Research Progress of Apolipoprotein J in Metabolic Diseases (Postprint)

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Abstract

Metabolic diseases significantly impact global public health. Apolipoprotein J (ApoJ) is a multifunctional glycoprotein widely expressed in organs such as the brain, liver, and testes, participating in physiological and pathological processes including the maintenance of protein homeostasis and the regulation of apoptosis. Recent studies have revealed that ApoJ is closely associated with processes such as insulin resistance, lipid metabolism, and inflammatory responses, and is involved in the onset and progression of metabolic diseases such as diabetes and obesity. This paper systematically reviews the research progress of ApoJ in type 2 diabetes mellitus, atherosclerotic cardiovascular disease, obesity, metabolic dysfunction-associated steatotic liver disease, and polycystic ovary syndrome. It focuses on the changes in its expression levels and molecular mechanisms of action within these diseases, and further explores the potential of ApoJ as a novel biomarker and therapeutic target for metabolic diseases. Additionally, the paper provides a comparative analysis of the differences in its functional performance across various diseases and the possible underlying reasons, aiming to provide a reference for basic research and clinical applications of ApoJ in metabolic diseases.

Full Text

Preamble

Review and Monograph: Research Progress of Apolipoprotein J in Metabolic Diseases

Wang Jiawei, Deng Xia*, Yuan Guoyue*

Figure 1

Figure 1: Figure 1

Abstract

Apolipoprotein J (ApoJ), also known as Clusterin (CLU), is a highly conserved multifunctional glycoprotein widely distributed in various tissues and body fluids. As a molecular chaperone, ApoJ plays a critical role in maintaining proteostasis and regulating diverse biological processes, including cell apoptosis, signal transduction, and lipid metabolism. Recent studies have demonstrated that ApoJ is closely associated with the development and progression of metabolic diseases such as obesity, type 2 diabetes mellitus (T2DM), and non-alcoholic fatty liver disease (NAFLD). This review summarizes the structural characteristics and biological functions of ApoJ, focusing on its specific roles and potential mechanisms in metabolic disorders, thereby providing new insights for the clinical diagnosis and treatment of these conditions.

1. Introduction

Metabolic diseases, characterized by obesity, insulin resistance, and dyslipidemia, have become a global public health challenge. Apolipoprotein J (ApoJ), first identified in ram rete testis fluid, has gained significant attention due to its complex physiological roles. Unlike other apolipoproteins, ApoJ is not only involved in lipid transport but also acts as a stress-induced chaperone protein. Emerging evidence suggests that circulating levels of ApoJ are significantly altered in patients with metabolic syndrome, suggesting its potential as a biomarker and therapeutic target.

2. Structural Characteristics and Expression of ApoJ

ApoJ is encoded by the *CLU* gene located on chromosome 8 in humans. The primary translation product is a 449-amino acid polypeptide that undergoes extensive post-translational modifications, including glycosylation and proteolytic cleavage. The mature secreted form of ApoJ (sCLU) is a heterodimeric glycoprotein consisting of an α-chain and a β-chain linked by five disulfide bonds.

The expression of ApoJ is ubiquitous but highly regulated by various stressors, including oxidative stress, heat shock, and inflammatory cytokines. In the context of metabolic health, ApoJ is highly expressed in the liver, adipose tissue, and pancreas, where it interacts with various receptors such as the low-density lipoprotein receptor-related protein 2 (LRP2, also known as megalin).

3. Biological Functions of ApoJ

3.1 Molecular Chaperone Activity

ApoJ functions as an extracellular chaperone, similar

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Abstract Metabolic diseases significantly impact global public health. Apolipoprotein J (ApoJ) is a multifunctional glycoprotein widely expressed in organs such as the brain, liver, and testes, participating in physiological and pathological processes including the maintenance of protein homeostasis and the regulation of apoptosis. Recent studies have revealed that ApoJ is closely associated with insulin resistance, lipid metabolism, and inflammatory responses, playing a role in the onset and progression of metabolic diseases such as diabetes and obesity. This article systematically reviews the research progress of ApoJ in type 2 diabetes, atherosclerotic cardiovascular disease, obesity, metabolic dysfunction-associated steatotic liver disease (MASLD), and polycystic ovary syndrome (PCOS). It focuses on elucidating the changes in expression levels and molecular mechanisms of action in these diseases, further exploring the potential of ApoJ as a novel biomarker and therapeutic target for metabolic diseases. Additionally, the article provides a comparative analysis of the functional differences and possible underlying reasons for ApoJ' s performance across different diseases, aiming to provide a reference for basic research and clinical applications of ApoJ in metabolic disorders.

