Review

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

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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.

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]

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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 dyslipidaemia[14] (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

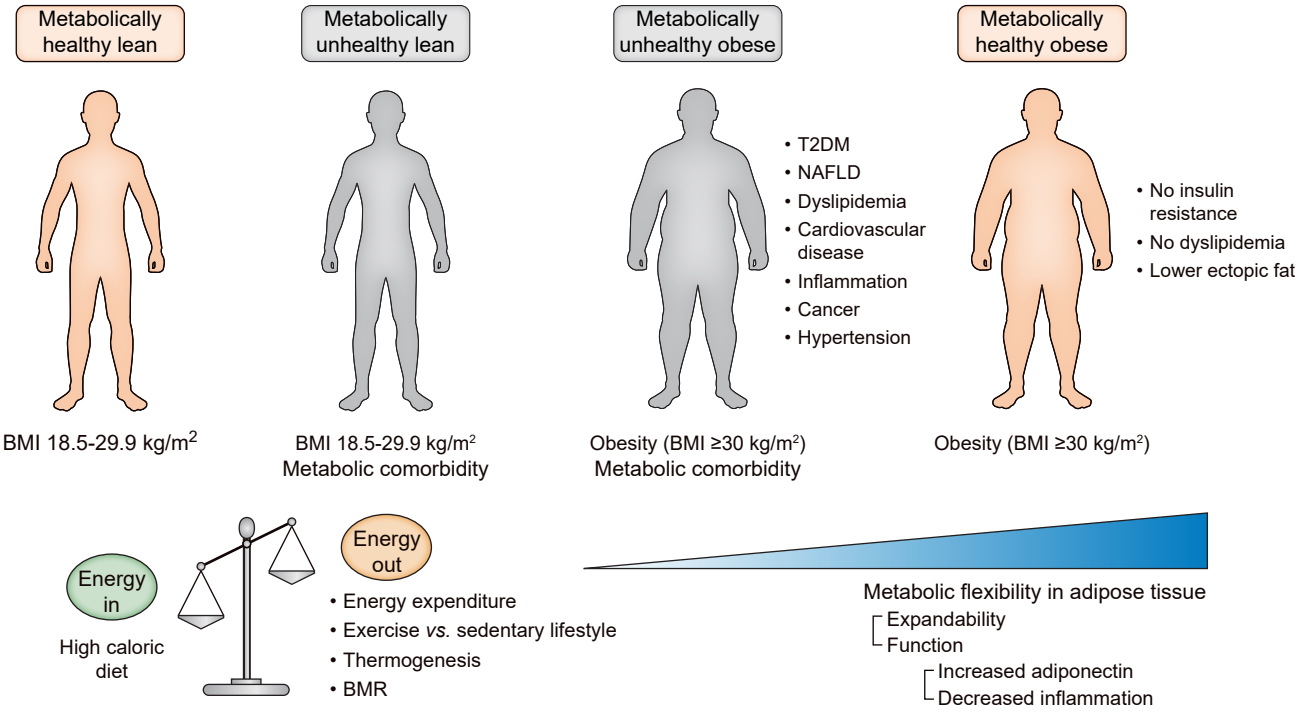

Fig. 1. Different types of obesity differing in coexistence of metabolic comorbidities. While some obese individuals do not display any metabolic abnormality, such as NAFLD, T2DM, or dyslipidemia (MHO), some lean individuals may develop NAFLD (MUL). Although the mechanism for the uncoupling between adiposity 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 β3-adrenergic receptor agonist, creates an excessive FFA load in plasma that cannot be cleared in the absence of adequate PPARα-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 rodents[47] 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 rodents[50] 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 PPARγ2 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 PPARγ2 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

