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Lipidomics of brown and white adipose tissue: implications for energy metabolism

Luiz O. Leiria^{3,4}, Yu-Hua Tseng^{1,2,*}

¹Joslin Diabetes Center, Section on Integrative Physiology and Metabolism, Harvard Medical School, Boston, MA, USA; Harvard Stem Cell Institute, Harvard University, Cambridge, MA, USA.

²Harvard Stem Cell Institute, Harvard University, Cambridge, MA, USA

³Department of Pharmacology, Ribeirao Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil

⁴Center for Research in Inflammatory Diseases (CRID), Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, São Paulo, Brazil.

Abstract

Adipose tissue exerts multiple vital functions that critically maintain energy balance, including storing and expending energy, as well as secreting factors that systemically modulate nutrient metabolism. Since lipids are the major constituents of the adipocytes, it is unsurprising that the lipid composition of these cells plays a critical role in maintaining their functions and communicating with other organs and cells. In both positive and negative energy balance conditions, lipids and free fatty acids secreted from adipocytes exert either beneficial or detrimental effects in other tissues, such as the liver, pancreas and muscle. The way the adipocytes communicate with other organs tightly depends on the nature of their lipidome composition. Notwithstanding, the lipidome composition of the adipocytes is affected by physiological factors such as adipocyte type, gender and age, but also by environmental cues such as diet composition, thermal stress and physical activity. Here we provide an updated overview on how the adipose tissue lipidome profile is shaped by different physiological and environmental factors and how these changes impact the way the adipocytes regulate whole-body energy metabolism.

Keywords

adipocytes; lipids; thermogenesis; lipokine

*Corresponding author: Yu-Hua Tseng, Ph.D., Joslin Diabetes Center, One Joslin Place, Boston, MA 02215, Phone: 617-309-1967, Fax: 617-309-2650, yu-hua.tseng@joslin.harvard.edu.

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Declaration of interests

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1. Impact of adipocytes' lipidomic profile on energy metabolism

The ability to store lipids in cells and tissues is a crucial characteristic of nearly all living species, from plants to mammals. Such ability serves to conserve energy for future use when energy sources become scarce. In order to prevent the effects of lipotoxicity, cells must be able to buffer and store excess lipids in an inert form known as „lipid droplets' (LDs), also referred to as oil bodies or lipid bodies [1,2]. Cells efficiently convert lipids and free-fatty acids (FFAs) into neutral lipids, such as TAGs, which are then incorporated into neutral LDs. In addition to serving as energy storing organelles, LDs also provide reservoirs of lipids for membrane synthesis [1,2].

Although nearly all cells of our body can save energy as stored lipids, white adipocytes are the ones with the highest capability to perform this role. Adipocytes are TAG-filled cells that exert many different roles, from energy storage to energy expenditure, depending on the adipocyte type [3]. There are three types of adipocytes, based on functions: (i) white adipocytes, the main cells composing white adipose tissue (WAT), are non-thermogenic and energy-storing type of fat cells, which contain an unilocular LD that occupy >95% of the cell volume; (ii) brown adipocytes are the main cell type constituting brown adipose tissue (BAT), the key organ responsible for defending body temperature. Brown adipocytes are thermogenic UCP1⁺ adipocytes, specialized in burning rather than storing energy and are composed of multilocular LDs dispersed in a mitochondrial rich cytoplasm; (iii) and finally the beige or “brite” (brown in white) adipocytes, which are inducible thermogenic cells that occur as clusters within WAT depots, exhibiting a mixed energy storage or spending function, and a mixed multilocular/unilocular/paucilocular morphology [3, 4, 5]. The smaller LDs of the thermogenic adipocytes facilitate the high rates of lipid metabolism and are necessary for the heat-generating function of these cells [6]. The release of FFAs from TAG stores takes place through the lipolysis of intracellular lipid stores [1,2,7,8]. This is a mechanism to redistribute the energy stored in adipocytes when it is demanded under negative energy balance conditions, such as exercise, cold exposure or fasting, thus providing lipid substrates for the maintenance of vital functions in other tissues [7,8]. Adipocyte lipolysis is triggered mainly by sympathetic stimuli of β -adrenergic receptors, initiating the sequential hydrolysis of TAGs through a cAMP-dependent pathway [1,7,8]. Lipolysis may dictate how adipocytes communicate with other organs in circumstances where the lipids or fatty acids serve as messengers. Besides mobilizing intracellular lipids for supporting mitochondrial activity under thermogenic adaptation, lipolysis allows for the secretion of lipid species from adipocytes that could signal in a hormone-like fashion to other tissues, thereby modulating gene expression and physiological function [9,10]. These lipid mediators are called lipokines [11]. Thus, the lipidome composition of the adipocyte plays a key role in allowing the adipocytes to activate thermogenic pathways, increase mitochondrial activity, and communicate energy status with other tissues [9,10,12,13].