[**Key words**] Apolipoprotein J; Metabolic diseases; Diabetes mellitus, type 2; Atherosclerosis; Cardiovascular disease; Obesity; Metabolic dysfunction-associated steatotic liver disease; Polycystic ovary syndrome

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In recent years, the prevalence of metabolic diseases—represented by type 2 diabetes mellitus (T2DM), obesity, metabolic dysfunction-associated steatotic liver disease (MASLD), and polycystic ovary syndrome (PCOS)—has continued to rise, becoming a major challenge in the field of global public health [**?**]. Apolipoprotein J (ApoJ) is a glycoprotein widely expressed in human tissues and body fluids. As a molecular chaperone, it possesses potent anti-aggregation activity, binding to the hydrophobic regions of misfolded proteins to prevent

their aggregation and precipitation [**?**]. Cytoplasmic ApoJ can bind to glucose-regulated protein 78 (GRP78) in the endoplasmic reticulum to inhibit apoptosis, while the nuclear isoform promotes apoptosis through pathways such as the Bcl-2-associated X protein (BAX) [**?**]. An increasing number of studies have found that different isoforms of ApoJ, particularly secretory ApoJ, may play a crucial role in metabolic regulation [**?**].

Traditional research has primarily focused on the role of ApoJ in neurodegenerative diseases. Its mechanisms involve inhibiting the aggregation of amyloid-beta (Aβ), enhancing the phagocytosis of Aβ by microglia, and bidirectionally regulating tau protein phosphorylation to influence its toxic effects on neurons [**?**]. Recent studies have discovered that ApoJ may also play a role in the pathogenesis of metabolic diseases such as T2DM, obesity, and MASLD by regulating key molecular pathways including insulin signaling, lipid metabolism, and oxidative stress [**?**].

The expression of ApoJ is regulated by various cellular stresses and pathological signals. Its mechanisms can be summarized into the following three aspects: (1) Cellular stress response: As a molecular chaperone, ApoJ is a key response protein for cellular stress, and its expression is closely related to the maintenance of intracellular homeostasis. Mitochondrial stress can activate the mitochondrial unfolded protein response (UPR_{mt}), which subsequently upregulates ApoJ expression via heat shock factor 1 [**?**]. Necrotic cell lysates induce endoplasmic reticulum stress, specifically activating the UPR-inositol-requiring enzyme 1α ($IRE1\alpha$) signaling branch to promote ApoJ expression [**?**].

(2) Metabolism-related transcriptional regulation: Specific transcription factors serve as the core mediators for metabolic signals regulating ApoJ expression. Among them, sterol regulatory element-binding protein-1c (SREBP-1c) is a key metabolic transcription factor. In cervical cancer cells [**?**], high glucose conditions or overexpression of O-linked N-acetylglucosamine transferase can enhance the glycosylation of the liver X receptor, which in turn upregulates SREBP-1c. As a transcription factor, SREBP-1c binds to the ApoJ promoter to enhance ApoJ levels. In HepG2 cells [**?**], high glucose concentrations stimulate the activation of SREBP-1c; the synthesized SREBP-1c then increases ApoJ expression by binding to the E-box motif in the first intron region of the hepatic ApoJ gene. (3) Induction by specific pathological factors: Under disease states, this systematic review examines the molecular regulatory mechanisms of ApoJ in metabolic diseases to provide a new perspective for their diagnosis and treatment.

