

An adipocentric perspective on the development and progression of non-alcoholic fatty liver disease

Eunyoung Lee^{1,2}, Hannelie Korf^{3,*}, Antonio Vidal-Puig^{1,4,5,*}

Summary

Alongside the liver, white adipose tissue (WAT) is critical in regulating systemic energy homeostasis. Although each organ has its specialised functions, they must work coordinately to regulate whole-body metabolism. Adipose tissues and the liver are relatively resilient and can adapt to an energy surplus by facilitating triglyceride (TG) storage up to a certain threshold level without significant metabolic disturbances. However, lipid storage in WAT beyond a “personalised” adiposity threshold becomes dysfunctional, leading to metabolic inflexibility, progressive inflammation, and aberrant adipokine secretion. Moreover, the failure of adipose tissue to store and mobilise lipids results in systemic knock-on lipid overload, particularly in the liver. Factors contributing to hepatic lipid overload include lipids released from WAT, dietary fat intake, and enhanced *de novo* lipogenesis. In contrast, extrahepatic mechanisms counteracting toxic hepatic lipid overload entail coordinated compensation through oxidation of surplus fatty acids in brown adipose tissue and storage of fatty acids as TGs in WAT. Failure of these integrated homeostatic mechanisms leads to quantitative increases and qualitative alterations to the lipidome of the liver. Initially, hepatocytes preferentially accumulate TG species leading to a relatively “benign” non-alcoholic fatty liver. However, with time, inflammatory responses ensue, progressing into more severe conditions such as non-alcoholic steatohepatitis, cirrhosis, and hepatocellular carcinoma, in some individuals (often without an early prognostic clue). Herein, we highlight the pathogenic importance of obesity-induced “adipose tissue failure”, resulting in decreased adipose tissue functionality (*i.e.* fat storage capacity and metabolic flexibility), in the development and progression of NAFL/NASH.

© 2023 The Author(s). Published by Elsevier B.V. on behalf of European Association for the Study of the Liver. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).



Introduction

The development of obesity-associated comorbidities, such as non-alcoholic fatty liver disease (NAFLD), depends on how functionally resilient the obese adipose tissue and other metabolically relevant organs are to the surplus of nutrients. The white adipose tissue (WAT) is the primary lipid storage organ and regulates systemic energy homeostasis by controlling metabolic flexibility and lipid fluxes to other organs. Additionally, WAT secretes adipokines that regulate energy balance and systemic glucose and lipid metabolism within distant target tissues, such as the liver, muscle, and brain.¹ During prolonged metabolic stress due to nutrient overload, a state of adipose failure/dysfunction ensues, resulting in the loss of its metabolic flexibility (MetFlex), insufficient lipid buffering capacity, and unsuppressed release of fatty acids from adipose tissues,² triggering a systemic maladaptive response to nutrient surplus, disrupting lipids fluxes, and increasing (fibro)inflammation.^{2,3} Adipose tissue inflammation, in turn, leads to an aberrant cytokine secretion profile. Additionally, the stressed adipose tissue secretes qualitatively/quantitatively altered extracellular vesicles (EVs), including exosomes, contributing to

local and distant homeostatic disruption. Combined, these adipose tissue-derived factors directly or indirectly disrupt lipid metabolism in the liver, initiating and propagating the development of NAFLD.

NAFLD includes diverse hepatic manifestations ranging from steatosis (non-alcoholic fatty liver [NAFL]) to the more aggressive non-alcoholic steatohepatitis (NASH). NASH is characterised by inflammation and hepatocyte damage, which trigger a fibrogenic response in the hepatic niche. Importantly, NASH and fibrosis are critical for disease progression towards cirrhosis and hepatocellular carcinoma.^{4,5} The development of NASH is a critical transitional step in the clinical progression of NAFLD. The number of patients with NAFLD is dramatically increasing, representing 32.4% of the population,⁶ and a proportional increase in NASH cases is expected. Recently, the importance of metabolic dysfunction in the development of fatty liver disease has been recognised (with the recently coined term MAFLD), mainly because hepatic triglyceride (TG) accumulation is associated with obesity, insulin resistance (IR), type 2 diabetes mellitus (T2DM) and hypertension.^{4,7} Notably, IR,^{8,9} adipose dysfunction,^{10,11} and gut dysbiosis^{12,13}

Keywords: adipose tissue biology; metabolic flexibility; inflammation; adipokines; cytokines; NAFLD; fatty acid flux; NASH.

Received 30 September 2022; received in revised form 20 December 2022; accepted 19 January 2023; available online 3 February 2023

* Corresponding authors. Addresses: Metabolic Research Laboratories, Wellcome Trust MRC Institute of Metabolic Science, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK (A. Vidal-Puig), or Laboratory of Hepatology, CHROMETA Department, KU Leuven, Leuven, Belgium (H. Korf).

E-mail addresses: ajv22@cam.ac.uk (A. Vidal-Puig), hannelie.korf@kuleuven.be (H. Korf).

<https://doi.org/10.1016/j.jhep.2023.01.024>



ELSEVIER

Key points

- Adipose tissues and the liver are relatively resilient to energy surpluses, as they can store excess energy as benign triglycerides and hence avoid metabolic disturbances.
- Adipose tissue dysfunction contributes to metabolic inflexibility, progressive inflammation, and aberrant adipokine secretion, ultimately leading to systemic insulin resistance and metabolic diseases.
- Increased circulating free fatty acids, caused by lipolysis in adipose tissue, are diverted to the liver.
- The interplay between altered adipose tissue biology and liver metabolism contributes to the development of NAFLD through various external and internal factors.
- Factors such as cytokines, adipokines, and exosomes secreted from adipose tissues play a crucial role in the development of NASH.
- Up to a point, expansion of healthy adipose tissue in individuals with metabolically healthy obesity can protect against NASH, T2DM, or dyslipidaemia by expanding healthy adipose tissues.
- Early interventions to prevent obesity-induced adipose tissue dysfunction, including promoting healthy adipose tissue expansion and/or increased oxidative capacity through BAT activation or WAT beiging, could be a therapeutic approach for NAFLD.

contribute to the development of NAFLD in patients with obesity, as part of the spectrum of metabolically unhealthy obesity (MUO). However, not all obese patients develop NAFLD, T2DM, or dyslipidaemia¹⁴ (Fig. 1), a phenotype known as metabolically healthy obesity (MHO), as they are protected from metabolic disturbances by efficient fat storage in healthy expandable adipose tissue.^{15,16} Notably, NAFLD can also be diagnosed in lean individuals (metabolically unhealthy lean). Despite their leanness, the contribution of adipose tissue failure to NAFLD in individuals with MUL, owing to limited capacity for adipose expansion, should not be dismissed.

In this review, we will discuss the crosstalk between adipose tissue and the liver from an adipocentric perspective, underlining the contribution of adipose tissue failure to the development of NAFLD. We further emphasise the therapeutic importance of early treatments aimed at restoring/maintaining adipose tissue function to prevent/reverse the development and progression of NAFLD.

Obesity-induced metabolic inflexibility within adipose tissue disrupts whole-body metabolism and fluxes

MetFlex is the capacity to rapidly switch from glucose to fatty acids as energy sources, for example, during the transition between feeding and fasting conditions.¹⁷ Notably, MetFlex is impaired in individuals with obesity or T2DM through defects in adipose tissue and skeletal muscle.^{18–21} At a mechanistic level, obese patients with T2DM exhibit metabolic inflexibility, as assessed by euglycemic-hyperinsulinemic clamp, due to defective glucose transport rather than defective glucose oxidation.²² Patients with NAFL also show impaired MetFlex associated with decreased insulin sensitivity and insulin-stimulated glucose disposal in adipose tissue and liver.²³ Glucose disposal after insulin stimulation is also reduced in non-obese, non-diabetic patients with NAFLD, although the increased glycerol in plasma indicates IR in their adipose tissues.²⁴

Additionally, the efficient diurnal fluctuation in nutritional fluxes is beneficial in optimising the MetFlex capacity of the

adipose tissue. However, in chronic overnutrition and obesity, the adipose tissue is highly susceptible to becoming metabolically inflexible, thereby failing to store and mobilise lipids quickly and efficiently. Moreover, the sustained excess of free fatty acids (FFAs) in circulation leads to systemic metabolic inflexibility affecting the liver and muscle, and promoting IR. Thus, obesity-associated metabolic inflexibility of the adipose tissue may promote the impairment of MetFlex in the liver and muscle.

Unleashing lipolysis in adipose tissue induces NAFLD

Insulin is an adipogenic hormone and a critical regulator of TG storage and lipolysis in adipose tissue in response to feeding and fasting. In the fed state, insulin suppresses ATGL (adipose TG lipase) and HSL (hormone-sensitive lipase), blocking lipolysis. Insulin also promotes glucose uptake and the production of glycerol 3-phosphate, an essential metabolite in TG synthesis that contributes to TG storage in adipose tissue.²⁵ These anabolic actions are impaired in obese insulin-resistant individuals,²⁶ contributing to elevated circulating FFAs.¹⁰ The pathogenic relevance of adipose tissue-leaked FFAs on NAFLD is demonstrated by experiments in *Abhd15* deficient mice, which showed enhanced lipolysis, resulting in systemic IR and NAFLD.^{27–29} Conversely, pharmacological inhibition of lipolysis using aglistatin, an inhibitor of ATGL, is sufficient to prevent obesity-induced IR and NAFLD in mice.³⁰

Defective TG storage in adipose tissue promotes NAFLD development

Humans with genetic and acquired forms of lipodystrophy develop IR, T2DM, hyperlipidaemia, and NAFLD.^{31,32} The relevance of “*adipose failure*” on NAFLD is highlighted by the phenotype of genetically engineered mice with selective defective TG storage in adipose tissue. Mouse models of lipodystrophy, including adipose tissue-specific insulin receptor-,³³ Raptor/mTORC1-,³⁴ and Hsl-³⁵ knockout mice, all develop hepatic steatosis. In these models, failure to buffer and handle FFA metabolism in adipose tissue redirects lipid fluxes to the liver. The release of FFAs from adipose tissue depends on the net balance

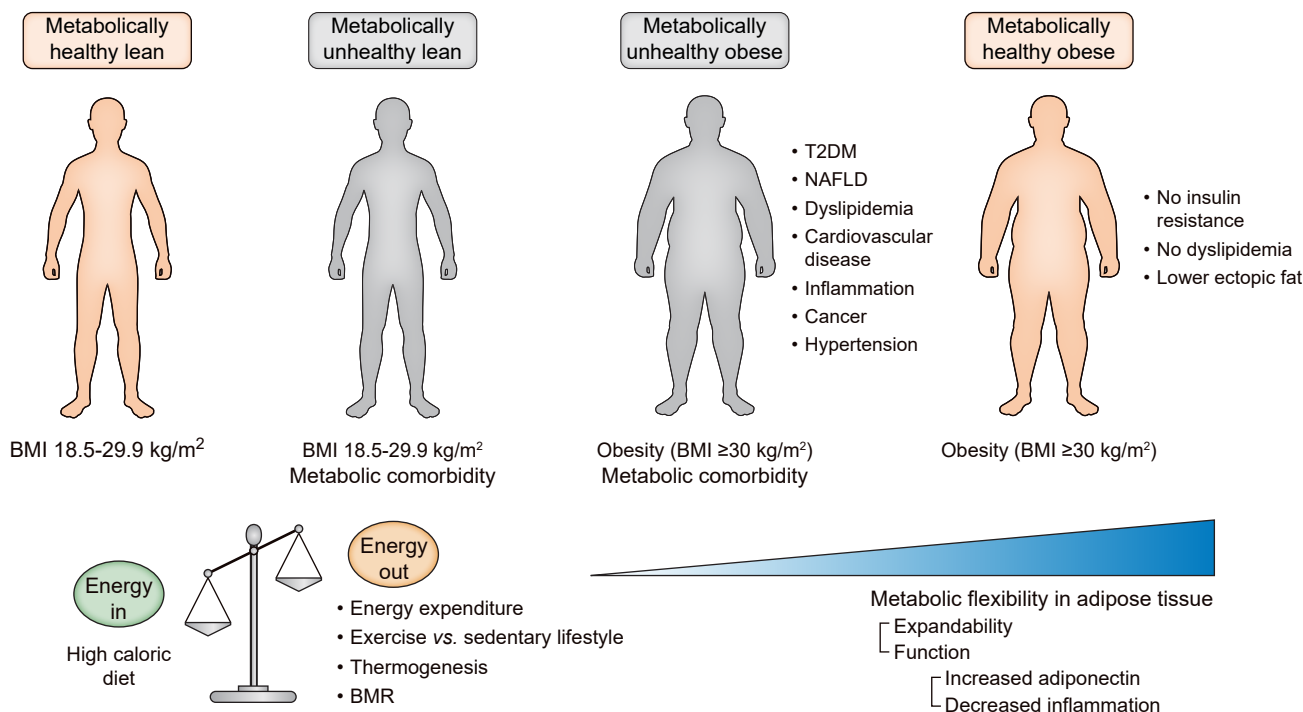


Fig. 1. Different types of obesity differing in coexistence of metabolic comorbidities. While some obese individuals do not display any metabolic abnormality, such as NAFLD, T2DM, or dyslipidemia (MHO), some lean individuals may develop NAFLD (MUL). Although the mechanism for the uncoupling between adiposity and NAFLD among individuals is unknown, metabolic inflexibility in adipose tissues might be one of the contributors to the development of metabolic comorbidities. BMR, basal metabolic rate; MHL, metabolically healthy lean; MUL, metabolically unhealthy lean; MUO, metabolically unhealthy obesity; MHO, metabolically healthy obesity; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus.

between lipolysis and FA re-esterification. Insulin promotes fat deposition by inhibiting lipolysis and stimulating FA re-esterification.^{36,37} Hepatic re-esterification of the FFAs derived from adipose tissue also significantly contributes to hepatic TG accumulation.³⁸ Notably, a unique insight from patients with pathogenic variants in the insulin receptor is that they develop hyperglycaemia without steatosis, indicating that a functional insulin receptor in the liver is required to promote FA re-esterification and TG accumulation.³⁹

