Z., Sebastiani, G., Ekstedt, M., Hagstrom, H., Nasr, P., et al. (2017). Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. Hepatology *65*, 1557–1565. https://doi.org/10.1002/hep.29085.
26. Iturbe-Rey, S., Maccali, C., Arrese, M., Aspichueta, P., Oliveira, C.P., Castro, R.E., Lapitz, A., Izquierdo-Sanchez, L., Bujanda, L., Perugorria, M.J., et al. (2025). Lipotoxicity-driven metabolic dysfunction-associated steatotic liver disease (MASLD). Atherosclerosis *400*, 119053. https://doi.org/10.1016/j.atherosclerosis.2024.119053.
27. Ali, S.M.J., and Lai, M. (2025). Metabolic dysfunction-associated steatotic liver disease. Ann. Intern. Med. *178*, ITC1–ITC16. https://doi.org/10.7326/ANNALS-24-02933.
28. Yamaguchi, K., Yang, L., McCall, S., Huang, J., Yu, X.X., Pandey, S.K., Bhanot, S., Monia, B.P., Li, Y.X., and Diehl, A.M. (2007). Inhibiting triglyceride synthesis improves hepatic steatosis but exacerbates liver damage and fibrosis in obese mice with nonalcoholic steatohepatitis. Hepatology *45*, 1366–1374. https://doi.org/10.1002/hep.21655.
29. Rong, S., Xia, M., Vale, G., Wang, S., Kim, C.W., Li, S., McDonald, J.G., Radhakrishnan, A., and Horton, J.D. (2024). DGAT2 inhibition blocks SREBP-1 cleavage and improves hepatic steatosis by increasing phosphatidylethanolamine in the ER. Cell Metab. *36*, 617–629.e7. https://doi.org/10.1016/j.cmet.2024.01.011.
30. Yu, X.X., Murray, S.F., Pandey, S.K., Booten, S.L., Bao, D., Song, X.Z., Kelly, S., Chen, S., McKay, R., Monia, B.P., et al. (2005). Antisense oligonucleotide reduction of DGAT2 expression improves hepatic steatosis and hyperlipidemia in obese mice. Hepatology *42*, 362–371. https://doi.org/10.1002/hep.20783.
31. Loomba, R., Morgan, E., Watts, L., Xia, S., Hannan, L.A., Geary, R.S., Baker, B.F., and Bhanot, S. (2020). Novel antisense inhibition of diacylglycerol O-acyltransferase 2 for treatment of non-alcoholic fatty liver disease: a multicentre, double-blind, randomised, placebo-controlled phase 2 trial. Lancet Gastroenterol. Hepatol. *5*, 829–838. https://doi.org/10.1016/S2468-1253(20)30186-2.
32. Loomba, R., Morgan, E., Yousefi, K., Li, D., Geary, R., Bhanot, S., and Alkhouri, N.; ION224-CS2 Investigators (2025). Antisense oligonucleotide DGAT-2 inhibitor, ION224, for metabolic dysfunction-associated steatohepatitis (ION224-CS2): results of a 51-week, multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet *406*, 821–831. https://doi.org/10.1016/S0140-6736(25)00979-1.
33. Choi, C.S., Savage, D.B., Kulkarni, A., Yu, X.X., Liu, Z.X., Morino, K., Kim, S., Distefano, A., Samuel, V.T., Neschen, S., et al. (2007). Suppression of diacylglycerol acyltransferase-2 (DGAT2), but not DGAT1, with antisense oligonucleotides reverses diet-induced hepatic steatosis and insulin resistance. J. Biol. Chem. *282*, 22678–22688. https://doi.org/10.1074/jbc.M704213200.
34. Calle, R.A., Amin, N.B., Carvajal-Gonzalez, S., Ross, T.T., Bergman, A., Aggarwal, S., Crowley, C., Rinaldi, A., Mancuso, J., Aggarwal, N., et al. (2021). ACC inhibitor alone or co-administered with a DGAT2 inhibitor in patients with non-alcoholic fatty liver disease: two parallel, placebo-controlled, randomized phase 2a trials. Nat. Med. *27*, 1836–1848. https://doi.org/10.1038/s41591-021-01489-1.
35. Morrow, M.R., Batchuluun, B., Wu, J., Ahmadi, E., Leroux, J.M., Mohammadi-Shemirani, P., Desjardins, E.M., Wang, Z., Tsakiridis, E.E., Lavoie, D.C.T., et al. (2022). Inhibition of ATP-citrate lyase improves NASH, liver fibrosis, and dyslipidemia. Cell Metab. *34*, 919–936.e8. https://doi.org/10.1016/j.cmet.2022.05.004.
36. Gautam, J., Wu, J., Lally, J.S.V., McNicol, J.D., Fayyazi, R., Ahmadi, E., Oniciu, D.C., Heaton, S., Newton, R.S., Rehal, S., et al. (2025). ACLY inhibition promotes tumour immunity and suppresses liver cancer. Nature *645*, 507–517. https://doi.org/10.1038/s41586-025-09297-0.
37. Cheng, D., Zinker, B.A., Luo, Y., Shipkova, P., De Oliveira, C.H., Krishna, G., Brown, E.A., Boehm, S.L., Tirucherai, G.S., Gu, H., et al. (2022). MGAT2 inhibitor decreases liver fibrosis and inflammation in murine NASH models and reduces body weight in human adults with obesity. Cell Metab. *34*, 1732–1748.e5. https://doi.org/10.1016/j.cmet.2022.10.007.
38. Libby, P. (2021). The changing landscape of atherosclerosis. Nature *592*, 524–533. https://doi.org/10.1038/s41586-021-03392-8.

Please cite this article in press as: Tilg et al., The many pathways driving liver inflammation in MASH, Cell Metabolism (2026), https://doi.org/10.1016/j.cmet.2026.02.018

39. Björkegren, J.L.M., and Lusis, A.J. (2022). Atherosclerosis: Recent developments. Cell *185*, 1630–1645. https://doi.org/10.1016/j.cell.2022.04.004.

40. Zhang, L., Shi, Y., Liang, B., and Li, X. (2024). An overview of the cholesterol metabolism and its proinflammatory role in the development of MASLD. Hepatol. Commun. *8*, e0434. https://doi.org/10.1097/HC9.0000000000000434.

41. Marí, M., Caballero, F., Colell, A., Morales, A., Caballeria, J., Fernandez, A., Enrich, C., Fernandez-Checa, J.C., and García-Ruiz, C. (2006). Mitochondrial free cholesterol loading sensitizes to TNF- and Fas-mediated steatohepatitis. Cell Metab. *4*, 185–198. https://doi.org/10.1016/j.cmet.2006.07.006.

42. Min, H.K., Kapoor, A., Fuchs, M., Mirshahi, F., Zhou, H., Maher, J., Kellum, J., Warnick, R., Contos, M.J., and Sanyal, A.J. (2012). Increased hepatic synthesis and dysregulation of cholesterol metabolism is associated with the severity of nonalcoholic fatty liver disease. Cell Metab. *15*, 665–674. https://doi.org/10.1016/j.cmet.2012.04.004.

43. Zhang, X., Coker, O.O., Chu, E.S., Fu, K., Lau, H.C.H., Wang, Y.X., Chan, A.W.H., Wei, H., Yang, X., Sung, J.J.Y., et al. (2021). Dietary cholesterol drives fatty liver-associated liver cancer by modulating gut microbiota and metabolites. Gut *70*, 761–774. https://doi.org/10.1136/gutjnl-2019-319664.

44. Itoh, M., Tamura, A., Kanai, S., Tanaka, M., Kanamori, Y., Shirakawa, I., Ito, A., Oka, Y., Hidaka, I., Takami, T., et al. (2023). Lysosomal cholesterol overload in macrophages promotes liver fibrosis in a mouse model of NASH. J. Exp. Med. *220*, e20220681. https://doi.org/10.1084/jem.20220681.

45. Ma, F., Longo, M., Meroni, M., Bhattacharya, D., Paolini, E., Mughal, S., Hussain, S., Anand, S.K., Gupta, N., Zhu, Y., et al. (2025). EHBP1 suppresses liver fibrosis in metabolic dysfunction-associated steatohepatitis. Cell Metab. *37*, 1152–1170.e7. https://doi.org/10.1016/j.cmet.2025.01.020.

46. Wang, X., Cai, B., Yang, X., Sonubi, O.O., Zheng, Z., Ramakrishnan, R., Shi, H., Valenti, L., Pajvani, U.B., Sandhu, J., et al. (2020). Cholesterol stabilizes TAZ in hepatocytes to promote experimental non-alcoholic steatohepatitis. Cell Metab. *31*, 969–986.e7. https://doi.org/10.1016/j.cmet.2020.03.010.

47. Saito, Y., Yin, D., Kubota, N., Wang, X., Filliol, A., Remotti, H., Nair, A., Fazlollahi, L., Hoshida, Y., Tabas, I., et al. (2023). A therapeutically targetable TAZ-TEAD2 pathway drives the growth of hepatocellular carcinoma via ANLN and KIF23. Gastroenterology *164*, 1279–1292. https://doi.org/10.1053/j.gastro.2023.02.043.

48. Dongiovanni, P., Petta, S., Mannisto, V., Mancina, R.M., Pipitone, R., Karja, V., Maggioni, M., Kakela, P., Wiklund, O., Mozzi, E., et al. (2015). Statin use and non-alcoholic steatohepatitis in at risk individuals. J. Hepatol. *63*, 705–712. https://doi.org/10.1016/j.jhep.2015.05.006.

49. Zhou, X.D., Kim, S.U., Yip, T.C.F., Petta, S., Nakajima, A., Tsochatzis, E., Boursier, J., Bugianesi, E., Hagström, H., Chan, W.K., et al. (2024). Long-term liver-related outcomes and liver stiffness progression of statin usage in steatotic liver disease. Gut *73*, 1883–1892. https://doi.org/10.1136/gutjnl-2024-333074.

50. Pramfalk, C., Parini, P., Gustafsson, U., Sahlin, S., and Eriksson, M. (2011). Effects of high-dose statin on the human hepatic expression of genes involved in carbohydrate and triglyceride metabolism. J. Intern. Med. *269*, 333–339. https://doi.org/10.1111/j.1365-2796.2010.02305.x.

51. Boutari, C., Rizos, C.V., Liamis, G., Skoumas, I., Rallidis, L., Garoufi, A., Kolovou, G., Sfikas, G., Tziomalos, K., Skalidis, E., et al. (2024). The effect of lipid-lowering treatment on indices of MASLD in familial hypercholesterolemia patients. Clin. Nutr. *43*, 84–91. https://doi.org/10.1016/j.clnu.2024.10.020.

52. Dichtl, W., Nilsson, L., Goncalves, I., Ares, M.P., Banfi, C., Calara, F., Hamsten, A., Eriksson, P., and Nilsson, J. (1999). Very low-density lipoprotein activates nuclear factor-kappaB in endothelial cells. Circ. Res. *84*, 1085–1094. https://doi.org/10.1161/01.res.84.9.1085.

53. Dichtl, W., Ares, M.P.S., Jönson, A.N., Jovinge, S., Pachinger, O., Giachelli, C.M., Hamsten, A., Eriksson, P., and Nilsson, J. (2002). Linoleic acid-stimulated vascular adhesion molecule-1 expression in endothelial cells depends on nuclear factor-kappaB activation. Metabolism *51*, 327–333. https://doi.org/10.1053/meta.2002.29963.

54. Furuta, K., Guo, Q., Pavelko, K.D., Lee, J.H., Robertson, K.D., Nakao, Y., Melek, J., Shah, V.H., Hirsova, P., and Ibrahim, S.H. (2021). Lipid-induced endothelial vascular cell adhesion molecule 1 promotes nonalcoholic steatohepatitis pathogenesis. J. Clin. Investig. *131*, e143690. https://doi.org/10.1172/JCI143690.

