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# Adipose tissue lipid metabolism: lipolysis

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White adipose tissue stores fatty acid (FA) as triglyceride in the lipid droplet organelle of highly specialized cells known as fat cells or adipocytes. Depending on the nutritional state and energy demand, hormonal and biochemical signals converge on activating an elegant and fundamental process known as lipolysis, which involves triglyceride hydrolysis to FAs. Almost six decades of work have vastly expanded our knowledge of lipolysis from enzymatic processes to complex protein assembly, disassembly, and post-translational modification. Research in recent decades ushered in the discovery of new lipolytic enzymes and coregulators and the characterization of numerous factors and signaling pathways that regulate lipid hydrolysis on transcriptional and post-transcriptional levels. This review will discuss recent developments with particular emphasis on the past two years in enzymatic lipolytic pathways and transcriptional regulation of lipolysis. We will summarize the positive and negative regulators of lipolysis, the adipose tissue microenvironment in lipolysis, and the systemic effects of lipolysis. The dynamic nature of adipocyte lipolysis is emerging as an essential regulator of metabolism and energy balance, and we will discuss recent developments in this area.

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## Introduction

White adipose tissue (WAT) triacylglycerol (TAG) is the primary energy reserve in higher eukaryotes [1]. During times of energy deprivation, WAT undergoes a shift toward the hydrolysis of TAG to generate fatty acids (FAs) and glycerol, a lipolysis process that is released for internal use and into the vasculature for use by other organs as energy substrates [2,3]. TAG is hydrolyzed sequentially to form diacylglycerol (DAG), then monoacylglycerol (MAG), with the liberation of a FA at each stage. MAG is hydrolyzed to release the final FA and glycerol. This lipid pool is in a constant state of flux, resulting from a largely futile cycle of lipolysis and re-esterification [2].

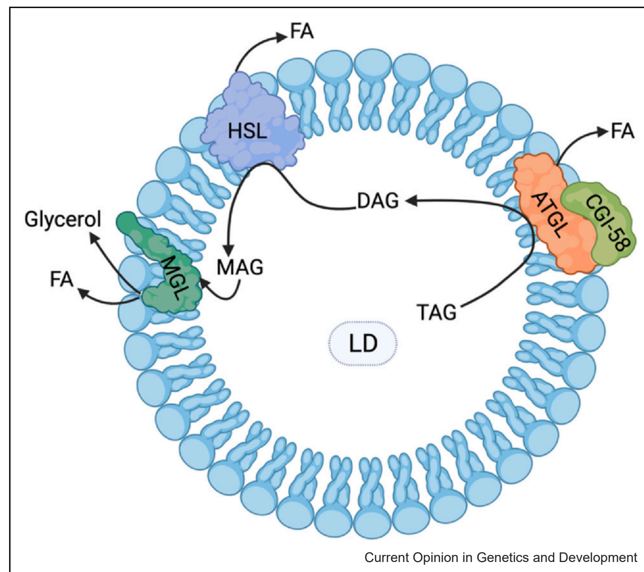
There are diverse fates of FAs inside and outside of adipocytes. FAs undergo oxidation to yield Adenosine triphosphate or heat production, re-esterification into TAGs, translocating as a cell membrane composition, or acting as signaling molecules to activate cellular metabolic and transcriptional programs. Adipocytes act as a signaling molecule, energy substrate in muscles and the liver, and utilization by white and brown adipose tissue (BAT) to activate thermogenic programs.

Although FAs are necessary for cellular energy as metabolic substrates for metabolic homeostasis, excessive amounts can lead to harmful effects by accumulating toxic lipid metabolites. This condition, known as lipotoxicity, can cause various negative processes, such as inflammation and insulin resistance when FAs overflow from adipocytes into nonadipose tissues. Lipotoxicity can induce cellular stress and dysfunction, leading to multiple forms of cell death. Hence, lipolysis is a highly controlled and dynamic cellular process for lipid and energy homeostasis, and dysregulation of lipolysis is detrimental and leads to metabolic pathogenesis.