Altered fat metabolism in NAFLD is secondary to adipocyte dysfunction

The liver has a predetermined lipid buffering capacity, which enables it to store the excess inflow of dietary- and adipose tissue-derived FFAs, conferring a certain degree of protection against local and systemic lipotoxicity. These anti-lipotoxic mechanisms involve upregulating FA oxidation and/or re-esterifying FFAs into metabolically harmless TGs that can be safely stored in the liver.⁴⁰ Increased circulating FFAs released from adipose tissue during fasting or in obesity reach the liver, activating peroxisome proliferator-activated receptor (PPAR) and thereby promoting FA oxidation. The anti-steatotic relevance of this mechanism is demonstrated by the development of steatosis during fasting in a hepatocyte-specific *Ppara* knockout mouse model.⁴¹ Moreover, promoting adipocyte lipolysis using CL316243, a β 3-adrenergic receptor agonist, creates an excessive FFA load in plasma that cannot be cleared in the absence of adequate PPAR α -mediated FA

oxidation.⁴¹ Resorting to hepatic FA oxidation as a homeostatic mechanism is either primarily decreased in people with NAFLD^{42,43} or insufficiently increased to counteract lipid load in NASH.⁴⁴

Other factors determining the size of the FFA pool in the liver are the contribution of *de novo* lipogenesis (DNL) and the secretion of very low-density lipoprotein (VLDL)-TG.⁴⁰ In patients with NAFLD, the release rate of VLDL-TG is increased in response to increased lipid flux into the liver. However, the increased secretion of lipoproteins is insufficient to compensate for the excess lipid supply, resulting in an increased absolute hepatic pool of TGs.^{10,45} Concerning DNL, Smith *et al.* recently reported that hepatic DNL activity increases in obese patients with NAFLD in parallel with increased intrahepatic TG content.⁹ Notably, hepatic DNL inversely correlates with hepatic and whole-body insulin sensitivity in obese patients with NAFLD. Furthermore, body weight reduction lowers hepatic TG content and decreases hepatic DNL.⁹ The type of diet is another factor modulating DNL. For example, fructose- and sucrose-sweetened beverages promoted hepatic DNL in healthy individuals.⁴⁶ A high-carbohydrate diet induces hepatic DNL by activating carbohydrate response element-binding protein (ChREBP) in rodents⁴⁷ and humans.⁴⁸ In contrast, the regulation of DNL by a high-fat diet (HFD) might depend on the percentage of unsaturated fatty acids. Diets rich in poly/monounsaturated fatty acids block sterol regulatory element-binding protein 1c (SREBP1c) activation and prevent the biosynthesis of FAs. Conversely, diets rich in saturated fat typically activate SREBP1c for the DNL programme, resulting in

increased FA biosynthesis, unsaturation and elongation.⁴⁹ Thus, the contribution of HFD-induced steatosis, particularly of saturated fat, is quantitatively more dependent on FA re-esterification than DNL in rodents⁵⁰ and humans.⁴⁸ Therefore, TG storage in the liver is determined by the balance between its output (the β -oxidation of FFAs and VLDL-TG secretion) and its input (*i.e.* DNL from glucose and re-esterification of FFAs in the liver) (Fig. 2).

However, when the lipid load exceeds the liver capacity threshold for TG deposition, specific lipid metabolites, such as ceramide and diacylglycerol, become overrepresented in the lipidome of the liver, mediating toxic effects, and leading to IR and metabolic stress.^{51,52} For instance, mice lacking PPAR γ 2 on an obese hyperphagic *ob/ob* background (POKO model) show a positive energy balance similar to *ob/ob* mice. However, they exhibit impaired adipose tissue expansion capacity and impaired MetFlex, resulting in elevated FFA release into the circulation. In this model, TG levels were decreased and ceramide levels increased in the liver and adipose tissue.⁵³ We recently demonstrated that the PPAR γ 2 isoform, preferentially expressed in adipose tissue, is a primary regulator of MetFlex in adipose tissue. Its ablation exerts a time-dependent, knock-on lipotoxic effect on other metabolically important organs, such as the liver.⁵⁴ Importantly, this result would indicate that an early metabolic inflexibility in adipose tissue is sufficient to trigger NAFLD and hepatic IR. Moreover, whole-body IR impairs insulin-mediated suppression of lipolysis in adipose tissue, leading to increased circulating FFAs despite increased insulin secretion, culminating in hyperinsulinemia. Of relevance, this level of hyperinsulinemia is sufficient to activate the SREBP-1c pathway in the liver and stimulate *de novo* FA synthesis. Thus, whereas obesity-induced systemic IR is associated with the inability to prevent hepatic glucose production, hyperinsulinemia resulting from systemic IR is sufficient to promote hepatic lipogenesis.^{39,55} This would indicate that the interplay between adipose tissue, pancreatic β -cells, and the liver contributes to NAFLD development.

Pathophysiology of aberrant adipose tissue biology on NAFLD development

WAT is very efficient in capturing nutrients when provided intermittently but has limited capacity to accommodate a chronic excess energy supply. Chronic overnutrition disrupts the physiological MetFlex and overstimulates the physiological mechanisms designed to increase storage capacity through adipocyte size (hypertrophy) and/or number (hyperplasia). Moreover, during expansion, WAT requires optimal coordination of mechanisms regulating adipogenesis, cell growth and the development of ancillary mechanisms controlling vascularisation, remodelling of extracellular matrix (ECM), infiltration of immune cells, and innervation. Moreover, hypertrophic and hyperplastic adipose tissue “*idiosyncratically*” disrupts an individual’s endocrine patterns, influencing the development of IR in the liver and other tissues. A long-term nutrient surplus evokes chronic activation of homeostatic responses designed to solve short-term metabolic stress situations, eventually reaching a maximal allostatic threshold.⁵⁶ Combined, these events lead to exhaustion and adipose tissue failure, which is characterised by metabolic dysfunction, reduced MetFlex, and increased inflammation. In the following sections, we discuss factors that promote adipose dysfunction and the underlying mechanisms interconnecting them with the development of NAFLD.

Roles of adipokines on NAFLD development

Obesity-induced leptin resistance and hyperleptinemia

Adipokines secreted from adipose tissue in response to physiological/pathological changes influence hepatic metabolism (summarised in Fig. 3). Numerous studies conducted in rodent models or humans with NAFLD have shown the link between hyperleptinemia and hepatic steatosis, fibrogenesis and carcinogenesis.⁵⁷ Hereto, Petrescu *et al.* reported that leptin exacerbates hepatic fibrosis and inflammation in a rodent model of cholestasis and that a leptin-neutralising antibody attenuates hepatic stellate cell (HSC) activation.⁵⁸ There is

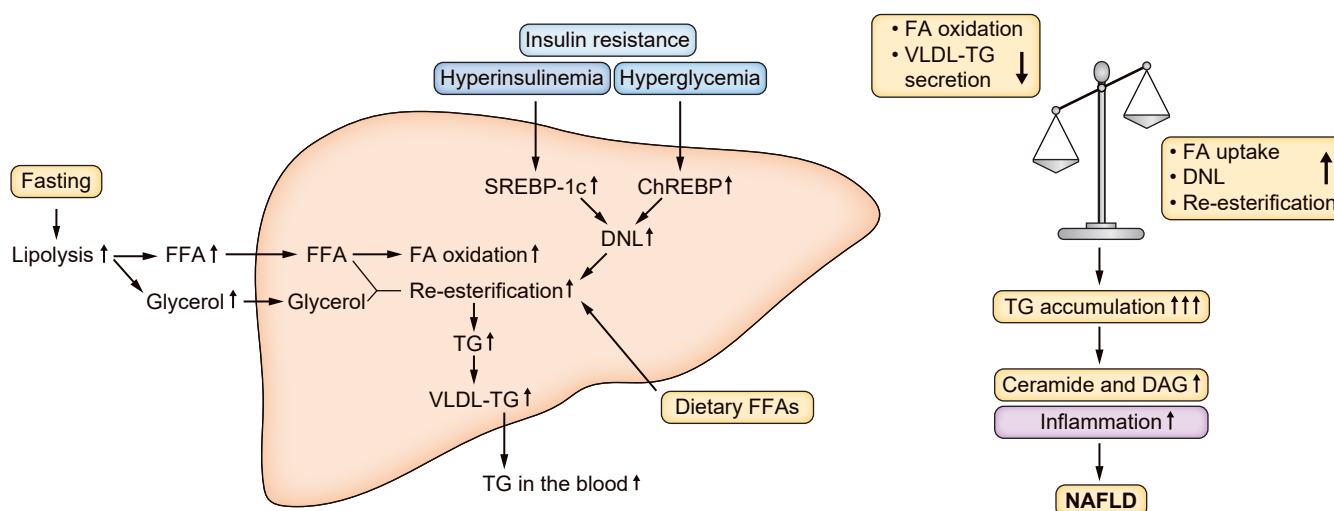


Fig. 2. The mechanism of TG accumulation in the liver and its consequences. Excessive FFAs in the circulation derived from the diet or adipose tissues promote TG accumulation in the liver. FFAs are also generated by DNL. In contrast, TG is utilised as an energy source or released from the liver as VLDL. Therefore, the imbalance between the FFA output (*i.e.* the β -oxidation of FFAs and VLDL-TG secretion) and input (*i.e.* DNL from glucose and re-esterification of FFAs in the liver) causes hepatic TG accumulation, leading to the development of NAFLD. DAG, diacylglycerol; DNL, *de novo* lipogenesis; FA, fatty acid; FFA, free fatty acid; NAFLD, non-alcoholic fatty liver disease; TG, triglyceride; VLDL, very low-density lipoprotein.

some evidence that leptin might contribute to the pathogenesis of NAFLD by acting directly on the liver. For example, the interaction of leptin with its hepatic receptor Ob-Rb activates JAK2 signalling pathways (reviewed in^{57,59}) in hepatocytes, Kupffer cells (KCs) and HSCs^{57,60} contributing to the development of NAFLD. Leptin is not synthesised in the healthy liver, but activated HSCs induce leptin production in the fibrotic liver.⁶¹ Leptin also activates KCs to induce the expression of TGF- β 1, which then activates HSCs and facilitates fibrosis.^{62,63} Regarding leptin's action on lipid metabolism in the liver, it differs between physiological and pathophysiological conditions. Hyperleptinemia increases DNL and TG content,⁶⁴ whereas attenuation of leptin signalling by administration of anti-leptin antibodies significantly reduced hepatic steatosis in mouse models of diet- or genetically induced obesity.⁶⁵ Thus, hyperleptinemia associated with leptin resistance promotes NAFLD. In contrast, activation of hepatic leptin signalling in a leptin-sensitive system ameliorates NAFLD, decreasing hepatic TG content and DNL-related gene expression (e.g. *Srebp-1c*, fatty acid synthase, and acetyl-CoA carboxylase 1.^{66,67} In support of leptin signalling's beneficial effect on NAFLD, liver-specific disruption of leptin signalling increases hepatic TG content,⁶⁸ whereas leptin treatment in patients with hypo-leptinemic lipodystrophy decreases DNL.⁶⁹

Besides the direct effects of leptin on the liver, there is strong evidence that most of leptin's effects are mediated through the central nervous system (CNS). Intracerebroventricular (ICV) leptin infusion increases VLDL secretion, reduces hepatic steatosis, and suppresses hepatic DNL.⁷⁰ Moreover, these effects of leptin are abrogated by hepatic branch vagotomy.⁷⁰ Also, ICV leptin infusion, but not

intraperitoneal leptin infusion, even has anti-steatotic effects in leptin-resistant mice with diet-induced obesity.⁷⁰ In agreement with these findings, ICV leptin treatment reduces steatosis in the lipodystrophy mouse model.⁷¹ Hence, obesity-induced hepatic steatosis is regulated by leptin, whether it is acting directly or indirectly on the liver. Moreover, leptin might have distinct stage-specific roles in the progression of NASH through its specific effects on different cell types in the liver.

Adiponectin as a biomarker of NAFL

Low adiponectin levels in adipose tissue and circulation are associated with the presence and severity of NAFLD.^{72,73} Adiponectin binds to AdipoR1 and AdipoR2 in the liver. Once it binds to its receptor, AMPK and PPAR α signalling is activated, which increases FA oxidation and decreases DNL, resulting in decreased TG content.^{74,75} Furthermore, adiponectin stimulates ceramidase activity, reducing lipotoxicity and improving insulin sensitivity.⁷⁶ In addition, adiponectin also inhibits the proliferation and migration of HSCs through AMPK activation, inhibiting fibrosis.^{77,78} Mice lacking adiponectin also exhibited exacerbated fibrogenesis in a carbon tetrachloride-induced cirrhotic mouse model.⁷⁹ In addition, adiponectin inhibits C-C motif chemokine ligand 2 (CCL2) expression in hepatocytes, contributing to the suppression of HFD-induced inflammation, including macrophage infiltration.⁸⁰ Paradoxically, several clinical studies have shown that adiponectin is increased in patients with liver fibrosis but decreased in those with steatosis.⁸¹ Thus, the pathophysiological roles of adiponectin in the development and progression of liver fibrosis remain to be clarified.

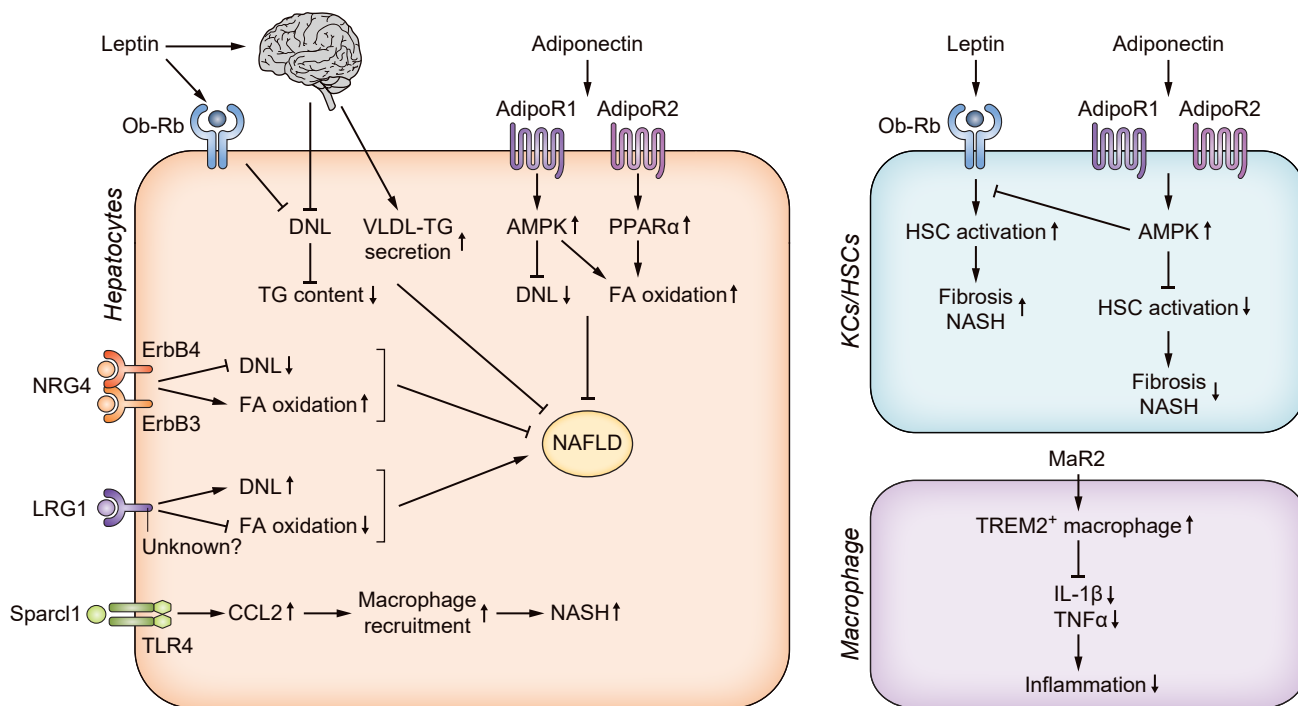


Fig. 3. The effect of adipokines on hepatic metabolism and inflammation. Adipokines directly or indirectly signal in hepatocytes, immune cells, or macrophages, leading to prevention or aggravation of NAFLD/NASH through multiple pathways. DNL, *de novo* lipogenesis; FA, fatty acid; NAFLD, non-alcoholic steatohepatitis; NASH, non-alcoholic steatohepatitis; TG, triglyceride; VLDL, very low-density lipoprotein.

