https://doi.org/10.1038/s42255-019-0145-5

Inter-organ cross-talk in metabolic syndrome

Christina Priest[1] and Peter Tontonoz[1,2,3]*

Maintenance of systemic homeostasis and the response to nutritional and environmental challenges require the coordination of multiple organs and tissues. To respond to various metabolic demands, higher organisms have developed a system of inter-organ communication through which one tissue can affect metabolic pathways in a distant tissue. Dysregulation of these lines of communication contributes to human pathologies, including obesity, diabetes, liver disease and atherosclerosis. In recent years, technical advances such as data-driven bioinformatics, proteomics and lipidomics have enabled efforts to understand the complexity of systemic metabolic cross-talk and its underlying mechanisms. Here, we provide an overview of inter-organ signals and their roles in metabolic control, and highlight recent discoveries in the field. We review peptide, small-molecule and lipid mediators secreted by metabolic tissues, as well as the role of the central nervous system in orchestrating peripheral metabolic functions. Finally, we discuss the contributions of inter-organ signalling networks to the features of metabolic syndrome.

The systemic metabolism of higher organisms involves a complex series of pathways that regulate energy and nutrient intake and disposition. Multiple organ systems work together to absorb, store, sense and use chemical energy, and must communicate with one another to maximize the efficiency of these processes. Dysfunction of these systems results in metabolic disease, which is quickly becoming one of the most pressing current public-health concerns.

Metabolic syndrome is a group of conditions, including hyperglycaemia, hypertension, abdominal obesity and dyslipidaemia, that increase the risk of cardiovascular disease, diabetes and associated morbidities. Current estimates suggest that more than one in three adults in the United States and approximately 40% of people over the age of 40 have metabolic syndrome, defined as exhibiting three or more of these risk factors[1]. Obesity is a marker of metabolic dysregulation and an enormous public-health concern in its own right; currently, 12% of adults are obese worldwide[2], and in the United States, more than two-thirds of adults are overweight or obese[3]. The global effects of metabolic disease are difficult to overstate. In 2015, more than 600 million adults and 100 million children globally were estimated to be obese[4]. Although statistics on the global incidence of metabolic syndrome do not exist, current estimates suggest that one-quarter of the global population—more than 1 billion people—has metabolic syndrome[5]. Markers of metabolic syndrome are also increasing, thus suggesting that this condition will be a pressing public-health concern in the coming decades. The global prevalence of diabetes, for example, is expected to increase from 8.8% to 10.4% by the year 2040 (ref. [6]). Currently, environmental interventions such as increased exercise and modified diet are the most effective treatments for metabolic syndrome[7,8]. Although pharmacologic strategies to target individual components of metabolic syndrome exist, none have yet been demonstrated to affect the root causes.

The aetiology of metabolic syndrome is believed to involve dysregulation of metabolic homeostasis. The molecular mechanisms that underlie both healthy and pathological metabolic states are still being elucidated. Tissues such as the liver, adipose, muscle and intestine have well-established roles in energy intake and utilization. However, how these organs interact with one another is still being uncovered. One key strategy for coordinating whole-body metabolism is communication between tissues via secreted factors. These include protein hormones, small molecules, lipids and other factors such as exosomes that relay important information about metabolic flux between physically distant cell types. Proper production and target-tissue action of such factors is important for metabolic homeostasis, and disruption of one or more of these signalling axes often underpins the development of metabolic disease. In recent years, several secreted mediators have been identified that may help to explain the links between individual risk factors and the development of metabolic syndrome. Understanding how organs communicate via secreted factors may also be the most promising avenue to discover therapeutic targets. Because many secreted factors are more easily manipulated than other determinants of metabolic disease (for example, genetic makeup or environmental factors), they may provide more tractable therapeutic opportunities. Modified synthetic secreted factors or inhibitors hold promise as pharmacological agents for interventions in metabolic syndrome.

In this Review, we summarize current knowledge about secreted factors involved in the coordination among key metabolic tissues. We additionally discuss links to metabolic disease as well as potential therapeutic applications.

Hepatokines and factors secreted by the liver

The liver plays essential roles in both glucose and lipid metabolism and is therefore central to the ability of organisms to respond to changing nutritional states. Given the liver's critical functions, declining metabolic health of the liver is unsurprisingly one of the first indications of metabolic disease. Hepatic steatosis, the accumulation of excess lipids in the liver, is correlated with obesity and cardiovascular disease and is an early indicator of insulin resistance[9]. Non-alcoholic fatty liver disease (NAFLD), encompassing mild steatosis to fibrosis and cirrhosis of the liver, is the most common liver disease in the United States, and its incidence increases dramatically with body mass index[10,11]. Liver dysfunction can have deleterious effects on whole-body metabolic health.

Factors secreted by the liver affect metabolism in distant tissues and exert wide-ranging effects (Fig. 1). These factors take diverse forms, from small molecules to secreted peptides to lipids. The term 'hepatokine' has been coined to indicate the group of hormones secreted by the liver, mostly in response to metabolic state. Accumulation of excess lipids in the liver is an important signal that triggers the production and release of bioactive molecules.

[1]Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA. [2]Department of Biological Chemistry, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA. [3]Molecular Biology Institute, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA. *e-mail: ptontonoz@mednet.ucla.edu

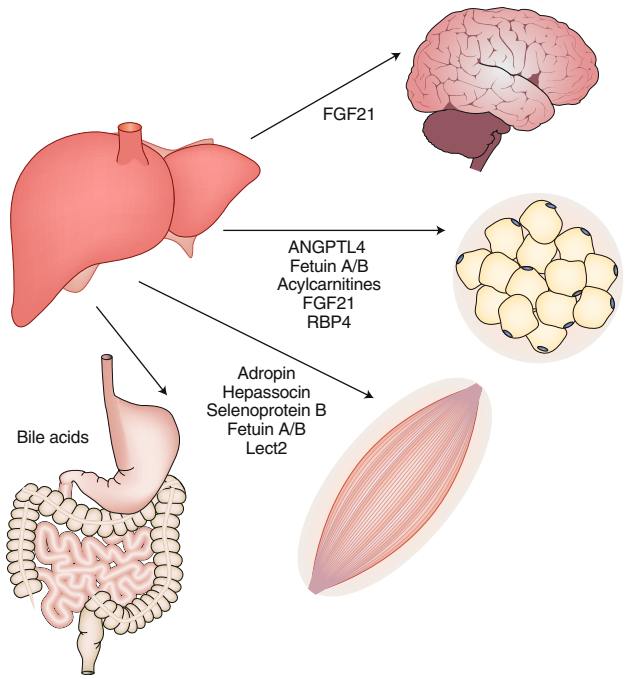

Fig. 1 | Liver-secreted factors. The liver has a central role in metabolism and communicates with other organ systems by using many secreted factors. These factors, including protein hepatokines, lipids and other small molecules, have diverse effects on target organs including the gut, muscle and adipose tissues, as well as the CNS, that help maintain energy homeostasis in response to rapidly changing nutritional states.

Altered levels of hepatokines in steatotic livers affect whole-body metabolism and provide a mechanism linking liver health to other components of metabolic syndrome.

Several hepatokines specifically highlight the links between accumulation of lipids in the liver and glucose intolerance and insulin resistance. Altered levels of these hepatokines may be used to identify individuals with metabolic dysregulation. Sex-hormone-binding globulin[12], a hepatokine involved in trafficking steroid hormones, shows diminished expression in steatotic livers, and low levels of sex-hormone-binding globulin are correlated with type 2 diabetes (T2D) risk[13]. Hepassocin is a protein involved in the regeneration of hepatocytes after liver injury[14]. Elevated levels of hepassocin are associated with NAFLD and are correlated with insulin resistance and elevated fasting glucose levels[15]. Angiopoietin-like 4 (ANGPTL4) is another peptide secreted from the liver and adipose tissue, whose expression is decreased in steatosis induced by a high-fat diet[16]. Levels of growth differentiation factor 15 (GDF15), a member of the TGFβ superfamily, are elevated in non-alcoholic steatohepatitis[17]. Recent studies in mice suggest that exogenous GDF15 might be used as a therapy for treating fatty liver disease[18].

Beyond simply indicating metabolic dysfunction, many hepatokines have been identified that actively modify metabolism in distant tissues. Several of these illuminate the connection between liver disease and impaired glucose metabolism. For example, ANGPTL4 expression increases glucose tolerance and insulin sensitivity, and additionally inhibits lipoprotein lipase in adipose tissue, thereby decreasing the clearance of triglycerides and lipoproteins from plasma[19]. Adropin expression is also diminished in steatotic livers[20]. This hepatokine, which is normally induced by feeding, decreases adiposity and insulin resistance. Although its molecular mechanism remains to be identified, this peptide enhances insulin signalling and improves mitochondrial function[21], thus suggesting that it has broad metabolic benefits. Fetuin A and B are liver-secreted proteins that have provided insights into the link between steatosis and T2D. Expression of the fetuins is elevated in steatotic livers, and these proteins have been reported to exert systemic effects that may contribute to insulin resistance[22,23]. For example, Fetuin A stimulates inflammatory-cytokine production in adipose tissue and macrophages[24].

Selenoprotein P is another hepatokine linked to insulin resistance[25]. This protein causes insulin resistance in mouse models, and its expression is elevated in humans with obesity and NAFLD[26], thus supporting a mechanistic link between fatty liver and the development of insulin resistance. Retinol-binding protein 4 (RBP4) was originally identified as a hepatokine that is elevated in people with T2D[27]. It has been shown to activate immune cells, thus contributing to adipose tissue inflammation and insulin resistance[28]. Although some studies have not found a correlation between RBP4 and insulin sensitivity, these observations may be explained by differences in RBP4 levels during circadian oscillation[29]. Lect2 is another peptide heptatokine correlated with obesity and insulin resistance in humans. It has been shown to cause insulin resistance in skeletal muscle, thus potentially contributing to the diabetic phenotype[30].

Fibroblast growth factor (FGF) 21 is a hepatic secreted factor with a particularly well-established link to human metabolic disease[31]. FGF21 is expressed in adipose, brain and possibly other tissues; however, most circulating FGF21 is produced by the liver in response to fasting or exercise[32]. This protein affects energy expenditure and insulin sensitivity, acting primarily in the central nervous system (CNS) and perhaps also directly on adipose tissue[33]. In adipose tissue, FGF21 signalling increases glucose uptake and decreases lipolysis. In the CNS, FGF21 promotes energy expenditure via sympathetic-nerve activation of brown adipose tissue (BAT)[34]. The potent effects of FGF21 in the CNS highlight the important role that the brain plays in regulating metabolism (Box 1). Levels of FGF21 are paradoxically elevated in obesity in humans and independently correlate with metabolic syndrome, thus suggesting possible resistance to FGF21 in this setting[35]. Nonetheless, administration of FGF21 shows beneficial metabolic effects in obese mice, including increased insulin sensitivity, decreased body mass, improved lipoprotein profiles and even lifespan extension[36]. People with T2D treated with an FGF21 analogue show decreased body weight, and decreased LDL and insulin levels[37]. Although long-term treatment with FGF21 may cause complications, including bone loss[38] and effects on female reproduction[39], this pathway still is a promising avenue for the treatment of metabolic syndrome in humans.