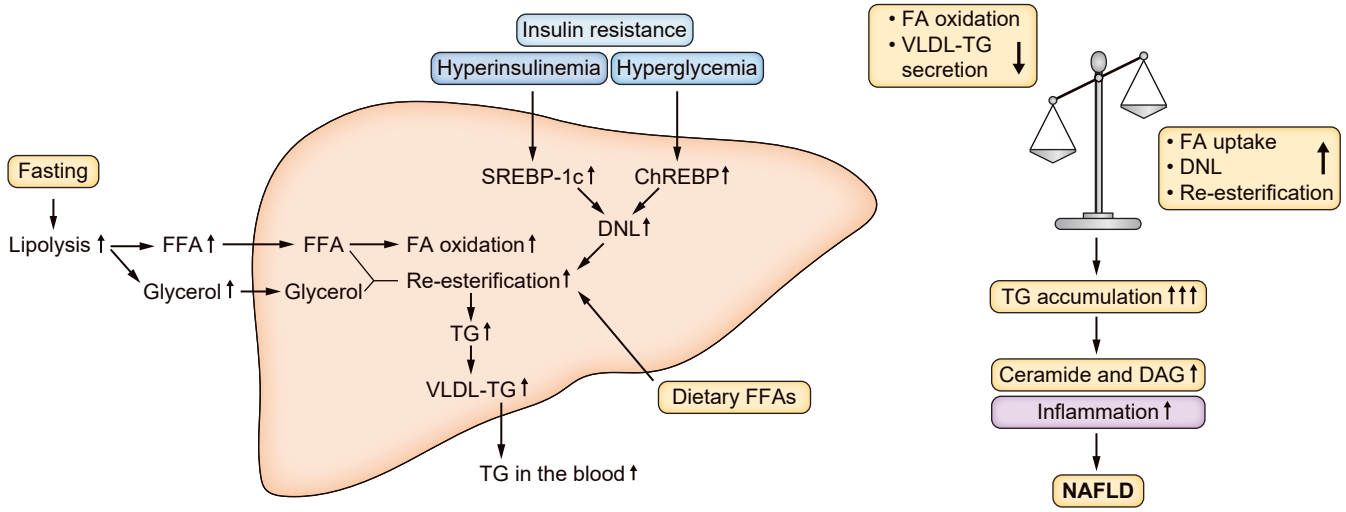

Fig. 2. The mechanism of TG accumulation in the liver and its consequences. Excessive FFAs in the circulation derived from the diet or adipose tissues promote TG accumulation in the liver. FFAs are also generated by DNL. In contrast, TG is utilised as an energy source or released from the liver as VLDL. 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-β1, 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 hypoleptinemic 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 PPARα 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.