Neuregulin 4, a batokine that improves hepatic lipid metabolism
The thermogenic brown and beige adipose tissue⁸² exert beneficial metabolic effects in preventing/reversing NAFLD by promoting negative energy balance and secreting endocrine signals, so-called batokines. More recently, Ahmed *et al.* reported that individuals with NAFLD with lower brown adipose tissue (BAT) activity had elevated hepatic fat content.⁸³ Moreover, there is evidence that BAT-based strategies to activate energy dissipation improve metabolic dysfunction in rodents and humans.^{82,84}

Neuregulin 4 (NRG4) is one of the batokines secreted by cold-activated BAT.^{85,86} NRG4 binds to receptors of tyrosine-protein kinases ErbB3 and ErbB4 expressed on hepatocytes, attenuating hepatic lipogenesis and increasing FA oxidation^{86,87}. Notably, the *Nrg4* gene is expressed in WAT and decreased in obese mice and humans.⁸⁶ Furthermore, *Nrg4* expression in epididymal WAT and BAT is decreased in diet-induced NASH models, and its genetic ablation increases the expression of genes involved in hepatic inflammation and fibrosis in mice.⁸⁸ NRG4 suppresses NASH-associated hepatocellular carcinoma by restraining liver tumour growth.⁸⁹

Of note, NRG4 also exhibits a paracrine role, contributing to the angiogenesis of adipose tissue.^{90,91} Moreover, NRG4 activates BMP8b signalling following cold exposure and is a mediator of neuro-vascular network remodelling in brown/beige adipose tissue.⁹¹ Therefore, NRG4 may exert an anti-steatotic effect directly in the liver and indirectly by improving adipose tissue functionality. Although there are many reports on the beneficial role of NRG4 on adipose tissue and the liver in rodent models, the relationship between plasma NRG4 levels and NAFLD in humans is less clear as different reports have shown either decreased^{92,93} or unaltered levels⁹⁴ in patients with NAFLD.

Adipose tissue-derived factors with a newly described role in NAFLD

Sparcl1

In the context of the hypertrophied adipocytes and chronically activated macrophages, WAT triggers the production of secreted protein acidic and rich cysteine-like protein 1 (Sparcl1), which promotes NASH progression through activation of Toll-like receptor 4 (TLR4) in hepatocytes.⁹⁵ TLR4 activation resulted in the elevation of CCL2 and, concomitantly, the recruitment of hepatic macrophages.⁹⁵ Moreover, Sparcl1 administration exacerbated liver injury and inflammation in the HFHC (high-fat and high-cholesterol) diet and HFD murine models of NASH. Of relevance, plasma Sparcl1 is increased in patients with NASH,⁹⁵ and inhibition of Sparcl1 signalling has been shown to prevent the development of NASH.⁹⁵ Hence, Sparcl1 is a potential pathogenic mediator that needs to be investigated in humans in more detail.

MaR2

Maresins (macrophage mediators in resolving inflammation) are synthesised from docosahexaenoic acid by 12-lipoxygenase and were discovered as novel macrophage mediators that promote the resolution of inflammation.⁹⁶ Additionally, Sugimoto *et al.* have reported that, in response to cold exposure or β 3-

adrenergic receptor activation, BAT-derived maresin 2 (MaR2) contributes to the suppression of hepatic inflammation.⁹⁷ MaR2 decreased the expression of proinflammatory genes in primary KCs and impeded the production of proinflammatory cytokines (IL-1 β and TNF α) at a protein level in lipopolysaccharide- or lipopolysaccharide-palmitate-treated macrophages. Mechanistically, MaR2 secreted from brown adipocytes targets the liver and promotes TREM2-positive macrophages that induce a protective, anti-inflammatory response during liver injury.^{97–100}

LRG1

Leucine-rich alpha-2-glycoprotein 1 (LRG1) is a secretory glycoprotein containing leucine-rich-repeat domains released from various tissues that was first identified in human serum.¹⁰¹ More recently, He *et al.* reported¹⁰² that serum LRG1 concentrations are increased in obese individuals and negatively correlate with BMI. Interestingly, LRG1 abundance increases in serum and adipose tissues in mouse models of diet- or genetically (*db/db* mice) induced obesity. By contrast, *Lrg1* KO mice exhibit decreased body weight and improved glucose tolerance with enhanced systemic insulin sensitivity. Mechanistically, increased LRG1 secretion from adipose tissues acts on the liver to increase DNL and decrease FAO, contributing to the development of NAFLD. Furthermore, secreted LRG1 from adipose tissues inhibits insulin signalling in the liver and promotes hyperglycaemia.¹⁰² The mechanism for the increase of LRG1 secretion from adipose tissues in obesity and its action on lipid metabolism in the liver remains to be clarified, but LRG1 seems to behave as a detrimental adipokine that aggravates obesity-induced NAFLD and systemic IR.

Roles of adipose tissue-derived EVs on NAFLD development

In addition to classical adipokines, adipose tissue is one of the most important sources of exosomes, which regulate systemic glucose and lipid metabolism.¹⁰³ The readers are referred to other outstanding reviews on the biogenesis of EVs and their pathological significance in metabolic diseases.¹⁰⁴ Among the numerous roles EVs play in metabolism and disease, a growing body of evidence indicates that EVs contribute to the pathogenesis of NAFLD. Exosomes secreted from adipose tissues signal to other tissues via the circulation. Studies conducted in mice showed that injecting isolated EVs from the adipose tissue-derived macrophages of obese mice into lean mice induces IR.¹⁰⁵ Recently, Fuchs *et al.* reported that plasma exosome concentrations in obese patients with NAFLD were higher than in obese patients without NAFLD. Additionally, treating mouse hepatocytes *in vitro* with the exosomes isolated from obese patients with NAFLD promoted IR.¹⁰⁶ The messages transmitted by exosomes include cargo extracellular microRNAs (miRNAs) that can regulate gene expression in distant organs such as the liver. Using genetically engineered mice deficient for the miRNA-processing enzyme (Dicer) in their adipose tissue (ADicer-KO), Thomou *et al.* demonstrated reduced levels of circulating exosomal miRNA.¹⁰⁷ Inversely, transplanting normal adipose tissue into ADicer-KO animals restored exosomal miRNA levels and their

capacity to regulate glucose. Interestingly, ADicer-KO mice showed increased plasma levels and hepatic transcription of *Fgf21* and adipose tissue-derived miR-99 b, a regulator of FGF21 expression. Of note, FGF21 is an essential regulator of metabolism and its association with lipodystrophy has been established.^{108,109} These experiments elegantly indicated that adipose tissue is an important source of circulating exosomal miRNAs that control specific transcriptional events in the liver.^{107,110}

Besides adipocyte-derived exosomes, hepatocyte-derived miRNAs in pathophysiological conditions, such as viral hepatitis, alcoholic hepatitis, and hepatocellular carcinoma, have been shown to activate HSCs or KCs, contributing to the progression of NASH.¹¹¹ Given the reports from human and rodent models, the involvement of exosomal miRNAs in the pathogenesis of NAFLD is of great interest. However, their role in lipid metabolism and usefulness as biomarkers and/or therapeutic targets in NAFLD remain to be determined.

Roles of proinflammatory cytokines from adipose tissue on NAFLD development

Obesity-induced inflammation in adipose tissue is generally proportional to the amount of fat stored. Therefore, one may think that the more obese the patient is, the more inflamed their adipose tissue will be. However, there is evidence that a subset of obese individuals are resilient to inflammation despite being very obese.^{14,112} Although it remains unknown what determines the natural course of NAFL or NASH, evidence indicates a direct relationship between inflammation in adipose tissue and the progression of NASH.^{112–115}

Adipocytes can expand their size and number in response to surplus nutrients (so-called hypertrophy/hyperplasia). In hypertrophic adipose tissue, the increased distance of adipocytes from vessels causes hypoxia within adipose tissue and promotes adipose tissue inflammation and dysfunction.^{116,117} In the adipose tissue of obese individuals, macrophages form a cellular complex called the crown-like structure (CLS) around dead adipocytes. In CLS, adipose tissue macrophages (ATMs) contribute to the clearance of cellular debris and remodelling of adipose tissue during the development of obesity.¹¹⁸ Moreover, hypertrophied adipocytes in obese individuals exhibit increased lipolysis, releasing FFAs, which activate TLR4 expressed on the cell surface of ATMs and increase the release of proinflammatory cytokines, including TNF α , IL1 β , and IL-6 through NF- κ B signalling. In addition, hypertrophied adipocytes release the chemokine CCL2, leading to further recruitment of macrophages to inflamed adipose tissues. This vicious cycle causes IR in adipocytes and other insulin-target tissues.

In contrast to those concepts, Zhu *et al.* generated transgenic mice expressing RID α/β , an adenovirus protein complex that inhibits mammalian inflammatory pathways, specifically in adipocytes and macrophages.¹¹⁹ In adipose tissues, RID α/β inhibits several inflammatory pathways. However, surprisingly, adipocyte-specific RID α/β expression rendered mice insulin resistant and impaired adipose tissue function, leading to higher liver weight under HFD-induced conditions, despite inflammatory genes being downregulated. Conversely, macrophage-specific RID α/β expression in mice did not influence HFD-induced insulin resistance.¹¹⁹ These results suggest

that crosstalk between adipocytes and macrophages is critical in maintaining adipose tissue function.

Defective macrophages also contribute to adipose tissue dysfunction. For instance, the macrophage-inducible C-type lectin (Mincle) increases the susceptibility of macrophages to promote CLS, resulting in infiltration of macrophages, which engulf dead adipocytes, exacerbating inflammation in adipose tissue, and promoting NAFLD/NASH in response to a HFD or genetically induced obesity in mice. Conversely, genetic loss of Mincle in macrophages promotes adipose tissue health, with decreased CLS formation and fibrosis,¹²⁰ and significantly decreases hepatic TG content.¹²⁰ Thus, inflammation in adipose tissue¹²¹ and the liver¹²² plays a critical role in the pathogenesis of NAFLD. Evidence included in this review indicates that inflammatory signals connecting adipose tissue and the liver promote liver injury and facilitate evolution toward NASH.

IL-6 is another proinflammatory cytokine. Wueest *et al.* reported that in HFD-fed mice with adipocyte-specific knockout of gp130, the signal transducer protein of the IL-6 family, steatosis and insulin sensitivity were improved in conjunction with a decrease in basal lipolysis rate and portal FFA levels.¹²³ Conversely, *IL6* mRNA expression in omental adipose tissue positively correlated with hepatic steatosis and IR in humans.¹²³ Moreover, elevated serum IL-6 level is also a risk factor for developing hepatocellular carcinoma in humans.¹²⁴ Nevertheless, the contribution of elevated circulating IL-6 to NASH development remains controversial. For example, IL-6-deficient mice paradoxically show IR along with steatosis and inflammation even when fed a standard chow diet.¹²⁵

TNF α is also a proinflammatory cytokine released from various cells, including adipocytes, macrophages in adipose tissue and KCs in the liver.¹²⁶ Similar to IL-6, TNF α expression in visceral adipose tissue is reported to be associated with the progression of NAFLD in obese patients.¹²⁷ Enhanced TNF α expression in the liver was also shown to drive the progression of NASH in mice.¹²⁸ Conversely, inhibition of TNF α signalling attenuated hepatic steatosis and fibrosis through suppression of KCs in a NASH model.¹²⁹ However, this result contradicts another study showing that hepatocyte-specific *Tnfr1* knockout mice are not protected from NASH.¹³⁰

CCL2 is a typical proinflammatory chemokine that triggers the recruitment of monocytes and is thought to play a role in the development of IR in adipose tissue and NAFLD.¹³¹ CCL2 levels in plasma, liver and/or visceral fat also increase in patients with NAFLD.^{132,133} CCL2 participates in the development of NAFL and its progression to NASH in mice with a hepatocyte-specific deficiency of small heterodimer partner, a nuclear receptor regulating bile acid and lipid metabolism. In these KO mice, lack of small heterodimer partner increased CCL2 production via NF- κ B signalling, which promotes macrophage recruitment, resulting in the development of NASH.¹³⁴ However, CCL2 is not essential in inducing NASH because steatosis and expression of proinflammatory genes can be induced in the liver in CCL2-deficient mice.¹³⁵

In addition to the local or systemic increase in proinflammatory cytokines, hypoxic conditions also trigger the onset of adipose tissue inflammation. Hypertrophy of adipocytes impedes adipose tissue oxygenation and induces defective adipose tissue remodelling, triggering adipose tissue inflammation, fibrosis, and systemic IR.¹¹⁶ Recently, Vincenza *et al.*

reported that adipose tissue oxygenation was decreased in patients with MUO and was positively associated with insulin sensitivity.¹¹⁷ In addition, adipose tissue oxygenation was negatively associated with *Serpine1*, the gene that encodes PAI-I. Notably, plasma PAI-1 levels were higher in patients with MUO than in their healthy obese counterparts.¹¹⁷ Similarly, PAI-1 levels were significantly elevated in obese patients with NAFLD compared to obese patients without NAFLD.¹⁰⁶ Since PAI-I was the only parameter differentially regulated in these cohorts, it may serve as a potential biomarker or a prognostic/diagnostic factor for the development of NAFLD. Therefore, our model of progressive adipose tissue dysfunction during obesity involves initial metabolic inflexibility characterised by increased leakage of FFAs, triggering inflammatory macrophage activation and mobilisation of monocytes through the CCL2 axis. In combination with the aberrant adipokine patterns, disruption of the exosome-mediated physiological cargo exchanges further exacerbates the release of inflammatory cytokines inside the adipose tissue (Fig. 4).