## Enzymatic control of lipolysis

Generation of FA and glycerol from stored TAG involves a series of highly coordinated enzymatic actions of lipases at the Lipid droplet (LD). The discovery of hormone-sensitive lipase (HSL) as a crucial hydrolase of TAGs was the first in a series of identification of other enzymes involved in lipolysis [4]. Along with HSL, Steinberg and colleagues also reported MAG hydrolysis by monoacylglycerol lipase (MGL) in adipocytes [4]. The maintenance of hormone-induced FA release in adipocytes of mice with HSL deficiency led to the concept of additional enzymes in the lipolytic pathways and led to the discovery of adipose triglyceride lipase (ATGL) or phospholipase-A2-ζ and α-/β-hydrolase domain-5 (ABHD5); also called comparative gene identification-58 (CGI-58) (Figure 1).

**Figure 1**




Generation of FA and glycerol from stored TAG involves a series of highly coordinated enzymatic actions of ATGL, HSL, and MGL at the LD. Enzymatic activity of ATGL is enhanced by CGI-58.

## Hormone-sensitive lipase

HSL exhibits the highest hydrolase activity against DAGs and Cholesterol esters, followed by TAG and MAG. Langin and colleagues recently published an extensive review on the function and regulation of HSL protein and expression of *Lipe*, a gene encoding HSL [5]. Humans and mice with HSL deficiency develop partial lipodystrophy associated with reduced Peroxisome Proliferator Activated Receptor Gamma (PPARγ) signaling in adipose tissue [6]. A recent report showed that advanced lipodystrophy and the reversed fatty liver phenotype in aged mice lacking adipocyte HSL were accompanied by improved glucose homeostasis compared with age-matched obese control mice [7]. The study suggests that inhibiting adipocyte HSL activity provokes adipocyte dysfunction, leading to tissue-specific insulin resistance, inflammation, and fat mass reduction. These progressive deteriorations of adipose tissue mass and function provoke fatty liver without affecting glucose homeostasis at this stage. When lipodystrophy advances, further blunting adipose tissue lipolysis, fatty liver reverses, and glucose homeostasis improves [7]. FA esters of hydroxy fatty acids (HFAs) called FAHFAs belong to oligomeric FA esters, known as estolides, and HSL was recently shown to hydrolyze estolide bonds on both TAG estolides and free FAHFAs [8]. Mice lacking HSL accumulate DAG in various tissues such as muscles, adipose tissue, and testis, demonstrating reduced FA mobilization and impaired PPARγ signaling [9]. A recent report by Kotzbeck et al. showed that HSL loss promoted Endoplasmic reticulum (ER) stress in both epididymal WAT (eWAT) and inguinal WAT of HSL knockout mice [10]. Still, inflammation and macrophage infiltration occurred mainly in eWAT, implicating fat-depot-specific function of HSL. Also, PPARγ activation reversed inflammation but not ER stress and DAG accumulation. These data indicate that neither reduction of DAG levels nor ER stress contribute to change in eWAT inflammation in HSL knockout mice [10].

## Adipose triglyceride lipase

ATGL is a 54-kDa hydrolase belonging to the family of patatin-like phospholipase domain-containing proteins (PNPLA) with specificity for TAG as a substrate. ABHD5, also known as CGI-58, plays an indispensable role in regulating the movement and activation of ATGL and other members of the PNPLA domain-containing family. The G0/G1 switch gene-2 (*G0S2*) encodes a protein discovered as a selective controller of ATGL, lowering its action in both cells and mice. G0S2 is primarily expressed in adipose tissue and mature adipocytes and interacts with ATGL to specifically prevent its TAG hydrolase activity. Similarly, hypoxia-induced lipid droplet-associated protein (HILPDA), also known as hypoxia-induced gene-2, is a peptide consisting of 63 amino acids and is related to G0S2 [11]. HILPDA has been found to obstruct ATGL activity, just like G0S2.

A recent report showed that ATGL and HSL participated in the metabolism of estolides and TAG estolides in distinct manners [8]. The researchers uncovered that ATGL could release FAHFAs from TAG estolides with high efficiency, either working alone or in conjunction with CGI-58. ATGL also played a crucial role in transesterification and remodeling reactions, creating TAG estolides with diverse acyl compositions. Few studies have also demonstrated the anabolic function of ATGL [12]. A recent paper from Patel et al. elegantly showed that ATGL transacylase activity was responsible for the biosynthesis of FAHFAs [13]. The authors showed that when both triglycerides and HFA are present, ATGL's transacylation activity can transfer an acyl chain from a triglyceride to HFA, forming FAHFA. ATGL mediates FAHFA release from FAHFA–TGs during lipolysis [13,14] and their research findings indicate that ATGL exhibits both catabolic and anabolic responses in mice and humans to regulate lipid metabolism.