Metabolic signals from the liver are not limited to protein hormones. Bile acids are well known for their roles in potentiating the absorption of lipids and vitamins in the intestine, as well as in facilitating cholesterol efflux. However, these molecules also act as hormones that control gene expression in distant tissues. Bile acid salts released into the intestine from the liver activate the bile acid receptor farnesoid X receptor (FXR), thus stimulating expression of FGF15 and FGF19 in enterocytes. Consequently, these hormones act on the liver by suppressing bile acid synthesis, thus creating a negative feedback loop[40]. Moreover, release of FGF15 from enterocytes after hepatic bile acid production decreases hepatic gluconeogenesis, thus indicating a role of the enterohepatic circulation in regulating metabolism[41]. Early studies of FXR-deficient and genetically obese mice have demonstrated that bile acid signalling also affects plasma lipid levels and insulin sensitivity[42–44], and these effects are linked to FXR-dependent gene regulation. Activation of hepatic FXR induces receptors that clear lipoproteins from the plasma and also inhibits the expression of gluconeogenic genes[45]. Plasma bile acids decrease blood glucose levels and increase insulin sensitivity through activation of TGR5, a G-protein-coupled receptor that is potently activated by bile acids[46]. TGR5 is expressed in the

Box 1 | CNS control of metabolism

Acting in concert with hormones and secreted factors, the CNS playa a critical role in control of peripheral metabolism. The CNS coordinates inputs from various organ systems and synthesizes responses that enable survival and procreation of organisms. The ways in which this coordination participates in the control of whole-body metabolism are only beginning to be understood. One important system in brain regulation of metabolism is the melanocortin system in the arcuate nucleus of the hypothalamus. Within this region, orexigenic neuropeptide Y/agouti-related peptide (NPY/AGRP) and anorexigenic pro-opiomelanocortin (POMC) neurons control energy expenditure, glucose metabolism and food-intake behaviour[192]. However, in humans, homeostatic control, reward, cognitive control and emotional pathways are involved in the control of food intake and other behaviours linked to metabolic disequilibrium[199]. Brain regions outside the hypothalamus, including the amygdala and hippocampus, respond to metabolic state and control systemic metabolism and behaviour[200]. Metabolic tissues in the periphery can also signal to the CNS, thus exerting effects on metabolic control as well as neuroprotective effects. Exercise has been shown to affect whole-body metabolism via NPY/AGRP and POMC neurons of the hypothalamus[201]. Several secreted factors with well-established effects on metabolism exert their effects via the CNS, including insulin, ghrelin, leptin and GLP-1. A more comprehensive understanding CNS pathways controlling metabolism has the potential to inform new therapies that address metabolic syndrome as well as neurodegenerative disorders linked to metabolism, such as Alzheimer's disease.

liver, immune cells, BAT, enteroendocrine cells and neurons in the intestine and brain[46,47]. Activation of TGR5 by bile acids affects both obesity, by increasing energy expenditure[48], and glucose homeostasis, by inducing GLP-1 secretion from the intestine[49]. The broad beneficial metabolic effects of TGR5 activation make activation of this receptor a promising avenue for therapy.

Lipid signals emanating from the liver have been identified. After cold exposure, the liver activates an HNF4α transcriptional program that generates acyl-carnitines from adipose-derived fatty acids. Acyl-carnitines are released from the liver and act as fuel for BAT, thereby increasing thermogenic output[50].

The liver is a central player in the control of organismal metabolic homeostasis in both normal physiology and metabolic disease. This organ secretes a wide variety of types of signals that affect metabolism in distant organs in myriad ways. Because dysregulation of this complex system is one of the first indicators of metabolic dysfunction, liver-secreted factors are likely to be predictive biomarkers for metabolic disease. Furthermore, given that accumulation of lipids in the liver is one of the earliest manifestations of metabolic disease, the effects of NAFLD on other organ systems, especially the link between fatty liver disease and insulin resistance, will continue to be active areas of study. A better understanding of how dysregulation of metabolism in the liver affects other organ systems may lead to new therapeutic strategies.

Adipokines and adipose-secreted factors

Owing to intensive investigation over the past several decades, the appreciation of adipose tissue function has moved far beyond the view of this organ as simply a site for energy storage. Adipose tissue is now recognized to also be an endocrine organ that engages in sophisticated cross-talk with other organ systems. As the primary site of energy storage and release, adipose tissue is uniquely positioned to signal the nutritional state of an organism and indeed has an important

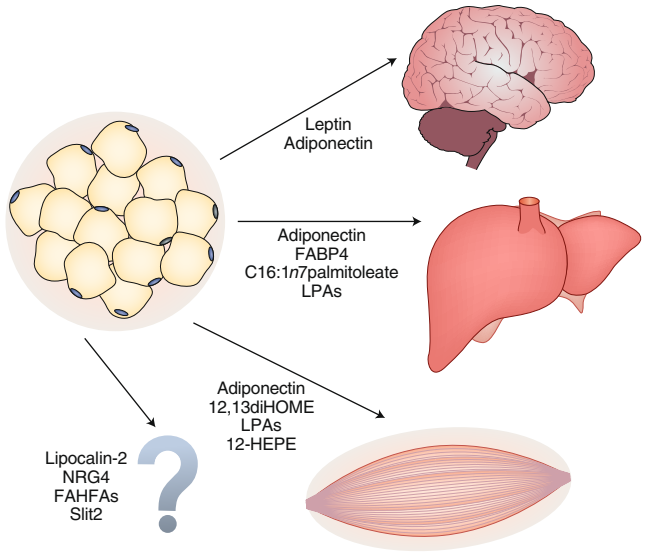

Fig. 2 | Adipose-secreted factors. Some adipose-secreted factors signal to the CNS to communicate nutritional state. Others, including adipokines and lipokines, have diverse effects on target organs including the liver and muscle. Some adipose-secreted factors with demonstrated effects on whole-body metabolism have target organs that are yet to be determined. FAHFAs, fatty acid esters of hydroxy fatty acids.

regulatory role in the control of systemic metabolism. In response to fasting, lipolysis in the adipose tissue releases fatty acids that provide fuel for mitochondrial oxidation and stimulate gluconeogenesis in the liver. Beyond these signals, numerous peptide and lipid hormones produced by adipose tissue have been identified, and many of these have been shown to have important effects on whole-body metabolism. The actions of various adipokines have been linked to obesity, diabetes, inflammation, atherosclerosis and liver disease (Fig. 2).

One key concept emerging over the past 30 years is that obesity and adipose tissue inflammation can disrupt proper adipose signalling, thus leading to deleterious effects in distant tissues. In fact, an increase in visceral fat is one of the strongest predictors of metabolic syndrome[51], thus supporting the idea that adipose tissue function is linked to systemic metabolic regulation and disease. One of the first indications that adipose-secreted factors, or adipokines, are linked to systemic metabolism was the discovery of adipsin[52], an adipose-secreted peptide also known as complement factor D, whose expression is decreased in obesity. Since then, the discovery of the key adipokines leptin and adiponectin has demonstrated that signals from adipose tissue can have dramatic effects on whole-body metabolism and has cemented the role of adipose tissue as an important endocrine organ.

Leptin is a hormone secreted from white adipose tissue (WAT) that negatively regulates food intake and increases energy expenditure[53] and has been extensively studied in relation to obesity. Leptin is a peptide that is produced by mature adipocytes and acts mainly on the CNS[54,55]. Levels of leptin are positively correlated with fat mass, and a decrease in leptin levels triggers several mechanisms in the organism that replenish nutrient stores. In addition to an increase in food intake and a decrease in energy expenditure, these include inhibition of energy-intensive processes, including reproduction and immune responses[56]. Leptin can also modulate whole-body metabolism, for example by increasing fatty acid oxidation via activation of 5′-AMP-activated protein kinase[57].

Adiponectin is also secreted by mature adipocytes[58]. In contrast to leptin levels, however, levels of adiponectin are inversely correlated with fat mass[59]. Adiponectin signalling increases insulin sensitivity[60] and has other beneficial metabolic effects, including reduced

adiposity[61], inflammation and atherosclerosis[62]. Adiponectin-target organs include the liver, where it decreases gluconeogenesis[63], the skeletal muscle, where it increases oxidation of fatty acids[64] and the brain, where it stimulates energy expenditure[61]. Although leptin and adiponectin have been well studied over the past two decades, more remains to be learned about their complex mechanisms of actions and their far-reaching metabolic consequences.

Since the discovery of leptin and adiponectin, dozens of other secreted factors from adipose tissue have been identified and implicated in the control of systemic metabolism, many of which remain to be fully understood. One of these is lipocalin-2, a member of the lipocalin family of transport proteins. Plasma lipocalin-2 levels have been correlated with adiposity, insulin resistance, increased inflammatory markers and cardiovascular disease[65,66]. However, studies in knockout mice have yielded inconclusive and sometimes conflicting results about the roles of lipocalins in systemic metabolism[67,68], and further study is required to clarify these roles. Neuregulin 4 (NRG4), a member of the epidermal growth factor family, is also produced by adipose tissue. Circulating levels are inversely correlated with obesity and stimulated by cold exposure[69]. NRG4 appears to have beneficial effects on metabolism, including improved glucose metabolism and reduced inflammation and steatosis, although the mechanisms underlying these effects are unclear[70].

Fatty acid–binding protein 4 (FABP4), also known as adipocyte protein 2 (aP2), is the major fatty acid–binding protein (FABP) in adipose tissue. Deficiency of this protein was initially observed to be correlated with increased insulin sensitivity[71]. In recent years, FABP4 has been found to be secreted from adipocytes and to act as an adipokine. In fact, FABP4 secreted by adipose tissue in response to fasting and lipolysis has been reported to stimulate hepatic gluconeogenesis[72]. Levels of FABP4 are elevated in obese humans, and inhibition of this protein has been proposed as a treatment for both atherosclerosis and diabetes[73]. Both small-molecule inhibitors of FABP4 and a monoclonal antibody against this peptide have been developed as potential therapeutics, and inactivation of FABP4 in obese mice has been shown to improve systemic glucose metabolism[74,75]. However, the utility of these therapies in humans remains to be determined.

The development of obesity can have deleterious effects on the secretome of adipose tissue. One hallmark of adipose tissue in obesity and diabetes is infiltration of the tissue with immune cells and increased secretion of pro-inflammatory cytokines. Several factors secreted by adipose tissue itself are pro-inflammatory and/or promote insulin resistance, including TNF, CRP and MCP-1 (ref. [76]). Resistin, another pro-inflammatory adipokine, promotes inflammation and insulin resistance in obesity by binding Toll-like receptor 4 (refs. [77,78]). These adipokines, in concert with inflammatory factors secreted by immune cells, contribute to inflammation of adipose tissue and the development of obesity-related metabolic disease, including atherosclerosis (Box 2).

Lipid signals, termed lipokines, have also emerged as a class of molecules that participate in inter-organ signalling in metabolism. Among the first of these to be identified was C16:1*n*7 palmitoleate, a lipid that is produced in adipose tissue in response to FABP deficiency and affects liver lipogenesis and insulin sensitivity in muscle. This lipid is produced in response to de novo lipogenesis in adipose tissue and subsequently increases insulin sensitivity in skeletal muscle[79]. Other lipokines include lysophosphatidic acids (LPAs). LPAs in circulation are primarily produced by WAT and are correlated with obesity[80]. These lipids have been implicated in the control of insulin secretion, hepatocyte glycogenolysis and skeletal muscle glucose utilization[81], and appear to have mostly negative effects on systemic metabolism.

Branched fatty acid esters of hydroxy fatty acids are another biologically relevant class of lipid signals from adipose tissue. A specifically well-studied subgroup of these compounds, palmitic acid esters of hydroxy stearic acids (PAHSAs), has been linked to glucose metabolism. Levels of PAHSAs are correlated with insulin sensitivity in humans[82]. Recent studies have shown that PAHSAs have anti-inflammatory effects, and increase glucose tolerance and insulin sensitivity in mice[83]. One group has observed no beneficial effects with PAHSA administration[84]; however, methodological differences among studies preclude direct comparison of the results[85]. Whether the PAHSA pathway can be harnessed for therapeutic benefit remains to be addressed.

