Adipose Tissue Lipokines: Recent Progress and Future Directions

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Beyond classical metabolic functions in energy storage and energy expenditure, adipose tissue is also a dynamic endocrine organ that secretes bioactive factors into blood plasma. Historically, studies of the adipose secretome have predominantly focused on polypeptide adipokines. Recently, adipose-derived blood-borne lipids ("lipokines") have emerged as a distinct class of endocrine factors. Lipokines are intimately connected to intracellular pathways of fatty acid metabolism and therefore uniquely poised to communicate the intracellular energy status of adipocytes to other nonadipose tissues including liver, muscle, and pancreas. Here, we discuss recent progress on our understanding of adipose-secreted lipokines as endocrine regulators of glucose and lipid metabolism. We also provide our perspective on future directions for adipose-secreted lipids, including limitations of the currently available experimental data as well as potential strategies for addressing the remaining open questions.

Adipose tissue is a major metabolic and endocrine organ involved in systemic energy, glucose, and lipid homeostasis. This endocrine function is mediated in part by adipose-secreted, blood-borne circulating factors (1). Historically, the most well-characterized adipose-secreted circulating factors have been proteins (e.g., adipokines) including leptin, adiponectin, and adipsin (2). With the growing prevalence of obesity and obesity-associated disorders including insulin resistance, type 2 diabetes, cardiovascular disease, and nonalcoholic fatty liver disease, adipose-secreted factors have attracted considerable attention for their central roles in the integration of systemic metabolism as well their therapeutic potential for the treatment of chronic metabolic disease.

Beyond polypeptide adipokines, the adipose tissue secretome comprises many other chemically distinct classes of bioactive molecules. One class of such non-peptide-secreted factors is fatty acid–derived bioactive lipids. While some adipose-secreted lipids are retained in the local adipose tissue environment, others are actively secreted into the circulation. This latter group of adipose-secreted blood-borne bioactive lipids are called "lipokines." Because of their presence in blood plasma, lipokines have been proposed to function as endocrine mediators of adipose cross talk to other tissues including pancreas, liver, and muscle via a diversity of both cell-surface and intracellular mechanisms of action (Fig. 1). Furthermore, these hydrophobic molecules are biochemically connected to intracellular pathways of fatty acid metabolism and therefore uniquely poised to communicate the energy status of adipocytes to other nonadipocyte cell types. Direct pharmacological studies using lipids, as well as complementary genetic manipulation of their biosynthesis or secretion pathways in adipose tissues, have emerged as important techniques for uncovering their functional roles in intercellular signaling (Table 1). Together, these studies have revealed an exciting and remarkably fertile world of adipose cross talk and integration of systemic metabolism mediated by adipose-derived endocrine lipids.

Here, we discuss recent progress on lipokines as endocrine regulators of glucose and lipid homeostasis. We begin with a historical perspective of bioactive lipids as constituents of the adipose secretome. We next discuss adipose-derived blood-borne lipokines that function as mediators of cross talk to nonadipose tissues. Lastly, we provide our perspectives on future directions for adipose-derived lipids, including limitations of the currently available experimental data and potential strategies for addressing these critical unanswered questions.

Biochemical Evidence for Bioactive Adipose-Secreted Lipids: A Historical Perspective

Bioactive lipids have long been recognized to be a bioactive component of the adipose secretome. The first observations were made >50 years ago when Shaw and Ramwell (3)

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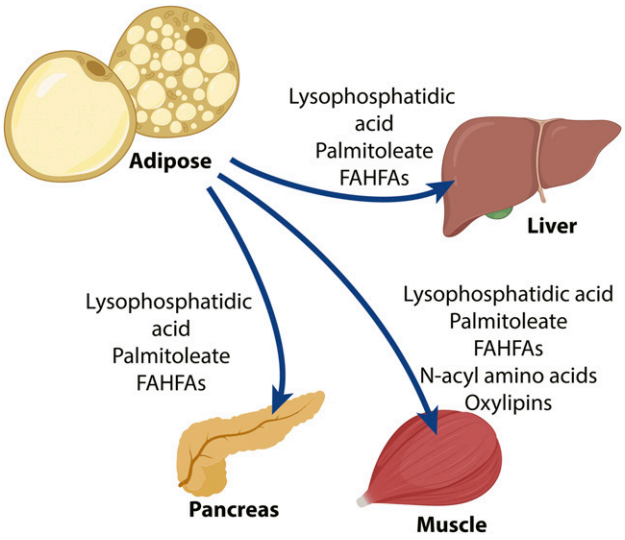