Mutations that impair the function of the *Pnpla2* gene result in a condition called neutral lipid storage disease with myopathy in humans [15], characterized by the abnormal accumulation of lipids in numerous tissues. Adipocyte-specific ATGL deletion reduces adipocyte lipolysis, serum lipids, systemic lipid oxidation, and expression of Peroxisome Proliferator Activated Receptor Alpha (PPARα) and PPARα target genes involved in lipid oxidation in adipose tissue and liver [16,17].

## Monoacylglycerol lipase

MGL is an enzyme with a molecular weight of 33 kDa that functions as a serine hydrolase [4]. It hydrolyzes both the 1- and 2-ester bonds of MAG and does not show catalytic activity against DAG, TAG, or CE in vitro. MGL has a structure containing an alpha-/beta-hydrolase fold, typical of known lipases. α-/β-hydrolase domain 6 (ABHD6) is also known to hydrolyze MAGs [18]. The absence of MGL in mice results in the accumulation of MAGs in various tissues and causes impaired intestinal lipid absorption, which moderately protects against the development of diet-induced obesity and hepatic steatosis in mice [19]. The phenotype of mice lacking MGL in adipocytes is yet to be determined [19]. Deficiency of ABHD6 also results in MAG accumulation in various tissues, and adipocyte-specific deletion of ABHD6 results in phenotypic changes, mostly under cold exposure [20]. Mice lacking ABHD6 in adipocytes demonstrate increased energy expenditure, resistance to cold-induced hyperthermia, increased glucose and oxidative metabolism in BAT, and increased eWAT expression of PGC1α, PPARα, and PPARγ without any concomitant changes in the thermogenic mitochondrial-uncoupling protein-1 levels [20].

## Transcriptional control of lipolysis

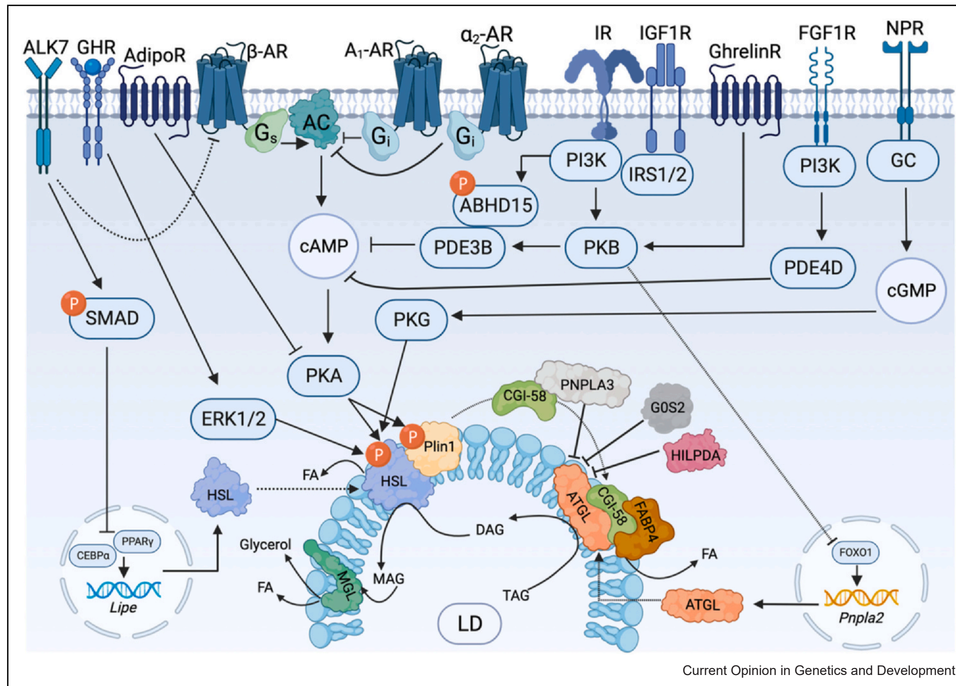
One of the effective mechanisms of controlling lipolysis is the transcriptional regulation in the promotors of the genes coding *Pnpla2* (ATGL) and *Lipe* (HSL). According to several studies, both target genes are regulated by the Peroxisome Proliferator Activated Receptor (PPAR) family. Both *Pnpla2* and *Lipe* are targets of PPARs, and a recent report showed that cysteine dioxygenase 1 engages with PPARγ and assists in enlisting Med24, a fundamental subunit of the mediator complex to promoters of *Pnpla2* and *Lipe* genes [21]. Other transcription factors that are known to induce adipogenesis, such as the G/C-box-binding factor specificity protein-1, E-box-binding transcription factor-E3, or CCAAT/enhancer-binding protein alpha (CEBPα), are also known to regulate both transcriptions of *Pnpla2* and *Lipe* [22]. The *Lipe* gene expression is controlled by sterol regulatory element-binding proteins. Growth hormones (GH) induce the Janus kinase 2/Signal transduction and activator and transcription 5 (STAT5) pathway as well as the Mitogen-activated protein (MAP) kinase pathway through the extracellular signal-regulated kinases 1/2 (ERK1/2) pathway [23]. Phospho-STAT5 will directly bind to the promoter region of the *Pnpla2* gene regulating the expression and initiating lipolysis [24,25]. Other than GH signaling, recently, the MAP kinase pathway through ERK-3 activated by the β3-adrenergic receptor could increase the forkhead box protein O1 (FOXO1)-mediated *Pnpla2* expression and stimulate lipolysis [26].