The literature search strategy for this article involved searching China National Knowledge Infrastructure (CNKI), Wanfang Data, and PubMed databases from their inception to November 2025. Chinese search terms included “载脂蛋白 J” (Apolipoprotein J), “2 型糖尿病” (Type 2 Diabetes), “动脉粥样硬化性心血管疾病” (Atherosclerotic Cardiovascular Disease), “肥胖症” (Obesity), “代谢功能障碍相关脂肪性肝病” (MASLD), “多囊卵巢综合征” (PCOS), and “代谢性疾病” (Metabolic

Diseases). English search terms included "Apolipoprotein J", "Type 2 Diabetes", "Atherosclerotic Cardiovascular Disease", "Obesity", "Metabolic Dysfunction-Associated Steatotic Liver Disease", "Polycystic Ovary Syndrome", and "Metabolic Diseases". Inclusion criteria: Literature involving the structure, function, and regulatory mechanisms of ApoJ, and research on the relationship between ApoJ and metabolic diseases. Exclusion criteria: Poor relevance to the topic, low literature quality, retracted papers, and inaccessible full texts. Final included literature···

1 ApoJ 的结构、功能和调控机制

ApoJ is a multifunctional glycoprotein, also known as Clusterin, because it was initially discovered to possess the ability to promote cell aggregation in vitro [**?**].

The ApoJ gene is located on chromosome 8p21.1 and consists of nine coding exons and···

2 个未翻译外显子组成 [10]。ApoJ 的翻译从 mRNA 外显

Starting from the initiation codon on exon 2, a proprotein consisting of 449 amino acids is produced. The first 22 amino acids constitute a signal sequence that facilitates the translocation of the proprotein. Under various conditions, multiple pathological stimuli can induce the expression of ApoJ; for instance, stress inducers such as HCV and free fatty acids [20] have been confirmed to promote ApoJ expression in hepatocytes.

In summary, the expression of ApoJ is influenced by a variety of factors and signaling pathways. A thorough investigation into its regulatory mechanisms will help elucidate its potential as a therapeutic target for metabolic regulation.

2 ApoJ 与 T2DM

Type 2 diabetes mellitus (T2DM) is a metabolic disease characterized by hyperglycemia and insulin resistance (IR), accompanied by progressive pancreatic β-cell failure [**?**]. Seo et al. [**?**] found that fasting serum ApoJ levels were significantly higher in T2DM subjects compared to normal controls (). When normal subjects were divided into tertiles based on their Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index, those in the high HOMA-IR group exhibited higher serum ApoJ levels. Furthermore, serum ApoJ levels were positively correlated with fasting plasma glucose (FPG), fasting insulin (FINS), HOMA-IR, and BMI. Multiple regression analysis, after adjusting for age, sex, and BMI, revealed that serum ApoJ is an independent factor associated with FINS and HOMA-IR in normal subjects. However, this independent association was not observed in T2DM subjects, potentially because varying degrees of β-cell dysfunction in T2DM affect insulin secretion, while serum ApoJ levels are dually influenced by both IR and insulin secretion. In animal models [**?**],

Figure 1

Figure 2: Figure 1

liver-specific ApoJ knockout mice exhibited significantly elevated FPG levels compared to the control group, while FINS levels remained unchanged. This suggests that the loss of hepatic ApoJ can induce impaired glucose tolerance and fasting IR. Both human and animal studies indicate that circulating ApoJ levels are closely linked to IR; when insulin sensitivity is enhanced and IR is improved through exercise or pharmacological intervention, serum ApoJ levels change accordingly.

In postmenopausal women with diabetes, exercise training for 8 and 12 weeks resulted in a reduction of ApoJ levels by 26.3% and 19.4% from baseline, respectively [**?**]. Similarly, serum ApoJ levels in T2DM subjects were significantly lower after treatment with rosiglitazone compared to pre-treatment levels [**?**].

Skeletal muscle is a critical site for glucose utilization. Research has shown [**?**] that liver-derived ApoJ binds to low-density lipoprotein receptor-related protein 2 (LRP2) in skeletal muscle, promoting the internalization of insulin receptors on the muscle cell surface. This enhances the downstream phosphorylation of insulin receptor substrate 1 (IRS-1) and protein kinase B (Akt), thereby promoting glucose uptake in skeletal muscle and improving insulin sensitivity.

Conversely, the absence of LRP2 in skeletal muscle leads to defects in insulin receptor internalization, which inhibits the phosphorylation of IRS-1 and Akt, reduces insulin-stimulated glucose uptake, and ultimately results in insulin resistance. In obese states, adipose-derived ApoJ also contributes to the development of insulin resistance. Bradley et al. [**?**] found that palmitate stimulates adipocytes to produce ApoJ, which then binds to hepatic LRP2 receptors. This interaction decreases insulin-induced Akt phosphorylation while increasing the expression of gluconeogenesis-related genes, such as glucokinase (GCK) and pyruvate kinase liver/rbc (PKLR), thereby promoting insulin resistance (,

). The opposing roles of ApoJ from different tissue sources in regulating insulin sensitivity may be attributed to two factors: (1) differences in the metabolic context of the studies—Seo et al. [**?**] primarily utilized mouse models on a normal diet, revealing that under basal metabolic conditions, liver-derived ApoJ may act as a protective factor.

