



Thematic Review Series: Adipose Biology

Beyond adiponectin and leptin: adipose tissue-derived mediators of inter-organ communication

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Abstract The breakthrough discoveries of leptin and adiponectin more than two decades ago led to a widespread recognition of adipose tissue as an endocrine organ. Many more adipose tissue-secreted signaling mediators (adipokines) have been identified since then, and much has been learned about how adipose tissue communicates with other organs of the body to maintain systemic homeostasis. Beyond proteins, additional factors, such as lipids, metabolites, noncoding RNAs, and extracellular vesicles (EVs), released by adipose tissue participate in this process. Here, we review the diverse signaling mediators and mechanisms adipose tissue utilizes to relay information to other organs. We discuss recently identified adipokines (proteins, lipids, and metabolites) and briefly outline the contributions of noncoding RNAs and EVs to the ever-increasing complexities of adipose tissue inter-organ communication. We conclude by reflecting on central aspects of adipokine biology, namely, the contribution of distinct adipose tissue depots and cell types to adipokine secretion, the phenomenon of adipokine resistance, and the capacity of adipose tissue to act both as a source and sink of signaling mediators.—Funcke, J-B., and P. E. Scherer. *Beyond adiponectin and leptin: adipose tissue-derived mediators of inter-organ communication*. *J. Lipid Res.* 2019. 60: 1648–1697.

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THE ENDOCRINE ERA OF ADIPOSE TISSUE

The roles of white adipose tissue (WAT) in long-term energy storage, thermal insulation, and mechanical protection

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and of brown adipose tissue (BAT) in nonshivering thermogenesis have long been appreciated (1). The concept that adipose tissue could serve as an endocrine organ, however, was only shaped after the discovery of its two most characteristic secretory products, leptin and adiponectin.

Leptin, identified in 1994, is a protein primarily produced by mature adipocytes (2, 3). It signals through the long isoform of the leptin receptor (LEPRb) and exerts the majority of its effects acting on the brain (2, 4–6). Its circulating levels reflect the filling state of adipose tissue depots and thus relate directly to the body's long-term energy stores (7, 8). The lowering of circulating leptin levels due to a reduction in adipose tissue mass triggers behavioral, metabolic, and endocrine responses that aim at replenishing and preserving the body's fuel reserves (9, 10). Among these responses are an increase in energy intake, a decrease in energy expenditure, and a reduction or elimination of highly energy-demanding processes, such as reproduction and immune-related processes (9, 10).

Abbreviations: AII, angiotensin II; AA, arachidonic acid; ACE, angiotensin-converting enzyme; AChE, acetylcholine esterase; ACRP30/ADIPOQ, adiponectin; ACVR, activin receptor; ADA, adenosine deaminase; AdipoR, adiponectin receptor; 2-AG, 2-arachidonoylglycerol; AGK, acylglycerol kinase; AGPAT, acylglycerol-3-phosphate acyltransferase; AGT, angiotensinogen; AIM2, absent in melanoma; ALK, activin receptor-like kinase; AMPD, AMP deaminase; AMPK, AMP-dependent protein kinase; ANG, angiopoietin; ANGPTL, angiopoietin-like protein; ANTR, angiotensin receptor; APLN, apelin; APLNR, apelin receptor; APPL1, adaptor protein containing PH domain, PTB domain, and leucine zipper motif 1; ATGL, adipose tissue triglyceride lipase; ATX, autotaxin; BAT, brown adipose tissue; BMP, bone morphogenic protein; BMPR2, bone morphogenic protein receptor 2; C3a, cleaved complement factor 3 fragment a; C3aR, cleaved complement factor 3 fragment a receptor; C3b, cleaved complement factor 3 fragment b; C3bBb, complement factor 3 convertase; CAD2, carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase; CAPI, adenylyl cyclase-associated protein 1; CARD11, caspase recruitment domain-containing protein 11; CAV1, caveolin 1; CB, cannabinoid receptor; CCL2, chemokine (C-C motif) ligand 2; CCRL2, chemokine (C-C motif) receptor-like 2; CDase, ceramidase; CDCN, cleaved decorin; CERK, ceramide kinase; CERS, (dihydro)ceramide synthase; CERT, ceramide transfer protein; CF, complement factor; CG, cathepsin G; CMKLR1, chemokine-like receptor 1; COL6, collagen VI; COL6A3, collagen VI a3 chain; COX, cyclooxygenase; C1P, ceramide-1-phosphate; C1TP, ceramide-1-phosphate

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Adiponectin, originally described in 1995 as “Acrp30” with additional reports following in 1996, is a protein exclusively produced by mature adipocytes (11–15). It forms low molecular weight trimers, intermediate molecular weight hexamers, and high molecular weight dodeca- to octadecamers (16). It signals through adiponectin receptor (AdipoR)1 and AdipoR2 and binds to the nonsignaling interacting protein, T-cadherin (15). It is found in circulation and critically involved in many signaling events from the adipocyte to other cell types and tissues (11). Its circulating levels are closely tied to the functional integrity of adipose tissue and decline with obesity (17, 18). Adiponectin functions as a powerful insulin sensitizer and suppressor of cell death and inflammation, directly promoting anti-diabetic and anti-atherosclerotic outcomes (16). It acts on the liver to decrease gluconeogenesis, on skeletal muscle to increase fatty acid oxidation, and on pancreatic β -cells and

cardiac muscle cells as a key anti-lipotoxic agent, exerting many of these functions on the basis of its effects on sphingolipids (19–22).

Adiponectin and leptin are clearly the two most widely studied adipocyte-derived factors with nearly 50,000 combined citations in PubMed identified with the name of these two adipokines as key search terms. Many reviews cover them extensively, so we do not want to belabor these two adipokines in detail here. However, suffice it to say that much still remains to be learned about both of these factors. While they are unquestionably important, their detailed mechanisms of action at the level of their target cells and organs, the underlying systemic resistance to the effects of these hormones, and their mutual effects on each other are yet to be better understood.

ADIPOSE TISSUE-SECRETED SIGNALING MEDIATORS

Screening endeavors undertaken in the wake of the discovery of leptin and adiponectin have revealed a vast spectrum of adipose tissue-secreted signaling mediators (see **Fig. 1** and **Table 1** for a compilation of central factors, some of which are portrayed in detail below) (23). The large diversity of adipose tissue secretory products may partially stem from the complex cellular composition of the tissue, which includes lipid-laden adipocytes, adipose tissue stromal cell populations of different adipogenic potentials, various immune cell populations, endothelial cells, pericytes, and neurons (24). While the term “adipokine” is commonly used to refer to adipose tissue-derived proteins

transfer protein; CSPG4, chondroitin sulfate proteoglycan 4; CTGF, connective tissue growth factor; CTRP3, complement factor 1q/tumor necrosis factor-related protein 3; CYP, cytochrome P450 oxidase; DAG, diacylglycerol; DAGL, diacylglycerol lipase; DARC, Duffy antigen/chemokine receptor; DEGS, (dihydro)ceramide desaturase; DHODH, dihydroorotate dehydrogenase; 12, 13-diHOME, 12, 13-dihydroxy-9Z-octadecenoic acid; DNAJC1, DnaJ heat shock protein family member C1; DPP4, dipeptidyl peptidase 4; EGF, epidermal growth factor; EH, epoxid hydrolase; EP, prostaglandin E receptor; ErbB4, epidermal growth factor receptor 4; ETP, endotrophin; EV, extracellular vesicle; FABP, fatty acid binding protein; FAHFA, fatty acid esters of hydroxy fatty acids; FAP α , dipeptidyl peptidase fibroblast activation protein α ; FASL, FAS ligand; FAT, fatty acid tranlocase; FATP, fatty acid transport protein; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; GALE, UDP-glucose-4-epimerase; GCS, glucosylceramide synthase; GFPT1, glutamine/fructose-6-phosphate aminotransferase 1; GlcCDase, glucosylceramidase; GLP1, glucagon-like peptide 1; GP130, glycoprotein 130; GPAT, glycerol-3-phosphate acyltransferase; GZMA, granzyme A; HDAC, histone deacetylase; HSL, hormone-sensitive lipase; IL, interleukin; IL1R, interleukin 1 receptor; IL1RAP, interleukin 1 receptor accessory protein; IL2R γ , interleukin 2 receptor γ ; IL4R α , interleukin 4 receptor α ; IL6R, interleukin 6 receptor; IL10R, interleukin 10 receptor; IL13R α 1, interleukin 13 receptor α 1; ILV, intraluminal vesicle; INT1, intelectin 1; KDSR, 3-ketodihydrosphingosine reductase; KHK, ketohexokinase; KLK7, kallikrein 7; KRT1, keratin 1; LAMP1, lysosomal-associated matrix protein 1; LAMR, laminin receptor; LCN, lipocalin; LCN2R, lipocalin 2 receptor; LEP, leptin; LEPR, leptin receptor; LF, lactoferrin; LILRB2, leukocyte Ig-like receptor B2; LIMP2, lysosome membrane protein 2; lncRNA, long noncoding RNA; LPA, lysophosphatidic acid; LPAR, lysophosphatidic acid receptor; LRP, LDL receptor-related protein; LPS, lipopolysaccharide; LPP, lipid phosphate phosphatase; M6P/IGF2R, mannose-6-phosphate/insulin-like growth factor 2 receptor; MCP1, monocyte chemoattractant protein 1; miRNA, microRNA; MMP9, matrix metalloproteinase 9; MVB, multivesicular body; NAMPT, nicotinamide phosphoribosyltransferase/visfatin; NLR4, NLR family CARD domain-containing 4; NLRP, NLR family pyrin domain-containing; NMN, nicotinamide mononucleotide; NOX, NADPH oxidase; NRG, neuregulin; NRP1, neuropilin 1; OMT, omentin; 5NT, 5'-nucleotidase; OPT, osteoprotegerin; 5-PAHSA, palmitic acid ester of 5-hydroxystearic acid; 9-PAHSA, palmitic acid ester of 5-hydroxystearic acid; PAI1, plasminogen activator inhibitor 1; PAR2, protease-activated receptor; PEDF, pigment epithelium-derived factor; PEDFR, pigment epithelium-derived factor; PGE, prostaglandin E; PK, protein kinase; PL, phospholipase; PLEKHA8, plectstrin homology domain-containing family A member 8; PLXDC, plexin domain-containing protein; PP, protein phosphatase; PRTN3, proteinase 3; RBP4, retinol-binding protein 4; RBPR2, retinol-binding protein 4 receptor 2; RETN, resistin; RISC, RNA-induced silencing complex; ROR1, receptor tyrosine kinase-like orphan receptor 1; SAA3, serum amyloid 3; SCD1, stearoyl-CoA desaturase 1; SERPIN

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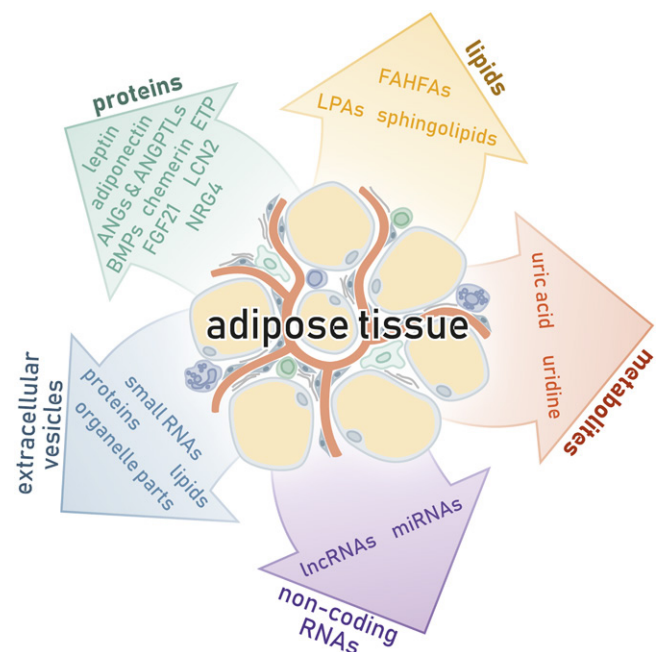


Fig. 1. Adipose tissue is a highly dynamic secretory organ that employs a plethora of adipokines (proteins, lipids, metabolites), non-coding RNAs, and EVs to relay information to other organs of the body.

