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Review

Excessive or sustained endoplasmic reticulum stress: one of the culprits of adipocyte dysfunction in obesity

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***Abstract*:** As the prevalence of obesity continues to rise globally, the research on adipocytes has attracted more and more attention. In the presence of nutrient overload, adipocytes are exposed to pressures such as hypoxia, inflammation, mechanical stress, metabolite, and oxidative stress that can lead to organelle dysfunction. Endoplasmic reticulum (ER) is a vital organelle for sensing cellular pressure, and its homeostasis is essential for maintaining adipocyte function. Under conditions of excess nutrition, ER stress (ERS) will be triggered by the gathering of abnormally folded proteins in the ER lumen, resulting in the activation of a signaling response known as the unfolded protein responses (UPRs), which is a response system to relieve ERS and restore ER homeostasis. However, if the UPRs fail to rescue ER homeostasis, ERS will activate pathways to damage cells. Studies have shown a role for disturbed activation of adipocyte ERS in the pathophysiology of obesity and its complications. Prolonged or excessive ERS in adipocytes can aggravate lipolysis, insulin resistance, and apoptosis and affect the bioactive molecule production. In addition, ERS also impacts the expression of some important genes. In view of the fact that ERS influences adipocyte function through various mechanisms, targeting ERS may be a viable strategy to treat obesity. This article summarizes the effects of ERS on adipocytes during obesity.

Keywords: adipocyte, endoplasmic reticulum stress, inflammation, insulin resistance, lipolysis, obesity

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Introduction

Obesity is one of the most prevalent health issues in modern society, which places a heavy burden on society.[1] In 2022, the World Health Organization (WHO) announced epidemiological data showing that obesity is widespread in different age groups worldwide, including 39 million children, 340 million adolescents, and 650 million adults, totaling more than 1 billion obese individuals. WHO estimates that approximately 167 million people will suffer from overweight or obese by 2025.[2] Both being overweight and obese have serious adverse effects on the occurrence and development of various diseases in different organs, such as type 2 diabetes mellitus (T2DM), cardiovascular and cerebrovascular diseases, non-alcoholic fatty liver disease (NAFLD), musculoskeletal diseases, chronic kidney disease (CKD), inflammatory bowel diseases, Alzheimer's disease, cancers, sleep apnea, as well as mental health problems.[3–5] Therefore, obesity poses a huge threat to human health.

The main feature of obesity is the expansion of white adipose tissue (WAT) accompanied by dysfunction, which is caused by a long-term imbalance between energy intake and expenditure. WAT is a major storage for excess energy and an endocrine organ, containing subcutaneous fat and visceral fat.[6] Perivascular adipose tissue (PVAT) is a special type of adipose tissue surrounding blood vessels that not only serves as a

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mechanical support for the vascular system but also plays a crucial role in the homeostasis of the vascular system. PVAT exhibits WAT, brown adipose tissue (BAT), and mixed phenotypes depending on their anatomical location. In abdominal PVAT, WAT is more abundant, while thoracic PVAT contains more BAT. These regional differences in PVAT are consistent with the clinical phenomenon that the abdominal aorta is more prone to atherosclerosis than the thoracic aorta. Obesity leads to elevated oxidative stress, and inflammatory and hypoxic states, which result in PVAT dysfunction.[7,8] Abdominal obesity formed by visceral fat dilation is a significant risk factor for metabolic syndrome and the pathological basis for the body in a state of chronic low-grade inflammation and insulin resistance (IR).[9,10] WAT is made up of generous adipocytes and extracellular matrix component (EMC), as well as a few other cell types. Adipocyte is the main component of WAT and is absolutely dominant in size.[11] Therefore, impaired adipocyte function is the most direct, initial, and major manifestation of WAT dysfunction.