## Molecular and cellular signals promoting lipolysis

The levels of TAG stores are regulated with great precision through the action of circulating hormones that promote adipocyte lipolysis ( Figures 1 and 2). Norepinephrine, a major catecholamine that engages adipocyte lipolysis, is released in response to cold stimulation from sympathetic nerve (SNS) endings that innervate adipose cells to facilitate nonshivering thermogenesis (NST) by activating G-protein-coupled receptors (GPCR) [27]. These GPCRs, including β1, β2, and β3-ARs, are coupled to Gs, leading to the activation of adenylyl cyclase, increasing the levels of cyclic AMP (cAMP) as a second messenger, and promoting protein kinase-A (PKA) activation mediating the actions of catecholamines. PKA then phosphorylates Perlipin1 (PLIN1), releasing CGI-58 to activate ATGL and phosphorylating HSL to promote its transfer from the cytosol to LDs. HSL then interacts with PLIN1 to increase its hydrolase activity for DAGs. The phosphorylation of PLIN1 is necessary for PKA-dependent lipolysis by releasing CGI-58 and interacting with ATGL and for proper LD recruitment and activation of HSL [2] (Figure 2). Other GPCRs, such as the olfactory and photoreceptive nonvisual opsins GPCRs, were shown to control lipolysis in WAT [28,29]. GPRC6A was another class of GPCRs shown to mediate the effect of osteocalcin and ornithine in promoting lipolysis and increasing ATGL levels [30]. Hypothalamus plays a crucial role in adipocyte lipolysis through adipose tissue SNS projections, and O-linked β-d-N-acetylglucosamine (O-GlcNAc) modification (O-GlcNAcylation), catalyzed by O-GlcNAc transferase (OGT) in the ventromedial hypothalamus (VMH), was shown to regulate VMH neuronal excitability and adipocyte lipolysis [31]. Similarly, mitochondrial architecture in the proopiomelanocortin (POMC)-expressing neurons in the arcuate nucleus of the hypothalamus was recently shown to regulate calcium homeostasis in POMC neurons and adipocyte lipolysis [32]. Adipocyte-secreted adipokine leptin acts in the hypothalamic region to stimulate the SNS-mediated adipocyte lipolysis [33]. Pharmacological activation of the SNS pathway by β3-AR agonist mirabegron was recently shown to induce lipolysis in humans' subcutaneous WAT (scWAT) [34], and stabilization of ERK-3 by β-adrenergic stimulation was shown to induce lipolysis by an increase in ATGL expression [26].