TABLE 1. Collection of various adipose tissue-derived proteins, lipids, and metabolites with information on essential characteristics and several references for further reading

Class	Name (Abbreviation)	Characteristics	References
Proteins	Angiotensin II (AII)	<p>Extracellular, generated</p> <p>Generated from serine protease inhibitor A8/angiotensinogen (SERPINA8/AGT) by combined activity of renin or cathepsins and angiotensin-converting enzyme 1 (ACE1) or chymases</p> <p>Signals through G protein-coupled angiotensin receptor (ANGTR)1 and ANGTR2</p> <p>Regulates adipose tissue stromal cell adipogenesis</p> <p>Regulates adipose tissue thermogenesis</p> <p>Regulates blood pressure</p> <p>Regulates cardiac and vascular functions</p> <p>Regulates energy expenditure</p> <p>Regulates fluid homeostasis</p> <p>Regulates glucose tolerance and insulin sensitivity</p> <p>Regulates inflammation</p> <p>Regulates WAT browning</p> <p>May regulate body weight</p> <p>Increases adipocyte lipid uptake and lipogenesis</p> <p>Increases adipose tissue stromal cell proliferation</p> <p>Decreases adipocyte lipolysis</p>	(453–455, 456–467)
Proteins	Adiponectin (ACRP30/ADIPOQ)	<p>Extracellular, secreted</p> <p>May be intracellular</p> <p>Signals through AdipoR1 and AdipoR2</p> <p>Binds T-cadherin</p> <p>Improves glucose tolerance and insulin sensitivity</p> <p>Maintains cardiac and vascular functions</p> <p>Regulates angiogenesis</p> <p>Regulates ceramide metabolism</p> <p>May regulate cancer growth and metastasis</p> <p>Increases adipocyte and skeletal muscle cell glucose uptake</p> <p>Increases adipocyte lipogenesis</p> <p>Increases adipose tissue stromal cell adipogenesis</p> <p>Increases β-cell survival</p> <p>Increases energy expenditure</p> <p>Increases hepatocyte and skeletal muscle cell fatty acid oxidation</p> <p>May increase β-cell glucose-stimulated insulin secretion</p> <p>Decreases adipose tissue stromal cell proliferation</p> <p>Decreases atherosclerosis</p> <p>Decreases hepatocyte lipogenesis</p> <p>Decreases inflammation</p> <p>Decreases liver gluconeogenesis</p> <p>Decreases liver steatosis</p>	(15, 16, 22, 156, 321, 468–476)
Proteins	Angiopietin 1 (ANG1)	<p>Extracellular, secreted</p> <p>Signals through TIE2 and integrin α5β5</p> <p>Improves glucose tolerance</p> <p>Regulates atherosclerosis</p> <p>Regulates cancer growth and metastasis</p> <p>Regulates inflammation</p> <p>Regulates vascular development and functions</p> <p>Increases angiogenesis</p> <p>Increases lymphangiogenesis</p> <p>Increases wound healing</p> <p>Decreases body weight gain</p>	(27, 28, 30, 33, 477–486)
Proteins	Angiopietin 2 (ANG2)	<p>Extracellular, secreted</p> <p>Signals through TIE2, integrin α3β1, and integrin α5β1</p> <p>Improves glucose tolerance and lipid metabolism</p> <p>Regulates atherosclerosis</p> <p>Regulates cancer growth and metastasis</p> <p>Regulates inflammation</p> <p>Regulates vascular development and functions</p> <p>Increases angiogenesis</p> <p>Increases lymphangiogenesis</p> <p>Decreases fibrosis</p>	(27, 28, 31, 482, 483, 485, 487–494)
Proteins	Angiopietin-like protein 2 (ANGPTL2)	<p>Intracellular and extracellular, secreted</p> <p>Signals through LILRB2 and integrin α5β1</p> <p>Binds the G protein-coupled angiotensin receptor 1 (AGTR1) (intracellular)</p> <p>Further glucose intolerance and insulin resistance (chronic exposure)</p> <p>Regulates vascular functions</p>	(34, 35, 37, 38, 495–503)

TABLE 1. Continued.

Class	Name (Abbreviation)	Characteristics	References
		Regulates hematopoiesis Increases atherosclerosis (chronic exposure) Increases cancer development, growth, and metastasis Increases inflammation Increases tissue integrity (acute exposure) Decreases tissue integrity (chronic exposure)	
Proteins	Angiopoietin-like protein 4 (ANGPTL4)	Extracellular, secreted Inhibits LPL and pancreatic lipase Cleavage fragments may have signaling functions May further glucose intolerance and insulin resistance Regulates lipid trafficking May increase atherosclerosis May increase inflammation Decreases lipoprotein breakdown in adipose tissue during fasting	(39, 43, 44, 53, 54)
Proteins	Angiopoietin-like protein 8 (ANGPTL8)	Extracellular, secreted Acts in concert with ANGPTL3 Inhibits LPL and endothelial lipase May further insulin resistance Regulates lipid trafficking Decreases lipoprotein breakdown in nonadipose tissues during feeding	(39, 50–52)
Proteins	Apelin (APLN)	Extracellular, secreted Signals through G protein-coupled APLN receptor (APLNR) Improves glucose tolerance and insulin sensitivity Maintains cardiac functions Regulates fluid homeostasis May regulate bone mass Increases adipocyte and skeletal muscle cell glucose uptake Increases adipose tissue thermogenesis Increases angiogenesis Increases energy expenditure Increases lymphangiogenesis Increases skeletal muscle cell mitochondrial biogenesis and fatty acid oxidation Increases white adipocyte browning Decreases adipose tissue stromal cell adipogenesis Decreases blood pressure Decreases body weight May decrease adipocyte lipolysis May decrease inflammation May decrease liver steatosis	(504–506, 507–518)
Proteins	Autotaxin (ATX)	Extracellular, secreted Exhibits PLD activity Generates most extracellular LPAs	(229, 236, 240–245)
Proteins	Bone morphogenic protein 2 (BMP2)	Extracellular, secreted Signals through ALK3 or ALK6 in complex with BMPR2, ACVR2a, or ACVR2b Maintains bone functions Regulates embryonic development May regulate cancer development, growth, metastasis, and chemoresistance May skew adipogenesis toward either white or brown phenotype Increases adipose tissue stromal cell adipogenesis	(59, 65, 67, 519–526)
Proteins	Bone morphogenic protein 3B (BMP3B)	Extracellular, secreted Signals through ALK4 in complex with ACVR2a or ACVR2b Improves glucose tolerance and insulin sensitivity Maintains neural functions Regulates bone development Increases activity Increases BAT activity Increases energy expenditure Increases food intake Decreases adipose tissue stromal cell adipogenesis Decreases body weight gain May decrease bone mass	(65, 79, 80, 527–529)

TABLE 1. Continued.

Class	Name (Abbreviation)	Characteristics	References
Proteins	Bone morphogenic protein 4 (BMP4)	<p>Extracellular, secreted</p> <p>Signals through ALK3 or ALK6 in complex with BMPR2, ACVR2a, or ACVR2b</p> <p>Improves glucose tolerance and insulin sensitivity</p> <p>Regulates embryonic development</p> <p>May regulate cancer development, growth, metastasis, and chemoresistance</p> <p>May skew adipose tissue stromal cell adipogenesis toward either white or brown phenotype</p> <p>Increase adipose tissue stromal cell adipogenesis</p> <p>Increases angiogenesis</p> <p>Increases BAT whitening</p> <p>Increases energy expenditure</p> <p>Increases food intake</p> <p>Increases WAT browning</p> <p>Increases WAT thermogenesis</p> <p>Decreases body weight gain</p> <p>Decreases brown adipocyte lipolysis</p> <p>Decreases BAT thermogenesis</p>	(59, 65, 67, 68, 76–78, 530–534)
Proteins	Bone morphogenic protein 8B (BMP8B)	<p>Extracellular, secreted</p> <p>Signals through ALK2, ALK3, or ALK6 in complex with BMPR2, ACVR2a, or ACVR2b</p> <p>Maintains reproductive functions</p> <p>Increases adipocyte lipolysis</p> <p>Increases adipose tissue thermogenesis</p> <p>Increases angiogenesis</p> <p>Increases brain sympathetic output to adipose tissue</p> <p>Increases energy expenditure</p> <p>Increases WAT browning</p> <p>May increase food intake</p> <p>Decreases body weight gain</p>	(65, 81, 82, 535–537)
Proteins	Clq/TNF-related protein 3 (CTRP3)	<p>Extracellular, secreted</p> <p>May inhibit signaling of bacterial lipopolysaccharide (LPS) through toll-like receptor 4 (TLR4)</p> <p>May bind lysosomal-associated matrix protein 1 (LAMP1) and lysosome membrane protein 2 (LIMP2)</p> <p>May improve insulin sensitivity</p> <p>Maintains cardiac and reproductive functions</p> <p>May maintain vascular functions</p> <p>May regulate fibrosis</p> <p>May regulate liver size</p> <p>Increases angiogenesis</p> <p>Increases cardiac muscle cell survival</p> <p>May increase bone mass</p> <p>May increase skeletal muscle stromal cell proliferation</p> <p>Decreases adipose tissue stromal cell adipogenesis</p> <p>Decreases inflammation</p> <p>Decreases liver gluconeogenesis</p> <p>Decreases liver steatosis</p> <p>May decrease skeletal muscle stromal cell myogenesis</p>	(538, 539–550)
Proteins	Chemerin	<p>Extracellular, secreted</p> <p>Signals through G protein-coupled CMKLR1 and GPR1</p> <p>Binds chemokine (C-C motif) receptor-like 2 (CCRL2)</p> <p>Acts as immune cell chemoattractant</p> <p>Impairs vascular functions</p> <p>May regulate adipose tissue stromal cell adipogenesis</p> <p>May regulate glucose tolerance and insulin sensitivity</p> <p>Increases bone mass loss</p> <p>Increases skeletal muscle cell insulin resistance</p>	(92–94, 106, 109–116)
Proteins	Chemokine (C-C motif) ligand 2/monocyte chemoattractant protein 1 (CCL2/MCP1)	<p>Extracellular, secreted</p> <p>Signals through G protein-coupled chemokine (C-C motif) receptor 2 (CCR2)</p> <p>Binds Duffy antigen/chemokine receptor (DARC)</p> <p>May further glucose intolerance and insulin resistance</p> <p>Acts as immune cell chemoattractant</p> <p>Regulates immune cell functions</p> <p>May regulate body weight gain</p> <p>Increases angiogenesis</p>	(551, 552–563)

TABLE 1. Continued.

Class	Name (Abbreviation)	Characteristics	References
		Increases cancer growth and metastasis Increases inflammation Increases liver steatosis Increases wound healing Decreases adipocyte and skeletal muscle cell glucose uptake	
Proteins	Complement factor D/ adipsin (CFD)	Extracellular, secreted Cleaves complement factor B (CFB) in complex with complement factor 3b (C3b), yielding the C3 convertase (C3bBb) of the alternative pathway of complement activation Accelerates C3 cleavage, C3a and C3b generation, as well as C3a signaling through G protein-coupled C3a receptor (C3aR) Improves glucose tolerance Fulfills crucial functions in immune defense Increases adipose tissue stromal cell adipogenesis Increases β -cell glucose-stimulated insulin secretion Increases cancer stemness and growth	(564, 565, 566–573)
Proteins	Dipeptidyl peptidase 4 (DPP4)	Extracellular, membrane-bound and secreted Exhibits serine protease activity, processing a variety of other Proteins Binds and/or signals through adenosine deaminase (ADA), caveolin 1 (CAV1), caspase recruitment domain-containing protein 11 (CARD11), dipeptidyl peptidase fibroblast activation protein α (FAP α), and others (membrane-bound) Binds and/or signals through mannose-6-phosphate/insulin-like growth factor 2 receptor (M6P/IGF2R) and G protein-coupled protease-activated receptor 2 (PAR2) (secreted) Binds different extracellular matrix components Furtheres glucose intolerance and insulin resistance Alters gastrointestinal microbiome Impairs β -cell functions Impairs gastrointestinal functions May impair cardiac and vascular functions Regulates immune cell functions May regulate bone mass Increases adipose tissue stromal cell proliferation Increases atherosclerosis Increases body weight gain Increases cancer development Increases fibrosis Increases inflammation Increases liver steatosis Decreases adipocyte, skeletal muscle cell, and vascular smooth muscle cell insulin sensitivity Decreases adipose tissue thermogenesis Decreases energy expenditure Decreases white adipocyte browning	(574, 575, 576–587)
Proteins	endotrophin (ETP)	Extracellular, generated C-terminal cleavage fragment of COL6A3 Furtheres glucose intolerance and insulin resistance Increases angiogenesis Increases cancer growth, metastasis, and chemoresistance Increases fibrosis Increases inflammation Increases liver steatosis May increase adipose tissue stromal cell adipogenesis Decreases energy expenditure May decrease adipocyte lipolysis	(118, 123–129, 588)
Proteins	Fatty acid binding protein 4 (FABP4)	Intracellular and extracellular, secreted Binds diverse lipids Binds hormone-sensitive lipase (HSL), PPAR γ , and keratin 1 (KRT1) (intracellular) Furtheres glucose intolerance and insulin resistance May maintain brown adipocyte thermogenesis Regulates immune cell functions Regulates lipid trafficking Regulates lipolysis Increases angiogenesis Increases atherosclerosis Increases β -cell glucose-stimulated insulin secretion	(589, 590, 591–602)

TABLE 1. Continued.

Class	Name (Abbreviation)	Characteristics	References
		Increases cancer growth and metastasis Increases cardiac dysfunction Increases inflammation Increases liver steatosis Decreases adipose tissue stromal cell adipogenesis	
Proteins	Fibroblast growth factor 21 (FGF21)	Extracellular, secreted Signals through FGFR1c and FGFR3c in complex with β -klotho Binds FGFR4 in complex with β -klotho Improves glucose tolerance and insulin sensitivity (not in humans) Regulates circadian rhythm Regulates brain sympathetic output to different tissues Increases adipose tissue glucose and fatty acid uptake, mitochondrial activity, and thermogenesis Increases β -cell glucose-stimulated insulin secretion (acute exposure) Increases bone mass loss Increases energy expenditure Increases hepatocyte fatty acid oxidation Increases life span Increases liver gluconeogenesis (acute exposure) Decreases β -cell glucose-stimulated insulin secretion (chronic exposure) Decreases body weight Decreases bone mass Decreases circulating triglycerides Decreases food intake Decreases growth Decreases hepatocyte lipogenesis Decreases liver gluconeogenesis (chronic exposure) Decreases liver glycogenolysis Decreases sugar and alcohol intake	(130, 134–136, 140, 141, 147, 151–155, 158)
Proteins	Intelectin 1/omentin (INTL1/OMT)	Extracellular, secreted Scarcely expressed in mouse adipose tissue Binds bacterial glycans Binds lactoferrin (LF) May partake in bacterial surveillance Maintains bone mass Maintains cardiac and vascular functions Increases adipocyte insulin sensitivity Increases adipose tissue stromal cell proliferation and survival May increase cancer cell death Decreases angiogenesis Decreases atherosclerosis Decreases inflammation May decrease cancer growth	(603, 604–615)
Proteins	Interleukin 1 β (IL1 β)	Intracellular and extracellular, secreted or generated Generated from pro-IL1 β by the NLRP1, NLRP3, NLR family CARD domain-containing 4 (NLRC4), and absent in melanoma 2 (AIM2) inflammasomes Alternatively generated from pro-IL1 β by various proteases such as proteinase 3 (PRTN3), granzyme A (GZMA), cathepsin G (CG), elastases, chymases, or chymotrypsin Signals through IL1 receptor α (IL1R α) in complex with IL1 receptor accessory protein (IL1RAP) Binds IL1 receptor β (IL1R β) either alone or in complex with IL1RAP Binds soluble IL1R α Binds soluble IL1 β either alone or in complex with IL1RAP Further glucose intolerance and insulin resistance Impairs β -cell functions Regulates immune cell functions May regulate brain sympathetic output to different tissues Increases activity Increases adipocyte insulin resistance and lipolysis Increases β -cell death Increases body temperature Increases BAT activity Increases energy expenditure Increases inflammation Increases liver steatosis May increase adipose tissue stromal cell proliferation	(616–618, 619–630)

TABLE 1. Continued.