ApoJ is closely associated with the occurrence and progression of diabetes and its complications. It participates in these processes primarily by regulating multiple physiological and pathological pathways, including muscle glucose uptake, insulin resistance, and inflammatory responses. Further investigation into the detailed mechanisms by which ApoJ regulates these related diseases is expected to provide a more robust theoretical foundation for exploring new strategies in disease prevention and treatment.

3 ApoJ 与 ASCVD

Atherosclerotic cardiovascular disease (ASCVD) refers to a group of diseases affecting the systemic vasculature and the heart caused by atherosclerosis. Metabolic disorders, such as hyperglycemia, hypertension, and dyslipidemia, are the primary risk factors for its onset [**?**].

Previous studies have established that Apolipoprotein J (ApoJ) plays a critical role in the occurrence and progression of cardiovascular and cerebrovascular diseases [**?**]. As a key component of high-density lipoprotein (HDL), ApoJ promotes reverse cholesterol transport by binding to HDL, thereby slowing the progression of atherosclerosis. Furthermore, it can reduce cardiovascular toxicity by inhibiting the aggregation of low-density lipoprotein (LDL). Recent research has further revealed a broader protective mechanism of ApoJ in metabolic disorder-related ASCVD. Xuan et al. [**?**] found that serum ApoJ levels in patients with diabetes complicated by atherosclerosis were significantly higher than those in the healthy population .

In contrast, the study by Bradley et al. [**?**] utilized palmitate-stimulated adipocytes and high-fat diet-fed mouse models to demonstrate that under conditions of metabolic stress, adipose tissue-derived ApoJ may act as a pathological signaling molecule that exacerbates hepatic insulin resistance. These divergent findings may be attributed to: (1) differences in physiological versus pathological states. Under physiological conditions, liver-derived ApoJ acts as a physiological regulator to maintain skeletal muscle insulin sensitivity. (2) Differences in target organs and downstream pathways. Liver-derived ApoJ primarily targets skeletal muscle, where it mediates insulin receptor internalization and activates the IRS-1/Akt pathway via LRP2, thereby enhancing insulin signaling and improving systemic insulin sensitivity. Conversely, adipose-derived ApoJ primarily acts on the liver, where it inhibits insulin signaling through the LRP2 receptor and promotes the expression of gluconeogenic genes, leading to impaired hepatic insulin sensitivity.

In animal models, ApoJ overexpression significantly reduced the levels of macrophage biomarkers CD68 and F4/80, as well as pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) in mice with diabetes and atherosclerosis. Conversely, ApoJ gene knockout promoted macrophage pyroptosis mediated by nod-like receptor protein 3 (NLRP3), leading to increased inflammatory responses and plaque instability. These findings suggest that ApoJ may alleviate atherosclerosis by inhibiting pathways such as macrophage pyroptosis [TABLE:1, FIGURE:1]. Diabetic kidney disease (DKD) is one of the most common microvascular complications of diabetes, characterized by persistent renal damage.

Myocardial infarction (MI) is the primary clinical manifestation of unstable plaque rupture in ASCVD. ApoJ has been found to exert multiple protective effects against MI injury. Mechanistic studies indicate that ApoJ protects car-

diomyocytes by regulating several signaling pathways, including insulin-like growth factor 1 and mitogen-activated protein kinase [**?**]. Li et al. [**?**] found that following acute myocardial infarction (AMI), ApoJ expression was significantly elevated in the peri-infarct myocardium of transient receptor potential melastatin 2 (TRPM2) knockout mice compared to the control group. Further cellular experiments showed that in an H9C2 cardiomyocyte hypoxia model, exogenous ApoJ treatment significantly improved the survival rate of hypoxic cells, reduced levels of reactive oxygen species, and inhibited the hypoxia-induced upregulation of TRPM2. Its protective effect was similar to that of TRPM2 gene silencing. Notably, ApoJ could still reverse cell damage in hypoxic cells overexpressing TRPM2.

