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Adipose tissue-liver cross talk in the control of whole-body metabolism: implications in non-alcoholic fatty liver disease

Vian Azzu,[1,2] Michele Vacca,[1] Samuel Virtue,[1] Michael Allison,[2] Antonio Vidal-Puig.[1,3]

1 Wellcome Trust-MRC Institute of Metabolic Science-Metabolic Research Laboratories, Level 4, Box 289, Addenbrooke's Hospital, Cambridge, CB2 0QQ, United Kingdom.

2 The Liver Unit, Department of Medicine, Cambridge University Hospitals NHS Foundation Trust, Cambridge Biomedical Campus, Hills Road, Cambridge, CB2 0QQ, United Kingdom.

3 Wellcome Trust Sanger Institute, Hinxton, CB10 1SA, United Kingdom.

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Adipose tissue, fatty acid flux, metabolism, non-alcoholic fatty liver disease

Abstract

Adipose tissue and the liver play a significant role in the regulation of whole body energy homeostasis, but they have not evolved to cope with the continuous, chronic, nutrient surplus seen in obesity. In this review, we detail how prolonged metabolic stress leads to adipose tissue dysfunction, inflammation and adipokine release that results in increased lipid flux to the liver. Overall, the upshot of hepatic fat accumulation alongside an insulin resistant state, is that hepatic lipid enzymatic pathways are modulated and overwhelmed, resulting in the selective build-up of toxic lipid species, which worsens the pro-inflammatory and pro-fibrotic shift observed in NASH.

Introduction: obesity and metabolic syndrome as a global health burden

Obesity develops as a result of a positive chronic energy balance defined as when caloric intake exceeds energy expenditure. It is emerging as one of the major factors limiting life-expectancy in developed countries, and is linked to an increased risk of metabolic syndrome (MetS) featuring insulin resistance (IR) and type 2 diabetes mellitus (T2DM), mixed dyslipidemia, and hypertension. Common complications include non-alcoholic fatty liver disease (NAFLD) (1), atherosclerosis (2) and cancer (3).

MetS is linked to an underlying impairment of glucose and lipid metabolism in various organs, including adipose tissue (AT) and the liver (4, 5), neither of which have evolved to cope with the continuous chronic nutrient surplus seen in obese states. In this review we consider how AT-liver cross talk goes awry during prolonged metabolic stress, focusing on lipid fluxes, peripheral IR, inflammation and hormonal signals. We will also discuss how dysregulation of these systems leads to fat accumulation within the liver.

Non-alcoholic fatty liver disease

The NAFLD spectrum includes histological features ranging from simple steatosis (NAFL) to steatohepatitis (NASH) and fibrosis ultimately leading to cirrhosis. Steatosis can be defined histologically (presence of lipid micro- or macro-vesicles in > 5% of hepatocytes) (6), chemically (intrahepatic triglyceride (TG) content >55mg/g of tissue) (7), or by imaging (e.g. >5% of liver fat fraction by magnetic resonance) (8). NAFL progresses to NASH when hepatocyte injury, inflammatory infiltrates and/or extracellular matrix deposition in the form of fibrosis develop (9). NASH places patients at risk of progression to cirrhosis and hepatocellular carcinoma, with consequent liver-related mortality or the need for liver transplantation (9). Epidemiological data suggest that NAFLD prevalence is 24% worldwide, with the highest rates reported in South America, Middle East, Asia, USA and Europe (1). The high rates of NAFLD are thought to be primarily related to the obesity epidemic especially during childhood and adolescence (1). However, considering NAFLD solely as a consequence of obesity is an oversimplification, since NAFLD can also develop in subjects

with a normal body mass index (BMI) (10) or low AT mass, thus suggesting that AT function rather than AT mass/obesity, could be a main driver of NAFLD.

The evolution of NAFL

A priori, there is little obvious reason why the liver should have such a dramatic capacity to accumulate fat compared to other non-adipose organs. This may stem from the fact AT and liver share an evolutionary origin in which metabolic cells are architecturally organized in close proximity with immune cells and blood vessels in order to coordinate the regulation of metabolic and immune responses (11). For example the fat body of Drosophila performs many of the functions of mammalian livers and AT in a single organ and has been used as a model to study obesity and metabolic diseases (11, 12). In mammals, NAFL itself may represent a maladaptation of physiological mechanisms designed for optimized nutrient storage. Firstly, fasting is a state where neutral lipid accumulation occurs in the liver. While this is presumed to be as a result of excess release of FFAs from the AT, it may be the liver has adapted to store these nutrients and then return the excess back to AT via very low density lipoproteins (VLDL) in the fed states, preserving them for later use. Equally, studies in mice of acute overfeeding demonstrate a transitory steatosis (13), which may represent a mechanism to deal with large infrequent influxes of nutrients present in evolution. The transient accumulation of lipid in liver would act to protect other organs when nutrient influx to the organism exceeds the capacity of the body's AT storage rate to deal with acute fat overload. As such, in obesity, NAFL may represent a 'least bad' option. Evidence from mice suggests that genetically preventing livers from accumulating fat in the context of the severely obese ob/ob mouse model improves liver insulin sensitivity at the cost of greatly worsening systemic insulin sensitivity (14).

Overall, the accumulation of large quantities of fat in NAFLD may represent a maladaptation of physiological systems in the liver designed to buffer short-term changes in nutritional status. We will now discuss the impact on the liver of the body's long-term lipid storage organ, AT, going awry.

The adipose tissue expandability hypothesis

One idea linking obesity with the development of NAFL is that of AT expandability (15). The concept is that each individual possesses an intrinsic limit on their capacity to store lipid in AT. Once this limit is reached, AT can no longer effectively store lipid, thus redirecting lipids toward other organs, most notably the liver. The mechanisms governing the limit on AT mass are not fully clarified. As AT mass increases dramatically with obesity (16), on a cellular level it leads to both adipocyte hyperplasia and hypertrophy. If not properly supported through appropriate extracellular matrix remodeling and neovascularization, adipocyte hypertrophy can result in adipocyte stress and cell death (17). Hypertrophic subcutaneous adipocytes have been shown to have a pro-inflammatory gene expression and are associated with greater rates of lipolysis, increased cytokine release, and IR (18, 19). Equally, intra-abdominal (visceral) adipocyte hypertrophy has been associated with dyslipidemia (20), suggested to be through excessive net delivery of FFAs to the portal circulation.