Besides transmembrane signaling, adipocyte-intrinsic signals are also emerging as regulators of lipolysis programs. The delivery of ATGL to lipid droplets relies on the presence of small Guanosine triphosphate-binding protein ARF1, its guanine-nucleotide exchange factor Golgi brefeldin A resistant guanine nucleotide exchange factor 1, and its effector coatomer protein I from the ER–Golgi transport machinery [35]. Lipid droplet-associated small GTPase Rab18 is essential in recruiting ATGL to lipid droplets through the ARF1/GBF1 pathway [36]. Circular RNA derived from protein tyrosine kinase 2 (PTK2) (circPTK2) induced lipolysis by sponging miR-182-5p and enhancing the stability of

**Figure 2**




Major pathways involved in positive and negative regulation of lipolysis. β-adrenergic receptors (β-AR) are coupled to Gs, leading to the activation of adenylyl cyclase, increasing the levels of cAMP as a second messenger, and PKA activation, mediating the actions of noradrenaline. PKA then phosphorylates PLIN1, releasing CGI-58 to activate ATGL and phosphorylating HSL to promote its transfer from the cytosol to LDs. CGI-58 interacts with FABP4 to increase ATGL activity. HSL then interacts with PLIN1 to increase its hydrolase activity for DAGs. HSL and PLIN1 are also phosphorylated by ERK1/2 and protein kinase G (PKG) through GHR and NP receptor (NPR) signals. PNPLA3 can compete with ATGL for binding to CGI-58, thereby sequestering CGI-58 away from ATGL. G0S2 and HILPDA interaction inhibits AGTL activity. The binding of natriuretic peptides (NP) to the NPR also activates PKG via GC-derived Guanosine 3',5'-cyclic monophosphate (cGMP). Insulin and IGF-1 activate PI3K and IRS1/2 that subsequently activate PKB and PDE3B, resulting in the hydrolysis of cAMP, blocking HSL and ATGL activation. Insulin binding blocks FOXO1 transcriptional function and also induces stabilization of PDE3B with ABHD15, which promotes cAMP degradation. Activation of ALK7 inhibits the expression of β-AR and causes phosphorylation of Suppressor of Mothers Against Decapentaplegic (SMAD) proteins to block transcription of *Lipe*. Ghrelin is recognized as having antilipolytic effects as it activates the PI3K pathway. Additionally, adiponectin can also hinder lipolysis by suppressing PKA by decreasing its regulatory subunit RIIα. FGF1 suppresses lipolysis through FGFR1 by inhibiting the cAMP/PKA axis via activation of PDE4D, which results in cAMP degradation. Activation of Gi-protein-coupled α2-ARs and A1-R inhibits AC and thereby reduces cAMP-dependent signaling to lipolysis.

juxtaposed with another zinc finger gene 1 (JAZF1) [37]. Micro RNAs (miR) are also emerging as important regulators of adipocyte lipolysis. miR-128 was shown to control adipocyte differentiation, lipid accumulation, and lipolysis [38], and ablation of miR-33 enhanced lipid uptake and impaired lipolysis [39]. Coiled-coil–helix-coiled–coil–helix domain-containing 10, a mitochondrial intermembrane protein enriched at the cristae junction, regulated lipolysis by modulating the levels of ATGL and HSL [40]. Other organelles, such as peroxisome, facilitate lipolysis through direct interaction with LD during fasting conditions [41].

## Molecular and cellular signals inhibiting lipolysis

Protein complexes formed at the LD are one of the best-known inhibitors of lipolytic programs (Figure 2). PNPLA3 can compete with ATGL for binding to CGI-58, thereby sequestering CGI-58 away from ATGL [42]. Ubiquitin-X domain adaptor 8 (UBDX8) can bind ATGL, promoting its segregation from the LD, followed by ubiquitination and proteasomal degradation [43]. ATGL is also ubiquitinated and degraded by interacting with prolyl isomerase Pin1 at Ser185/Pro186 residues in the PNPLA domain [44]. The levels of the ATGL protein are also regulated by two types of E3 ligases, UBR1 and UBR2, which are part of a system called the N-end rule pathway [45]. This pathway recognizes specific N-terminal residues of short-lived proteins and targets them for degradation through the proteasome. The researchers showed that mice with a genetic modification that makes the ATGL protein resistant to degradation by the N-end rule pathway (called AtglF2A/F2A) had increased lipolysis and are protected against obesity and fatty liver disease induced by a high-fat diet [45]. In contrast to the role of O-GlcNAc and OGT activity in VMH neurons to promote lipolysis mentioned above [31], a mouse model with the adipocyte-specific

knockout of OGT causes loss of PLIN1 O-GlcNAc, which leads to increased PLIN1 phosphorylation and increased lipolysis [46].