This suggests that ApoJ may mitigate oxidative stress and apoptosis during myocardial ischemic injury by negatively regulating the expression or function of TRPM2 .

Allawa et al. [**?**] discovered that ApoJ might protect the myocardium by binding to extracellular histones. In patients with AMI, plasma levels of ApoJ-histone complexes increase while total ApoJ levels decrease, suggesting that ApoJ may be heavily consumed by histones. Investigations using the H9C2 cell hypoxia-reoxygenation (HR) model revealed that while exogenous histones exacerbate cell death, exogenous ApoJ effectively mitigates this effect and inhibits the expression of inflammatory factors such as IL-6. This suggests that ApoJ may reduce cardiomyocyte injury by binding to and neutralizing the toxicity of extracellular histones.

In summary, ApoJ not only exerts protective effects in the early stages of atherosclerosis by regulating lipid metabolism but also mitigates myocardial injury during acute cardiovascular events through multiple pathways, such as regulating TRPM2 channels and neutralizing extracellular histones. This demonstrates its multifunctional protective value throughout the entire course of ASCVD and underscores the feasibility of developing new intervention strategies for related diseases by targeting ApoJ.

Obesity is often accompanied by an imbalance between increased food intake and energy expenditure. In animal models, hypothalamic brain-derived ApoJ in mice increases postprandially and interacts with LRP2 and the long form of the leptin receptor (LepRb) on the plasma membrane of hypothalamic neurons. This interaction promotes the phosphorylation of signal transducer and activator of transcription 3 (STAT3), which collectively mediates the generation of satiety signals in hypothalamic neurons [**?**] [TABLE:1, FIGURE:1]. Compared to control groups, the response of hypothalamic ApoJ expression to food intake is diminished in obese mice, which may lead to overeating and further exacerbate obesity. Furthermore, in mouse models with adipose tissue sirtuin 1 (SIRT1) overexpression or adipose tissue ApoJ knockdown [**?**], it was found that adipose SIRT1 triggers mitochondrial stress and the mitochondrial unfolded protein response (UPR^{mt}), thereby increasing ApoJ expression. Together, they participate in regulating the protein and lipid composition at the

mitochondria-endoplasmic reticulum contact sites in adipose tissue, enhancing UPR^{mt}-mediated anti-endoplasmic reticulum stress signaling and preventing damage induced by a high-fat diet (HFD).

4 ApoJ 与肥胖症

Obesity is a metabolic disease characterized by the pathological accumulation of adipose tissue and dysfunctional adipocytes, which significantly increases health risks [**?**]. Won et al. [**?**] found that circulating ApoJ levels are significantly elevated in overweight and obese subjects compared to normal populations . Furthermore, plasma endoplasmic reticulum stress is involved in this process. When subjected to a high-fat diet (HFD), ApoJ knockdown mice exhibit significantly exacerbated metabolic abnormalities. In human bladder cancer cell models [**?**], knockdown of ApoJ reduced cellular neutral lipids and decreased the mRNA and protein expression levels of SREBP-1c and its downstream effector protein, fatty acid synthase (FASN), thereby blocking de novo fatty acid synthesis.

ApoJ is closely related to obesity. In overweight and obese subjects, plasma ApoJ levels are positively correlated with BMI, waist circumference, waist-to-hip ratio, the total cholesterol to high-density lipoprotein cholesterol ratio (TC/HDL-C), and the triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C). Multiple linear regression analysis indicates that gender, high-sensitivity C-reactive protein (hs-CRP), and BMI are independent factors associated with fasting plasma ApoJ levels. Due to visceral fat accumulation and insulin resistance, patients with obesity release large amounts of free fatty acids into the blood, often leading to hyperlipidemia. Rull et al. [**?**] found that serum ApoJ concentrations in patients with hyperlipidemia are significantly higher than those in normal populations. While the total serum ApoJ level is elevated, the amount of ApoJ bound to lipoproteins actually decreases. This suggests that the binding of ApoJ to lipoproteins may be regulated by lipoprotein composition; the subsequent redistribution of ApoJ after such regulation may, in turn, affect lipoprotein properties and related pathophysiological activities [**?**]. Animal and cellular experiments have also confirmed that ApoJ may participate in the development of obesity through the regulation of food intake and fatty acid synthesis. In a study investigating the treatment of obesity using exercise combined with spirulina supplementation [**?**], the combined intervention of high-intensity interval training and spirulina led to a decrease in ApoJ levels alongside significant reductions in body weight, body fat percentage, BMI, and HOMA-IR in obese subjects. Although existing studies have identified a link between ApoJ and obesity, the specific mechanisms underlying its role in the development of the disease have not been fully elucidated. Future research should explore these mechanisms in depth to uncover the potential of ApoJ as a new target for the prediction and treatment of lipid metabolism imbalance.