The 'lean NAFL' paradigm

The AT expandability hypothesis is attractive as it explains several clinical and epidemiological observations regarding NAFLD progression. Not all individuals present with NAFLD at the same BMI. The AT expandability hypothesis would postulate different individuals have different intrinsic limits on the capacity to expand their AT depots. On reaching their limits at different levels of adiposity, they begin to develop IR and subsequently NAFLD. Equally, epidemiologically, different populations exhibit different susceptibilities to obesity-associated metabolic complications. Asian populations from the Indian and Chinese communities exhibit metabolic complications found in obese Caucasians at comparable frequencies when reaching a BMI of 28 rather than 30 (21). So-called 'lean NAFLD' is mainly prevalent in Asia but affects up to 20% of Europeans and Americans, and is characterized by individuals with normal BMI but an 'obese' metabolic phenotype with impaired insulin sensitivity, hyperinsulinemia, and hypertriglyceridemia (22, 23). Although the causes are not fully delineated, it is believed that lean NAFLD arises as a consequence of a combination of unhealthy lifestyles (diets enriched in fructose, or westernized pattern of nutrition; sedentary habits), genetic risk factors, and abnormal AT function (Figure 1). In

contrast, different studies have suggested that lean NASH subjects are characterized by an early impairment of white AT expandability and flexibility, increased AT IR and FFA release, and are more prone to develop NASH (22, 23). A lipodystrophy-like phenotype in the general population (with limited subcutaneous fat mass, and expansion of different visceral AT deposits and/or lower body fat mass) may therefore explain part of the metabolic unhealthiness in lean individuals (24, 25).

The lipodystrophy paradigm

The most extreme example of limited AT expansion is exhibited by individuals with either genetic or acquired defects in AT development. This set of disorders are known as lipodystrophies. While a complex and heterogenous population, lipodystrophic individuals are characterized by low or no fat mass. Despite being lean, they are variably, and in some cases, extremely insulin resistant and exhibit much higher rates of NAFL, NASH progression, and cardiometabolic complications than would be expected based simply on their degree of adiposity (26). The clinical observations regarding patients with lipodystrophies are further supported by mouse models of lipodystrophy. For example, A/ZIP mice carry a transgene that causes a complete failure in AT formation, and develop substantial NAFL, with liver weights more than double those of controls (27).

However, this picture is more complex; the absence of AT also causes a lack of adipokines, with dramatic effects on whole body metabolism and IR. For example studies show that treating lipodystrophic patients with leptin can reverse hyperphagia and result in amelioration of metabolic abnormalities (28). Furthermore, mice lacking white fat also lack leptin and are hyperphagic (29). Treating such mice with leptin ameliorates both IR and reduces NAFLD (29).

A flux perspective on how fat accumulates in the liver

The degree of steatosis in the liver is determined by the flux of fat through the hepatocyte. The levels of fat in the liver are set by the quantity of lipid that the liver either produces or takes up from the bloodstream, and the capacity for the liver to export or burn it. If either side of the liver fat equation changes, it will lead to an increase or decrease in liver fat

levels. Once uptake/production of fat comes back into equilibrium with export/oxidation a new steady state concentration of liver fat will be established. We can therefore consider steatosis through the prism of turnover equations (30). The degree of steatosis in the liver can be considered as the pool size in a turnover equation, where rate of 'synthesis' (ksyn) is composed of de novo lipogenesis (DNL), hepatic free fatty acid (FFA) uptake and lipoprotein uptake. In turn, rate of 'degradation' (kdeg) comprises the processes of fatty acid oxidation and export. The equation for pool size, [P], is [P] = ksyn/kdeg, where ksyn has the units of mass and kdeg is expressed as fractional removal over time.

The fat present in the liver is constantly turning over and the amount of fat accumulated can be altered by changes in ksyn, kdeg or both. If ksyn increases without a change in kdeg then the pool size expands until the two processes balance again. For example, if ksyn for the whole liver is 2 mg/g liver/hour and kdeg is 2%/g liver/hour, then the pool size will be 2/0.02 = 100 mg/g liver; the liver will contain 10% fat. If ksyn increases two-fold to 4 mg/g liver/hour, the pool size will double to 4/0.02 = 200 mg/g and the liver will contain 20% fat (Figure 2).

Thus, while many mechanisms may exist to explain how ksyn or kdeg may be changed, the absolute degree of steatosis represents a turnover issue. Therefore, if fluxes of fat to the liver increase, even in states of neutral energy balance, unless they are matched by active increases in fatty acid oxidation or export (collectively kdeg) then steatosis will occur (Figure 2, middle panel).

One immediate consequence of flux model is that under physiological conditions if ksyn is increased, export of lipid from the liver will increase even if no active change in kdeg occurs. Several studies have indeed demonstrated that this is the case. In healthy subjects (<5% liver fat) FFA fluxes to the liver correlate with VLDL secretion (31) and intrahepatic TG levels (pool size) correlates with VLDL secretion, consistent with kdeg being a fraction of the pool disposed per unit of time. In NAFL this relationship between TG pool size and VLDL secretion breaks down (31, 32) suggesting an upper limit on TG export capacity from liver (33).

Conversely, a setting of an inherently low VLDL production will also change steatosis levels, assuming ksyn remains constant. When overexpressed, the PNPLA3 polymorphism I148M results in low VLDL secretion rates in cultured hepatocytes. In vivo, however, VLDL secretion rates from carriers of the I148M polymorphism remain constant in absolute terms but

represent a lower proportion of the total lipid pool (consistent with the concept kdeg is fractional). In this setting, consistent with our model, the consequences of a genetic limit on kdeg are not reduced VLDL production but an expansion of the pool size until a new equilibrium is reached (34) (Figure 2, right panel). Equally, the same applies to the E167K substitution in TM6SF2, resulting in decreased VLDL secretion and an increased propensity towards a fibrotic liver phenotype (35, 36), but a lower cardiovascular risk (37). Recently, Helsley *et al.* have shown that MBOAT7-driven acylation of lysophosphatidylinositols in humans is protective against obesity-associated NAFLD progression by altering hepatic lipid droplet flux (38). In the following sections we will discuss how changes in AT may drive fatty acid fluxes to liver beyond its export capacity.