Class	Name (Abbreviation)	Characteristics	References
		Decreases adipocyte glucose uptake Decreases adipose tissue stromal cell adipogenesis Decreases body weight May decrease adipose tissue lipid uptake May decrease gastrointestinal lipid uptake	
Proteins	Interleukin 4 (IL4)	Extracellular, secreted Signals through IL4 receptor α (IL4R α) in complex with IL2 receptor γ (IL2R γ) or IL13 receptor $\alpha 1$ (IL13R $\alpha 1$) Binds soluble IL4R α Improves glucose tolerance and insulin sensitivity Skews adipose tissue stromal cell adipogenesis toward brown phenotype Regulates adipocyte lipolysis Regulates adipose tissue and skeletal muscle stromal cell adipogenesis Regulates body weight gain Regulates immune cell functions Regulates inflammation May regulate atherosclerosis Increases WAT browning May increase adipose tissue stromal cell proliferation May increase energy expenditure	(631, 632–643)
Proteins	Interleukin 6 (IL6)	Extracellular, secreted Signals through glycoprotein 130 (GP130) in complex with membrane-bound or soluble IL6 receptor (IL6R) Binds soluble GP130 and soluble IL6R Regulates α - and β -cell functions Regulates body weight Regulates glucose tolerance and insulin sensitivity Regulates immune cell functions Regulates inflammation Regulates liver steatosis Increases adipocyte lipolysis Increases body temperature Increases cancer development, growth, metastasis, and chemoresistance Increases energy expenditure Increases skeletal muscle cell fatty acid oxidation Increases WAT browning Decreases activity Decreases food intake	(198, 644–654)
Proteins	Interleukin 10 (IL10)	Extracellular, secreted Signals through IL10 receptor α (IL10R α) in complex with IL10 receptor β (IL10R β) Maintains cardiac functions Regulates glucose tolerance and insulin sensitivity Regulates immune cell functions Regulates liver steatosis May regulate body weight gain May increase cancer stemness, growth, and chemoresistance Decreases fibrosis Decreases inflammation May decrease adipose tissue stromal cell adipogenesis May decrease adipose tissue thermogenesis May decrease energy expenditure May decrease WAT browning	(558, 645, 650, 655, 656–664)
Proteins	Leptin (LEP)	Extracellular, secreted Signals through leptin receptor isoform b (LEPRb) Binds short and soluble leptin receptor isoforms (<i>e.g.</i> LEPRa) Informs brain on long-term energy stores Regulates body weight gain Regulates bone mass Regulates brain sympathetic output to different tissues Regulates food intake and energy expenditure Regulates glucose tolerance and insulin sensitivity Regulates immune cell functions Regulates reproduction May regulate body temperature May regulate hematopoiesis	(5, 9, 665, 666, 667–677)

TABLE 1. Continued.

Class	Name (Abbreviation)	Characteristics	References
		<p>Increases adipocyte lipolysis</p> <p>Increases adipocyte, hepatocyte, and skeletal muscle cell fatty acid oxidation</p> <p>Increases angiogenesis</p> <p>Increases BAT activity</p> <p>Increases inflammation</p> <p>Increases skeletal muscle cell glucose uptake</p> <p>Increases wound healing</p> <p>May increase adipose tissue stromal cell proliferation</p> <p>May increase blood pressure</p> <p>May increase WAT browning</p> <p>Decreases adipocyte glucose uptake</p> <p>Decreases adipocyte, hepatocyte, and skeletal muscle cell lipogenesis</p>	
Proteins	Lipocalin 2 (LCN2)	<p>Intracellular and extracellular, secreted</p> <p>Binds iron-chelating siderophores</p> <p>Binds LCN2 receptor and LRP2</p> <p>Regulates intracellular iron stores</p> <p>May regulate adipose tissue stromal cell adipogenesis</p> <p>May regulate adipocyte glucose uptake</p> <p>May regulate body weight gain</p> <p>May regulate BAT activity</p> <p>May regulate fibrosis</p> <p>May regulate glucose tolerance and insulin sensitivity</p> <p>May regulate liver steatosis</p> <p>May regulate vascular functions</p>	(167, 173 , 174, 178, 183–187, 190, 192–194)
Proteins	Neuregulin 4 (NRG4)	<p>Extracellular, membrane-bound and secreted</p> <p>Signals through ErbB4</p> <p>Improves glucose tolerance and insulin sensitivity</p> <p>Maintains neural functions</p> <p>May regulate immune functions</p> <p>Increases angiogenesis</p> <p>May increase BAT activity</p> <p>May increase hepatocyte survival</p> <p>Decreases body weight gain</p> <p>Decreases hepatocyte lipogenesis</p> <p>Decreases inflammation</p> <p>Decreases liver steatosis</p> <p>May decrease fibrosis</p>	(200 , 201, 203–205, 212, 213, 678, 679)
Proteins	Nicotinamide phosphoribosyltransferase/visfatin (NAMPT)	<p>Intracellular and extracellular, secreted</p> <p>Generates nicotinamide mononucleotide (NMN) for NAD synthesis (intracellular)</p> <p>Acts as immune cell chemoattractant (extracellular)</p> <p>Regulates body weight gain</p> <p>Regulates food intake</p> <p>Regulates glucose tolerance and insulin sensitivity</p> <p>Regulates inflammation</p> <p>Increases β-cell glucose-stimulated insulin secretion</p> <p>Increases brown adipocyte thermogenesis</p> <p>Increases cancer growth and chemoresistance</p> <p>Increases immune cell survival</p> <p>Increases physical activity</p> <p>Decreases fibrosis</p> <p>Decreases liver steatosis</p>	(680–682 , 683–694)
Proteins	Resistin (RETN)	<p>Extracellular, secreted</p> <p>May bind and/or signal through TLR4, cleaved decorin (cDCN), receptor tyrosine kinase-like orphan receptor 1 (ROR1), and adenylyl cyclase-associated protein 1 (CAP1)</p> <p>Expressed in mouse adipocytes, but scarcely expressed in human adipocytes</p> <p>May be expressed in human immune cells</p> <p>Further glucose intolerance and insulin resistance (not in humans)</p> <p>May regulate brain sympathetic output to different tissues</p> <p>Increases adipocyte lipolysis</p> <p>Increases angiogenesis</p> <p>Increases atherosclerosis</p> <p>Increases inflammation</p>	(695 , 696–707)

TABLE 1. Continued.

Class	Name (Abbreviation)	Characteristics	References
		<p>May increase adipose tissue stromal cell proliferation Decreases adipocyte and skeletal muscle cell glucose uptake Decreases adipocyte insulin sensitivity Decreases adipose tissue stromal cell adipogenesis</p>	
Proteins	Retinol-binding protein 4 (RBP4)	<p>Extracellular, secreted Binds retinol Binds and signals through stimulated by retinoic acid 6 (STRA6) Binds RBP4 receptor 2 (RBPR2) Signals through TLR4 May further glucose intolerance and insulin resistance Regulates adipose tissue stromal cell adipogenesis Regulates immune cell functions Increases cancer stemness and growth Increases inflammation May increase blood pressure May increase liver steatosis May increase mitochondrial dysfunction Decreases adipocyte insulin sensitivity</p>	(708, 709–720)
Proteins	Secreted frizzled-related protein 5 (SFRP5)	<p>Extracellular, secreted Inhibits wingless-related integration site (WNT)5a, WNT5b, and WNT11 May exhibit additional signaling capacities May bind different extracellular matrix components Maintains cardiac and vascular functions May regulate adipocyte insulin sensitivity May regulate adipocyte mitochondrial function May regulate adipose tissue stromal cell adipogenesis May regulate body weight gain May regulate glucose tolerance and insulin sensitivity Increases angiogenesis Decreases β-cell proliferation Decreases inflammation Decreases liver steatosis and fibrosis</p>	(721, 722–731)
Proteins	Serine protease inhibitor A12/vaspin (SERPINA12/VASP)	<p>Extracellular, secreted Inhibits kallikrein 7 (KLK7) May inhibit acetylcholine esterase (AChE) Signals through GRP78 in complex with DnaJ heat shock protein family member C1 (DNAJC1) and/or voltage-dependent anion channel (VDAC) Binds different extracellular matrix components Improves glucose tolerance and insulin sensitivity Maintains vascular functions Maintains β-cell functions Increases adipose tissue stromal cell adipogenesis Increases skeletal muscle cell glucose uptake and insulin sensitivity Increases β-cell glucose-stimulated insulin secretion May increase bone mass Decreases atherosclerosis Decreases food intake Decreases ER stress Decreases inflammation Decreases liver steatosis</p>	(732, 733–744)
Proteins	Serine protease inhibitor E1/plasminogen activator inhibitor 1 (SERPINE1/PAI1)	<p>Extracellular, secreted Inhibits tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA) Signals through LRP1 Binds and signals through uPA in complex with uPA receptor (uPAR) and LRP1 Binds vitronectin and inhibits its binding and signaling through integrin αVβ3, integrin αVβ5, and uPAR May further glucose intolerance and insulin resistance Maintains cellular senescence Regulates angiogenesis Regulates cancer growth and metastasis Regulates cell migration Regulates wound healing May regulate adipose tissue stromal cell adipogenesis May regulate bone mass May regulate ceramide metabolism</p>	(278, 745, 746, 747–757)

TABLE 1. Continued.

Class	Name (Abbreviation)	Characteristics	References
		Increases atherosclerosis May increase body weight gain May increase inflammation Decreases fibrinolysis Decreases hematopoiesis Decreases life span May decrease adipocyte glucose uptake	
Proteins	Serine protease inhibitor F1/pigment epithelium-derived factor (SERPIN1/PEDF)	Extracellular, secreted May be intracellular No known protease inhibitory functions Binds and/or signals through PEDF receptor/adipose tissue triglyceride lipase (PEDFR/ATGL), laminin receptor (LAMR), LRP6, and plexin domain-containing protein (PLXDC)1 and PLXDC2 Inhibits cell surface F1-ATPase May regulate PPAR α (intracellular) Binds different extracellular matrix components Maintains neuronal functions Regulates fibrosis Regulates immune cell functions Regulates inflammation May regulate glucose tolerance and insulin sensitivity Increases adipocyte, hepatocyte, and skeletal muscle cell lipolysis Increases cancer cell death and differentiation Decreases adipose tissue stromal cell adipogenesis Decreases angiogenesis Decreases cancer growth and metastasis Decreases liver steatosis	(758, 759, 760–771)
Proteins	Serum amyloid A3 (SAA3)	Extracellular, secreted Not expressed in humans Signals through TLR2 and TLR4 May bind to HDL Acts as immune cell chemoattractant May regulate immune cell functions May increase body weight gain May increase inflammation May increase liver steatosis	(772, 773–783)
Proteins	Transforming growth factor β (TGF β)	Extracellular, secreted Signals through ALK1, ALK2, ALK3, or ALK5 in complex with TGF β receptor 2 (TGFB β R2) Binds connective tissue growth factor (CTGF) Binds different extracellular matrix components Furtheres glucose intolerance and insulin resistance Increases adipose tissue stromal cell proliferation Increases fibrosis Increases inflammation Increases liver steatosis Decreases adipocyte fatty acid oxidation Decreases adipose tissue stromal cell adipogenesis Decreases adipose tissue thermogenesis	(784–786, 787–793)
Proteins	TNF ligand superfamily member 10/TNF-related apoptosis-inducing ligand (TNFSF10/TRAIL)	Extracellular, membrane-bound and secreted Signals through TRAIL receptor (TRAILR)1 and TRAILR2 Binds TRAILR3, TRAILR4, and osteoprotegerin (OPG) Improves glucose tolerance and insulin sensitivity Regulates adipocyte metabolism Regulates immune cell functions Increases adipose tissue stromal cell proliferation Increases adipose tissue stromal cell and adipocyte inflammation Decreases adipose tissue stromal cell adipogenesis Decreases atherosclerosis Decreases body weight Decreases liver steatosis Decreases systemic inflammation	(794, 795, 796–807)
Proteins	TNF ligand superfamily member 2/TNF α (TNFSF2/TNFA)	Extracellular, membrane-bound and secreted Signals through TNF receptor (TNFR)1 and TNFR2 Furtheres glucose intolerance and insulin resistance	(802, 808–810, 811–821)

TABLE 1. Continued.