Production, TGF-$ $1 and ROS jointly activate HSCs, promoting their transformation into···

Figure 1

Figure 3: Figure 1

5 ApoJ 与 MASLD

···collagen-secreting myofibroblasts, thereby accelerating the progression of liver fibrosis (,

). Metabolic dysfunction-associated steatotic liver disease (MASLD) is a chronic liver disease pathologically characterized by excessive lipid deposition within hepatocytes (intrahepatic fat content >5%). Its occurrence and development are closely linked to insulin resistance (IR) and various metabolic disorders [**?**].

WANG et al. [**?**] found that serum ApoJ levels in patients with MASLD were significantly higher than those in non-MASLD populations (), and the prevalence of MASLD was markedly increased in individuals with high serum ApoJ levels. After adjusting for multiple confounding factors—including total cholesterol (TC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and high-sensitivity C-reactive protein (hs-CRP)—multiple linear regression analysis demonstrated that serum ApoJ levels were significantly positively correlated with the fatty liver index. This suggests that circulating ApoJ content may serve as a serum biomarker for MASLD progression.

ApoJ promotes the pathological process of MASLD by regulating lipid metabolism in hepatocytes and the progression of liver fibrosis through multiple pathways, including the mediation of mTOR ubiquitin-proteasome degradation and fibroblast proliferation. In-depth research into these regulatory networks is expected to provide new insights for targeted therapeutic strategies for MASLD. Furthermore, DUAN et al. [**?**] reported that in oleic acid (OA)-treated Huh7 cells, OA promotes intracellular lipid accumulation in a dose-dependent manner ...

6 ApoJ 与 PCOS

Polycystic Ovary Syndrome (PCOS) is a highly heterogeneous chronic endocrine and metabolic disorder. Its core characteristics involve the coexistence of reproductive dysfunction and metabolic abnormalities [**?**].

Seo et al. [**?**] found that serum Apolipoprotein J (ApoJ) levels in patients with PCOS are significantly higher than those in control groups. ApoJ levels correlate positively with fasting insulin (FINS), free fatty acids (FFA), HOMA-IR, and HOMA-β, while correlating negatively with the glucose disposal rate (GDR). In PCOS patients, an elevated HOMA2-IR in the fasting state and a decreased GDR under insulin-stimulated conditions are indicative of insulin resistance (IR). Following treatment with the insulin sensitizer pioglitazone, PCOS patients exhibited decreased serum ApoJ levels, reduced HOMA2-IR, and increased GDR. This is consistent with previous findings that rosiglitazone treat-

Figure 1

Figure 4: Figure 1

ment improves IR in subjects with Type 2 Diabetes Mellitus (T2DM) while simultaneously lowering serum ApoJ levels. Furthermore, research has demonstrated that serum ApoJ levels are positively correlated with the risk of PCOS. When the study population was divided into tertiles based on serum ApoJ levels, both the middle and highest tertiles showed a higher risk of PCOS compared to the lowest tertile. Multiple linear regression analysis further suggested that serum ApoJ levels in PCOS patients are independently associated with BMI and HOMA-IR [**?**]. Consequently, ApoJ may serve as a relevant biomarker for insulin resistance in patients with polycystic ovary syndrome.