BAT is a specialized adipose tissue that allows mammals to thermoregulate by producing heat from futile metabolic cycles. These cycles consume a large quantity of energy in the form of fatty acids and glucose and contribute to a high metabolic rate. Consequently, increasing BAT thermogenic activity has been considered as a therapeutic avenue to increase energy expenditure and decrease adiposity and its concurrent negative health outcomes. Although the relevance of BAT to human biology has long been questioned, decreased levels of BAT have been observed in obese individuals, thus suggesting that BAT activity negatively correlates with metabolic disease in humans[86]. Beyond BAT, a subset of white adipocytes can be induced to contribute to thermogenesis in response to cold or hormonal stimuli. Termed beige adipocytes, these cells affect energy expenditure and glucose metabolism. Secreted factors from other metabolic tissues, including FGF21 from the liver and irisin from muscle, can cause a metabolically beneficial increase in beige adipocytes, termed 'browning'[87].

In addition to increasing energy expenditure, BAT activity remodels organismal metabolism by signalling to distant tissues. In response to activation of the transcriptional coregulator PRDM16, beige adipocytes secrete a fragment of the protein Slit2, which induces thermogenesis and results in increased energy expenditure and improved glucose clearance[88]. The transcription factor IRF4 in BAT inhibits expression of myostatin, a myokine that inhibits skeletal muscle function. Through inhibition of myostatin, IRF4

Box 2 | Role of the immune system in vascular metabolic health

The components of metabolic syndrome contribute to the development of atherosclerosis and cardiovascular disease, which are major public-health concerns in their own right. One-quarter of adult deaths in industrialized countries can be attributed to atherosclerosis, and cardiovascular disease is the leading cause of death worldwide[193]. Dyslipidaemia, specifically an excess of cholesterol-rich low-density lipoprotein (LDL), is the single most important risk factor in the development of this disease[194]. Effective treatments, including statins, have been developed to treat dyslipidaemia. However, inflammation is also accepted to be a major contributor to atherogenesis[195,196]. Accumulation of LDL particles in the vascular endothelium activates components of the innate and adaptive immune responses, thus resulting in recruitment of immune cells and release of inflammatory signals. Mechanistic links between the improved cholesterol clearance and reduced inflammation have been elucidated in recent years. For example, liver X receptors, sterol-responsive transcription factors that improve reverse cholesterol transport, exert their atheroprotective effects both by promoting cholesterol efflux and by reducing inflammation[197]. Recent studies have suggested that increased inflammation contributes to the risk of heart attack even after LDL-cholesterol lowering and that regression of atherosclerotic plaques depends on the resolution of inflammatory signaling[198]. In light of these discoveries, future therapies for cardiovascular disease should enable the targeting of both dyslipidaemia and inflammation as underlying causes.

signalling in BAT results in increased mitochondrial function and exercise capacity in skeletal muscle via activation of the mammalian target of rapamycin pathway[89].

Improvements in lipidomics have additionally enabled the discovery of lipokines from BAT. The first of these is 12,13-diHOME, a lipokine produced from BAT in humans and mice in response to exercise. This lipid causes increased uptake and oxidation of fatty acids in skeletal muscle[90], providing a link between BAT and the beneficial effects of exercise. Another lipokine produced by BAT is the lipid 12-HEPE, which is secreted in response to cold exposure and β-adrenergic signalling, and promotes glucose uptake by muscle and adipose tissues, thus improving glucose metabolism[91].

Increased adiposity is highly correlated with metabolic disease and is also the most visible trait associated with dysregulation of metabolism. As the site of energy storage and a potent endocrine organ, adipose tissue plays a central role in regulating organismal metabolism. Inflammation of this tissue is correlated with disrupted signalling and deleterious effects on health, including insulin resistance and atherosclerosis. The extent to which dysregulation of adipose tissue causes or results from dysregulation of metabolism in other organ systems is an open question. Further insight into the roles of adipose tissue in metabolic disease, including the roles of BAT in human biology and disease, will be provided by the continued study of adipose signalling factors, including previously understudied classes of mediators, such as lipokines and other lipid signals.

Myokines and muscle-secreted factors

Medical science and conventional wisdom have long indicated that exercise has beneficial effects on metabolism and overall health. Exercise is effective in treating and preventing many of the hallmarks of metabolic syndrome. However, the molecular mechanisms that underpin the effects of exercise on these conditions remain an area of active investigation. Muscle contraction has benefits on metabolism beyond consuming excess energy directly. Muscle tissue undergoes extensive adaptation to increased exercise, including increased expression of enzymes involved in beta-oxidation and glycogen metabolism. Exercise also increases the sensitivity of adipose tissue to epinephrine-stimulated lipolysis and increases the utilization of intramuscular triglycerides, thus suggesting that muscle contractions can affect distant tissues[90].

The effects of exercise on metabolism are increasingly being shown to depend heavily on muscle-secreted factors, known as myokines, which have varied and far-reaching effects (Fig. 3). Some evidence indicates that the effects of muscle contractions persist even in the absence of cross-talk between muscle and the CNS[92]. Muscle has been predicted to secrete hundreds of factors, many of which have not been characterized[93]. Many myokines are secreted in response to muscle contractions, and many have been shown to increase energy expenditure, decrease inflammation and have neuroprotective effects. Although myokines can have autocrine, paracrine and endocrine effects, here we focus on myokines that allow the muscle to signal to distant tissues and affect whole-body metabolism.

One of the earliest-discovered myokines was interleukin (IL) 6, a circulating peptide with effects on liver, adipose and endocrine tissues[94]. IL-6 was first identified as a myokine after observations that its plasma levels markedly increase after exercise in proportion to muscle mass, up to 100-fold, even in the absence of exercise-induced muscle damage[95]. This observation is consistent with findings that immune responses do not have a role in exercise-induced increases in IL-6, which is produced by myoblasts[96]. The circumstances of IL-6 secretion by muscle also suggest that the role of this myokine is primarily regulation of metabolism rather than immune responses. For example, IL-6 release is reduced by high glycogen levels in muscle and by ingestion of glucose during exercise[97]. These data suggest a role of IL-6 in the response to muscular energy stores.

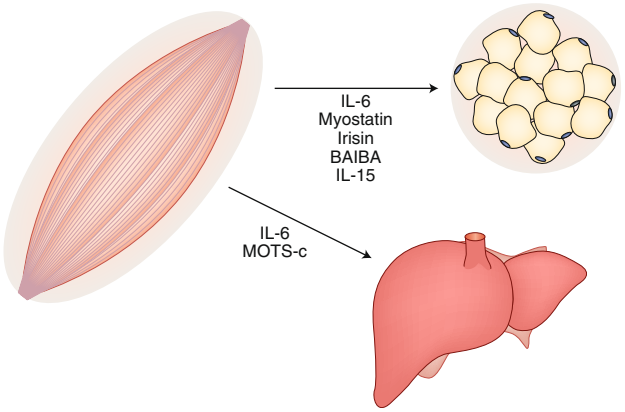

Fig. 3 | Muscle-secreted factors. Muscle-secreted factors or 'myokines' have effects on the adipose and liver that potentiate the beneficial effects of exercise on metabolism.

IL-6 production after exercise is believed to potentiate the beneficial effects of exercise on the metabolism of distant tissues. Infusion of recombinant IL-6 into humans has been found to increase whole-body insulin sensitivity in hyperinsulinaemic/euglycaemic clamp studies[98]. Additionally, IL-6 activates hepatic production of glucose during exercise[99] and increases systemic fatty acid oxidation[100]. However, recombinant IL-6 alone is insufficient to increase glucose production or uptake, thus suggesting that it may work in concert with other factors[100]. Individuals with obesity and metabolic syndrome exhibit elevated basal levels of IL-6, thus possibly suggesting resistance to IL-6 signalling under these conditions[101]. This possibility complicates the clinical promise of IL-6 treatment.

Myostatin, a well-described myokine that negatively regulates muscle growth[102], also has effects on whole-body metabolism. In addition to its inhibitory effects on muscle, this secreted protein regulates adipose tissue mass and function[103,104]. Increased myostatin expression is correlated with obesity[105], thereby providing further evidence that myokine signalling is perturbed by metabolic disease and that obesity can negatively affect muscle function. Ablation of myostatin potentiates the beneficial effects of long-term exercise[105], thus raising the possibility that inhibition of this pathway might be a viable avenue for treatment of metabolic syndrome. In contrast, levels of follistatin, a negative regulator of myostatin, increase after exercise[106]. There is some debate regarding the origin of circulating follistatin, and its effects on metabolism remain under investigation[107].

Studies in lean and obese humans have shown that exercise induces browning of subcutaneous fat (as evidenced by increased thermogenic gene expression) and increases insulin sensitivity in the absence of substantial changes in body composition[108]. This observation provides another mechanism through which exercise may improve overall metabolism, even in the absence of a decrease in adipose tissue. Exercise can also affect whole-body metabolism via the well-characterized transcriptional coactivator PGC1α. Stimulation of this protein by muscle contraction results in increased expression of Fndc5, a membrane protein whose cleavage product is secreted as the protein hormone irisin[109]. Irisin stimulates white adipose cells to express uncoupling protein 1 (UCP1), thus contributing to browning of these cells and promoting thermogenesis. Browning of WAT increases energy expenditure, which in turn decreases adiposity and increases insulin sensitivity. In addition, irisin has been shown to have neuroprotective effects in the brain via induction of bone-derived neurotrophic factor[110].

PGC1α promotes the expression of other secreted factors in addition to irisin, and other myokines that have yet to be described may also be under its control[109]. One other myokine under the

control of PGC1α is beta-aminoisobutryic acid (BAIBA). This small molecule is secreted from myocytes after muscle contraction. In addition to reducing insulin resistance in muscle, BAIBA induces WAT browning and hepatic fatty acid oxidation, thereby increasing energy expenditure[111].

Because exercise and oxidative metabolism are intrinsically linked, mitochondrial factors have been hypothesized to play a role in adaptation to exercise. The mitochondrial-encoded peptide MOTS-c is expressed in the muscle, liver and brain[112]. Exogenous MOTS-c has a host of beneficial metabolic effects when administered to mice, including increased energy expenditure, increased glucose utilization and fatty acid oxidation, and decreased lipid accumulation in the liver[112]. Plasma levels of this peptide are correlated with obesity and markers of insulin resistance in humans[113].

IL-15 is a putative myokine produced by skeletal muscle that has anabolic effects in this tissue[114]. IL-15 decreases both lipid deposition in preadipocytes and WAT mass overall. Thus, although it has not yet been observed in plasma, it may act as a myokine regulating adipose tissue[115,116]. This hypothesis is consistent with observations that IL-15 is inversely correlated with adipose tissue mass and abdominal adiposity in humans[116]. Expression of IL-15 in mouse skeletal muscle has been shown to reduce abdominal adipose mass, thus suggesting a causative connection between IL-15 and adiposity[116].

Additional potential myokines have been identified that affect bone formation[117], increase vascularization of muscle[118] and have cardioprotective effects[119]—beneficial functions consistent with adaptation to exercise. Exercise is now well appreciated to exert positive effects on markers of metabolic syndrome, thereby suggesting causal linkages. The secretome of skeletal muscle remains largely uncharacterized, and additional mechanisms through which muscle exerts control over whole-body metabolism are likely to be discovered. The study of muscle tissue and its adaptation to exercise continues to be a promising avenue for the discovery of secreted factors that might be harnessed as metabolic therapies.

