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Metabolism and Target Organ Damage

Review

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Metrnl plays a crucial role in the regulation of glycolipid metabolism

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Abstract

An imbalance in the metabolism of glycolipids largely causes numerous metabolic diseases that negatively affect human health. Metrnl plays an important role in glycolipid metabolism and regulates glucose and lipid metabolism through multiple mechanisms. However, the expression level of Metrnl in diseases related to glycolipid metabolism remains controversial. Metrnl can increase the utilization of glucose by tissue cells in glucose metabolism and reduce the adverse effects of a high-glucose environment on the body; in lipid metabolism, it can affect the composition and level of blood lipids, reduce the accumulation of fat, and promote the browning of white fat. The clinical efficacy of exogenously administered recombinant Metrnl needs to be further investigated and verified. This review presents an overview of Metrnl, emphasizing its role in glycolipid metabolism and its association with related diseases. It offers a theoretical foundation for the clinical treatment of glycolipid metabolism-related conditions.

Keywords: Glucose metabolism, lipid metabolism, Metrnl, diabetes, obesity, metabolism

INTRODUCTION

Investigating adipokines may enhance human health, reduce socioeconomic burdens, and tackle clinical challenges related to various chronic metabolic diseases. Metrnl, a novel class of adipokine that is widely

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distributed in the human body, is also known as Meteorin-like, Comtin, Subfatin, Interleukin-39, Interleukin-41, Meteorin-β, and Metrn-β/Metrnβ. It controls inflammation, neurodevelopment, lipid metabolism, energy expenditure, white fat browning, insulin sensitization, and inflammation. Metrnl facilitates muscle regeneration, glucose absorption, and fat oxidation in skeletal muscle, attracting considerable study in recent years[1,2].

The human body contains many Metrnl, expressed in the skin, neurological system, adipose tissue, mucosal tissue, and activated macrophages. It is extensively disseminated throughout the body and is expressed to differing extents in various tissues and organs. At the same time, Metrnl can play multiple biological roles as a neurotrophic factor, adipokine, and inflammatory factor, and it is important in certain diseases and in regulating metabolism[3]. Nevertheless, current research is still exploratory regarding the specific mechanism of Metrnl's role in glycolipid metabolism. Most current research results are based on animal models, and human clinical data have not yet been standardized. Therefore, more studies are needed to verify whether Metrnl has similar expression properties and functional patterns in humans. In this review, we will summarize the relationship between the role of Metrnl in glycolipids and related diseases, and discuss and look forward to the problems that may be encountered in clinical applications [Figure 1]. These investigations will improve our knowledge of how Metrnl enhances glucose and lipid metabolism and could offer fresh ideas for future treatment approaches.

OVERVIEW OF METRNL

Development of Metrnl

Metrnl demonstrates various biological activities, with its active form being induced by exercise or cold stimulation. Nishino *et al.* identified the Metrnl homologous protein Metrn in 2004[4]. Given Metrn's evident role in the central nervous system and its designation as a direct target of PAX2/5/8 in ear development, Jørgensen *et al.* characterized the Metrnl protein for the first time in 2012. They showed its function as an analogous Metrn-like neurotrophic factor. Subsequently, Jørgensen *et al.* detected low levels of Metrnl messenger RNA in auditory vesicles[5,6]. Li *et al.* identified elevated Metrnl expression in adult rats' subcutaneous white adipose tissue (WAT) subjected to a specific diet by gene sequence detection and bioinformatics methodologies[7]. Their finding was validated by the production of recombinant proteins and antibodies, with findings from both Jørgensen's and Li's laboratories indicating that Metrnl is a novel adipokine. Although Metrnl shares a similar gene sequence and is homologous to the neurotrophic factor Meteorin, its expression in the mouse brain is minimal. At the same time, it is significantly concentrated in subcutaneous adipose tissue. Therefore, Metrnl is also called "Subfatin", i.e., a highly expressed protein in subcutaneous fat[3,8-10], also known as adipokine.