55. Tilg, H., Moschen, A.R., and Szabo, G. (2016). Interleukin-1 and inflammasomes in alcoholic liver disease/acute alcoholic hepatitis and nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. Hepatology *64*, 955–965. https://doi.org/10.1002/hep.28456.

56. Wang, X., Wang, Y., Antony, V., Sun, H., and Liang, G. (2020). Metabolism-associated molecular patterns (MAMPs). Trends Endocrinol. Metab. *31*, 712–724. https://doi.org/10.1016/j.tem.2020.07.001.

57. Wen, H., Gris, D., Lei, Y., Jha, S., Zhang, L., Huang, M.T.H., Brickey, W.J., and Ting, J.P.Y. (2011). Fatty acid-induced NLRP3-ASC inflammasome activation interferes with insulin signaling. Nat. Immunol. *12*, 408–415. https://doi.org/10.1038/ni.2022.

58. Vandanmagsar, B., Youm, Y.H., Ravussin, A., Galgani, J.E., Stadler, K., Mynatt, R.L., Ravussin, E., Stephens, J.M., and Dixit, V.D. (2011). The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. Nat. Med. *17*, 179–188. https://doi.org/10.1038/nm.2279.

59. Nielsen, S., Guo, Z., Johnson, C.M., Hensrud, D.D., and Jensen, M.D. (2004). Splanchnic lipolysis in human obesity. J. Clin. Investig. *113*, 1582–1588. https://doi.org/10.1172/JCI21047.

60. Rosso, C., Kazankov, K., Younes, R., Esmaili, S., Marietti, M., Sacco, M., Carli, F., Gaggini, M., Salomone, F., Møller, H.J., et al. (2019). Crosstalk between adipose tissue insulin resistance and liver macrophages in non-alcoholic fatty liver disease. J. Hepatol. *71*, 1012–1021. https://doi.org/10.1016/j.jhep.2019.06.031.

61. Xia, J.Y., Holland, W.L., Kusminski, C.M., Sun, K., Sharma, A.X., Pearson, M.J., Sifuentes, A.J., McDonald, J.G., Gordillo, R., and Scherer, P.E. (2015). Targeted induction of ceramide degradation leads to improved systemic metabolism and reduced hepatic steatosis. Cell Metab. *22*, 266–278. https://doi.org/10.1016/j.cmet.2015.06.007.

62. Koh, E.H., Yoon, J.E., Ko, M.S., Leem, J., Yun, J.Y., Hong, C.H., Cho, Y.K., Lee, S.E., Jang, J.E., Baek, J.Y., et al. (2021). Sphingomyelin synthase 1 mediates hepatocyte pyroptosis to trigger non-alcoholic steatohepatitis. Gut *70*, 1954–1964. https://doi.org/10.1136/gutjnl-2020-322509.

63. Xie, C., Yagai, T., Luo, Y., Liang, X., Chen, T., Wang, Q., Sun, D., Zhao, J., Ramakrishnan, S.K., Sun, L., et al. (2017). Activation of intestinal hypoxia-inducible factor 2alpha during obesity contributes to hepatic steatosis. Nat. Med. *23*, 1298–1308. https://doi.org/10.1038/nm.4412.

64. Zhang, Y., Wang, X., Lin, J., Liu, J., Wang, K., Nie, Q., Ye, C., Sun, L., Ma, Y., Qu, R., et al. (2024). A microbial metabolite inhibits the HIF-2alpha-ceramide pathway to mediate the beneficial effects of time-restricted feeding on MASH. Cell Metab. *36*, 1823–1838.e6. https://doi.org/10.1016/j.cmet.2024.07.004.

65. Alsamman, S., Christenson, S.A., Yu, A., Ayad, N.M.E., Mooring, M.S., Segal, J.M., Hu, J.K.H., Schaub, J.R., Ho, S.S., Rao, V., et al. (2020). Targeting acid ceramidase inhibits YAP/TAZ signaling to reduce fibrosis in mice. Sci. Transl. Med. *12*, eaay8798. https://doi.org/10.1126/scitranslmed.aay8798.

66. Jiang, J., Gao, Y., Wang, J., Huang, Y., Yang, R., Zhang, Y., Ma, Y., Wen, Y., Luo, G., Zhang, S., et al. (2025). Hepatic sphingomyelin phosphodiesterase 3 promotes steatohepatitis by disrupting membrane sphingolipid metabolism. Cell Metab. *37*, 1119–1136.e13. https://doi.org/10.1016/j.cmet.2025.01.016.

67. Luukkonen, P.K., Zhou, Y., Sädevirta, S., Leivonen, M., Arola, J., Orešič, M., Hyötyläinen, T., and Yki-Järvinen, H. (2016). Hepatic ceramides dissociate steatosis and insulin resistance in patients with non-alcoholic fatty liver disease. J. Hepatol. *64*, 1167–1175. https://doi.org/10.1016/j.jhep.2016.01.002.

68. Donnelly, K.L., Smith, C.I., Schwarzenberg, S.J., Jessurun, J., Boldt, M.D., and Parks, E.J. (2005). Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. J. Clin. Investig. *115*, 1343–1351. https://doi.org/10.1172/JCI23621.

69. Li, Z., Yang, S., Lin, H., Huang, J., Watkins, P.A., Moser, A.B., Desimone, C., Song, X.Y., and Diehl, A.M. (2003). Probiotics and antibodies to TNF

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inhibit inflammatory activity and improve nonalcoholic fatty liver disease. Hepatology *37*, 343–350. https://doi.org/10.1053/jhep.2003.50048.

70. Liao, Y., Chen, Q., Liu, L., Huang, H., Sun, J., Bai, X., Jin, C., Li, H., Sun, F., Xiao, X., et al. (2024). Amino acid is a major carbon source for hepatic lipogenesis. Cell Metab. *36*, 2437–2448.e8. https://doi.org/10.1016/j.cmet.2024.10.001.

71. Zhang, X.J., She, Z.G., Wang, J., Sun, D., Shen, L.J., Xiang, H., Cheng, X., Ji, Y.X., Huang, Y.P., Li, P.L., et al. (2021). Multiple omics study identifies an interspecies conserved driver for nonalcoholic steatohepatitis. Sci. Transl. Med. *13*, eabg8117. https://doi.org/10.1126/scitranslmed.abg8117.

72. Luukkonen, P.K., Porthan, K., Ahlholm, N., Rosqvist, F., Dufour, S., Zhang, X.M., Lehtimäki, T.E., Seppänen, W., Orho-Melander, M., Hodson, L., et al. (2023). The PNPLA3 I148M variant increases ketogenesis and decreases hepatic de novo lipogenesis and mitochondrial function in humans. Cell Metab. *35*, 1887–1896.e5. https://doi.org/10.1016/j.cmet.2023.10.008.

73. Govaere, O., Petersen, S.K., Martinez-Lopez, N., Wouters, J., Van Haele, M., Mancina, R.M., Jamialahmadi, O., Bilkei-Gorzo, O., Lassen, P.B., Darlay, R., et al. (2022). Macrophage scavenger receptor 1 mediates lipid-induced inflammation in non-alcoholic fatty liver disease. J. Hepatol. *76*, 1001–1012. https://doi.org/10.1016/j.jhep.2021.12.012.

74. Fuchs, C.D., Radun, R., Dixon, E.D., Mlitz, V., Timelthaler, G., Halilbasic, E., Herac, M., Jonker, J.W., Ronda, O.A.H.O., Tardelli, M., et al. (2022). Hepatocyte-specific deletion of adipose triglyceride lipase (adipose triglyceride lipase/patatin-like phospholipase domain containing 2) ameliorates dietary induced steatohepatitis in mice. Hepatology *75*, 125–139. https://doi.org/10.1002/hep.32112.

75. Zhang, P., Liu, J., Lee, A., Tsaur, I., Ohira, M., Duong, V., Vo, N., Watari, K., Su, H., Kim, J.Y., et al. (2024). IL-22 resolves MASLD via enterocyte STAT3 restoration of diet-perturbed intestinal homeostasis. Cell Metab. *36*, 2341–2354.e6. https://doi.org/10.1016/j.cmet.2024.08.012.

76. Zhang, Y., Jiang, Q., Liang, X., Qian, Q., Xiong, J., Liu, C., Xu, J., Wang, N., Xu, Y., Zhou, P., et al. (2024). Coagulation Factor VII fine-tunes hepatic steatosis by blocking AKT-CD36-mediated fatty acid uptake. Diabetes *73*, 682–700. https://doi.org/10.2337/db23-0814.

77. Gallage, S., Ali, A., Barragan Avila, J.E., Seymen, N., Ramadori, P., Joerke, V., Zizmare, L., Aicher, D., Gopalsamy, I.K., Fong, W., et al. (2024). A 5:2 intermittent fasting regimen ameliorates NASH and fibrosis and blunts HCC development via hepatic PPARalpha and PCK1. Cell Metab. *36*, 1371–1393.e7. https://doi.org/10.1016/j.cmet.2024.04.015.

78. Clifford, B.L., Sedgeman, L.R., Williams, K.J., Morand, P., Cheng, A., Jarrett, K.E., Chan, A.P., Brearley-Sholto, M.C., Wahlström, A., Ashby, J.W., et al. (2021). FXR activation protects against NAFLD via bile-acid-dependent reductions in lipid absorption. Cell Metab. *33*, 1671–1684.e4. https://doi.org/10.1016/j.cmet.2021.06.012.

79. Weiss, J.M., Palmieri, E.M., Gonzalez-Cotto, M., Bettencourt, I.A., Megill, E.L., Snyder, N.W., and McVicar, D.W. (2023). Itaconic acid underpins hepatocyte lipid metabolism in non-alcoholic fatty liver disease in male mice. Nat. Metab. *5*, 981–995. https://doi.org/10.1038/s42255-023-00801-2.

80. Tilg, H., Adolph, T.E., and Trauner, M. (2022). Gut-liver axis: Pathophysiological concepts and clinical implications. Cell Metab. *34*, 1700–1718. https://doi.org/10.1016/j.cmet.2022.09.017.

81. Miele, L., Valenza, V., La Torre, G., Montalto, M., Cammarota, G., Ricci, R., Mascianà, R., Forgione, A., Gabrieli, M.L., Perotti, G., et al. (2009). Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease. Hepatology *49*, 1877–1887. https://doi.org/10.1002/hep.22848.

82. Mishra, S.P., Wang, B., Jain, S., Ding, J., Rejeski, J., Furdui, C.M., Kitzman, D.W., Taraphder, S., Brechot, C., Kumar, A., et al. (2023). A mechanism by which gut microbiota elevates permeability and inflammation in obese/diabetic mice and human gut. Gut *72*, 1848–1865. https://doi.org/10.1136/gutjnl-2022-327365.

83. Nie, Q., Luo, X., Wang, K., Ding, Y., Jia, S., Zhao, Q., Li, M., Zhang, J., Zhuo, Y., Lin, J., et al. (2024). Gut symbionts alleviate MASH through a secondary bile acid biosynthetic pathway. Cell *187*, 2717–2734.e33. https://doi.org/10.1016/j.cell.2024.03.034.

84. Kuang, J., Wang, J., Li, Y., Li, M., Zhao, M., Ge, K., Zheng, D., Cheung, K.C.P., Liao, B., Wang, S., et al. (2023). Hyodeoxycholic acid alleviates non-alcoholic fatty liver disease through modulating the gut-liver axis. Cell Metab. *35*, 1752–1766.e8. https://doi.org/10.1016/j.cmet.2023.07.011.

85. Fuchs, C.D., Simbrunner, B., Baumgartner, M., Campbell, C., Reiberger, T., and Trauner, M. (2025). Bile acid metabolism and signalling in liver disease. J. Hepatol. *82*, 134–153. https://doi.org/10.1016/j.jhep.2024.09.032.