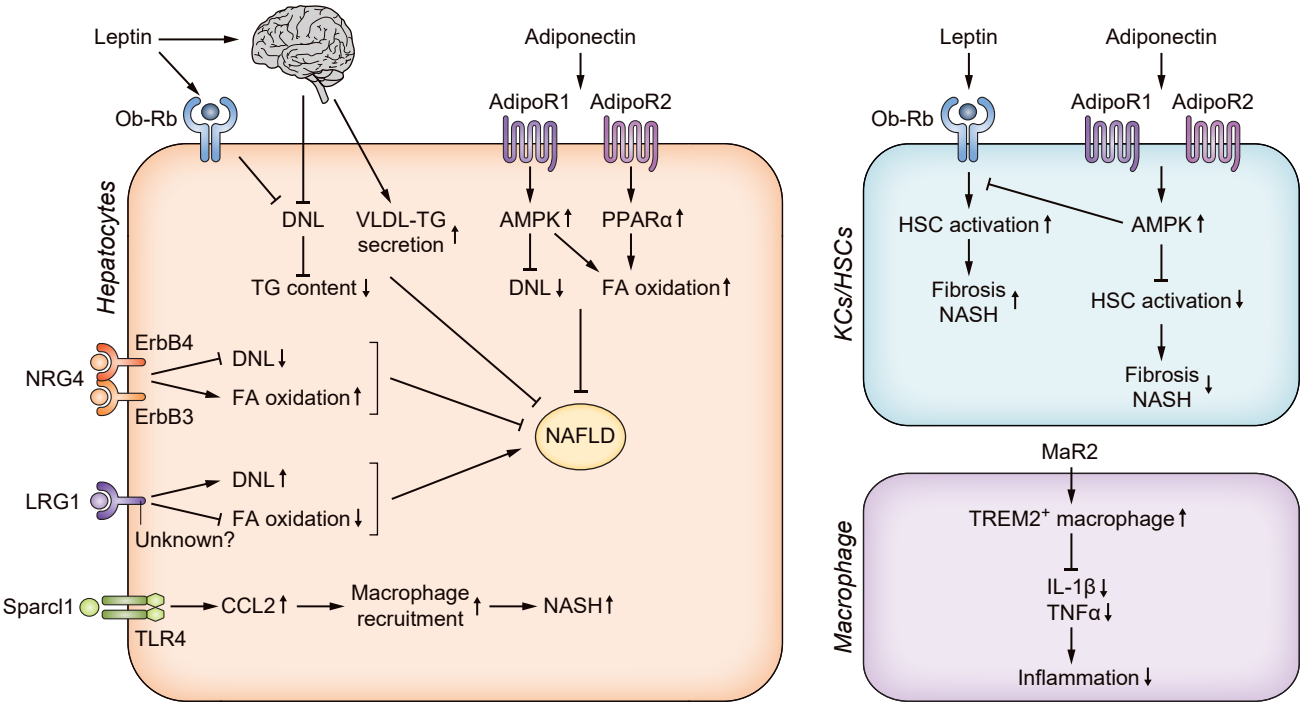

Fig. 3. The effect of adipokines on hepatic metabolism and inflammation. Adipokines directly or indirectly signal in hepatocytes, immune cells, or macrophages, leading to prevention or aggravation of NAFLD/NASH through multiple pathways. DNL, *de novo* lipogenesis; FA, fatty acid; NAFLD, non-alcoholic 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 tissue[82] 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 levels[94] 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, Sugimto *et al.* have reported that, in response to cold exposure or β3-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-1β and TNFα) 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.* reported[102] 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 TNFα, IL1β, and IL-6 through NF-κB 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 RIDα/β, an adenovirus protein complex that inhibits mammalian inflammatory pathways, specifically in adipocytes and macrophages.[119] In adipose tissues, RIDα/β inhibits several inflammatory pathways. However, surprisingly, adipocyte-specific RIDα/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 RIDα/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 tissue[121] and the liver[122] 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]

TNFα 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, TNFα expression in visceral adipose tissue is reported to be associated with the progression of NAFLD in obese patients.[127] Enhanced TNFα expression in the liver was also shown to drive the progression of NASH in mice.[128] Conversely, inhibition of TNFα 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-κB 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 insulin[140] 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