Structure of metrnl

Metrnl precursor protein contains 311 amino acids, with a molecular weight of about 34,000 Da. The Metrnl precursor protein lacks a transmembrane domain, rendering mature Metrnl a non-membrane protein that can be secreted to function extracellularly; the N-terminal segment of the Metrnl precursor protein has a signal peptide consisting of 45 amino acids. The Metrnl precursor protein, upon entering the endoplasmic reticulum for processing, undergoes hydrolysis of its signal peptide by the signal peptidase present in the inner lumen of the endoplasmic reticulum. Therefore, mature Metrnl contains 266 amino acids, and its molecular weight is about 30,000 Da[3,9,11]. The Metrnl proteins in mice and humans share 239 identical amino acids, representing 77% similarity, while Metrnl displays around 40% amino acid identity with Metrn. The prediction of N-glycosylation sites in Metrnl identifies a single potential N-glycosylation site at amino acid 103 in mouse Metrnl, differing from Metrn[5,8]. The *Metrnl* genes are found on human chromosome *17q25.3* and mouse chromosome *11qE2*, and the cyclic chromosome 17 syndrome has been linked to the *Metrnl* gene's precise placement near the end of the q-arm of human chromosome 17[3,6,7,12].

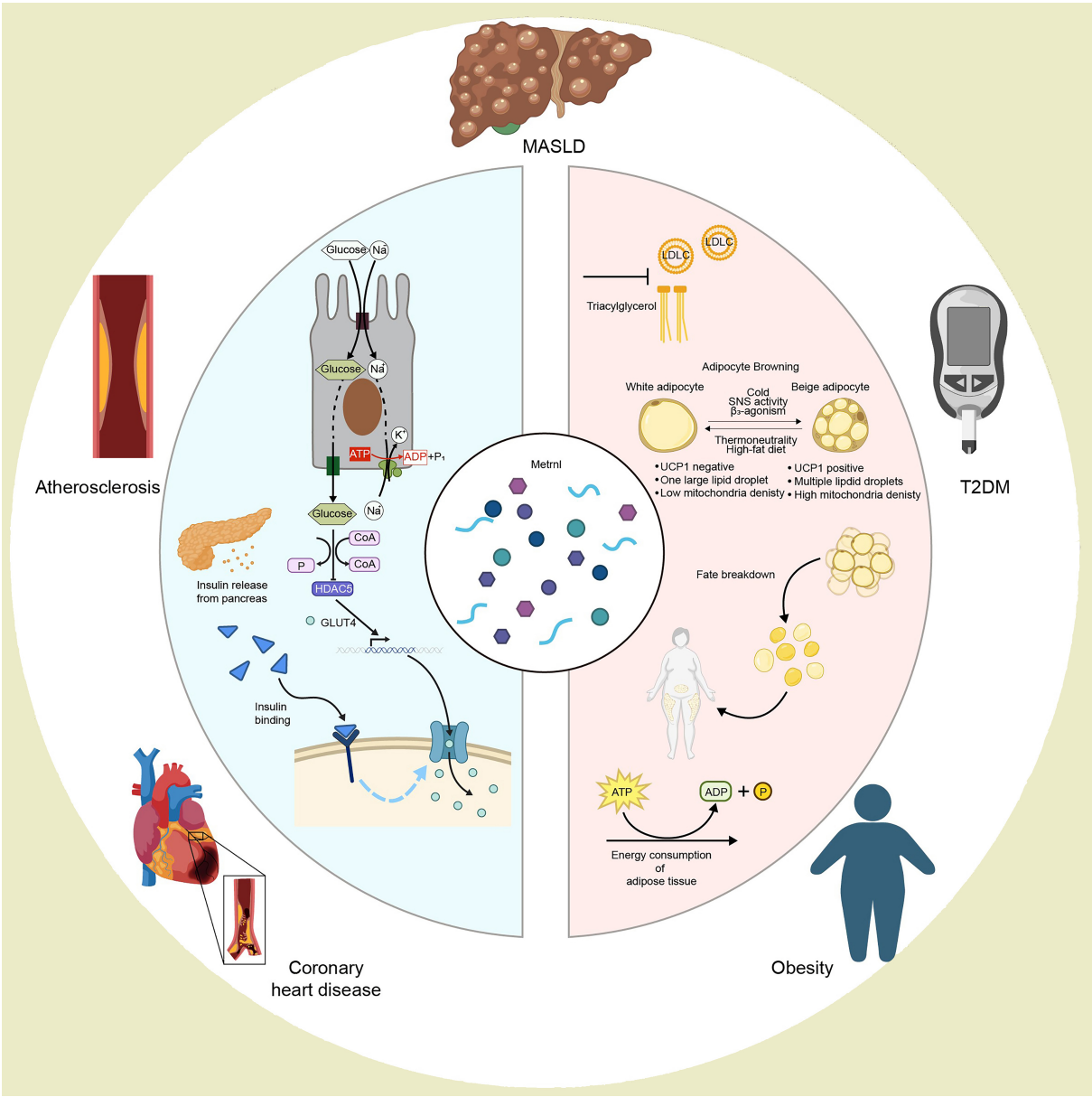

Figure 1. Role of metrnl in glycolipid metabolism and related diseases. MASLD: Metabolic dysfunction-associated steatotic liver disease; T2DM: type 2 diabetes; HDAC5: histone deacetylase 5; GLUT4: glucose transporter type 4; ATP: adenosine triphosphate; ADP: adenosine diphosphate; LDLC: low-density lipoprotein cholesterol; SNS: sympathetic nervous system; UCP1: uncoupling protein 1.

Various results suggest that Metrnl is evolutionarily conserved and reveal the importance of Metrnl in biology and medicine, especially in nervous system function and metabolic regulation.

Metrnl plays an essential role in biology and medicine

The biological functions of Metrnl are broad and diverse. Research indicates that physical activity and cold settings enhance the synthesis of Metrnl in muscular and adipose tissues, demonstrating a substantial link between exercise and Metrnl levels. Metrnl is a neurotrophic factor that supports spiral ganglion neuron survival *in vivo* and stimulates synapse formation and neuroblast migration *in vitro*. Second, Metrnl increases beige fat thermogenesis by modifying immune-adipose interactions, contributing to cold acclimation. Third, by enhancing adipose function and counteracting the effects of obesity-induced insulin

resistance, Metrnl plays a significant role in the biology of WAT. It also has a major impact on immune response regulation, wound healing, and vascularization. By controlling lipid metabolism and glucose tolerance, Metrnl shows promise in treating metabolic disorders like obesity and type 2 diabetes (T2DM)[13-15].

