Adipose Signals Regulating Distal Organ Health and Disease

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Excessive adiposity in obesity is a significant risk factor for development of type 2 diabetes (T2D), nonalcoholic fatty liver disease, and other cardiometabolic diseases. An unhealthy expansion of adipose tissue (AT) results in reduced adipogenesis, increased adipocyte hypertrophy, adipocyte hypoxia, chronic low-grade inflammation, increased macrophage infiltration, and insulin resistance. This ultimately culminates in AT dysfunction characterized by decreased secretion of antidiabetic adipokines such as adiponectin and adipsin and increased secretion of proinflammatory prodiabetic adipokines including RBP4 and resistin. This imbalance in adipokine secretion alters the physiological state of AT communication with target organs including pancreatic β-cells, heart, and liver. In the pancreatic β-cells, adipokines are known to have a direct effect on insulin secretion, gene expression, cell death, and/or dedifferentiation. For instance, impaired secretion of adipsin, which promotes insulin secretion and β-cell identity, results in β-cell failure and T2D, thus presenting a potential druggable target to improve and/or preserve β-cell function. The cardiac tissue is affected by both the classic white AT–secreted adipokines and the newly recognized brown AT (BAT)-secreted BATokines or lipokines that alter lipid deposition and ventricular function. In the liver, adipokines affect hepatic gluconeogenesis, lipid accumulation, and insulin sensitivity, underscoring the importance of adipose-liver communication in the pathogenesis of nonalcoholic fatty liver disease. In this perspective, we outline what is currently known about the effects of individual adipokines on pancreatic β-cells, liver, and the heart.

Obesity, clinically defined as a BMI of $\geq$30 kg/m^2, has become a major epidemic worldwide (1). Anatomically, obesity is manifested by increased adipose tissue (AT) mass that results in an excess burden of diseases like type 2 diabetes (T2D), heart disease, and certain types of cancers. Research over the past decade has made it evident that the obesity link to metabolic disease depends on not only the traditionally known function of AT as an energy storage reservoir but also its role as a major endocrine organ. Since the description of adipsin as the first adipokine in 1987, the AT is now known to control metabolism via secretion of a large number of adipokines (peptide mediators), lipid mediators, and RNA molecules in the form of extracellular vesicles (EVs) (2). These adipocyte-secreted factors mediate the AT communications with and control functions of major organs such as pancreas, heart, and liver. For example, adipokines such as adipsin promote pancreatic β-cell function (insulin secretion) and survival (3,4). In this article, we will explore AT communication to the pancreas, liver, and heart via its secreted factors and shed light on how this communication is disrupted in a state of AT dysfunction.

AT Dysfunction: A Communication Failure

There are three major types of AT: white adipocytes that reside in white AT (WAT), comprising >95% of adipose mass; brown adipocytes within brown AT (BAT), comprising 1–2% of fat; and beige/brite adipocytes that are interspersed within the WAT and can transform into brown-like adipocytes in response to cold exposure or adrenergic stimulation. White adipocytes with a large unilocular lipid droplet are mainly responsible for AT expansion in obesity. In contrast, brown and beige adipocytes have multilocular droplets and high mitochondrial density to dissipate heat through uncoupled respiration, a unique feature that could potentially be used to combat obesity (5). AT dysfunction has mainly been described in WAT; however, recent studies

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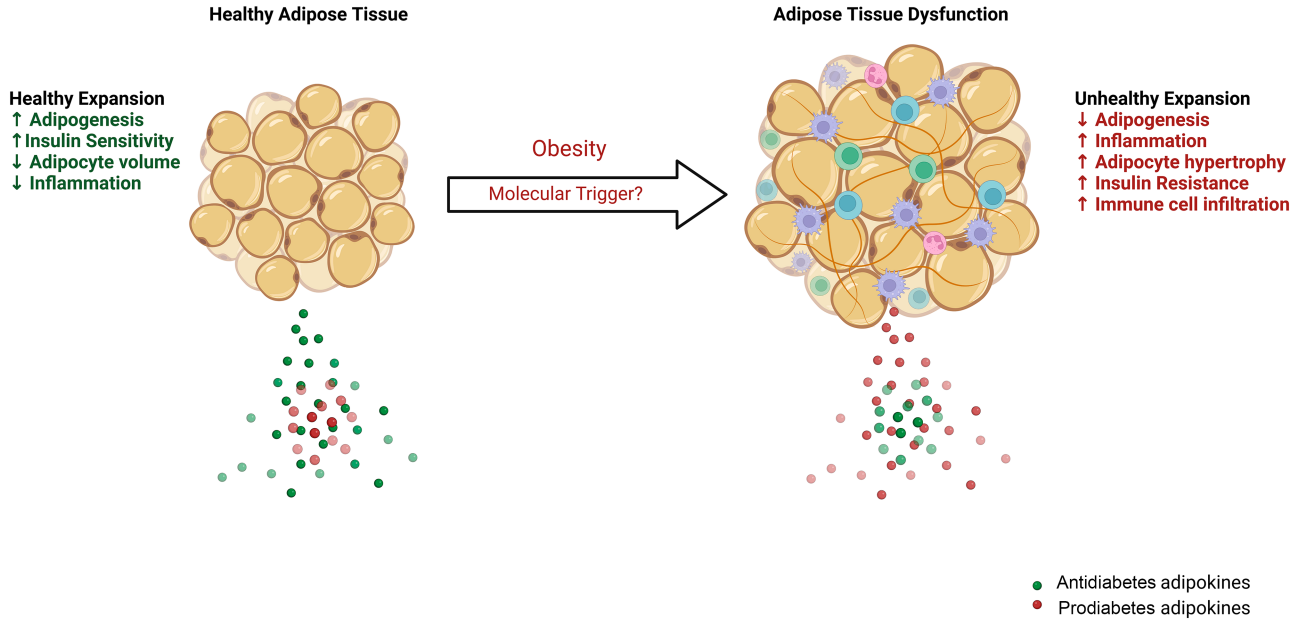