Figure 1—Schematic of adipose-derived endocrine lipids that mediate cross talk from adipose to other peripheral metabolic tissues.

demonstrated that adipose tissues secrete prostaglandins, a class of bioactive arachidonic acid–derived signaling lipids. Subsequently, adipose prostaglandins were shown to exhibit diverse autocrine/paracrine bioactivities in vitro and in animal models including potent antilipolytic activity and stimulation of thermogenesis (4). Adipocyte-conditioned media transfer experiments have uncovered additional adipocyte-secreted paracrine lipids and lipid-derived metabolites including monobutyrin (5) and β-hydroxybutyrate (6).

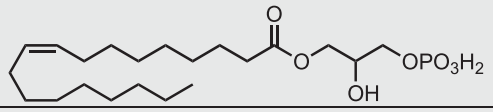
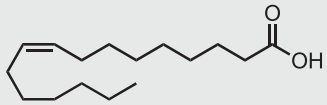
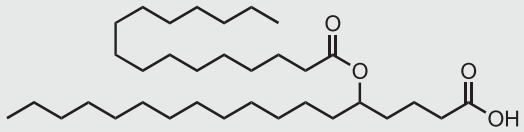
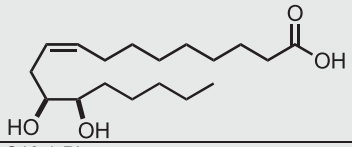
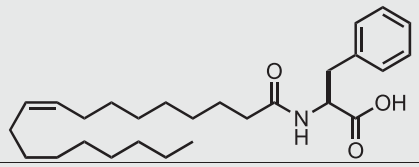
For many years, the function of adipose-secreted lipids was thought to be restricted to local autocrine/paracrine action within the adipose tissue. Even adipose-produced lipophilic hormones such as cortisol were established to be locally acting and functionally dissociated from the circulating, adrenal gland–derived pools (7). Consequently, it remained an open question as to whether adipose-derived lipids could contribute to the blood plasma and whether those molecules could function in an endocrine manner. Unlike for polypeptide adipokines, for which primary sequence (e.g., presence of an N-terminal signal peptide) and expression profiling (e.g., adipose enrichment) could easily provide clues about plasma localization and adipose-specific expression, similar analyses for adipose-derived lipids were simply not possible because lipids are not themselves genetically encoded molecules. With the recent widespread accessibility of mass spectrometry technologies and the ability to create tissue-specific transgenic or knockout mouse models, there is a growing appreciation that many adipose-derived endocrine lipids substantially contribute to the plasma metabolome and exert diverse actions on peripheral metabolic tissues. Below, we discuss recent examples of the structural and functional diversity of lipokines secreted from white and brown adipose tissues.

Adipocyte-Secreted ATX/Lysophosphatidic Acid Promotes Insulin Resistance

One of the first examples of an adipocyte-derived blood-borne lipid was lysophosphatidic acid (LPA). In 1998, LPA was originally identified as a secreted trophic lipid from differentiated 3T3-F442A adipocytes that could promote preadipocyte proliferation by acting on preadipose LPAR1, one of the five cell-surface LPA receptors (8,9). Several years later, autotaxin (ATX) (gene name *Enpp2*) was also identified to be an adipocyte-secreted enzyme responsible for extracellular adipose LPA biosynthesis (10). Adipose ATX expression was increased in genetically obese *db/db* mice and upon high-fat diet feeding, providing a provocative link between increased nutrient availability and adipose-derived LPA biosynthesis (11). Importantly, both ATX and LPA were found in blood plasma, suggesting that adipocyte-derived ATX-LPA may function in an endocrine manner. Consistent with this notion, pharmacological administration of LPA promoted systemic insulin resistance by acting at the pancreas, liver, and muscle. For instance, direct administration of LPA to mice impaired glucose-stimulated insulin secretion in an LPAR1/2/3-depenent manner (12). LPA was also shown to antagonize insulin signaling and inhibit mitochondrial respiration in muscle tissue and C2C12 cells in vitro (13). Finally, in hepatocytes, LPA inhibited insulin signaling in an LPAR3-dependent manner (14).