ROLE OF METRNL IN GLUCOSE METABOLISM

Regulation of energy metabolism

Adipokines and other secreted proteins control glucose uptake and release, which controls glucose homeostasis. Chronic high-fat diets or a lack of physical activity can lead to obesity, which can alter glucose metabolism and cause insulin resistance and diabetes mellitus. It has been found that the secretion of Metrnl increases during muscle contraction, and the increased expression of Metrnl can increase the inhibition of histone deacetylase 5 (HDAC5) through AMP-activated protein kinase α2 (AMPKα2), and the phosphorylated HDAC5 can interact with 14-3-3 protein and isolate HDAC5 in the cytoplasm[16] so that the inhibitory effect of HDAC5 on GLUT4 is lost. The transcriptional activation of GLUT4 is promoted, and it enters adipocytes, muscle, and cardiomyocytes via the GLUT-4 (glucose transporter-4) transporter, a complex process involving different enzymes and mediators. Therefore, enhancing cellular glucose absorption and facilitating the influx of glucose from the extracellular environment into the cell, together with glucose synthesis, ultimately reduces blood glucose levels and sustains glucose homeostasis inside the body. By altering immune-fat interactions to promote thermogenesis, which raises total body energy expenditure, Metrnl also adjusts to cold conditions. Exercise and mild cold exposure encourage the body to convert WAT to brown adipose tissue (BAT), which speeds up metabolism and helps people lose weight. Yan *et al.* conducted a Zebrafish-based study employing the CRISPR/Cas9 system to knock down gluk2, a protein involved in cold sensing within peripheral sensory neurons. Their findings identified Metrnl as a differentially expressed gene, suggesting its potential involvement in the biological changes following gluk2 knockdown. This underscores Metrnl's significance in cold perception, adaptation to low temperatures, and regulating energy metabolism[17-20].

Improvement of insulin resistance

Insulin resistance and the relative deficiency of insulin production by pancreatic β-cells are significant contributors to dysregulated blood glucose levels. The inadequate insulin production by pancreatic β-cells is an important factor contributing to the dysregulation of blood glucose levels in individuals with T2DM[21]. Enhancing insulin sensitivity is a critical focus of investigation in managing T2DM and metabolic syndrome. Research indicates that Metrnl enhances energy expenditure in mice and augments insulin sensitivity by promoting the expression of genes linked to brown fat thermogenesis, and serum Metrnl levels are connected with insulin resistance[22,23].