The lipidome profile of adipocytes can be directly remodeled under the influence of changes in dietary composition and quantity, but also can be modified by negative energy balance conditions that affect lipid turnover and enzymatic machinery activity, such as thermal stress, physical activity, fasting and cachexia [14–16]. Lipid species trigger specific signaling pathways and largely differ in their properties as well as in their capacity to

interfere with cell function. As a consequence, the dynamic alterations in the lipid profile, stimulated by the aforementioned environmental or dietary cues, play a pivotal role in the changes in tissue function and gene profile observed in those conditions. Over the last decade a number of studies have shed light on the effects of different signaling lipids in different aspects of energy homeostasis, such as glucose and lipid metabolism, substrate availability and energy expenditure [13–17]. Since adipose tissue, either thermogenic and non-thermogenic fat, plays a central role in storing, biotransforming and redistributing lipid species, it is plausible that adipocytic lipidome profiles closely link to whole body energy metabolism.

2. Differences between brown and white fat lipidome profile

The distinct lipidomes of white, beige, and brown adipocytes reflect their different organelle composition and cell functions. In a lipidomic analysis of primary white, beige and brown adipocytes, Schweizer and colleagues [18] reveal major differences between the thermogenic fat cells and the non-thermogenic white adipocytes. This study demonstrates that thermogenic adipocytes possess higher contents of phosphatidylethanolamine (PE) and phosphatidylcholine (PC) fractions, with longer ($C > 36$) and more polyunsaturated species, as well as cardiolipin (CL) than those in white adipocytes. Because CLs constitute major components of mitochondrial inner membranes, and are indicators of mitochondrial mass, the higher amounts of CL in the thermogenic fat reflect the higher mitochondrial content in brown and beige adipocytes in comparison to white adipocytes [19,20]. Nevertheless, the incidence of longer PUFAs in BAT/beige fat reflects the pivotal role of elongases, especially Elov13, in thermogenic adaptation. Interestingly, the manner that thermogenic adipocytes and white adipocytes adapt their lipid profiles in response to adrenergic stimuli substantially differs [18]. For instance, β -adrenergic stimulation of brown, but not white, adipocytes led to the enhanced biosynthesis of saturated lyso-PC (LPC), which can stimulate UCP1-mediated proton leak [21]. In line with these findings, LPC16:0 levels positively correlate with BAT activity in humans exposed to cold [21].

A study performed in the distinct adipose tissue depots from mice confirmed the higher abundance of phospholipids such as PEs and PCs in BAT in comparison to subcutaneous and perigonadal WAT [21]. These phospholipids were predominantly composed by polyunsaturated LCFAs, especially DHA, which is known to improve membrane fluidity. FFAs were higher in BAT, while DAG and TAG levels were higher in WAT [22]. As already mentioned, these lipidomic alterations consistently respond to the particular cellular demands of each cell type. Thus, it is conceivable that free fatty acids are more abundant in BAT due to the need for prompt utilization of FFA for FA oxidation and UCP1 activation, while the predominance of TAGs and DAGs in WAT reflects the primary function of these cells, which is to store energy in the form of TAGs.