86. Pasolli, E., Asnicar, F., Manara, S., Zolfo, M., Karcher, N., Armanini, F., Beghini, F., Manghi, P., Tett, A., Ghensi, P., et al. (2019). Extensive unexplored human microbiome diversity revealed by over 150,000 genomes from metagenomes spanning age, geography, and lifestyle. Cell *176*, 649–662.e20. https://doi.org/10.1016/j.cell.2019.01.001.

87. Loomba, R., Seguritan, V., Li, W., Long, T., Klitgord, N., Bhatt, A., Dulai, P.S., Caussy, C., Bettencourt, R., Highlander, S.K., et al. (2017). Gut microbiome-based metagenomic signature for non-invasive detection of advanced fibrosis in human nonalcoholic fatty liver disease. Cell Metab. *25*, 1054–1062.e5. https://doi.org/10.1016/j.cmet.2017.04.001.

88. Hoyles, L., Fernández-Real, J.M., Federici, M., Serino, M., Abbott, J., Charpentier, J., Heymes, C., Luque, J.L., Anthony, E., Barton, R.H., et al. (2018). Molecular phenomics and metagenomics of hepatic steatosis in non-diabetic obese women. Nat. Med. *24*, 1070–1080. https://doi.org/10.1038/s41591-018-0061-3.

89. Carr, R.M., Li, Y., Chau, L., Friedman, E.S., Lee, J.J., Adorini, L., Erickson, M., Zaru, L., Shringarpure, R., MacConell, L., et al. (2023). An integrated analysis of fecal microbiome and metabolomic features distinguish non-cirrhotic NASH from healthy control populations. Hepatology *78*, 1843–1857. https://doi.org/10.1097/HEP.0000000000000474.

90. Nychas, E., Marfil-Sánchez, A., Chen, X., Mirhakkak, M., Li, H., Jia, W., Xu, A., Nielsen, H.B., Nieuwdorp, M., Loomba, R., et al. (2025). Discovery of robust and highly specific microbiome signatures of non-alcoholic fatty liver disease. Microbiome *13*, 10. https://doi.org/10.1186/s40168-024-01990-y.

91. Wei, J., Luo, J., Yang, F., Dai, W., Pan, X., and Luo, M. (2024). Identification of commensal gut bacterial strains with lipogenic effects contributing to NAFLD in children. iScience *27*, 108861. https://doi.org/10.1016/j.isci.2024.108861.

92. Ponziani, F.R., Bhoori, S., Castelli, C., Putignani, L., Rivoltini, L., Del Chierico, F., Sanguinetti, M., Morelli, D., Paroni Sterbini, F., Petito, V., et al. (2018). Hepatocellular carcinoma is associated with gut microbiota profile and inflammation in nonalcoholic fatty liver disease. Hepatology *69*, 107–120. https://doi.org/10.1002/hep.30036.

93. Oh, T.G., Kim, S.M., Caussy, C., Fu, T., Guo, J., Bassirian, S., Singh, S., Madamba, E.V., Bettencourt, R., Richards, L., et al. (2020). A universal gut-microbiome-derived signature predicts cirrhosis. Cell Metab. *32*, 878–888.e6. https://doi.org/10.1016/j.cmet.2020.06.005.

94. Xu, Z., and Knight, R. (2015). Dietary effects on human gut microbiome diversity. Br. J. Nutr. *113*, S1–S5. https://doi.org/10.1017/S0007114514004127.

95. Ni, Y., Qian, L., Siliceo, S.L., Long, X., Nychas, E., Liu, Y., Ismaiah, M.J., Leung, H., Zhang, L., Gao, Q., et al. (2023). Resistant starch decreases intrahepatic triglycerides in patients with NAFLD via gut microbiome alterations. Cell Metab. *35*, 1530–1547.e8. https://doi.org/10.1016/j.cmet.2023.08.002.

96. Sookoian, S., Salatino, A., Castaño, G.O., Landa, M.S., Fijalkowky, C., Garaycoechea, M., and Pirola, C.J. (2020). Intrahepatic bacterial metataxonomic signature in non-alcoholic fatty liver disease. Gut *69*, 1483–1491. https://doi.org/10.1136/gutjnl-2019-318811.

97. Carpino, G., Del Ben, M., Pastori, D., Carnevale, R., Baratta, F., Overi, D., Francis, H., Cardinale, V., Onori, P., Safarikia, S., et al. (2020). Increased liver localization of lipopolysaccharides in human and experimental NAFLD. Hepatology *72*, 470–485. https://doi.org/10.1002/hep.31056.

98. Pang, J., Xu, W., Zhang, X., Wong, G.L., Chan, A.W., Chan, H.Y., Tse, C.H., Shu, S.S., Choi, P.C., Chan, H.L., et al. (2017). Significant positive association of endotoxemia with histological severity in 237 patients with non-alcoholic fatty liver disease. Aliment. Pharmacol. Ther. *46*, 175–182. https://doi.org/10.1111/apt.14119.

Please cite this article in press as: Tilg et al., The many pathways driving liver inflammation in MASH, Cell Metabolism (2026), https://doi.org/10.1016/j.cmet.2026.02.018

99. Han, Y.H., Onufer, E.J., Huang, L.H., Sprung, R.W., Davidson, W.S., Czepielewski, R.S., Wohltmann, M., Sorci-Thomas, M.G., Warner, B.W., and Randolph, G.J. (2021). Enterically derived high-density lipoprotein restrains liver injury through the portal vein. Science *373*, eabe6729. https://doi.org/10.1126/science.abe6729.

100. Miyamoto, Y., Kikuta, J., Matsui, T., Hasegawa, T., Fujii, K., Okuzaki, D., Liu, Y.C., Yoshioka, T., Seno, S., Motooka, D., et al. (2024). Periportal macrophages protect against commensal-driven liver inflammation. Nature *629*, 901–909. https://doi.org/10.1038/s41586-024-07372-6.

101. Spruss, A., Kanuri, G., Wagnerberger, S., Haub, S., Bischoff, S.C., and Bergheim, I. (2009). Toll-like receptor 4 is involved in the development of fructose-induced hepatic steatosis in mice. Hepatology *50*, 1094–1104. https://doi.org/10.1002/hep.23122.

102. Henao-Mejia, J., Elinav, E., Jin, C., Hao, L., Mehal, W.Z., Strowig, T., Thaiss, C.A., Kau, A.L., Eisenbarth, S.C., Jurczak, M.J., et al. (2012). Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. Nature *482*, 179–185. https://doi.org/10.1038/nature10809.

103. Yuan, J., Chen, C., Cui, J., Lu, J., Yan, C., Wei, X., Zhao, X., Li, N., Li, S., Xue, G., et al. (2019). Fatty liver disease caused by high-alcohol-producing Klebsiella pneumoniae. Cell Metab. *30*, 675–688.e7. https://doi.org/10.1016/j.cmet.2019.08.018.

104. Meijnikman, A.S., Davids, M., Herrema, H., Aydin, O., Tremaroli, V., Rios-Morales, M., Levels, H., Bruin, S., de Brauw, M., Verheij, J., et al. (2022). Microbiome-derived ethanol in nonalcoholic fatty liver disease. Nat. Med. *28*, 2100–2106. https://doi.org/10.1038/s41591-022-02016-6.

105. Aron-Wisnewsky, J., Vigliotti, C., Witjes, J., Le, P., Holleboom, A.G., Verheij, J., Nieuwdorp, M., and Clément, K. (2020). Gut microbiota and human NAFLD: disentangling microbial signatures from metabolic disorders. Nat. Rev. Gastroenterol. Hepatol. *17*, 279–297. https://doi.org/10.1038/s41575-020-0269-9.

106. Lau, H.C.H., Zhang, X., and Yu, J. (2025). Gut microbiome in metabolic dysfunction-associated steatotic liver disease and associated hepatocellular carcinoma. Nat. Rev. Gastroenterol. Hepatol. *22*, 619–638. https://doi.org/10.1038/s41575-025-01089-1.

107. Netea, M.G., Balkwill, F., Chonchol, M., Cominelli, F., Donath, M.Y., Giamarellos-Bourboulis, E.J., Golenbock, D., Gresnigt, M.S., Heneka, M.T., Hoffman, H.M., et al. (2017). A guiding map for inflammation. Nat. Immunol. *18*, 826–831. https://doi.org/10.1038/ni.3790.

108. Crespo, J., Cayón, A., Fernández-Gil, P., Hernández-Guerra, M., Mayorga, M., Domínguez-Díez, A., Fernández-Escalante, J.C., and Pons-Romero, F. (2001). Gene expression of tumor necrosis factor alpha and TNF-receptors, p55 and p75, in nonalcoholic steatohepatitis patients. Hepatology *34*, 1158–1163. https://doi.org/10.1053/jhep.2001.29628.

109. Kamari, Y., Shaish, A., Vax, E., Shemesh, S., Kandel-Kfir, M., Arbel, Y., Olteanu, S., Barshack, I., Dotan, S., Voronov, E., et al. (2011). Lack of interleukin-1alpha or interleukin-1beta inhibits transformation of steatosis to steatohepatitis and liver fibrosis in hypercholesterolemic mice. J. Hepatol. *55*, 1086–1094. https://doi.org/10.1016/j.jhep.2011.01.048.

110. Moschen, A.R., Molnar, C., Enrich, B., Geiger, S., Ebenbichler, C.F., and Tilg, H. (2011). Adipose and liver expression of interleukin (IL)-1 family members in morbid obesity and effects of weight loss. Mol. Med. *17*, 840–845. https://doi.org/10.2119/molmed.2010.00108.

111. Tilg, H., and Moschen, A.R. (2011). IL-1 cytokine family members and NAFLD: neglected in metabolic liver inflammation. J. Hepatol. *55*, 960–962. https://doi.org/10.1016/j.jhep.2011.04.007.

112. Csak, T., Pillai, A., Ganz, M., Lippai, D., Petrasek, J., Park, J.K., Kodys, K., Dolganiuc, A., Kurt-Jones, E.A., and Szabo, G. (2014). Both bone marrow-derived and non-bone marrow-derived cells contribute to AIM2 and NLRP3 inflammasome activation in a MyD88-dependent manner in dietary steatohepatitis. Liver Int. *34*, 1402–1413. https://doi.org/10.1111/liv.12537.

113. Yang, G., Lee, H.E., and Lee, J.Y. (2016). A pharmacological inhibitor of NLRP3 inflammasome prevents non-alcoholic fatty liver disease in a mouse model induced by high fat diet. Sci. Rep. *6*, 24399. https://doi.org/10.1038/srep24399.

114. Sawada, K., Chung, H., Softic, S., Moreno-Fernandez, M.E., and Divanovic, S. (2023). The bidirectional immune crosstalk in metabolic dysfunction-associated steatotic liver disease. Cell Metab. *35*, 1852–1871. https://doi.org/10.1016/j.cmet.2023.10.009.

115. Hammerich, L., and Tacke, F. (2023). Hepatic inflammatory responses in liver fibrosis. Nat. Rev. Gastroenterol. Hepatol. *20*, 633–646. https://doi.org/10.1038/s41575-023-00807-x.

116. Byrne, C.D., Armandi, A., Pellegrinelli, V., Vidal-Puig, A., and Bugianesi, E. (2025). Metabolic dysfunction-associated steatotic liver disease: a condition of heterogeneous metabolic risk factors, mechanisms and comorbidities requiring holistic treatment. Nat. Rev. Gastroenterol. Hepatol. *22*, 314–328. https://doi.org/10.1038/s41575-025-01045-z.

117. Chen, V.L., Kuppa, A., Oliveri, A., Chen, Y., Ponnandy, P., Patel, P.B., Palmer, N.D., and Speliotes, E.K. (2025). Human genetics of metabolic dysfunction-associated steatotic liver disease: from variants to cause to precision treatment. J. Clin. Investig. *135*, e186424. https://doi.org/10.1172/JCI186424.