A study investigated glucose tolerance in mice with adipocyte-specific overexpression of Metrnl and those with adipocyte-specific Metrnl knockout. The findings indicated that adipocyte-specific Metrnl knockout exacerbated insulin resistance caused by a high-fat diet. In contrast, adipocyte-specific overexpression of Metrnl mitigated insulin resistance induced by a high-fat diet or leptin deficiency in mice. Moreover, adipocyte-specific overexpression of Metrnl mitigated insulin resistance caused by a high-fat diet or leptin deficiency in mice. Later studies indicated that peroxisome proliferator-activated receptor γ (PPARγ) inhibitors and PPARγ knockouts inhibited the insulin resistance associated with Metrnl.

Additional studies revealed that both peroxisome PPARγ inhibitors and peroxisome *PPARγ* gene knockdown could block the insulin-sensitizing effect of Metrnl. This suggests that adipocyte Metrnl could improve insulin resistance from a high-fat diet by activating the peroxisome PPARγ pathway. Thus, Metrnl

may be an inherent insulin-sensitizing agent[9]. This study offers novel approaches and targets for the treatment of T2DM.

ROLE OF METRNL IN LIPID METABOLISM

Influence on the composition and level of blood lipids

Subcutaneous adipose tissue exhibits significant levels of Metrnl expression. Adipocytes are a key cell type for lipid storage, and they can regulate adipocyte differentiation and upregulate lipid metabolism-related genes via *PPARδ*[2,24]. Some studies have examined the role of Metrnl in lipid metabolism. According to a study that examined the lipid composition of Metrnl systemic knockout mice, Metrnl gut-specific knockout mice, and Metrnl liver-specific knockout mice, the mice's lipid levels did not significantly change under normal dietary conditions. However, following high-fat dietary feeding, the mice's serum lipid parameters did not change. Still, the systemic and liver-specific knockout mice displayed varied degrees of altered lipid levels *in vivo*[25]. The results of this experiment showed that different components of blood lipids are controlled by tissue-specific Metrnl. Adipose metabolism modifies blood triglycerides (TG), while liver metabolism controls blood high-density lipoprotein cholesterol (HDL-C)[26]. It can be seen that when the body is stimulated by external factors (such as a long-term high-fat diet disrupting the body's homeostasis), Metrnl affects the blood lipid level. Still, when the body is stable, Metrnl does not regulate blood lipids[25]. Metrnl in different tissues may have different or opposite effects on the body. Metrnl knockout mice from various tissues were creatively used as research participants in this project. Through a controlled study, it investigated the function of Metrnl in lipid metabolism at a more thorough tissue level, which might serve as a guide for further investigations. In conclusion, Metrnl can effectively regulate blood lipid levels and influence lipid metabolism.

Reducing fat accumulation

Fat accumulation releases various cellular inflammatory factors, adipokines, and vasoactive peptides, leading to various metabolic diseases. Upregulating Metrnl protein may help reduce fat by enhancing metabolism in systemic tissues, as exercise causes an increase in intramuscular Metrnl. Metrnl and peripheral tissue metabolism have been linked in several studies. It has also been demonstrated that increasing Metrnl in adipose tissue enhances insulin sensitivity by upregulating *PPAR-γ*, and plasma Metrnl roughly doubles following acute resistance exercise in tandem with increased intramuscular Metrnl. Using a real-time fluorescence quantitative nucleic acid amplification detection method, Rao *et al.* discovered elevated amounts of Metrnl in cardiac and skeletal muscle[5]. According to a study, mice on a high-fat diet had noticeably higher levels of Metrnl in their muscles after exercise. At the same time, the levels of Metrnl, acyl-coenzyme A oxidase 1, and triglyceride lipase in adipose tissue were also significantly increased, all of which were conducive to the decomposition of fat metabolism. These findings suggest that exercise-induced muscle damage increases Metrnl levels in adipose tissue, where Metrnl effectively reduces fat storage, making it a potential treatment target for chronic obesity[27,28]. In comparison to subcutaneous fat, the accumulation of cardiac fat poses a heightened risk for chronic diseases, including cardiovascular and cerebrovascular conditions. Research conducted on serum Metrnl levels and visceral fat area in patients with T2DM in China revealed a negative correlation between serum Metrnl levels and visceral fat obesity in these patients[29]. This adverse correlation is likely to manifest in individuals with T2DM. Du *et al.* employed dual-energy X-ray absorptiometry (DXA) to measure the visceral fat area and discovered that Metrnl levels were independently and inversely correlated with visceral fat accumulation[30].