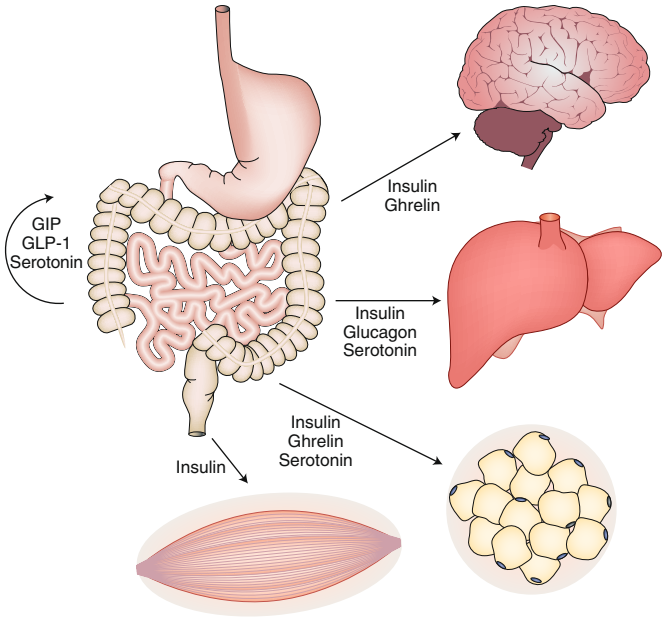

Fig. 4 | Gut- and endocrine-secreted factors. Factors secreted by the pancreas in response to nutrient uptake include the well-characterized hormones insulin and glucagon. Hormones secreted by the gut, including ghrelin and the incretin hormones GIP and GLP-1, potentiate nutrient uptake and storage. Hormones secreted from the gut and endocrine system act on the CNS and modify food intake, and also have effects on target organs including the liver, muscle and adipose tissue.

Secreted gastrointestinal and endocrine factors

The pancreas has long been studied for its central role in endocrine control of metabolism. Secreted insulin and glucagon together regulate a large portion of glucose homeostasis, and disruption of this system in diabetes is a major health concern (Fig. 4). Insulin and glucagon secretion act in concert with factors secreted from the gut in response to nutrient absorption, thereby coordinating efficient nutrient metabolism and regulating energy utilization.

Insulin is perhaps the best-characterized of any secreted factor. For almost a century, insulin has been studied as a factor dysregulated in individuals with high blood glucose[120]. Insulin is a peptide hormone released in response to increased blood glucose from pancreatic beta cells, and it is the primary signal coordinating the response of an organism to ingestion of nutrients. In adipose and muscle tissues, insulin triggers translocation of the Glut4 glucose transporter to the cell membrane, where it potentiates glucose absorption and rapidly decreases blood glucose[121]. In the liver, insulin inhibits gluconeogenesis and promotes the synthesis of glycogen and lipids, so that energy can be stored for later use[122]. Insulin can cross the blood–brain barrier and signal in the CNS, thereby modulating reward pathways and food-intake behaviour[123]. Insulin has well-established effects on cell growth, metabolism and survival, and the molecular mechanisms underlying insulin signalling have been studied extensively. Insulin exerts its effects via activation of the insulin receptor, which in turn activates cascades of downstream signalling proteins including the MAPK and PI3K pathways[124].

Insulin replacement is the dominant therapeutic approach to treating type 1 diabetes, and recent advances in formulation have improved the outcomes of insulin therapy for this disease[125]. The therapeutic potential of insulin in people with T2D, who are resistant to insulin, is somewhat more complicated. Insulin resistance is one of the cornerstones of metabolic syndrome, and treatment of this symptom has a beneficial effect on patients, including prevention of the deleterious vascular effects of hyperglycaemia[126]. However, treatment of people with T2D with insulin or insulin sensitizers can increase obesity, owing to the lipogenic effects of insulin. As the disease progresses, increasing insulin resistance coupled with declining reserves of insulin necessitate increasingly large doses to maintain effective therapy[127]. Nevertheless, insulin remains a mainstay therapy for people with T2D, and advances in delivery have improved treatment outcomes[128].

Glucagon, a peptide hormone secreted from pancreatic alpha cells in response to fasting, acts in opposition to insulin and allows organisms to adapt to nutrient-scarce conditions[129]. Glucagon acts in the liver by increasing glycogenolysis and gluconeogenesis while inhibiting glycogen synthesis. Although these actions may contribute to hyperglycaemia in the context of T2D, glucagon has several beneficial metabolic effects. Glucagon signalling increases fatty acid oxidation and counteracts dyslipidaemia, thus suggesting that agonism of glucagon signalling may be a therapeutic avenue for treating metabolic syndrome[130]. Treatment with glucagon has also been shown to have anti-obesogenic effects[131], which are at least partially mediated by stimulation of FGF21 (ref. [132]).

As the primary site of nutrient absorption, the gastrointestinal tract signals to remote tissues during digestion and acts in concert with insulin secretion in maximizing nutrient storage and utilization. Peptides released from enteroendocrine cells in the gut, including glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1), increase insulin secretion in the pancreas in response to glucose absorption[133]. Together known as the incretin hormones, GIP and GLP-1 are primarily responsible for the incretin effect: the observation that insulin secretion in response to oral glucose administration is higher than that elicited by intravenous glucose. In individuals with T2D this effect is blunted, owing

to diminished sensitivity of the pancreas to GIP[134]. Although GIP is a more potent activator of insulin secretion in individuals without diabetes[135], resistance to GIP signalling in people with T2D suggests that GLP-1 is the more promising therapeutic target in T2D[136]. Activation of GLP-1 signalling decreases plasma glucose and has other beneficial metabolic effects, including decreased food intake and increased weight loss[137,138]. GLP-1 secretion is inhibited in obesity[139], but patients who have undergone gastric bypass surgery show elevated levels of GLP-1 secretion, which may mediate some of the beneficial effects of this intervention on metabolic health[140]. GLP-1 agonists have also been shown to reduce the risk of cardiovascular events in people with T2D, and GLP-1 has multiple beneficial effects in the cardiovascular system, including reducing both inflammation and the progression of atherosclerosis[141]. These observations suggest that activation of this pathway has broad therapeutic potential for individuals with metabolic syndrome.

In the liver, the incretin hormones are degraded by dipeptidyl-peptidase 4 (DPP-4). Increased activity of DPP-4 is associated with insulin resistance and lipid accumulation in the liver, and inhibition of this protein is a potential therapy for diabetes and liver disease[142]. Another gut peptide, peptide Y (PYY) may act synergistically with GLP-1 in decreasing food intake[143].

Ghrelin is a factor released from the gastric mucosa that was identified 20 years ago as an agonist for the growth hormone secretagogue receptor 1α (GHSR1α)[144]. It was quickly identified as an important metabolic regulator acting on the CNS and increasing food intake and consequently fat mass[145]. Since then, many additional functions have been ascribed to this protein hormone, including modulating taste sensation, anxiety and circadian rhythms[146]. Ghrelin has additionally been implicated in signalling to other organs important for whole-body metabolism. For example, ghrelin has been reported to modulate thermogenesis in BAT[147] and lipid utilization in WAT[148]. Ghrelin receptors are most highly expressed in the brain but can also be found in other organs, including the pancreas[149]. Because of its positive effect on food intake, antagonism of the ghrelin pathway has been explored as a potential therapeutic avenue for obesity. Unfortunately, knockout studies of ghrelin and its receptor have yielded mixed results, and have suggested that inhibition of ghrelin alone may be insufficient to ameliorate diet-induced obesity[146]. Inhibition of ghrelin signalling has been proposed as a treatment for T2D, although the effects of ghrelin on glucose metabolism depend heavily on its post-translational acylation[150,151]. Interestingly, ghrelin improves glucose clearance in diabetic mice without affecting adiposity[152] and decreases inflammation in several tissues. Administration of ghrelin has been shown to ameliorate the inflammatory effects of a high-fat diet in the liver and muscle, to have beneficial effects on glucose metabolism[153,154] and to increase fatty acid oxidation in skeletal muscle[155]. Ghrelin treatment may additionally exert cardioprotective effects in rodents and humans with metabolic syndrome[156].

Serotonin, a well-studied neurotransmitter that was first identified as a factor secreted from the gut[157], also plays a role in metabolic signalling, particularly in the adaptation to fasting. Peripheral serotonin, which is secreted primarily by the intestinal mucosa, has effects on glucose metabolism in the pancreas, liver and adipose. In the pancreas, serotonin increases beta-cell mass, glucose sensitivity and insulin production[158,159]. In the liver, serotonin facilitates the adaptation to fasting by increasing gluconeogenesis and decreasing glucose uptake[160]. In the adipose, serotonin improves lipolysis, inhibits lipogenesis and increases glucose tolerance[160,161].

Secreted factors from the gastrointestinal tract show potential promise in the treatment of metabolic syndrome. Modulation of the ghrelin and the incretin hormone pathways is under investigation as a therapy in humans and has shown promise in the treatment of metabolic syndrome. Moreover, the gut is host to a large and important portion of the microbiome. Potential interactions between gut microbes and the metabolism in distant organs under physiological and pathological conditions is an area of active investigation, and ongoing studies in this area may open new avenues for the treatment of metabolic syndrome.

Secreted factors and the vasculature

Metabolic health has long been understood to be intimately related to cardiovascular health. Dysfunctional lipid metabolism and inflammation are major factors underlying atherosclerosis. A host of secreted factors from metabolically important organs are released into the circulation and influence the complex pathogenesis of cardiovascular disease (Fig. 5). For example, secreted signals acting on the vasculature affect hypertension, a major contributor to cardiovascular events. Investigation of the functions of vascular-acting factors continues to provide insight into the links among obesity, hypertension, insulin resistance and cardiovascular disease.

Hypertension, one of the hallmarks of metabolic syndrome, is closely associated with dysregulation of metabolism[162]. Recent observations suggest that salt intake, long established as a risk factor for hypertension, is an independent risk factor for obesity, even when food intake is considered[163]. A high-salt diet can affect adipokine expression, thereby providing one mechanism for this connection. Excess salt levels have been reported to induce adipogenesis and the production of inflammatory adipokines in adipocytes, thus providing a mechanism by which salt can exacerbate obesity, hypertension and adipose inflammation[164]. Moreover, obesity regulates the production of secreted factors affecting blood pressure. Intestinal mediators, including GLP-1 and ghrelin, have been shown to decrease blood pressure and to be decreased in obesity[165]. Obesity causes adipocytes to overproduce components of the renin-angiotensin system, thereby increasing blood pressure and exacerbating adipose inflammation and atherogenesis[166]. Plasma adiponectin, which is lowered in obesity, reduces blood pressure in obese mice at least in part via regulation of the SGLT2 sodium/glucose cotransporter in the kidneys[167,168].

Adiponectin and other adipokines affect the development of atherosclerosis, a complex process exacerbated by inflammation and dyslipidaemia, both of which are components of metabolic syndrome. Adiponectin has been shown to decrease atherogenesis in mouse models[169]; consequently, reduced adiponectin in obesity may exacerbate this pathology. Adiponectin also exhibits cardioprotective effects. Overexpression of adiponectin ameliorates cardiac hypertrophy and reduces myocardial infarct size in mouse models[170,171]. Low adiponectin levels have been correlated with atherosclerosis in humans; these observations may therefore have clinical relevance[172]. FABP4, an adipokine that links adipose tissue to liver lipogenesis and insulin sensitivity in muscle, also affects atherogenesis. FABP4 deficiency decreases atherosclerosis in mice and has been demonstrated to affect macrophage cholesterol trafficking and inflammation[173,174].

Myokines may have roles in the development of atherosclerosis. Overexpression of PGC1α, which is also elevated after exercise, ameliorates atherosclerosis in mice[175]. The PGC1α target irisin is inversely correlated with atherosclerosis in patients receiving dialysis[176]. BAIBA has been shown to reduce vascular inflammation[177]. These myokines provide potential mechanisms through which exercise directly exerts beneficial effects on the vasculature, although additional factors probably remain to be identified.