Class	Name (Abbreviation)	Characteristics	References
		Regulates immune cell functions Increases adipocyte lipolysis Increases adipose tissue stromal cell proliferation Increases atherosclerosis Increases body weight loss Increases ER stress Increases inflammation Increases mitochondrial dysfunction Decreases adipose tissue stromal cell adipogenesis Decreases adipose tissue thermogenesis	
Proteins	TNF ligand superfamily member 6/Fas ligand (TNFSF6/FASL)	Extracellular, membrane-bound and secreted Signals through FAS Furtheres glucose intolerance and insulin resistance Regulates immune cell functions Increases adipocyte insulin resistance Increases adipose tissue stromal cell proliferation Increases body weight Increases brown adipocyte lipolysis Increases inflammation Increases liver steatosis Increases mitochondrial dysfunction	(802, 822, 823–827)
Proteins	Vascular endothelial growth factor A (VEGFA)	Extracellular, secreted Maybe intracellular Signals through VEGF receptor (VEGFR)1 and VEGFR2 May bind to neuropilin 1 (NRP1) May bind different extracellular matrix components Regulates glucose tolerance and insulin sensitivity Regulates vascular permeability May regulate adipose tissue stromal cell osteogenesis and adipogenesis Increases adipose tissue stromal cell proliferation Increases angiogenesis Increases brown adipocyte mitochondrial function and survival Increases energy expenditure Increases vasculogenesis Increases white adipocyte browning Increases white adipocyte lipolysis Increases WAT sympathetic innervation Increases WAT vascularization May increase inflammation	(828, 829, 830–841)
Proteins	Vascular endothelial growth factor D (VEGFD)	Extracellular, secreted Signals through VEGFR2 and VEGFR3 Acts as immune cell chemoattractant Regulates glucose tolerance and insulin sensitivity Regulates lymphangiogenesis Regulates WAT inflammation May regulate liver steatosis May regulate vascular permeability May increase angiogenesis May increase vasculogenesis	(828, 829, 842–845)
Proteins	Xanthine oxidoreductase (XOR)	Intracellular and extracellular, secreted Exhibits dehydrogenase and oxidase activities Interconvertible dehydrogenase and oxidase forms (XDH and XO) Generates uric acid Can generate reactive oxygen and nitrogen species Regulates adipose tissue stromal cell adipogenesis	(371, 372, 376, 379, 384, 403, 404, 405, 409–414)
Lipids	12,13-Dihydroxy-9Z-octadecenoic acid (12,13-diHOME)	Intracellular and extracellular Generated from linoleic acid by combined activity of cytochrome P450 oxidases (CYPs) and epoxide hydrolase (EH)1-4 May act as peroxisome PPAR γ ligand (intracellular) Regulates immune cell functions Increases brown adipocyte and skeletal muscle cell fatty acid uptake and oxidation Increases BAT and skeletal muscle lipid uptake Decreases atherosclerosis	(846–849)

TABLE 1. Continued.

Class	Name (Abbreviation)	Characteristics	References
Lipids	2-Arachidonoylglycerol (2-AG)	Intracellular and extracellular Generated from arachidonic acid (AA)-containing diacylglycerols (DAG) by DAG lipases (DAGL) Signals through G protein-coupled cannabinoid receptor (CB)1 and CB2, GPR55, and transient receptor potential cation channel subfamily V member 1 (TRPV1) Binds to FABP3, FABP5, and FABP7 May act as PPAR α and/or PPAR γ ligand (intracellular) Acts as immune cell chemoattractant Regulates brain sympathetic output to different tissues Regulates glucose tolerance and insulin sensitivity Regulates immune cell functions Regulates social and food reward Increases adipocyte insulin sensitivity and glucose uptake Increases adipose tissue stromal cell adipogenesis Increases atherosclerosis Increases β -cell glucose-stimulated insulin secretion Increases body weight Increases food intake Increases gastrointestinal energy absorption Increases liver steatosis Decreases adipose tissue thermogenesis Decreases energy expenditure Decreases mitochondrial biogenesis Decreases white adipocyte browning Decreases WAT, liver, and skeletal muscle glycogenesis	(850, 851, 852–863)
Lipids	4-Hydroxynonenal (4-HNE)	Intracellular and extracellular Generated from unsaturated lipid acyl chains by reactive oxygen species-mediated peroxidation followed by nonenzymatic decomposition Strong electrophile that covalently modifies lipids, Proteins, and nucleic acids May further glucose intolerance and insulin resistance Increases apoptosis Increases autophagy Increases body weight gain Increases ER stress Increases mitochondrial dysfunction Increases mitophagy Increases oxidative stress Decrease β -cell glucose-stimulated insulin secretion Decreases adipose tissue and skeletal muscle insulin sensitivity Decreases adipose tissue stromal cell adipogenesis Decreases adipose tissue stromal cell proliferation	(864–866, 867–878)
Lipids	Ceramide-1-phosphates (C1Ps)	Intracellular and extracellular Generated from ceramides by CERK Stimulate AA-releasing cytosolic PLA2 α Inhibit TNF-releasing TACE Inhibit acid SMase Bind to C1P transfer protein (C1PTP) Further glucose intolerance Regulate immune cell functions Regulate inflammation Increase body weight gain Increase inflammation	(251, 296, 345, 879–886)
Lipids	Ceramides	Intracellular and extracellular Generated by multiple mechanisms, de novo synthesis and salvage Stimulate PP1, PP2A, and PP2C Stimulate PKC ζ Stimulate the NLRP3 inflammasome Bind ceramide transfer protein (CERT) Further glucose intolerance and insulin resistance Increase cancer development Increase ER stress Increase inflammation Increase liver steatosis Increase mitochondrial dysfunction Increase cell death (various cell types) Decrease adipose tissue stromal cell adipogenesis	(251, 256, 261, 264, 268, 273, 290, 296, 297, 299, 301–304, 316)

TABLE 1. Continued.

Class	Name (Abbreviation)	Characteristics	References
		Decrease adipose tissue thermogenesis Decrease β -cell glucose-stimulated insulin secretion Decrease insulin sensitivity (various cell types) Decrease WAT browning	
Lipids	<i>cis</i> -Palmitoleic acid	Intracellular and extracellular Generated from palmitate by stearoyl-CoA desaturase 1 (SCD1) Alternatively generated from stearate or <i>cis</i> -oleate by desaturation and/or chain shortening Inhibits SCD1 Improves glucose tolerance and insulin sensitivity Maintains cardiac and vascular functions May regulate liver steatosis Increases β -cell proliferation and glucose-stimulated insulin secretion Increases hepatocyte and skeletal muscle cell insulin sensitivity Increases hepatocyte, skeletal muscle cell, and β -cell survival May increase adipocyte and skeletal muscle cell glucose uptake May increase adipose tissue stromal cell proliferation and survival May increase cancer growth Decreases atherosclerosis Decreases inflammation	(311, 887–889, 890–900)
Lipids	Glucosylceramides	Intracellular and extracellular Generated from ceramides by GCS Bind pleckstrin homology domain-containing family A member 8 (PLEKHA8) Substrate for complex glycosphingolipid synthesis May further glucose intolerance and insulin resistance May increase fibrosis May increase inflammation	(251, 337–344)
Lipids	Lysophosphatidic acids (LPAs)	Intracellular and extracellular Generated by multiple mechanisms Signal through G protein-coupled LPAR1–6 (extracellular) May act as PPAR γ ligands (intracellular) Intermediates of glycerolipid synthesis Further glucose intolerance and insulin resistance Increase adipose tissue stromal cell proliferation Decrease adipose tissue stromal cell adipogenesis Decrease β -cell glucose-stimulated insulin secretion	(223, 224, 226, 227, 229–231, 233, 236, 238, 239)
Lipids	Palmitic acid	Intracellular and extracellular Taken up from ingested food (exogenous) Also generated by multiple mechanisms (endogenous) Signals through GPR40 Signals through TLR4 (high exposure) Also stimulates different PKC isoforms (e.g., PKC ϵ and PKC θ) (likely indirect, high exposure) Also stimulates PKR (likely indirect, high exposure) Also stimulates the NLRP3 inflammasome (likely indirect, high exposure) Binds diverse FABPs, fatty acid transport proteins (FATPs), and fatty acid translocase (FAT) Affects lipid membrane properties (e.g., fluidity and permeability) Prime substrate for ceramide synthesis Substrate for energy generation Substrate for structural component and signaling mediator synthesis Regulates glucose tolerance and insulin sensitivity Regulates immune cell functions May regulate adipose tissue stromal cell proliferation and adipogenesis May regulate atherosclerosis May regulate body weight gain May regulate energy expenditure May regulate food intake May regulate liver steatosis Increases β -cell glucose-stimulated insulin secretion (low exposure) Increases cell death (various cell types, high exposure) Increases ceramide generation (high exposure) Increases enteroendocrine cell hormone release (low exposure) Increases ER stress (high exposure) Increases inflammation (high exposure) Increases mitochondrial dysfunction (high exposure) Increases oxidative stress (high exposure)	(628, 901–903, 904–914)

TABLE 1. Continued.

Class	Name (Abbreviation)	Characteristics	References
Lipids	Palmitic acid ester of 5-hydroxystearic acid (5-PAHSA)	Intracellular and extracellular Produced by unknown mechanisms May signal through GPR40 and GPR120 May improve glucose tolerance and insulin sensitivity May increase adipose tissue stromal cell adipogenesis May increase adipocyte glucose uptake May increase β -cell glucose-stimulated insulin secretion May increase L-cell GLP1 secretion May decrease inflammation	(215–221, 222)
Lipids	Palmitic acid ester of 9-hydroxystearic acid (9-PAHSA)	Intracellular and extracellular Produced by unknown mechanisms May signal through GPR40 and GPR120 May improve glucose tolerance and insulin sensitivity May increase adipose tissue stromal cell adipogenesis May increase adipocyte glucose uptake May increase β -cell glucose-stimulated insulin secretion May increase L-cell GLP1 secretion May decrease inflammation	(215–221, 222)
Lipids	Prostaglandin E2 (PGE2)	Intracellular and extracellular Generated from AA by combined activity of cyclooxygenase (COX)1 and COX2 and PGE synthase (PGES)1, PGES2, or PGES3 Signals through G protein-coupled PGE receptor (EP)1-4 May improve glucose tolerance and insulin sensitivity Regulates atherosclerosis Regulates fibrosis Regulates immune cell functions Regulates inflammation Regulates liver steatosis May regulate lipid trafficking Skews adipose tissue stromal cell adipogenesis toward brown phenotype May increase activity May increase BAT activity May increase WAT browning Decreases adipose tissue stromal cell adipogenesis Decreases white adipocyte lipolysis May decrease body weight gain May decrease food intake	(915 , 916–927)
Lipids	Sphingomyelins	Intracellular and extracellular Generated from ceramides by SMSs May regulate adipose tissue development May regulate glucose tolerance and insulin sensitivity May regulate liver steatosis May regulate mitochondrial functions	(251 , 262, 289, 331–334, 335 , 336)
Lipids	Sphingosine-1-phosphate (S1P)	Intracellular and extracellular Generated from sphingosine by sphingosine kinases Signals through G protein-coupled S1PR1–5 Also stimulates CIAP2 Also stimulates TRAF2 Also inhibits HDAC1 and HDAC2 May regulate glucose tolerance and insulin sensitivity May regulate vascular functions May regulate liver steatosis May increase adipose tissue stromal cell proliferation May increase β -cell glucose-stimulated insulin secretion May increase hepatocyte and skeletal muscle cell glucose uptake May increase hepatocyte and β -cell survival May increase hepatocyte lipogenesis May increase inflammation May decrease adipose tissue stromal cell adipogenesis	(251 , 276, 296 , 348–350, 353, 355–357, 360, 361, 363, 365)
Metabolites	Uric acid	Intracellular and extracellular Product of purine base degradation Acts as anti-oxidant (extracellular) Acts as pro-oxidant (intracellular) Stimulates the NLRP3 inflammasome (intracellular) Stimulates NOX (intracellular) Furtheres glucose intolerance and insulin resistance Impairs vascular and kidney functions Increases blood pressure	(371 , 372 , 376, 379, 385, 393, 395–402)

TABLE 1. Continued.

Class	Name (Abbreviation)	Characteristics	References
		Increases inflammation Increases liver steatosis Increases mitochondrial dysfunction	
Metabolites	Uridine	Intracellular and extracellular May require metabolism for signaling Substrate for RNA and DNA synthesis Substrate for glycogen deposition Substrate for protein and lipid glycosylation Improves glucose tolerance (acute exposure) May regulate glucose tolerance and insulin sensitivity (chronic exposure) Essential for fasting-induced decrease in body temperature (acute exposure) Increases body weight gain (chronic exposure) May increase body temperature (low concentration exposure) May increase cancer development (chronic exposure) May increase liver steatosis (chronic exposure) Decreases body temperature (high concentration) Decreases energy expenditure (acute exposure)	(418, 419, 421 , 424–429)

References in bold indicate reviews.

exclusively, it has occasionally been used to refer to the entirety of signaling mediators secreted by adipose tissue, and it is this latter definition that will be applied here.

Adipose tissue forms circumscribed depots in the body that differ in their cellular composition and character (24, 25). Whereas dermal, subcutaneous, and visceral depots exist in both humans and mice, the occurrence of depots in the bone marrow, skeletal muscle, and pancreas depends on several factors, including species, sex, age, and nutritional state (25). While the cellular differences between these adipose tissue depots immediately suggest quantitatively and possibly even qualitatively distinct patterns of adipokine secretion, thorough assessments of depot-specific production have been carried out for only few adipose tissue-derived factors.