Promotion of white fat browning

Metrnl is a new adipokine significantly expressed in brown and WAT. The browning process, also referred to as "browning" or "reionization" from WAT to BAT, is facilitated by Metrnl, according to studies. This browning increases energy expenditure and thermogenesis, causing weight loss and improved glucolipid

metabolism[24,31-33]. Metrnl increases the activation of the alternate pathway in adipocyte macrophages and eosinophil-dependent IL-4/IL-13 expression, which in turn stimulates catecholamine secretion and the upregulation of genes linked to β-oxidation and thermogenesis, including Uncoupling protein-1, thereby promoting beige adiposity[5,34]. UCP-1 is a mitochondrial proton carrier uncoupling protein that uncouples oxidative phosphorylation and allows mitochondrial energy to be dissipated as heat[35] rather than accumulated as fat. Therefore, Metrnl can promote white fat browning to a certain extent to stimulate energy expenditure.

Furthermore, gonadal adipose tissue is a WAT primarily found in the visceral and abdominal areas. The function of Metrnl in WAT may extend to gonadal adipose tissue. Metrnl functions as an insulin-sensitizing factor *in vivo* and enhances insulin secretion by resolving pancreatic β-cell dysfunction, which may affect gonadal adipose tissue's function and metabolic activity.

THE ROLE OF METRNL IN GLYCOLIPID METABOLISM-RELATED DISEASES

The major research advances in Metrnl in disorders related to glycolipid metabolism have been briefly summarized in Table 1, followed by a detailed review of the major roles of Metrnl in disorders related to glycolipid metabolism.

Obesity

Obesity, one of the most common diseases in the world today, is a significant risk factor for metabolic and cardiovascular disorders. The alterations in circulation Metrnl levels in obese people are debated[3,39,40]. Subcutaneous WAT in both humans and rodents had the highest amount of Metrnl expression, according to real-time polymerase chain reaction (PCR). Furthermore, expression was detected in omental adipose tissue, subcutaneous adipose tissue, perivascular adipose tissue, interscapular adipose tissue, and several other tissues, including the liver, spleen, muscle, heart, thymus, forebrain, midbrain, and hindbrain. Insulin resistance in obesity is linked to a higher concentration of macrophages in adipose tissue. Metrnl levels have been observed to be lower in obese patients than in healthy people. However, following bariatric surgery, such as a laparoscopic sleeve gastrectomy, obese patients' Metrnl levels are noticeably elevated[41]. Some experiments, though, have come to the opposite conclusion. For instance, scientists established mouse models of normal and high-fat diets for controlled tests. Mice on a high-fat diet demonstrated considerably greater levels of Metrnl, according to their detection of Metrnl expression in several organs[37].

The findings demonstrated that mice's WAT's Metrnl level may be particularly raised by a high-fat diet. However, they had no discernible impact on the levels of Metrnl in the skeletal muscle, colon, liver, kidney, or other organs of mice. As a result, it is thought that obesity can particularly increase Metrnl in adipose tissue and that there may be a mechanism for feedback control to enhance metabolism *in vivo*[35,42]. Löffler *et al.* demonstrated that compared to lean children, obese children's adipose tissue had higher levels of Metrnl expression[42]. In their investigation of adipocytes in obese children, AlKhairi *et al.* also discovered that Metrnl hindered adipocyte development, which led to a rise in adipocyte volume but a decrease in adipogenic cells, indicating that blood Metrnl was elevated in fat individuals[43,44]. Furthermore, several studies have demonstrated a negative relationship between the area of visceral fat and circulating Metrnl[45].