3. Adipocyte lipidome and metabolic syndrome

Environmental factors such as a high-fat-high-sugar based diet and a sedentary lifestyle are key factors leading to metabolic maladaptation which ultimately yields obesity and type-2 diabetes, among other metabolic diseases and comorbidities [23,24]. Obesity-induced

insulin resistance in glucose demanding tissues such as adipocytes and skeletal muscle, precedes fasting hyperglycemia and type-2 diabetes [25]. There are multiple mechanisms proposed to explain the onset of insulin resistance in these tissues, and among those, the remodeling of the lipidome composition of adipose tissue has been overlooked although of potentially crucial importance. Because adipose tissue acts as a deposit for fatty acids acquired from ingested nutrients, high-fat diets can remodel the adipocytes' lipidomic profile, which in turn can interfere with insulin signaling, thus driving insulin resistance [26,27].

Excessive supplies of both saturated and unsaturated FAs lead to the accumulation of ceramides into adipose tissues and skeletal muscle, most likely as a result of activation of the sphingolipid recycling pathway [26]. Importantly, ceramides are found at higher levels in the visceral adipose tissue of both obese humans and mice [27–29]. Ceramide serves as a major hub of sphingolipid metabolism and is composed of sphingosine, a long-chain amino alcohol, with an N-linked fatty acyl group of various carbon chain lengths [26]. The ceramide molecule also constitutes the backbone of complex sphingolipids and can convert into sphingosine, catalyzed by the enzyme ceramidase [26]. Abundance of ceramides as well as other sphingolipid species are strongly associated with insulin resistance in skeletal muscle and adipocytes. At the molecular level, ceramides impair the Akt activation and GLUT4 translocation to the membrane [30], thus reducing the efficacy of insulin to promote glucose uptake into the cells. The proinflammatory environment in the adipose tissue of obese mice also re-feeds the ceramide biosynthetic pathway, since the elevated TNF α levels in the adipose tissue of ob/ob mice increase the expression of the enzymes taking part in ceramide biosynthesis in adipose tissue, such as nSMase, aSMase, and SPT [31]. In addition, elevated levels of ceramides in subcutaneous adipose tissue of obese patients correlate with hepatic steatosis [27]. Furthermore, adipose tissue-specific deletion of *Sptlc*, the first enzyme in the sphingolipid biosynthesis cascade, can prevent hepatic steatosis induced by high-fat diet [29], providing a link between adipose accumulation of ceramides and hepatic steatosis. The adipose-specific *Sptlc* knockout mice also exhibit adipose tissue browning and higher energy expenditure [29]. These studies highlight the important role of adipose lipid metabolism in systemic energy homeostasis.

During adipocyte expansion, fat cells undergo drastic remodeling of lipidome compositions in order to maintain plasma membrane integrity and functionality. In healthy obesity, the lipid remodeling involves the accumulation of PUFAs containing phospholipids (PL) in contrast with diminished MUFAs and SFAs containing PL [32]. However, the maintenance of membrane integrity occurs at the expense of the increased concentration of ethanolamine plasmalogens containing arachidonic acid, thus favoring a proinflammatory environment. Interestingly, the levels of PUFA-containing PL are much lower in morbidly obese patients in comparison with those in healthy obese subjects, indicating that the adipocytes were unable to compensate for the dramatic morphological changes in extreme obesity [32]. This study suggests that the lipidome remodeling in the adipocytes may be necessary for cellular hypertrophy and tissue expansion. But at the same time, this poses uncertainty concerning whether the lipidome changes are also partially a cause of the cellular lipid disturbances. The authors also found an increase in the proportion of triglycerides composed with C18 fatty acids rather than the C16 ones, and a combined regulation of the lipidome adaptation