Figure 1—Adipose tissue dysfunction in a setting of obesity. Under conditions of caloric excess and metabolic stress, the AT undergoes an unhealthy expansion characterized by an array of features distinguishable from an otherwise healthy expansion. These include reduced adipogenesis, increased adipocyte hypertrophy, increased immune cell infiltration, chronic low-grade inflammation, and decreased insulin sensitivity. Adipocyte dysfunction results in an imbalance in the secretion of adipokines, with higher secretion of proinflammatory prodiabetes adipokines (red dots) and lower secretion of anti-inflammatory antidiabetes adipokines (green dots). This impairs the AT's physiological communication to the adipokine-effector organs such as pancreatic β-cells, liver, and heart.

have outlined BAT dysfunction associated with reduced thermogenic capacity and altered production of brown fat–specific adipokines, also known as BATokines.

A unique feature of WAT is its incredible ability to expand under conditions of nutritional excess to adapt to metabolic stress, an attribute not commonly found in nonneoplastic tissues. During obesity, WAT can expand by hypertrophy and proliferation and/or differentiation of newborn adipocytes. This continued expansion may become unhealthy and is characterized by inadequate vascularization, diffusion-limited hypoxia, fibrosis, or macrophage infiltration with chronic low-grade inflammation (6). This is accompanied by reduced adipogenesis, reduced thermogenic capacity, and diminished insulin sensitivity, resulting in cardiometabolic diseases such as T2D. This mechanistic link has made it increasingly clear that adipocyte function is an important determinant of metabolic health. In particular, there is a group of patients termed metabolically healthy obese who, despite having obesity, do not suffer from the "typical" metabolic complications such as hypertension, dyslipidemia, and hyperglycemia. However, what mediates adipocyte dysfunction or an unhealthy adipose expansion in obesity is not clear. Potential mechanisms might include molecular factors that initiate the expression of proinflammatory cytokines and chemokines such as IL-1β, IL-6, and TNF-α that promote infiltration of immune cells in the AT. Ultimately, adipocyte dysfunction ensues creating an imbalance between production of insulin-sensitizing antidiabetic adipokines (including adipsin and adiponectin) and proinflammatory prodiabetic adipokines (RBP4 and resistin) (Fig. 1). The altered production of adipokines dramatically changes the way AT communicates with neighboring and distal organs such as pancreas, liver, and heart. In the sections below we will review major adipokines regulating the physiological functions of these organs and how adipose dysfunction in diseased states leads to the so-called "communication failure" resulting in pathological outcomes.

Even during the recent coronavirus disease 2019 (COVID-19) pandemic, results of several clinical studies pointed toward worse prognosis following COVID-19 infection in patients who had overweight or obesity, hinting at an involvement of adipose dysfunction. Our laboratory was the first to provide clinical evidence that hyperglycemia in acute COVID-19 infection is predominantly due to insulin resistance and associated with 50% reductions in adiponectin (7). We demonstrated that severe acute respiratory syndrome coronavirus 2 can directly infect adipocytes in vitro. Moreover, adiponectin-to-leptin ratios were significantly decreased in patients with COVID-19, connecting AT dysfunction, metabolic disease, and viral infection.

ADIPOSE COMMUNICATION TO PANCREAS

Adipokines, lipokines, and EVs (e.g., exosomes) establish a variety of communications with the pancreas, particularly β-cells. The field of study of pancreatic islets as targets of adipokines began with the discovery of leptin receptor on the surface of β-cells (8). Subsequent studies showed the presence of several other adipokine receptors