Adipose tissue is highly dynamic and able to respond to changes in nutritional state (e.g., during feeding or fasting or with obesity) with acute and chronic adjustments in both its metabolism and cellularity (26). These metabolic and cellular adjustments are usually accompanied by pronounced shifts in adipokine secretion with immediate effects on systemic homeostasis (26). With obesity, such shifts in adipokine secretion may directly contribute to the development of insulin resistance, hepatic steatosis, type 2 diabetes, and cardiovascular disease (26).

PROTEINS

Angiopoietins and angiopoietin-like proteins

The family of angiopoietins (ANGs) and ANG-like proteins (ANGPTLs) consists of several structurally similar but functionally distinct proteins.

ANG1 and ANG2 regulate angiogenesis and vascular function and exert their effects by signaling through the tyrosine kinase with Ig and epidermal growth factor (EGF) homology domains 2 (TIE2) expressed by endothelial cells and certain populations of monocytes and macrophages, as well as integrins $\alpha\beta 5$, $\alpha 3\beta 1$, and $\alpha 3\beta 1$ expressed by a

variety of cells (27, 28). Obesity and fasting decrease ANG1 and ANG2 expression in WAT, while cold exposure increases ANG2 expression in BAT (29–31). Overexpression of ANG1 from injected plasmid DNA slows the body weight gain in obese leptin-deficient *ob/ob* mice, whereas overexpression of a stabilized ANG1 variant from a viral vector reduces diabetic nephropathy and improves glucose tolerance in obese leptin receptor-deficient *db/db* mice (30, 32, 33). Inducing adipocyte-specific overexpression of ANG2 in mice elicits increased WAT angiogenesis and an anti-inflammatory secretion profile, offering protection from high-fat diet-induced obesity and improving glucose and lipid metabolism (31). Treating mice with an ANG2-neutralizing antibody conversely decreases WAT angiogenesis, increases WAT inflammation and fibrosis, and results in metabolic deterioration (31). ANG1 and ANG2 thus appear to have beneficial effects on systemic metabolism.

ANGPTL2 also affects vascular function, but does so in a TIE2-independent fashion by engaging integrin $\alpha 5\beta 1$ and the leukocyte Ig-like receptor B2 (LILRB2) (34). ANGPTL2 expression in WAT and BAT is increased with hypoxia, ER stress, and obesity (35, 36). Its circulating levels correlate positively with adiposity and markers of inflammation and insulin resistance (35, 36). In mice, endothelial cell-specific overexpression of ANGPTL2 results in vascular dysfunction and facilitates vascular inflammation and atherosclerosis when combined with ApoE deficiency, whereas adipocyte-specific overexpression causes increased WAT inflammation, glucose intolerance, and insulin resistance (35, 37). ANGPTL2-deficient mice, in turn, exhibit improved insulin sensitivity and are protected from high-fat diet-induced metabolic and vascular deterioration (35, 37, 38). ANGPTL2 thus has detrimental effects on systemic metabolism, at least under the conditions tested.

ANGPTL3, ANGPTL4, and ANGPTL8 regulate triglyceride trafficking and metabolism (39). ANGPTL3 and ANGPTL8 act in concert to inhibit LPL and endothelial lipase, while ANGPTL4 acts alone to inhibit LPL and pancreatic lipase (39–41). ANGPTL3 and ANGPTL4 also undergo

proteolytic cleavage, generating C-terminal fragments that may exert alternative signaling functions (42–44). ANGPTL3 is primarily produced by the liver, ANGPTL4 primarily by WAT and BAT, and ANGPTL8 by WAT and BAT as well as the liver (45–47). Fasting increases ANGPTL4 expression in WAT and BAT, suppressing local LPL activity and thus hydrolytic release of fatty acids from triglyceride-rich lipoproteins, redirecting them to other energy-demanding tissues (47). Conversely, upon feeding, ANGPTL3 and ANGPTL8 mediate the suppression of lipases in energy-demanding tissues, allowing white and brown adipocytes to replenish their lipid reserves (39). ANGPTL3- and ANGPTL8-deficient mice display improved triglyceride clearance, but no or only slight improvements in insulin sensitivity, even upon high-fat challenge (48–52). In line with its role in redirecting triglyceride-rich lipoproteins from WAT and BAT to other organs, mice lacking ANGPTL4 exhibit increased fatty acid uptake into WAT during fasting (47). Adipocyte-specific deletion of ANGPTL4 in mice improves triglyceride clearance and glucose tolerance with increased triglyceride uptake into WAT, BAT, and liver (53). In the setting of a high-fat diet, adipocyte-specific deletion of ANGPTL4 improves glucose tolerance and insulin sensitivity, while curbing inflammation and atherosclerosis (53). Specific overexpression of ANGPTL4 in adipocytes, in turn, causes dyslipidemia and exacerbates the detrimental metabolic effects of a high-fat diet (54). Similarly, humans harboring loss-of-function alleles of *ANGPTL3*, *ANGPTL4*, or *ANGPTL8* display decreased triglyceride levels and increased triglyceride clearance (55–58).

Bone morphogenic proteins

The bone morphogenic protein (BMP) family belongs to the transforming growth factor β (TGF β) superfamily, and its members have central functions in the development and maintenance of many tissues (59). They signal through complexes of one of seven different type I receptors, the activin receptor-like kinases 1–7 (ALK1–7), with one of three different type II receptors, the BMP receptor 2 (BMPR2) and the activin receptor (ACVR)2a and ACVR2b, that are expressed by a wide range of cells (59). In mice, the specific deletion of ALK3 in brown adipocyte progenitors impairs BAT formation, while its deletion in mature white adipocytes alleviates high-fat diet-induced WAT inflammation and insulin resistance (60, 61).

BMP2 and BMP4 regulate the commitment and differentiation of adipose tissue stromal cells and the maintenance of adipocytes. They signal through ALK3 or ALK6 in conjunction with BMPR2, ACVR2a, or ACVR2b (62–65). BMP2 and BMP4 are expressed in WAT and BAT, and the expression of BMP4 correlates positively with adiposity and adipocyte size (66–68). Both promote the commitment of adipose tissue stromal cells to the adipogenic lineage, which involves the repression of the anti-adipogenic zinc finger protein 521 (ZFP521) and activation of the pro-adipogenic zinc finger protein 423 (ZFP423) (69–73). They also appear to skew adipogenesis toward either a white or brown adipocyte phenotype, although in vitro experiments have been unsuccessful to determine what combination of factors (e.g.,

dose, time, and duration of treatment, or cell type) determines the exact outcome (66, 68, 74–77). Adipocyte-specific overexpression of BMP4 in mice results in decreased WAT and increased BAT weights, increased WAT angiogenesis and browning, BAT whitening, yet overall increased energy expenditure and improved glucose tolerance and insulin sensitivity (66, 78). Intriguingly, the specific deletion of BMP4 in adipocytes causes increased WAT and BAT weights, decreased WAT angiogenesis, and BAT whitening, as well as disturbed glucose tolerance and insulin sensitivity (66, 78). Similar effects are observed using viral vectors to overexpress BMP4 either systemically or locally in BAT (68, 77).

Another member of the BMP family that is implicated in the regulation of adipose tissue stromal cell adipogenic differentiation is BMP3B. It signals through ALK4 and ACVR2a or ACVR2b, and its production in WAT and BAT increases with obesity (65, 79). Suppressing BMP3B expression in adipose tissue stromal cells increases their adipogenic potential, while overexpressing BMP3B decreases it (79). On a high-fat diet, mice with adipocyte-specific overexpression of BMP3B display decreased WAT weight and adipocyte size, increased BAT thermogenic marker expression, food consumption, activity, and energy expenditure, and improved glucose tolerance and insulin sensitivity (80).

BMP8B is a BMP family member that may particularly regulate BAT function. It signals through a combination of ALK2, ALK3, or ALK6 and BMPR2, ACVR2a, or ACVR2b (65). It is expressed in WAT and BAT, and its expression in BAT is decreased during fasting and increased during feeding and with obesity, as well as upon cold exposure (67, 81). Mice lacking BMP8B display decreased body temperature and impaired cold-induced thermogenesis with reduced oxygen consumption and BAT sympathetic input (81). On a high-fat diet, these mice furthermore exhibit increased body weight gain, but also decreased food intake (81). Apart from directly acting on adipocytes to increase their lipolytic capacity, BMP8B augments the vessel density and neuronal innervation of adipose tissue and prompts the brain to increase the sympathetic output to it (81, 82).

BMP2, BMP3B, BMP4, and BMP8B thus appear to have favorable effects on metabolic homeostasis.

While BMP7 has also been described to have a role in the regulation of BAT formation and function, it has, to our knowledge, never been unambiguously established that it is produced by adipose tissue (67, 74, 76, 83–86).

Chemerin

Chemerin acts as a chemokine and is produced as a pro-protein that undergoes stepwise C-terminal proteolytic processing to generate multiple variants differing greatly in their respective activity (87–90). Chemerin signals through the chemokine-like receptor 1 (CMKLR1) and the G protein-coupled receptor (GPR)1 and also binds to the non-signaling C-C chemokine receptor-like 2 (CCRL2), all of which are expressed by a variety of cells (91–94). It circulates mostly in its pro-form, and its total circulating levels correlate positively with age, adiposity, triglycerides, and blood pressure (95–102). Apart from its role in immune cell chemotaxis, in vitro experiments implicate chemerin to act on

endothelial and vascular smooth muscle cells, promoting vascular dysfunction on skeletal muscle cells fueling insulin resistance and on osteoclasts instigating bone resorption (98, 103–108). A direct action of chemerin on adipose tissue stromal cell adipogenic differentiation or on adipocyte function has remained controversial though (91, 109–111). Chemerin-deficient mice display increased skeletal muscle but decreased WAT insulin sensitivity, as well as mild glucose intolerance; whereas mice overexpressing chemerin specifically in the liver exhibit improved glucose tolerance (112). In contrast, treatment with chemerin exacerbates the obesity-associated glucose intolerance in *ob/ob* mice, *db/db* mice, and mice fed a high-fat diet (113). The deletion of CMKLR1 was reported to either not affect or, in another study, decrease glucose tolerance in mice on regular or high-fat diets, while the deletion of GPR1 decreases glucose tolerance in mice on a high-fat diet (110, 111, 114–116). More advanced mouse models may need to be used to clarify the effects of this signaling axis on metabolic homeostasis, such as overexpression or deletion of chemerin or its receptors in a time- and cell type-controlled manner. Such approaches are essential to effectively deconvolute developmental effects from effects on mature cells and tissues (38, 117).

Endotrophin

Endotrophin (ETP) constitutes a C-terminal cleavage fragment of the collagen VI $\alpha 3$ chain (COL6A3) that is released from mature collagen VI (COL6) following secretion (118). While diverse integrins and the chondroitin sulfate proteoglycan 4 (CSPG4) may act as receptors for COL6, a specific receptor for ETP has not yet been identified (118, 119). ETP levels are strongly associated with adipose tissue dysfunction. Similarly, COL6A3 expression in WAT correlates positively with adiposity and with markers of WAT inflammation and is decreased upon anti-diabetic thiazolidinedione treatment (120, 121). Following this pattern, the circulating ETP levels correlate positively with adiposity and markers of insulin resistance, and actually predict the therapeutic response to thiazolidinedione treatment (121). Adipocytes have the unique ability to support the growth of breast cancer cells not only *in vitro* but also *in vivo* in the local microenvironment of the mammary gland. COL6A3-derived ETP was singled out as one of the key adipokines involved in this process (122, 123). Studies in the mouse mammary tumor virus/polyomavirus middle T antigen (MMTV-PyMT) model of breast cancer highlighted ETP as a major driver of tumor growth, metastasis formation, and chemoresistance (123–125). In MMTV-PyMT mice, functional elimination of COL6 or treatment with an ETP-neutralizing antibody or with thiazolidinediones decreases tumor growth, metastasis, and chemoresistance (123–125). Mammary epithelial cell-specific overexpression of ETP, in turn, increases tumor inflammation, angiogenesis, and fibrosis, while it also decreases tumor hypoxia and promotes tumor metastasis by initiating epithelial-mesenchymal transition (123–125). Intact TGF β signaling is required for ETP's effects on tumor epithelial-mesenchymal transition and is partially required for its

effect on tumor fibrosis (124). It is, however, not required for its effects on inflammation and angiogenesis (124). The negative impact of ETP on tumor progression and chemoresistance is in fact highly relevant for human breast cancer as well (126). ETP has more recently also been demonstrated to aggravate the inflammatory and fibrotic consequences of liver damage and advance the development of liver cancer (127). COL6A3 and ETP, moreover, act as drivers of metabolic deterioration in obesity (128). COL6-deficient *ob/ob* mice and mice fed a high-fat diet exhibit increased WAT adipocyte size and decreased WAT inflammation and liver steatosis, as well as improved triglyceride clearance, glucose tolerance, and insulin sensitivity (128). Consistent with ETP being the key constituent of COL6, adipocyte-specific overexpression of ETP aggravates WAT inflammation and fibrosis, enhances dyslipidemia, liver steatosis, and impaired glucose tolerance and insulin sensitivity in mice fed a high-fat diet, while antibody neutralization of ETP results in the opposite effects (129). ETP thus exerts unfavorable effects on systemic metabolism.