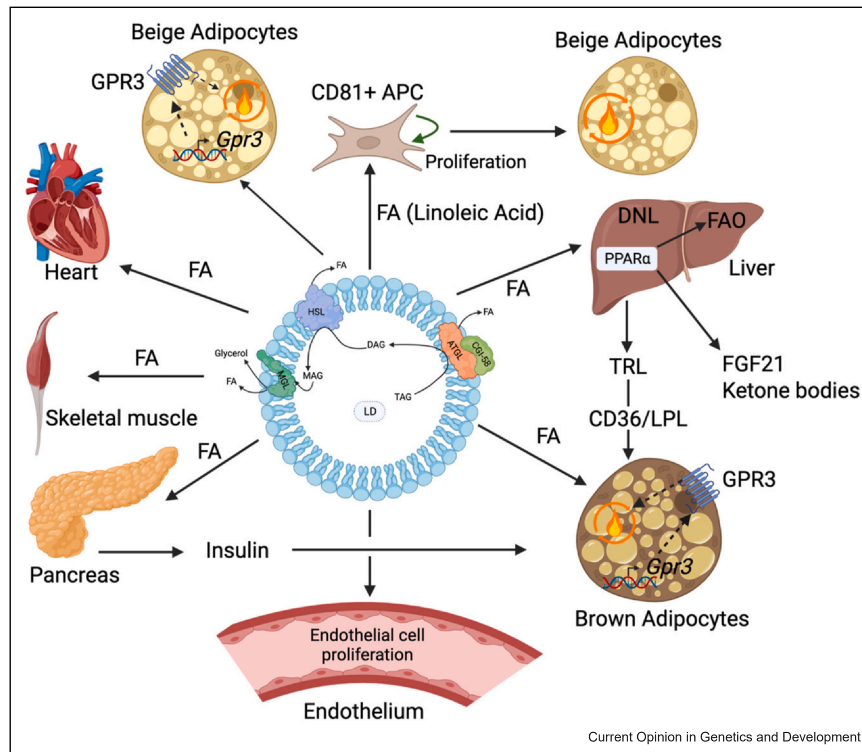
Hormonal signals such as insulin or insulin-like growth factor-1 (IGF-1) inhibit lipolysis by binding to the insulin receptor or IGF receptor (Figure 2) [2]. This binding activates insulin receptor substrate-1/2 (IRS1/2), phosphatidylinositol-3-kinase (PI3K), PDK1, and PKB, which then activate PDE3B, leading to the hydrolysis of cAMP [47]. Insulin suppresses the transcription of *Pnpla2* through the phosphorylation of FOXO1 by PKB, leading to the inhibition of nuclear translocation of FOXO1 [48]. Insulin binding also induces stabilization of PDE3B with ABHD15, which promotes cAMP degradation [49] (Figure 2). Using similar mechanism, FGF1 suppresses lipolysis through FGFR1 by inhibiting cAMP/PKA axis via activation of PDE4D, which results in cAMP degradation [50]. Adenosine and alpha-2 receptor agonists also inhibit lipolysis by reducing cAMP levels by activating adenosine-A1 receptors ($A_1$-AR) and $\alpha_2$-AR, respectively, coupled with Gi proteins, inhibiting adenylate cyclase and cAMP synthesis (Figure 2) [51]. PAQR11, a scaffolding protein, progesterone, and Adipoq receptor family member, regulates PDE4D levels in adipose tissue [52]. PAQR11 modulates the WAT cAMP level by regulating PDE4D degradation through the SKP1–CUL1–FBXO2 E3 ligase complex [52].