For the determination of the endocrine contribution of adipose-derived LPA, three different adipose-specific ATX knockout mice were generated and characterized (15–17). Dusaulcy et al. (15) and Nishimura et al. (16) both generated adipose-specific ATX knockout mice using *aP2*-cre. Dusaulcy et al. (15) reported that their mice exhibit dramatic depletion of ATX in brown and white fat with no changes to ATX in other tissues. This was associated with an ∼40% reduction in circulating LPA levels, demonstrating that adipose tissues are a significant contributor to total extracellular LPA. Following high-fat diet feeding, Dusaulcy et al. showed that adipose-specific ATX knockout animals have improved glucose tolerance despite an overall increased adiposity. Similarly, Nishimura et al. (16) reported that adipose-specific ATX knockout mice also exhibited dramatically improved glucose and insulin tolerance compared with high-fat diet–fed littermates, but with an associated hypermetabolic phenotype, which was ascribed to increased brown adipose thermogenesis. Most recently, Brandon et al. (17) generated adipose-specific ATX knockouts using the more specific *Adipoq*-cre driver. In contrast to the other models, these knockout mice did not show any changes in glucose homeostasis but did exhibit protection from diet-induced hepatic steatosis, an effect that was associated with decreased gene expression for hepatic triglyceride synthesis genes. While specific downstream receptors and cell types responsible for the metabolic phenotypes for each of these knockout mice have not been fully characterized, overall it appears that loss of adipose-derived LPA results in improved systemic glucose and lipid homeostasis.

Table 1—Summary of adipose tissue lipokines, their molecular and physiologic regulation, and proposed target tissues and endocrine functions

Lipokine class	Representative chemical structure and name	Metabolic enzymes	Regulation	Signaling and known functions	Target tissues	Receptor or mechanism of action
LPA	C18:1-LPA 	ATX	Plasma levels increased by high-fat diet	Antagonism of insulin signaling	Adipose, pancreas, liver, muscle	LPAR1-5
Palmitoleate		SCD1	Plasma levels increased by carbohydrate intake	Insulin sensitizing	Liver, muscle	Not known
FAHFAs	5-PAHSA 	CEL, AIG1, ADTRP	Plasma and adipose tissue levels suppressed by high-fat diet and suppressed in insulin-resistant humans	Insulin sensitizing, anti-inflammatory	Adipose, pancreas, gut, liver	GPR120, GPR40
Oxylipins	12,13-diHOME 	EPHX1/2, ALOX12	Plasma levels elevated in cold-exposed mice and humans	Stimulation of fatty acid uptake and cellular respiration	Adipose, muscle	Involves translocation of CD36 and FATP1 to plasma membrane
N-acyl amino acids	C18:1-Phe 	PM20D1, FAAH	Plasma levels elevated in chronically cold exposed mice	Stimulation of mitochondrial uncoupling and cellular respiration	Adipose, muscle	Import to cells and binding to mitochondrial SLC25 transporters

Adipose-Secreted Palmitoleate Is an Insulin-Sensitizing Lipid Metabolite

The monounsaturated fatty acid palmitoleate was identified as an adipose-derived circulating lipid in 2008. Previously, ablation of both *Fabp4* and *Fabp5* was shown to produce a mouse model with remarkable resistance to metabolic syndrome, including protection from diet-induced obesity, insulin resistance, and fatty liver disease (18). Because *Fabp4* and *Fabp5* encode fatty acid–binding proteins, Cao et al. (19) hypothesized that alterations of an individual or specific set of fatty acid mediators might be responsible for these systemic metabolic phenotypes. Cao et al. (19) showed that palmitoleate was selectively elevated in multiple tissues and blood plasma from *Fabp4*/*5* double knockout mice compared with control animals. Furthermore, palmitoleate biosynthesis was stimulated by lipogenesis in adipose tissues, directly linking its production to adipose nutritional state.