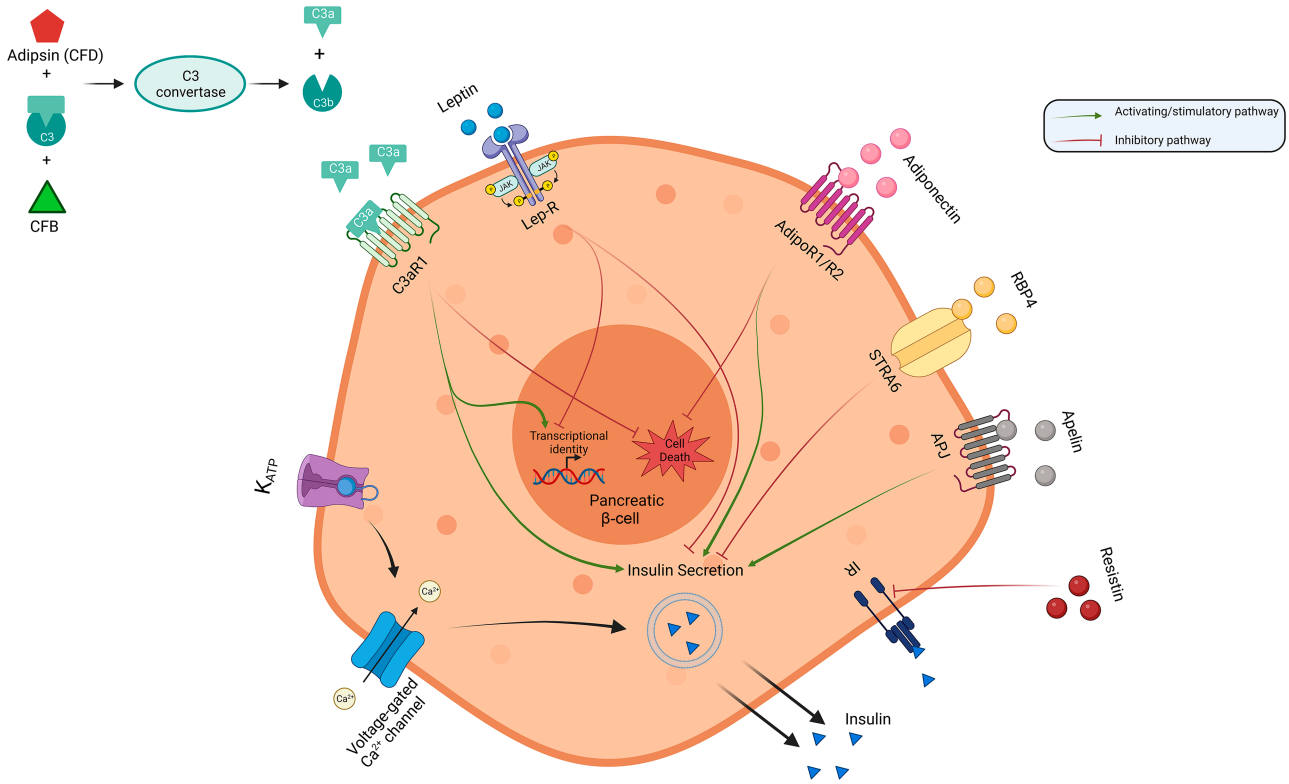

Figure 2—Adipokines with direct effects on pancreatic β-cells. Most adipokines bind to their receptors on the β-cell surface and signal via their cognate receptors to stimulate or inhibit insulin secretion and alter β-cell transcriptional identity, β-cell death and/or dedifferentiation. For example, C3a, the downstream active product of adipsin pathway, binds and activates its G-protein–coupled receptor C3aR1. The resulting downstream signaling pathway promotes GSIS, maintains β-cell transcriptional identity, and promotes survival by dampening both β-cell death and dedifferentiation. AdipoR1/R2, adiponectin receptor 1/receptor 2; APJ, apelin receptor; CFB, complement factor B; CFD, complement factor D (Adipsin); C3aR1, C3a receptor 1; IR, insulin receptor; Lep-R, leptin receptor; RBP4, retinol binding protein 4; STRA6, stimulated by retinoic acid 6 receptor.

on β-cells, including adiponectin receptors (AdipoR1 and AdipoR2), C3aR1 (downstream of adipsin and C3a), apelin receptor (APJ), and RBP4 receptor STRA6 (3,9) (Fig. 2).

Adipsin/complement factor D (CFD) is a serine protease belonging to the alternative complement pathway that catalyzes the production of C3 convertase, which then cleaves C3 to generate C3a and C3b. Adipsin levels are severely reduced in mouse models of obesity and diabetes (10). Moreover, adipsin knockout mice display severe impairment of glucose tolerance following high-fat diet (HFD)-induced obesity. This effect was attributed to decreased insulin secretion from the pancreatic β-cells. In contrast, supplementing adipsin to diabetic *db/db* mice resulted in an improvement in glucose tolerance due to increased insulin secretion. This beneficial effect of adipsin was found to be mediated by C3a, an active product of its downstream pathway, which can then act on C3aR1 on pancreatic β-cells. C3a was found to enhance glucose-stimulated insulin secretion (GSIS) on pancreatic islets. C3aR1 antagonism or agonism also inhibited or potentiated insulin secretion, respectively (3). Downstream of adipsin/C3a in the β-cells, an effector known as dual specificity protein phosphatase 26 (DUSP26) was identified. Gain- and loss-of-function experiments with DUSP26 in β-cells revealed that this phosphatase plays a crucial role in the maintenance of β-cell identity and regulation of apoptotic pathways. In addition to its effect on insulin secretion, adipsin also affects β-cell survival and function. Chronic overexpression of adipsin in *db/db* mice prevents β-cell failure by dampening both β-cell death and dedifferentiation (4). Interestingly, unlike with other insulin secretagogues prolonged adipsin overexpression does not result in β-cell exhaustion, making adipsin/C3a/DUSP26 pathway an attractive target for potential treatment of T2D.

