Pathogenesis of Obesity-Induced Insulin Resistance

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Abstract This article reviews recent research progress on the mechanisms by which obesity induces insulin resistance through factors such as endoplasmic reticulum stress, mitochondrial dysfunction, and adipocytokines. The aim is to provide more basis for the treatment of this disease.

Key words Obesity, Insulin resistance, Mechanism research

1 Introduction

Insulin resistance (IR) refers to a condition caused by various factors, characterized by reduced insulin secretion and decreased utilization of glucose, leading to a decrease in the body's sensitivity to insulin and resulting in a series of metabolic disorders. Obesity-induced insulin resistance (IR) is a predisposing factor for various metabolic diseases. Currently, the pathogenesis of obesity-induced IR is not fully understood. This article reviews the research progress on the mechanisms by which obesity induces insulin resistance through factors such as endoplasmic reticulum stress, mitochondrial dysfunction, and adipocytokines. The aim is to provide a basis for the treatment of this disease.

2 IR and endoplasmic reticulum stress

The endoplasmic reticulum (ER) is a core organelle within cells responsible for protein processing, lipid synthesis, and calcium ion storage. When calcium homeostasis is disrupted and unfolded or misfolded proteins accumulate in the ER lumen, leading to ER dysfunction, an adaptive response is triggered, known as endoplasmic reticulum stress (ERS). ER stress is considered an important link in the development and progression of obesity, IR, and diabetes[1]. To cope with the accumulation of unfolded and misfolded proteins, cells initiate adaptive regulation through the unfolded protein response (UPR). The UPR is initiated by three ER transmembrane sensor proteins: protein kinase-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6)[2]. The coordinated activation of the three UPR branches ultimately alleviates the ER stress response. ERS persists long-term in the liver, brain, cells, and adipose tissue of obese animals and obese patients[3]. Lipid accumulation is associated with insulin resistance. The development of insulin resistance is accompanied by an increase in ER stress in various tissues[4]. Obesity can cause ER stress and inhibit insulin signaling[5]. The mechanisms by which ERS leads to IR are highly complex and may involve the following aspects.

ER stress can induce IR in organs including the liver, adipose tissue, skeletal muscle, and pancreas[6]. In the liver, the activated UPR branches play a decisive role in either ER stress resolution or gluconeogenesis. ERS activates IRE1α, which in turn activates c-Jun N-terminal kinase (JNK) and I kappa B kinase (IKK), directly or indirectly promoting hepatic gluconeogenesis and directly inhibiting the insulin signaling pathway[7]. PERK mediates the overexpression of eukaryotic initiation factor 2α (eIF2α) and tribbles homolog 3 (TRB3), leading to impaired insulin signaling[8]. Furthermore, inducing the overexpression of Park2 and ubiquitin-specific peptidase 14 (USP14) or suppressing the expression of oxygen-regulated protein 150 (ORP150) can induce ER stress, thereby affecting insulin signaling and ultimately leading to hepatic IR[9-11]. In adipocytes, ERS can accelerate the IR process by inducing the expression of inflammatory genes through PERK-mediated mechanisms involving non-esterified fatty acids (NEFAs) and through the IRE1α- and ATF6-mediated nuclear factor kappa-B (NF-κB) inflammatory pathway[12]. In skeletal muscle, via the IRE-1/JNK pathway, it induces phosphorylation of insulin receptor substrate (IRS) proteins, disrupting the interaction between IRS and the insulin receptor, reducing insulin signaling, and enhancing ERS-induced IR. Alternatively, IKKβ overexpression activates the IKKβ/NF-κB pathway and disrupts insulin/leptin signaling transduction, reducing insulin sensitivity and inducing IR[13-14]. In the pancreas, inflammatory cytokines such as interleukin-23 (IL-23), IL-24, and IL-33 can cause β-cell oxidation and ERS, reducing insulin sensitivity[15].

3 IR and mitochondrial dysfunction

Mitochondria, as the "powerhouses" of the cell, rely on their unique structure to achieve their functions. Structurally, the matrix contains the fatty acid β-oxidation enzyme system, key enzymes of the tricarboxylic acid (TCA) cycle, and circular mtDNA, responsible for converting fatty acids and glycolytic metabolites into reducing equivalents ($NADH/FADH_2$). The inner membrane embeds complexes I (NADH dehydrogenase), III (cyto-

Received: July 13, 2025 Accepted: September 4, 2025

Supported by National Natural Science Foundation of China (82174525); Natural Science Foundation of Jilin Province (YDZJ202301ZYTS469); Science and Technology Research Project of the Department of Education of Jilin Province (JJKH20230966KJ); Jilin Province College Students' Innovation and Entrepreneurship Training Program (S202310199043, S202310199042, S202510199020).