Targeting adipose tissue to prevent and treat NAFLD before it evolves into NASH

No FDA-permitted therapeutics for NAFLD exist. Attempts to target advanced fibroinflammatory stages have failed, partly because once the inflammatory cascade is activated, it is almost impossible to identify a single target that can contain it. Nevertheless, elucidation of the pathophysiology of NAFLD has suggested several molecular targets that may act on the early metabolic events controlling the flow and accumulation of

reactive lipid species in the liver with the potential to delay the natural history of the disease. Some of them involve improving the function of the adipose tissue and other peripheral metabolic organs to improve liver lipid fluxes, which ameliorate steatosis and abort the early stages of inflammation and fibrosis. The concept is to intervene early to prevent its progression to the advanced irreversible forms of liver disease, namely cirrhosis and hepatocellular carcinoma. In the next section, we provide an adipocentric therapeutic perspective on NAFLD and discuss its potential synergic effects on alleviating the vicious cycle responsible for the worsening of NAFLD.

FGF21 analogue as an insulin sensitiser through the action of adipose tissue

FGF21 plays an essential role in regulating glucose and lipid metabolism, acting through the co-receptor complex of β -klotho and one of the FGF receptors (FGFR1c, FGFR2c, and FGFR3c).¹³⁶ β -Klotho is expressed primarily in the liver, pancreas, and adipose tissue. Notably, circulating FGF21 is mainly secreted from the liver during fasting,¹³⁷ protecting against NAFLD through its actions on the liver and also in adipose tissue.^{138,139} For instance, FGF21 increases glucose uptake in WAT independently of insulin¹⁴⁰ and suppresses lipolysis during fasting.¹⁴¹ Also, FGF21 is induced by cold exposure in BAT and WAT, promoting browning in inguinal WAT.^{142,143} In line with these reports, AKR-001 (also known as efruxifermin), a long-acting Fc-FGF21 fusion protein, reduces postprandial FFA levels in patients with T2DM by suppressing lipolysis in adipose tissues,^{141,144} increasing adiponectin levels

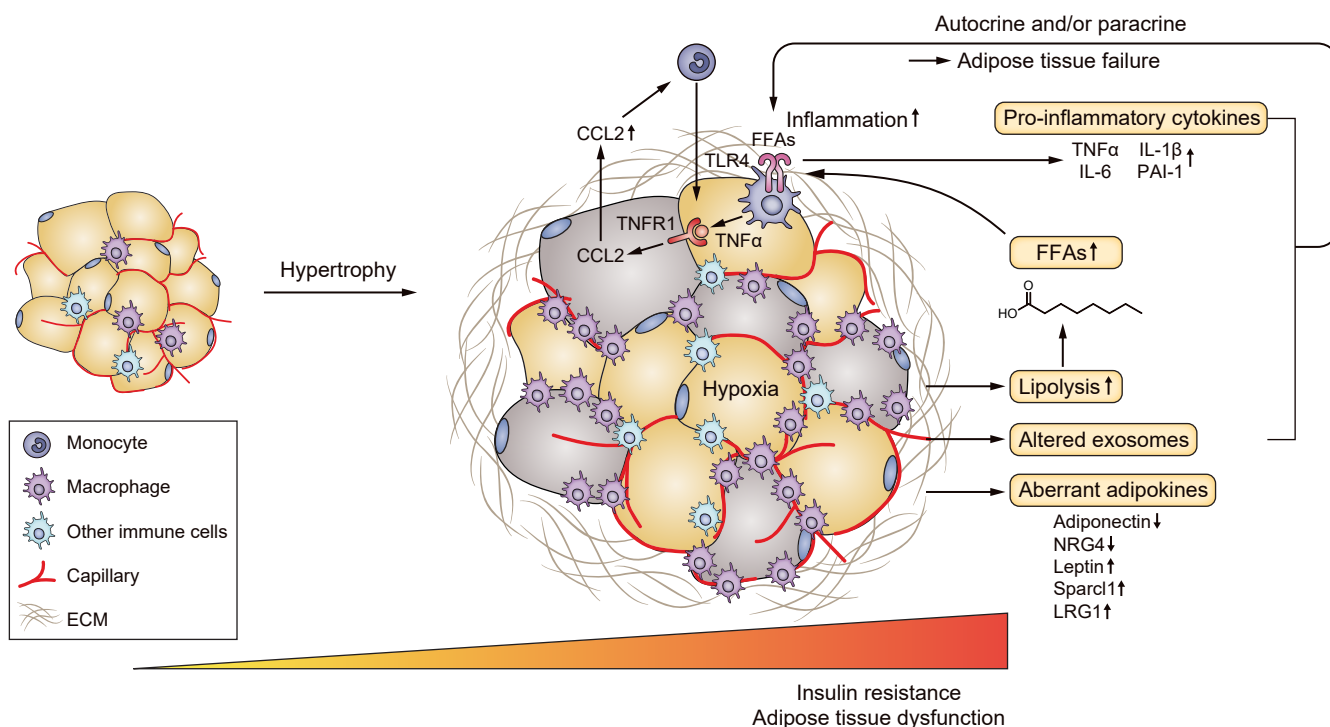


Fig. 4. Aberrant adipose biology caused by obesity. Obesity-induced adipocyte hypertrophy and progressive adipose tissue dysfunction induce insulin resistance and metabolic inflexibility characterised by increased leakage of FFAs, leading to increased pro-inflammatory cytokines and aberrant adipokine patterns, further aggravating adipose tissue dysfunction. ECM, extracellular matrix; FFAs, free fatty acids.

and enhancing systemic insulin sensitivity.¹⁴⁵ Furthermore, efruxifermin suppresses hepatic fat content and a fibrosis marker PRO-C3 in individuals with NASH.¹⁴⁶ Also, pegbelfermin, a recombinant PEGylated human FGF21 analogue, increases HDL and circulating adiponectin levels and decreases fibrosis markers, such as PAI-1, PRO-C3, and YKL-40,¹⁴⁷ reflecting decreased hepatic fat content and fibrosis in individuals with NASH.¹⁴⁸ As mentioned, circulating PAI-1 levels are increased in individuals with MUO and obese patients with NAFLD. PRO-C3 is an N-terminal type III collagen propeptide and is recognised as a new and more beneficial fibrosis marker that reflects the degree of liver fibrosis in NASH.¹⁴⁹ YLK-40 is also a novel inflammatory marker.¹⁵⁰ Despite these beneficial effects, FGFR1c, the primary FGF21 receptor, shows little or no expression in hepatocytes.¹⁵¹ Moreover, mice deficient in liver-specific β -klotho showed that the anti-steatotic effect of FGF21 is mediated through the CNS.¹⁵² Notably, the systemic insulin-sensitising effect of FGF21, mediated by adipose tissue,¹⁵² might indirectly influence hepatic fat accumulation. Although it is still unclear whether FGF21 inhibits lipid metabolism in the liver directly¹³⁸ or indirectly through the CNS and/or adipose tissue,¹⁵² by suppressing lipolysis, potentiating glucose uptake, inducing beiging, and upregulating circulating adiponectin, it should ameliorate NAFLD. The molecular and physiological action of FGF21 on metabolism is reviewed in detail in.^{136,153}

GLP-1 receptor agonists prevent NAFLD by acting synergistically on adipose tissue and the liver

GLP-1 is a gut hormone secreted from enteroendocrine L-cells that potentiates glucose-induced insulin secretion. GLP-1 receptor agonists, including several GLP-1 analogues, have been used widely to treat T2DM.¹⁵⁴ Such wide clinical use of GLP-1 receptor agonists has provided evidence of their effectiveness in ameliorating NAFLD.^{155,156} However, whether GLP-1R is^{157,158} or is not^{159,160} expressed in the liver remains controversial. Therefore, it is unclear whether the anti-steatotic effect of GLP-1 might directly affect hepatocytes. Nevertheless, GLP-1 and GLP-1 receptor agonists inhibit hepatic glucose production,^{161,162} contributing to the glucose-lowering effect. Significantly, GLP-1 receptor agonists increase satiety and effectively reduce food intake through their action on the brain, leading to a consequential reduction in body weight.¹⁶³

Furthermore, in addition to their anorexigenic actions, GLP-1 analogues have been shown to act directly on adipose tissues to reduce macrophage infiltration in epididymal WAT in mice.¹⁶⁴ GLP-1 treatment decreased the expression of inflammatory cytokine genes, such as IL-6, TNF α , and CCL2, in adipose tissue by suppressing the NF- κ B pathway.¹⁶⁴ Some other reports show that GLP-1 improves insulin sensitivity in adipose tissue.^{165,166} Also, a clinical study showed that liraglutide, a GLP-1 analogue, decreases body weight, hepatic TG content, and visceral fat in people with obesity.¹⁶⁷ Notably, semaglutide also effectively induces NASH resolution in humans.¹⁶⁸ Accordingly, the synergic effects of GLP-1 on adipose tissue and the liver contribute to ameliorating adipose tissue inflammation and steatosis. However, to establish GLP-1 analogues as a treatment for NASH, the contribution of its effects in adipose tissue and other organs require clarification.

PPAR γ agonists as a paradigm of promoting adipose tissue health to treat NASH

PPAR γ belongs to a nuclear receptor superfamily and is critical in regulating lipid and glucose metabolism.¹⁶⁹ PPAR γ is abundantly expressed in white and brown adipocytes, and its activation promotes lipid anabolism by enhancing adipogenic and lipogenic expression.^{2,53,169} PPAR γ is also essential for adipocyte differentiation, and its activation renders adipocytes sensitive to insulin, increasing lipid synthesis and uptake.¹⁶⁹ Therefore, PPAR γ agonists such as pioglitazone have been used to treat diabetes mellitus.¹⁶⁹ Pioglitazone increases insulin-induced suppression of lipolysis¹⁷⁰ in T2DM. It also improves adipose tissue IR in patients with NASH, decreasing hepatic TG content and necroinflammation.¹⁷¹ Furthermore, pioglitazone promotes adipose tissue redistribution, reduces visceral fat, increases adiponectin levels, and improves liver histology¹⁷² in people with NASH.

Mechanistically, adipocyte-specific PPAR γ activation in transgenic mice improves whole-body insulin sensitivity and the adipokine profile and suppresses macrophage infiltration into adipose tissue.¹⁷³ In addition, PPAR γ 2 prevents lipotoxicity by promoting adipose tissue expansion and improving MetFlex,⁵⁴ limiting the inflow of lipids into the liver.⁵³

Physiologically, PPAR γ 1 can be found in the liver,¹⁷⁴ where PPAR γ target genes promote DNL¹⁷⁵ and FFA uptake,¹⁷⁶ leading to an increase in hepatic TG. PPAR γ 2 can be induced *de novo* in the liver under increased lipid flow and adipose tissue dysfunction, contributing to safe fat accumulation as TG. Consistent with these results, hepatocyte-specific PPAR γ knockout mice were protected from fat accumulation in the liver.^{177,175} Administering a PPAR γ agonist, such as pioglitazone, may initially worsen TG accumulation in the liver if the expression of PPAR γ is still increased, but this effect is overcome when the trophic effects mediated by PPAR γ in adipose tissue take over and divert lipid fluxes away from the liver into the adipose tissue. Moreover, activation of PPAR γ in immune cells also exerts anti-inflammatory effects. PPAR γ is also expressed in ATMs, and the deletion of PPAR γ in macrophages impairs its anti-inflammatory and homeostatic functions.¹⁷⁸ In addition, PPAR γ in macrophages and HSCs exerts anti-inflammatory and anti-fibrotic effects.^{179,180,181} In line with these findings, another PPAR γ agonist, rosiglitazone, prevented the expression of inflammatory and fibrosis-related genes in mice following hepatocyte-specific *Pparg* knockout.¹⁷⁷ In fact, in many clinical trials, PPAR γ agonists reduced liver fibrosis and improved glucose tolerance in patients with NASH superimposed on T2DM.^{182,183} Improving the health of the adipose tissue and changing the fluxes of nutrients towards the adipose tissue comes at the price of increasing BMI,¹⁸⁴ which might hamper the amelioration of NAFLD in the long term. Moreover, muraglitazar and saroglitazar, dual agonists of PPAR α and PPAR γ , have been shown to reduce hepatic fat content,^{185,186} while lanifibranor, a pan-PPAR agonist, improved NASH resolution without worsening fibrosis in a phase IIb trial.¹⁸⁷

Thyroid hormone receptor- β agonists prevent NAFLD via an increase in the degradation of FAs in the liver

The thyroid hormone (TH) regulates glucose and energy metabolism. However, a growing body of evidence suggests that hypothyroidism is associated with NAFLD independently