Non-secretory ApoJ interacts with the mammalian target of rapamycin (mTOR). Specifically, ApoJ binds to the mTOR kinase domain, thereby competitively inhibiting the binding of the ubiquitin ligase F-box/WD repeat domain-containing protein 7 (FBW7) to mTOR. This prevents the degradation of mTOR by the ubiquitin-proteasome system, thus involving ApoJ in hepatic lipid metabolism ,

. Intracellular non-secretory ApoJ also participates in hepatic lipid deposition through sterol O-acyltransferase 2 (SOAT2) [**?**]. In Huh7 cells, both nutritional stress (free fatty acids) and viral stress (HCV) can induce Golgi apparatus fragmentation, prompting the migration of ApoJ to endoplasmic reticulum-Golgi contact sites. There, ApoJ specifically binds to SOAT2 via its N-terminal intrinsically disordered region. This interaction not only stabilizes the SOAT2 protein but also significantly enhances its enzymatic activity, catalyzing the esterification of free cholesterol into cholesterol esters (CE). As neutral lipids, these newly formed CEs are stored in large quantities within lipid droplets. The expansion and accumulation of these lipid droplets within hepatocytes ultimately drive the development of hepatic steatosis.

PCOS is closely associated with metabolic factors such as IR, obesity, and hyperlipidemia. Advancing molecular research into the liver and ovarian tissues of PCOS patients is expected to further elucidate the reasons for elevated serum ApoJ levels and its potential prospects in the future treatment of PCOS. Beyond its involvement in the aforementioned pathological processes of hepatic lipid metabolism disorders, ApoJ also plays a critical role in the occurrence and progression of liver fibrosis. Research by Liu et al. [**?**] demonstrated that, compared to control groups, ApoJ expression is significantly altered in both human subjects and mice.

7 总结与展望

ApoJ, as a multifunctional glycoprotein, has garnered increasing attention for its central role in maintaining cellular homeostasis, stress response, and metabolic

Figure 1

Figure 5: Figure 1

regulation. Compared to previous literature, this review not only covers classic fields such as diabetes and obesity but also incorporates the latest research progress on ApoJ in cutting-edge areas such as MASLD and PCOS. It systematically elucidates the expression changes, functions, and molecular mechanisms of ApoJ in the aforementioned variety of metabolic diseases.

ApoJ expression is generally elevated in metabolic diseases such as type 2 diabetes and obesity, and is closely correlated with disease progression, making it a promising biomarker for the development of metabolic disorders. Simultaneously, its protective effects—demonstrated in improving insulin sensitivity, delaying the progression of diabetic nephropathy, and alleviating atherosclerosis—reveal its potential as a therapeutic intervention target.

However, the contradictory roles of ApoJ across different diseases (for instance, promoting lipid deposition and fibrosis in the liver while exerting protective effects in the kidney) are noteworthy. Its expression is significantly upregulated in fibrotic liver tissue, and serum ApoJ levels are positively correlated with the degree of liver fibrosis. In studies using carbon tetrachloride to induce liver fibrosis in ApoJ-overexpressing mice, it was found that these mice exhibited increased serum ALT and AST levels, enhanced activation of hepatic stellate cells (HSCs), increased hepatic collagen deposition, and greater macrophage infiltration. Furthermore, profibrotic and inflammatory genes were upregulated, suggesting that ApoJ can accelerate the process of injury-induced liver fibrosis. Investigating its mechanism of action, oxidative stress increases ApoJ expression; the upregulated ApoJ then interacts with RAN binding protein 2 to promote the SUMOylation of STAT3. As a post-translational modification, SUMOylation induces the nuclear translocation of STAT3, subsequently activating its signaling pathway. This activation triggers the increased expression of transforming growth factor beta 1 (TGF-$ $1) and the production of reactive oxygen species (ROS).

Note: ApoJ: Apolipoprotein J; LRP2: Low-density lipoprotein receptor-related protein 2; GCK: Glucokinase; PKLR: Pyruvate kinase L/R type; IRS-1: Insulin receptor substrate 1; Akt: Protein kinase B; mTOR: Mammalian target of rapamycin; FBW7: F-box/WD repeat-containing protein 7; STAT3: Signal transducer and activator of transcription 3; TGF-$ $1: Transforming growth factor beta 1; ROS: Reactive oxygen species; CaMK1D: Calcium/calmodulin-dependent protein kinase 1D; DRP1: Dynamin-related protein 1; NLRP3: NOD-like receptor protein 3; LepRb: Leptin receptor isoform b.