Adipose tissue as a regulator of lipid flux to the liver

AT is critical for determining the fluxes of lipid to the liver in both the fasting and fed states. Importantly multiple processes that become dysregulated in obese AT are able to affect the delivery of fatty acids to the liver.

Fatty acid turnover rates in the fasting and fed states

Basal and post-prandial fatty acid turnover rates in obese individuals have been reported to be elevated on a whole organism level (39, 40) and particularly in the context of upper body obesity (41, 42). As such obesity represents a state whereby lipid flux to the liver is elevated, promoting an increase in hepatic TG pool size.

In the fasted state the main contributor to the increased fatty acid turnover rate is likely to be lipolysis. Elevations in lipolysis have been suggested to be driven by cell autonomous changes in adipocytes (39), such as an increased prevalence of hypertrophic adipocytes with greater lipolytic rates (43). However, other studies have suggested that net FFA release per adipocyte is low in obesity – instead increased whole body rates of FFA appearance are driven simply by greater fat mass (40). This concept is supported by evidence from radiocarbon dating of lipids in AT. The fatty acids in the AT of obese subjects and subjects with familial combined hyperlipidaemia are nearly twice as old as those from lean

individuals – suggesting obesity and metabolic diseases are characterized by a low lipid turnover per gram of AT (44).

The fed state is more difficult to dissect. Increased fatty acid turnover rates in the fed state can be broadly grouped into either a failure of AT to take up lipids or a failure of insulin to suppress lipolysis. In the fed state, the major source of lipid for storage in AT comes in the form of the TG-rich lipoproteins (chylomicrons and VLDL). The TGs in these lipoproteins are hydrolysed by lipoprotein lipase (LPL), which can have one of two fates – they can either be transported across the endothelium into the adipocyte to be stored as TG, or they can exit AT as FFAs (a process known as 'spillover'). Spillover rates are generally thought to be higher for chylomicrons (~30%) than VLDL (~5%) (45); however, one study has reported VLDL spillover could be as high as 70% (46). Intriguingly, spillover from chylomicrons into the circulation has been reported to be higher for women than men, and reduced with obesity, raising doubts over how much this process is responsible for higher FFA fluxes in obese vs. lean individuals (47). Conversely, splanchnic spillover of FFA into the portal circulation may be more relevant for FFA hepatic delivery. Two studies have reported that visceral fat exhibits high rates of spillover (48), and that this is increased in obesity (47). Equally chylomicrons and VLDL may not be fully hydrolyzed, resulting in lipoprotein remnants. These can also be taken up by the liver and potentially contribute to NAFL (49). Further complexity comes in that fatty acids can be recycled by the liver into VLDL (50). Therefore, post-prandial elevations in lipid fluxes to the liver can be driven by a) insufficient suppression of lipolysis (39); b) spillover of fatty acids from hydrolyzed lipoproteins (48); or c) partially hydrolyzed remnant lipoprotein particles (40).

Interestingly, the liver can also signal to AT to modulate lipolysis. Angiopoietin-like protein 4 (ANGPTL4) is mainly produced in the liver and is an important endocrine regulator of lipid metabolism (51). It suppresses LPL activity (52) and stimulates AT lipolysis by activating cAMP in adipocytes (53). Additionally, ANGPTL4's suppressive function on LPL is enhanced when TG-rich lipoproteins are enriched in apoC-I or apoC-III lipoproteins, a condition frequently seen in hepatic IR; these apolipoproteins displace the enzyme from lipid droplets, thus rendering the enzyme more susceptible to ANGPTL4 inactivation. This evidence suggests that the changes of lipoproteins composition observed in NAFLD can modulate

peripheral AT function, contributing the vicious cycle of fatty acid fluxes between liver and AT (54, 55).

While the precise balance and importance of these processes remains contested, across virtually all studies there is a general agreement that elevated fatty acid fluxes at the systemic level promote NAFL, especially when the efficiency of export or oxidation of fatty acids is not able to counterbalance it.

The importance of AT distribution

In terms of fatty acid fluxes, upper body obesity is associated with increased fatty acid turnover rates in both fasting and fed states relative to lower body obesity. Furthermore, lower body fat has a relative preference for hydrolysis of fatty acids from VLDL versus chylomicrons compared to upper body fat (56). Overall this would help to reduce the proposed futile cycle where by fatty acids are recirculated between liver and AT in the fed state (40), thus reducing the flux of lipid through the liver.

During the development of obesity, not all fat accumulation is equal. Each standard deviation increase in subcutaneous AT (SAT) mass decreases the likelihood of IR by 48%, whereas each standard deviation increase of visceral AT (VAT) mass increases likelihood of IR by 80% (57). One reason why some humans are more likely to develop metabolic sequelae of obesity may be related to their differential increase of SAT and VAT mass, which can vary with sex and genetics (58). Indeed, the preferential expansion of VAT has been associated with cardiometabolic risk (20) and NAFLD progression (59). In a large study, 115 obese patients undergoing bariatric surgery, a model based on microarray analysis of SAT/VAT was able to accurately predict NAFLD histology (obese only, NAFL, NASH) (60). Macrophages in VAT from patients with NASH, and supernatants of cultured macrophages had increased levels of cytokines and chemokines compared with control subjects (60), thus suggesting along with other studies that omental inflammation results in increased inflammatory mediators in the portal system which subsequently drive NASH (59, 61, 62). However, it should also be noted that there are studies suggesting that AT distribution is not important for NAFLD progression. In a large population of biopsy-proven NAFLD patients, Fracanzani *et al.* suggest that 55% of patients without visceral obesity had NASH, with a

milder metabolic impairment than obese patients with NAFLD (63), possibly suggesting that once NASH develops, intra-hepatic events become more relevant than AT dysfunction or AT distribution.