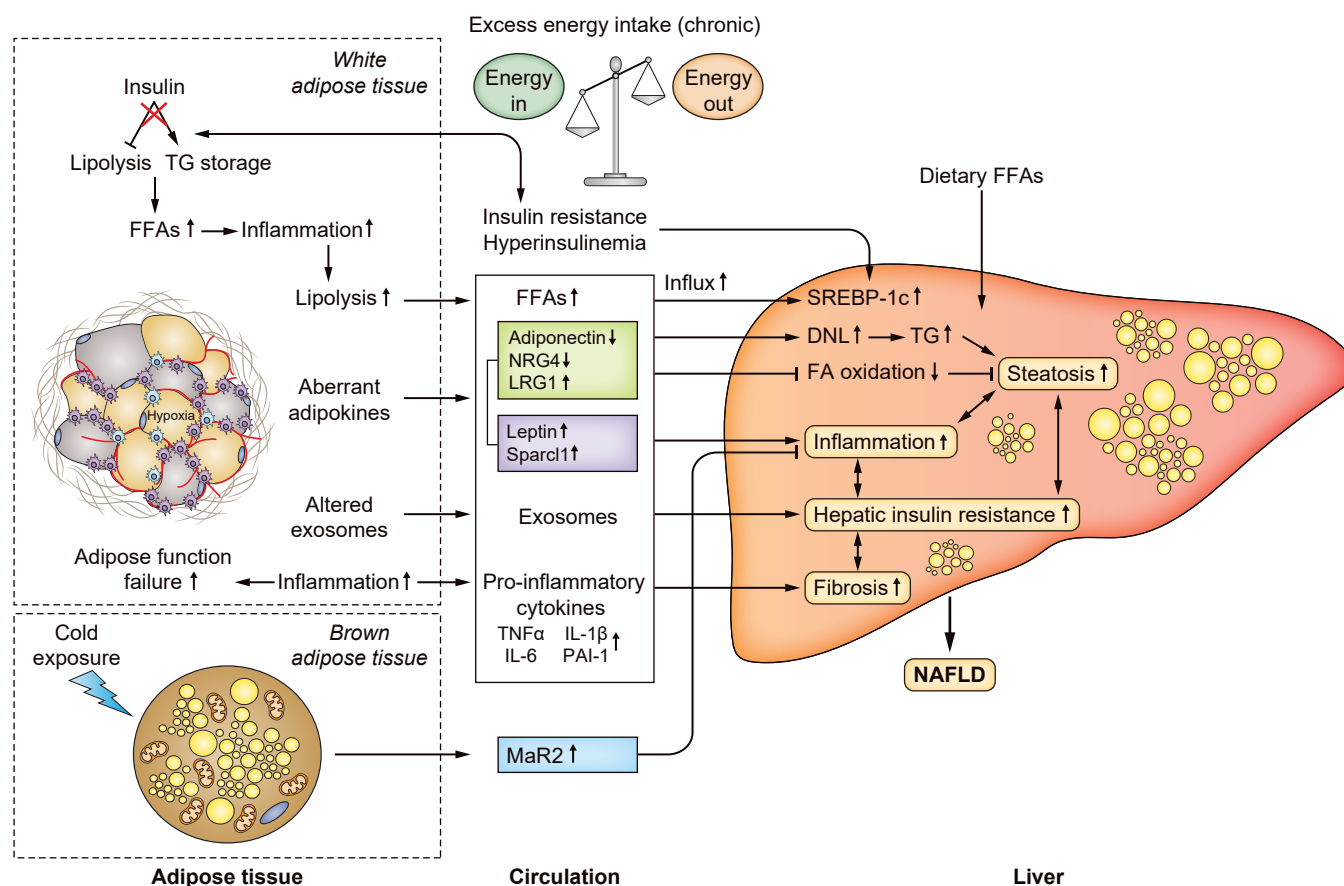


Fig. 5. Crosstalk between adipose tissue and liver in obesity, inducing the development of NAFLD. Adipose tissue dysfunction in obesity alters the levels of FFAs, adipokines, exosomes, and pro-inflammatory cytokines in the circulation, contributing to TG accumulation in the liver. Therefore, alleviating obesity-induced adipose tissue dysfunction promoted by healthy adipose tissue expansion and/or brown adipose tissue activation could prevent TG accumulation in the liver. DNL, *de novo* lipogenesis; FA, fatty acid; FFA, free fatty acid; NAFLD, non-alcoholic fatty liver disease; TG, triglyceride; VLDL, very low-density lipoprotein.

of known metabolic risk factors,^{188,189,190} although conflicting findings were reported.^{191,192} Indeed, TH affects hepatic lipid metabolism, increasing DNL through direct activation of its nuclear receptors $\text{THR}\alpha$, $\text{THR}\beta$, or through indirect activation of other transcription factors, such as SREBP1c, ChREBP, and liver X receptors.¹⁹³ In addition, TH increases β -oxidation of FAs, mitophagy, the activity of hepatic lipase, and cholesterol synthesis and clearance. Therefore, TH prevents steatosis via increased degradation of FAs despite stimulating DNL.¹⁹³

While $\text{THR}\alpha$ is highly expressed in the heart and bone, $\text{THR}\beta$ is predominantly expressed in hepatocytes.¹⁹⁴ Their roles in lipid metabolism were studied in mice with a dominant negative mutation in Thrb or Thra .¹⁹⁵ Thrb mutant mice exhibited increases in serum FFAs and total TG as well as steatosis, which was associated with increased expression of lipogenic enzymes and decreased FA oxidation.¹⁹⁵ By contrast, Thra mutant mice showed a decrease in liver weight and expression of lipogenic enzymes, suggesting that the two THR isoforms play distinct roles in lipid metabolism in the liver.¹⁹⁵ In line with this finding, individuals with a loss-of-function mutation in $\text{THR}\beta$ exhibited increased steatosis.¹⁹⁶ For this reason, liver-specific THR agonists have received much attention as candidate therapeutics against NAFLD. Especially resmetirom (MGL-3196), a selective $\text{THR}\beta$ agonist, was reported to reduce hepatic TG in patients with NASH^{197,198} in phase II and more recently phase III¹⁹⁹ clinical trials.

Conclusions

As discussed in this review, adipose tissue dysfunction could affect IR locally and systemically. Hypertrophy of adipocytes induced during obesity is associated with adipose tissue inflammation and IR, resulting in metabolic inflexibility and limiting adipose tissue expandability. Moreover, mediators secreted from adipose tissue induce increased systemic FFAs, aberrant adipokines, altered exosomes (and their genetic and protein cargo), and increased proinflammatory cytokines, all of which influence TG metabolism, IR, inflammation, and fibrosis in the liver, culminating in the development of NAFLD (Fig. 5). Synergising with altered adipose tissue biology, alterations of intrinsic liver metabolism, gut microbiota and autonomic nervous system activity could become risk factors for NAFLD. However, we posit the value of early interventions aimed at reversing obesity-induced adipose tissue dysfunction by promoting healthy adipose tissue expansion and/or increased oxidative capacity in brown fat, as strategies to redirect lipids away from the liver. Early coordination of these interventions seems a safe strategy to prevent and revert NAFL before it triggers an uncontrollable and irreversible inflammatory cascade, beyond the reach of the limited therapeutic options available.

Affiliations

¹Metabolic Research Laboratories, Wellcome Trust MRC Institute of Metabolic Science, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK; ²Department of Medical Physiology, Chiba University, Graduate School of Medicine, Chiba, Japan; ³Laboratory of Hepatology, CHROMETA Department, KU Leuven, Leuven, Belgium; ⁴Centro de Investigación Príncipe Felipe, Valencia, Spain; ⁵Cambridge University Nanjing Centre of Technology and Innovation, Nanjing, China.

Abbreviations

ATMs, adipose tissue macrophages; BAT, brown adipose tissue; CCL2, C–C motif chemokine ligand 2; ChREBP, carbohydrate response element-binding protein; CLS, crown-like structure; CNS, central nervous system; DNL, *de novo* lipogenesis; ECM, extracellular matrix; EVs, extracellular vesicles; FFAs, free fatty acids; HFHC, high-fat and high-cholesterol; HSCs, hepatic stellate cells; ICV, intracerebroventricular; IR, insulin resistance; KCs, Kupffer cells; LRG1, leucine-rich alpha-2-glycoprotein 1; MetFlex, metabolic flexibility; MHL, metabolically healthy lean; MHO, metabolically healthy obesity; Mincl, macrophage-inducible C-type lectin; miRNAs, microRNAs; MUL, metabolically unhealthy lean; MUO, metabolically unhealthy obesity; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NRG4, neuregulin 4; PAI-1, plasminogen activator inhibitor; Sparcl1, secreted protein acidic and rich cysteine-like protein 1; SREBP-1c, sterol regulatory element-binding protein-1c; T2DM, type 2 diabetes; TG, triglyceride; TH, thyroid hormone; THR, thyroid hormone receptor; TLR4, Toll-like receptor 4; VLDL, very-low-density lipoprotein-triglyceride; WAT, white adipose tissue.

Financial support

This study was supported by a research grant from The Research Foundation – Flanders (FWO); Fonds voor Wetenschappelijk Onderzoek – Vlaanderen (G082018N, Belgium) and funding from KU Leuven (C14/18/087 & AKUL/19/039, Belgium). Financial support was also received from the Belgian Association for the Study of the Liver (ELM-E0140), Gilead Sciences (10112761/2020, Belgium), UZ Leuven (KOOR) (RT0599) and a research grant from the Belgian Week of Gastroenterology (BWGE) (10065941/2021). Furthermore, this study was supported by MRC MDU (MC_UU_12012/2, United Kingdom), H2020 EPoS (Elucidating Pathways of Steatohepatitis grant agreement 634413, United Kingdom), the British Heart Foundation (RG/18/7/33636, United Kingdom), and the LITMUS Innovative Medicines Initiative 2 (IMI2) Joint (777377, Belgium). Furthermore, this study was supported by Grants-in-Aid from the Ministry of Education, Science, Sports and Culture of Japan (22H02800, Japan).

Conflict of interest

The authors declare no conflicts of interest related to this work. Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

E.L., H.K., and A.V.P. designed the concept of manuscript and wrote. All authors reviewed and approved the manuscript.

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2023.01.024>.

References

Author names in bold designate shared co-first authorship

- [1] Deng Y, Scherer PE. Adipokines as novel biomarkers and regulators of the metabolic syndrome. *Ann N Y Acad Sci* 2010;1212:E1–E19.
- [2] Virtue S, Vidal-Puig A. It's not how fat you are, it's what you do with it that counts. *Plos Biol* 2008;6:e237.
- [3] Shi H, Kokoeva MV, Inouye K, Zsameli I, Yin H, Flier JS. TLR4 links innate immunity and fatty acid-induced insulin resistance. *J Clin Invest* 2006;116:3015–3025.
- [4] Powell EE, Wong VW, Rinella M. Non-alcoholic fatty liver disease. *Lancet* 2021;397:2212–2224.
- [5] **Loomba R, Friedman SL, Shulman GI.** Mechanisms and disease consequences of nonalcoholic fatty liver disease. *Cell* 2021;184:2537–2564.
- [6] Riazi K, Azhari H, Charette JH, Underwood FE, King JA, Afshar EE, et al. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2022;7:851–861.
- [7] **Eslam M, Newsome PN,** Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. *J Hepatol* 2020;73:202–209.
- [8] Korenblat KM, Fabbri E, Mohammed BS, Klein S. Liver, muscle, and adipose tissue insulin action is directly related to intrahepatic triglyceride content in obese subjects. *Gastroenterology* 2008;134:1369–1375.
- [9] Smith GI, Shankaran M, Yoshino M, Schweitzer GG, Chondronikola M, Beals JW, et al. Insulin resistance drives hepatic *de novo* lipogenesis in nonalcoholic fatty liver disease. *J Clin Invest* 2020;130:1453–1460.
- [10] Fabbri E, Mohammed BS, Magkos F, Korenblat KM, Patterson BW, Klein S. Alterations in adipose tissue and hepatic lipid kinetics in obese men and women with nonalcoholic fatty liver disease. *Gastroenterology* 2008;134:424–431.
- [11] Beals JW, Smith GI, Shankaran M, Fuchs A, Schweitzer GG, Yoshino J, et al. Increased adipose tissue fibrogenesis, not impaired expandability, is associated with nonalcoholic fatty liver disease. *Hepatology* 2021;74:1287–1299.
- [12] Loomba R, Seguritan V, Li W, Long T, Klitgord N, Bhatt A, et al. Gut microbiome-based metagenomic signature for non-invasive detection of advanced fibrosis in human nonalcoholic fatty liver disease. *Cell Metab* 2017;25:1054–1062.e1055.
- [13] **Alferink LJM, Radjabzadeh D,** Erler NS, Vojinovic D, Medina-Gomez C, Uitterlinden AG, et al. Microbiomics, metabolomics, predicted metagenomics, and hepatic steatosis in a population-based study of 1,355 adults. *Hepatology* 2021;73:968–982.
- [14] Smith GI, Mittendorfer B, Klein S. Metabolically healthy obesity: facts and fantasies. *J Clin Invest* 2019;129:3978–3989.
- [15] Rasouli N, Raue U, Miles LM, Lu T, Di Gregorio GB, Elbein SC, et al. Pioglitazone improves insulin sensitivity through reduction in muscle lipid and redistribution of lipid into adipose tissue. *Am J Physiol Endocrinol Metab* 2005;288:E930–E934.
- [16] Tran TT, Yamamoto Y, Gesta S, Kahn CR. Beneficial effects of subcutaneous fat transplantation on metabolism. *Cell Metab* 2008;7:410–420.
- [17] Goodpaster BH, Sparks LM. Metabolic flexibility in health and disease. *Cell Metab* 2017;25:1027–1036.
- [18] Blaak EE, van Aggel-Leijssen DP, Wagenmakers AJ, Saris WH, van Baak MA. Impaired oxidation of plasma-derived fatty acids in type 2 diabetic subjects during moderate-intensity exercise. *Diabetes* 2000;49:2102–2107.
- [19] Kelley DE, Goodpaster B, Wing RR, Simoneau JA. Skeletal muscle fatty acid metabolism in association with insulin resistance, obesity, and weight loss. *Am J Physiol* 1999;277:E1130–E1141.
- [20] Tinius RA, Blankenship MM, Furgal KE, Cade WT, Pearson KJ, Rowland NS, et al. Metabolic flexibility is impaired in women who are pregnant and overweight/obese and related to insulin resistance and inflammation. *Metabolism* 2020;104:154142.
- [21] McQuaid SE, Hodson L, Neville MJ, Dennis AL, Cheeseman J, Humphreys SM, et al. Downregulation of adipose tissue fatty acid trafficking in obesity: a driver for ectopic fat deposition? *Diabetes* 2011;60:47–55.
- [22] Galgani JE, Heilbronn LK, Azuma K, Kelley DE, Albu JB, Pi-Sunyer X, et al. Metabolic flexibility in response to glucose is not impaired in people with type 2 diabetes after controlling for glucose disposal rate. *Diabetes* 2008;57:841–845.
- [23] Brouwers B, Schrauwen-Hinderling VB, Jelenik T, Gemmink A, Havekes B, Bruls Y, et al. Metabolic disturbances of non-alcoholic fatty liver resemble the alterations typical for type 2 diabetes. *Clin Sci (Lond)* 2017;131:1905–1917.
- [24] Bugianesi E, Gastaldelli A, Vanni E, Gambino R, Cassader M, Baldi S, et al. Insulin resistance in non-diabetic patients with non-alcoholic fatty liver disease: sites and mechanisms. *Diabetologia* 2005;48:634–642.
- [25] Petersen MC, Shulman GI. Mechanisms of insulin action and insulin resistance. *Physiol Rev* 2018;98:2133–2223.