Leptin, traditionally known for its central nervous system–driven effect on regulation of food intake and energy expenditure, is now known to have effects on a variety of metabolic tissues including pancreatic β-cells. Studies have shown that leptin inhibits GSIS on pancreatic islets ex vivo and decreases circulating insulin levels in vivo (11). Leptin induces changes in gene expression of β-cells such as downregulation of *Ins* and *Pp1* and upregulation of *Socs3*. Leptin has been shown to stimulate the proliferation of islet cells from fetal but not adult rats, suggesting that leptin might play a role in determining β-cell mass at birth. Leptin has been shown to both increase and decrease apoptotic cell death in pancreatic β-cells, though the exact mechanism is not yet clear. Studies on the role

of leptin signaling in β-cells in vivo have yielded inconsistent results, which could be due to underlying differences in the Cre recombinase transgenic models used (4). D'souza and Kieffer restored LepR specifically to pancreatic β-cells in *db/db* mice and found no effect on body weight, glucose homeostasis, insulin secretion, or islet architecture. Collectively, these data show that LepR signaling on β-cells is not sufficient to overcome the metabolic consequences in *db/db* mice, while suggesting that effects of leptin on β-cells play a minor role in T2D (12).

Adiponectin is an adipokine with remarkably high levels in the circulation compared with other peptide hormones. Rodent and human pancreatic β-cells express the adiponectin receptors AdipoR1 and AdipoR2 (9). AdipoR1 is the major isoform in mice, whereas expression of both isoforms is similar in humans. Studies with β-cell lines and pancreatic islets have shown that adiponectin potentiates GSIS (13). However, the mechanism by which adiponectin stimulates insulin secretion is ill defined, as adiponectin treatment was shown to have no effect on ATP generation, cell membrane potential, cytosolic calcium concentration, or AMPK activation. Adiponectin is also known for its antiapoptotic effect on pancreatic β-cells under a variety of conditions, including serum starvation, exposure to cytokines, and glucolipotoxicity (7,14). This antiapoptotic effect of adiponectin on β-cells has been shown to be mediated by changes in extracellular signal–regulated kinase (ERK) and protein kinase B (PI3K-AKT) phosphorylation or increases in ceramide catabolism and formation of sphingosine-1-phosphate (7,13,14).

Resistin, an adipokine that was first shown to induce insulin resistance in obesity, is now linked by several reports to impaired β-cell function in mouse models of T2D (15). Investigators of studies with adenoviral vectors expressing resistin have found that this adipokine induces β-cell insulin resistance and blunts the insulin response to glucose (16). Resistin also decreases the viability of murine β-cells along with downregulation of insulin receptor (17). However, results of recent studies have shown that resistin expression is increased in islets from individuals with T2D, indicating a local nonadipocyte source acting on β-cells (18). Visfatin, also known as external nicotinamide phosphoribosyltransferase (eNAMPT) is an adipokine enzyme involved in the biosynthesis of NAD. Visfatin is secreted by adipocytes in nonclassical secretory pathway. Female but not male *Nampt*$^{+/-}$ mice show impaired glucose tolerance and defects in insulin secretion that have been attributed to lack of NAD^+ biosynthetic activity in β-cells (19). Visfatin has also been shown to play a role in protection against β-cell apoptosis, islet inflammation, and β-cell transcriptional identity (20). Fatty acid binding protein 4 (FABP4), also known as adipocyte protein 2 (AP2), is an adipokine with a role in glucose metabolism and adipocyte lipolysis. The exact direct effect of FABP4 on β-cells is still not clear, with some studies describing a positive effect on pancreatic islet GSIS (21), whereas others show that FABP4 negatively affects insulin secretion and β-cell viability (22). Apelin is another peptide hormone secreted by the AT whose G-protein–coupled receptor, known as the apelin receptor (APJ), is found on pancreatic β-cells. Deletion of APJ receptor on β-cells has been shown to reduce β-cell mass, impair glucose tolerance, and reduce GSIS (23). Several other adipose-secreted factors such as Nesfatin-1, RBP4, FGF21, SFRP5, DPP-4, and Vaspin (24) have been found to affect pancreatic β-cell function (Table 1), underscoring the importance of maintenance of healthy adipose-pancreas communication through regulated adipokine secretion.

ADIPOSE COMMUNICATION TO HEART

ATs can modulate cardiovascular health and disease. While visceral fat correlates with cardiac disease, brown fat is considered beneficial (25,26). The underlying molecular links for many of these processes remain to be elucidated. However, some adipokines are known to target the heart and contribute to improved or worsened heart function (or disease state). Under physiological conditions, there is a balance between proinflammatory and anti-inflammatory adipokines that tips toward the latter in cardiometabolic diseases. In fact, serum levels of adipokines are altered in patients not only with obesity, diabetes, and metabolic syndrome but also with arrhythmia, myocardial infarction, and heart failure (27,28).