by intake of FAs from diet through CD36 transporter and the elongation by the elongase Elovl6 [32]. These data were recently validated in a murine model of high-fat diet-induced obesity (DIO). Adipose tissue depots (BAT, eWAT and ingWAT) from DIO mice exhibit an accumulation of TAGs with a total length of 54 carbons and a concomitant decrease of TAGs with 48 and 50 carbons, indicating that C16 acyl chains were replaced by C18 acyl chains [17]. Thus, it appears that an overall increase of longer and polyunsaturated triglycerides and phospholipid species in adipose tissue is a common phenomenon in obese rodents and humans. Both studies indicate that lipidomic remodeling of adipose tissue in obesity is likely associated with the nature of the FAs acquired from diet and is also regulated by an enhanced activity of elongase Elovl6. However, to date there is no direct evidence showing the impact of the Elovl6 depletion on the adipocyte expansion and lipidome profile under high-fat feeding.

The endocannabinoid system (ECS) also importantly influences the regulation of energy homeostasis [33, 34]. Endocannabinoids are lipid mediators that regulate a number of physiological and cognitive processes via binding to the cannabinoid receptor. ECS regulates energy metabolism either by acting in the central nervous system where they stimulate food intake, or in the periphery by promoting adipogenesis [33, 34]. The circulating levels of one of the most relevant endocannabinoid lipids, 2-arachidonoyl glycerol (2-AG), was found to positively correlate with visceral adiposity and negatively correlate with insulin sensitivity [35]. Thus, activation of peripheral and adipose ECS may contribute to increased visceral adiposity and insulin resistance in human obesity [35]. In line with this, the specific deletion of CB1-R, either in the central nervous system or in adipose tissue, protects mice against diet-induced obesity [36, 37].

It has been proposed that increased circulating levels of branched chain amino acids (BCAA) are strongly linked to obesity and insulin resistance [38, 39]. A recent study by Yoneshiro and colleagues [40] has demonstrated that BAT controls the BCAA levels by promoting the clearance and metabolism of these compounds, suggesting a potential mechanism in which higher BAT mass or activity would benefit the whole-body energy metabolism. Importantly, the uptake of BCAA in BAT through the transporter SLC25A44 is followed by BCAA catabolism and subsequent *de novo* synthesis of monomethyl branched chain fatty acids (mmBCFAs) [40]. Even though it remains unclear whether mmBCFAs are the actual effectors of the BCAA-promoted thermogenesis in BAT, the fact that the expression of rate-limiting enzymes involved in the catabolism of BCAAs is decreased in the adipose tissue of both obese mice and humans with insulin resistance, suggests that these metabolic reactions and subsequent biosynthesis of mmBCFAs do indeed have involvement in the regulation of insulin sensitivity in adipose tissue [41, 42]. Accordingly, mmBCFA content in adipose tissue of obese patients is lower than in lean subjects and is further increased after weight loss [43]. Moreover, mmBCFA levels in adipose tissue also positively correlate with insulin sensitivity [43]. Studies in which the enzymes responsible for the BCAA catabolism are deleted specifically in adipose tissue depots are necessary for properly addressing the role of mmBCFA in glucose homeostasis and thermogenesis. Another class of endogenous branched fatty acids that possess insulin sensitizing effects are the branched fatty acid esters of hydroxy fatty acids (FAHFAs) [13]. FAHFAs are biosynthesized in the adipose tissue and are regulated by fasting and high-fat feeding. When administered into

mice, FAHFs can improve insulin sensitivity, increase insulin secretion from pancreas, and blunt the inflammatory process in adipose tissue [13].