Various other hormones, including adiponectin and ghrelin, can act as regulators of lipolysis. Adiponectin, derived from adipocytes, is crucial in safeguarding against obesity-related metabolic conditions [53]. Adiponectin has demonstrated its capacity to obstruct lipolysis by inhibiting HSL activation through the PKA pathway. Moreover, adiponectin reduces the levels of PKA RIIα, the regulatory subunit of PKA, thereby negatively impacting its protein stability. The inhibitory effect of adiponectin on lipolysis is nullified when RIIα is overexpressed [54]. In summary, adiponectin not only enhances insulin-induced suppression of lipolysis but also independently obstructs the process of lipolysis. Studies have revealed that ghrelin directly attenuates lipolysis in WAT by activating the PI3K–PKB–PDE3B axis (Figure 2) [55]. However, the effect of ghrelin on lipolysis remains unclear, as ghrelin infusion in humans was found to acutely increase lipolysis and free FA release while impairing glucose uptake into skeletal muscle [56]. Other secreted factors such as Activin B, Activin E, and growth/differentiation factor-3 binding to the activin-receptor-1c (also called activin-receptor-like kinase 7, Alk7) could block lipolysis through downregulation of β-AR expression and the phosphorylation of Suppressor of Mothers Against Decapentaplegic transcription factors, which in turn, inhibit CEBPα and PPARγ expression and thereby decrease *Lipe* gene transcription [57–59] (Figure 2). Noncoding RNAs are also emerging as a potent inhibitor of lipolysis. A recent study by Zhang et al. showed that small nucleolar RNA C/D box 46 (SNORD46) blocked IL-15-induced, FER kinase-dependent phosphorylation of CD36 and MGL in adipocytes, leading to inhibition lipolysis [60]. miR-425 inhibits lipolysis by blocking Cab39–AMPK pathway and miR-145 blocks lipolysis by directly targeting *Foxo1* and *Abhd5* to attenuate ATGL function and expression [61].

## Adipose tissue microenvironment control of lipolysis

Immune cells are one of the best-known cell types in adipose tissue that regulate adipocyte lipolysis. Immune cells secrete cytokines such as tumor necrosis factor-alpha, interleukin-6 (IL6), IL1-b, IL-4, IL-15, IL-17a, IL-21, and interferon-gamma is known to influence lipolysis. ER stress protein inositol-requiring protein-1 (IRE1) was recently shown to mediate inflammation-induced lipolysis and adipocyte-specific knockout of IRE1-blocked adipocyte lipolysis and increased plasma TAG levels after bacterial toxin stimulus [62]. Immune cells can also function to regulate lipolysis negatively. Adipose tissue macrophages (ATM) regulate age-related decline in lipolysis by catecholamine degradation through the action of inflammasome and monoamine oxidase-a (MAOA), an enzyme known to degrade catecholamines [63]. The regulatory T cells (Tregs) were recently shown to suppress visceral eWAT diurnal adipocyte lipolysis [64]. The clock gene Basic Helix-Loop-Helix ARNT Like 1, specifically in Tregs, enabled eWAT Tregs to enforce a diurnal rhythm in eWAT lipolysis, causing an increase in the suppression of fat breakdown throughout the day [64]. These results highlight the significance of the cell's internal biological clock in ensuring optimal lipolytic function. Single-nuclei adipocyte RNA-seq from adipocytes lacking IL10Rα showed a marked increase in *Lipe* levels in the thermogenic adipocyte cluster, hinting toward an inhibitory role of IL10 on lipolysis [65]. Adipocytes also consist of B-cell-activating factor receptors, and B-cell activating factor overexpression was shown to induce lipolysis in scWAT [66]. Besides immune cells, the crosstalk between endothelium and adipocytes in the adipose tissue is crucial for adipose tissue homeostasis, exemplified by angiogenesis during WAT expansion. A recent report by Monelli et al. showed that when the PI3K pathway is activated in endothelial cells (EC), it causes ECs to proliferate, specifically in WAT [67]. The researchers found that polyamines released by ECs are the critical mediators of communication and stimulate adipocyte lipolysis and FA release. The ECs then use these FAs for energy production to support their proliferation [67]. These findings provide new insights into the biology of ECs in

**Figure 3**




Recent developments in the local and systemic tissue crosstalk mediated by lipolysis to regulate energy and lipid homeostasis. FA released by adipocytes during fasting and b-adrenergic stimulation can function as PPARα ligands in the liver to upregulate a transcriptional program involved in increasing FA oxidation, FGF21, and ketone bodies, and BAT thermogenic activity. FA released by adipocytes during fasting and β-adrenergic stimulation also leads to insulin secretion from the pancreas that stimulates the uptake of FA-induced TRL from the liver in BAT for optimal thermogenesis. The heart and skeletal muscle use both glucose- and adipocyte- derived FA as an energy substrate for normal function. Linoleic acid from adipocyte lipolysis acts on a pool of CD81+ beige APC for proliferation and conversion into beige adipocytes for optimal thermogenesis. Lipolytic signal also enhances the transcription of Gpr3, a gene encoding GPR3. GPR3 is a constitutively active GPCR that activates the cAMP/PKA pathway to increase thermogenesis in beige and brown adipocytes. FA from adipocyte lipolysis also increases EC proliferation.