Pharmacological evidence for the link between adipose tissue fatty acid fluxes and NAFLD

One interesting clinical paradox is that rosiglitazone and pioglitazone, thiazolidinediones (TZDs) that activate PPARγ, have been demonstrated to be anti-steatogenic in humans (64-67). In preclinical models, overexpression of PPARγ in the liver leads to massive NAFL (68), whereas ablating PPARγ prevents TG accumulation in liver even in the genetically obese ob/ob mouse model (14). However, the systemic effects of the activation of a potently lipogenic transcription factor on improving NAFL can be explained in light of the AT expandability hypothesis. Increasing AT function through activating PPARγ increases AT capacity to store fat, as well as restoring the function of AT in terms of both lipid uptake and release (69). Fatty acid transporters and lipases are known PPARγ target genes (70). Increase AT expansion capacity and function allows fat to be channeled away from liver and into AT. As a side effect, TZD treatment increases body weight (71), however despite increasing BMI, clinical outcomes in terms of liver function and insulin sensitivity are improved in response to TZDs, confirming that AT function rather than mass is crucial for the metabolic outcomes of obese patients.

Importantly, TZDs may also improve NAFL through regulating fatty acid fluxes. For example, pioglitazone increases AT mass, improves AT insulin sensitivity, thus leading to suppressed AT lipolysis and decreased circulating FFA and triglycerides (66, 69). This reduces the flux of fatty acids to liver and, as a consequence, the pool size of intrahepatic lipid.

Diverting systemic lipid fluxes away from liver to combat NAFLD

While reducing the total flux of lipid around the body is desirable in order to reduce the flux of FFA to the liver (decreasing hepatic ksyn), an alternative approach is to eliminate fatty

acids through oxidation (increasing kdeg). Several lines of evidence support the concept that both approaches have therapeutic benefit.

Serum levels of ketone bodies are used as a proxy measure of hepatic FA oxidation, and have been reported as increased (22), unchanged (72) or decreased (73-75) in obesity or NAFLD. This is likely explained by the ketone body being measured, the extent of metabolic disease severity (e.g. the presence of T2D), and the fasting/fed state of the subjects. For example, in the context of mitochondrial dysfunction in NAFLD (76), the lack of efficient shuttling of acetyl co-A into the mitochondrial tricarboxylic acid cycle leads to an increase in β-hydroxybutyrate levels (22). However, as hepatic steatosis and glycemia worsen, ketogenesis may become progressively impaired (75), thus lowering ketone body levels. Mechanistically, increasing fatty acid oxidation directly in the liver has been done both genetically and pharmacologically. Pharmacologically two studies used mitochondrial uncouplers (dinitrophenol in a slow release form called 'controlled-release mitochondrial protonophore' and niclosamide ethanolamine) which principally accumulated in liver. These drugs work by short-circuiting the mitochondrial inner membrane, preventing the proton gradient from being used for ATP synthesis. Instead the mitochondrial proton gradient generated by the electron transport chain is dissipated as heat. In both studies, uncoupling mitochondria led to reduced liver fat, improved insulin sensitivity and improved markers of hepatic function (77, 78). Genetically, hepatocyte-specific PGC1β activation is able to induce mitochondrial oxidative phosphorylation and FA oxidation, thus prevent hepatic lipid overload and ensuing inflammation and fibrosis (79).

Equally, diverting lipid fluxes away from liver can prevent NAFL. Brown AT (BAT) is a thermogenic organ, which physiologically uncouples oxidative phosphorylation from ATP generation using the protein uncoupler UCP1. At room temperature, mice are already under considerable thermal stress and female C57Bl6/J mice do not exhibit substantial diet induced obesity or NAFL. Moving mice to a thermoneutral environment shuts down BAT, increases weight gain in both male and female mice, worsens NAFL in males and leads to the development of NAFL in females (80). BAT may be particularly effective at preventing liver fat accumulation as it not only clears fatty acids from the circulation but removes entire lipoprotein particles, reducing multiple sources of lipid flux that can be potentially directed to the liver (80). There is limited data in humans showing that individuals with

higher levels of BAT have a reduced probability of T2DM and obesity (81), as well as NAFLD (82), implying that activation of BAT and/or beiging of white fat may be a viable therapeutic option in the future [reviewed in (83)].

Adipose tissue, insulin resistance and hyperglycaemia as worsening factors of NAFL

As a result of chronic positive energy balance and of the subsequent development of obesity, adipocytes enlarge and become dysfunctional. As adipocytes reach their maximal storage capacity adipose tissue fails to store lipid appropriately redirecting it to other organs where it causes insulin resistance through lipotoxic mechanisms. Various studies have shown that preventing adipose tissue from forming can have adverse metabolic consequences (27), and allowing re-expansion of white fat ameliorates this phenotype (84). Peripheral IR and the subsequent hyperinsulinemia are both associated with NAFL and NASH progression (23, 85). The adipose tissue expandability and lipotoxicity hypotheses are reviewed here (15), but details of the molecular mechanisms leading to AT IR and its systemic metabolic complications is out of the scope of this review article [widely reviewed in (17, 86, 87)] but there are at least two major reasons that justify the association of AT IR with altered hepatic lipid fluxes and metabolism. Firstly, under physiological conditions, insulin induces a post-prandial inhibition of AT FFA release by directly or indirectly repressing the activity of adipose triglyceride lipase and hormone-sensitive lipase; these effects are inhibited in obesity and AT IR (88, 89) and increase circulating FFA levels (22, 23). Secondly, peripheral IR in obesity and NAFLD is associated with hyperinsulinemia (22, 23, 90). Insulin regulates multiple facets of liver biology, with perhaps the two most canonical functions being to suppress the release of glucose and to promote the synthesis of lipid from carbohydrate. In healthy states these two processes are coupled. In the fed state, when glucose and lipids are coming from the gut to the liver, insulin levels are high. Dietary lipids are stored by AT and carbohydrates are used as oxidative substrate.