The endoplasmic reticulum (ER) is an important organelle that has the function of synthesizing, folding, and transporting proteins, as well as being responsible for lipid synthesis and calcium homeostasis.[12,13] As a pressure sensor, the accumulation of abnormally folded proteins in the ER lumen leads to the imbalance of ER homeostasis. In the excess energy states such as obesity and T2DM, where adipocytes are exposed to multiple stresses such as hypoxia, inflammation, mechanical stress, metabolite, and oxidative stress, complex signaling networks called the unfolded protein responses (UPRs) in adipocytes are activated, including transcriptional induction of ER chaperones and translation attenuation, thus triggering a series of ER stress (ERS) responses.[14–16] The UPRs signaling pathways consist of three typical branches: inositol-requiring enzyme 1 and X-box binding protein 1 (IRE1-XBP1), protein kinase R-like endoplasmic reticulum kinase and eukaryotic initiation factor 2α (PERK-eIF2α), and activating transcription factor 6 (ATF6).[17–19] Although ERS is conducive to eliminate the accretion of misfolded/unfolded proteins, prolonged or excessive ERS promotes the development of programmed cell death and interferes with normal cellular function. Activation of ERS is strongly associated with many metabolic diseases, such as obesity and NAFLD, making ERS a promising therapeutic target for these diseases.[20,21] ERS is a momentous factor contributing to the dysfunction of hypertrophic adipocytes, which causes abnormalities in WAT.[22] Currently, increasing evidence supporting a causal link between ERS and adipocyte dysfunction in obesity has been reported. However, there is a lack of comprehensive review about the impact of ERS on adipocytes during obesity. Hence, there is a need to review the existing research to draw more attention and provide thoughts for exploration.

ERS and lipolysis

Pro-inflammatory cytokines and excessive metabolites such as free fatty acid (FFA) derived from WAT enter the bloodstream and flow to other organs, bringing about metabolic damage to tissues and eventually progressing to various complications, such as NAFLD, cardiovascular diseases, and T2DM.[23–25] In mammals, fatty acids are stored in adipocytes in the form of triacylglycerol (TG), which constructs the main energy reserve. The hydrolysis of TG in adipocytes, known as lipolysis, generates glycerol and FFA. Lipolysis is regulated by multiple signaling pathways and is a complex process in adipocytes in which TG is catabolized to glycerol and FFA catalyzed by lipolytic enzymes.[26–28] Due to the lack of glycerol kinase in regular adipocytes, glycerol is rarely reused to resynthesis TG; instead, it is released into the bloodstream along with FFA to provide energy for different tissues. Adipocyte lipolysis is a crucial procedure for controlling the plasma FFA concentration and modulating metabolic homeostasis via the Randle glucose-fatty acid cycle.[29] The abnormalities in lipolysis pathways lead to the increase of circulating FFA, which can contribute to lipotoxicity and IR in obesity. ERS can regulate adipocyte lipolysis. cAMP-dependent protein kinase A (PKA) and extracellular signal-regulated kinase-1/2 (ERK1/2) are major signals adjusting lipolysis.[30–33] In the PKA-stimulated downstream lipolytic cascade, the key to complete activation of hormone-sensitive lipase (HSL) is the phosphorylation of HSL and lipid droplet-associated protein perilipin A, and then the transfer of HSL from the cytoplasm to the surface of lipid droplet.[34] Adipose triglyceride lipase (ATGL) is another vital lipolytic enzyme that may be indirectly activated in PKA-mediated lipolysis.[35] Lipolysis-derived FFA may amplify the WAT lipolysis, inflammation, and IR by activating

toll-like receptor 4 in immune and non-immune cells to release more pro-inflammatory cytokines.[36] The research on adipocyte lipolysis discussed below is not limited to obesity, to provide broader research perspectives.