WAT and demonstrate how the microenvironment influences WAT homeostatic conditions.

## Local and systemic effects of lipolysis

Energy-demanding tissues such as the liver, heart, BAT, and pancreas show direct consequences of perturbations in lipolysis (Figure 3). During fasting and β3-adrenergic stimulation, adipocyte ATGL action controls hepatic PPARα transcriptional function and production of FGF21 and ketone bodies [68]. β3-adrenergic stimulation also induces a thermogenic response in BAT, and the authors show that ATGL function in white adipocytes also elicits a tertiary response in BAT through hepatic PPARα activation [68]. ATGL is present in BAT, but recent reports have indicated a dispensable role of ATGL in BAT thermogenesis [16]. The thermogenic activity of BAT is influenced by the availability of nutrients or the breakdown of fats in WAT. This implies that the energy substrates circulating in the body are adequate to support NST. Previous assumptions that the cold intolerance observed in ATGL knockout mice was due to BAT dysfunction were probably incorrect, as it has been discovered that the mice suffer from severe cardiomyopathy [69]. ATGL lipolytic function in WAT under cold exposure and β3-AR stimulation also results in insulin secretion from pancreatic beta cells that facilitate triglyceride-rich lipoprotein (TRL) uptake in BAT for optimal BAT function [70]. Mice lacking ATGL die early due to heart failure [71]. However, when ATGL was overexpressed in the hearts of these mice, their heart failure was prevented, and they had normal heart function and lifespan. Accordingly, adipocyte-specific ATGL depletion and pharmacological treatment with Atglistatin, a pharmacological inhibitor of ATGL, protect mice from catecholamine-induced cardiac damage by decreasing cardiac hypertrophy, cardiac fibrosis, and inflammation [72].

The lipolytic program plays a significant role in remodeling cell-intrinsic and adipose tissue niche. FAs from lipolysis activate PPAR pathways to regulate gene expression. Lipolytic signal also enhances the transcription of *Gpr3*, a gene encoding G-protein-coupled receptor 3 (GPR3). GPR3 is a constitutively active GPCR that activates cAMP/PKA pathway to increase thermogenesis in beige and brown adipocytes [73]. Lipolytic products also potentiate the proliferation of cells in the WAT niche. WAT lipolysis increases the proliferation of thermogenic beige precursor cell (adipocyte precursor cells (APC)) in the WAT niche to increase adipose thermogenesis [74]. The researcher showed that linoleic acid released from adipocyte lipolysis increases β-oxidation and prostanoid release with a subsequent increase in CD81+ beige APC proliferation [74]. As discussed, FA also causes EC proliferation due to the crosstalk between the endothelium and adipocytes [67].

## Conclusion

Despite lipolysis being recognized as important for many years, the identification of essential proteins has only occurred in recent decades. Our understanding of lipolysis and its effects on cellular metabolism, including adipose tissue, has been significantly expanded with the discovery of crucial lipolytic enzymes and various regulatory proteins and mechanisms. As more enzymes and regulatory proteins are discovered, the intricate nature of the hormonal and intracellular signaling network that controls the lipolytic pathway has become increasingly apparent. Investigating the involvement of lipolytic products and intermediates in nonadipose tissues could reveal new insights into the role of lipolysis and its connection to metabolic diseases. Our view of lipolysis has drastically evolved from the actions of three lipases to a complex interactome or 'lipolysome' [75]. The adipose tissue lipolytic pathway has been the subject of intense investigation, and mutant mouse lines have been developed for most lipases. Additionally, the identification of lipase inhibitors has created a timely opportunity to achieve a quantitative understanding of lipolysis and its regulatory network. The severe symptoms observed in various tissues such as adipose tissue, pancreas, liver, heart, and skeletal muscle due to the defect in lipolysis highlight the importance of maintaining a balance between lipid mobilization, utilization, and storage in most tissues. Therefore, by examining the mechanisms that govern lipolysis in adipose and nonadipose tissues, we can enhance our comprehension of lipid metabolism and identify novel therapeutic targets for managing metabolic conditions such as type-2 diabetes, fatty liver disease, and heart failure.

## Data Availability

No data were used for the research described in the article.

## Declaration of Competing Interest

The authors have no conflict of interest to declare.

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- • of special interest
- •• of outstanding interest


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