118. Roden, M., and Shulman, G.I. (2019). The integrative biology of type 2 diabetes. Nature *576*, 51–60. https://doi.org/10.1038/s41586-019-1797-8.

119. Ferreyra Solari, N.E., Inzaugarat, M.E., Baz, P., De Matteo, E., Lezama, C., Galoppo, M., Galoppo, C., and Cherñavsky, A.C. (2012). The role of innate cells is coupled to a Th1-polarized immune response in pediatric nonalcoholic steatohepatitis. J. Clin. Immunol. *32*, 611–621. https://doi.org/10.1007/s10875-011-9635-2.

120. Rau, M., Schilling, A.K., Meertens, J., Hering, I., Weiss, J., Jurowich, C., Kudlich, T., Hermanns, H.M., Bantel, H., Beyersdorf, N., et al. (2016). Progression from nonalcoholic fatty liver to nonalcoholic steatohepatitis is marked by a higher frequency of Th17 cells in the liver and an increased Th17/resting regulatory T cell ratio in peripheral blood and in the liver. J. Immunol. *196*, 97–105. https://doi.org/10.4049/jimmunol.1501175.

121. Henning, J.R., Graffeo, C.S., Rehman, A., Fallon, N.C., Zambirinis, C.P., Ochi, A., Barilla, R., Jamal, M., Deutsch, M., Greco, S., et al. (2013). Dendritic cells limit fibroinflammatory injury in nonalcoholic steatohepatitis in mice. Hepatology *58*, 589–602. https://doi.org/10.1002/hep.26267.

122. Syn, W.K., Oo, Y.H., Pereira, T.A., Karaca, G.F., Jung, Y., Omenetti, A., Witek, R.P., Choi, S.S., Guy, C.D., Fearing, C.M., et al. (2010). Accumulation of natural killer T cells in progressive nonalcoholic fatty liver disease. Hepatology *51*, 1998–2007. https://doi.org/10.1002/hep.23599.

123. Dudek, M., Pfister, D., Donakonda, S., Filpe, P., Schneider, A., Laschinger, M., Hartmann, D., Hüser, N., Meiser, P., Bayerl, F., et al. (2021). Auto-aggressive CXCR6+ CD8 T cells cause liver immune pathology in NASH. Nature *592*, 444–449. https://doi.org/10.1038/s41586-021-03233-8.

124. Ma, C., Kesarwala, A.H., Eggert, T., Medina-Echeverz, J., Kleiner, D.E., Jin, P., Stroncek, D.F., Terabe, M., Kapoor, V., ElGindi, M., et al. (2016). NAFLD causes selective CD4(+) T lymphocyte loss and promotes hepatocarcinogenesis. Nature *531*, 253–257. https://doi.org/10.1038/nature16969.

125. Pfister, D., Núñez, N.G., Pinyol, R., Govaere, O., Pinter, M., Szydlowska, M., Gupta, R., Qiu, M., Deczkowska, A., Weiner, A., et al. (2021). NASH limits anti-tumour surveillance in immunotherapy-treated HCC. Nature *592*, 450–456. https://doi.org/10.1038/s41586-021-03362-0.

126. Hai, S., Li, X., Xie, E., Wu, W., Gao, Q., Yu, B., Hu, J., Xu, F., Zheng, X., Zhang, B.H., et al. (2024). Intestinal IL-33 promotes microbiota-derived trimethylamine N -oxide synthesis and drives metabolic dysfunction-associated steatotic liver disease progression by exerting dual regulation on HIF-1alpha. Hepatology *82*, 184–198. https://doi.org/10.1097/HEP.0000000000000985.

127. Johnson, E.L., Heaver, S.L., Waters, J.L., Kim, B.I., Bretin, A., Goodman, A.L., Gewirtz, A.T., Worgall, T.S., and Ley, R.E. (2020). Sphingolipids produced by gut bacteria enter host metabolic pathways impacting ceramide levels. Nat. Commun. *11*, 2471. https://doi.org/10.1038/s41467-020-16274-w.

128. Le, H.H., Lee, M.T., Besler, K.R., and Johnson, E.L. (2022). Host hepatic metabolism is modulated by gut microbiota-derived sphingolipids. Cell Host Microbe *30*, 798–808.e7. https://doi.org/10.1016/j.chom.2022.05.002.

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129. Klag, K., Ott, D., Tippetts, T.S., Nicolson, R.J., Tatum, S.M., Bauer, K.M., Stephen-Victor, E., Weis, A.M., Bell, R., Weagley, J., et al. (2025). Dietary fat disrupts a commensal-host lipid network that promotes metabolic health. Cell Metab. *38*, 157–173.e9. https://doi.org/10.1016/j.cmet.2025.10.007.

130. Sato, Y., Atarashi, K., Plichta, D.R., Arai, Y., Sasajima, S., Kearney, S.M., Suda, W., Takeshita, K., Sasaki, T., Okamoto, S., et al. (2021). Novel bile acid biosynthetic pathways are enriched in the microbiome of centenarians. Nature *599*, 458–464. https://doi.org/10.1038/s41586-021-03832-5.

131. Paik, D., Yao, L., Zhang, Y., Bae, S., D'Agostino, G.D., Zhang, M., Kim, E., Franzosa, E.A., Avila-Pacheco, J., Bisanz, J.E., et al. (2022). Human gut bacteria produce TH17-modulating bile acid metabolites. Nature *603*, 907–912. https://doi.org/10.1038/s41586-022-04480-z.

132. Brown, E.M., Clardy, J., and Xavier, R.J. (2023). Gut microbiome lipid metabolism and its impact on host physiology. Cell Host Microbe *31*, 173–186. https://doi.org/10.1016/j.chom.2023.01.009.

133. Oh, S.F., Praveena, T., Song, H., Yoo, J.S., Jung, D.J., Erturk-Hasdemir, D., Hwang, Y.S., Lee, C.C., Le Nours, J., Kim, H., et al. (2021). Host immunomodulatory lipids created by symbionts from dietary amino acids. Nature *600*, 302–307. https://doi.org/10.1038/s41586-021-04083-0.

134. Yang, T., Hu, X., Cao, F., Yun, F., Jia, K., Zhang, M., Kong, G., Nie, B., Liu, Y., Zhang, H., et al. (2025). Targeting symbionts by apolipoprotein L proteins modulates gut immunity. Nature *643*, 210–218. https://doi.org/10.1038/s41586-025-08990-4.

135. Kanno, T., Nakajima, T., Miyako, K., and Endo, Y. (2023). Lipid metabolism in Th17 cell function. Pharmacol. Ther. *245*, 108411. https://doi.org/10.1016/j.pharmthera.2023.108411.

136. Adolph, T.E., and Tilg, H. (2024). Western diets and chronic diseases. Nat. Med. *30*, 2133–2147. https://doi.org/10.1038/s41591-024-03165-6.

137. Tilg, H., and Moschen, A.R. (2015). Food, immunity, and the microbiome. Gastroenterology *148*, 1107–1119. https://doi.org/10.1053/j.gastro.2014.12.036.

138. Si, J., Vázquez-Castellanos, J.F., Gregory, A.C., Decommer, L., Rymenans, L., Proost, S., Centelles Lodeiro, J., Weger, M., Notdurfter, M., Leitner, C., et al. (2022). Long-term life history predicts current gut microbiome in a population-based cohort study. Nat Aging *2*, 885–895. https://doi.org/10.1038/s43587-022-00286-w.

139. Pendyala, S., Walker, J.M., and Holt, P.R. (2012). A high-fat diet is associated with endotoxemia that originates from the gut. Gastroenterology *142*, 1100–1101.e2. https://doi.org/10.1053/j.gastro.2012.01.034.

140. Stenman, L.K., Holma, R., Eggert, A., and Korpela, R. (2013). A novel mechanism for gut barrier dysfunction by dietary fat: epithelial disruption by hydrophobic bile acids. Am. J. Physiol., Gastrointest. Liver Physiol. *304*, G227–G234. https://doi.org/10.1152/ajpgi.00267.2012.

141. Lefebvre, C., Tiffay, A., Breemeersch, C.E., Dreux, V., Bôle-Feysot, C., Guérin, C., Breton, J., Maximin, E., Monnoye, M., Déchelotte, P., et al. (2024). Sex-dependent effects of a high fat diet on metabolic disorders, intestinal barrier function and gut microbiota in mouse. Sci. Rep. *14*, 19835. https://doi.org/10.1038/s41598-024-70931-4.

142. Gulhane, M., Murray, L., Lourie, R., Tong, H., Sheng, Y.H., Wang, R., Kang, A., Schreiber, V., Wong, K.Y., Magor, G., et al. (2016). High fat diets induce colonic epithelial cell stress and inflammation that is reversed by IL-22. Sci. Rep. *6*, 28990. https://doi.org/10.1038/srep28990.

143. Devkota, S., Wang, Y., Musch, M.W., Leone, V., Fehlner-Peach, H., Nadimpalli, A., Antonopoulos, D.A., Jabri, B., and Chang, E.B. (2012). Dietary-fat-induced taurocholic acid promotes pathobiont expansion and colitis in Il10-/- mice. Nature *487*, 104–108. https://doi.org/10.1038/nature11225.

144. Kawano, Y., Edwards, M., Huang, Y., Bilate, A.M., Araujo, L.P., Tanoue, T., Atarashi, K., Ladinsky, M.S., Reiner, S.L., Wang, H.H., et al. (2022). Microbiota imbalance induced by dietary sugar disrupts immune-mediated protection from metabolic syndrome. Cell *185*, 3501–3519.e20. https://doi.org/10.1016/j.cell.2022.08.005.

145. Febbraio, M.A., and Karin, M. (2021). "Sweet death": Fructose as a metabolic toxin that targets the gut-liver axis. Cell Metab. *33*, 2316–2328. https://doi.org/10.1016/j.cmet.2021.09.004.

146. Todoric, J., Di Caro, G., Reibe, S., Henstridge, D.C., Green, C.R., Vrbanac, A., Ceteci, F., Conche, C., McNulty, R., Shalapour, S., et al. (2020). Fructose stimulated de novo lipogenesis is promoted by inflammation. Nat. Metab. *2*, 1034–1045. https://doi.org/10.1038/s42255-020-0261-2.

147. Vasques-Monteiro, I.M.L., Silva-Veiga, F.M., Miranda, C.S., de Andrade Gonçalves, É.C.B., Daleprane, J.B., and Souza-Mello, V. (2021). A rise in Proteobacteria is an indicator of gut-liver axis-mediated nonalcoholic fatty liver disease in high-fructose-fed adult mice. Nutr. Res. *91*, 26–35. https://doi.org/10.1016/j.nutres.2021.04.008.

148. Zhao, S., Jang, C., Liu, J., Uehara, K., Gilbert, M., Izzo, L., Zeng, X., Trefely, S., Fernandez, S., Carrer, A., et al. (2020). Dietary fructose feeds hepatic lipogenesis via microbiota-derived acetate. Nature *579*, 586–591. https://doi.org/10.1038/s41586-020-2101-7.

149. Kim, J.Y., Wang, L.Q., Sladky, V.C., Oh, T.G., Liu, J., Trinh, K., Eichin, F., Downes, M., Hosseini, M., Jacotot, E.D., et al. (2022). PIDDosome-SCAP crosstalk controls high-fructose-diet-dependent transition from simple steatosis to steatohepatitis. Cell Metab. *34*, 1548–1560.e6. https://doi.org/10.1016/j.cmet.2022.08.005.

150. Gu, L., Zhu, Y., Nandi, S.P., Lee, M., Watari, K., Bareng, B., Ohira, M., Liu, Y., Sakane, S., Carlessi, R., et al. (2025). FBP1 controls liver cancer evolution from senescent MASH hepatocytes. Nature *637*, 461–469. https://doi.org/10.1038/s41586-024-08317-9.