BAT is associated with lower risk of congestive heart failure, hypertension, and atrial fibrillation (25). The overall levels of BAT decrease both with age and obesity (25). The proposed cardioprotective effect of BAT is poorly studied, and only a handful of BATokines targeting the heart have been well described to date (Fig. 3). Prominent examples include FGF21, NRG4, and 12,13-diHOME (29). FGF21 is a cold-activated BATokine, which protects against fibrosis and cardiac hypertrophy (29). In addition, FGF21 levels have been negatively associated with atherosclerosis and diabetic cardiomyopathy (30). The lipokine 12,13-diHOME has been shown to enhance cardiac function after BAT transplantation in mice (29). Neuregulin 4 (NRG4) protects against insulin resistance and alleviates myocardial injury in a model of diabetic cardiomyopathy (31). Along with BATokines, BAT also secretes EVs like exosomes that target the heart (32). Treatment of obese mice with BAT exosomes improved the overall metabolic state (lower body weight, blood glucose, and adiposity), reduced lipid accumulation in the heart, and partially restored worsened ventricular function triggered by HFD (32). Secretion of exosomes by BAT is directly regulated by β-3 adrenergic receptor, which also controls the exosome cargo and thereby influences whether exosomes elicit beneficial or detrimental effects (33). In fact, with use of a β-3 antagonist BAT exosomes exacerbate angiotensin II–mediated heart failure signaling, while in the absence of the antagonist BAT exosomes acted in a protective manner by preventing adverse cardiac remodeling (33).

Table 1—Summary of adipokines that are altered in metabolic diseases and their demonstrated effects on pancreatic β-cells

Adipokine	Levels in metabolic diseases (obesity and T2D)	Effect on pancreatic β-cells
Leptin	Increased	Inhibits GSIS, may increase proliferation
Adiponectin	Decreased	Increases GSIS and insulin sensitivity, antiapoptotic effect
Adipsin	Increased in obesity but decreased in T2D and patients with β-cell failure	Enhances insulin secretion and maintains β-cell mass by reducing death and dedifferentiation
Resistin	Increased in obesity, increased or unchanged in T2D	Decreases GSIS and expression of insulin receptors
eNAMPT/Visfatin	Increased	Positive effect on insulin secretion and transcriptional identity of β-cells
FABP4	Increased	Negatively affects β-cell viability; effect on insulin secretion is unclear
Chemerin	Increased	Promotes GSIS and β-cell identity
Apelin	Decreased	Promotes β-cell function
Nesfatin-1	Increased	Enhances GSIS
RBP4	Increased	Impairs GSIS and β-cell function
SFRP5	Increased	Negative effects on β-cell function
DPP4	Increased	Cleaves GLP-1 to reduce GSIS
Vaspin	Increased	Blocks degradation of secreted insulin
FGF21	Increased	Increases β-cell proliferation, increases insulin transcription
MCP-1	Increased	Increases amylin expression

GLP-1, glucagon-like peptide 1.

In addition to visceral AT, subcutaneous AT, and BAT, the heart is also affected by adipokines secreted locally by epicardial (EAT) and pericardial AT. Since EAT lacks fascia and is in contact with the myocardium, adipokines secreted by EAT directly target the heart. In healthy hearts, EAT protects and supports the heart due to its relatively high expression of thermogenic genes, similar to BAT (34). However, in diseases such as obesity the EAT becomes inflammatory and expands (35). This can result in adipocyte infiltration of the myocardium, perturbing electrical conduction to enable arrhythmia development (35). EAT is also a local source of free fatty acids, the preferred energy source of the heart; yet, lipid overload observed in pathological conditions is detrimental to heart function (35). Adipokines that are known to be secreted by EAT include leptin and visfatin, which act in a profibrotic manner. Leptin, in particular, is considered a predictor of poor outcomes in patients with heart failure or coronary heart disease (28). Yet, leptin has also been observed to be antilipotoxic in the context of obesity and decreases the severity of acute myocardial infarction (27,28). Adiponectin is also secreted by EAT and is known to be antiatherosclerotic and displays decreased expression in acute myocardial infarction and heart failure (27,34). C1q/TNF-related protein 3 (CTRP3), which acts in a way similar to how adiponectin acts, displays lower expression in atrial fibrillation and protects against atrial fibrosis and structural remodeling triggered by inflammation (28). Apelin, another protective adipokine secreted by EAT, has a positive inotropic effect and protects against fibrosis, apoptosis, and ischemia and reperfusion injury (27). Apelin levels are lower in patients with coronary heart disease and atrial fibrillation (27,28). Another adipokine regulating structural remodeling is omentin, which is reduced in patients with atrial fibrillation, obesity, and coronary artery disease (CAD) and negatively correlates with heart failure and hypertension (27,28). EAT also secretes adrenomedullin, which is decreased in CAD and attenuates cardiac hypertrophy and fibrosis (34). Lastly, EAT exosomes from patients with atrial fibrillation have been shown to be secreted in higher amounts and contain a proinflammatory cargo (35). Similar results have been found for CAD as well (36). How these EAT exosomes could alter cardiac function remains to be elucidated.

Reversing the inflammatory state of EAT in obesity and other diseases or boosting the BAT activity could serve as therapeutic strategies to decrease cardiovascular risk and potentially reverse the pathological changes triggered by proinflammatory adipokines seen in structural heart disease.