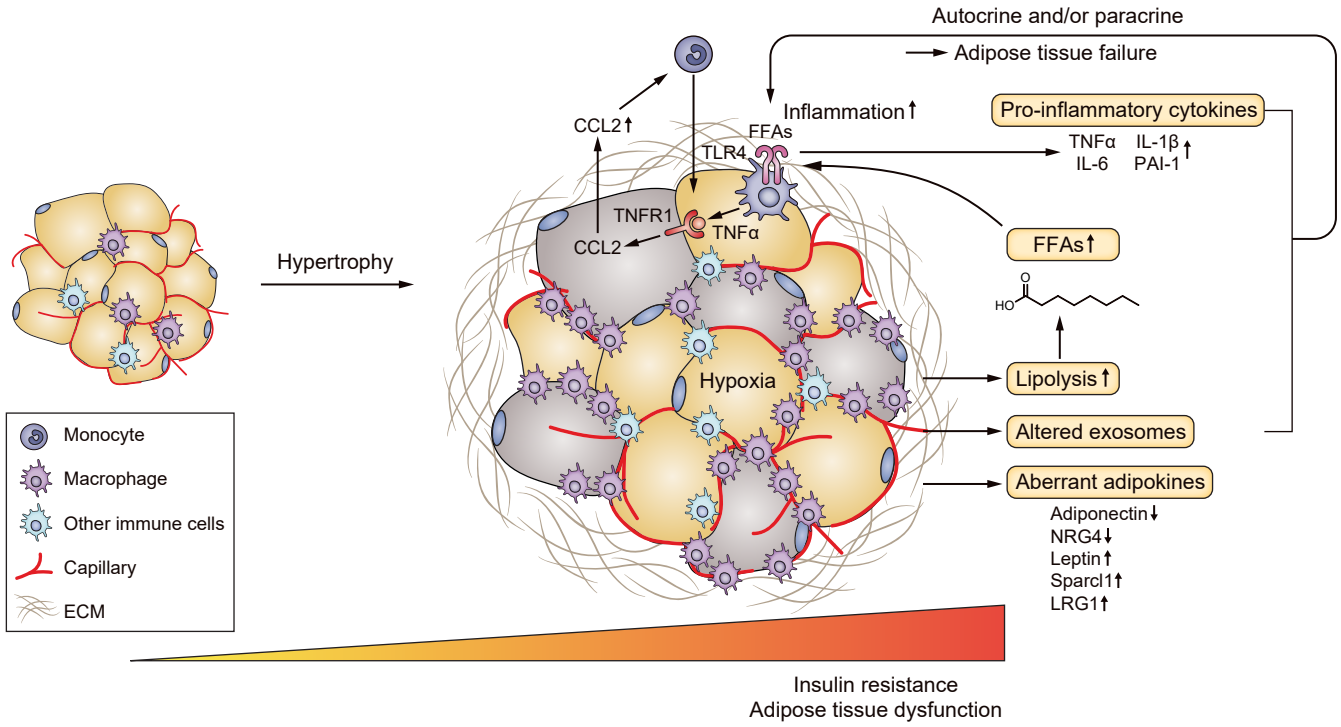

Fig. 4. Aberrant adipose biology caused by obesity. Obesity-induced adipocyte hypertrophy and progressive adipose tissue dysfunction induce insulin resistance and metabolic inflexibility characterised by increased leakage of FFAs, leading to increased pro-inflammatory cytokines and aberrant adipokine 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 directly[138] 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, TNFα, and CCL2, in adipose tissue by suppressing the NF-κB 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.

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

PPARγ belongs to a nuclear receptor superfamily and is critical in regulating lipid and glucose metabolism.[169] PPARγ is abundantly expressed in white and brown adipocytes, and its activation promotes lipid anabolism by enhancing adipogenic and lipogenic expression.[2,53,169] PPARγ is also essential for adipocyte differentiation, and its activation renders adipocytes sensitive to insulin, increasing lipid synthesis and uptake.[169] Therefore, PPARγ agonists such as pioglitazone have been used to treat diabetes mellitus.[169] Pioglitazone increases insulin-induced suppression of lipolysis[170] 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 histology[172] in people with NASH.

Mechanistically, adipocyte-specific PPARγ activation in transgenic mice improves whole-body insulin sensitivity and the adipokine profile and suppresses macrophage infiltration into adipose tissue.[173] In addition, PPARγ2 prevents lipotoxicity by promoting adipose tissue expansion and improving MetFlex,[54] limiting the inflow of lipids into the liver.[53]

Physiologically, PPARγ1 can be found in the liver,[174] where PPARγ target genes promote DNL[175] and FFA uptake,[176] leading to an increase in hepatic TG. PPARγ2 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 PPARγ knockout mice were protected from fat accumulation in the liver.[177,175] Administering a PPARγ agonist, such as pioglitazone, may initially worsen TG accumulation in the liver if the expression of PPARγ is still increased, but this effect is overcome when the trophic effects mediated by PPARγ in adipose tissue take over and divert lipid fluxes away from the liver into the adipose tissue. Moreover, activation of PPARγ in immune cells also exerts anti-inflammatory effects. PPARγ is also expressed in ATMs, and the deletion of PPARγ in macrophages impairs its anti-inflammatory and homeostatic functions.[178] In addition, PPARγ in macrophages and HSCs exerts anti-inflammatory and anti-fibrotic effects.[179,180,181] In line with these findings, another PPARγ 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, PPARγ 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 PPARα and PPARγ, 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