If the degree of IR in the liver is less than that of the periphery, then the liver may be in a state of relatively elevated insulin action thus inducing sterol regulatory element-binding

353 protein 1c (SREBP-1c), which i) promotes DNL, ii) negatively feeds back on insulin signaling
354 leading to decreased glycogen synthesis and increased gluconeogenesis, and iii) directly
355 promotes gluconeogenesis. The net effect is thus the induction of NAFL and
356 hyperglycaemia (91), which is worsened by progressive hepatic fat accumulation and the
357 development of hepatic IR.

358 Excess carbohydrate replenishes glycogen stocks, directly promotes DNL, and the
359 downstream products are channeled into DNL for the purpose of conversion into energy-
360 dense fatty acids for long-term storage (92-94). The high carbohydrate load is
361 compounded by a 'western' diet containing fructose, which is recognized to be a potent
362 substrate and activator of DNL (95). Increased intracellular glucose levels activate the
363 glucose sensor carbohydrate response element-binding protein (ChREBP), which
364 promotes glycolysis and gene expression of DNL genes in the liver (96). In animal models
365 of obesity, the specific deletion of hepatic ChREB prevents NAFL and reduces plasma
366 levels of TGs, also ameliorating IR and glucose intolerance (92). Intriguingly, ChREBP
367 expression correlates with the degree of steatosis in patients with NASH, however, its
368 expression decreases in presence of severe hepatic IR (97). In NAFLD, the combined
369 action of hyperinsulinemia and hyperglycemia on SREBP1 and ChREBP, results in
370 induction of DNL desaturation and elongation genes (91) and upregulation of hepatic FFA
371 production (98-100), which is estimated to account for 26% of hepatic lipids (101).

372

373 Adipose tissue inflammation in NAFL

374 AT contains a large and diverse immune cell repertoire that is modulated in a primarily pro-
375 inflammatory manner by obesity. AT in obese individuals is characterized by an increased AT
376 inflammatory cell infiltrate (102, 103). Dysfunctional adipocytes act as antigen presenting
377 cells, presenting MHC Class II complex proteins (104-108) and producing pro-inflammatory
378 NFkB-dependent cytokines. These include TNFα (109), IL6 (110), IL1β (111, 112), MCP1/CCL2
379 (102, 109, 113, 114), RANTES/CCL5 (108, 109, 114, 115) and MCP4/CCL13 (binding both to
380 CCR2 and CCR5) (108, 116), which reshape the inflammatory infiltrates in the AT of obese
381 subjects (103). Overall, the prominent features of the AT inflammatory cell infiltrate in

obesity is an increased composition of cells having a 'pro-inflammatory' role and a relative reduction of 'anti-inflammatory' cells (117, 118).

Although the molecular mechanisms linking immune cell regulation to IR are outside the scope of this article [reviewed in (119)], we will briefly discus how inflammatory pathways can directly interfere with AT IR and lipolysis (120), thus potentially leading to NASH progression (19).

Macrophage inflammatory status controls adipose tissue lipolysis

Recent evidence has suggested that macrophages within AT are able to regulate lipolysis. This observation initially came from the fact that genetic deletions within macrophages led to the browning of white fat (121). Both browning of white fat and lipolysis are under the control of monoamines, in particular norepinephrine (122), and changes in macrophage polarization status can alter monoamine degradation rate (121) through the monoamine oxidase pathway and the norepinephrine transporter (123). This suggests that changes in macrophage inflammatory status in obesity could potentially regulate lipolysis. This concept was given further weight by the finding that specific populations of macrophages are in close proximity with nerve endings and that they reduced catecholamine delivery to adipocytes (124). Whether the effect of macrophages on catecholamines is relevant for human lipolysis and if and how this could regulate fatty acid fluxes to liver remains to be determined. In addition to directly regulating catecholamines, cytokines such as TNFα have also been shown to drive lipolysis. Recently, it has been shown that inflammation can promote AT lipolysis by causing aberrant MAPK signaling. MAPK activates the β3-adrenergic receptor (β3AR) on serine 247, promoting lipolysis (125). Importantly, this activation could explain the higher rates of basal AT lipolysis present in obesity, which can drive excess FFA fluxes to the liver.

Hormonal cross talk between AT and liver

In addition to cytokines produced by AT, it is now well recognized that AT is a major endocrine organ producing a large array of hormones. In the following section, we will

411 review the role of different AT-produced hormones and how they can signal to the liver to
412 promote NAFL.

413 Congenital loss of leptin results in severe obesity in humans and rodents, and its restoration
414 through recombinant protein ameliorates the phenotype (126), thus generating hope in
415 future weight loss therapies. Indeed, leptin replacement in lipodystrophy dramatically
416 improves the metabolic phenotype of these patients (127). It is thought to decrease NAFLD
417 through reducing hyperphagia (28), further evidence reveals that this occurs independently
418 of reduced calorie consumption (128).

419 However, increased AT mass in obesity results in increased secretion of the hormone leptin.
420 Meta-analyses show a robust association between increased leptin during obesity and
421 association with NAFLD severity (129) and hepatic IR (130). It is important to note, however,
422 that obesity is also characterized by a leptin resistant state (131). Zhao *et al.* recently
423 demonstrated that in the context of obesity, partial leptin reduction restores hypothalamic
424 leptin sensitivity, leads to reduced food intake, increased energy expenditure, and improved
425 insulin sensitivity (132). Hackl and colleagues have shed further light on the mechanism by
426 showing that intrathecal leptin delivery in mice protects from steatosis by promoting
427 hepatic TG export and decreasing DNL independently of caloric intake (133). This discovery
428 requires hepatic vagal innervation, suggesting that leptin ameliorates MetS centrally via the
429 parasympathetic autonomic nervous system rather than directly acting on the liver. In
430 contrast to its effects on hepatic lipid handling, there is also evidence that leptin has a
431 fibrogenic effect on the liver, which is mediated through the sympathetic autonomic
432 nervous system, namely via norepinephrine's stimulation of hepatic stellate cell activation
433 (134, 135). Some evidence also suggests that leptin may act directly on liver cells, for
434 example by enhancing the release of TNFα by Kupffer cell cultures (136) and potentiating
435 the effect of TGFβ on cultured hepatic stellate cell activation in the presence of Kupffer cell
436 medium (137).