Inflammatory mediators produced by the immune system are subject to changes in metabolism and are a major contributor to cardiovascular disease (Box 2). Numerous studies have suggested links between levels of trimethylamine *N*-oxide (TMAO), a choline-derived metabolite produced in the intestine and liver, and diet. Moreover, plasma levels of TMAO have been correlated with atherosclerosis. The mechanism underlying this association appears to be the activation of endothelial inflammation by TMAO[178]. FMO3,

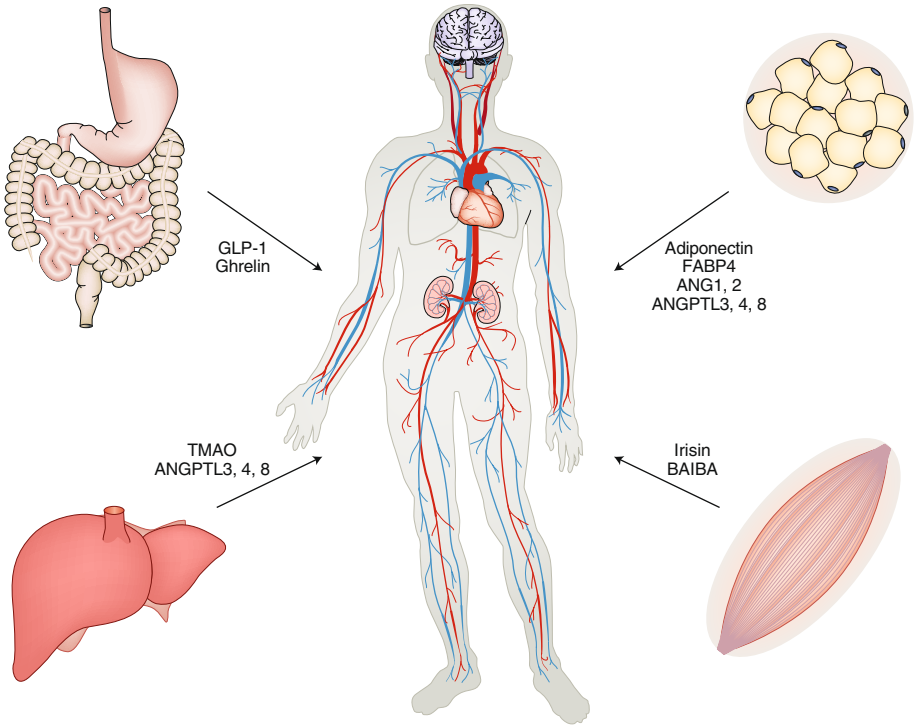

Fig. 5 | Secreted factors and the vasculature. Various factors secreted from the gut, adipose, muscle and liver affect the vasculature. These include members of the angiopoietin and angiopoietin-like families of proteins, which mediate angiogenesis and lipid metabolism, as well as hormones and small molecules that affect blood pressure and vascular inflammation—important factors in the development of atherosclerosis.

the enzyme that produces TMAO, has been shown to respond to insulin, thus suggesting a connection to diabetes-related atherosclerosis[179], and TMAO has also been implicated in the browning of WAT[180]. Therapeutic strategies aimed at modulating the TMAO pathway have yet to be developed.

Other adipose-secreted factors have effects on the vasculature related to angiogenesis. These factors include members of the angiopoietin and angiopoietin-like families. Angiopoietin 1 and 2 (ANG1 and ANG2) are mediators that are expressed in adipose tissue and affect angiogenesis and vascular function[181,182]. Their expression is reduced in WAT in obesity[183], thus suggesting that this pathway may be disrupted by metabolic disease. Expression of these proteins has been demonstrated to have beneficial metabolic consequences, a finding at least in part attributable to effects on adipose angiogenesis[182,184,185]. Plasma levels of another member of this family of proteins, angiopoietin-like 2 (ANGPTL2), increase with obesity and are correlated with insulin resistance[186]. Expression of ANGPTL2 worsens atherosclerosis in mice and exacerbates insulin resistance in mice[187]; consequently, its increased expression may contribute to metabolic syndrome. ANGPTL3, ANGPTL4 and ANGPTL8 are produced by liver and adipose tissue and regulate triglyceride metabolism by collectively inhibiting lipoprotein lipase, endothelial lipase and pancreatic lipase[188]. Loss-of-function alleles of these proteins have been linked to decreased triglyceride levels in humans[189], and deletion of ANGPTL4 in a mouse model has been found to ameliorate inflammation and atherosclerosis[190].

Cardiovascular diseases are enormous public-health concerns on their own; however, hypertension and atherosclerosis should be viewed as key components of metabolic syndrome. Common mechanisms are likely to contribute to cardiovascular and whole-body metabolic health. As a complement to existing therapies (those targeting plasma cholesterol levels, for example), future therapies or preventive strategies for cardiovascular disease show promise in inhibiting inflammatory signals from the adipose tissue or liver. As more is understood about the links between metabolic health and its effects on the vasculature, more avenues for interventions in these diseases are likely to be elucidated.

Box 3 | Exosomes in metabolism

The study of exosomes, small membrane-bound extracellular compartments that may contain proteins, lipids, coding and non-coding RNAs, or signalling molecules, is an emerging field of study. The secretion of exosomes is a controlled process known to respond to nutrient-related cues, including fasting, refeeding and obesity, thus suggesting that this method of communication may play a role in responses to changing nutritional states[202,203]. In support of this idea, exosome secretion from WAT increases in response to obesity, whereas BAT produces exosomes in response to cold exposure[204,205]. Exosomes have also been shown to elicit changes in the metabolic states of target tissues. For example, exosomes collected from the WAT in mice fed a high-fat diet have been reported to disrupt glucose homeostasis, increase inflammation and exacerbate atherosclerosis when administered to recipient mice[206]. These studies suggest that exosome secretion may be a method allowing cells and tissues to rapidly exchange cellular components in response to nutritional changes. The study of exosomes expands the landscape in the search for inter-organ mediators that might be exploited as targets in therapies for metabolic diseases.

Conclusions

Over the past several decades, the rich diversity of signals that mediate inter-organ communication in the control of whole-body metabolism have come to be appreciated. From peptide hormones to small molecules to lipids, these factors coordinate myriad processes in target organs, thus enabling responses to fluctuating nutritional states. Here, we have discussed factors secreted from classical

metabolically relevant organs. These systems interact with factors secreted from the bone, the immune system and even the microbiome, and consequently influence metabolism. These interactions are currently active areas of investigation.

As techniques improve, additional ways in which tissues communicate in maintaining homeostasis, and how these networks are perturbed by disease, will undoubtedly be discovered. Advances in proteomics and lipidomics are likely to enable the identification of new secreted factors by analysis of plasma in normal and diseased states. Improved sequencing and advanced data-processing techniques are expected to continue to provide insight into genes that affect metabolic traits across tissues[191,192], thereby elucidating new pathways, or new roles for established pathways, in inter-organ communication. Studies on emerging classes of factors, including exosomes (Box 3), may also yield unexpected insights that are now only beginning to be appreciated. Investigation of secreted factors and their roles in inter-organ communication has the potential to address many unresolved questions in the field of metabolism, including the mechanisms through which organs alter catabolism in the overfed state and how organisms sense and regulate body mass. The study of secreted factors in control of metabolism continues to hold promise for the study of metabolic regulation and the identification of new therapeutic targets for treatment of human metabolic disorders.

Received: 30 July 2019; Accepted: 5 November 2019;
Published online: 9 December 2019