4. Lipidome dynamics in adaptive thermogenesis

Thermogenesis is the process of heat production in living organisms. It occurs in all homeothermic animals, and also in a few species of thermogenic plants [44,45]. In mammals, the thermogenic fat, namely BAT and beige fat, are the main tissues orchestrating the thermogenic adaptation in response to cold in order to maintain body temperature. Although UCP1-independent mechanisms of heat generation have been recently reported [46], the promotion of uncoupled mitochondrial respiration through UCP1 stands as the key mechanism leading to heat generation in thermogenic fat. As can be seen in the examples listed below, many distinct changes in the lipidome profiles of adipose tissue may govern the thermogenic machinery by either directly activating UCP1 or by shaping the environment for the proper function of the thermogenic machinery.

4.1. Free-fatty acids

In addition to the transcriptional changes in UCP1 expression during adaptive thermogenesis, its activation by FFAs is essential for the proper function of UCP1 [47]. Moreover, alterations in the lipidome composition are also required for heat generation [9,48,49]. In order to support the high demand for fuel utilization in the thermogenic fat, the adipocytes obtain large amounts of FAs by promoting FA uptake through transporters such as FATP1 and CD36, and by the stimulation of the *de novo* lipogenesis machinery [49,50,51]. The enhanced intake and *de novo* synthesis of FAs is accompanied by the higher rates of TAG lipolytic breakdown and consumption of the resultant FAs by the mitochondrial thermogenic machinery. It is currently understood that the thermogenic activation of BAT under cold, requires FAs released from lipolytic breakdown of TAGs in white fat rather than BAT [52,53]. The uptake of FFA into BAT is supported by insulin-mediated translocation of the aforementioned FA transporters [53]. Under short-term cold exposure or acute β -adrenergic stimulation, lipolysis of WAT promotes the release of FFA which ultimately leads to insulin secretion from pancreatic β -cells. The surge of circulating insulin results in an increased translocation of CD36 to the plasma membrane of brown fat, thereby leading to the clearance of circulatory FFA and activation of UCP1-mediated thermogenesis [54] (Fig. 1).

4.2. Structural lipids

In combination with the enhanced FA turnover in the thermogenic fat, changes in the activity of the enzymatic machinery for FA metabolism also promote profound alterations in the lipidomic landscape. UCP1 is abundantly expressed in the mitochondrial inner membrane of brown adipose tissues, which implies that both the function and structure of UCP1 are affected and likely regulated by the surrounding phospholipid molecules in the mitochondrial inner membrane [19,20]. Cardiolipins (CL, [(1',3'-bis(1,2-dioleoyl)-sn-glycero-3-phospho)-sn-glycerol (sodium salt)]) serve as a major lipid component of the mitochondrial inner membrane that accounts for approximately 20% of the total mitochondrial lipid content [19,20]. CL is a diphosphatidylglycerol molecule, which is

composed of one PG molecule and one cytidine diphosphate diacylglycerol molecule by the enzyme cardiolipin synthase 1 (CRLS1). The presence of CL can stabilize UCP1-associated oligomeric and monomeric forms resulting in enhanced proton transport activity [55]. Importantly, PG and CL metabolism is activated in both brown and white fat of mice housed in cold environment [56]. While the total CL content remains unchanged in the adipose tissues of cold-exposed mice, the concentrations of certain lower abundant CL species (such as those containing PG species with 18:1, 16:1, and 16:0 fatty acid tails) are significantly higher in BAT of cold-challenged animals [56]. Consistent with these findings, CRLS1 was upregulated upon cold exposure in brown adipocytes, and the BAT-specific deletion of *Crls1* mice display reduced energy expenditure and impaired glucose homeostasis [48].

Combining RNAseq and lipidomics analyses, Marcher et al., have identified an increase in the concentration of glycerophospholipid species, as well as the genes involved in the biosynthesis of these lipid species, in BAT from mice exposed to cold [14]. They additionally found a pronounced accumulation of several TAG species containing long- and very-long-chain saturated fatty acyls along with higher levels of the C18:0, C20:0, and C22:0 acyl chains in TAG in the BAT of cold-exposed mice [14]. The accumulation could be explained by enrichment of the elongation pathway, especially *Elovl3*, the gene encoding the main enzyme involved in the elongation of fatty-acids in brown adipocytes. The elongation of fatty-acids in the BAT during adaptive thermogenesis may be a natural way to provide more suitable fuel for UCP1 activation, since LCFAs are known to more efficiently activate UCP1 [44].