In conclusion, the expression level of Metrnl in the obese population may be related to factors such as age, racial differences, or geographic environment, and more specific and comprehensive clinical data are needed for verification in the future. In obesity, there is an increase in the number of macrophages within adipose tissue, which correlates with insulin resistance. Metrnl exhibits an anti-inflammatory effect, potentially regulating the release of inflammatory factors and inhibiting inflammation in adipose and

Table 1. Advances in metrnl research in diseases related to glycolipid metabolism

Principal investigator	Nationality	Content of research	Research methodology	Research progress
Ding *et al.*[35]	China	Obesity	One hundred eighty-two participants in the cross-sectional study had their serum Metrnl concentrations determined using the ELISA assay	Individuals who were overweight or obese had lower serum Metrnl levels, which were also linked to negative lipid profiles on their own
Lin *et al.*[36]	China	Diabetes Mellitus	Groups of DKD, DKD + Metrnl-/-, and DKD + Metrnl+/+ were randomly assigned to twenty-four db/db mice. ELISA was used to measure the plasma Metrnl concentrations. Kidney tissues were analyzed using qRT-PCR and western blotting	Increased renal Metrnl expression can improve renal injury by decreasing the creation of fibrotic molecules like α-SMA and downregulating the expression of components in the TGF-β1/Smads signaling pathway in the renal tissues of T2DM mice
Zheng *et al.*[37]	China	Atherosclerosis	BM transplantation of mice for vascular reactivity analysis	ApoE knockdown exacerbated atherosclerosis in mice with atherosclerosis and decreased endothelium and circulating Metrnl levels
Wang *et al.*[38]	China	MASLD	Serum Metrnl and MASLD and metabolic indicators were correlated using Spearman's correlation analysis, and the factors influencing the development of MASLD in 183 individuals were examined using logistic regression analysis	Reduced serum Metrnl is an independent risk factor for developing MASLD, and Metrnl is strongly associated with MASLD and metabolic disease indicators

T2DM: Type 2 diabetes; MASLD: metabolic dysfunction-associated steatotic liver disease; ELISA: enzyme-linked immunosorbent assay; DKD: diabetic kidney disease; qRT-PCR: quantitative real-time polymerase chain reaction; α-SMA: alpha-smooth muscle actin.

muscle tissues through macrophage activation, which Metrnl may modulate by influencing these macrophages. Thus, it shows potential for reducing the inflammatory response induced by lipid accumulation.

Metrnl and T2DM

T2DM is a prominent metabolic disorder that is distinguished by the presence of numerous distinct types of diabetes that are caused by insulin resistance or deficiency. Certain adipokines, including lipocalin, FABP4, and leptin, are secreted by adipose tissue and are responsible for maintaining glucose metabolic homeostasis[46]. Furthermore, T2DM is linked to a significant burden of chronic inflammation. Metrnl enhances anti-inflammatory cytokines by stimulating IL-4 expression[5,16]. Multiple pieces of data indicate that Metrnl is independently correlated with coronary artery disease (CAD) and T2DM[2,16] and is inversely related to insulin resistance and inflammation. Evidence indicates that patients with T2DM and CAD exhibit elevated production of pro-inflammatory cytokines, suggesting that Metrnl may contribute to the pathophysiology of CAD and T2DM[2,45]. The association between serum Metrnl levels and T2DM remains controversial. Following extended hypoglycemic therapy, Metrnl levels may rise concomitantly with regulating blood glucose levels[47,48]. While Chung *et al.* discovered elevated serum levels of Metrnl, Zheng *et al.* and Lee *et al.* revealed low serum levels of Metrnl in patients with recently diagnosed T2DM[35,37,49]. So, there may be a dynamic correlation between Metrnl and blood glucose levels, which can be used as a monitoring indicator of the clinical efficacy of diabetes mellitus. Recently, Song *et al.* discovered that Metrnl accelerated cutaneous wound healing by promoting angiogenesis in normal and diabetic mice. This finding suggests that Metrnl may be able to protect against diabetic vascular endothelial dysfunction. This offers research evidence and guidance for the subsequent stages of clinical translation[21]. Some scholars have experimentally investigated the potential of Metrnl in treating T2DM by using recombinant Metrnl because of its function in regulating glucose metabolism. For instance, researchers employed Metrnl knockout rodents fed a high-fat diet as a model. They discovered that the acute intravenous injection of recombinant Metrnl had no hypoglycemic effect. Furthermore, the insulin resistance exacerbated by adipocyte Metrnl deficiency was not improved by the intravenous injection of Metrnl for one week. However, recombinant Metrnl administered intraperitoneally has been shown to enhance glucose tolerance

in mice with T2DM induced by a high-fat diet, which is advantageous for treating T2DM[50]. It can be seen that the effectiveness of exogenously administered Metrnl in maintaining glucose homeostasis depends on factors such as the dosage and mode of administration, and the effective concentration profile of Metrnl and its metabolism or absorption pathway in the human body need to be further investigated in the future in order to achieve a good therapeutic efficacy[14,51,52].