Palmitoleate is distinct from other common mono- and polyunsaturated fatty acids by the position of its double bond: whereas palmitoelate is an n-7 fatty acid, other common fatty acids are n-3 fatty acids (e.g., eicosapentaenoic acid, high in fish), n-6 fatty acids (e.g., linoleic acid, high in nuts and seed oils), and n-9 fatty acids (e.g., oleic acid, high in olive oil). This small structural change may explain the distinct bioactivity of palmitoleate compared with other fatty acids. In the original report, palmitoleate in the triglyceride-esterified form TG-palmitoleate was demonstrated to function as an insulin sensitizer in both the liver and muscle tissues when reinfused to mice. This bioactivity was not observed with TG-palmitate, establishing that the double bond position in palmitolate is an important determinant of the insulin-sensitizing effects. At a whole-body level, infusion with palmitolate resulted in increased glucose infusion rate and disposal rate under hyperinsulinemic-euglycemic clamp conditions. Cao et al. proposed that palmitoleate is an adipose-secreted lipid metabolite that improves systemic insulin sensitivity by action on both liver and muscle.

Concurrent with and since the original publication, additional studies in vitro and in mice have confirmed a positive effect of palmitolate on insulin sensitivity. For instance, palmitolate-stimulated glucose uptake in rat L6 skeletal muscle cells (20), promoted insulin signaling in cultured

hepatocytes (21), and increased insulin sensitivity in the spontaneously diabetic KK-Ay mouse model (22). However, measurements of circulating palmitoleate in humans have revealed a more complex relationship between this lipid and insulin sensitivity. For instance, some studies have found a positive association of plasma palmitoleate levels with insulin sensitivity (23), while others have not (24). Therefore, while palmitoleate is generally agreed to be released from adipose tissues and can exert insulin-sensitizing bioactivity when pharmacologically applied to cells or animals, many questions still remain open about its endogenous physiologic roles and relevance to human metabolic health. An important and complicating aspect relates to measurements of palmitoleate itself: palmitoleate can be found in both *cis* and *trans* forms, both of which can be endogenously synthesized and also taken in as part of diet, and found in "free" fatty acid form as well as esterified into other types of lipids such as triglycerides or phospholipids. Not all studies to date have reported the specific form of palmitoleate measured or functionally tested. Specific dissection of the functional roles for specific palmitoleate forms (*cis* vs. *trans*, free vs. esterified) as well as genetic models that selectively abolish palmitoleate biosynthesis or secretion from adipose would clarify these important questions.

Adipose-Secreted FAHFAs Are Orphan Antidiabetic Lipid Metabolites

Yore et al. (25) used adipose-specific GLUT4-overexpressing mice to identify a family of orphan lipids called fatty acid hydroxy fatty acids (FAHFAs). Previously, adipose-specific overexpression of the facultative GLUT GLUT4 led to improved glucose tolerance despite increased adiposity, suggesting the presence of an adipose-derived insulin-sensitizing factor (26). Hypothesizing that a lipid biosynthesized via GLUT4-stimulated lipogenesis was the responsible factor, Yore et al. (25) applied untargeted lipidomics to these mice and identified dramatic elevation of FAHFAs in adipose tissues and blood plasma. This large lipid class, which was a previously unknown family of lipids, encompasses many structurally distinct members differing in either the hydroxy acyl chain or the main fatty acid acyl chain. FAHFAs were reported to be secreted by adipocytes into blood plasma and dynamically regulated by fasting and high-fat diet feeding. In humans, FAHFA levels in both adipose tissues and plasma are correlated with insulin sensitivity and decreased in insulin-resistant states.

Functionally, FAHFAs exhibit antidiabetic effects in mice. The most well-characterized FAHFA species are those of the PAHSA (palmitic acid esters of hydroxy stearic acid) subclass. Direct administration of 5-PAHSA or 9-PAHSA to mice leads to improved glucose tolerance and enhanced systemic insulin sensitivity (25,27,28). This antidiabetic effect appears to be mediated by diverse autocrine, paracrine, and endocrine actions. Within the adipose tissue, PAHSAs promote glucose uptake, augment the antilipolytic effects of insulin, and suppress proinflammatory cytokine production from adipose tissue macrophages (25). Beyond adipose, in the pancreas PAHSAs enhance glucose-stimulated insulin secretion and β-cell survival; the latter effect appears to be via attenuation of ER stress (28). PAHSAs also directly act on enteroendocrine cells to promote GLP-1 secretion. Lastly, certain PAHSAs also have direct effects on the liver to reduce basal as well as glucagon-stimulated glucose production (27). The diverse effects of FAHFAs on specific cell types appear to be mediated by specific cell-surface receptors on each cell type. Candidate free fatty acid G-protein–coupled receptors that have been proposed include the free fatty acid receptors GPR120 and GPR40 (25,29). While some of these anti-inflammatory effects of FAHFAs have been reproduced, others have disputed the antidiabetic actions of FAHFAs (30). These differences which may be at least partially accounted for by technical issues in the experimental procedures (31).