During obesity, the inflammatory response of adipocytes is dependent or independent of ERS. Inflammation, ERS, and lipolysis in adipocytes can form malignant interactions. The inflammatory response is the downstream of ERS. Inflammatory cytokines can exacerbate ERS and promote adipocyte lipolysis, releasing excessive FFA, which in turn enhances adipocyte inflammatory response and ERS, starting a vicious cycle.[37,38] Tumor necrosis factor α (TNF-α) has been reported to promote lipolysis in differentiated human adipocytes through activation of ERK signal and elevation of intracellular cAMP, as activated cAMP-dependent PKA leads to hyperphosphorylation of perilipin.[39] Foley et al. showed that inhibiting IRE1 kinase activity was sufficient to block adipocyte-autonomous lipolysis from multiple inflammatory ligands. They suggested that IRE1 kinase activity, rather than RNase activity, regulated inflammation-induced adipocyte lipolysis, that is, independent of typical UPR signal.[40] Xia et al. found that the chemical chaperone tauroursodeoxycholic acid (TUDCA) inhibited TNF-α-stimulated ERS and lipolysis in 3T3-L1 adipocytes. Its potential mechanism might be related to the inhibition of the IRE-c-Jun N-terminal kinase (JNK) signaling pathway, which influenced the expression of perilipin A.[41] Wang et al. reported that administration of curcumin or TUDCA inhibited ERS-related lipolysis induced by the high-fat diet feeding, at least in part via suppression of cAMP/PKA/HSL signal.[42] The ERS inducer tunicamycin has been reported to induce lipolysis in cultured human adipocytes.[43] Deng et al. explored the effect of ERS inducers on lipolysis in rat adipocytes, demonstrating that ERS elicits lipolysis by activating cAMP/PKA and ERK1/2 signals in adipocytes.[44] In addition to mammals, ERS was found to promote cAMP/PKA signal-mediated lipolysis and apoptosis of adipocytes in grass carp. [45] Amiodarone is an antiarrhythmic drug with hepatotoxicity. Hubel et al. established a mouse model of repetitive amiodarone administration. Amiodarone-caused liver injury was at least partly due to induced ERS-dependent lipolysis in epididymis WAT (eWAT), which increased circulating FFA level, resulting in increased hepatotoxic FFA accumulation. Besides, amiodarone up-regulated the phosphorylation of JNK and the expression of its downstream target TNF-α in eWAT.[46] 4-phenyl butyric acid (PBA) is a chemical chaperone known to reduce ERS in vitro and in vivo. Xiong et al. established a rat model of high-altitude hypoxia using a hypobaric chamber and found that hypoxia exposure displayed significant ERS and lipolysis in WAT. Treatment with PBA effectively reduced hypoxia-induced lipolysis via cAMP-PKA-HSL/perilipin pathway.[47] The accumulation of asymmetrical dimethylarginine (ADMA) is common in advanced CDK. Zhou et al. reported that ADMA induced lipolysis in 3T3-L1 adipocytes by reducing perilipin-A expression, rather than affecting the expression or activity of lipases. ADMA also promoted the expression of inflammatory cytokines such as TNF-α, interleukin (IL)-6, and monocyte chemotactic protein-1 (MCP-1) via activating nuclear factor-κB (NF-κB). Blocking ADMA-caused inflammatory responses with NF-κB inhibitor also partially inhibited the lipolysis. Treatment with ERS inhibitor completely eliminated ADMA-triggered lipolysis and inflammatory responses in cultured adipocytes.[48] Zhu et al. found that in a rat model of CKD constructed via a five-sixths nephrectomy, visceral WAT underwent enhanced lipolysis and ERS, while PBA markedly alleviated lipolysis, mainly by blocking the activation of ATGL.[49]

The ER is rich in chaperones and oxidoreductases that control proper protein folding and ER-related degradation of abnormally folded proteins. The lipotoxic of FFA and overproduction of reactive oxygen species (ROS) disrupt the redox state of the ER, increasing the frequency of abnormally folded proteins.[50] The major pathways of oxidative protein folding consist of ER oxidoreductase 1 (Ero1) and the protein disulfide isomerase (PDI) family. Normally, Ero1 re-oxidizes and re-activates PDI to promote the formation of disulfide bonds, thus improving protein folding. However, this process consumes O_2 and produces H_2O_2, and over-activation of the Ero1-PDI system can lead to ER peroxidation, which in turn exacerbates ERS.[51–53] Homocysteine is a noxious sulfur-containing amino acid produced in the process of methionine metabolism.[54] Yan et al. established a hyperhomocysteinemia (HHcy) mouse model fed with a high-methionine diet and demonstrated that homocysteine activated lipolysis in WAT through activating HIF1α/

Table 1. Human, mouse or cell models of ERS-related lipolysis.

Model type	Inducer of ERS	The signal molecules involved in lipolysis
3T3-L1 adipocyte[41]	TNF-α	IRE-JNK signal-mediated decline in perilipin-A expression
Mouse model[42]	A high-fat diet	cAMP/PKA-mediated phosphorylation of HSL
Human adipocyte[43]	Tunicamycin	Not mentioned
Rat adipocyte[44]	Thapsigargin; tunicamycin; brefeldin A	cAMP/PKA and ERK1/2 signals accompanied by phosphorylation of perilipin and HSL and activation of cellular lipases
Mouse model[46]	Amiodarone	Increased the level of p-HSL
Rat model[47]	Using hypobaric chamber to establish high-altitude hypoxia	cAMP/PKA signal-mediated phosphorylation of perilipin and HSL
3T3-L1 adipocyte[48]	Asymmetrical dimethylarginine	Decreased perilipin-A expression; No alteration of lipase expression or activity
Rat model[49]	A five-sixths nephrectomy to establish chronic kidney disease	Activation of ATGL
Mouse model[55]	A high-methionine diet	Increased the level of ATGL and p-HSL

ERS, Endoplasmic reticulum stress.