- [26] Coppack SW, Evans RD, Fisher RM, Frayn KN, Gibbons GF, Humphreys SM, et al. Adipose tissue metabolism in obesity: lipase action in vivo before and after a mixed meal. *Metabolism* 1992;41:264–272.
- [27] Xia W, Pessentheiner AR, Hofer DC, Amor M, Schreiber R, Schoiswohl G, et al. Loss of ABHD15 impairs the anti-lipolytic action of insulin by altering PDE3B stability and contributes to insulin resistance. *Cell Rep* 2018;23:1948–1961.
- [28] Stöckli J, Zadoorian A, Cooke KC, Deshpande V, Yau B, Herrmann G, et al. ABHD15 regulates adipose tissue lipolysis and hepatic lipid accumulation. *Mol Metab* 2019;25:83–94.
- [29] Chavez JA, Gridley S, Sano H, Lane WS, Lienhard GE. The 47kDa Akt substrate associates with phosphodiesterase 3B and regulates its level in adipocytes. *Biochem Biophys Res Commun* 2006;342:1218–1222.
- [30] Schweiger M, Romauch M, Schreiber R, Grabner GF, Hütter S, Kotzbeck P, et al. Pharmacological inhibition of adipose triglyceride lipase corrects high-fat diet-induced insulin resistance and hepatosteatosis in mice. *Nat Commun* 2017;8:14859.
- [31] Garg A, Wilson R, Barnes R, Arioglu E, Zaidi Z, Gurakan F, et al. A gene for congenital generalized lipodystrophy maps to human chromosome 9q34. *J Clin Endocrinol Metab* 1999;84:3390–3394.
- [32] Albert JS, Yerges-Armstrong LM, Horenstein RB, Pollin TI, Sreenivasan UT, Chai S, et al. Null mutation in hormone-sensitive lipase gene and risk of type 2 diabetes. *N Engl J Med* 2014;370:2307–2315.
- [33] Softic S, Boucher J, Solheim MH, Fujisaka S, Haering MF, Homan EP, et al. Lipodystrophy due to adipose tissue-specific insulin receptor knockout results in progressive NAFLD. *Diabetes* 2016;65:2187–2200.
- [34] Lee PL, Tang Y, Li H, Guertin DA. Raptor/mTORC1 loss in adipocytes causes progressive lipodystrophy and fatty liver disease. *Mol Metab* 2016;5:422–432.
- [35] Xia B, Cai GH, Yang H, Wang SP, Mitchell GA, Wu JW. Adipose tissue deficiency of hormone-sensitive lipase causes fatty liver in mice. *Plos Genet* 2017;13:e1007110.
- [36] Campbell PJ, Carlson MG, Hill JO, Nurjhan N. Regulation of free fatty acid metabolism by insulin in humans: role of lipolysis and reesterification. *Am J Physiol* 1992;263:E1063–E1069.
- [37] Frayn KN, Shadid S, Hamlani R, Humphreys SM, Clark ML, Fielding BA, et al. Regulation of fatty acid movement in human adipose tissue in the postabsorptive-to-postprandial transition. *Am J Physiol* 1994;266:E308–E317.
- [38] Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. *J Clin Invest* 2005;115:1343–1351.
- [39] Sekizkardes H, Chung ST, Chacko S, Haymond MW, Startzell M, Walter M, et al. Free fatty acid processing diverges in human pathologic insulin resistance conditions. *J Clin Invest* 2020;130:3592–3602.
- [40] Scorletti E, Carr RM. A new perspective on NAFLD: focusing on lipid droplets. *J Hepatol* 2022;76:934–945.
- [41] Montagner A, Polizzi A, Fouché E, Ducheix S, Lippi Y, Lasserre F, et al. Liver PPAR α is crucial for whole-body fatty acid homeostasis and is protective against NAFLD. *Gut* 2016;65:1202–1214.
- [42] Naguib G, Morris N, Yang S, Fryzek N, Haynes-Williams V, Huang WA, et al. Dietary fatty acid oxidation is decreased in non-alcoholic fatty liver disease: a palmitate breath test study. *Liver Int* 2020;40:590–597.
- [43] Moore MP, Cunningham RP, Meers GM, Johnson SA, Wheeler AA, Ganga RR, et al. Compromised hepatic mitochondrial fatty acid oxidation and reduced markers of mitochondrial turnover in human NAFLD. *Hepatology* 2022;76:1452–1465.
- [44] Dasarathy S, Yang Y, McCullough AJ, Marczewski S, Bennett C, Kalhan SC. Elevated hepatic fatty acid oxidation, high plasma fibroblast growth factor 21, and fasting bile acids in nonalcoholic steatohepatitis. *Eur J Gastroenterol Hepatol* 2011;23:382–388.
- [45] Fabbri E, Magkos F, Mohammed BS, Pietka T, Abumrad NA, Patterson BW, et al. Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. *Proc Natl Acad Sci U S A* 2009;106:15430–15435.
- [46] Geidl-Flueck B, Hochuli M, Németh Á, Eberl A, Derron N, Köfeler HC, et al. Fructose- and sucrose- but not glucose-sweetened beverages promote hepatic de novo lipogenesis: a randomized controlled trial. *J Hepatol* 2021;75:46–54.
- [47] Yamashita H, Takenoshita M, Sakurai M, Bruick RK, Henzel WJ, Shillinglaw W, et al. A glucose-responsive transcription factor that regulates carbohydrate metabolism in the liver. *Proc Natl Acad Sci U S A* 2001;98:9116–9121.
- [48] Luukkonen PK, Sädevirta S, Zhou Y, Kayser B, Ali A, Ahonen L, et al. Saturated fat is more metabolically harmful for the human liver than unsaturated fat or simple sugars. *Diabetes care* 2018;41:1732–1739.
- [49] Azzu V, Vacca M, Kamzolas I, Hall Z, Leslie J, Carobbio S, et al. Suppression of insulin-induced gene 1 (INSIG1) function promotes hepatic lipid remodeling and restrains NASH progression. *Mol Metab* 2021;48:101210.
- [50] Duarte JA, Carvalho F, Pearson M, Horton JD, Browning JD, Jones JG, et al. A high-fat diet suppresses de novo lipogenesis and desaturation but not elongation and triglyceride synthesis in mice. *J Lipid Res* 2014;55:2541–2553.
- [51] Petersen MC, Shulman GI. Roles of diacylglycerols and ceramides in hepatic insulin resistance. *Trends Pharmacol Sci* 2017;38:649–665.
- [52] Byrne CD, Targher G. NAFLD: a multisystem disease. *J Hepatol* 2015;62:S47–S64.
- [53] Medina-Gomez G, Gray SL, Yetukuri L, Shimomura K, Virtue S, Campbell M, et al. PPAR gamma 2 prevents lipotoxicity by controlling adipose tissue expandability and peripheral lipid metabolism. *Plos Genet* 2007;3:e64.
- [54] Virtue S, Petkevicius K, Moreno-Navarrete JM, Jenkins B, Hart D, Dale M, et al. Peroxisome proliferator-activated receptor γ 2 controls the rate of adipose tissue lipid storage and determines metabolic flexibility. *Cell Rep* 2018;24:2005–2012.e2007.
- [55] Shimomura I, Matsuda M, Hammer RE, Bashmakov Y, Brown MS, Goldstein JL. Decreased IRS-2 and increased SREBP-1c lead to mixed insulin resistance and sensitivity in livers of lipodystrophic and ob/ob mice. *Mol Cell* 2000;6:77–86.
- [56] Virtue S, Vidal-Puig A. Adipose tissue expandability, lipotoxicity and the Metabolic Syndrome—an allostatic perspective. *Biochim Biophys Acta* 2010;1801:338–349.
- [57] Jiménez-Cortegana C, García-Galey A, Tami M, Del Pino P, Carmona I, López S, et al. Role of leptin in non-alcoholic fatty liver disease. *Bio-medicines* 2021;9.
- [58] Petrescu AD, Grant S, Williams E, An SY, Seth N, Shell M, et al. Leptin enhances hepatic fibrosis and inflammation in a mouse model of cholestasis. *Am J Pathol* 2022;192:484–502.
- [59] Martínez-Uña M, López-Mancheño Y, Diéguez C, Fernández-Rojo MA, Novelle MG. Unraveling the role of leptin in liver function and its relationship with liver diseases. *Int J Mol Sci* 2020;21.
- [60] Saxena NK, Ikeda K, Rockey DC, Friedman SL, Anania FA. Leptin in hepatic fibrosis: evidence for increased collagen production in stellate cells and lean littermates of ob/ob mice. *Hepatology* 2002;35:762–771.
- [61] Potter JJ, Rennie-Tankesley L, Mezey E. Influence of leptin in the development of hepatic fibrosis produced in mice by *Schistosoma mansoni* infection and by chronic carbon tetrachloride administration. *J Hepatol* 2003;38:281–288.
- [62] Ikejima K, Takei Y, Honda H, Hirose M, Yoshikawa M, Zhang YJ, et al. Leptin receptor-mediated signaling regulates hepatic fibrogenesis and remodeling of extracellular matrix in the rat. *Gastroenterology* 2002;122:1399–1410.
- [63] Wang J, Leclercq I, Brymora JM, Xu N, Ramezani-Moghadam M, London RM, et al. Kupffer cells mediate leptin-induced liver fibrosis. *Gastroenterology* 2009;137:713–723.
- [64] Wu L, Chen G, Liu W, Yang X, Gao J, Huang L, et al. Intramuscular injection of exogenous leptin induces adiposity, glucose intolerance and fatty liver by repressing the JAK2-STAT3/PI3K pathway in a rat model. *Gen Comp Endocrinol* 2017;252:88–96.
- [65] Zhao S, Zhu Y, Schultz RD, Li N, He Z, Zhang Z, et al. Partial leptin reduction as an insulin sensitization and weight loss strategy. *Cell Metab* 2019;30:706–719.e706.
- [66] Tang X, Li J, Xiang W, Cui Y, Xie B, Wang X, et al. Metformin increases hepatic leptin receptor and decreases steatosis in mice. *J Endocrinol* 2016;230:227–237.
- [67] Lim DW, Bose S, Wang JH, Choi HS, Kim YM, Chin YW, et al. Modified SJH alleviates FFAs-induced hepatic steatosis through leptin signaling pathways. *Sci Rep* 2017;7:45425.
- [68] Huynh FK, Levi J, Denroche HC, Gray SL, Voshol PJ, Neumann UH, et al. Disruption of hepatic leptin signaling protects mice from age- and diet-related glucose intolerance. *Diabetes* 2010;59:3032–3040.
- [69] Baykal AP, Parks EJ, Shamburek R, Syed-Abdul MM, Chacko S, Cochran E, et al. Leptin decreases de novo lipogenesis in patients with lipodystrophy. *JCI Insight* 2020;5.
- [70] Hackl MT, Fürsinn C, Schuh CM, Krssak M, Carli F, Guerra S, et al. Brain leptin reduces liver lipids by increasing hepatic triglyceride secretion and lowering lipogenesis. *Nat Commun* 2019;10:2717.
- [71] Asilmaz E, Cohen P, Miyazaki M, Dobrzyn P, Ueki K, Fayzikhodjaeva G, et al. Site and mechanism of leptin action in a rodent form of congenital lipodystrophy. *J Clin Invest* 2004;113:414–424.
- [72] Savvidou S, Hytioglou P, Orfanou-Koumerkeridou H, Panderis A, Frantzoulis P, Goulis J. Low serum adiponectin levels are predictive of