Regarding pathways of FAHFA biosynthesis and metabolism, several enzymes have been identified as candidate FAHFA metabolic enzymes. These include carboxy ester lipase (CEL), an enzyme previously characterized to hydrolyze cholesterol esters, as well as the membrane hydrolases AIG1 and ADTRP, which exhibit selectivity for hydrolyzing FAHFA over other lipid classes (32,33). AIG/ADTRP double knockout mice were reported to have dramatically elevated brown fat FAHFAs and exhibited modestly reduced body weight but no changes to glucose disposal or insulin sensitivity (34). These data suggest the likely presence of additional, and potentially tissue-specific, alternative metabolic pathways for FAHFA metabolism, which still remain molecularly uncharacterized.

Brown Fat–Secreted Oxylipins Promote Adipose and Muscle Fatty Acid Uptake

The brown fat secretome has attracted considerable attention in recent years with regard to strategy for "capturing" the metabolic benefits of this cell type without direct adrenergic activation or cold exposure. One such class of brown fat–secreted metabolites is oxylipins, a structurally diverse family of oxidized polyunsaturated fatty acid derivatives. The two best studied brown fat–secreted oxylipins are 12,13-diHOME, generated by dihydroxylation of linoleic acid, and 12-HEPE, a lipid from hydroxylation of docosahexaenoic acid (35–37). Lynes et al. (35) identified 12,13-diHOME as a brown fat–secreted metabolite by lipidomic profiling of plasma from mice and humans following cold exposure (35). Biosynthetic enzymes for 12,13-diHOME, including epoxide hydrolases (*Ephx1* and *Ephx2*), were selectively upregulated in brown fat after chronic cold exposure. 12,13-diHOME, also called isoleukotoxin diol, was originally identified as a proinflammatory, toxic metabolite (38). In contrast, Lynes et al. (35) and Stanford et al. (36) demonstrated that 12,13-diHOME exhibited metabolically beneficial bioactivities by promoting fatty acid uptake and cellular respiration in brown fat and skeletal muscle in vitro and in mice, a bioactivity

associated with plasma membrane translocation of the fatty acid transporters CD36 and FATP1.

In more recent studies, Leiria et al. (37) showed that brown fat secretes several products of the 12-lipoxygenase enzyme (12-LO, gene name *Alox12*), including 12-HEPE, into conditioned media in vitro and blood plasma in mice and humans. Importantly, brown fat–specific deletion of 12-LO in mice abolished cold-induced increases in 12-HEPE in the blood. Functionally, these knockout mice exhibited reduced body temperature following cold exposure and blunted norepinephrine-stimulated oxygen consumption, demonstrating that 12-HEPE can act in an autocrine manner to stimulate thermogenesis and energy expenditure. Additional functional studies demonstrated that 12-HEPE, like 12,13-diHOME, significantly increased glucose uptake of C2C12 myotubes in vitro and muscle tissues in vivo. Taken together, these data demonstrate that brown fat–secreted oxylipins can act in both an autocrine and an endocrine manner to promote fatty acid and glucose uptake in brown fat and muscle. To date, the specific cell-surface receptors responsible for these effects have not been established, though certain G-protein–coupled receptors and TRP ion channels are potential candidates (39).

Brown Fat–Secreted PM20D1/N-acyl Amino Acids Stimulate Mitochondrial Respiration and Whole-Body Energy Expenditure