Fibroblast growth factor 21

Fibroblast growth factor (FGF) 15/19, FGF21, and FGF23 form the endocrine subgroup of the FGF family (130). They generally have a low heparin- and heparan sulfate-binding capacity, allowing them to leave their place of production and enter circulation (130). FGF21 signals through complexes of FGF receptor (FGFR)1c or FGFR3c with β -klotho as a coreceptor, and binds to, but does not signal through, complexes of FGFR4 with β -klotho (131–133). FGF21 is primarily produced by the liver, but is also expressed in WAT, BAT, and the brain, and possibly skeletal muscle, cardiac muscle, and the pancreas [reviewed in (130)]. Under most conditions, circulating FGF21 primarily derives from the liver where its production increases upon fasting and exercise as well as with high carbohydrate or low protein intake (130). Possible extra-hepatic contributions to the circulating FGF21 levels may occur from BAT upon cold exposure or from skeletal and cardiac muscle upon disturbances of cellular metabolism or mitochondrial function (130). The exact contributions of WAT to circulating pools of FGF21 remain to be clarified. Circulating FGF21 levels are increased with obesity, lipodystrophy, and pancreatitis (130). FGF21 has been extensively studied in mice, monkeys, and humans. Its main effects may relate to decreasing body weight (134–139), sugar and alcohol consumption (140, 141), circulating triglycerides and insulin (134–139), and bone mass (139, 142, 143), while in parallel increasing WAT and BAT glucose uptake, mitochondrial activity, and thermogenesis (136, 144–154) as well as circulating adiponectin (138, 139, 155–157). FGF21 also decreases circulating glucose and improves glucose tolerance and insulin sensitivity in mice (134–136), but may not do so in non-human primates and humans (137–139). Effects on dyslipidemia seem to be preserved in all cases. While FGF21 may exert many of its effects by direct action on the brain, local effects on WAT and BAT nonetheless occur and could be physiologically relevant (140, 141, 147, 150, 158–161). Direct FGF21 signaling was reported to increase white and

brown adipocyte glucose uptake (134, 153, 162, 163), thermogenic marker expression (144, 146, 150), and adiponectin secretion (153, 155–157), decrease white adipocyte lipolysis (153, 164), and promote white adipocyte-initiated cold-induced WAT beiging (154), partly through autocrine and paracrine effects of adipocyte-produced FGF21 (146, 154, 157). Other studies failed to demonstrate such effects of direct FGF21 signaling or adipocyte-produced FGF21 (148, 153, 165, 166). Adipocyte-specific deletions of either FGFR1 or β -klotho abolish FGF21's acute effects on glucose tolerance and insulin sensitivity in mice (137, 145, 153, 155, 161). Adiponectin has been identified as a crucial mediator of FGF21's gluco regulatory actions (156, 157). We had proposed a direct linear relationship between the activation of PPAR γ by thiazolidinediones, local production of FGF21, and local production as well as systemic release of adiponectin, eventually resulting in an effective reduction in blood and tissue ceramide levels with associated improvements in insulin sensitivity (156). It may thus be the absence of the FGF21-triggered adiponectin surge that explains how defects in adipose tissue FGF21 signaling impact its effects on glucose tolerance and insulin sensitivity. Taken together, FGF21 has mostly beneficial effects on systemic metabolism, some of which may, however, not fully translate from rodents to man.

Lipocalin 2

The lipocalin (LCN) family encompasses several structurally similar proteins that bind and transport small hydrophobic molecules, such as retinol, fatty acids, and steroids (167). LCN2 binds iron-chelating siderophores produced by bacterial and mammalian cells, including 2,3-dihydroxybenzoic acid, 2,5-dihydroxybenzoic acid, and catechol (168–172). LCN2 binds to the LCN2 receptor (LCN2R) and the LDL receptor-related protein (LRP)2, which either increases or decreases intracellular iron stores depending on whether LCN2 is loaded with iron or not (168–172). Human LCN2 can also form covalent homodimers as well as heterodimers with matrix metalloproteinase 9 (MMP9), while murine LCN2 lacks the cysteine residue required for these interactions (173). The circulating LCN levels correlate positively with adiposity, markers of inflammation, and markers of insulin resistance (174–182). Studies with LCN2-deficient mice on either a regular or high-fat diet yielded variable results in that these mice were reported to have increased, decreased, or unchanged body weight gain, altered WAT, BAT, and endothelial cell function, cold intolerance, liver steatosis, and improved, worsened, or unchanged glucose tolerance and insulin sensitivity (178, 183–191). Studies involving either the overexpression of LCN2 or treatment with LCN2 have equally failed to paint a clearer picture of LCN2's effects on adipose tissue stromal cell adipogenic differentiation, adipocyte function, and metabolic homeostasis (167, 174, 182, 184, 189–194). Surprisingly, despite the central role that iron plays in adipocyte function, the vast majority of these studies on LCN2 did not address iron homeostasis (167, 174, 182, 184, 189–196). As in the case of chemerin, the use of more advanced mouse models enabling an inducible

tissue-specific overexpression or deletion of LCN2 or its receptors may be required to refine our assessment of LCN2's effects on systemic metabolism. We should not be surprised by the wide array of effects reported. This range of phenotypes seen under different conditions is characteristic of what has been observed for many factors involved in inflammatory responses, where beneficial and detrimental effects are in a tug of war, and the net effects differ between acute and chronically challenged states (197–199).

Neuregulin 4

The neuregulin (NRG) family belongs to the EGF superfamily and its members are mostly known for their functions in the development and maintenance of the nervous system (200). Akin to other NRGs, NRG4 is produced as a transmembrane pro-protein that undergoes N-terminal proteolytic processing to release a soluble ligand (201). It signals through the EGF receptor 4 (ErbB4) that is expressed by a wide range of cells (200, 201). NRG4 is expressed in WAT and BAT where its production increases upon cold exposure and decreases with obesity (201–205). Its circulating levels were reported to correlate positively, negatively, or not at all with adiposity and markers of insulin resistance (206–211), yielding a rather unclear picture of its behavior. NRG4-deficient mice fed a high-fat diet display increased body weight gain, decreased WAT and BAT vessel density, increased WAT inflammation, liver steatosis, and impaired glucose tolerance and insulin sensitivity (201, 204, 205). While similar effects occur in high-fat-challenged ErbB4-deficient mice, opposite effects can be achieved by adipocyte- or hepatocyte-specific overexpression of NRG4 (201, 203, 204, 212, 213). This argues for beneficial effects of NRG4 on metabolic homeostasis. Of note though, humans harboring loss-of-function alleles of *NRG4* display reduced to nearly absent fasting C-peptide levels, but no apparent alterations of glucose homeostasis, calling for further studies addressing the translatability of above findings (214).

LIPIDS

Fatty acid esters of hydroxy fatty acids

Fatty acid esters of hydroxy fatty acids (FAHFAs) are produced by still poorly understood enzymatic and nonenzymatic processes (215, 216). Differences in acyl chain length, saturation, and hydroxylation of the constituent fatty acids allow for the generation of more than a hundred distinct FAHFA species of which palmitic acid esters of 5- and 9-hydroxystearic acid (5-PAHSA and 9-PAHSA) are the best studied ones (215, 216). 9-PAHSA and possibly also 5-PAHSA signal through the GPR40 and GPR120 expressed by a variety of cells (215, 217, 218). They are produced by BAT and WAT where their production increases with glucose uptake, de novo lipogenesis, and possibly lipid oxidation, and they may be found in food (215, 216, 219, 220). Low circulating 5-PAHSA levels are moreover associated with markers of insulin resistance (215). Administration of 5- and 9-PAHSA to lean or obese mice increases

glucagon-like peptide 1 (GLP1) and insulin secretion, decreases circulating glucose levels, and improves glucose tolerance and insulin sensitivity (215, 218). 5-PAHSA and 9-PAHSA may directly act on adipose tissue stromal cells to promote adipogenic differentiation, and in adipocytes to increase insulin-stimulated glucose uptake, in L-cells to increase GLP1 secretion, in β -cells to increase glucose-stimulated insulin secretion, and in macrophages to decrease activation and pro-inflammatory cytokine release (215, 219–221). Of note though, another study featuring both *in vitro* and *in vivo* experiments was unable to confirm any of the above-mentioned effects of 5- and 9-PAHSA (217). Whether central aspects of the experimental setups used by individual studies may have contributed to different outcomes remains to be addressed though (222).

Lysophosphatidic acids

Lysophosphatidic acids (LPAs) consist of a glycerol backbone, a phosphate group, and an ester-bound acyl chain of differing length and saturation (223). They are generated both *intra-* and *extracellularly* and their circulating levels increase with obesity (223, 224). They can be produced by acylation of glycerol 3-phosphate by glycerol-3-phosphate acyltransferases (GPATs), phosphorylation of monoacylglycerol by acylglycerol kinases (AGKs), head group modification of other lysophospholipids involving phospholipase (PL)D activity, or deacylation of phosphatidic acids involving PLA1 or PLA2 activity (223). LPAs can subsequently be degraded by deacylation involving PLA1 or PLA2 activity, dephosphorylation by lipid phosphate phosphatases (LPPs), or acylation by acylglycerol-3-phosphate acyltransferases (AGPATs) (223). Intracellular LPAs are crucial intermediates of glycerolipid synthesis and may possibly function as endogenous PPAR γ ligands, while extracellular LPAs act as lipid mediators signaling through six widely expressed G protein-coupled LPA receptors (LPAR1–6) (223). Administration of LPAs to mice diminishes glucose-stimulated insulin secretion and glucose tolerance (224). LPAs may also directly increase adipose tissue stromal cell proliferation, decrease adipose tissue stromal cell adipogenic differentiation by downregulation of PPAR γ 2, increase hepatocyte glycogenolysis, and decrease β -cell glucose-stimulated insulin secretion (224–236). Mice deficient in LPAR1 display pronounced developmental defects and delays with a reduced body size and weight, but also increased adipose tissue mass and adipocyte size, enhanced adipocyte glucose transporter 4 (GLUT4) expression, and elevated circulating leptin levels (237–239). Furthermore, when fed a high-fat diet, these mice do not gain body weight or adipose tissue mass and also do not exhibit the expected increase in food intake (238). Chemical inhibition of LPAR1 and LPAR3 in high-fat diet-fed mice increases adipose tissue mass, adipose tissue PPAR γ 2 expression, and adipocyte size, skeletal muscle glucose utilization, liver glycogen storage, and pancreatic islet mass, and improves glucose tolerance and insulin sensitivity (224, 239). Circulating LPAs are mainly generated from lysophosphatidylcholines by the PLD activity of autotaxin (ATX), an enzyme primarily produced by adipocytes (229,

240–244). ATX secretion by WAT and BAT and circulating ATX levels are increased with obesity and correlate positively with markers of glucose intolerance and insulin resistance (229, 243–249). While a homozygous loss of ATX is embryonically lethal in mice, a heterozygous loss of ATX is tolerated and, upon high-fat feeding, results in decreased circulating LPA levels, body weight gain, and adipose tissue accrual as well as improved glucose tolerance and insulin sensitivity (240–242, 250). Mice with adipocyte-specific deletion of ATX also display decreased circulating LPA levels and improved glucose tolerance, but intriguingly increased adipose tissue accrual, adipose tissue PPAR γ 2 expression, and adipocyte size (244). Mice overexpressing ATX conversely display increased circulating LPA levels, body weight gain, and adipose tissue accrual, yet no alterations of glucose homeostasis (236).

Taken together, LPAs appear to have mostly detrimental effects on systemic metabolism.

Sphingolipids

The sphingolipid superfamily is characterized by a sphingoid backbone (e.g., sphingosine) and, depending on the respective subfamily, a specific head group, an amide-bound acyl chain, and, in certain cases, also an ester-bound acyl chain (251). Their *de novo* synthesis begins with the generation of 3-ketodihydrosphingosine from serine and palmitoyl-CoA by serine palmitoyltransferases (SPTs) (251). This is succeeded by a reduction to dihydrosphingosine by 3-ketodihydrosphingosine reductase (KDSR), an acylation to dihydroceramides by (dihydro)ceramide synthases (CERSs), and a conversion to ceramides by (dihydro)ceramide desaturases (DEGSs) (251). Ceramides can be modified further by addition of different head groups, such as phosphatidylcholine by sphingomyelin synthases (SMSs) or glucose by glucosylceramide synthase (GCS) (251). They can alternatively be acylated to acylceramides by diacylglycerol acyltransferases (DGATs), deacylated to sphingosine by ceramidases (CDases), or phosphorylated to ceramide-1-phosphates (C1Ps) by ceramide kinase (CERK) (251). Sphingosine too can be phosphorylated by sphingosine kinases (SPHKs) yielding sphingosine-1-phosphate (S1P) (251). Additional “salvage pathways” exist for ceramide generation from sphingomyelins, glucosylceramides, sphingosine, and C1P that involve SMases, glucosylceramidases (GlcCDases), CERSs, and C1P phosphatases, respectively (251).

While a near-complete reduction of SPT activity due to a homozygous loss of either SPT long chain subunit 1 or 2 (SPTLC1 or SPTLC2) is embryonically lethal in mice, a partial reduction due to heterozygous loss of SPTLC2 or by chemical SPT inhibition alleviates glucose intolerance, insulin resistance, WAT inflammation, liver steatosis, and atherosclerosis, as well as cardiac and vascular dysfunction in different mouse and rat models of obesity, diabetes, and cardiovascular disease (252–269). Highlighting the importance of balanced *de novo* sphingolipid synthesis for adipose tissue function, mice with adipocyte-specific deletion of SPTLC1 or SPTLC2 display age-dependent lipodystrophy and metabolic deterioration (270, 271). This is,

however, a complex pathway, as another study demonstrates that adipocyte-specific deletion of *SPTLC2* can also result in protection from high-fat diet-induced metabolic disturbances (268).