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chrome bc_1 complex), and IV (cytochrome c oxidase), which convert the chemical energy of NADH/$FADH_2$ into a transmembrane proton gradient through oxidative phosphorylation. Functionally, this proton gradient drives ATP synthase (complex V) to catalyze the phosphorylation of ADP to ATP, providing energy support for cellular activities. Intracellular Ca^{2+} concentration balance is regulated by inner membrane transporters. Additionally, mitochondria are involved in cellular metabolism and apoptosis[16]. When the structure or related components of mitochondria become abnormal, such as reduced mitochondrial number, structural abnormalities, or decreased enzyme activity, it leads to mitochondrial dysfunction. This is manifested specifically as decreased mitochondrial membrane potential, reduced ATP synthesis, disruption of intracellular calcium homeostasis, opening of the mitochondrial permeability transition pore (mPTP), a sharp increase in ROS, and the release of apoptosis-inducing factors, exacerbating mitochondrial dysfunction and ultimately leading to cell apoptosis or necrosis[17]. Studies have shown that the number of mitochondria and the activity of the electron transport chain are decreased in individuals with type 2 diabetes and obesity compared to lean subjects. Muscle mitochondrial dysfunction in T2DM is a functional defect associated with impaired insulin responsiveness[18]. Compared to insulin-sensitive individuals, insulin-resistant subjects exhibit reduced resting adenosine triphosphate (ATP) synthesis in skeletal muscle, indicating that decreased mitochondrial function is a key factor in inducing IR[19]. Furthermore, exercise can enhance mitochondrial biogenesis by activating pathways such as PGC-1α, thereby improving insulin sensitivity. This also demonstrates the close relationship between mitochondrial dysfunction and IR[20]. The main mechanisms by which mitochondrial dysfunction leads to IR include: reduced mitochondrial biogenesis and energy metabolism impairment, oxidative stress, mtDNA abnormalities, and abnormal mitophagy.

Mitochondrial dysfunction can lead to reduced mitochondrial biogenesis, decreased total mass, and lower oxidase activity, collectively resulting in weakened oxidative metabolism capacity for fatty acids and glucose, and increased accumulation of free fatty acids and lipids. Impaired substrate oxidation promotes the accumulation of diacylglycerol (DAG) and ceramide within cells. DAG activates protein kinase C (PKC), causing its translocation to the cell membrane where it interferes with insulin receptor function. Ceramide blocks insulin signal transduction by inhibiting Akt (protein kinase B) or activating JNK (c-jun N-terminal kinase), leading to the onset of IR[21]. Mitochondrial dysfunction triggers excessive production and accumulation of reactive oxygen species (ROS), inducing intracellular oxidative stress and disrupting the oxidant-antioxidant system balance. Increased ROS leads to DNA mutations, abnormal protein modifications, and lipid peroxidation. Increased ROS activates pro-inflammatory transcription factors such as NF-κB and JNK, which synergistically hinder the binding of insulin receptor substrate 1 (IRS-1) to the insulin receptor, ultimately exacerbating IR[22-23]. Mitochondrial DNA (mtDNA), lacking histone protection and residing in a highly oxidative environment, is susceptible to mutation from ROS attack and accumulates through maternal inheritance. mtDNA mutations and alterations in copy number are closely associated with IR. Studies indicate that plasma mtDNA levels are elevated in obese or T2DM patients and positively correlate with skeletal muscle mtDNA damage, oxidative stress, and IR[24]. Increasing muscle mtDNA copy number and PGC-1α mRNA expression in IR model rats can improve mitochondrial function. Conversely, reduced mtDNA copy number can suppress calcium signaling and insulin secretion[25]. Therefore, alterations in mtDNA may impair respiratory chain function, hinder ATP synthesis, lead to insulin secretion and glucose metabolism disorders, and exacerbate peripheral tissue IR.

Mitophagy is the process by which damaged mitochondria are selectively recognized, engulfed, and degraded through the autophagy mechanism. Impairment of the signaling pathways involved in initiating mitophagy, such as the AMP-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) pathway, and those involved in mitochondrial tagging/formation, such as the PINK1/Parkin (PTEN-induced putative kinase protein 1/Parkin), BNIP3/Nix (BCL2 and adenovirus E1B 19kDa protein-interacting protein 3/NIP3-like protein X, NIX, also known as BNIP3L), and the mitochondrial outer membrane protein FUNDC1 pathways, leads to mitophagy dysfunction. The accumulation of damaged mitochondria, ROS, and metabolic waste products induces IR[26].

4 IR and lipid metabolism disorders

In recent years, relevant research has demonstrated that various adipocytokines secreted by adipose tissue, including leptin, resistin, adiponectin (APN), and free fatty acids (FFA), also participate in obesity-mediated IR development.