ERO1α-dependent ER overoxidation and ERS, which released excess FFA and the FFA was eventually absorbed by hepatocytes, leading to hepatic steatosis.[55] The above ERS-related lipolysis models of adipocytes or adipose tissue are listed in Table 1.

ERS and IR

ERS has been considered an important mechanism of obesity-related IR.[56,57] In general, insulin activates cellular procedures by binding to the insulin receptor on the cytomembrane, mediating the activation of insulin receptor tyrosine kinases and subsequent tyrosine phosphorylation of downstream signal molecules such as insulin receptor substrate (IRS) proteins, which then activate the phosphatidylinositol 3-kinase (PI3K) signal pathway, ultimately contributing to insulin signal transduction. [58,59] Li et al. found that ERS inducer tunicamycin caused the autophagy defect and impaired insulin sensitivity in adipocytes, partly due to the upregulation of IRE1-JNK pathway, which is a direct repressor of cytoplasmic insulin signaling, as the activated JNK pathway can phosphorylate IRS-1 at Ser307. Moreover, the autophagy defect further aggravated ERS and IR.[60] Zhou et al. reported that ERS downregulated insulin receptors in adipocytes via autophagy-dependent ER-related degradation, but had little effect on insulin receptor tyrosine phosphorylation, thereby inhibiting the downstream signal of the insulin receptor. They found that pretreatment with ER chemical chaperone rescued tunicamycin-induced ERS, insulin receptor reduction, and IR in adipocytes. Although the autophagy inhibitor 3-methyladenine significantly alleviated the decreased insulin receptor induced by ERS, it could not save the downstream signal of insulin receptor in adipocytes, which is consistent with the fact that ERS also affects insulin signaling through other mechanisms.[61]

GLUT4 is an insulin-responsive glucose transporter. When insulin binds to its receptor, it starts a series of events that cause GLUT4 to transfer from the intracellular chamber and insert into the plasma membrane.[62,63] In adipocytes, the attenuated insulin sensitivity in obesity and T2DM is due to the insulin-stimulated GLUT4 translocation defect and decreased expression.[64,65] It has been found that activation of ERS in adipocytes repressed GLUT4 expression at the gene transcriptional level, possibly by increasing the expression of CAAT/enhancer binding protein

Table 2. Effect of ERS on the expression of bioactive molecules.

Gene name	Role in obesity	Expression regulated by ERS
Resistin	Adverse	Downregulation
Adpsin	Protective	Downregulation
Adipolin	Protective	Downregulation
Adiponectin	Protective	Downregulation
TNF-α/MCP-1/IL-6/IL-1β	Adverse	Upregulation

ERS, Endoplasmic reticulum stress.

homologous protein-10 (CHOP10).[66] The CHOP10 protein has marked homology with other CAAT/enhancer binding proteins (C/EBPs), and it can interact dominantly and negatively with other C/EBPs to inhibit the transcription of their targets.[67] CHOP10 is a suppressor of C/EBPα activity and expression, while C/EBPα is an activator of GLUT4 expression.[68,69] This suggests that adipocyte ERS activation inhibits GLUT4 expression as an additional mechanism benefiting IR in obesity. ERp44 is a member of the PDI family that preferentially assists in the intracellular localization of ER enzymes lacking the ER retention motif and recognizes folded proteins in the secretion pathway.[70,71] Ubc9 is the only E2 conjugating enzyme in the post-translational modified SUMO system. Xie et al. found that overnutrition increased the Ubc9 level in adipocytes and underwent SUMOylation conversion. Adipocyte-specific Ubc9 deletion protected mice from high-fat diet-induced obesity and IR by alleviating ERS in WAT.[72] Mechanistically, ERp44 showed the highest change in SUMOylation level of ER-related substrates after palmitic acid stimulated adipocytes. Loss of Ubc9 led to the deficiency of SUMOylation in ERp44, enhancing its degradation and inhibiting its covalent binding to Ero1α, an oxidase present in the ER but lacking ER retention motif, thereby relieving lipotoxic-induced ERS by boosting the secretion of Ero1α.[73,74] Intestinal hormone glucagon-like peptide 1 (GLP-1) is effective in improving blood glucose in T2DM.[75] GLP-1 has been reported to reduce the expression of ATF4 and CHOP by curbing the mTOR signaling pathway, thereby ameliorating ERS-induced impairment of insulin signaling in adipocytes.[76] Progranulin is an important growth factor that promotes IR. Guo et al reported that progranulin enhanced adipocyte autophagy-mediated insulin sensitivity reduction in adipocytes, at least partially via activating oxidative stress and ERS.[77]