Ceramides form a pivotal sphingolipid subfamily that is implicated in causing many of the metabolic sequelae of excessive saturated fatty acid intake (272, 273). Circulating ceramides associate with VLDLs and LDLs, extracellular vesicles (EVs), and possibly also albumin (272). Their levels in circulation as well as in tissues, such as WAT, skeletal muscle, and liver, increase with obesity and correlate positively with markers of inflammation and insulin resistance (268, 274–295). Ceramides can activate protein phosphatase (PP)1, PP2A, and PP2C, protein kinase (PK)C ζ , and the NLR family pyrin domain-containing (NLRP)3 inflammasome, suppress mitochondrial β -oxidation, and promote ER stress (273, 296). They directly decrease the insulin sensitivity of adipose tissue stromal cells, adipocytes, skeletal and cardiac muscle cells, endothelial cells, vascular smooth muscle cells, and kidney cells (256, 261, 264, 297–308). They also decrease adipose tissue stromal cell adipogenic differentiation, white adipocyte browning, and β -cell insulin production, increase adipocyte inflammatory marker expression, and promote β -cell, cardiac muscle cell, and kidney cell death (268, 276, 308–315). Ceramides differ in the length and saturation of their amide-bound acyl chains, mostly resulting from the acyl-CoA preference of the CERS isoform involved in their synthesis (251). CERS1 prefers C18, CERS2 C20–26, CERS5 C16, and CERS6 C14–16 acyl-CoA (251). Mice deficient in either CERS1, CERS5, or CERS6 display improved glucose homeostasis upon high-fat feeding, whereas mice (partially) deficient in CERS2 not only display impaired glucose homeostasis upon high-fat feeding, but also develop liver steatosis and cancer (290, 294, 316–320). Comparable metabolic improvements are seen in high-fat diet-fed mice with either brown adipocyte- or hepatocyte-specific deletions of CERS6 (290). This implicates ceramides with rather short amide-bound C14–C18 acyl chains as prime mediators of saturated fatty acid-induced glucose intolerance and insulin resistance.

Similar to upstream SPT activity, a near-complete reduction of downstream DEGS activity due to a homozygous loss of *DEGS1* results in incompletely penetrant embryonic lethality in mice (255). Mice with a heterozygous loss of *DEGS1* are viable and display increased insulin sensitivity (255). In line with these observations, chemical *DEGS1* inhibition offers partial protection from glucose intolerance and insulin resistance upon high-fat feeding (307).

Ceramide degradation is intimately connected to adiponectin signaling, as the engagement of AdipoR1 and AdipoR2 is associated with increased ceramidase activity, which may stem from the receptors themselves (117, 321–324). Adiponectin-deficient mice display not only impaired glucose tolerance and insulin sensitivity, but also increased ceramide and decreased sphingosine and SIP levels in WAT and liver as well as exacerbated responses upon experimental induction of β -cell and cardiac muscle cell death (117, 321). Treatment with adiponectin or overexpression of it decreases tissue ceramide levels, normalizes

glucose homeostasis upon high-fat feeding, and restrains β -cell and cardiac muscle cell death, likely through induction of ceramide degradation and SIP production (321). In mice, WAT-, liver-, or skeletal muscle-restricted overexpression of AdipoR1 or AdipoR2 decreases local ceramide levels and increases local insulin sensitivity (321, 322, 325). When either WAT or liver is targeted, not only local but also distant tissue ceramide levels diminish and glucose tolerance and insulin sensitivity improve, suggesting a dynamic inter-tissue exchange of ceramides (322). In agreement, overexpression of acid ceramidase in either WAT or liver decreases tissue and circulating ceramide levels and augments systemic metabolism (326). Intriguingly, adiponectin itself may play a role in this exchange of ceramides by stimulating the release of ceramide-rich EVs from cells following T-cadherin but not AdipoR1 or AdipoR2 engagement (327). In addition, consistent with adaptor protein containing PH domain, PTB domain, and leucine zipper motif 1 (APPL1) being a key downstream mediator of adiponectin signaling, global APPL1 overexpression decreases cardiac ceramide accumulation, insulin resistance, and damage, and improves systemic metabolism upon high-fat feeding (328).

Sphingomyelins are ceramide derivatives whose circulating levels increase with obesity and, dependent on the length of their amide-bound acyl chain, correlate positively with markers of insulin resistance (251, 276, 287, 288, 291, 329, 330). Mice deficient in *SMS1* display incompletely penetrant neonatal lethality, age-dependent lipodystrophy, and disturbed glucose tolerance with pronounced mitochondrial dysfunction and oxidative stress in WAT and pancreas (331, 332). In contrast, mice deficient in *SMS2* display augmented glucose tolerance and insulin sensitivity and partial protection from high-fat diet-induced obesity and metabolic deterioration (262, 333, 334). These differences may arise not only from the differential expression of *SMS1* and *SMS2* in specific tissues, but also from the distinct subcellular localizations of both enzymes, and thus may be due to subcellular differences in sphingomyelin generation (335). Alterations of sphingomyelin synthesis can furthermore influence the levels of ceramides and ceramide derivatives such as glucosylceramides (335). The loss or chemical inhibition of acid SMase, for instance, decreases liver ceramide levels and steatosis, glucose intolerance, and insulin resistance in mice fed a high-fat diet (289, 336).

Glucosylceramides are also ceramide derivatives and themselves form the basis for the synthesis of more complex glycosphingolipids (251). Not much is known about whether and how glucosylceramide levels in circulation and in tissues change with obesity, glucose intolerance, and insulin resistance. A homozygous loss of *GCS* results in embryonic lethality in mice, and the metabolic consequences of a heterozygous loss of *GCS* have not yet been studied (337, 338). While hepatocyte-specific deletion of *GCS* is without apparent impact on systemic metabolism, not even upon high-fat challenge, chemical inhibition of *GCS* curtails WAT inflammation and liver steatosis, fibrosis, and inflammation and improves glucose tolerance and insulin sensitivity in *ob/ob* mice and mice fed a high-fat diet (339–344).

Thus, while there appears to be an involvement, much remains to be uncovered concerning the role of glucosylceramides and glycosphingolipids in obesity and obesity-associated diseases.

CIPs and SIP are lipid mediators formed by the phosphorylation of ceramides and sphingosine, respectively (251). CIPs stimulate the enzymatic activity of the arachidonic acid-releasing cytosolic PLA2 α and inhibit those of TNF-releasing TNF-converting enzyme (TACE) and acid SMase (251, 296). Arguing for mostly detrimental effects of CIPs on systemic metabolism, CERK-deficient mice exhibit decreased body weight gain and decreased WAT adipocyte size, as well as reduced macrophage infiltration and inflammation (345). As a consequence, they show improved glucose tolerance upon high-fat feeding (345).

SIP not only signals through five widely-expressed G protein-coupled SIP receptors (S1PR1–5), but also stimulates the enzymatic activities of TNF receptor-associated factor 2 (TRAF2) and cellular inhibitor of apoptosis 2 (CIAP2) and inhibits those of histone deacetylase (HDAC)1 and HDAC2 (251, 296). In circulation, SIP associates with ApoM on HDL and with albumin (251, 296). Its circulating levels increase with obesity as well as upon fasting and correlate positively with markers of insulin resistance and inflammation (276, 283, 346–351). SIP directly acts on adipose tissue stromal cells to increase proliferation and decrease adipogenic differentiation, prompts adipocytes to increase inflammatory marker expression, triggers hepatocytes to increase inflammatory marker expression, survival, glucose uptake, and lipid accumulation, and leads to an overall decrease in insulin sensitivity (276, 348, 350, 352–361). It also triggers skeletal muscle cells to increase glucose uptake, β -cells to increase survival and glucose-stimulated insulin secretion, vascular smooth muscle cells to increase tone, and endothelial cells to increase immune cell adhesion and permeability (276, 348, 350, 352–361). SPHK1-deficient mice display decreased circulating SIP levels and are variably reported to exhibit either decreased WAT inflammation, liver inflammation and steatosis, and improved glucose tolerance and insulin resistance or increased β -cell death and worsened glucose tolerance and insulin sensitivity (349, 356, 357, 359). While chemical inhibition of SPHK1 has yielded similarly inconsistent results, SPHK1 overexpression from an integrated transgene or from viral vectors was uniformly reported to have beneficial metabolic effects (346, 349, 353, 355, 362). In contrast, not only overexpression but also deletion of SPHK2 results in increased circulating SIP levels and improved glucose tolerance and insulin resistance in mice (361, 363, 364). Targeting SIP signaling rather than SIP production has provided more consistent results. To this end, either combined chemical modulation of S1PR1 and S1PR3–5, chemical inhibition of S1PR2, or deletion of S1PR2 results in augmented glucose homeostasis in different mouse models of obesity and diabetes (348, 350, 360, 365–370).

As in the case of other signaling mediators, more sophisticated models and methods may be required to disentangle acute and chronic effects of altered CIPs and SIP production and signaling on different cells and tissues.

Uric acid

Uric acid is a product of purine base degradation, a process that begins with the conversion of adenine and guanine nucleotides to hypoxanthine and xanthine, respectively, and concludes with the conversion of hypoxanthine to xanthine to uric acid (371, 372). Uric acid is produced by adipose tissue, the liver, and skeletal muscle and excreted primarily by the kidneys and secondarily by the liver (372). It is also degraded by uricase, an enzyme that is present in mice and rats, but absent in humans, resulting in overall higher circulating and tissue uric acid levels in the latter (371, 372). The circulating uric acid levels increase with obesity, liver steatosis, type 2 diabetes, and kidney disease and may predict the development of the metabolic syndrome (373–389). Uric acid exerts anti-oxidant effects in the extracellular environment where it can scavenge reactive oxygen and nitrogen species, including superoxide anions (O_2^-), peroxynitrite anions ($ONOO^-$), and NO, but pro-oxidant effects in the intracellular environment where it can activate the NLRP3 inflammasome and NADPH oxidase (NOX) (379, 385, 390–395). NADPH oxidase activation by uric acid triggers its translocation to the mitochondria, induces mitochondrial oxidative stress, suppresses β -oxidation, and promotes de novo lipogenesis (379, 393, 394). Uric acid directly increases adipocyte and hepatocyte inflammatory marker expression, hepatocyte lipid accumulation, and vascular smooth muscle cell proliferation, and decreases hepatocyte and endothelial cell insulin sensitivity as well as endothelial cell proliferation (376, 379, 385, 393, 395–402). Chemical inhibition of uricase in mice and rats results in elevated circulating uric acid levels, raised blood pressure, diminished WAT, liver skeletal muscle, and vessel insulin sensitivity, evident liver steatosis and inflammation, kidney dysfunction, as well as disturbed glucose tolerance and insulin sensitivity (394, 395, 400, 401).

The final steps of purine base degradation, the conversion of hypoxanthine to xanthine to uric acid, are carried out by the multifunctional enzyme, xanthine oxidoreductase (XOR), that occurs in two distinct forms, a dehydrogenase form (XDH) and an oxidase form (XO) (403, 404). XOR is produced as XDH and can be converted to XO either reversibly by cysteine residue oxidation or irreversibly by limited proteolysis (403, 404). Secreted XDH undergoes rapid turnover to XO, which then binds to the surface of endothelial cells (403, 404). XOR can utilize a wide range of substrates (403, 404). While substrate oxidation by XDH consumes NAD^+ to produce NADH, substrate oxidation by XO consumes oxygen (O_2) to produce mainly hydrogen peroxide (H_2O_2) but also O_2^- (403, 404). Depending on pH, O_2 tension, and substrate availability, XDH can also utilize O_2 as an electron acceptor and thus act as a source of reactive oxygen species (403, 404). Moreover, both XDH and XO can generate reactive nitrogen species by substrate or NADH oxidation with concomitant reduction of nitrate (NO_3^-) to nitrite (NO_2^-) to NO (403, 404). XOR is expressed in WAT, liver, and skeletal muscle, and its

production and activity in WAT and liver increase with obesity (382, 385, 405, 406). XOR partakes in the regulation of adipogenesis, and mice with a homozygous loss of XOR display decreased fat mass and early lethality, although comparable XOR deficiency in humans is nonlethal (405, 407, 408). Mice with a heterozygous loss of XOR display age-dependent body and WAT weight gain and WAT dysfunction with increased oxidative stress and inflammation, as well as glucose intolerance and insulin resistance, all of which are exacerbated on a high-fat diet (409). Chemical inhibition of XO, in contrast, not only lowers the circulating uric acid levels, but also preserves WAT and liver function and augments glucose homeostasis in *db/db* mice as well as mice fed a high-fat diet (376, 379, 384). The outcome of manipulating XOR thus appears to depend on which aspects of XOR biology are targeted.

Uric acid production is tightly linked to fructose intake (371, 372). Following cellular uptake, fructose can undergo unrestrained phosphorylation by ketohexokinase (KHK), which yields fructose-1-phosphate and consumes cellular ATP (371, 372). The accompanying depletion of cellular phosphate triggers an activation of AMP deaminase (AMPD), degradation of adenine nucleotides, XOR-dependent production of uric acid, and uric acid-mediated inhibition of AMP-dependent protein kinase (AMPK) (371, 372). High-fructose feeding of mice and rats causes elevated circulating uric acid levels, cardiac, vascular, and kidney dysfunction with increased oxidative stress, inflammation, and fibrosis, as well as disturbed glucose homeostasis, all of which can be mitigated by chemical XO inhibition (383, 399, 410–414).

Taken together, this argues for mostly detrimental effects of elevated uric acid levels on systemic metabolism.