ADIPOSE COMMUNICATION TO LIVER

A hallmark of obesity and AT dysfunction is the development of hepatic steatosis and metabolic (dysfunction)-associated

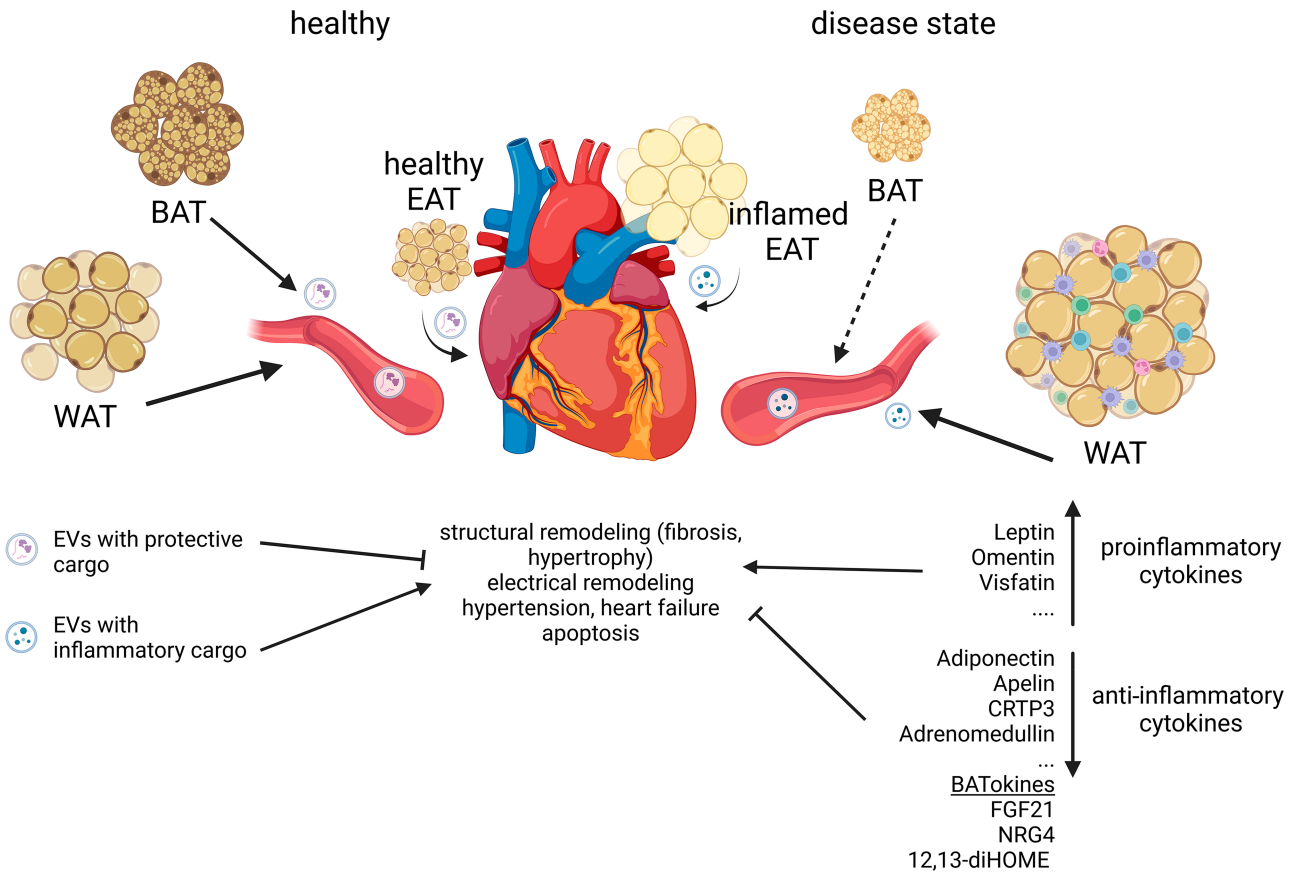

Figure 3—Adipose communication to heart. In the healthy state, the WAT and the brown-like EAT mostly secrete EVs with protective cargo and anti-inflammatory cytokines, which protect against structural and electrical remodeling of the heart. The BAT secretes protective BATokines like FGF21, NRG4, and 12,13-diHOME. In the diseased state, WAT and EAT become inflamed and expand. In addition, more proinflammatory cytokines and EVs with inflammatory cargo are secreted resulting in detrimental changes to the heart that include fibrosis, electrical remodeling, and apoptosis.

fatty liver disease (MAFLD) (37), also known as nonalcoholic fatty liver disease, which occurs in 25% of people with obesity and 50% of people with T2D. MAFLD can lead to nonalcoholic steatohepatitis (NASH) and ultimately to cirrhosis and hepatocellular. Ectopic fat deposition is a common feature of both obesity and lipodystrophy, and it could play a unique role in liver disease, since adipose-liver communication can occur directly via the portal vein. Visceral WAT exhibits high rates of lipolysis and free fatty acid release and is directly associated with insulin resistance and hepatic steatosis. By contrast, fatty acid esters of hydroxy fatty acids are anti-inflammatory bioactive lipids, primarily adipose derived, that improve hepatic insulin sensitivity while suppressing hepatic glucose production via a cAMP-dependent pathway (38). Mesothelial-derived adipocytes are highly responsive to inflammatory signals and secrete high levels of IL-6 and IL-8 following stimulation, reflecting the heterogeneity of the adipocyte pool even within specific adipose depots. Nevertheless, an inflammatory response seems to facilitate adipose expansion and remodeling. In mice on HFD, an impaired local proinflammatory response leads to decreased intestinal barrier function, increased hepatic steatosis, and metabolic dysfunction (39).