References

1. Aguilar, M., Bhuket, T., Torres, S., Liu, B. & Wong, R. J. Prevalence of the metabolic syndrome in the United States, 2003-2012. *J. Am. Med. Assoc.* **313**, 1973–1974 (2015).
2. Afshin, A., Reitsma, M. B. & Murray, C. J. L. Health effects of overweight and obesity in 195 countries. *N. Engl. J. Med.* **377**, 1496–1497 (2017).
3. Ogden, C. L., Carroll, M. D., Kit, B. K. & Flegal, K. M. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. *J. Am. Med. Assoc.* **307**, 483–490 (2012).
4. Gregg, E. W. & Shaw, J. E. Global health effects of overweight and obesity. *N. Engl. J. Med.* **377**, 80–81 (2017).
5. Saklayen, M. G. The global epidemic of the metabolic syndrome. *Curr. Hypertens. Rep.* **20**, 12 (2018).
6. Ogurtsova, K. et al. IDF Diabetes Atlas: global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res. Clin. Pract.* **128**, 40–50 (2017).
7. Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. *Lancet Diabetes Endocrinol.* **3**, 866–875 (2015).
8. Ryan, D. H. & Diabetes Prevention Program Research Group. Diet and exercise in the prevention of diabetes. *Int. J. Clin. Pract. Suppl.*, 28–35 (2003).
9. Yoo, H. J. & Choi, K. M. Hepatokines as a link between obesity and cardiovascular diseases. *Diabetes Metab. J.* **39**, 10–15 (2015).
10. Browning, J. D. & Horton, J. D. Molecular mediators of hepatic steatosis and liver injury. *J. Clin. Invest.* **114**, 147–152 (2004).
11. Bellentani, S. et al. Risk factors for alcoholic liver disease. *Addict. Biol.* **5**, 261–268 (2000).
12. Ding, E. L. et al. Sex hormone-binding globulin and risk of type 2 diabetes in women and men. *N. Engl. J. Med.* **361**, 1152–1163 (2009).
13. Ding, L., Wendl, M. C., Koboldt, D. C. & Mardis, E. R. Analysis of next-generation genomic data in cancer: accomplishments and challenges. *Hum. Mol. Genet.* **19**, R188–R196 (2010). R2.
14. Li, C. Y. et al. Recombinant human hepassocin stimulates proliferation of hepatocytes in vivo and improves survival in rats with fulminant hepatic failure. *Gut* **59**, 817–826 (2010).
15. Wu, H. T. et al. The role of hepassocin in the development of non-alcoholic fatty liver disease. *J. Hepatol.* **59**, 1065–1072 (2013).
16. Wang, Y. et al. Angiopoietin-like protein 4 improves glucose tolerance and insulin resistance but induces liver steatosis in high-fat-diet mice. *Mol. Med. Rep.* **14**, 3293–3300 (2016).
17. Koo, B. K. et al. Growth differentiation factor 15 predicts advanced fibrosis in biopsy-proven non-alcoholic fatty liver disease. *Liver Int.* **38**, 695–705 (2018).
18. Kim, K. H. et al. Growth differentiation factor 15 ameliorates nonalcoholic steatohepatitis and related metabolic disorders in mice. *Sci. Rep.* **8**, 6789 (2018).
19. Dijk, W. et al. Angiopoietin-like 4 promotes intracellular degradation of lipoprotein lipase in adipocytes. *J. Lipid Res.* **57**, 1670–1683 (2016).
20. Kutlu, O. et al. Serum adropin levels are reduced in adult patients with non-alcoholic fatty liver disease. *Med. Princ. Pract.* **28**, 463–469 (2019).
21. Gao, S. et al. Therapeutic effects of adropin on glucose tolerance and substrate utilization in diet-induced obese mice with insulin resistance. *Mol. Metab.* **4**, 310–324 (2015).
22. Meex, R. C. et al. Fetuin B is a secreted hepatocyte factor linking steatosis to impaired glucose metabolism. *Cell Metab.* **22**, 1078–1089 (2015).
23. Pal, D. et al. Fetuin-A acts as an endogenous ligand of TLR4 to promote lipid-induced insulin resistance. *Nat. Med.* **18**, 1279–1285 (2012).
24. Mukhopadhyay, S. & Bhattacharya, S. Plasma fetuin-A triggers inflammatory changes in macrophages and adipocytes by acting as an adaptor protein between NEFA and TLR-4. *Diabetologia* **59**, 859–860 (2016).
25. Misu, H. et al. A liver-derived secretory protein, selenoprotein P, causes insulin resistance. *Cell Metab.* **12**, 483–495 (2010).
26. Choi, H. Y. et al. Increased selenoprotein P levels in subjects with visceral obesity and nonalcoholic fatty liver disease. *Diabetes Metab. J.* **37**, 63–71 (2013).
27. Yang, Q. et al. Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. *Nature* **436**, 356–362 (2005).
28. Moraes-Vieira, P. M. et al. RBP4 activates antigen-presenting cells, leading to adipose tissue inflammation and systemic insulin resistance. *Cell Metab.* **19**, 512–526 (2014).
29. Kotnik, P., Fischer-Posovszky, P. & Wabitsch, M. RBP4: a controversial adipokine. *Eur. J. Endocrinol.* **165**, 703–711 (2011).
30. Lan, F. et al. LECT2 functions as a hepatokine that links obesity to skeletal muscle insulin resistance. *Diabetes* **63**, 1649–1664 (2014).
31. Kliewer, S. A. & Mangelsdorf, D. J. A dozen years of discovery: insights into the physiology and pharmacology of FGF21. *Cell Metab.* **29**, 246–253 (2019).
32. Staiger, H., Keuper, M., Berti, L., Hrabe de Angelis, M. & Häring, H. U. Fibroblast growth factor 21-metabolic role in mice and men. *Endocr. Rev.* **38**, 468–488 (2017).
33. Bookout, A. L. et al. FGF21 regulates metabolism and circadian behavior by acting on the nervous system. *Nat. Med.* 19, (1147–1152 (2013).
34. Owen, B. M. et al. FGF21 acts centrally to induce sympathetic nerve activity, energy expenditure, and weight loss. *Cell Metab.* **20**, 670–677 (2014).
35. Zhang, X. et al. Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans. *Diabetes* **57**, 1246–1253 (2008).
36. Zhang, Y. et al. The starvation hormone, fibroblast growth factor-21, extends lifespan in mice. *eLife* **1**, e00065 (2012).
37. Gaich, G. et al. The effects of LY2405319, an FGF21 analogue, in obese human subjects with type 2 diabetes. *Cell Metab.* **18**, 333–340 (2013).
38. Wei, W. et al. Fibroblast growth factor 21 promotes bone loss by potentiating the effects of peroxisome proliferator-activated receptor γ. *Proc. Natl Acad. Sci. USA* **109**, 3143–3148 (2012).
39. Owen, B. M. et al. FGF21 contributes to neuroendocrine control of female reproduction. *Nat. Med.* **19**, 1153–1156 (2013).
40. Inagaki, T. et al. Fibroblast growth factor 15 functions as an enterohepatic signal to regulate bile acid homeostasis. *Cell Metab.* **2**, 217–225 (2005).
41. Potthoff, M. J. et al. FGF15/19 regulates hepatic glucose metabolism by inhibiting the CREB-PGC-1α pathway. *Cell Metab.* **13**, 729–738 (2011).
42. Sinal, C. J. et al. Targeted disruption of the nuclear receptor FXR/BAR impairs bile acid and lipid homeostasis. *Cell* **102**, 731–744 (2000).
43. Watanabe, M. et al. Bile acids lower triglyceride levels via a pathway involving FXR, SHP, and SREBP-1c. *J. Clin. Invest.* **113**, 1408–1418 (2004).
44. Zhang, Y. et al. Activation of the nuclear receptor FXR improves hyperglycaemia and hyperlipidemia in diabetic mice. *Proc. Natl Acad. Sci. USA* **103**, 1006–1011 (2006).
45. Calkin, A. C. & Tontonoz, P. Transcriptional integration of metabolism by the nuclear sterol-activated receptors LXR and FXR. *Nat. Rev. Mol. Cell Biol.* **13**, 213–224 (2012).
46. van Nierop, F. S. et al. Clinical relevance of the bile acid receptor TGR5 in metabolism. *Lancet Diabetes Endocrinol.* **5**, 224–233 (2017).
47. Keitel, V. et al. The bile acid receptor TGR5 (Gpbar-1) acts as a neurosteroid receptor in brain. *Glia* **58**, 1794–1805 (2010).
48. Watanabe, M. et al. Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. *Nature* **439**, 484–489 (2006).
49. Thomas, C. et al. TGR5-mediated bile acid sensing controls glucose homeostasis. *Cell Metab.* **10**, 167–177 (2009).
50. Simcox, J. et al. Global analysis of plasma lipids identifies liver-derived acylcarnitines as a fuel source for brown fat thermogenesis. *Cell Metab.* **26**, 509–522.e506 (2017).
51. Shah, R. V. et al. Visceral adiposity and the risk of metabolic syndrome across body mass index: the MESA Study. *JACC Cardiovasc. Imaging* **7**, 1221–1235 (2014).
52. Cook, K. S. et al. Adipsin: a circulating serine protease homolog secreted by adipose tissue and sciatic nerve. *Science* **237**, 402–405 (1987).
53. Zhang, Y. et al. Positional cloning of the mouse obese gene and its human homologue. *Nature* **372**, 425–432 (1994).

54. Cohen, P. et al. Selective deletion of leptin receptor in neurons leads to obesity. *J. Clin. Invest.* **108**, 1113–1121 (2001).
55. Guo, K. et al. Disruption of peripheral leptin signalling in mice results in hyperleptinemia without associated metabolic abnormalities. *Endocrinology* **148**, 3987–3997 (2007).
56. Flier, J. S. & Maratos-Flier, E. Leptin's physiologic role: does the emperor of energy balance have no clothes? *Cell Metab.* **26**, 24–26 (2017).
57. Minokoshi, Y. et al. Leptin stimulates fatty-acid oxidation by activating AMP-activated protein kinase. *Nature* **415**, 339–343 (2002).
58. Scherer, P. E., Williams, S., Fogliano, M., Baldini, G. & Lodish, H. F. A novel serum protein similar to C1q, produced exclusively in adipocytes. *J. Biol. Chem.* **270**, 26746–26749 (1995).
59. Arita, Y. et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem. Biophys. Res. Commun.* **257**, 79–83 (1999).
60. Yamauchi, T. et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nat. Med.* **7**, 941–946 (2001).
61. Qi, Y. et al. Adiponectin acts in the brain to decrease body weight. *Nat. Med.* **10**, 524–529 (2004).
62. Wang, Z. V. & Scherer, P. E. Adiponectin, the past two decades. *J. Mol. Cell Biol.* **8**, 93–100 (2016).
63. Combs, T. P., Berg, A. H., Obici, S., Scherer, P. E. & Rossetti, L. Endogenous glucose production is inhibited by the adipose-derived protein Acrp30. *J. Clin. Invest.* **108**, 1875–1881 (2001).
64. Muoio, D. M., Dohm, G. L., Fiedorek, F. T. Jr., Tapscott, E. B. & Coleman, R. A. Leptin directly alters lipid partitioning in skeletal muscle. *Diabetes* **46**, 1360–1363 (1997).
65. Auguet, T. et al. Upregulation of lipocalin 2 in adipose tissues of severely obese women: positive relationship with proinflammatory cytokines. *Obesity (Silver Spring)* **19**, 2295–2300 (2011).
66. Fernandez-García, C. E. et al. Lipocalin-2, a potential therapeutic target in advanced atherosclerosis. *Atherosclerosis* **278**, 321–322 (2018).
67. Guo, H. et al. Lipocalin-2 deficiency impairs thermogenesis and potentiates diet-induced insulin resistance in mice. *Diabetes* **59**, 1376–1385 (2010).
68. Law, I. K. et al. Lipocalin-2 deficiency attenuates insulin resistance associated with aging and obesity. *Diabetes* **59**, 872–882 (2010).
69. Wang, G. X. et al. The brown fat-enriched secreted factor Nrg4 preserves metabolic homeostasis through attenuation of hepatic lipogenesis. *Nat. Med.* **20**, 1436–1443 (2014).
70. Pfeifer, A. NRG4: an endocrine link between brown adipose tissue and liver. *Cell Metab.* **21**, 13–14 (2015).
71. Hotamisligil, G. S. et al. Uncoupling of obesity from insulin resistance through a targeted mutation in aP2, the adipocyte fatty acid binding protein. *Science* **274**, 1377–1379 (1996).
72. Cao, H. et al. Adipocyte lipid chaperone AP2 is a secreted adipokine regulating hepatic glucose production. *Cell Metab.* **17**, 768–778 (2013).
73. Furuhashi, M. et al. Treatment of diabetes and atherosclerosis by inhibiting fatty-acid-binding protein aP2. *Nature* **447**, 959–965 (2007).
74. Zhang, M., Zhu, W. & Li, Y. Small molecule inhibitors of human adipocyte fatty acid binding protein (FABP4). *Med. Chem.* **10**, 339–347 (2014).
75. Burak, M. F. et al. Development of a therapeutic monoclonal antibody that targets secreted fatty acid-binding protein aP2 to treat type 2 diabetes. *Sci. Transl. Med.* **7**, 319ra205 (2015).
76. Barchetta, I., Cimini, F. A., Ciccarelli, G., Baroni, M. G. & Cavallo, M. G. Sick fat: the good and the bad of old and new circulating markers of adipose tissue inflammation. *J. Endocrinol. Invest.* **42**, 1257–1272 (2019).
77. Steppan, C. M. et al. The hormone resistin links obesity to diabetes. *Nature* **409**, 307–312 (2001).
78. Tarkowski, A., Bjersing, J., Shestakov, A. & Bokarewa, M. I. Resistin competes with lipopolysaccharide for binding to toll-like receptor 4. *J. Cell. Mol. Med.* **14**, 1419–1431 (2010). (6B).
79. Cao, H. et al. Identification of a lipokine, a lipid hormone linking adipose tissue to systemic metabolism. *Cell* **134**, 933–944 (2008).
80. Ferry, G. et al. Autotaxin is released from adipocytes, catalyzes lysophosphatidic acid synthesis, and activates preadipocyte proliferation. Up-regulated expression with adipocyte differentiation and obesity. *J. Biol. Chem.* **278**, 18162–18169 (2003).
81. Rancoule, C. et al. Lysophosphatidic acid impairs glucose homeostasis and inhibits insulin secretion in high-fat diet obese mice. *Diabetologia* **56**, 1394–1402 (2013).
82. Yore, M. M. et al. Discovery of a class of endogenous mammalian lipids with anti-diabetic and anti-inflammatory effects. *Cell* **159**, 318–332 (2014).
83. Syed, I. et al. Palmitic acid hydroxystearic acids activate GPR40, which is involved in their beneficial effects on glucose homeostasis. *Cell Metab.* **27**, 419–427.e414 (2018).
84. Pflimlin, E. et al. Acute and repeated treatment with 5-PAHSA or 9-PAHSA isomers does not improve glucose control in mice. *Cell Metab.* **28**, 217–227. e213 (2018).
85. Syed, I. et al. Methodological issues in studying PAHSA biology: masking PAHSA effects. *Cell Metab.* **28**, 543–546 (2018).
86. van Marken Lichtenbelt, W. D. et al. Cold-activated brown adipose tissue in healthy men. *N. Engl. J. Med.* **360**, 1500–1508 (2009).
87. Lee, P. et al. Irisin and FGF21 are cold-induced endocrine activators of brown fat function in humans. *Cell Metab.* **19**, 302–309 (2014).
88. Svensson, K. J. et al. A secreted Slit2 fragment regulates adipose tissue thermogenesis and metabolic function. *Cell Metab.* **23**, 454–466 (2016).
89. Kong, X. et al. Brown adipose tissue controls skeletal muscle function via the secretion of myostatin. *Cell Metab.* **28**, 631–643.e633 (2018).
90. Stanford, K. I. et al. 12,13-diHOME: an exercise-induced lipokine that increases skeletal muscle fatty acid uptake. *Cell Metab.* **27**, 1111–1120. e1113 (2018).
91. Leiria, L. O. et al. 12-Lipoxygenase regulates cold adaptation and glucose metabolism by producing the omega-3 lipid 12-HEPE from brown fat. *Cell Metab.* **30**, 768–783.e767 (2019).
92. Mohr, T. et al. Long-term adaptation to electrically induced cycle training in severe spinal cord injured individuals. *Spinal Cord* **35**, 1–16 (1997).
93. Bortoluzzi, S., Scannapieco, P., Cestaro, A., Danieli, G. A. & Schiaffino, S. Computational reconstruction of the human skeletal muscle secretome. *Proteins* **62**, 776–792 (2006).
94. Pedersen, B. K. & Febbraio, M. A. Muscle as an endocrine organ: focus on muscle-derived interleukin-6. *Physiol. Rev.* **88**, 1379–1406 (2008).
95. Fischer, C. P. Interleukin-6 in acute exercise and training: what is the biological relevance? *Exerc. Immunol. Rev.* **12**, 6–33 (2006).
96. Hiscock, N., Chan, M. H., Bisucci, T., Darby, I. A. & Febbraio, M. A. Skeletal myocytes are a source of interleukin-6 mRNA expression and protein release during contraction: evidence of fiber type specificity. *FASEB J.* **18**, 992–994 (2004).
97. Febbraio, M. A. et al. Glucose ingestion attenuates interleukin-6 release from contracting skeletal muscle in humans. *J. Physiol. (Lond.)* **549**, 607–612 (2003).
98. Carey, A. L. et al. Interleukin-6 increases insulin-stimulated glucose disposal in humans and glucose uptake and fatty acid oxidation in vitro via AMP-activated protein kinase. *Diabetes* **55**, 2688–2697 (2006).
99. Febbraio, M. A., Hiscock, N., Sacchetti, M., Fischer, C. P. & Pedersen, B. K. Interleukin-6 is a novel factor mediating glucose homeostasis during skeletal muscle contraction. *Diabetes* **53**, 1643–1648 (2004).
100. Steensberg, A. et al. Acute interleukin-6 administration does not impair muscle glucose uptake or whole-body glucose disposal in healthy humans. *J. Physiol. (Lond.)* **548**, 631–638 (2003).
101. Pedersen, B. K. & Febbraio, M. A. Muscles, exercise and obesity: skeletal muscle as a secretory organ. *Nat. Rev. Endocrinol.* **8**, 457–465 (2012).
102. McPherron, A. C., Lawler, A. M. & Lee, S. J. Regulation of skeletal muscle mass in mice by a new TGF-beta superfamily member. *Nature* **387**, 83–90 (1997).
103. McPherron, A. C. & Lee, S. J. Suppression of body fat accumulation in myostatin-deficient mice. *J. Clin. Invest.* **109**, 595–601 (2002).
104. Feldman, B. J., Streeper, R. S., Farese, R. V. Jr. & Yamamoto, K. R. Myostatin modulates adipogenesis to generate adipocytes with favorable metabolic effects. *Proc. Natl Acad. Sci. USA* **103**, 15675–15680 (2006).
105. Hittel, D. S., Berggren, J. R., Shearer, J., Boyle, K. & Houmard, J. A. Increased secretion and expression of myostatin in skeletal muscle from extremely obese women. *Diabetes* **58**, 30–38 (2009).
106. Hansen, J. et al. Exercise induces a marked increase in plasma follistatin: evidence that follistatin is a contraction-induced hepatokine. *Endocrinology* **152**, 164–171 (2011).
107. Hansen, J. S. & Plomgaard, P. Circulating follistatin in relation to energy metabolism. *Mol. Cell. Endocrinol.* **433**, 87–93 (2016).
108. Otero-Díaz, B. et al. Exercise induces white adipose tissue browning across the weight spectrum in humans. *Front. Physiol.* **9**, 1781 (2018).
109. Boström, P. et al. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature* **481**, 463–468 (2012).
110. Wrann, C. D. et al. Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway. *Cell Metab.* **18**, 649–659 (2013).
111. Roberts, L. D. et al. β-Aminoisobutyric acid induces browning of white fat and hepatic β-oxidation and is inversely correlated with cardiometabolic risk factors. *Cell Metab.* **19**, 96–108 (2014).
112. Lee, C. et al. The mitochondrial-derived peptide MOTS-c promotes metabolic homeostasis and reduces obesity and insulin resistance. *Cell Metab.* **21**, 443–454 (2015).
113. Du, C. et al. Circulating MOTS-c levels are decreased in obese male children and adolescents and associated with insulin resistance. *Pediatr. Diabetes* **19**, 1058–1064 (2018).
114. Nielsen, A. R. & Pedersen, B. K. The biological roles of exercise-induced cytokines: IL-6, IL-8, and IL-15. *Appl. Physiol. Nutr. Metab.* **32**, 833–839 (2007).