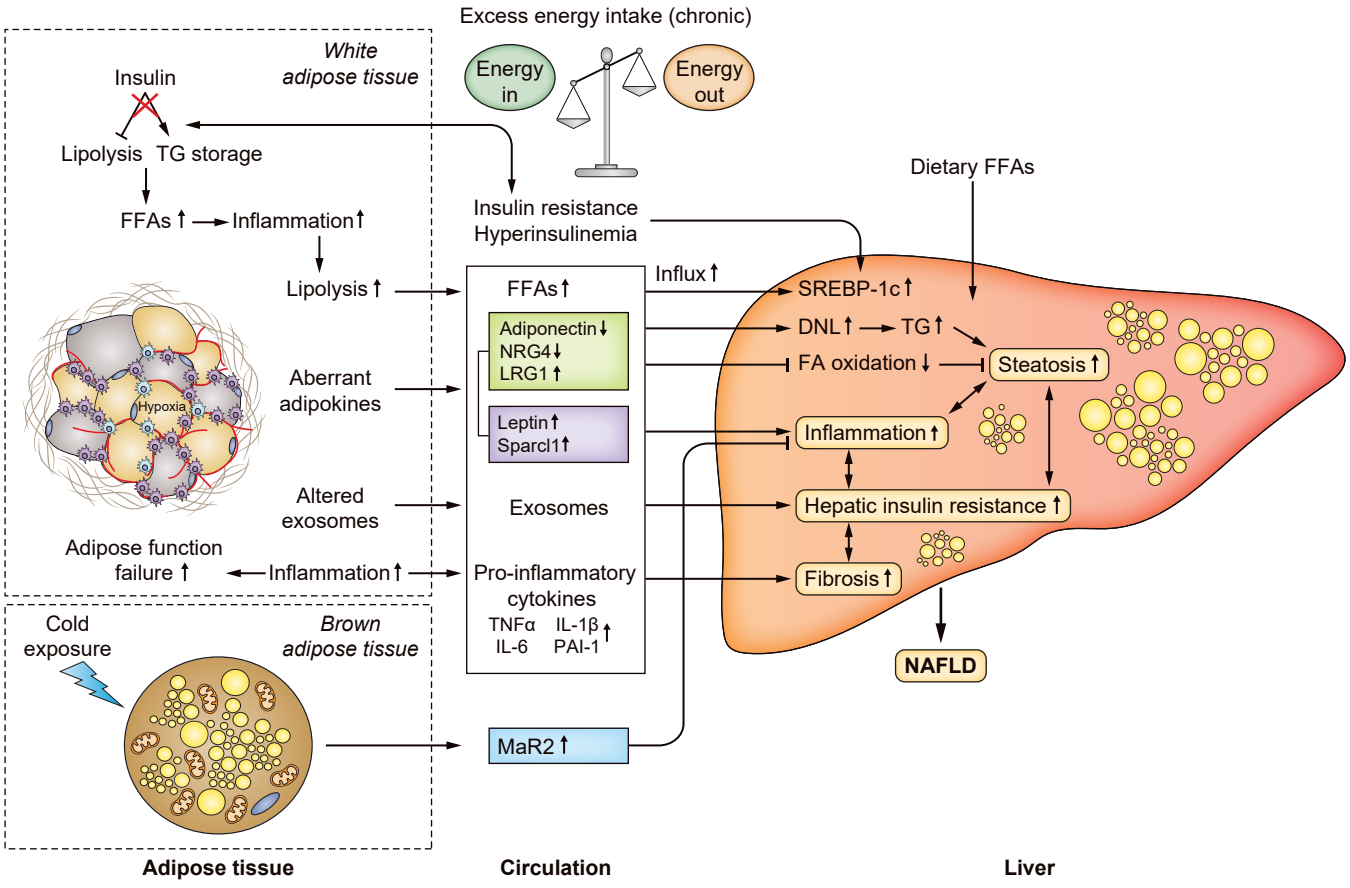

Fig. 5. Crosstalk between adipose tissue and liver in obesity, inducing the development of NAFLD. Adipose tissue dysfunction in obesity alters the levels of FFAs, adipokines, exosomes, and pro-inflammatory cytokines in the circulation, contributing to TG accumulation in the liver. Therefore, alleviating 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 THRα, THRβ, 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 THRα is highly expressed in the heart and bone, THRβ 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 THRβ 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 THRβ agonist, was reported to reduce hepatic TG in patients with NASH[197,198] in phase II and more recently phase III[199] 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.

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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; Mincle, 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.

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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

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