437 Unlike most adipokines which are increased in obesity, animal studies and epidemiological
438 data show that decreased adiponectin is associated with obesity-related metabolic
439 complications such as IR, dyslipidemia and cardiometabolic disease (138, 139). Reduced
440 levels of adiponectin in obesity result from increased proportional VAT and mean adipocyte
441 diameter, which have been shown to result in reduced secretion of adiponectin (140). When

injected into diabetic animals, adiponectin is able to lower circulating glucose primarily through PPAR-mediated decrease of glycogenolysis and gluconeogenesis (141). Adiponectin is also able to inhibit DNL in the liver, stimulate FA oxidation through signaling via AMPK (142), and increase ceramidase activity thus preventing or reversing diet-induced steatosis, IR, and glucose intolerance (143). As well as signaling through its AdipoR receptors, adiponectin is able to mediate insulin sensitization in the liver by upregulation of hepatic IRS-2 via an IL6-dependent pathway (144). Therefore, adiponectin acts pleiotropically to regulate glucolipid metabolism and insulin sensitivity in peripheral tissues and its lowering in obesity potentiates adverse metabolic outcomes (145) as well as being associated with progressive liver fibrosis in NASH (146).

Although most adipokine factors are predominantly produced by white AT, neuregulin 4 (Nrg4), is produced predominantly by BAT or beige adipocytes (147, 148). Regulated by BMP8b (149), it has a direct effect on AT, inducing AT angiogenesis, reducing AT hypoxia (150) and modulating the AT adipokine profile towards a more healthy pattern (151). Work in mice has shown that Nrg4 deficiency results in increased hepatic inflammation and fibrosis in the context of a high fat diet, and mice transgenic for Nrg4 in AT alone markedly reduces these elements of NASH (151) and reduces hepatic lipogenesis (152). Human data indicates that there is reduced serum Nrg4 in human NAFLD (153) and it is suggested that Nrg4 levels fall with increasing adiposity, thereby having a role in the progressive change in AT phenotype with adiposity.

A further mechanism by which AT and the liver interact is via secreted microRNAs (miRNAs) or extracellular vesicles, failure of which has been associated with adverse metabolic events (154, 155); the precise details of these mechanisms are outside the scope of this work and may be reviewed here (156). Despite being a topic at its infancy, the role of exosomes in AT-liver interactions is a promising area that seems certain to attract more scientific interest in the future.

Liver lipotoxicity and the development of NASH

So far, we have discussed AT-liver cross talk that lead to the accumulation of fat seen in NAFL. However, it is widely believed that neutral lipids, which are the major constituent of

472 microscopically visible lipid droplets in liver, are relatively benign. In this section we will
473 discuss lipid species that are responsible for the transition from NAFL to NASH.

474 Lipidomic studies show that although most hepatic lipids accumulate as inert TGs that are
475 relatively non-toxic in NAFL, progression from NAFL to NASH and fibrosis is associated with
476 the accumulation of toxic lipid species. This includes (but is not limited to) intermediates in
477 TG synthesis (e.g. diacylglycerols (100, 163), saturated fatty acids (SFA) (164, 165)), free
478 cholesterol (166, 167), ceramides (99, 168), and complex lipids (e.g. glycerophospholipids,
479 sphingolipids). NAFL to NASH transition has also been associated with deficiency in lipid
480 species that are essential for cellular integrity such as phospholipids, omega-3
481 polyunsaturated fatty acids (PUFAs), or PUFA-derived specialized pro-resolving mediators)
482 [reviewed in detail here (169)].

483 The relative contribution of the specific lipid metabolic pathways could explain why, at the
484 same degree of hepatic lipid accumulation, some individuals develop hepatic lipotoxicity
485 and NASH, while others have a more benign outcome. The type of lipids accumulating in the
486 liver will be impacted by the genetic background of the subjects, their environment,
487 underlying AT and systemic metabolic dysfunction (e.g. IR, hyperinsulinemia, increased
488 circulating FFA) as well as lifestyle habits (diet and exercise).

489 For example, ChREBP and SREBP1c have overlapping but distinct roles on lipid metabolism
490 (170): they both promote DNL although exerting differential effects on lipid remodeling
491 genes like desaturases and elongases. Although high liver ChREBP expression results in
492 greater steatosis, reduced SFA/increased monounsaturated fatty acids protect against IR
493 (92, 97), whereas high liver SREBP1c expression remains associated with IR (171). Indeed,
494 Chiappini *et al.* showed that the lipidomic signature in NASH (compared to NAFL) is related
495 to alterations of elongase and desaturase enzymes involved in the synthesis of long chain FA
496 and very long-chain fatty acids, and that the lipids species that are selectively accumulated
497 in the context of NASH constituted a mixture highly toxic to human hepatic cells (172).

498 The interaction between systemic metabolic health and the hepatic lipidome becomes more
499 complex when taking into account the different nutrients enriched in specific dietary
500 patterns: for example, in overweight/obese subjects overfeeding with SFA and
501 carbohydrates leads to increased hepatic lipid deposition (164, 173) compared to feeding
502 with unsaturated fat (which suppresses lipolysis) (164). Furthermore, SFAs appear more

powerful than monounsaturated fatty acids at inducing steatosis and hepatic IR, and increasing harmful ceramide levels (99, 164). Additionally, SFAs can cause lipotoxic damage by directly binding and activating hepatocyte plasma membrane receptors that induce hepatocyte apoptosis (174).

Mechanistically, lipotoxic lipids have been associated with increased endoplasmic reticulum stress, mitochondrial dysfunction, the development of hepatic IR and activation of the inflammasome. Therefore, lipotoxicity is able to promote virtually all know processes that are hepatotoxic, thus promoting NASH progression.