115. Carbó, N. et al. Interleukin-15 mediates reciprocal regulation of adipose and muscle mass: a potential role in body weight control. *Biochim. Biophys. Acta* **1526**, 17–24 (2001).
116. Quinn, L. S., Strait-Bodey, L., Anderson, B. G., Argilés, J. M. & Havel, P. J. Interleukin-15 stimulates adiponectin secretion by 3T3-L1 adipocytes: evidence for a skeletal muscle-to-fat signalling pathway. *Cell Biol. Int.* **29**, 449–457 (2005).
117. Hamrick, M. W., McNeil, P. L. & Patterson, S. L. Role of muscle-derived growth factors in bone formation. *J. Musculoskelet. Neuronal Interact.* **10**, 64–70 (2010).
118. Ouchi, N. et al. Follistatin-like 1, a secreted muscle protein, promotes endothelial cell function and revascularization in ischemic tissue through a nitric-oxide synthase-dependent mechanism. *J. Biol. Chem.* **283**, 32802–32811 (2008).
119. Oshima, Y. et al. Follistatin-like 1 is an Akt-regulated cardioprotective factor that is secreted by the heart. *Circulation* **117**, 3099–3108 (2008).
120. Macleod, J. J. Pancreatic extract and diabetes. *Can. Med. Assoc. J.* **12**, 423–425 (1922).
121. Klip, A., McGraw, T. E. & James, D. E. 30 sweet years of GLUT4. *J. Biol. Chem.* **294**, 11369–11381 (2019).
122. Titchenell, P. M., Lazar, M. A. & Birnbaum, M. J. Unraveling the regulation of hepatic metabolism by insulin. *Trends Endocrinol. Metab.* **28**, 497–505 (2017).
123. Liu, S. & Borgland, S. L. Insulin actions in the mesolimbic dopamine system. *Exp. Neurol.* **320**, 113006 (2019).
124. Guo, S. Insulin signalling, resistance, and the metabolic syndrome: insights from mouse models into disease mechanisms. *J. Endocrinol.* **220**, T1–T23 (2014).
125. Mathieu, C., Gillard, P. & Benhalima, K. Insulin analogues in type 1 diabetes mellitus: getting better all the time. *Nat. Rev. Endocrinol.* **13**, 385–399 (2017).
126. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* **352**, 837–853 (1998).
127. Riddle, M., Umpierrez, G., DiGenio, A., Zhou, R. & Rosenstock, J. Contributions of basal and postprandial hyperglycaemia over a wide range of A1C levels before and after treatment intensification in type 2 diabetes. *Diabetes Care* **34**, 2508–2514 (2011).
128. Wallia, A. & Molitch, M. E. Insulin therapy for type 2 diabetes mellitus. *J. Am. Med. Assoc.* **311**, 2315–2325 (2014).
129. Lin, H. V. & Accili, D. Hormonal regulation of hepatic glucose production in health and disease. *Cell Metab.* **14**, 9–19 (2011).
130. Habegger, K. M. et al. The metabolic actions of glucagon revisited. *Nat. Rev. Endocrinol.* **6**, 689–697 (2010).
131. Day, J. W. et al. A new glucagon and GLP-1 co-agonist eliminates obesity in rodents. *Nat. Chem. Biol.* **5**, 749–757 (2009).
132. Kim, T. et al. Glucagon receptor signalling regulates energy metabolism via hepatic farnesoid X receptor and fibroblast growth factor 21. *Diabetes* **67**, 1773–1782 (2018).
133. Nauck, M. A. & Meier, J. J. Incretin hormones: their role in health and disease. *Diabetes Obes. Metab.* **20**, 5–21 (2018). (Suppl. 1).
134. Muscelli, E. et al. Separate impact of obesity and glucose tolerance on the incretin effect in normal subjects and type 2 diabetic patients. *Diabetes* **57**, 1340–1348 (2008).
135. Nauck, M. A., Bartels, E., Orskov, C., Ebert, R. & Creutzfeldt, W. Additive insulinotropic effects of exogenous synthetic human gastric inhibitory polypeptide and glucagon-like peptide-1-(7-36) amide infused at near-physiological insulinotropic hormone and glucose concentrations. *J. Clin. Endocrinol. Metab.* **76**, 912–917 (1993).
136. Nauck, M. A. et al. Preserved incretin activity of glucagon-like peptide 1 [7-36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. *J. Clin. Invest.* **91**, 301–307 (1993).
137. Flint, A., Raben, A., Astrup, A. & Holst, J. J. Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. *J. Clin. Invest.* **101**, 515–520 (1998).
138. Verdich, C. et al. A meta-analysis of the effect of glucagon-like peptide-1 (7-36) amide on ad libitum energy intake in humans. *J. Clin. Endocrinol. Metab.* **86**, 4382–4389 (2001).
139. Ranganath, L. R. et al. Attenuated GLP-1 secretion in obesity: cause or consequence? *Gut* **38**, 916–919 (1996).
140. Laferrère, B. Effect of gastric bypass surgery on the incretins. *Diabetes Metab.* **35**, 513–517 (2009).
141. Drucker, D. J. The cardiovascular biology of glucagon-like peptide-1. *Cell Metab.* **24**, 15–30 (2016).
142. Zhong, J., Maiseyeu, A., Davis, S. N. & Rajagopalan, S. DPP4 in cardiometabolic disease: recent insights from the laboratory and clinical trials of DPP4 inhibition. *Circ. Res.* **116**, 1491–1504 (2015).
143. Svane, M. S. et al. Peptide YY and glucagon-like peptide-1 contribute to decreased food intake after Roux-en-Y gastric bypass surgery. *Int. J. Obes. (Lond.)* **40**, 1699–1706 (2016).
144. Kojima, M. et al. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature* **402**, 656–660 (1999).
145. Tschöp, M., Smiley, D. L. & Heiman, M. L. Ghrelin induces adiposity in rodents. *Nature* **407**, 908–913 (2000).
146. Colldén, G., Tschöp, M. H. & Müller, T. D. Therapeutic potential of targeting the ghrelin pathway. *Int. J. Mol. Sci.* **18**, E798 (2017).
147. Yasuda, T., Masaki, T., Kakuma, T. & Yoshimatsu, H. Centrally administered ghrelin suppresses sympathetic nerve activity in brown adipose tissue of rats. *Neurosci. Lett.* **349**, 75–78 (2003).
148. Theander-Carrillo, C. et al. Ghrelin action in the brain controls adipocyte metabolism. *J. Clin. Invest.* **116**, 1983–1993 (2006).
149. Gnanapavan, S. et al. The tissue distribution of the mRNA of ghrelin and subtypes of its receptor, GHS-R, in humans. *J. Clin. Endocrinol. Metab.* **87**, 2988 (2002).
150. Gauna, C. et al. Ghrelin stimulates, whereas des-octanoyl ghrelin inhibits, glucose output by primary hepatocytes. *J. Clin. Endocrinol. Metab.* **90**, 1055–1060 (2005).
151. Gauna, C. et al. Administration of acylated ghrelin reduces insulin sensitivity, whereas the combination of acylated plus unacylated ghrelin strongly improves insulin sensitivity. *J. Clin. Endocrinol. Metab.* **89**, 5035–5042 (2004).
152. Sun, Y., Asnicar, M., Saha, P. K., Chan, L. & Smith, R. G. Ablation of ghrelin improves the diabetic but not obese phenotype of ob/ob mice. *Cell Metab.* **3**, 379–386 (2006).
153. Li, Y. et al. Administration of ghrelin improves inflammation, oxidative stress, and apoptosis during and after non-alcoholic fatty liver disease development. *Endocrine* **43**, 376–386 (2013).
154. Gortan Cappellari, G. et al. Unacylated ghrelin reduces skeletal muscle reactive oxygen species generation and inflammation and prevents high-fat diet-induced hyperglycemia and whole-body insulin resistance in rodents. *Diabetes* **65**, 874–886 (2016).
155. Kraft, E. N., Cervone, D. T. & Dyck, D. J. Ghrelin stimulates fatty acid oxidation and inhibits lipolysis in isolated muscle from male rats. *Physiol. Rep.* **7**, e14028 (2019).
156. Khatib, M. N. et al. Effect of ghrelin on mortality and cardiovascular outcomes in experimental rat and mice models of heart failure: a systematic review and meta-analysis. *PLoS One* **10**, e0126697 (2015).
157. Erspamer, V. & Asero, B. Identification of enteramine, the specific hormone of the enterochromaffin cell system, as 5-hydroxytryptamine. *Nature* **169**, 800–801 (1952).
158. Kim, H. et al. Serotonin regulates pancreatic beta cell mass during pregnancy. *Nat. Med.* **16**, 804–808 (2010).
159. Paulmann, N. et al. Intracellular serotonin modulates insulin secretion from pancreatic beta-cells by protein serotonylation. *PLoS Biol.* **7**, e1000229 (2009).
160. Sumara, G., Sumara, O., Kim, J. K. & Karsenty, G. Gut-derived serotonin is a multifunctional determinant to fasting adaptation. *Cell Metab.* **16**, 588–600 (2012).
161. Oh, C. M. et al. Regulation of systemic energy homeostasis by serotonin in adipose tissues. *Nat. Commun.* **6**, 6794 (2015).
162. Tanaka, M. & Itoh, H. Hypertension as a metabolic disorder and the novel role of the gut. *Curr. Hypertens. Rep.* **21**, 63 (2019).
163. Ma, Y., He, F. J. & MacGregor, G. A. High salt intake: independent risk factor for obesity? *Hypertension* **66**, 843–849 (2015).
164. Lee, M., Sorn, S. R., Lee, Y. & Kang, I. Salt induces adipogenesis/lipogenesis and inflammatory adipocytokines secretion in adipocytes. *Int. J. Mol. Sci.* **20**, E160 (2019).
165. Zhu, Z., Xiong, S. & Liu, D. The gastrointestinal tract: an initial organ of metabolic hypertension? *Cell. Physiol. Biochem.* **38**, 1681–1694 (2016).
166. Frigolet, M. E., Torres, N. & Tovar, A. R. The renin-angiotensin system in adipose tissue and its metabolic consequences during obesity. *J. Nutr. Biochem.* **24**, 2003–2015 (2013).
167. Ohashi, K. et al. Adiponectin replenishment ameliorates obesity-related hypertension. *Hypertension* **47**, 1108–1116 (2006).
168. Zhao, Y. et al. Sodium intake regulates glucose homeostasis through the PPARδ/adiponectin-mediated SGLT2 pathway. *Cell Metab.* **23**, 699–711 (2016).
169. Okamoto, Y. et al. Adiponectin reduces atherosclerosis in apolipoprotein E-deficient mice. *Circulation* **106**, 2767–2770 (2002).
170. Shibata, R. et al. Adiponectin-mediated modulation of hypertrophic signals in the heart. *Nat. Med.* **10**, 1384–1389 (2004).
171. Shibata, R. et al. Adiponectin protects against myocardial ischemia-reperfusion injury through AMPK- and COX-2-dependent mechanisms. *Nat. Med.* **11**, 1096–1103 (2005).
172. Juárez-Rojas, J. G. et al. Association of adiponectin with subclinical atherosclerosis in a Mexican-mestizo population. *Arch. Med. Res.* **48**, 73–78 (2017).