- advanced hepatic fibrosis in patients with NAFLD. *J Clin Gastroenterol* 2009;43:765–772.
- [73] Zhang H, Niu Y, Gu H, Lu S, Zhang W, Li X, et al. Low serum adiponectin is a predictor of progressing to nonalcoholic fatty liver disease. *J Clin Lab Anal* 2019;33:e22709.
- [74] Yamauchi T, Nio Y, Maki T, Kobayashi M, Takazawa T, Iwabu M, et al. Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. *Nat Med* 2007;13:332–339.
- [75] Awazawa M, Ueki K, Inabe K, Yamauchi T, Kaneko K, Okazaki Y, et al. Adiponectin suppresses hepatic SREBP1c expression in an AdipoR1/LKB1/AMPK dependent pathway. *Biochem Biophys Res Commun* 2009;382:51–56.
- [76] Holland WL, Miller RA, Wang ZV, Sun K, Barth BM, Bui HH, et al. Receptor-mediated activation of ceramide activity initiates the pleiotropic actions of adiponectin. *Nat Med* 2011;17:55–63.
- [77] Caligiuri A, Bertolani C, Guerra CT, Aleffi S, Galastri S, Trappoliere M, et al. Adenosine monophosphate-activated protein kinase modulates the activated phenotype of hepatic stellate cells. *Hepatology* 2008;47:668–676.
- [78] Handy JA, Saxena NK, Fu P, Lin S, Mells JE, Gupta NA, et al. Adiponectin activation of AMPK disrupts leptin-mediated hepatic fibrosis via suppressors of cytokine signaling (SOCS-3). *J Cell Biochem* 2010;110:1195–1207.
- [79] Kamada Y, Tamura S, Kiso S, Matsumoto H, Saji Y, Yoshida Y, et al. Enhanced carbon tetrachloride-induced liver fibrosis in mice lacking adiponectin. *Gastroenterology* 2003;125:1796–1807.
- [80] Ryu J, Hadley JT, Li Z, Dong F, Xu H, Xin X, et al. Adiponectin alleviates diet-induced inflammation in the liver by suppressing MCP-1 expression and macrophage infiltration. *Diabetes* 2021;70:1303–1316.
- [81] Udomsinprasert W, Honsawek S, Poovorawan Y. Adiponectin as a novel biomarker for liver fibrosis. *World J Hepatol* 2018;10:708–718.
- [82] Wang W, Seale P. Control of brown and beige fat development. *Nat Rev Mol Cell Biol* 2016;17:691–702.
- [83] Ahmed BA, Ong FJ, Barra NG, Blondin DP, Gunn E, Oreskovich SM, et al. Lower brown adipose tissue activity is associated with non-alcoholic fatty liver disease but not changes in the gut microbiota. *Cell Rep Med* 2021;2:100397.
- [84] Becher T, Palanisamy S, Kramer DJ, Eljalby M, Marx SJ, Wibmer AG, et al. Brown adipose tissue is associated with cardiometabolic health. *Nat Med* 2021;27:58–65.
- [85] Rosell M, Kaforou M, Frontini A, Okolo A, Chan YW, Nikolopoulou E, et al. Brown and white adipose tissues: intrinsic differences in gene expression and response to cold exposure in mice. *Am J Physiol Endocrinol Metab* 2014;306:E945–E964.
- [86] Wang GX, Zhao XY, Meng ZX, Kern M, Dietrich A, Chen Z, et al. The brown fat-enriched secreted factor Nrg4 preserves metabolic homeostasis through attenuation of hepatic lipogenesis. *Nat Med* 2014;20:1436–1443.
- [87] Chen Z, Wang GX, Ma SL, Jung DY, Ha H, Altamimi T, et al. Nrg4 promotes fuel oxidation and a healthy adipokine profile to ameliorate diet-induced metabolic disorders. *Mol Metab* 2017;6:863–872.
- [88] Guo L, Zhang P, Chen Z, Xia H, Li S, Zhang Y, et al. Hepatic neuregulin 4 signaling defines an endocrine checkpoint for steatosis-to-NASH progression. *J Clin Invest* 2017;127:4449–4461.
- [89] Zhang P, Chen Z, Kuang H, Liu T, Zhu J, Zhou L, et al. Neuregulin 4 suppresses NASH-HCC development by restraining tumor-prone liver microenvironment. *Cell Metab* 2022;34:1359–1376.e1357.
- [90] Nugroho DB, Ikeda K, Barinda AJ, Wardhana DA, Yagi K, Miyata K, et al. Neuregulin-4 is an angiogenic factor that is critically involved in the maintenance of adipose tissue vasculature. *Biochem Biophys Res Commun* 2018;503:378–384.
- [91] Pellegrinelli V, Peirce VJ, Howard L, Virtue S, Türei D, Senzacqua M, et al. Adipocyte-secreted BMP8b mediates adrenergic-induced remodeling of the neuro-vascular network in adipose tissue. *Nat Commun* 2018;9:4974.
- [92] Tutunchi H, Mobasser M, Aghamohammadzadeh N, Hooshyar J, Naeini F, Najafipour F. Serum neuregulin 4 (NRG-4) level and non-alcoholic fatty liver disease (NAFLD): a case-control study. *Int J Clin Pract* 2021;75:e14555.
- [93] Dai YN, Zhu JZ, Fang ZY, Zhao DJ, Wan XY, Zhu HT, et al. A case-control study: association between serum neuregulin 4 level and non-alcoholic fatty liver disease. *Metabolism* 2015;64:1667–1673.
- [94] De Munck Tji, Boesch M, Verhaegh P, Masclee AAM, Jonkers D, van Pelt JF, et al. Is there a role for neuregulin 4 in human nonalcoholic fatty liver disease? *PLoS One* 2021;16:e0251822.
- [95] Liu B, Xiang L, Ji J, Liu W, Chen Y, Xia M, et al. Sparcl1 promotes nonalcoholic steatohepatitis progression in mice through upregulation of CCL2. *J Clin Invest* 2021;131.
- [96] Serhan CN, Yang R, Martinod K, Kasuga K, Pillai PS, Porter TF, et al. Maresins: novel macrophage mediators with potent antiinflammatory and proresolving actions. *J Exp Med* 2009;206:15–23.
- [97] Sugimoto S, Mena HA, Sansbury BE, Kobayashi S, Tsuji T, Wang CH, et al. Brown adipose tissue-derived MaR2 contributes to cold-induced resolution of inflammation. *Nat Metab* 2022;4:775–790.
- [98] Esparza-Baquer A, Labiano I, Sharif O, Agirre-Lizaso A, Oakley F, Rodrigues PM, et al. TREM-2 defends the liver against hepatocellular carcinoma through multifactorial protective mechanisms. *Gut* 2021;70:1345–1361.
- [99] Jaitin DA, Adlung L, Thaiss CA, Weiner A, Li B, Descamps H, et al. Lipid-associated macrophages control metabolic homeostasis in a trem2-dependent manner. *Cell* 2019;178:686–698.e614.
- [100] Labiano I, Agirre-Lizaso A, Olaizola P, Echebarria A, Huici-Izagirre M, Olaizola I, et al. TREM-2 plays a protective role in cholestasis by acting as a negative regulator of inflammation. *J Hepatol* 2022;77:991–1004.
- [101] Haupt H, Baudner S. [Isolation and characterization of an unknown, leucine-rich 3.1-S-alpha2-glycoprotein from human serum (author's transl)]. *Hoppe Seylers Z Physiol Chem* 1977;358:639–646.
- [102] He S, Ryu J, Liu J, Luo H, Lv Y, Langlais PR, et al. LRG1 is an adipokine that mediates obesity-induced hepatosteatosis and insulin resistance. *J Clin Invest* 2021;131.
- [103] Kita S, Maeda N, Shimomura I. Interorgan communication by exosomes, adipose tissue, and adiponectin in metabolic syndrome. *J Clin Invest* 2019;129:4041–4049.
- [104] Dorairaj V, Sulaiman SA, Abu N, Abdul Murad NA. Extracellular vesicles in the development of the non-alcoholic fatty liver disease: an update. *Bio-molecules* 2020;10.
- [105] Ying W, Riopel M, Bandyopadhyay G, Dong Y, Birmingham A, Seo JB, et al. Adipose tissue macrophage-derived exosomal miRNAs can modulate in vivo and in vitro insulin sensitivity. *Cell* 2017;171:372–384.e312.
- [106] Fuchs A, Samovski D, Smith GI, Cifarelli V, Farabi SS, Yoshino J, et al. Associations among adipose tissue immunology, inflammation, exosomes and insulin sensitivity in people with obesity and nonalcoholic fatty liver disease. *Gastroenterology* 2021;161:968–981.e912.
- [107] Thomou T, Mori MA, Dreyfuss JM, Konishi M, Sakaguchi M, Wolfrum C, et al. Adipose-derived circulating miRNAs regulate gene expression in other tissues. *Nature* 2017;542:450–455.
- [108] Spolcová A, Holubová M, Mikulášková B, Nagelová V, Stofková A, Lacinová Z, et al. Changes in FGF21 serum concentrations and liver mRNA expression in an experimental model of complete lipodystrophy and insulin-resistant diabetes. *Physiol Res* 2014;63:483–490.
- [109] Miehle K, Ebert T, Kralisch S, Hoffmann A, Kratzsch J, Schlögl H, et al. Serum concentrations of fibroblast growth factor 21 are elevated in patients with congenital or acquired lipodystrophy. *Cytokine* 2016;83:239–244.
- [110] Korf H, van der Merwe S. Adipose-derived exosomal MicroRNAs orchestrate gene regulation in the liver: is this the missing link in nonalcoholic fatty liver disease? *Hepatology* 2017;66:1689–1691.
- [111] Szabo G, Momen-Heravi F. Extracellular vesicles in liver disease and potential as biomarkers and therapeutic targets. *Nat Rev Gastroenterol Hepatol* 2017;14:455–466.
- [112] Blüher M. Metabolically healthy obesity. *Endocr Rev* 2020;41.
- [113] Azzu V, Vacca M, Virtue S, Allison M, Vidal-Puig A. Adipose tissue-liver cross talk in the control of whole-body metabolism: implications in nonalcoholic fatty liver disease. *Gastroenterology* 2020;158:1899–1912.
- [114] Korf H, Boesch M, Meelberghs L, van der Merwe S. Macrophages as key players during adipose tissue-liver crosstalk in nonalcoholic fatty liver disease. *Semin Liver Dis* 2019;39:291–300.
- [115] du Plessis J, van Pelt J, Korf H, Mathieu C, van der Schueren B, Lannoo M, et al. Association of adipose tissue inflammation with histologic severity of nonalcoholic fatty liver disease. *Gastroenterology* 2015;149:635–648.e614.
- [116] Lee YS, Kim JW, Osborne O, Oh DY, Sasik R, Schenk S, et al. Increased adipocyte O2 consumption triggers HIF-1 α , causing inflammation and insulin resistance in obesity. *Cell* 2014;157:1339–1352.
- [117] Cifarelli V, Beeman SC, Smith GI, Yoshino J, Morozov D, Beals JW, et al. Decreased adipose tissue oxygenation associates with insulin resistance in individuals with obesity. *J Clin Invest* 2020;130:6688–6699.
- [118] Sun K, Kusminski CM, Scherer PE. Adipose tissue remodeling and obesity. *J Clin Invest* 2011;121:2094–2101.
- [119] Zhu Q, An YA, Kim M, Zhang Z, Zhao S, Zhu Y, et al. Suppressing adipocyte inflammation promotes insulin resistance in mice. *Mol Metab* 2020;39:101010.

- [120] Tanaka M, Ikeda K, Suganami T, Komiya C, Ochi K, Shirakawa I, et al. Macrophage-inducible C-type lectin underlies obesity-induced adipose tissue fibrosis. *Nat Commun* 2014;5:4982.
- [121] Kawai T, Autieri MV, Scalia R. Adipose tissue inflammation and metabolic dysfunction in obesity. *Am J Physiol Cell Physiol* 2021;320:C375–C391.
- [122] Peiseler M, Schwabe R, Hampe J, Kubes P, Heikenwälder M, Tacke F. Immune mechanisms linking metabolic injury to inflammation and fibrosis in fatty liver disease - novel insights into cellular communication circuits. *J Hepatol* 2022;77:1136–1160.
- [123] Wueest S, Item F, Lucchini FC, Challa TD, Müller W, Blüher M, et al. Mesenteric fat lipolysis mediates obesity-associated hepatic steatosis and insulin resistance. *Diabetes* 2016;65:140–148.
- [124] Aleksandrova K, Boeing H, Nöthlings U, Jenab M, Fedirko V, Kaaks R, et al. Inflammatory and metabolic biomarkers and risk of liver and biliary tract cancer. *Hepatology* 2014;60:858–871.
- [125] Matthews VB, Allen TL, Risis S, Chan MH, Henstridge DC, Watson N, et al. Interleukin-6-deficient mice develop hepatic inflammation and systemic insulin resistance. *Diabetologia* 2010;53:2431–2441.
- [126] Luster MI, Germolec DR, Yoshida T, Kayama F, Thompson M. Endotoxin-induced cytokine gene expression and excretion in the liver. *Hepatology* 1994;19:480–488.
- [127] Jorge ASB, Andrade JMO, Paraíso AF, Jorge GCB, Silveira CM, de Souza LR, et al. Body mass index and the visceral adipose tissue expression of IL-6 and TNF-alpha are associated with the morphological severity of non-alcoholic fatty liver disease in individuals with class III obesity. *Obes Res Clin Pract* 2018;12:1–8.
- [128] Henaó-Mejía J, Elinav E, Jin C, Hao L, Mehal WZ, Strowig T, et al. Inflammation-mediated dysbiosis regulates progression of NAFLD and obesity. *Nature* 2012;482:179–185.
- [129] Tomita K, Tamiya G, Ando S, Ohsumi K, Chiyo T, Mizutani A, et al. Tumour necrosis factor alpha signalling through activation of Kupffer cells plays an essential role in liver fibrosis of non-alcoholic steatohepatitis in mice. *Gut* 2006;55:415–424.
- [130] Bluemel S, Wang Y, Lee S, Schnabl B. Tumour necrosis factor alpha receptor 1 deficiency in hepatocytes does not protect from non-alcoholic steatohepatitis, but attenuates insulin resistance in mice. *World J Gastroenterol* 2020;26:4933–4944.
- [131] Nio Y, Yamauchi T, Iwabu M, Okada-Iwabu M, Funata M, Yamaguchi M, et al. Monocyte chemoattractant protein-1 (MCP-1) deficiency enhances alternatively activated M2 macrophages and ameliorates insulin resistance and fatty liver in lipoatrophic diabetic A-ZIP transgenic mice. *Diabetologia* 2012;55:3350–3358.
- [132] Kirovski G, Dorn C, Huber H, Moleda L, Niessen C, Wobser H, et al. Elevated systemic monocyte chemoattractant protein-1 in hepatic steatosis without significant hepatic inflammation. *Exp Mol Pathol* 2011;91:780–783.
- [133] Haukeland JW, Damås JK, Konopski Z, Löberg EM, Haaland T, Goverud I, et al. Systemic inflammation in nonalcoholic fatty liver disease is characterized by elevated levels of CCL2. *J Hepatol* 2006;44:1167–1174.
- [134] Zou A, Magee N, Deng F, Lehn S, Zhong C, Zhang Y. Hepatocyte nuclear receptor SHP suppresses inflammation and fibrosis in a mouse model of nonalcoholic steatohepatitis. *J Biol Chem* 2018;293:8656–8671.
- [135] Kassel KM, Guo GL, Tawfik O, Luyendyk JP. Monocyte chemoattractant protein-1 deficiency does not affect steatosis or inflammation in livers of mice fed a methionine-choline-deficient diet. *Lab Invest* 2010;90:1794–1804.
- [136] Flippo KH, Potthoff MJ. Metabolic messengers: FGF21. *Nat Metab* 2021;3:309–317.
- [137] Inagaki T, Dutchak P, Zhao G, Ding X, Gautron L, Parameswara V, et al. Endocrine regulation of the fasting response by PPARalpha-mediated induction of fibroblast growth factor 21. *Cell Metab* 2007;5:415–425.
- [138] Fisher FM, Estall JL, Adams AC, Antonellis PJ, Bina HA, Flier JS, et al. Integrated regulation of hepatic metabolism by fibroblast growth factor 21 (FGF21) in vivo. *Endocrinology* 2011;152:2996–3004.
- [139] Queen NJ, Bates R, Huang W, Xiao R, Appana B, Cao L. Visceral adipose tissue-directed FGF21 gene therapy improves metabolic and immune health in BTBR mice. *Mol Ther Methods Clin Dev* 2021;20:409–422.
- [140] Kharitonov A, Shivanova TL, Koester A, Ford AM, Micanovic R, Galbreath EJ, et al. FGF-21 as a novel metabolic regulator. *J Clin Invest* 2005;115:1627–1635.
- [141] Hotta Y, Nakamura H, Konishi M, Murata Y, Takagi H, Matsumura S, et al. Fibroblast growth factor 21 regulates lipolysis in white adipose tissue but is not required for ketogenesis and triglyceride clearance in liver. *Endocrinology* 2009;150:4625–4633.
- [142] Abu-Odeh M, Zhang Y, Reilly SM, Ebadat N, Keinan O, Valentine JM, et al. FGF21 promotes thermogenic gene expression as an autocrine factor in adipocytes. *Cell Rep* 2021;35:109331.
- [143] Fisher FM, Kleiner S, Douris N, Fox EC, Mepani RJ, Verdegue F, et al. FGF21 regulates PGC-1 α and browning of white adipose tissues in adaptive thermogenesis. *Genes Dev* 2012;26:271–281.
- [144] Arner P, Pettersson A, Mitchell PJ, Dunbar JD, Kharitonov A, Rydén M. FGF21 attenuates lipolysis in human adipocytes - a possible link to improved insulin sensitivity. *FEBS Lett* 2008;582:1725–1730.
- [145] Kaufman A, Abuqayyas L, Denney WS, Tillman EJ, Rolph T. AKR-001, an FGF21 analog, showed sustained pharmacodynamic effects on insulin sensitivity and lipid metabolism in type 2 diabetes patients. *Cell Rep Med* 2020;1:100057.
- [146] Harrison SA, Ruane PJ, Freilich BL, Neff G, Patil R, Behling CA, et al. Efruxifermin in non-alcoholic steatohepatitis: a randomized, double-blind, placebo-controlled, phase 2a trial. *Nat Med* 2021;27:1262–1271.
- [147] Charles ED, Neuschwander-Tetri BA, Pablo Frias J, Kundu S, Luo Y, Tirucherai GS, et al. Pegbelfermin (BMS-986036), PEGylated FGF21, in patients with obesity and type 2 diabetes: results from a randomized phase 2 study. *Obesity (Silver Spring)* 2019;27:41–49.
- [148] Abdelmalek MF, Charles ED, Sanyal AJ, Harrison SA, Neuschwander-Tetri BA, Goodman Z, et al. The FALCON program: two phase 2b randomized, double-blind, placebo-controlled studies to assess the efficacy and safety of pegbelfermin in the treatment of patients with nonalcoholic steatohepatitis and bridging fibrosis or compensated cirrhosis. *Contemp Clin Trials* 2021;104:106335.
- [149] Hansen JF, Juul Nielsen M, Nyström K, Leeming DJ, Lagging M, Norkrans G, et al. PRO-C3: a new and more precise collagen marker for liver fibrosis in patients with chronic hepatitis C. *Scand J Gastroenterol* 2018;53:83–87.
- [150] Roslind A, Johansen JS. YKL-40: a novel marker shared by chronic inflammation and oncogenic transformation. *Methods Mol Biol* 2009;511:159–184.
- [151] Fon Tacer K, Bookout AL, Ding X, Kurosu H, John GB, Wang L, et al. Research resource: comprehensive expression atlas of the fibroblast growth factor system in adult mouse. *Mol Endocrinol* 2010;24:2050–2064.
- [152] Lan T, Morgan DA, Rahmouni K, Sonoda J, Fu X, Burgess SC, et al. FGF19, FGF21, and an FGFR1/ β -klotho-activating antibody act on the nervous system to regulate body weight and glycemia. *Cell Metab* 2017;26:709–718.e703.
- [153] Geng L, Lam KSL, Xu A. The therapeutic potential of FGF21 in metabolic diseases: from bench to clinic. *Nat Rev Endocrinol* 2020;16:654–667.
- [154] Drucker DJ. Mechanisms of action and therapeutic application of glucagon-like peptide-1. *Cell Metab* 2018;27:740–756.
- [155] Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet* 2016;387:679–690.
- [156] Gastaldelli A, Marchesini G. Time for Glucagon like peptide-1 receptor agonists treatment for patients with NAFLD? *J Hepatol* 2016;64:262–264.
- [157] Gupta NA, Mells J, Dunham RM, Grakoui A, Handy J, Saxena NK, et al. Glucagon-like peptide-1 receptor is present on human hepatocytes and has a direct role in decreasing hepatic steatosis in vitro by modulating elements of the insulin signaling pathway. *Hepatology* 2010;51:1584–1592.
- [158] Svegliati-Baroni G, Saccomanno S, Rychlicki C, Agostinelli L, De Minicis S, Candelaresi C, et al. Glucagon-like peptide-1 receptor activation stimulates hepatic lipid oxidation and restores hepatic signalling alteration induced by a high-fat diet in nonalcoholic steatohepatitis. *Liver Int* 2011;31:1285–1297.
- [159] Wei Y, Mojsos S. Tissue-specific expression of the human receptor for glucagon-like peptide-1: brain, heart and pancreatic forms have the same deduced amino acid sequences. *FEBS Lett* 1995;358:219–224.
- [160] Körner M, Stöckli M, Waser B, Reubi JC. GLP-1 receptor expression in human tumors and human normal tissues: potential for in vivo targeting. *J Nucl Med* 2007;48:736–743.
- [161] Prigeon RL, Quddusi S, Paty B, D'Alessio DA. Suppression of glucose production by GLP-1 independent of islet hormones: a novel extrapancreatic effect. *Am J Physiol Endocrinol Metab* 2003;285:E701–E707.
- [162] Seghier M, Rebelos E, Gastaldelli A, Astiarraga BD, Casolaro A, Barsotti E, et al. Direct effect of GLP-1 infusion on endogenous glucose production in humans. *Diabetologia* 2013;56:156–161.