4.3. 12-HEPE

Cold exposure accelerates the lipid turnover in adipocytes, which includes enhanced uptake, utilization, metabolism and secretion. As a consequence, certain lipid species produced by the activated enzymatic pathways can regulate metabolic processes for cold adaptation. Oxygenases such as LOX, COX, and Cyp450, are stimulated to produce oxidized lipid species, known as oxylipins, during adaptive thermogenesis [9,49, 57,58]. The oxylipins can regulate cellular fuel mobilization and activate UCP1, thereby supporting thermogenesis [9,49,57,58]. Recently, our group has demonstrated that 12-LOX activity in BAT is required for cold adaptation due to its capacity to biosynthesize and release the oxylipin 12-hydroxyeicosapentaenoic acid (12-HEPE) from BAT [9] (Fig. 1). Chemical inhibition or BAT-specific deletion of 12-LOX in mice leads to an impaired capacity to maintain body temperature under acute cold challenge. 12-HEPE is a metabolite of omega-3 PUFA EPA via the activity of 12-LOX. In mice, 12-HEPE promotes glucose uptake into BAT and skeletal muscle through activation of the PI3K-mTOR-Akt-Glut pathway, thus improving glucose homeostasis. In humans, circulating levels of 12-HEPE are elevated in response to oral treatment with β 3-adrenergic agonist mirabegron and negatively correlate with body mass index and insulin resistance [9]. A recent study has demonstrated that circulating levels of 12-HEPE are higher in human subjects with detectable BAT activity (BATpos), in comparison with those with undetectable BAT activity [59]. Moreover, 12-HEPE levels were significantly increased by cold exposure only in the BATpos group, supporting the notion that 12-HEPE is a cold-induced lipokine produced by BAT in humans [59]. These findings shed light on a new role for lipoxygenases and their oxylipin products in the regulation of

glucose metabolism and adaptive thermogenesis in both mice and humans. Although the mechanism for the glucose shuttling effect was detailed, further studies are warranted to elucidate the mechanism by which 12-HEPE support thermogenesis.

4.4. 12,13-diHOME

12,13-diHOME is the product of cyp450 epoxygenase and epoxide hydrolase from linoleic acid. It was identified as a cold-induced oxylipin in the circulation of mice and humans using both untargeted and targeted LC-MS/MS lipidomic analysis [49]. An initial study found that the levels of 12,13-diHOME were significantly lower in obese individuals and negatively correlated with triglyceride and circulating markers of liver function [49]. These findings were validated in other large human cross-sectional studies [60,61]. 12,13-diHOME supports thermogenesis by shuttling FA into brown adipocytes (Figure 1). As a consequence of facilitating lipid utilization, treatment of DIO mice with 12,13-diHOME significantly reduces circulatory triglycerides' levels [49]. This oxylipin is also secreted under physical exercise in both humans and mice to support muscle activity by mediating FA uptake into the skeletal muscle [62]. Importantly, brown fat appears to be the major site of 12,13-diHOME production in response to cold or exercise challenge. It is worth mentioning that circulating levels of 12,13-diHOME and 12-HEPE are strongly correlated with BAT activity as measured by radiolabeled glucose uptake [9,49,59], suggesting that these lipids could serve as surrogate biomarkers for BAT activation in humans.