151. Wang, Z., Klipfell, E., Bennett, B.J., Koeth, R., Levison, B.S., Dugar, B., Feldstein, A.E., Britt, E.B., Fu, X., Chung, Y.M., et al. (2011). Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature *472*, 57–63. https://doi.org/10.1038/nature09922.

152. Zhu, W., Gregory, J.C., Org, E., Buffa, J.A., Gupta, N., Wang, Z., Li, L., Fu, X., Wu, Y., Mehrabian, M., et al. (2016). Gut microbial metabolite TMAO enhances platelet hyperreactivity and thrombosis risk. Cell *165*, 111–124. https://doi.org/10.1016/j.cell.2016.02.011.

153. Schiattarella, G.G., Sannino, A., Toscano, E., Giugliano, G., Gargiulo, G., Franzone, A., Trimarco, B., Esposito, G., and Perrino, C. (2017). Gut microbe-generated metabolite trimethylamine-N-oxide as cardiovascular risk biomarker: a systematic review and dose-response meta-analysis. Eur. Heart J. *38*, 2948–2956. https://doi.org/10.1093/eurheartj/ehx342.

154. Ma, R., Shi, G., Li, Y., and Shi, H. (2024). Trimethylamine N-oxide, choline and its metabolites are associated with the risk of non-alcoholic fatty liver disease. Br. J. Nutr. *131*, 1915–1923. https://doi.org/10.1017/S0007114524000631.

155. Koh, A., Molinaro, A., Ståhlman, M., Khan, M.T., Schmidt, C., Mannerås-Holm, L., Wu, H., Carreras, A., Jeong, H., Olofsson, L.E., et al. (2018). Microbially produced imidazole propionate impairs insulin signaling through mTORC1. Cell *175*, 947–961.e17. https://doi.org/10.1016/j.cell.2018.09.055.

156. Mastrangelo, A., Robles-Vera, I., Mañanes, D., Galán, M., Femenía-Muiña, M., Redondo-Urzainqui, A., Barrero-Rodríguez, R., Papaioannou, E., Amores-Iniesta, J., Devesa, A., et al. (2025). Imidazole propionate is a driver and therapeutic target in atherosclerosis. Nature *645*, 254–261. https://doi.org/10.1038/s41586-025-09263-w.

157. Wang, Y., Kory, N., BasuRay, S., Cohen, J.C., and Hobbs, H.H. (2019). PNPLA3, CGI-58, and inhibition of hepatic triglyceride hydrolysis in mice. Hepatology *69*, 2427–2441. https://doi.org/10.1002/hep.30583.

158. Lindén, D., Ahnmark, A., Pingitore, P., Ciociola, E., Ahlstedt, I., Andréasson, A.C., Sasidharan, K., Madeyski-Bengtson, K., Zurek, M., Mancina, R.M., et al. (2019). Pnpla3 silencing with antisense oligonucleotides ameliorates nonalcoholic steatohepatitis and fibrosis in Pnpla3 I148M knock-in mice. Mol. Metab. *22*, 49–61. https://doi.org/10.1016/j.molmet.2019.01.013.

159. Armisen, J., Rauschecker, M., Sarv, J., Liljeblad, M., Wernevik, L., Niazi, M., Knöchel, J., Eklund, O., Sandell, T., Sherwood, J., et al. (2025). AZD2693, a PNPLA3 antisense oligonucleotide, for the treatment of MASH in 148M homozygous participants: two randomized phase I trials. J. Hepatol. *83*, 31–42. https://doi.org/10.1016/j.jhep.2024.12.046.

160. Fabbrini, E., Rady, B., Koshkina, A., Jeon, J.Y., Ayyar, V.S., Gargano, C., DiProspero, N., Wendel, S., Hegge, J., Hamilton, H., et al. (2024). Phase 1 trials of PNPLA3 siRNA in I148M homozygous patients with MAFLD. N. Engl. J. Med. *391*, 475–476. https://doi.org/10.1056/NEJMc2402341.

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161. Dongiovanni, P., Petta, S., Maglio, C., Fracanzani, A.L., Pipitone, R., Mozzi, E., Motta, B.M., Kaminska, D., Rametta, R., Grimaudo, S., et al. (2015). Transmembrane 6 superfamily member 2 gene variant disentangles nonalcoholic steatohepatitis from cardiovascular disease. Hepatology *61*, 506–514. https://doi.org/10.1002/hep.27490.

162. Prill, S., Caddeo, A., Baselli, G., Jamialahmadi, O., Dongiovanni, P., Rametta, R., Kanebratt, K.P., Pujia, A., Pingitore, P., Mancina, R.M., et al. (2019). The TM6SF2 E167K genetic variant induces lipid biosynthesis and reduces apolipoprotein B secretion in human hepatic 3D spheroids. Sci. Rep. *9*, 11585. https://doi.org/10.1038/s41598-019-47737-w.

163. Li, B.T., Sun, M., Li, Y.F., Wang, J.Q., Zhou, Z.M., Song, B.L., and Luo, J. (2020). Disruption of the ERLIN-TM6SF2-APOB complex destabilizes APOB and contributes to non-alcoholic fatty liver disease. PLOS Genet. *16*, e1008955. https://doi.org/10.1371/journal.pgen.1008955.

164. Tanaka, Y., Shimanaka, Y., Caddeo, A., Kubo, T., Mao, Y., Kubota, T., Kubota, N., Yamauchi, T., Mancina, R.M., Baselli, G., et al. (2020). LPIAT1/MBOAT7 depletion increases triglyceride synthesis fueled by high phosphatidylinositol turnover. Gut *70*, 180–193. https://doi.org/10.1136/gutjnl-2020-320646.

165. Alharthi, J., Bayoumi, A., Thabet, K., Pan, Z., Gloss, B.S., Latchoumanin, O., Lundberg, M., Twine, N.A., McLeod, D., Alenizi, S., et al. (2022). A metabolic associated fatty liver disease risk variant in MBOAT7 regulates toll like receptor induced outcomes. Nat. Commun. *13*, 7430. https://doi.org/10.1038/s41467-022-35158-9.

166. Dutta, T., Sasidharan, K., Ciociola, E., Pennisi, G., Noto, F.R., Kovooru, L., Kroon, T., Lindblom, A., Du, Y., Pirmoradian, M., et al. (2024). Mitochondrial amidoxime-reducing component 1 p.Ala165Thr increases protein degradation mediated by the proteasome. Liver Int. *44*, 1219–1232. https://doi.org/10.1111/liv.15857.

167. Ciociola, E., Dutta, T., Sasidharan, K., Kovooru, L., Noto, F.R., Pennisi, G., Petta, S., Mirarchi, A., Maurotti, S., Scopacasa, B., et al. (2024). Downregulation of the MARC1 p.A165 risk allele reduces hepatocyte lipid content by increasing beta-oxidation. Clin. Mol. Hepatol. *31*, 445–459. https://doi.org/10.3350/cmh.2024.0642.

168. Luukkonen, P.K., Tukiainen, T., Juuti, A., Sammalkorpi, H., Haridas, P.A.N., Niemelä, O., Arola, J., Orho-Melander, M., Hakkarainen, A., Kovanen, P.T., et al. (2020). Hydroxysteroid 17-β dehydrogenase 13 variant increases phospholipids and protects against fibrosis in nonalcoholic fatty liver disease. JCI Insight *5*, e132158. https://doi.org/10.1172/jci.insight.132158.

169. Vilar-Gomez, E., Liang, T., Yates, K., Wilson, L., Loomba, R., and Chalasani, N. (2023). The protection conferred by HSD17B13 rs72613567 on hepatic fibrosis is likely mediated by lowering ballooning and portal inflammation. Clin. Gastroenterol. Hepatol. *21*, 2981–2983.e3. https://doi.org/10.1016/j.cgh.2022.11.002.

170. Mak, L.Y., Gane, E., Schwabe, C., Yoon, K.T., Heo, J., Scott, R., Lee, J.H., Lee, J.I., Kweon, Y.O., Weltman, M., et al. (2023). A phase I/II study of ARO-HSD, an RNA interference therapeutic, for the treatment of non-alcoholic steatohepatitis. J. Hepatol. *78*, 684–692. https://doi.org/10.1016/j.jhep.2022.11.025.

171. Baselli, G.A., Jamialahmadi, O., Pelusi, S., Ciociola, E., Malvestiti, F., Saracino, M., Santoro, L., Cherubini, A., Dongiovanni, P., Maggioni, M., et al. (2022). Rare *ATG7* genetic variants predispose to severe fatty liver disease. J. Hepatol. *77*, 596–606. https://doi.org/10.1016/j.jhep.2022.03.031.

172. Negoita, F., Blomdahl, J., Wasserstrom, S., Winberg, M.E., Osmark, P., Larsson, S., Stenkula, K.G., Ekstedt, M., Kechagias, S., Holm, C., et al. (2019). PNPLA3 variant M148 causes resistance to starvation-mediated lipid droplet autophagy in human hepatocytes. J. Cell. Biochem. *120*, 343–356. https://doi.org/10.1002/jcb.27378.

173. Sinha, R.A. (2024). Thyroid hormone-mediated selective autophagy and its implications in countering metabolic dysfunction-associated steatotic liver disease. Endocrinol. Metab. (Seoul) *39*, 686–692. https://doi.org/10.3803/EnM.2024.2068.

174. Harrison, S.A., Bedossa, P., Guy, C.D., Schattenberg, J.M., Loomba, R., Taub, R., Labriola, D., Moussa, S.E., Neff, G.W., Rinella, M.E., et al. (2024). A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. N. Engl. J. Med. *390*, 497–509. https://doi.org/10.1056/NEJMoa2309000.

175. Ng, S.W.K., Rouhani, F.J., Brunner, S.F., Brzozowska, N., Aitken, S.J., Yang, M., Abascal, F., Moore, L., Nikitopoulou, E., Chappell, L., et al. (2021). Convergent somatic mutations in metabolism genes in chronic liver disease. Nature *598*, 473–478. https://doi.org/10.1038/s41586-021-03974-6.

176. Wang, Z., Zhu, S., Jia, Y., Wang, Y., Kubota, N., Fujiwara, N., Gordillo, R., Lewis, C., Zhu, M., Sharma, T., et al. (2023). Positive selection of somatically mutated clones identifies adaptive pathways in metabolic liver disease. Cell *186*, 1968–1984.e20. https://doi.org/10.1016/j.cell.2023.03.014.

177. Azzu, V., Vacca, M., Virtue, S., Allison, M., and Vidal-Puig, A. (2020). Adipose tissue-liver cross talk in the control of whole-body metabolism: implications in nonalcoholic fatty liver disease. Gastroenterology *158*, 1899–1912. https://doi.org/10.1053/j.gastro.2019.12.054.

178. Hotamisligil, G.S., Shargill, N.S., and Spiegelman, B.M. (1993). Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science *259*, 87–91. https://doi.org/10.1126/science.7678183.

179. Tilg, H., Ianiro, G., Gasbarrini, A., and Adolph, T.E. (2025). Adipokines: masterminds of metabolic inflammation. Nat. Rev. Immunol. *25*, 250–265. https://doi.org/10.1038/s41577-024-01103-8.

180. Kern, P.A., Saghizadeh, M., Ong, J.M., Bosch, R.J., Deem, R., and Simsolo, R.B. (1995). The expression of tumor necrosis factor in human adipose tissue. Regulation by obesity, weight loss, and relationship to lipoprotein lipase. J. Clin. Investig. *95*, 2111–2119. https://doi.org/10.1172/JCI117899.

181. Fried, S.K., Bunkin, D.A., and Greenberg, A.S. (1998). Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. J. Clin. Endocrinol. Metab. *83*, 847–850. https://doi.org/10.1210/jcem.83.3.4660.

182. Mohamed-Ali, V., Goodrick, S., Rawesh, A., Katz, D.R., Miles, J.M., Yudkin, J.S., Klein, S., and Coppack, S.W. (1997). Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. J. Clin. Endocrinol. Metab. *82*, 4196–4200. https://doi.org/10.1210/jcem.82.12.4450.