A number of adipose-derived signaling factors, or adipokines, exert beneficial or deleterious effects on hepatic metabolism and pathogenesis (Fig. 4). Leptin indirectly improves hepatic steatosis via central activation, though leptin may also promote hepatic activation of AMPK (40). Adiponectin improves insulin sensitivity in part by acting on its membrane receptors AdipoR1 and AdipoR2 to suppress hepatic glucose output via phosphorylation of AMPK, in addition to lowering the hepatic content of proinflammatory ceramides and inhibiting the fibrogenic effects of transforming growth factor-β (41). Another liver-protective adipokine, secreted frizzled-related protein 5 (SFRP5), is decreased in obesity, and its loss leads to increased liver fibrosis via hepatic stellate cell activation by the Wnt5a pathway (42). Asprosin, a C-terminal cleavage product of fibrillin-1, was discovered to be produced primarily in subcutaneous WAT and reportedly stimulates hepatic glucose release while inhibiting browning of WAT (43,44), but other studies have cast doubt on the reproducibility of these findings (45). Brown fat is enriched in the adipose-derived hepatoprotective hormone NRG4, which contains an epidermal growth factor–like domain and activates *ErbB3/4* signaling in hepatocytes, attenuating lipogenesis and

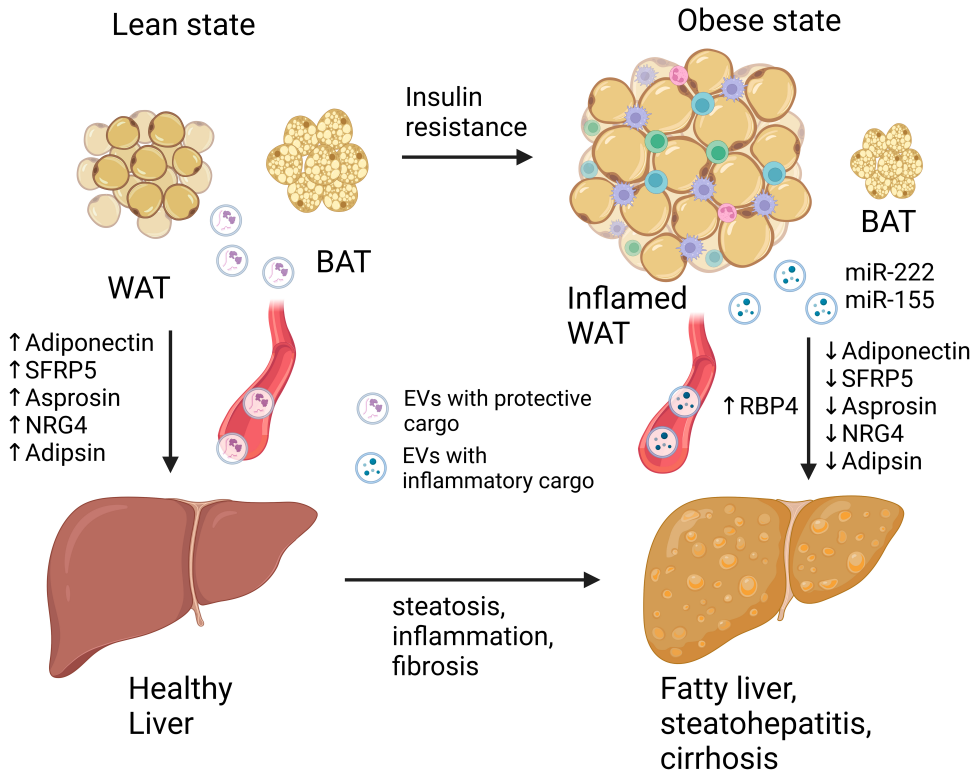

Figure 4—Adipose communication to liver. AT can secrete hepatoprotective hormones in the healthy lean state, such as adiponectin, SFRP5, asprosin, NRG4, and adipsin. However, in unhealthy adipose expansion and insulin resistance, adipose dysfunction and inflammation lead to ectopic fat deposition, including hepatosteatosis and downregulation of the above hepatoprotective factors. In addition, there are increased levels of other factors that promote hepatic dysfunction and further insulin resistance, such as RBP4 and exosome-derived miRNAs. Together these illustrate the interrelatedness of obesity and liver disease due to the secretion of important regulatory factors from AT. NRG4, neuregulin 4; RBP4, retinol binding protein 4; SFRP5, secreted frizzled-related protein 5.

hepatic steatosis in mice. Circulating NRG4 levels are reduced in obesity, and its deficiency may exacerbate a protumor immune environment in a mouse model of NASH, though the direct relevance to human NASH remains unclear. Adipsin/complement factor D controls alternative activation of the complement system and reduces hepatic gluconeogenesis and inflammation in diabetic mice (46). In contrast to the above beneficial factors, RBP4 produced by visceral adipocytes, and especially liver, promotes adipose inflammation leading to hepatic steatosis and insulin resistance, and elevated circulating RBP4 increases hepatic expression of gluconeogenic enzymes such as *Pepck* (47).