4.5. Long-Chain Acylcarnitines

Both 12-HEPE and 12,13-diHOME are produced by activated BAT with an autocrine activity that promotes fuel mobilization under cold. However, other secreted lipids that are not biosynthesized by BAT can also regulate BAT thermogenesis under cold. That is the case for the long-chain acylcarnitines (LCAC), which are biosynthesized in the liver upon short-term cold exposure or β 3-adrenergic stimuli, and then secreted to activate UCP1 in BAT [10] (Fig. 1). LCAC production in the liver requires HNF4 α activation, which directly regulates the expression of genes involved in acylcarnitine metabolism. Activation of HNF4 α requires FFA release from WAT upon lipolysis [10]. Moreover, FFAs serve as the substrates for LCAC biosynthesis in the liver [10]. Thus, short-term cold adaptation involves an inter-organ network between WAT, liver and BAT, which requires the use of lipid species as messengers to interconnect them and support thermogenesis.

4.6. Plasmalogens

Plasmalogens are plasmenyl-phospholipids that have an ether bond in position sn-1 to an alkenyl group, and have abundant expression in many human tissues, especially cardiac and neural tissues [63]. Biosynthesis of plasmalogens is catalyzed by the peroxisomal matrix enzymes GNPAT and AGPS. The first steps of the plasmalogens' biosynthesis takes place at the luminal side of the peroxisome membrane [63]. Peroxisomes are multifunctional organelles found abundant in BAT, and among many other functions, these structures enable the biosynthesis of plasmalogens, which seem to play a crucial role in mitochondrial dynamics under cold conditions.

Peroxisomes' biogenesis involves proteins called peroxins. Three of these factors, Pex3, Pex16, and Pex19, were found increased in BAT and iWAT of mice exposed to cold [64]. Park and colleagues have shown that peroxisomes' biogenesis is enhanced in the BAT and beige fat of cold-exposed mice as a consequence of Prdm-16 mediated increase in Pex16 expression. Deletion of Pex16 in adipocytes prevented the mitochondrial fission and mtDNA copy number induced by cold, resulting in mitochondrial dysfunction along with a severe impairment in the thermogenic capacity. Transgenic mice harboring an adipose-specific deletion of GNPAT, the rate-limiting enzyme for plasmalogen synthesis, phenocopied adipocyte-specific Pex16 knockout mice. Furthermore, supplementation with plasmalogens rescued mitochondrial function and restored thermogenesis in Pex16-AKO mice, indicating that peroxisomes regulated adipose tissue thermogenesis by producing and directing plasmalogens to mitochondria to mediate mitochondrial fission [64].

5. Conclusions and perspectives

The longstanding notion that lipids could merely serve as an energy supply for cells, or as substrates for composing cell membranes, has significantly evolved over the last few years. It has been noted that lipids play a critical role in metabolism by triggering their specific signaling pathways to regulate cellular function and processes such as differentiation, gene expression, apoptosis, mitochondrial bioenergetics, and substrate uptake, among others. Clearly, all the studies herein mentioned indicate that the adipocyte lipidome profile adapts to dietary composition and intake, thermal stress, and physical activity. Furthermore, the lipidome remodeling is not only a result of adaptation to these conditions, but also actively regulates the cellular processes, leading to changes in adipocyte function that are required during environmental challenges, such as adaptive thermogenesis or high fat feeding. Moreover, the role of the lipids as messengers in inter-organ communication has attracted great attention. The lipokines produced by adipose tissue, the liver, or other organs, has proven to play a key role in metabolic regulation by way of a complex inter-organ network in response to energy status and demands.

The recent emergence of novel LC-MS/MS based lipidomic platforms for quantification of a broad range of lipid species, associated with very specific gene editing tools, has enabled researchers to better understand the physiological role of lipids that were previously unknown or had no annotated signaling pathway or function. Yet there persist a large amount of orphan lipids without defined actions, indicating an enormous avenue of research lay ahead to understand the complex networks and targets of these lipids in different contexts, from health to disease. Studies using molecular or chemical approaches to specifically delete or inactivate the rate-limiting enzymes for lipid metabolite production will help to understand the function, source, and flux of the lipids that regulate adipocyte functions, and their wider implications for whole-body metabolism. Beyond the importance of the physiological relevance of lipid species, the characterization of the targets to which they bind in order to promote certain biological effects can be of great utility in the development of new therapeutic approaches for combating metabolic diseases.