Overall, in the early phases of NAFL, the liver prevents lipotoxicity by inducing the remodelling of the lipidome (the conversion of more harmful lipids in inert ones e.g. via elongation and desaturation), exporting excess fat into lipoproteins, and oxidizing the remnant lipids. As the efficiency of mitochondrial β-oxidation (76, 175) and of lipoprotein synthesis (23, 176) is impaired in NASH, this leads to the promotion of the extra-mitochondrial (microsomal and peroxisomal) oxidation (76, 175) and of Ω-oxidation (that is required for very long FAs). These processes are metabolically less efficient than mitochondrial β-oxidation, and generate a dramatic amplification of ROS production thus worsening the lipotoxic milieu and causing further dysfunction of hepatocytes and apoptosis, thereby worsening the pro-inflammatory and pro-fibrotic shift observed in NASH [reviewed here (175)].

Conclusion

In this review we put forward a largely adipocentric view of NAFLD development. We propose that adipose tissue can impact on the liver by regulating the flux of lipids to it, by the production of cytokines and hormones that can affect hepatocyte function and by signaling through exosomal pathways (Figure 3). Although we believe adipose tissue function is a critical driver of NAFL and NASH, as evidenced by the association between obesity and these diseases, we do not disregard the importance of intrinsic changes in hepatic biology. Hepatic insulin resistance, lipid export capacity, lipid oxidative capacity and lipid synthetic capacity can all mediate aspects of NAFLD. However, we believe that considering NAFLD a disease of fat accumulation, without taking into account the

cooperative role that the liver and adipose tissue play in controlling lipid metabolism is akin to trying to solve a jigsaw puzzle with half the pieces missing.

Conflicts of interest

The authors declare no conflicts in relation to this manuscript

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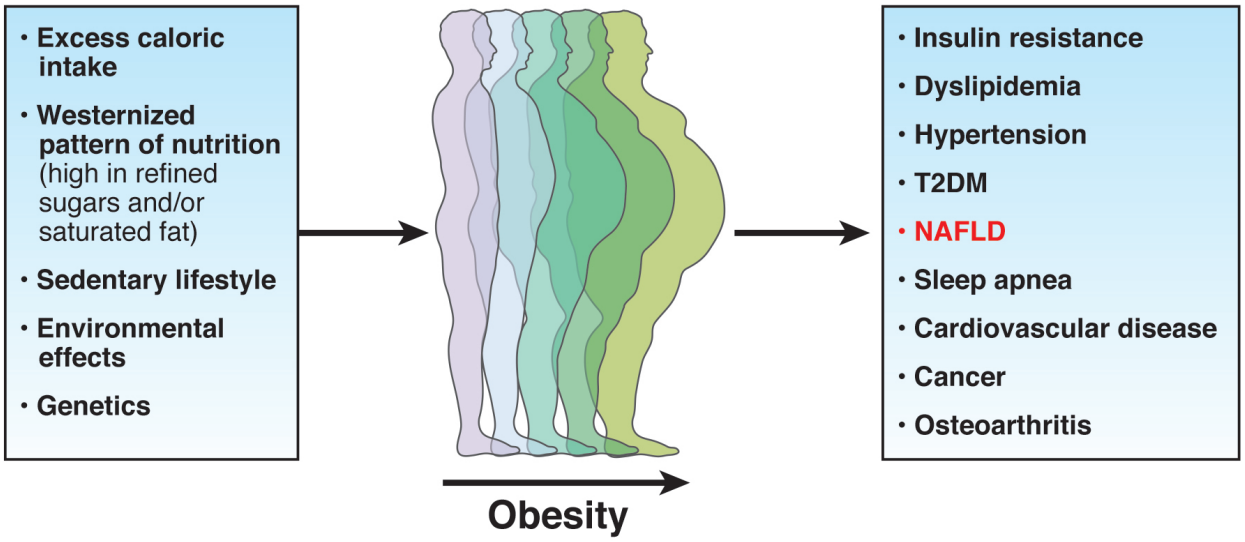
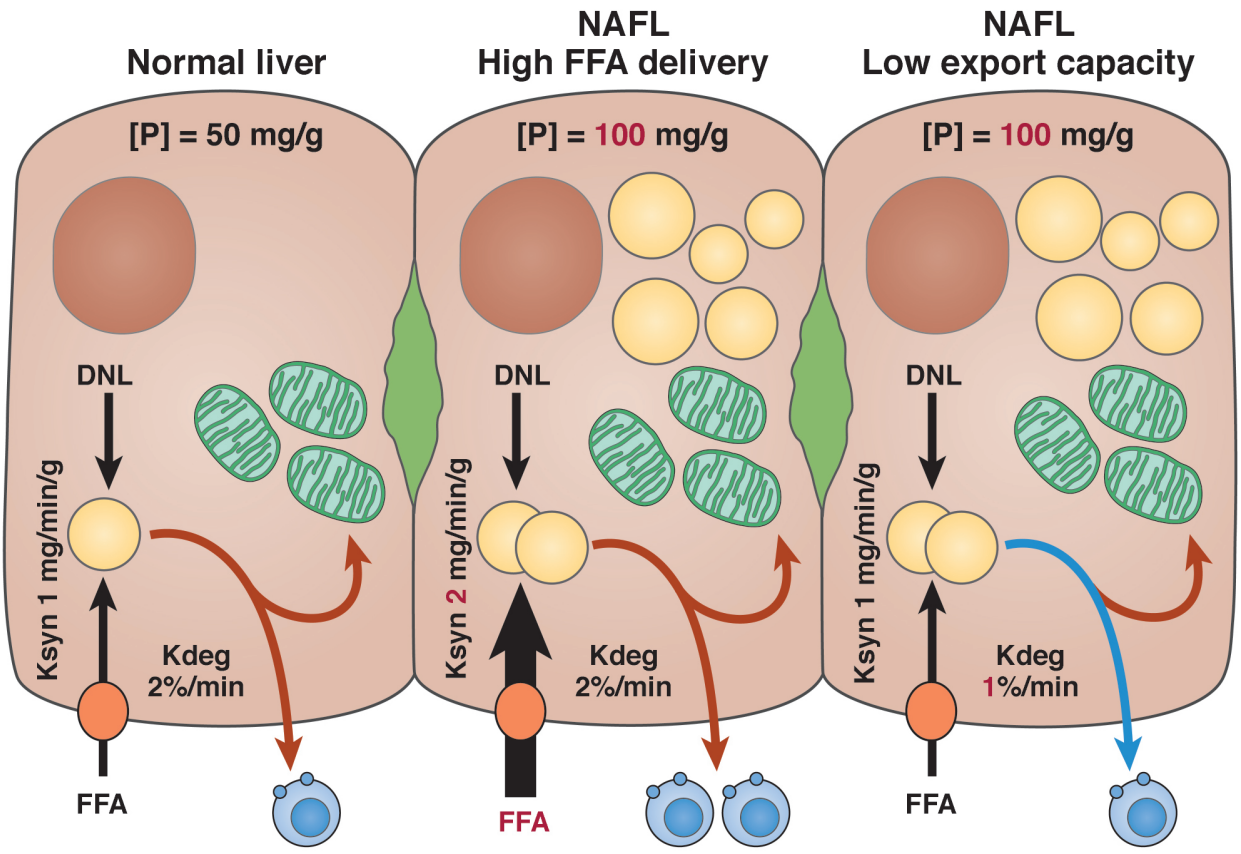
Figure Legends