Figure 1 Physiological and pathological roles of ApoJ in metabolic diseases Table 1 Expression levels of ApoJ in metabolic diseases and its key signaling pathways ApoJ Level

2 型糖尿病

Elevated serum levels of liver-derived Apolipoprotein J (ApoJ) interact with skeletal muscle LRP2, leading to increased phosphorylation of IRS-1 and Akt, which subsequently improves peripheral insulin sensitivity. Conversely, palmitate-induced adipose-derived ApoJ targets hepatic LRP2, inhibiting Akt phosphorylation and upregulating the expression of GCK and PKLR, thereby inducing the primary signaling pathways of hepatic insulin resistance (IR). In diabetic nephropathy, glomerular expression levels of ApoJ are increased; specifically, podocyte KLF6 promotes the release of ApoJ, which is then taken up by the proximal tubules via LRP2. This process activates CaMK1D and increases the phosphorylation of DRP1 at S637, inhibiting mitochondrial fission and alleviating renal injury. In atherosclerotic cardiovascular disease, elevated serum ApoJ levels inhibit NLRP3 activation, thereby suppressing macrophage pyroptosis and reducing inflammatory responses and plaque instability, which mitigates atherosclerosis. Furthermore, ApoJ inhibits TRPM2 expression, reducing oxidative stress and apoptosis to protect the myocardium. Regarding appetite regulation, food intake increases hypothalamic ApoJ levels, which act through the LRP2/LepRb complex to increase STAT3 phosphorylation, thereby mediating satiety signals. In metabolic dysfunction-associated steatotic liver disease (MASLD), elevated serum ApoJ binds to the mTOR kinase domain, competitively inhibiting the binding of FBW7 to mTOR. This reduces mTOR degradation and promotes hepatic lipid deposition. Additionally, oxidative stress-induced ApoJ upregulation interacts with RanBP2 to promote STAT3 SUMOylation, leading to increased TGF-$ $1 and ROS levels, which activates hepatic stellate cells and drives liver fibrosis.

Note: ApoJ: Apolipoprotein J; LRP2: Low-density lipoprotein receptor-related protein 2; IRS-1: Insulin receptor substrate 1; Akt: Protein kinase B; GCK: Glucokinase; PKLR: Pyruvate kinase L/R type; IR: Insulin resistance; KLF6: Krüppel-like factor 6; CaMK1D: Calcium/calmodulin-dependent protein kinase 1D; DRP1: Dynamin-related protein 1; NLRP3: NOD-like receptor protein 3; TRPM2: Transient receptor potential cation channel subfamily M member 2; LepRb: Leptin receptor isoform b; STAT3: Signal transducer and activator of transcription 3; mTOR: Mechanistic target of rapamycin; FBW7: F-box/WD repeat-containing protein 7; RanBP2: RAN binding protein 2; TGF-$ $1: Transforming growth factor $ $1; ROS: Reactive oxygen species.

The core challenge for targeted intervention lies in the functional heterogeneity of ApoJ. This divergence may stem from the presence of tissue-specific receptors, the preferential expression of different ApoJ isoforms in specific tissues, and the modulation of its conformation and function by the local tissue microenvironment. The authors declare no conflicts of interest.

Future research must employ precision analytical techniques, such as isoform identification, to move beyond systemic observations and into tissue- and isoform-specific mechanisms. It is essential to further elucidate the sophisti-

cated regulatory networks of ApoJ in metabolic diseases. Such advancements will pave the way for the development of novel ApoJ-based diagnostic biomarkers and targeted therapeutic strategies, ultimately contributing to the individualized and precise prevention and control of metabolic diseases.

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Abstract

Bariatric surgery has emerged as a highly effective intervention for severe obesity, leading not only to significant weight loss but also to profound metabolic improvements. This study examines the longitudinal changes in lipoprotein composition and functional characteristics following surgical intervention. While traditional lipid profiles—such as total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides—typically show marked improvement, the qualitative shifts in lipoprotein particles are equally critical for cardiovascular risk reduction.

Our findings indicate that bariatric surgery induces a shift toward larger, less dense LDL particles and enhances the protective functional capacity of high-density lipoproteins (HDL). Specifically, there is a measurable increase in HDL-mediated cholesterol efflux capacity and a reduction in the inflammatory markers associated with various lipoprotein fractions. These changes contribute to a more favorable anti-atherogenic profile, suggesting that the benefits of bariatric surgery extend beyond simple caloric restriction to include fundamental remodeling of lipid metabolism. Understanding these compositional and functional shifts is essential for evaluating the long-term cardiovascular outcomes of bariatric procedures in patients with metabolic syndrome.