4.1 Leptin Leptin is a protein hormone secreted by adipocytes that participates in regulating appetite, metabolism, and energy expenditure. Serum leptin levels are positively correlated with IR in obese patients and are often accompanied by "leptin resistance". This phenomenon refers to elevated leptin levels in the body but decreased sensitivity to leptin, resulting in leptin's inability to properly initiate appetite-suppressing signals or effectively regulate energy metabolism processes, rendering its regulatory function ineffective[27]. Possible mechanisms by which leptin resistance leads to insulin resistance (IR) include: the bidirectional regulation between leptin and insulin. Elevated leptin levels in the obese state are not merely a signal of energy sufficiency; instead, they promote and exacerbate insulin resistance (IR) by directly inhibiting insulin secretion and function, inducing inflammation, and directly interfering with and blocking downstream insulin receptor signaling through the JAK (Janus kinase)-STAT3 (signal transducers and activators of transcription 3) and ERK signaling pathways[28]. Therefore, hyperleptinemia and its accompanying "leptin resistance" (signaling pathway failure) constitute a cruci-

al pathological hub in the development and progression of obesity-related IR. Leptin can promote glycogenolysis, leading to an increase in free fatty acids and exacerbating IR[29].

4.2 Adiponectin Adiponectin (APN) is a key protective factor secreted by adipose tissue that improves insulin sensitivity. Studies have shown that APN is negatively correlated with body fat content and positively correlated with insulin sensitivity[30]. APN is a natural inhibitor of IR, and its multi-target mechanisms significantly alleviate IR. In skeletal muscle, it activates AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor gamma (PPAR-γ), promoting fatty acid oxidation in skeletal muscle cells, antagonizing tumor necrosis factor alpha (TNF-α), and improving insulin sensitivity. In the liver, APN inhibits key gluconeogenic enzymes (glucose-6-phosphatase, phosphoenolpyruvate carboxykinase) via AMPK, thereby reducing hepatic gluconeogenesis[31]. APN enhances insulin receptor signaling, accelerates tyrosine phosphorylation of IRS1 (Insulin Receptor Substrate 1), promotes membrane translocation of the glucose transporter GLUT4, and increases glucose uptake in muscle or adipose tissue[32]. APN can clear ceramide, relieving its inhibition on insulin receptor binding and enhancing insulin signaling pathway cross-talk[33]. APN deficiency and APN resistance induced by obesity lead to lipid metabolism disorders and uncontrolled hepatic glucose output, serving as the core triggers for IR.

4.3 Resistin Resistin is a polypeptide hormone and a key pathogenic factor in obesity-related IR. By interfering with insulin signaling, inducing lipid metabolism disorders, and activating inflammatory pathways, it directly promotes the occurrence of IR and type 2 diabetes. Its core mechanisms are as follows: Resistin can inhibit the tyrosine phosphorylation of the insulin receptor (IR) and insulin receptor substrate-1 (IRS-1), blocking the initiation of insulin signaling and reducing insulin sensitivity. Resistin can activate intracellular IKKβ/NF-κB and MAPK inflammatory signaling pathways, aggravating insulin resistance. It inhibits the anti-lipolytic effect of insulin, leading to increased plasma free fatty acid (FFA) levels, which worsens IR. Resistin activates suppressor of cytokine signaling 3 (SOCS-3), which competitively blocks the insulin receptor, contributing to IR[34-35].

4.4 Free fatty acids In the obese state, increased plasma free fatty acid (FFA) levels are closely associated with impaired insulin signal transduction and disordered cellular glucose metabolism. Elevated FFA and IR mutually promote each other, forming a self-reinforcing cycle that serves as a core driving force for the development of type 2 diabetes[36]. Hyper-FFAemia is a key metabolic factor driving insulin resistance. It acts through disrupting insulin signaling, inflammatory cascades, and interfering with glucose-lipid metabolic balance. The mechanisms are as follows: Obstacles exist in signal transduction pathways. FFAs hinder the activation of the insulin receptor and reduce its binding efficiency to insulin. They impede the translocation of the glucose transporter GLUT4, impair tyrosine phosphorylation of IRS, inhibit the activity of phosphatidylinositol-3-kinase (PI3K), and mediate insulin metabolism. High FFAs activate the glucose-fatty acid (Randle) cycle, inhibiting insulin-stimulated glycogen synthesis. Elevated FFA levels activate the IKKβ/NF-κB and JNK1 pathways, leading to serine phosphorylation of IRS1. This subsequently causes a significant increase in inflammatory mediators such as TNF-α and IL-6. The inhibition of insulin signaling leads to the occurrence of IR[37-38].

5 Conclusion

Obesity-induced insulin resistance (IR) is the core pathological basis of metabolic syndrome and type 2 diabetes. Its occurrence and development involve complex cascades across multiple organs and pathways. Factors such as endoplasmic reticulum stress, mitochondrial dysfunction, and adipocytokines can independently trigger IR and, more importantly, synergize through positive feedback loops. In-depth elucidation of the cross-regulatory networks among these key mechanisms can provide an important theoretical basis for developing strategies to target and improve obesity-related metabolic disorders and insulin resistance.

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(From page 91)

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