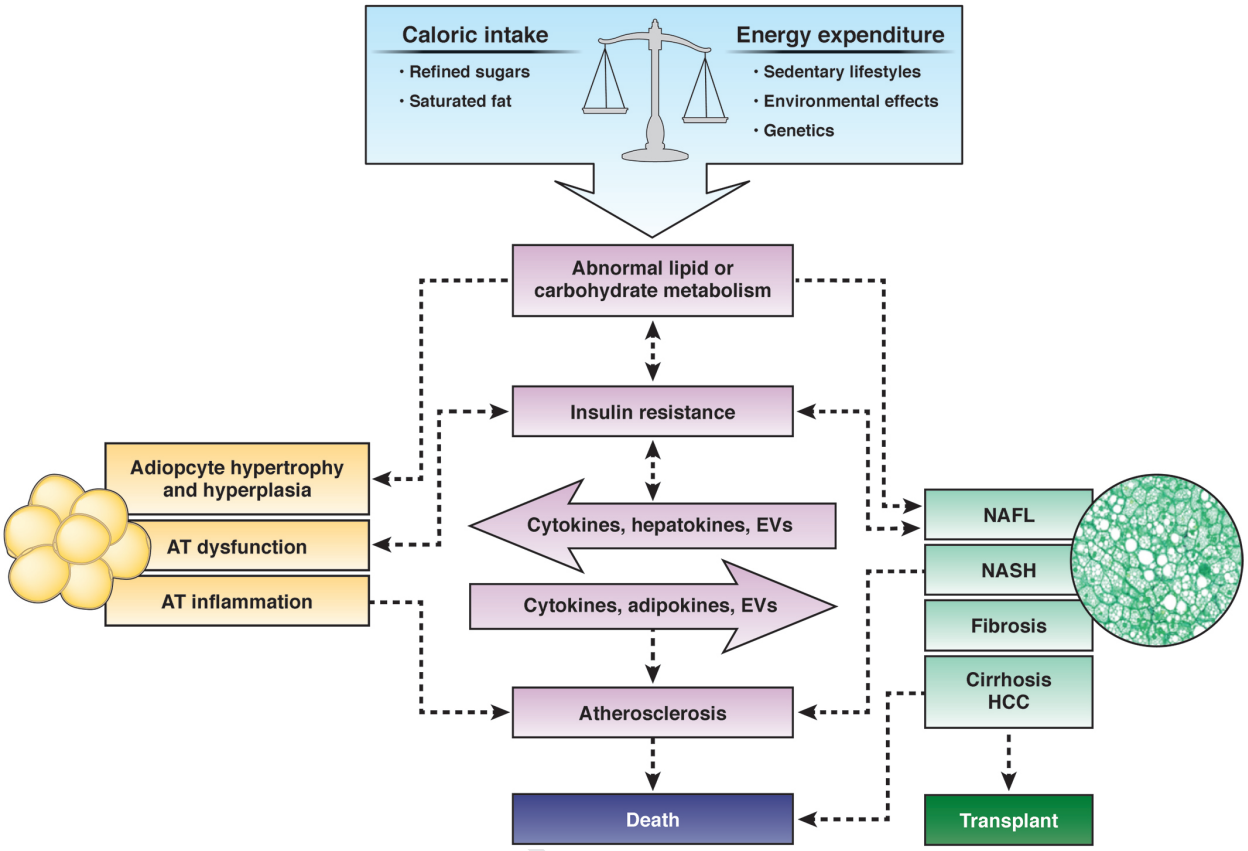
Figure 1: Causes and consequences of obesity

Figure 2: Metabolic fluxes and NAFLD

Figure 3: Interaction of adipose tissue, inflammation and liver in obesity




Normal liver
[P] = 50 mg/g
DNL
Ksyn 1 mg/min/g
Kdeg
2%/min
FFA
NAFL
High FFA delivery
[P] = 100 mg/g
DNL
Ksyn 2 mg/min/g
Kdeg
2%/min
FFA
NAFL
Low export capacity
[P] = 100 mg/g
DNL
Ksyn 1 mg/min/g
Kdeg
1%/min
FFA


Caloric intake
• Refined sugars
• Saturated fat
Energy expenditure
• Sedentary lifestyles
• Environmental effects
• Genetics
Abnormal lipid or carbohydrate metabolism
Insulin resistance
Adiopcyte hypertrophy and hyperplasia
AT dysfunction
AT inflammation
Cytokines, hepatokines, EVs
Cytokines, adipokines, EVs
NAFL
NASH
Fibrosis
Cirrhosis HCC
Atherosclerosis
Death
Transplant


SIGMA-ALDRICH