- [163] **Secher A, Jelsing J**, Baquero AF, Hecksher-Sørensen J, Cowley MA, Dalbøge LS, et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. *J Clin Invest* 2014;124:4473–4488.
- [164] Lee YS, Park MS, Choung JS, Kim SS, Oh HH, Choi CS, et al. Glucagon-like peptide-1 inhibits adipose tissue macrophage infiltration and inflammation in an obese mouse model of diabetes. *Diabetologia* 2012;55:2456–2468.
- [165] Jiang Y, Wang Z, Ma B, Fan L, Yi N, Lu B, et al. GLP-1 improves adipocyte insulin sensitivity following induction of endoplasmic reticulum stress. *Front Pharmacol* 2018;9:1168.
- [166] Zhang F, Chen Z, Wu D, Tian L, Chen Q, Ye Y, et al. Recombinant human GLP-1 beinaglutide regulates lipid metabolism of adipose tissues in diet-induced obese mice. *iScience* 2021;24:103382.
- [167] Neeland IJ, Marso SP, Ayers CR, Lewis B, Oslica R, Francis W, et al. Effects of liraglutide on visceral and ectopic fat in adults with overweight and obesity at high cardiovascular risk: a randomised, double-blind, placebo-controlled, clinical trial. *Lancet Diabetes Endocrinol* 2021;9:595–605.
- [168] Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *N Engl J Med* 2021;384:1113–1124.
- [169] Lehrke M, Lazar MA. The many faces of PPAR γ . *Cell* 2005;123:993–999.
- [170] Gastaldelli A, Casolaro A, Ciocciaro D, Frascerra S, Nannipieri M, Buzzigoli E, et al. Decreased whole body lipolysis as a mechanism of the lipid-lowering effect of pioglitazone in type 2 diabetic patients. *Am J Physiol Endocrinol Metab* 2009;297:E225–E230.
- [171] Gastaldelli A, Harrison SA, Belfort-Aguilar R, Hardies LJ, Balas B, Schenker S, et al. Importance of changes in adipose tissue insulin resistance to histological response during thiazolidinedione treatment of patients with nonalcoholic steatohepatitis. *Hepatology* 2009;50:1087–1093.
- [172] Gastaldelli A, Sabatini S, Carli F, Gaggini M, Bril F, Belfort-DeAguiar R, et al. PPAR γ -induced changes in visceral fat and adiponectin levels are associated with improvement of steatohepatitis in patients with NASH. *Liver Int* 2021;41:2659–2670.
- [173] Sugii S, Olson P, Sears DD, Saberi M, Atkins AR, Barish GD, et al. PPAR γ activation in adipocytes is sufficient for systemic insulin sensitization. *Proc Natl Acad Sci U S A* 2009;106:22504–22509.
- [174] Bedoucha M, Atzpodien E, Boelsterli UA. Diabetic KKAY mice exhibit increased hepatic PPAR γ 1 gene expression and develop hepatic steatosis upon chronic treatment with antidiabetic thiazolidinediones. *J Hepatol* 2001;35:17–23.
- [175] Matsusue K, Haluzik M, Lambert G, Yim SH, Gavrilova O, Ward JM, et al. Liver-specific disruption of PPAR γ in leptin-deficient mice improves fatty liver but aggravates diabetic phenotypes. *J Clin Invest* 2003;111:737–747.
- [176] **Wolf Greenstein A, Majumdar N**, Yang P, Subbaiah PV, Kineman RD, Cordoba-Chacon J. Hepatocyte-specific, PPAR γ -regulated mechanisms to promote steatosis in adult mice. *J Endocrinol* 2017;232:107–121.
- [177] Lee SM, Pusec CM, Norris GH, De Jesus A, Diaz-Ruiz A, Muratalla J, et al. Hepatocyte-specific loss of PPAR γ protects mice from NASH and increases the therapeutic effects of rosiglitazone in the liver. *Cell Mol Gastroenterol Hepatol* 2021;11:1291–1311.
- [178] Bassaganya-Riera J, Misyak S, Guri AJ, Hontecillas R. PPAR γ is highly expressed in F4/80(hi) adipose tissue macrophages and dampens adipose-tissue inflammation. *Cell Immunol* 2009;258:138–146.
- [179] Morán-Salvador E, Titos E, Rius B, González-Pérez A, García-Alonso V, López-Vicario C, et al. Cell-specific PPAR γ deficiency establishes anti-inflammatory and anti-fibrogenic properties for this nuclear receptor in non-parenchymal liver cells. *J Hepatol* 2013;59:1045–1053.
- [180] **Luo W, Xu Q, Wang Q**, Wu H, Hua J. Effect of modulation of PPAR γ activity on Kupffer cells M1/M2 polarization in the development of non-alcoholic fatty liver disease. *Sci Rep* 2017;7:44612.
- [181] **Ni XX, Li XY, Wang Q**, Hua J. Regulation of peroxisome proliferator-activated receptor-gamma activity affects the hepatic stellate cell activation and the progression of NASH via TGF- β 1/Smad signaling pathway. *J Physiol Biochem* 2021;77:35–45.
- [182] Yen FS, Yang YC, Hwu CM, Wei JC, Huang YH, Hou MC, et al. Liver-related long-term outcomes of thiazolidinedione use in persons with type 2 diabetes. *Liver Int* 2020;40:1089–1097.
- [183] Bril F, Kalavalapalli S, Clark VC, Lomonaco R, Soldevila-Pico C, Liu IC, et al. Response to pioglitazone in patients with nonalcoholic steatohepatitis with vs without type 2 diabetes. *Clin Gastroenterol Hepatol* 2018;16:558–566.e552.
- [184] Cusi K, Orsak B, Bril F, Lomonaco R, Hecht J, Ortiz-Lopez C, et al. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. *Ann Intern Med* 2016;165:305–315.
- [185] Fernandez M, Gastaldelli A, Triplitt C, Hardies J, Casolaro A, Petz R, et al. Metabolic effects of muraglitazar in type 2 diabetic subjects. *Diabetes Obes Metab* 2011;13:893–902.
- [186] Siddiqui MS, Idowu MO, Parmar D, Borg BB, Denham D, Loo NM, et al. A phase 2 double blinded, randomized controlled trial of saroglitazar in patients with nonalcoholic steatohepatitis. *Clin Gastroenterol Hepatol* 2021;19:2670–2672.
- [187] Francque SM, Bedossa P, Ratziu V, Anstee QM, Bugianesi E, Sanyal AJ, et al. A randomized, controlled trial of the pan-PPAR agonist lanifibranor in NASH. *N Engl J Med* 2021;385:1547–1558.
- [188] Chung GE, Kim D, Kim W, Yim JY, Park MJ, Kim YJ, et al. Non-alcoholic fatty liver disease across the spectrum of hypothyroidism. *J Hepatol* 2012;57:150–156.
- [189] **Bano A, Chaker L**, Plompen EP, Hofman A, Dehghan A, Franco OH, et al. Thyroid function and the risk of nonalcoholic fatty liver disease: the rotterdam study. *J Clin Endocrinol Metab* 2016;101:3204–3211.
- [190] D'Ambrosio R, Campi I, Maggioni M, Perbellini R, Giammona E, Stucchi R, et al. The relationship between liver histology and thyroid function tests in patients with non-alcoholic fatty liver disease (NAFLD). *PLoS One* 2021;16:e0249614.
- [191] **Lee KW, Bang KB**, Rhee EJ, Kwon HJ, Lee MY, Cho YK. Impact of hypothyroidism on the development of non-alcoholic fatty liver disease: a 4-year retrospective cohort study. *Clin Mol Hepatol* 2015;21:372–378.
- [192] Jaruvongvanich V, Sanguankeo A, Upala S. Nonalcoholic fatty liver disease is not associated with thyroid hormone levels and hypothyroidism: a systematic review and meta-analysis. *Eur Thyroid J* 2017;6:208–215.
- [193] **Hatzigelaki E, Paschou SA, Schön M**, Psaltopoulou T, Roden M. NAFLD and thyroid function: pathophysiological and therapeutic considerations. *Trends Endocrinology Metabolism: TEM* 2022;33:755–768.
- [194] Abel ED, Boers ME, Pazos-Moura C, Moura E, Kaulbach H, Zakaria M, et al. Divergent roles for thyroid hormone receptor beta isoforms in the endocrine axis and auditory system. *J Clin Invest* 1999;104:291–300.
- [195] Araki O, Ying H, Zhu XG, Willingham MC, Cheng SY. Distinct dysregulation of lipid metabolism by unliganded thyroid hormone receptor isoforms. *Mol Endocrinol* 2009;23:308–315.
- [196] Chaves C, Bruinstroop E, Refetoff S, Yen PM, Anselmo J. Increased hepatic fat content in patients with resistance to thyroid hormone beta. *Thyroid* 2021;31:1127–1134.
- [197] Harrison SA, Bashir MR, Guy CD, Zhou R, Moylan CA, Frias JP, et al. Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet* 2019;394:2012–2024.
- [198] Harrison SA, Bashir M, Moussa SE, McCarty K, Pablo Frias J, Taub R, et al. Effects of resmetirom on noninvasive endpoints in a 36-week phase 2 active treatment extension study in patients with NASH. *Hepatol Commun* 2021;5:573–588.
- [199] Lucas J, Abdelmalek M, Baum S, Harrison S, Hennen J, Taub B. Abstract #1184634: effect of resmetirom, a selective thyroid hormone receptor beta agonist, on hepatic hypothyroidism in a 52-week non-cirrhotic NASH phase 3 clinical trial. *Endocr Pract* 2022;28:S154.