Role of Metrnl in atherosclerosis and coronary heart disease

Insulin resistance, inflammation, and dyslipidemia are important risk factors for atherosclerosis. Liu *et al.* found that in diabetic or nondiabetic patients, lower blood Metrnl concentrations were significantly associated with CAD. As the quantity of stenotic arteries in individuals with coronary heart disease escalates, serum Metrnl levels diminish; concurrently, an increase in the severity of coronary artery stenosis correlates with a further decline in serum Metrnl levels[53,54]. A substantial negative association was also identified between serum Metrnl and the Gensini score, an angiographic scoring system for evaluating the severity of coronary stenosis and the number of stenotic arteries[13]. The more severe the lesion, the lower the Metrnl level. The basic pathological change of coronary heart disease is atherosclerosis of coronary arteries[55], and vascular endothelial cell injury is the early critical link in the development of atherosclerosis. Some researchers found that Metrnl has a very obvious continuous distribution in the vascular endothelium, and at the same time, vascular endothelial cells can also secrete Metrnl. In addition, Metrnl activates *AMPK/PPARδ* signaling and ameliorates macrophage-associated inflammation[56]. Later, employing Metrnl and ApoE, this experimental group also created a double knockout mouse model of vascular endothelial cells. They then used aortic oil-red O staining to compare the size of aortic atherosclerotic plaques while detecting pro- and anti-inflammatory cytokines. The results showed that endothelial damage, inflammatory cell infiltration, and inflammatory cell infiltration in vascular endothelial cells of Metrnl and ApoE double knockout mice were more pronounced than those in ApoE knockout mice with atherosclerosis-susceptible plaques[37]. Additionally, endothelial injury, inflammatory cell infiltration and chronic inflammation were more severe in Metrnl and ApoE knockout mice than in mice with atherosclerosis-susceptible texture[13]. This implies that Metrnl may decrease the progression of coronary heart disease and have a beneficial protective and preventative effect on those at high risk. Metrnl's capacity to enhance glycolipid metabolism and its potential anti-inflammatory properties are linked to its impact on coronary heart disease. According to studies, the epidermis, activated macrophages, and mucosal tissues exhibit significant Metrnl expression levels[57]. Numerous cytokines, including those activated by tumor necrosis factor-α, interleukin-17α, interleukin-12, and interleukin-4, and those blocked by γ-interferon and transforming growth factor-β, can control the production of Metrnl by bone marrow macrophages (i.e., M2-type macrophages)[58]. However, high levels of Metrnl can also enhance the production of genes linked to anti-inflammatory cytokines, decrease the inflammatory response of tissues, and encourage the alternative activation of M2-type macrophages in adipose tissue. Therefore, by reducing the inflammatory response process in atherosclerosis, Metrnl can protect the vascular endothelium and control glucose and lipid metabolism[34,45,54,59]. Coronary heart disease is linked to low blood Metrnl, and Metrnl may protect against coronary heart disease. This mechanism can be explained by several indications, such as the correlation between lower blood Metrnl and E-selectin, intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), brachial-ankle pulse wave velocity, carotid intima-media thickness, and low-density lipoprotein (LDL) cholesterol[60].