ERS and adipokines

Except for storing excess energy, WAT is also an active endocrine tissue that secretes bioactive molecules, including unique adipokines and conventional cytokines. Secretory profile of hypertrophic adipocytes is shifted toward the pro-inflammatory spectrum.[78,79] ERS participates in adjusting the expression of multiple bioactive molecules in adipocytes (Table 2). Resistin is an adipokine that damages glucose metabolism.[80] In rodents, resistin is almost entirely derived from adipocytes. In obese mice, the circulating resistin level is increased, but its gene expression in WAT is paradoxically decreased.[81,82] Martina et al. found that ERS decreases the gene transcription of resistance in adipocytes, concerning at least three transcription factors. The action of ERS on resistin transcript level in adipocytes appears to be a joint result of reducing the expression of activated transcription factors, including C/EBPα and peroxisome proliferator-activated receptor (PPARγ), and increasing the expression of inhibitory factors such as CHOP10.[83] Adpsin is an adipokine that can maintain insulin secretion function of β-cells to improve glucose tolerance.[84] The lightened transcription of Adipsin in adipocytes of obese mice has relevance to ERS-mediated downregulation of PPARγ.[85] Takashi et al reported that adipolin is an anti-inflammatory and insulin-sensitive adipokine, which is reduced in WAT and plasma of obese rodent models. Palmitic acid and ERS inducers significantly inhibit adipolin transcription in adipocytes.[86] Adiponectin is a protective adipocytokine with the effects of anti-inflammation, anti-apoptosis, and promoting insulin sensitivity. The

expression and secretion of adiponectin are dropped in adipocytes in obesity.[87] ERS is relevant to modulating adiponectin expression.[88] WAT is in a hypoxic state during obesity, which activates the PERK and IRE1 signal pathways in adipocytes, thus suppressing adiponectin expression by activating ERS.[89] The hypoxia-caused decline of adiponectin is also mediated by CHOP, which attenuates the transcriptional activity of adiponectin promoter. The RNA interference of CHOP partially rescued the inhibition of adiponectin transcription induced by hypoxia in adipocytes.[90] In addition, ERS can diminish adiponectin levels through advancing autophagy-dependent degradation of adiponectin.[91] As the chaperone protein, PDI family heavily exists in the ER and is markedly induced by the UPRs.[92] PDIA4 pertains to the PDI family. The lessening of adiponectin expression in adipocytes stimulated by palmitate was concerned with the upregulation of PDIA4. Pharmacological and genetic disturbance of PDIA4 could rescue the adiponectin expression in hypertrophic adipocytes.[93]