183. van der Poorten, D., Milner, K.L., Hui, J., Hodge, A., Trenell, M.I., Kench, J.G., London, R., Peduto, T., Chisholm, D.J., and George, J. (2008). Visceral fat: a key mediator of steatohepatitis in metabolic liver disease. Hepatology *48*, 449–457. https://doi.org/10.1002/hep.22350.

184. Moschen, A.R., Molnar, C., Geiger, S., Graziadei, I., Ebenbichler, C.F., Weiss, H., Kaser, S., Kaser, A., and Tilg, H. (2010). Anti-inflammatory effects of excessive weight loss: potent suppression of adipose interleukin 6 and tumour necrosis factor alpha expression. Gut *59*, 1259–1264. https://doi.org/10.1136/gut.2010.214577.

185. Kopp, H.P., Kopp, C.W., Festa, A., Krzyzanowska, K., Kriwanek, S., Minar, E., Roka, R., and Schernthaner, G. (2003). Impact of weight loss on inflammatory proteins and their association with the insulin resistance syndrome in morbidly obese patients. Arterioscler. Thromb. Vasc. Biol. *23*, 1042–1047. https://doi.org/10.1161/01.ATV.0000073313.16135.21.

186. Fain, J.N., Madan, A.K., Hiler, M.L., Cheema, P., and Bahouth, S.W. (2004). Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. Endocrinology *145*, 2273–2282. https://doi.org/10.1210/en.2003-1336.

187. Sabio, G., Das, M., Mora, A., Zhang, Z., Jun, J.Y., Ko, H.J., Barrett, T., Kim, J.K., and Davis, R.J. (2008). A stress signaling pathway in adipose tissue regulates hepatic insulin resistance. Science *322*, 1539–1543. https://doi.org/10.1126/science.1160794.

188. Huang, C.C., Yeh, H.Y., Lin, R., Liao, T.L., Shen, H.C., Yang, Y.Y., and Lin, H.C. (2024). Inhibition of visceral adipose tissue-derived pathogenic signals by activation of adenosine A(2A)R improves hepatic and cardiac dysfunction of NASH mice. Am. J. Physiol., Gastrointest. Liver Physiol. *326*, G385–G397. https://doi.org/10.1152/ajpgi.00104.2023.

189. Chen, M., Li, Y., Zhu, J.Y., Mu, W.J., Luo, H.Y., Yan, L.J., Li, S., Li, R.Y., Yin, M.T., Li, X., et al. (2025). Exercise-induced adipokine Nrg4 alleviates MASLD by disrupting hepatic cGAS-STING signaling. Cell Rep. *44*, 115251. https://doi.org/10.1016/j.celrep.2025.115251.

190. Rohm, T.V., Dos Reis, F.C.G., Cunha E Rocha, K., Isaac, R., Strayer, S., Murphy, C., Bandyopadhyay, G., Gao, H., Ganguly, S., Nguyen, T., et al. (2025). MASH adipose tissue macrophages secrete extracellular vesicles that activate liver fibrosis in obese male mice. Gastroenterology *169*, 691–704.e9. https://doi.org/10.1053/j.gastro.2025.03.033.

191. du Plessis, J., van Pelt, J., Korf, H., Mathieu, C., van der Schueren, B., Lannoo, M., Oyen, T., Topal, B., Fetter, G., Nayler, S., et al. (2015). Association of adipose tissue inflammation with histologic severity of nonalcoholic fatty liver disease. Gastroenterology *149*, 635–648.e14. https://doi.org/10.1053/j.gastro.2015.05.044.

192. Shen, W., Middleton, M.S., Cunha, G.M., Delgado, T.I., Wolfson, T., Gamst, A., Fowler, K.J., Alazraki, A., Trout, A.T., Ohliger, M.A., et al. (2023). Changes in abdominal adipose tissue depots assessed by MRI correlate with hepatic histologic improvement in non-alcoholic steatohepatitis. J. Hepatol. *78*, 238–246. https://doi.org/10.1016/j.jhep.2022.10.027.

193. Boesch, M., Lindhorst, A., Feio-Azevedo, R., Brescia, P., Silvestri, A., Lannoo, M., Deleus, E., Jaekers, J., Topal, H., Topal, B., et al. (2024). Adipose tissue macrophage dysfunction is associated with a breach of vascular integrity in NASH. J. Hepatol. *80*, 397–408. https://doi.org/10.1016/j.jhep.2023.10.039.

194. Hutchison, A.L., Tavaglione, F., Romeo, S., and Charlton, M. (2023). Endocrine aspects of metabolic dysfunction-associated steatotic liver disease (MASLD): Beyond insulin resistance. J. Hepatol. *79*, 1524–1541. https://doi.org/10.1016/j.jhep.2023.08.030.

195. Angulo, P., Kleiner, D.E., Dam-Larsen, S., Adams, L.A., Bjornsson, E.S., Charatcharoenwitthaya, P., Mills, P.R., Keach, J.C., Lafferty, H.D., Stahler, A., et al. (2015). Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology *149*, 389–397.e10. https://doi.org/10.1053/j.gastro.2015.04.043.

196. Sanyal, A.J., Van Natta, M.L., Clark, J., Neuschwander-Tetri, B.A., Diehl, A., Dasarathy, S., Loomba, R., Chalasani, N., Kowdley, K., Hameed, B., et al. (2021). Prospective study of outcomes in adults with nonalcoholic fatty liver disease. N. Engl. J. Med. *385*, 1559–1569. https://doi.org/10.1056/NEJMoa2029349.

197. Kim, H.Y., Rosenthal, S.B., Liu, X., Miciano, C., Hou, X., Miller, M., Buchanan, J., Poirion, O.B., Chilin-Fuentes, D., Han, C., et al. (2025). Multi-modal analysis of human hepatic stellate cells identifies novel therapeutic targets for metabolic dysfunction-associated steatotic liver disease. J. Hepatol. *82*, 882–897. https://doi.org/10.1016/j.jhep.2024.10.044.

198. Meng, F., Wang, K., Aoyama, T., Grivennikov, S.I., Paik, Y., Scholten, D., Cong, M., Iwaisako, K., Liu, X., Zhang, M., et al. (2012). Interleukin-17 signaling in inflammatory, Kupffer cells, and hepatic stellate cells exacerbates liver fibrosis in mice. Gastroenterology *143*, 765–776.e3. https://doi.org/10.1053/j.gastro.2012.05.049.

199. Wree, A., Eguchi, A., McGeough, M.D., Pena, C.A., Johnson, C.D., Canbay, A., Hoffman, H.M., and Feldstein, A.E. (2014). NLRP3 inflammasome activation results in hepatocyte pyroptosis, liver inflammation, and fibrosis in mice. Hepatology *59*, 898–910. https://doi.org/10.1002/hep.26592.

200. Mridha, A.R., Wree, A., Robertson, A.A.B., Yeh, M.M., Johnson, C.D., Van Rooyen, D.M., Haczeyni, F., Teoh, N.C.H., Savard, C., Ioannou, G.N., et al. (2017). NLRP3 inflammasome blockade reduces liver inflammation and fibrosis in experimental NASH in mice. J. Hepatol. *66*, 1037–1046. https://doi.org/10.1016/j.jhep.2017.01.022.

201. Kaufmann, B., Kui, L., Reca, A., Leszczynska, A., Kim, A.D., Booshehri, L.M., Wree, A., Friess, H., Hartmann, D., Broderick, L., et al. (2022). Cell-specific deletion of NLRP3 inflammasome identifies myeloid cells as key drivers of liver inflammation and fibrosis in murine steatohepatitis. Cell. Mol. Gastroenterol. Hepatol. *14*, 751–767. https://doi.org/10.1016/j.jcmgh.2022.06.007.

202. Dong, J., Viswanathan, S., Adami, E., Singh, B.K., Chothani, S.P., Ng, B., Lim, W.W., Zhou, J., Tripathi, M., Ko, N.S.J., et al. (2021). Hepatocyte-specific IL11 cis-signaling drives lipotoxicity and underlies the transition from NAFLD to NASH. Nat. Commun. *12*, 66. https://doi.org/10.1038/s41467-020-20303-z.

203. Widjaja, A.A., Lim, W.W., Viswanathan, S., Chothani, S., Corden, B., Dasan, C.M., Goh, J.W.T., Lim, R., Singh, B.K., Tan, J., et al. (2024). Inhibition of IL-11 signalling extends mammalian healthspan and lifespan. Nature *632*, 157–165. https://doi.org/10.1038/s41586-024-07701-9.

204. Kalligeros, M., Henry, L., and Younossi, Z.M. (2024). Metabolic dysfunction-associated steatotic liver disease and its link to cancer. Metabolism *160*, 156004. https://doi.org/10.1016/j.metabol.2024.156004.

205. Friedman, S.L. (2024). Hepatic fibrosis and cancer: the silent threats of metabolic syndrome. Diabetes Metab. J. *48*, 161–169. https://doi.org/10.4093/dmj.2023.0240.

206. Vaz, J., Jepsen, P., Strömberg, U., Midlöv, P., Eriksson, B., Buchebner, D., and Hagström, H. (2025). Metabolic dysfunction-associated steatotic liver disease has become the most common cause of hepatocellular carcinoma in Sweden: A nationwide cohort study. Int. J. Cancer *156*, 40–51. https://doi.org/10.1002/ijc.35097.

207. Park, E.J., Lee, J.H., Yu, G.Y., He, G., Ali, S.R., Holzer, R.G., Osterreicher, C.H., Takahashi, H., and Karin, M. (2010). Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. Cell *140*, 197–208. https://doi.org/10.1016/j.cell.2009.12.052.

208. Grohmann, M., Wiede, F., Dodd, G.T., Gurzov, E.N., Ooi, G.J., Butt, T., Rasmiena, A.A., Kaur, S., Gulati, T., Goh, P.K., et al. (2018). Obesity drives STAT-1-dependent NASH and STAT-3-dependent HCC. Cell *175*, 1289–1306.e20. https://doi.org/10.1016/j.cell.2018.09.053.

209. He, G., Dhar, D., Nakagawa, H., Font-Burgada, J., Ogata, H., Jiang, Y., Shalapour, S., Seki, E., Yost, S.E., Jepsen, K., et al. (2013). Identification of liver cancer progenitors whose malignant progression depends on autocrine IL-6 signaling. Cell *155*, 384–396. https://doi.org/10.1016/j.cell.2013.09.031.

210. Hotamisligil, G.S. (2017). Inflammation, metaflammation and immunometabolic disorders. Nature *542*, 177–185. https://doi.org/10.1038/nature21363.

211. Huang, J., Wang, M., Wu, Y., Kumar, R., and Lin, S. (2022). Serum high-sensitive C-reactive protein is a simple indicator for all-cause among individuals with MAFLD. Front. Physiol. *13*, 1012887. https://doi.org/10.3389/fphys.2022.1012887.

212. Ridker, P.M., Everett, B.M., Thuren, T., MacFadyen, J.G., Chang, W.H., Ballantyne, C., Fonseca, F., Nicolau, J., Koenig, W., Anker, S.D., et al. (2017). Antiinflammatory therapy with canakinumab for atherosclerotic disease. N. Engl. J. Med. *377*, 1119–1131. https://doi.org/10.1056/NEJMoa1707914.

213. Xie, W., Gan, J., Zhou, X., Tian, H., Pan, X., Liu, W., Li, X., Du, J., Xu, A., Zheng, M., et al. (2024). Myocardial infarction accelerates the progression of MASH by triggering immunoinflammatory response and induction of periosti. Cell Metab. *36*, 1269–1286.e9. https://doi.org/10.1016/j.cmet.2024.04.020.