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Abbreviations

12-HEPE	12-Hydroxyeicosapentaenoic acid
12,13-diHOME	12,13-dihydroxy-9Z-octadecenoic
AGPS	alkyl-glycerone phosphate synthase
Akt	protein kinase B
aSMase	acid sphingomyelinase
cAMP	cyclic adenosine monophosphate
CD36	cluster of differentiation 36
COX	cyclooxygenase
CRLS1	Cardiolipin Synthase 1
Cyp450	cytochrome P450
DAG	diacylglycerol
DHA	docosahexaenoic acid
Elovl3	ELOVL fatty acid elongase 3
Elovl6	ELOVL fatty acid elongase 6
EPA	eicosapentaenoic acid
FAs	fatty acids
Fatp1	fatty acid transport protein 1
FFAs	free-fatty acids
GLUT-1	glucose transporter protein isoform 1
GLUT-4	glucose transporter protein isoform 4
GNPAT	glyceronephosphate O-acyltransferase
GPCR	g-protein coupled receptor
HNF4α	Hepatocyte Nuclear Factor 4α
LCFA	long-chain fatty acid

LC-MS/MS	Liquid Chromatography Mass Spectrometry
LOX	lipoxygenase
mtDNA	mitochondrial DNA
mTOR	mammalian target of rapamycin
MUFAs	monounsaturated fatty acids
nSMase	neutral sphingomyelinase
ob/ob	leptin deficient
Pex3	peroxisomal biogenesis factor 3
Pex16	peroxisomal biogenesis factor 16
Pex19	peroxisomal biogenesis factor 19
PI3K	phosphatidylinositol-3-kinase
PUFAs	polyunsaturated fatty acids
SFAs	saturated fatty acids
Sptlc	serine palmitoyltransferase (gene)
SPT	serine palmitoyltransferase (protein)
TAG	triacylglycerol
TNFα	tumor necrosis factor-alpha
UCP1	Uncoupling protein 1

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Highlights:

- Adipose tissue (AT) lipidome profiles influence global energy metabolism.
- Distinct white and brown AT lipidomes reflect their physiological functions.
- Obesity-induced changes in AT lipidomics contribute to metabolic dysfunction.
- AT-produced lipids govern energy metabolism.

Fig. 1. Lipid network activated by cold exposure.

In BAT, cold exposure triggers a sympathetic-driven pathway consisting of lipolytic breakdown of TAG in precursor fatty acids such as alpha-linolenic acid and linoleic acid, which in turn undergo a sequence of enzymatic reactions to yield 12-HEPE and 12,13-diHOME, respectively. These oxylipins support thermogenesis by stimulating the translocation of glucose and fatty acid transporters, thus allowing the substrate entrance and utilization by the brown adipocytes. In WAT, lipolysis triggered by cold stimuli allows the secretion of FFA, which can migrate to BAT and directly stimulate UCP1-dependent thermogenesis. WAT-released FFA can also promote glucose-stimulated insulin secretion from pancreatic β -cells at short-term cold exposure. The secreted insulin subsequently facilitates glucose and FFA uptake into BAT in order to provide fuel to be used as substrate for UCP1 activation. FFA released from WAT lipolysis also triggers a transcriptional network in the liver involving the transcriptional factor HNF4 α , which stimulates the expression of genes involved in long-chain acylcarnitine (LCAC) metabolism. LCAC can then activate UCP1-dependent thermogenesis in BAT during cold challenge. IR: insulin receptor; TAG: triacylglycerol; FFA: free fatty acids; LCAC: long-chain acylcarnitine; EPA: eicosapentaenoic acid; LA: linoleic acid; FAO: fatty-acid oxidation.