Apart from adipokines, ERS alters the production of pro-inflammatory cytokines in adipocytes during obesity.[79] ER chemical chaperones can effectively abolish adipocyte ERS and downstream inflammatory response triggered by multiple stimuli. ERS inducer thapsigargin stimulates adipocytes to produce monocyte chemoattractant protein-1 (MCP-1), interleukin-6 (IL-6), and TNF-α.[94] ERS inducer tunicamycin also provokes adipocytes to generate TNF-α and IL-6, which are blocked by ER chemical chaperones.[95] ERS in adipocytes can also be activated by FFA. The pivotal downstream target of FFA-caused ERS is IκB kinase β (IKKβ), a major mediator in regulating inflammation and IR. Both ER chemical chaperone and PERK deletion can weaken the activation of IKKβ in adipocytes to interrupt FFA-induced expression of TNF-α and IL-6, and improve insulin signal.[37] Oxidized low-density lipoprotein promotes the expression of TNF-α and MCP-1 by activating adipocyte ERS.[96] Homocysteine can promote MCP-1 and TNF-α expression in part through activating ERS in adipocytes, thus impairing insulin signaling.[97] In hypertrophic adipocytes, autophagy is inhibited, which can activate ERS-mediated inflammation, resulting in increased expression of MCP-1, IL-6, and IL-1β.[98] Homeobox a5 (Hoxa5) is a noteworthy transcription factor abundantly expressed in WAT.[99] Cao et al. reported that a high-fat diet decreased the Hoxa5 expression in WAT. Hoxa5 acted to attenuate adipocyte ERS and inflammatory responses by blocking the PERK-eIF2α signaling pathway.[100] During obesity, the abnormal accumulation of EMC in WAT is involved in WAT inflammation and fibrosis, in which collagen XV is very abundant.[101] Focal adhesion kinase (FAK) is the main downstream moderator of integrin β1, which is phosphorylated and activated upon binding of integrin β1 to EMC proteins.[102,103] It has been shown that the FAK-PI3K-Ca2+ signal pathway was enabled by connecting with α3β1 integrin.[104] Li et al. have demonstrated that collagen XV caused intracellular $Ca^{2}+$ imbalance by activating the integrin β1/FAK axis, which triggered ERS mainly the IRE1α-XBP1 pathway, thus promoting the production of inflammatory cytokines.[105]

ERS and apoptosis

ERS is associated with adipocyte apoptosis. Huang et al. reported that docosahexaenoic acid (DHA) induced apoptosis of grass carp adipocytes through ERS, and B-cell lymphoma-2-related ovarian killer (BOK) may be an important link between ERS and apoptosis. BOK is considered to be a pro-apoptotic member of the BCL-2 family, handling the mitochondrial apoptosis pathway. DHA significantly increased the transcript of BOK, which was blocked by the ERS inhibitor.[106] Beclin-1 is a basic composition of the class III PI3K complex, which is necessary for autophagosome formation and vesicle transport. Ablation of Beclin-1 in adipocytes has made them more sensitive to the ERS-stimulated apoptotic signal. The inhibition of ERS by Beclin-1 is a crucial player in maintaining adipocyte survival and WAT homeostasis in obesity.[107] ERS triggered adipocyte apoptosis by increasing intracellular FFA and $Ca^{2}+$ levels. Adiponectin was able to attenuate ERS-induced adipocyte apoptosis by activating the AMPK signaling pathway via binding to adiponectin receptors and inhibiting ATF2 transcription through upregulation of PPARα.[108]

ERS and mitochondrial dysfunction

There is a cross-talk between the ER and mitochondria, which are closely linked both physically and functionally.[109] Laura Jacksch et al. treated human differentiated adipocytes from Chub-S7 cell line and primary abdominal subcutaneous adipocytes from lean and obese individuals with

tunicamycin to induce ERS and evaluate mitochondrial function. Chronic ERS caused by obesity leads to increased oxidative stress, and decreased antioxidant protection, as well as inefficient mitochondrial oxidative capacity, diminished membrane potential, and increased mitochondrial fragmentation in human adipocytes. These human data indicate that adipocyte mitochondrial inefficiency is driven by ERS and aggravated during obesity. Adipocyte ERS induced by overnutrition can lead to mitochondrial dysfunction.[110] Nisha et al. found that treatment of 3T3-L1 adipocytes with tunicamycin significantly increased intracellular ROS and reduced mitochondrial biosynthesis.[111] Manuel et al. found that the active-site cysteines of PDI were succinated during glucotoxicity-caused mitochondrial stress, diminishing PDI oxidoreductase activity and induced protein folding disorder, which led to increased ERS in adipocytes under the high glucose condition and in the epididymal WAT of db/db mice. After targeting mitochondrial stress in adipocytes under high glucose conditions with the chemical uncoupler niclosamide, PAI protein succination, and ERS were reduced. Succination of PDI can link mitochondrial stress and ERS in adipocytes during diabetes.[112]