214. Chew, N.W.S., Mehta, A., Goh, R.S.J., Zhang, A., Chen, Y., Chong, B., Chew, H.S.J., Shabbir, A., Brown, A., Dimitriadis, G.K., et al. (2025). Cardiovascular-liver-metabolic health: recommendations in screening, diagnosis, and management of metabolic dysfunction-associated steatotic liver disease in cardiovascular disease via modified Delphi approach. Circulation *151*, 98–119. https://doi.org/10.1161/CIRCULATIONAHA.124.070535.

215. Gries, J.J., Lazarus, J.V., Brennan, P.N., Siddiqui, M.S., Targher, G., Lang, C.C., Virani, S.S., Lavie, C.J., Isaacs, S., Arab, J.P., et al. (2025). Interdisciplinary perspectives on the co-management of metabolic dysfunction-associated steatotic liver disease and coronary artery disease. Lancet Gastroenterol. Hepatol. *10*, 82–94. https://doi.org/10.1016/S2468-1253(24)00310-8.

216. Ridker, P.M., Bhatt, D.L., Pradhan, A.D., Glynn, R.J., MacFadyen, J.G., and Nissen, S.E.; PROMINENT, REDUCE-IT, and STRENGTH Investigators (2023). Inflammation and cholesterol as predictors of cardiovascular events among patients receiving statin therapy: a collaborative analysis of three randomised trials. Lancet *401*, 1293–1301. https://doi.org/10.1016/S0140-6736(23)00215-5.

217. Mantovani, A., Allavena, P., Sica, A., and Balkwill, F. (2008). Cancer-related inflammation. Nature *454*, 436–444. https://doi.org/10.1038/nature07205.

Please cite this article in press as: Tilg et al., The many pathways driving liver inflammation in MASH, Cell Metabolism (2026), https://doi.org/10.1016/j.cmet.2026.02.018

218. Carlsson, L.M.S., Sjöholm, K., Jacobson, P., Andersson-Assarsson, J.C., Svensson, P.A., Taube, M., Carlsson, B., and Peltonen, M. (2020). Life expectancy after bariatric surgery in the Swedish Obese Subjects Study. N. Engl. J. Med. *383*, 1535–1543. https://doi.org/10.1056/NEJMoa2002449.

219. Hardvik Åkerström, J., Santoni, G., von Euler Chelpin, M., Chidambaram, S., Markar, S.R., Maret-Ouda, J., Ness-Jensen, E., Kauppila, J.H., Holmberg, D., and Lagergren, J. (2023). Decreased risk of esophageal adenocarcinoma after gastric bypass surgery in a cohort study from 3 Nordic countries. Ann. Surg. *278*, 904–909. https://doi.org/10.1097/SLA.0000000000006003.

220. Mantovani, A., Petracca, G., Beatrice, G., Csermely, A., Tilg, H., Byrne, C.D., and Targher, G. (2022). Non-alcoholic fatty liver disease and increased risk of incident extrahepatic cancers: a meta-analysis of observational cohort studies. Gut *71*, 778–788. https://doi.org/10.1136/gutjnl-2021-324191.

221. Chan, K.E., Ong, E.Y.H., Chung, C.H., Ong, C.E.Y., Koh, B., Tan, D.J.H., Lim, W.H., Yong, J.N., Xiao, J., Wong, Z.Y., et al. (2024). Longitudinal outcomes associated with metabolic dysfunction-associated steatotic liver disease: a meta-analysis of 129 studies. Clin. Gastroenterol. Hepatol. *22*, 488–498.e14. https://doi.org/10.1016/j.cgh.2023.09.018.

222. Allen, A.M., Hicks, S.B., Mara, K.C., Larson, J.J., and Therneau, T.M. (2019). The risk of incident extrahepatic cancers is higher in non-alcoholic fatty liver disease than obesity - A longitudinal cohort study. J. Hepatol. *71*, 1229–1236. https://doi.org/10.1016/j.jhep.2019.08.018.

223. Li, W., and Wang, W. (2025). Unravelling the obesity paradox in MASLD patients with extrahepatic cancer. Gut *74*, 501–503. https://doi.org/10.1136/gutjnl-2024-333087.

224. Ridker, P.M., MacFadyen, J.G., Thuren, T., Everett, B.M., Libby, P., and Glynn, R.J.; CANTOS Trial Group (2017). Effect of interleukin-1beta inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. Lancet *390*, 1833–1842. https://doi.org/10.1016/S0140-6736(17)32247-X.

225. Tacke, F., Puengel, T., Loomba, R., and Friedman, S.L. (2023). An integrated view of anti-inflammatory and antifibrotic targets for the treatment of NASH. J. Hepatol. *79*, 552–566. https://doi.org/10.1016/j.jhep.2023.03.038.

226. Tincopa, M.A., Anstee, Q.M., and Loomba, R. (2024). New and emerging treatments for metabolic dysfunction-associated steatohepatitis. Cell Metab. *36*, 912–926. https://doi.org/10.1016/j.cmet.2024.03.011.

227. Souza, M., Al-Sharif, L., Antunes, V.L.J., Huang, D.Q., and Loomba, R. (2025). Comparison of pharmacological therapies in metabolic dysfunction-associated steatohepatitis for fibrosis regression and MASH resolution: Systematic review and network meta-analysis. Hepatology *82*, 1523–1533. https://doi.org/10.1097/HEP.0000000000001254.

228. Newsome, P.N., and Loomba, R. (2025). Therapeutic horizons in metabolic dysfunction-associated steatohepatitis. J. Clin. Investig. *135*, e186425. https://doi.org/10.1172/JCI186425.

229. Sanyal, A.J., Newsome, P.N., Kliers, I., Østergaard, L.H., Long, M.T., Kjær, M.S., Cali, A.M.G., Bugianesi, E., Rinella, M.E., Roden, M., et al. (2025). Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. N. Engl. J. Med. *392*, 2089–2099. https://doi.org/10.1056/NEJMoa2413258.

230. da Silva Lima, N., Cabaleiro, A., Novoa, E., Riobello, C., Knerr, P.J., He, Y., Esquinas-Román, E.M., González-García, I., Prevot, V., Schwaninger, M., et al. (2024). GLP-1 and GIP agonism has no direct actions in human hepatocytes or hepatic stellate cells. Cell. Mol. Life Sci. *81*, 468. https://doi.org/10.1007/s00018-024-05507-6.

231. Zafer, M., Tavaglione, F., Romero-Gómez, M., and Loomba, R. (2025). Review article: GLP-1 receptor agonists and glucagon/GIP/GLP-1 receptor dual or triple agonists-mechanism of action and emerging therapeutic landscape in MASLD. Aliment. Pharmacol. Ther. *61*, 1872–1888. https://doi.org/10.1111/apt.70196.

232. Romero-Gómez, M., Lawitz, E., Shankar, R.R., Chaudhri, E., Liu, J., Lam, R.L.H., Kaufman, K.D., and Engel, S.S.; MK-6024 P001 Study Group (2023). A phase IIa active-comparator-controlled study to evaluate the efficacy and safety of efinopegdutide in patients with non-alcoholic fatty liver disease. J. Hepatol. *79*, 888–897. https://doi.org/10.1016/j.jhep.2023.05.013.

233. Sanyal, A.J., Bedossa, P., Fraessdorf, M., Neff, G.W., Lawitz, E., Bugianesi, E., Anstee, Q.M., Hussain, S.A., Newsome, P.N., Ratziu, V., et al. (2024). A phase 2 randomized trial of survodutide in MASH and fibrosis. N. Engl. J. Med. *391*, 311–319. https://doi.org/10.1056/NEJMoa2401755.

234. Loomba, R., Hartman, M.L., Lawitz, E.J., Vuppalanchi, R., Boursier, J., Bugianesi, E., Yoneda, M., Behling, C., Cummings, O.W., Tang, Y., et al. (2024). Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. N. Engl. J. Med. *391*, 299–310. https://doi.org/10.1056/NEJMoa2401943.

235. Sanyal, A.J., Kaplan, L.M., Frias, J.P., Brouwers, B., Wu, Q., Thomas, M.K., Harris, C., Schloot, N.C., Du, Y., Mather, K.J., et al. (2024). Triple hormone receptor agonist retatrutide for metabolic dysfunction-associated steatotic liver disease: a randomized phase 2a trial. Nat. Med. *30*, 2037–2048. https://doi.org/10.1038/s41591-024-03018-2.

236. Francque, S.M., Bedossa, P., Ratziu, V., Anstee, Q.M., Bugianesi, E., Sanyal, A.J., Loomba, R., Harrison, S.A., Balabanska, R., Mateva, L., et al. (2021). A randomized, controlled trial of the pan-PPAR agonist lanifibranor in NASH. N. Engl. J. Med. *385*, 1547–1558. https://doi.org/10.1056/NEJMoa2036205.

237. Kliewer, S.A., and Mangelsdorf, D.J. (2019). A dozen years of discovery: insights into the physiology and pharmacology of FGF21. Cell Metab. *29*, 246–253. https://doi.org/10.1016/j.cmet.2019.01.004.

238. Rose, J.P., Morgan, D.A., Sullivan, A.I., Fu, X., Inigo-Vollmer, M., Burgess, S.C., Meyerholz, D.K., Rahmouni, K., and Potthoff, M.J. (2025). FGF21 reverses MASH through coordinated actions on the CNS and liver. Cell Metab. *37*, 1515–1529.e6. https://doi.org/10.1016/j.cmet.2025.04.014.

239. Choi, M., Schneeberger, M., Fan, W., Bugde, A., Gautron, L., Vale, K., Hammer, R.E., Zhang, Y., Friedman, J.M., Mangelsdorf, D.J., et al. (2023). FGF21 counteracts alcohol intoxication by activating the noradrenergic nervous system. Cell Metab. *35*, 429–437.e5. https://doi.org/10.1016/j.cmet.2023.02.005.

240. Flippo, K.H., Trammell, S.A.J., Gillum, M.P., Aklan, I., Perez, M.B., Yavuz, Y., Smith, N.K., Jensen-Cody, S.O., Zhou, B., Claflin, K.E., et al. (2022). FGF21 suppresses alcohol consumption through an amygdalo-striatal circuit. Cell Metab. *34*, 317–328.e6. https://doi.org/10.1016/j.cmet.2021.12.024.

241. Harrison, S.A., Frias, J.P., Neff, G., Abrams, G.A., Lucas, K.J., Sanchez, W., Gogia, S., Sheikh, M.Y., Behling, C., Bedossa, P., et al. (2023). Safety and efficacy of once-weekly efruxifermin versus placebo in non-alcoholic steatohepatitis (HARMONY): a multicentre, randomised, double-blind, placebo-controlled, phase 2b trial. Lancet Gastroenterol. Hepatol. *8*, 1080–1093. https://doi.org/10.1016/S2468-1253(23)00272-8.

242. Noureddin, M., Rinella, M.E., Chalasani, N.P., Neff, G.W., Lucas, K.J., Rodriguez, M.E., Rudraraju, M., Patil, R., Behling, C., Burch, M., et al. (2025). Efruxifermin in compensated liver cirrhosis caused by MASH. N. Engl. J. Med. *392*, 2413–2424. https://doi.org/10.1056/NEJMoa2502242.

243. Loomba, R., Sanyal, A.J., Kowdley, K.V., Bhatt, D.L., Alkhouri, N., Frias, J.P., Bedossa, P., Harrison, S.A., Lazas, D., Barish, R., et al. (2023). Randomized, controlled trial of the FGF21 analogue pegozafermin in NASH. N. Engl. J. Med. *389*, 998–1008. https://doi.org/10.1056/NEJMoa2304286.

244. Loomba, R., Kowdley, K.V., Rodriguez, J., Kim, N.J., Alvarez, A.M., Morrow, L., Jeglinski, B., Clawson, A., Chowdhury, S., Bain, G., et al. (2025). Efimosfermin alfa (BOS-580), a long-acting FGF21 analogue, in participants with phenotypic metabolic dysfunction-associated steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2a trial. Lancet Gastroenterol. Hepatol. *10*, 734–745. https://doi.org/10.1016/S2468-1253(25)00067-6.