Other fat-derived signaling molecules involved in adipose-liver communication include miRNAs packaged in EVs or exosomes, which are decreased in humans with lipodystrophy. Rescue of miRNA machinery in adipose-specific deletion of Dicer enzyme improved glucose tolerance and reduced hepatic *Fgf21* mRNA and circulating FGF21, regulated by miR-99b released by brown adipocytes (48). In other work investigators found that miR-222 attenuated insulin-induced AKT phosphorylation in liver by repressing IRS-1 expression (49). AT macrophages also release exosome-derived miRNAs including miR-155, which is upregulated in obesity and targets PPARγ in distal tissues, leading to insulin resistance and impaired insulin-mediated suppression of hepatic glucose production (50). This underscores the importance of adipose inflammation in mediating distant effects on nonadipose tissues in the metabolic syndrome.

TARGETING AT DYSFUNCTION TO TREAT METABOLIC DISEASES: FUTURE PERSPECTIVES AND CHALLENGES

A growing number of adipokines and other active circulating factors secreted by the AT have established roles in maintenance of functions of distal organs such as pancreas, heart, and liver. There is a considerable ongoing effort on making the AT healthy again (or reversing adipocyte dysfunction) by targeting AT inflammation and/or altering gene expression or adipocyte secretion pattern. However, these strategies are challenging, since they target a much later stage post–disease development. The exact molecular mediators that trigger AT inflammation and dysfunction have not yet been identified. Targeting specific adipokines can provide unique opportunities to better understand the pathophysiology and treatment of T2D, nonalcoholic fatty liver disease, arrhythmias, and other cardiometabolic diseases. Potential new approaches include reconstitution of adipokine function, such as supplementing adipsin/C3a in β-cell failure, and/or activation or inhibition of adipokine

receptors, such as selective C3aR1 agonists to improve insulin secretion and β-cell function and AdipoR1 to restore insulin sensitivity. Directly targeting C3aR1 may also be challenging given concerns with anaphylaxis. Whether biased C3aR1 agonists offer promise remains to be determined.

One challenge in translating adipokine-related therapeutic strategies is the difference in the biology of these adipokines across species. For instance, circulating adipsin levels are higher in mice compared with humans. This could be because mouse adipsin is glycosylated and more stable. Resistin in rodents is almost exclusively produced by white adipocytes, whereas in humans it is synthesized and released from other cell types within WAT such as macrophages. Human and mouse vaspin share about 62% amino acid identity, owing to differences in levels of glycosylation and downstream actions. On the other hand, adipokines such as adiponectin and its receptors are highly conserved between mice and humans. Thus, it is important to take these similarities or differences in adipokine biology between mice and humans into consideration in developing adipokine-based therapies.

In addition, adipose-secreted exosomal miRNAs might provide new strategies to distinguish metabolically healthy versus unhealthy obesity. The bioactive molecules such as miRNAs and some adipokines transported in adipocyte-derived EVs are likely to exert their functions in circulation and modulate distal targets. One potential synergistic approach would be to package known anti-inflammatory, antidiabetic miRNAs (like miR-690 and miR-146a) and adipokines (like adiponectin and adipsin) into EVs for administration in individuals with T2D, for instance. Compared with other biological therapeutics, EVs also offer advantages of higher stability, ability to store for longer periods, and easily controlled dosing (51).

Understanding the heterogeneity of dysfunctional AT poses an opportunity to develop drugs that can change the distribution of the ATs, shifting toward a metabolically healthy subtype. It is now clear that distinct subpopulations of adipocytes exist in WAT that undergo dynamic changes under situations of metabolic stress. In recent single-cell or single-nuclei RNA-sequencing studies, such as those of Emont et al. (52), investigators identified subpopulations of human and mouse adipocytes at single-cell resolution. Interestingly, they found human adipocyte clusters with differential expression of adipokines. One such cluster, hAd3, which had a higher expression of antidiabetic adipokines ADIPOQ and CFD/ADIPSIN, was found to be lower in individuals with higher BMI (BMI range of 40–50 kg/m^2). Development of drugs that can promote activation of one cluster over another can offer an alternative approach to modify adipose function. There is reason to speculate that differential secretion of adipokines arising from dysfunction-associated heterogeneity in adipocytes may lead to shift in heterogeneity of cell types in adipokine-targeted distal tissues. For example, there are heterogenous subpopulations of pancreatic β-cells that undergo dynamic changes under situations of metabolic stress and T2D (53). We recently identified a subset of β-cells marked by high CD63 expression that exhibit higher mitochondrial respiration and enhanced GSIS that are diminished in mouse models of and in humans with T2D (54). Although it is unclear how much of these changes in β-cell subpopulations are mediated by obesity and adipose dysfunction, potentially secondary to dysregulated adipokine secretion, it is possible that changes in the hAd3 (or others) adipocyte cluster could result in decreased adipsin or alterations in other adipokines that might perturb β-cell subsets and lead to diminished CD63^{hi} β-cells. The mechanism may involve either a direct action of adipsin/C3a on β-cell function and survival or an indirect effect mediated through another cell type or organ. How specific adipokines and adipocyte secreted factors might affect the different β-cell subpopulations is an area of considerable interest that may have broad implications for prevention and treatment of T2D. Finally, approaches that combine boosting adipocyte health (hence, promote physiological balance of adipokine secretion) and target disease-specific adipokines may represent ideal future strategies to ameliorate the growing burden of metabolic diseases.

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