A second class of brown fat–secreted metabolites are the N-acyl amino acids, a family of fatty acid–amino acid conjugates. These unusual lipids had been endogenously detected in adipose and other mammalian tissues, but their physiologic functions remained mysterious (40). In 2016, we deorphanized the secreted enzyme PM20D1 as an N-acyl amino acid biosynthetic enzyme highly enriched in brown versus white adipose (41). Adipose expression of *Pm20d1* was increased by adrenergic agonists and cold exposure in mice and antidiabetic thiazolidinediones in humans (42). Plasma N-acyl amino acids are also elevated following chronic cold exposure (41,43,44). Functionally, N-acyl amino acids exhibited autocrine/paracrine and endocrine activities as direct stimulators of cellular respiration in adipocytes as well as nonadipocytes such as C2C12 muscle cells (41,45,46). Structure-activity studies demonstrated a remarkable specificity to the specific structural features that promote mitochondrial respiration: only those N-acyl amino acids with neutral amino acid head groups and medium desaturated fatty acid chains, such as that present in N-oleoyl-phenylalanine and N-oleoyl-leucine, exhibited bioactivity (46). Administration of these thermogenic N-acyl amino acids to mice with diet-induced obesity increased whole-body energy expenditure, reduced adiposity, and improved glucose clearance. Importantly, these effects were not observed with pharmacological administration of the corresponding fatty acid alone, establishing that the intact amino acid–fatty acid conjugate is required for this bioactivity.

One mechanism by which N-acyl amino acids stimulate respiration appears to be direct import to cells and action by uncoupling mitochondrial respiration. Two lines of evidence support such a pathway. First, N-acyl amino acids can directly stimulate respiration on isolated mitochondria, demonstrating that intracellular signal transduction pathways are not formally required for this respiratory bioactivity. Second, N-acyl amino acids directly bind to mitochondrial SLC25 transporters including the adenine nucleotide translocases (SLC25A4 and SLC25A5). These mitochondrial inner membrane carriers are known to function as fatty acid–stimulated proton translocators (41). Therefore, N-acyl amino acids mimic the action of other mitochondrial uncouplers such as UCP1 and dinitrophenol. Beyond this "direct" pathway, N-acyl amides have also been reported to act as ligands at cell-surface G-protein–coupled receptors and ion channels. Whether these other cell-surface mechanisms are involved in N-acyl amino acid bioactivity on cellular respiration remains to be determined.

Genetic manipulation of PM20D1- or PM20D1-associated factors has also provided additional insights into the regulation and function of N-acyl amino acids. For instance, direct viral overexpression of PM20D1 from the liver was sufficient to elevate circulating N-acyl amino acids and produced a hypermetabolic phenotype characterized by reduced adiposity and resistance to diet-induced weight gain (41). We also found that PM20D1 could be coactivated by lipoprotein association (43). Consequently, elevation of lipoproteins, such as in the APOE-KO mouse, was sufficient to drive PM20D1 activity, N-acyl amino acid biosynthesis, and a hypermetabolic phenotype despite hyperlipidemia and hypercholesterolemia. Conversely, global PM20D1 knockout mice, while not having global depletion of N-acyl amino acids due to compensatory alternative biosynthetic pathways, nevertheless exhibited bidirectional dysregulation of circulating N-acyl amino acids (44,47). PM20D1 knockout mice exhibit insulin resistance and impaired glucose homeostasis following high-fat or Western diets in the absence of any changes to adiposity, demonstrating that changes to circulating N-acyl amino acids can contribute to systemic insulin resistance.

Lastly, the potential role of N-acyl amino acids in human metabolic health remains unknown. Nevertheless, polymorphisms in human *PM20D1*, including a missense I380T mutation, are linked to obesity (42), suggesting a potential role for N-acyl amino acids in human energy balance.

The Road Ahead

Several distinct classes of lipokines have now been identified in blood plasma, and, largely with use of pharmacological approaches in cells and in mice, their endocrine functions in glucose and lipid homeostasis are also beginning to be uncovered. Taken together, these data strongly suggest that adipose-derived lipids represent another endocrine axis by which adipose tissues communicate with nonadipose cell types and tissues. Nevertheless, in our opinion there remain three major gaps in our knowledge

about lipokine structure and function *1*): structure-activity studies of lipokine bioactivity, *2*) upstream and downstream protein regulation of lipokine levels and function, and *3*) genetic evidence for physiologic lipokine circuits in the context of an intact organism. We propose that future experimental data addressing questions in these three outstanding areas could dramatically improve our understanding of lipokines in intercellular communication and metabolic homeostasis.