245. Wang, X., Wang, L., Geng, L., Tanaka, N., and Ye, B. (2023). Resmetirom ameliorates NASH-model mice by suppressing STAT3 and NF-κB signaling pathways in an RGS5-dependent manner. Int. J. Mol. Sci. *24*, 5843. https://doi.org/10.3390/ijms24065843.

246. Harrison, S.A., Bashir, M.R., Guy, C.D., Zhou, R., Moylan, C.A., Frias, J.P., Alkhouri, N., Bansal, M.B., Baum, S., Neuschwander-Tetri, B.A.,

Please cite this article in press as: Tilg et al., The many pathways driving liver inflammation in MASH, Cell Metabolism (2026), https://doi.org/10.1016/j.cmet.2026.02.018

et al. (2019). Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet *394*, 2012–2024. https://doi.org/10.1016/S0140-6736(19)32517-6.

247. Byrne, C.D., Targher, G., and Tilg, H. (2024). Thyroid hormone receptor-beta agonists: new MASLD therapies on the horizon. Gut *73*, 573–581. https://doi.org/10.1136/gutjnl-2023-330596.

248. Wong, C.K., and Drucker, D.J. (2025). Antiinflammatory actions of glucagon-like peptide-1-based therapies beyond metabolic benefits. J. Clin. Investig. *135*, e194751. https://doi.org/10.1172/JCI194751.

249. Tilg, H., and Targher, G. (2025). Lessons from incretin-based therapy in MASH and obesity. Nat. Rev. Gastroenterol. Hepatol. *22*, 531–533. https://doi.org/10.1038/s41575-025-01096-2.

250. Rakipovski, G., Rolin, B., Nøhr, J., Klewe, I., Frederiksen, K.S., Augustin, R., Hecksher-Sørensen, J., Ingvorsen, C., Polex-Wolf, J., and Knudsen, L.B. (2018). The GLP-1 analogs liraglutide and semaglutide reduce atherosclerosis in ApoE(-/-) and LDLr(-/-) mice by a mechanism that includes inflammatory pathways. JACC Basic Transl. Sci. *3*, 844–857. https://doi.org/10.1016/j.jacbts.2018.09.004.

251. Ros-Madrid, I., Cano-Mármol, R.P., Ferrer-Gomez, M., and Ramos-Molina, B. (2025). Anti-inflammatory properties of GLP-1 receptor agonists and other ancillary benefits from a pharmacological perspective. Can. J. Physiol. Pharmacol. *103*, 369–377. https://doi.org/10.1139/cjpp-2025-0148.

252. Xue, S., Wasserfall, C.H., Parker, M., Brusko, T.M., McGrail, S., McGrail, K., Moore, M., Campbell-Thompson, M., Schatz, D.A., Atkinson, M.A., et al. (2008). Exendin-4 therapy in NOD mice with new-onset diabetes increases regulatory T cell frequency. Ann. N. Y. Acad. Sci. *1150*, 152–156. https://doi.org/10.1196/annals.1447.049.

253. le Kim Chung, K., Hosaka, T., Yoshida, M., Harada, N., Sakaue, H., Sakai, T., and Nakaya, Y. (2009). Exendin-4, a GLP-1 receptor agonist, directly induces adiponectin expression through protein kinase A pathway and prevents inflammatory adipokine expression. Biochem. Biophys. Res. Commun. *390*, 613–618. https://doi.org/10.1016/j.bbrc.2009.10.015.

254. Shiraishi, D., Fujiwara, Y., Komohara, Y., Mizuta, H., and Takeya, M. (2012). Glucagon-like peptide-1 (GLP-1) induces M2 polarization of human macrophages via STAT3 activation. Biochem. Biophys. Res. Commun. *425*, 304–308. https://doi.org/10.1016/j.bbrc.2012.07.086.

255. Wong, C.K., McLean, B.A., Baggio, L.L., Koehler, J.A., Hammoud, R., Rittig, N., Yabut, J.M., Seeley, R.J., Brown, T.J., and Drucker, D.J. (2024). Central glucagon-like peptide 1 receptor activation inhibits Toll-like receptor agonist-induced inflammation. Cell Metab. *36*, 130–143.e5. https://doi.org/10.1016/j.cmet.2023.11.009.

256. Krasner, N.M., Ido, Y., Ruderman, N.B., and Cacicedo, J.M. (2014). Glucagon-like peptide-1 (GLP-1) analog liraglutide inhibits endothelial cell inflammation through a calcium and AMPK dependent mechanism. PLOS One *9*, e97554. https://doi.org/10.1371/journal.pone.0097554.

257. Martins, F.F., Marinho, T.S., Cardoso, L.E.M., Barbosa-da-Silva, S., Souza-Mello, V., Aguila, M.B., and Mandarim-de-Lacerda, C.A. (2022). Semaglutide (GLP-1 receptor agonist) stimulates browning on subcutaneous fat adipocytes and mitigates inflammation and endoplasmic reticulum stress in visceral fat adipocytes of obese mice. Cell Biochem. Funct. *40*, 903–913. https://doi.org/10.1002/cbf.3751.

258. Jara, M., Norlin, J., Kjær, M.S., Almholt, K., Bendtsen, K.M., Bugianesi, E., Cusi, K., Galsgaard, E.D., Geybels, M., Gluud, L.L., et al. (2025). Modulation of metabolic, inflammatory and fibrotic pathways by semaglutide in metabolic dysfunction-associated steatohepatitis. Nat. Med. *31*, 3128–3140. https://doi.org/10.1038/s41591-025-03799-0.

259. He, Y., Chen, Y., Qian, S., van Der Merwe, S., Dhar, D., Brenner, D.A., and Tacke, F. (2025). Immunopathogenic mechanisms and immunoregulatory therapies in MASLD. Cell. Mol. Immunol. *22*, 1159–1177. https://doi.org/10.1038/s41423-025-01307-5.

260. Lefere, S., Puengel, T., Hundertmark, J., Penners, C., Frank, A.K., Guillot, A., de Muynck, K., Heymann, F., Adarbes, V., Defrêne, E., et al. (2020). Differential effects of selective- and pan-PPAR agonists on experimental steatohepatitis and hepatic macrophages☆. J. Hepatol. *73*, 757–770. https://doi.org/10.1016/j.jhep.2020.04.025.

261. Cooreman, M.P., Butler, J., Giugliano, R.P., Zannad, F., Dzen, L., Huot-Marchand, P., Baudin, M., Beard, D.R., Junien, J.L., Broqua, P., et al. (2024). The pan-PPAR agonist lanifibranor improves cardiometabolic health in patients with metabolic dysfunction-associated steatohepatitis. Nat. Commun. *15*, 3962. https://doi.org/10.1038/s41467-024-47919-9.

262. Li, X., Rao, Z., Hu, W., Lu, W., and Luo, Y. (2025). Treating metabolic dysfunction-associated steatohepatitis: The fat-trimming FGF21 approach. Obes. Rev. *26*, e13861. https://doi.org/10.1111/obr.13861.

263. Yu, Y., Li, S., Liu, Y., Tian, G., Yuan, Q., Bai, F., Wang, W., Zhang, Z., Ren, G., Zhang, Y., et al. (2015). Fibroblast growth factor 21 (FGF21) ameliorates collagen-induced arthritis through modulating oxidative stress and suppressing nuclear factor-kappa B pathway. Int. Immunopharmacol. *25*, 74–82. https://doi.org/10.1016/j.intimp.2015.01.005.

264. Inia, J.A., Attema, J., de Ruiter, C., Menke, A.L., Caspers, M.P.M., Verschuren, L., Wilson, M., Arlantico, A., Brightbill, H.D., Jukema, J.W., et al. (2024). Therapeutic effects of FGF21 mimetic bFKB1 on MASH and atherosclerosis in Ldlr-/-.Leiden mice. FASEB J. *38*, e70087. https://doi.org/10.1096/fj.202401397R.

265. Theofilis, P., Oikonomou, E., Karakasis, P., Pamporis, K., Dimitriadis, K., Kokkou, E., Lambadiari, V., Siasos, G., Tsioufis, K., and Tousoulis, D. (2025). FGF21 analogues in patients with metabolic diseases: systematic review and meta-analysis of randomised controlled trials. Liver Int. *45*, e70016. https://doi.org/10.1111/liv.70016.

266. Vacca, M., Kamzolas, I., Harder, L.M., Oakley, F., Trautwein, C., Hatting, M., Ross, T., Bernardo, B., Oldenburger, A., Hjuler, S.T., et al. (2024). An unbiased ranking of murine dietary models based on their proximity to human metabolic dysfunction-associated steatotic liver disease (MASLD). Nat. Metab. *6*, 1178–1196. https://doi.org/10.1038/s42255-024-01043-6.

267. Hsu, C.L., and Loomba, R. (2024). From NAFLD to MASLD: implications of the new nomenclature for preclinical and clinical research. Nat. Metab. *6*, 600–602. https://doi.org/10.1038/s42255-024-00985-1.

268. Jamialahmadi, O., De Vincentis, A., Tavaglione, F., Malvestiti, F., Li-Gao, R., Mancina, R.M., Alvarez, M., Gelev, K., Maurotti, S., Vespasiani-Gentilucci, U., et al. (2024). Partitioned polygenic risk scores identify distinct types of metabolic dysfunction-associated steatotic liver disease. Nat. Med. *30*, 3614–3623. https://doi.org/10.1038/s41591-024-03284-0.

269. Colella, F., Henderson, N.C., and Ramachandran, P. (2025). Dissecting the mechanisms of MASLD fibrosis in the era of single-cell and spatial omics. J. Clin. Investig. *135*, e186421. https://doi.org/10.1172/JCI186421.

270. Hong, S.E., Mun, S.J., Lee, Y.J., Yoo, T., Suh, K.S., Kang, K.W., Son, M.J., Kim, W., and Choi, M. (2025). Single-cell eQTL analysis identifies genetic variation underlying metabolic dysfunction-associated steatohepatitis. Nat. Genet. *57*, 1638–1648. https://doi.org/10.1038/s41588-025-02237-8.

271. Martin, O.P., Wallace, M.S., Oetheimer, C., Patel, H.B., Butler, M.D., Wong, L.P., Huang, P., Elbaz, J., Costentin, C., Salloum, S., et al. (2025). Single-cell atlas of human liver and blood immune cells across fatty liver disease stages reveals distinct signatures linked to liver dysfunction and fibrogenesis. Nat. Immunol. *26*, 1596–1611. https://doi.org/10.1038/s41590-025-02255-y.

272. Zhang, Y.H., Xie, R., Dai, C.S., Gao, H.W., Zhou, G., Qi, T.T., Wang, W.Y., Wang, H., and Cui, Y.M. (2025). Thyroid hormone receptor-beta agonist HSK31679 alleviates MASLD by modulating gut microbial sphingolipids. J. Hepatol. *82*, 189–202. https://doi.org/10.1016/j.jhep.2024.08.008.

273. Targher, G., Mantovani, A., Byrne, C.D., and Tilg, H. (2025). Recent advances in incretin-based therapy for MASLD: from single to dual or triple incretin receptor agonists. Gut *74*, 487–497. https://doi.org/10.1136/gutjnl-2024-334023.

274. Gleeson, M., Bishop, N.C., Stensel, D.J., Lindley, M.R., Mastana, S.S., and Nimmo, M.A. (2011). The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. Nat. Rev. Immunol. *11*, 607–615. https://doi.org/10.1038/nri3041.

275. Schwabe, R.F., Tacke, F., Sugimoto, A., and Friedman, S.L. (2025). Antifibrotic therapies for metabolic dysfunction-associated steatotic liver disease. JHEP Rep. *7*, 101421. https://doi.org/10.1016/j.jhepr.2025.101421.