173. Makowski, L. et al. Lack of macrophage fatty-acid-binding protein aP2 protects mice deficient in apolipoprotein E against atherosclerosis. *Nat. Med.* **7**, 699–705 (2001).
174. Makowski, L., Brittingham, K. C., Reynolds, J. M., Suttles, J. & Hotamisligil, G. S. The fatty acid-binding protein, aP2, coordinates macrophage cholesterol trafficking and inflammatory activity. Macrophage expression of aP2 impacts peroxisome proliferator-activated receptor gamma and IκB kinase activities. *J. Biol. Chem.* **280**, 12888–12895 (2005).
175. Shimba, Y. et al. Skeletal muscle-specific PGC-1α overexpression suppresses atherosclerosis in apolipoprotein E-knockout mice. *Sci. Rep.* **9**, 4077 (2019).
176. Lee, M. J. et al. Irisin, a novel myokine is an independent predictor for sarcopenia and carotid atherosclerosis in dialysis patients. *Atherosclerosis* **242**, 476–482 (2015).
177. Sawada, M., Yamamoto, H., Ogasahara, A., Tanaka, Y. & Kihara, S. β-aminoisobutyric acid protects against vascular inflammation through PGC-1β-induced antioxidative properties. *Biochem. Biophys. Res. Commun.* **516**, 963–968 (2019).
178. Seldin, M. M. et al. Trimethylamine N-oxide promotes vascular inflammation through signalling of mitogen-activated protein kinase and nuclear factor-κB. *J. Am. Heart Assoc.* **5**, e002767 (2016).
179. Miao, J. et al. Flavin-containing monooxygenase 3 as a potential player in diabetes-associated atherosclerosis. *Nat. Commun.* **6**, 6498 (2015).
180. Schugar, R. C. et al. The TMAO-producing enzyme flavin-containing monooxygenase 3 regulates obesity and the beiging of white adipose tissue. *Cell Rep.* **19**, 2451–2461 (2017).
181. Dallabrida, S. M. et al. Adipose tissue growth and regression are regulated by angiopoietin-1. *Biochem. Biophys. Res. Commun.* **311**, 563–571 (2003).
182. An, Y. A. et al. Angiopoietin-2 in white adipose tissue improves metabolic homeostasis through enhanced angiogenesis. *eLife* **6**, e24071 (2017).
183. Voros, G. et al. Modulation of angiogenesis during adipose tissue development in murine models of obesity. *Endocrinology* **146**, 4545–4554 (2005).
184. Jung, Y. J. et al. The effects of designed angiopoietin-1 variant on lipid droplet diameter, vascular endothelial cell density and metabolic parameters in diabetic db/db mice. *Biochem. Biophys. Res. Commun.* **420**, 498–504 (2012).
185. Lee, S. et al. Renoprotective effect of COMP-angiopoietin-1 in db/db mice with type 2 diabetes. *Nephrol. Dial. Transplant.* **22**, 396–408 (2007).
186. Tabata, M. et al. Angiopoietin-like protein 2 promotes chronic adipose tissue inflammation and obesity-related systemic insulin resistance. *Cell Metab.* **10**, 178–188 (2009).
187. Horio, E. et al. Role of endothelial cell-derived angptl2 in vascular inflammation leading to endothelial dysfunction and atherosclerosis progression. *Arterioscler. Thromb. Vasc. Biol.* **34**, 790–800 (2014).
188. Kersten, S. New insights into angiopoietin-like proteins in lipid metabolism and cardiovascular disease risk. *Curr. Opin. Lipidol.* **30**, 205–211 (2019).
189. Romeo, S. et al. Rare loss-of-function mutations in ANGPTL family members contribute to plasma triglyceride levels in humans. *J. Clin. Invest.* **119**, 70–79 (2009).
190. Aryal, B. et al. Absence of ANGPTL4 in adipose tissue improves glucose tolerance and attenuates atherogenesis. *JCI Insight* **3**, 97918 (2018).
191. Lusis, A. J. et al. The Hybrid Mouse Diversity Panel: a resource for systems genetics analyses of metabolic and cardiovascular traits. *J. Lipid Res.* **57**, 925–942 (2016).
192. Seldin, M. M. et al. A strategy for discovery of endocrine interactions with application to whole-body metabolism. *Cell Metab.* **27**, 1138–1155. e1136 (2018).
193. Heron, M. Deaths: leading causes for 2010. *Natl Vital Stat. Rep.* **62**, 1–96 (2013).
194. Goldstein, J. L. & Brown, M. S. A century of cholesterol and coronaries: from plaques to genes to statins. *Cell* **161**, 161–172 (2015).
195. Libby, P. & Hansson, G. K. Inflammation and immunity in diseases of the arterial tree: players and layers. *Circ. Res.* **116**, 307–311 (2015).
196. Gisterå, A. & Hansson, G. K. The immunology of atherosclerosis. *Nat. Rev. Nephrol.* **13**, 368–380 (2017).
197. Lee, S. D. & Tontonoz, P. Liver X receptors at the intersection of lipid metabolism and atherogenesis. *Atherosclerosis* **242**, 29–36 (2015).
198. Rahman, K. & Fisher, E. A. Insights from pre-clinical and clinical studies on the role of innate inflammation in atherosclerosis regression. *Front. Cardiovasc. Med.* **5**, 32 (2018).
199. Farr, O. M., Li, C. R. & Mantzoros, C. S. Central nervous system regulation of eating: insights from human brain imaging. *Metabolism* **65**, 699–713 (2016).
200. Soto, M., Cai, W., Konishi, M. & Kahn, C. R. Insulin signalling in the hippocampus and amygdala regulates metabolism and neurobehavior. *Proc. Natl Acad. Sci. USA* **116**, 6379–6384 (2019).
201. He, Z. et al. Cellular and synaptic reorganization of arcuate NPY/AgRP and POMC neurons after exercise. *Mol. Metab.* **18**, 107–119 (2018).
202. Tkach, M. & Théry, C. Communication by extracellular vesicles: where we are and where we need to go. *Cell* **164**, 1226–1232 (2016).
203. Crewe, C. et al. An endothelial-to-adipocyte extracellular vesicle axis governed by metabolic state. *Cell* **175**, 695–708.e613 (2018).
204. Chen, Y. et al. Exosomal microRNA miR-92a concentration in serum reflects human brown fat activity. *Nat. Commun.* **7**, 11420 (2016).
205. Deng, Z. B. et al. Adipose tissue exosome-like vesicles mediate activation of macrophage-induced insulin resistance. *Diabetes* **58**, 2498–2505 (2009).
206. Xie, Z. et al. Adipose-derived exosomes exert proatherogenic effects by regulating macrophage foam cell formation and polarization. *J. Am. Heart Assoc.* **7**, e007442 (2018).

Author contributions

C.P. and P.T. prepared the original draft and revised the manuscript. C.P. prepared the figures.

Competing interests

The authors declare no competing interests.

Additional information

Correspondence should be addressed to P.T.

Peer review information Primary Handling Editor: Elena Bellafante.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.