ERS and other functions

ERS adjusts the expression of some important genes in adipocytes. PPARα is a ligand-dependent transcription factor that regulates genes associated with lipid metabolism, and PPARα expression is reduced in WAT of obese mice.[113] Studies have shown that activation of the PPARα signal in adipocytes may ameliorate obesity.[114,115] Jungin et al. investigated the regulatory mechanism of PPARα gene transcription in adipocytes under inflammatory conditions. They found that nitric oxide (NO) secreted by activated macrophages downregulated PPARα expression in adipocytes, at least partially by inducing ERS. NO-mediated ERS in adipocytes decreased the occupation of transcription factor Sp1 at the binding site in the proximal promoter region of PPARα, then inhibiting the transcription of PPARα.[116] As a key protein for adipocytes to integrate inflammation and metabolism, the six transmembrane proteins of prostate 2 (STAMP2) play an important role in maintaining metabolic homeostasis. Mice with STAMP2 gene deletion in visceral fat developed spontaneous metabolic disease even on a normal diet.[117] ERS inducers could markedly decrease STAMP2 expression in adipocytes. In mechanism, C/EBPα directly bound to and activated the STAMP2 promoter, while ERS reduced Stamp2 transcription by lessening the expression of C/EBPα.[118] Nuclear transcription factor-Y A (NF-YA) is an evolutionarily conserved transcription factor that can regulate the expression of adipocyte-specific genes. It has been reported that ERS inhibited NF-YA expression in adipocytes at the transcriptional level, which may be related to the decrease of PPARγ. Activation of PPARγ could alleviate the inhibition of NF-YA expression by ERS.[119] The transcriptional regulator TRIP-Br2 is specifically up-regulated in obese visceral fat. TRIP-Br2 deficiency can protect mice from obesity and related complications.[120] Qiang et al. found that the TRIP-Br2 expression in obese visceral adipocytes was regulated by inflammatory cytokines and FFA-activated ERS. ERS promoted TRIP-Br2 expression by up-regulating the transcription factor GATA3. In turn, the increase of TRIP-Br2 further facilitated ERS-induced inflammatory response.[121] Fatty acid–binding protein 4 (FABP4) is highly expressed in adipocytes and primarily controls lipid metabolism pathways. As a lipid chaperone, FABP4 is secreted along with lipolysis in adipocytes. Raised circulating FABP4 level is pertinent to obesity.[122,123] The relationship between Chlamydia pneumoniae infection and metabolic syndrome has been demonstrated.[124,125] Nirwana et al. investigated that Chlamydia pneumoniae infection caused ERS in adipocytes, which promoted lipolysis-related FABP4 secretion by eliciting elevated mitochondrial ROS and cytosolic Ca2+. Chlamydia pneumoniae-induced lipolysis and FABP4 secretion were inhibited by utilizing the ER chemical chaperone, CHOP gene silencing, and mitochondrial ROS scavenger. Moreover, ERS inducers also promoted FABP4 secretion in adipocytes.[126]

ERS in adipocytes as a potential target for obesity management

Inhibiting ERS could be a therapeutic intervention against the morphological and functional alterations of overall adipose tissue depots in obesity. The ERS inhibitor TUDCA, as a bile acid conjugated to taurine with chemical chaperone activity, has emerged as a therapeutic strategy to minimize obesity-related adipose tissue dysfunction and metabolic disorders. TUDCA has been