Structure-Activity Studies of Lipokine Bioactivity

Many lipokines are based on a similar structural backbone, but with important chemical differences for specific species within the class. For instance, the N-acyl amino acids are all fatty acid–amino acid amide conjugates but differ in terms of specific fatty acids or amino acids; the FAHFAs are all fatty acid esters, differing in fatty acid, oxidation location, and stereochemistry; and the oxylipins are all oxidized polyunsaturated fatty acids but, once again, differing in oxidations in the form of oxygen atoms and double bonds. How these structural differences translate into potential functional differences remains a central yet largely unanswered question. Chemical synthesis of individual candidate structures differing in stereochemistry and sites of oxidation, coupled with functional in vitro and/or in vivo assays, will be required to address this important issue. Knowledge of active versus inactive structures could help guide the production of synthetic derivatives with improved pharmacokinetics, pharmacodynamic, or oral bioavailability properties, analogous to the development of dexamethasone and other synthetic analogs of the corticosteroids. Furthermore, such studies could also identify structurally inactive isomers, which could be subsequently used to control for potential nonspecific effects associated with pharmacological application of hydrophobic substances to cells or in animals.

Upstream and Downstream Protein Regulation of Lipokine Levels and Function

All classical metabolite signaling pathways have molecularly characterized upstream proteins involved in the regulation of metabolite levels and also downstream proteins involved in metabolite signaling and function. For instance, corticosteroid signaling involves upstream biosynthetic enzymes (CYP11B1, CYP21A1), plasma carrier proteins (SERPINA6, albumin), and downstream intracellular receptors (MR and GR). By contrast, our understanding of the upstream and downstream regulation of many adipose-derived secreted lipids remains largely preliminary. We only have some understanding of their biosynthetic machinery or downstream receptor targets and essentially no holistic, integrated view of their molecular regulation or systemic functions. Achieving this level of pathway mapping for individual adipose lipokines remains an important and still largely unmet goal. Knowledge of these pathway regulators would enable new mouse models for interrogating metabolic consequences following genetic manipulation of endogenous lipokine levels. These pathway regulators could also provide genetic handles for identifying polymorphisms or loss-of-function mutations linked to metabolic disease in humans.

Genetic Evidence for Physiologic Lipokine Circuits

Endocrine circuits have classically been established by surgical ablation of hormone biosynthesis and rescue of those effects by pharmacological administration of the candidate hormones. Genetic knockout models have been similarly used to establish endocrine factors for tissues that cannot themselves be surgically removed (e.g., liver-derived FGF21). With only a few exceptions (15–17), equivalent experimental evidence for adipose-derived lipokines has not yet been established. In part, this has been due to a technical barrier in creating genetic mouse models with both selective and also complete ablation of lipokines. For instance, rather than the anticipated insulin-resistant mouse that would be predicted for ablation of a palmitoleate biosynthetic pathway, global knockout of SCD1 instead produces a hypermetabolic, insulin-sensitive mouse (48). This SCD1 knockout phenotype may be due to a combination of both changes to other SCD1 substrates beyond palmitate alone and also other compensatory metabolic pathways for palmitoleate biosynthesis. Multiple gene knockouts may be required to generate these models. While from a technical point of view this question remains by far the most challenging to address, nevertheless robust genetic models for lipokine loss-of-function studies in mice or humans will provide important evidence to concretely establish endogenous roles of these blood-borne factors in interorgan metabolic communication.

Summary

The adipose secretome is a rich source of endocrine molecules that mediate intercellular communication between adipose and other tissues. Beyond classical polypeptide adipokines, in recent years there has been a growing recognition that adipose-secreted endocrine lipids, including LPA, palmitoleate, FAHFAs, oxylipins, and N-acyl amino acids, constitute another important class of adipose-derived chemical messengers. Complementary pharmacological and genetic studies have identified endocrine functions for these lipid molecules in mediating cross talk to the pancreas, liver, and muscle. Such lipid-mediated signaling may in fact represent a more general endocrine mechanism for interorgan metabolic communication (49,50). We propose that future studies should focus on the determination of lipokine structure-activity relationships, identification of upstream and downstream proteins involved in regulating lipokine levels and activity, and development of robust genetic models that provide evidence for physiologic lipokine circuits in the context of an intact organism. Lastly, considering that synthetic analogs of other endocrine lipophilic hormones have already been approved as drugs (e.g., dexamethasone, levothyroxine, and obeticholic acid), how adipose-derived endocrine lipid pathways might be translated into real therapeutic opportunities for obesity,

insulin resistance, type 2 diabetes, and other chronic metabolic diseases remains an exciting and potentially fertile area for future work.

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