Uridine

Uridine is the nucleoside of the pyrimidine base, uracil, and provides the basis of substrates that are essential for RNA and DNA synthesis, glycogen deposition, and protein and lipid glycosylation (415). Its *de novo* synthesis usually begins with the formation of dihydroorotate from glutamine, bicarbonate (HCO_3^-), ATP, and aspartate by the tri-functional enzyme, carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase (CAD2), followed by the conversion of dihydroorotate to orotate by dihydroorotate dehydrogenase (DHODH), of orotate to UMP by the bi-functional enzyme, UMP synthase (UMPS), and of UMP to uridine by 5'-nucleotidase (5NT) (415). Its degradation, in turn, is carried out by uridine phosphorylases (UPPs) (415). Uridine is produced by the liver and WAT and cleared by the liver (416–419). Both endogenous and exogenous uridine (introduced either orally or intraperitoneally) undergo continuous and rapid clearance by the liver, mostly through degradation by Kupffer cells and endothelial cells, but also through biliary excretion by hepatocytes (416–419). The circulating uridine levels are tightly regulated, increase with obesity and upon fasting, exercise, and ingestion of ethanol, glucose, and fructose, and decrease with lipodystrophy and upon ingestion of amino acids (418–421). Strikingly, while the liver produces

most of the circulating uridine in the fed state, adipose tissue is doing so in the fasted state (418, 419). Not much is known about how uridine signals and no dedicated uridine receptor has been identified yet. Uridine may indeed exert most of its effects by being metabolized to either UDP, UDP-glucose, or UTP, which can signal through different G protein-coupled purinoreceptors (i.e., P2YR2, P2YR4, P2YR6, and P2YR14) or to UDP-hexosamines and UDP-*N*-acetyl-hexosamines, which can alter the glycosylation and thus the activity of distinct proteins and lipids (422, 423).

Acute treatment of humans, rats, and mice with a high dose of uridine results in a transient decrease in body temperature, while a low dose may cause a slight increase instead (418, 424, 425). In extension, the fasting-associated decrease in body temperature was found to be critically dependent on uridine production by adipose tissue (418). In mice, uridine treatment also increases the circulating leptin level, decreases the metabolic rate, and improves glucose tolerance in aged and in high-fat diet-fed animals (418). Uridine's effects on both body temperature and glucose homeostasis apparently involve active leptin signaling, as uridine treatment of *ob/ob* mice evokes an exacerbated decrease in body temperature, but unexpectedly also worsens glucose homeostasis (418).

Prolonged disturbances of uridine homeostasis in either direction appear to be mostly detrimental. As such, dietary supplementation of uridine in mice for several days to weeks promotes body weight gain, alters liver protein acetylation and glycosylation, stimulates liver glycogen and lipid accumulation, blunts liver insulin sensitivity, and disturbs glucose homeostasis (426–428). Intriguingly, lowering uridine levels by chemical inhibition of DHODH or overexpression of UPP1 also induces liver lipid accumulation and blunts liver and systemic insulin sensitivity, but improves glucose tolerance (426, 427). Elevating uridine levels by UPP1 deletion, in turn, does not affect liver insulin sensitivity, but similarly blunts systemic insulin sensitivity, improves glucose tolerance, and may furthermore promote spontaneous tumorigenesis (427, 429).

The ER stress response, specifically the mRNA splicing-dependent production of the short isoform of X-box binding protein 1 (XBPs), plays a central role in uridine metabolism (430). In the fed state, XBPs levels are high in hepatocytes and pro-opiomelanocortin neurons of the arcuate nucleus and low in adipocytes, whereas the opposite can be observed in the fasted state (419, 431, 432). XBPs upregulation in adipose tissue seems to be tied to active lipolysis with higher XBPs levels detectable not only upon fasting, but also with obesity and cancer-associated cachexia (419). XBPs acts as a transcription factor that stimulates uridine *de novo* synthesis by inducing CAD2 as well as uridine conversion to UDP-hexosamines and UDP-*N*-acetyl-hexosamines by inducing both glutamine/fructose-6-phosphate aminotransferase 1 (GFPT1) and UDP-glucose 4-epimerase (GALE) (419, 431–433). Highlighting its role in promoting uridine production, adipocyte-specific deletion of XBPs abolishes the fasting-induced increase in uridine (419). Mice with adipocyte-specific overexpression of XBPs display elevated circulating and adipose tissue

uridine levels, increased activity, energy expenditure, and body heat loss, decreased body weight and body temperature, and protection from obesity upon high-fat feeding or with leptin deficiency (419). Suggesting mostly favorable effects of XBPIs induction, hepatocyte- or pro-opiomelanocortin neuron-specific XBPIs overexpression augments glucose homeostasis, and cardiac muscle cell-specific XBPIs overexpression alleviates ischemia-reperfusion damage in mice (431–433).

Much remains to be learned about how short- and long-term disturbances of uridine homeostasis impact systemic metabolism and about whether manipulations of uridine metabolism may yield therapeutic benefits.

NONCODING RNAs

Long noncoding RNAs

Contrary to lasting assumptions, the majority of the genome is transcribed, at least under some conditions (434). Long noncoding RNAs (lncRNAs) originate from the transcription of intergenic and genic portions of the genome, both in the sense and antisense direction (434). They are, by definition, over 200 nucleotides long, not translated into proteins, and may regulate gene transcription and nuclear domain organization as well as RNA and protein function (434). Most lncRNAs are localized in the nucleus, lowly abundant, and poorly conserved (434). Only a small fraction (hundreds to thousands) of the predicted 20,000–100,000+ lncRNAs in humans may indeed have specific functions (434). lncRNAs are found in EVs, raising the possibility that EV-associated lncRNAs released from adipose tissue function as regulators of distant tissue function (435). Recent reviews provide an excellent overview of the role of lncRNAs in the regulation of adipose tissue function and systemic metabolism (436–438).

MicroRNAs

MicroRNAs (miRNAs) either originate from introns or are transcribed from dedicated genes (439). They are released from pri- and pre-miR precursors by successive processing involving the microprocessor complex in the nucleus as well as DICER in the cytoplasm (439). At the end of their processing, they are 20–24 nucleotides long and incorporated into the RNA-induced silencing complex (RISC). As a RISC component, they regulate mRNA translation and stability, usually resulting in a repression of protein expression (439). They are more conserved than lncRNAs and show a wide range of abundance (439). Strikingly though, only less than 100 of the adipose tissue-expressed miRNAs appear to be regulated by obesity in either humans or mice (439). Distinct populations of miRNAs are released from cells associated mostly with components of the RISC, but also associated with lipoproteins and EVs (440–442). Adipose tissue is a major source of circulating EV-associated miRNAs, and recent reviews offer much insight into how adipose tissue-derived miRNAs shape metabolic homeostasis (439).

EVs

EVs are an eminent means of intercellular communication (435, 443–445). They carry a large variety of cargo, including organelle parts, proteins, and lipids, as well as small coding and noncoding RNAs (e.g., mRNAs, lncRNAs, and miRNAs), delivering them from one cell to another. Cells secrete EVs in an orderly process that is controlled by intra- and intercellular signals, including nutrient-related cues (435, 443–445). Determined by their biogenesis, ectosomes (also called microvesicles) with a diameter of 50–1,000 nm and exosomes with a diameter of 50–150 nm can be distinguished (435, 443–445). While ectosomes bud directly from the plasma membrane, exosomes are generated by inward budding of endosomal membranes to create multivesicular bodies (MVBs) containing intraluminal vesicles (ILVs, i.e., unreleased exosomes) followed by either degeneration through fusion of the ILVs with the MVB membrane, degradation through fusion of the MVBs with lysosomes, or release through fusion of the MVBs with the plasma membrane (435, 443–445). Accordingly, ectosomes are released in an immediate fashion and exosomes in a delayed fashion (435, 443–445). EVs are capable of delivering their cargo to specific cells and tissues by binding to and rolling on target cell surfaces, which subsequently allows for receptor interaction and fusion by fusogenic interactions, endocytosis, macropinocytosis, or phagocytosis (435, 443–445).

Obesity alters the cargo and increases the release of EVs from WAT, while cold exposure does so in BAT and browning WAT (446, 447). Establishing a role for adipose tissue-derived EVs in the regulation of systemic metabolism, EVs collected from WAT of high-fat diet-fed mice elicit glucose intolerance and insulin resistance when injected into wild-type mice and exacerbate atherosclerosis when injected in ApoE-deficient mice (447, 448). Highlighting the contribution of macrophages to these effects, WAT macrophage EVs from high-fat diet-fed mice are sufficient to disrupt glucose homeostasis when injected into wild-type mice, whereas WAT macrophage EVs of regular diet-fed mice are capable of augmenting glucose homeostasis instead (449). WAT EVs of high-fat diet-fed mice may also induce monocyte homing to adipose tissue and the liver, promote local monocyte proliferation and differentiation, and increase macrophage pro-inflammatory cytokine production (447, 448, 450). Taken together, these observations allude to a vicious cycle of obesity-associated shifts in the adipose tissue EV secretion profile, immune cell infiltration, and inflammation.

EVs serve as a means of communication not only between adipose tissue and other organs but also between different cell populations within adipose tissue itself. Regarding this aspect of adipose tissue biology, we recently uncovered an extensive EV-mediated local exchange of cellular components between adipocytes and endothelial cells that is governed by the nutritional state (451). In WAT of mice, the cellular origin and destination as well as the cargo of the transferred EVs changes upon fasting, feeding, and with obesity (451). Fasting, for instance, results in an increased EV-mediated transfer of cellular components

from WAT endothelial cells to adipocytes as well as an enrichment of WAT EVs in proteins involved in central cellular signaling pathways, mitochondrial respiration, oxidative stress defense, and hypoxia response and a depletion of WAT EVs in proteins involved in lipid and amino acid metabolism (451). The highly dynamic character of this EV-mediated local exchange alludes to the possibility that it might primarily serve to rapidly and efficiently redistribute cellular components between different cell populations within WAT, thus lending heightened metabolic flexibility to the tissue as a whole.

Altogether, EVs released from adipose tissue into circulation may exert mostly beneficial effects on systemic metabolism in the lean state but detrimental effects in the obese state. Related to this, much remains to be learned about exactly how adipose tissue communicates with other organs by means of EV exchange, the sending cells, and the receiving cells, as well as the nature of the transmitted message.

PERSPECTIVE

There is clearly a wide variety of signaling mediators and mechanisms that adipose tissue utilizes to communicate with other organs of the body. At the systemic level, we deal with adipose tissue as a whole, distributed throughout the body in the form of discrete depots.

The contribution of specific depots and cell populations within them to the overall production frequently remains to be defined for many adipose tissue-derived factors. Likewise, the manner in which physiological and pathophysiological states, such as fasting, aging, and obesity, affect the production of certain factors by distinct depots and cell types awaits elucidation. Particularly with respect to fibrosis and inflammation, it has become clear that the effects observed commonly involve a cross-talk of multiple different cell types with net output from all participating populations. A fundamental impediment to more refined studies of adipose tissue-emergent signals is the present dearth of methods to measure and manipulate the production of distinct signaling mediators by specific adipose tissue depots and cell populations *in vivo*.

There are several signaling molecules, such as leptin and FGF21, which exert mostly beneficial effects on systemic metabolism, yet also display elevated circulating levels in pathophysiological states tightly associated with metabolic disturbances. The mechanistic basis by which certain pathophysiological states alter the signaling capacity and character of distinct factors is of immense interest. Reduced responsiveness to the metabolically favorable actions of leptin and FGF21 in the obese state, for instance, evoked still controversial ideas of leptin and FGF21 resistance that have been probed in numerous studies, altogether providing no coherent model (130, 452). To reliably define the role that a specific signaling mediator plays in metabolic disease remains challenging. It requires careful modulation of the abundance and/or activity of the respective factor and its receptor(s), while concomitantly monitoring systemic metabolism and cellular signaling. At

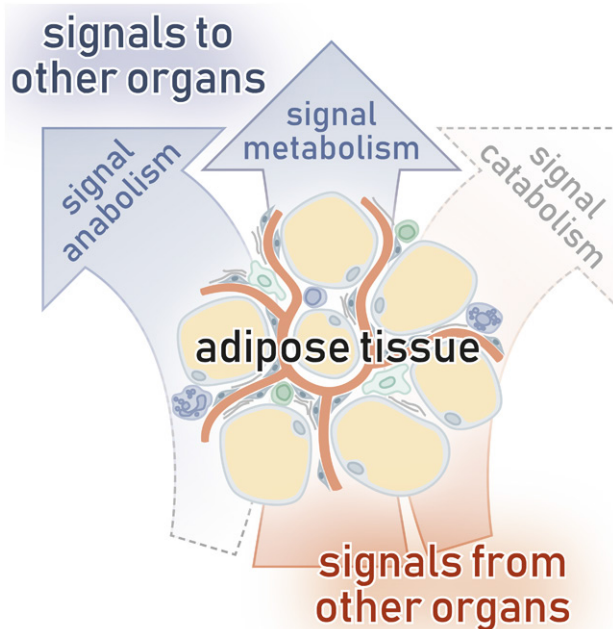


Fig. 2. Adipose tissue partakes in inter-organ communication by producing new signaling mediators (“signal anabolism”) as well as by converting or degrading signaling mediators reaching it from other organs (“signal metabolism” and “signal catabolism”).

the same time, focusing unduly on either individual cell types and tissues or isolated signaling pathways has to be avoided. More sophisticated *in vivo* models that enable these types of modifications are likely to make crucial contributions to such efforts.

Above, we solely discussed signaling mediators that are actively produced by adipose tissue. Adipose tissue is, however, also capable of degrading signaling mediators that derive from or that are destined for other organs (**Fig. 2**). It thus partakes in inter-organ communication as a source as well as a sink of signals. Future endeavors should thus consider not only the anabolism but also the metabolism and catabolism of signals by adipose tissue when evaluating its contributions to systemic metabolic and cellular homeostasis. **EB**

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