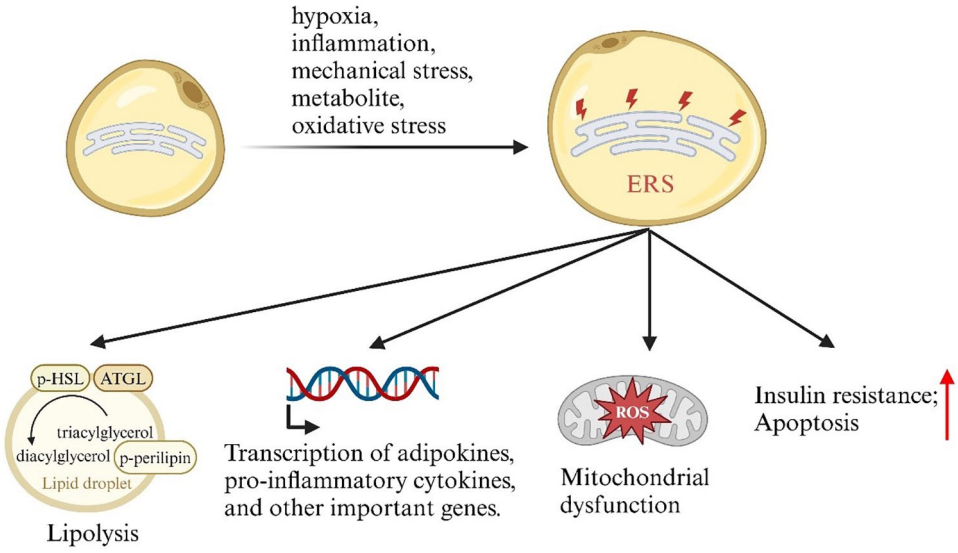

Figure 1. The effects of ERS on the hypertrophic adipocyte.
Source. This mechanism diagram was created with BioRender.com.
ERS, Endoplasmic reticulum stress.

approved by the US administration for clinical application of cholelithiasis and cholestatic liver disease. Thus, TUDCA treatment may also be a feasible therapeutic agent for obesity management.[127] Due to the limited amount of human subcutaneous adipose tissue (SAT) biopsies, peripheral blood mononuclear cells (PBMCs) can be used as surrogate cells for studying metabolic syndrome, diabetes, and obesity. Abdelkrim Khadi et al. collected SAT and PBMCs from nondiabetes human lean and obese subjects at baseline and after physical exercise. Obese individuals had higher levels of ERS markers in SAT and PBMCs compared to lean individuals and could be improved by physical exercise. This suggests that regular moderate physical exercise could be an effective non-pharmacological approach to alleviate ERS and maintain metabolic homeostasis.[128] Sandra et al. reported that after receiving calorie restriction, obese individuals lost weight, raised insulin sensitivity, and reduced serum inflammation levels, as well as decreased ERS in PBMCs.[129] Gregor et al. collected SAT samples from obese subjects before and 1 year after gastric bypass surgery and found that after the surgery, the subjects experienced weight loss and improved insulin sensitivity. The ERS markers of SAT significantly decreased with weight loss, indicating that weight loss is also a considerable method of mitigating ERS in adipose tissue of obese subjects.[130] In general, Pharmacological regulators of ERS or weight loss including physical exercise, dietary interventions, and surgery may be promising clinical options for relieving ERS in adipose tissue and obesity management.

Current limitations of knowledge and future directions

Since ERS in adipose tissue is primarily afflicted by obesity, the development of novel treatments for obesity may provide new insights into mitigating ERS. Although pharmacological inhibitors of ERS have therapeutic potential as new targets for metabolic diseases, obesity is adjusted by multiple factors and variables, making it a highly complicated disease for which a single therapeutic approach is usually less effective. The current lifestyle management strategies such as caloric restriction and physical activity are often inadequate. In addition to lifestyle changes, treatments for obesity generally include pharmacotherapy and bariatric surgery.[131] Pharmacotherapeutics contain anti-inflammatory drugs, antioxidant agents, lipid-lowering medications, and anti-obesity medications. Moreover, alternative strategies for confronting obesity are being explored, including regulation of the gut microbiome, anti-obesity vaccines, and gene therapy. With the continuous research and understanding of the pathophysiological mechanism of obesity, personalized and

multimodal obesity treatment will be the future direction.[132]

Conclusion

On a global scale, the gradual increase in the prevalence of obesity over the past several decades is regarded as a serious threat to public health. The rising obesity epidemic and its related complications have made adipocytes an important topic of scientific research and a target for therapeutic intervention. The ER controls the correct folding of peptides and proteins through a variety of chaperones and enzymes on its membrane. When the overloaded protein folding exceeds the processing capacity, the ER folding process will be disordered, leading to the accumulation of misfolded/unfolded proteins in the ER lumen and ultimately triggering ERS. With the progression of obesity, excessive or sustained ERS disrupts adipocyte functions, including lipolysis, IR, apoptosis, bioactive molecule production, mitochondrial dysfunction, and impacting the expression of some important genes, thereby affecting WAT (Figure 1). Growing evidence implies that severe ERS in adipocytes plays a crucial role in the pathogenesis of obesity-related metabolic diseases, and alleviating ERS in adipocytes may be a potential target for obesity management.

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Consent for publication

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Author contributions

Yu Jiang: Conceptualization; Project administration; Writing – original draft.

Jia-Qi Guo: Data curation; Formal analysis.

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