Metrnl and metabolic dysfunction-associated steatotic liver disease

The clinicohistopathological condition known as metabolic dysfunction-associated steatotic liver disease, or MASLD, shares histological characteristics with alcoholic liver injury. Non-alcoholic fatty liver disease, or NAFLD, was renamed as metabolic dysfunction-associated fatty liver disease (MAFLD) in 2020 by the Asian Pacific Association for the Study of the Liver (APASL) and other organizations. The American

Association for the Study of Liver Diseases (AASLD) and other organizations formally changed the name to MASLD in 2023. It includes a variety of conditions ranging from mild steatosis to more serious types that can lead to cirrhosis, fibrosis, and hepatocellular cancer. The global prevalence of MASLD is rising, with estimates ranging from 10% to 50%. The global prevalence of MASLD is increasing, with estimates ranging from 10% to 50%. The disease is linked to comorbidities, including obesity, T2DM, insulin resistance, and cardiovascular disease[61]. Studies have shown that insulin resistance and adipokines are closely related to the development of MASLD. Some scholars conducted a case-control study by selecting patients with MASLD and healthy people who underwent physical examination simultaneously[62,63]. Multifactorial logistic regression analysis revealed that decreased serum Metrnl levels in patients are an independent risk factor for developing MASLD[64]. Through a randomized controlled trial, Liu *et al.* demonstrated that serum Metrnl in MAFLD was independently related to systolic blood pressure and creatinine and that it was positively correlated with diastolic blood pressure, waist circumference (WC), body mass index (BMI), systolic blood pressure, γ-GGT, and creatinine[27]. No researchers have demonstrated the role of Metrnl in NAFLD/MAFLD/MASLD through animal trials. The only study to show that Metrnl overexpression improved fulminant hepatitis in mice was conducted by Du *et al.*[65]. It is unknown how serum Metrnl levels relate to MASLD, and more research is necessary to determine the exact mechanism of action.

DISCUSSION

In the field of glycolipid metabolism, the key role of Metrnl has been confirmed by numerous animal experiments and clinical studies. It is hoped that the next research direction for Metrnl should focus on its translation in the clinic. In adipocytes, Metrnl can regulate adipocyte differentiation, upregulate lipid metabolism-related genes, attenuate inflammatory responses, promote fat remodeling, and improve insulin resistance via *PPAR*δ. In addition, Metrnl ameliorates macrophage-associated inflammation and improves glycemia by regulating lipoprotein metabolism, elevating plasma HDL-C, decreasing TG levels, and attenuating hepatic glucose xenogenesis[24,27]. Metrnl stimulates energy expenditure and improves insulin resistance, promotes regulation of adipose oxidation, and expresses anti-inflammatory cytokines, which have a potential role in T2DM, obesity, dyslipidemia, coronary heart disease, and other diseases. Although Metrnl regulates several signaling pathways, the receptors or proteins that directly interact with Metrnl and the physiological mechanisms of Metrnl remain unclear. For the treatment of T2DM, there is currently no effective exogenous recombinant Metrnl dose or delivery system. Nevertheless, research has shown that Metrnl has positive benefits for several diseases[20,21]. Therefore, further studies on the expression level and mechanism of Metrnl in various glycolipid metabolism diseases will help better understand its role in promoting glycolipid metabolism. In the future, it might serve as a novel therapeutic target and monitoring marker for disorders linked to lipid metabolism. New methods for identifying and treating coronary microvascular dysfunction will be made possible by investigating the unique role and mechanism of Metrnl. In addition, Metrnl is highly expressed in M2-type macrophages and modulates macrophage expression of various cytokines and chemokines. M2-type macrophages are anti-inflammatory, function in angiogenesis and wound healing, and correlate with the helper T-cell 2 (Th2) response. To enhance adipose tissue thermogenesis and upregulate the expression of the anti-inflammatory cytokines transforming growth factor beta and IL-10 in adipose tissue, Metrnl stimulates eosinophil-dependent and promotes the activation of adipose tissue macrophages, increasing IL-4 expression. M1-type macrophages display pro-inflammatory properties during macrophage polarisation, whereas M2-type macrophages show anti-inflammatory properties. Macrophages of the M1 and M2 types have various markers. M1-type macrophages have markers like IL1a, IL1b, IL6, NOS2, *etc.*, whereas M2-type macrophages have markers like CD163, ARG1, PPARG, CD206, CD115, *etc.* Due to the high expression of Metrnl in M2-type macrophages, it can be a potential marker for recognizing and differentiating M2-type macrophages, along with markers such as CD206 and CD163[17,21,66]. However, the potential of Metrnl as a marker needs to be validated by further

studies; its specific expression in macrophage subpopulations identified in different tissues and pathological conditions can be confirmed in the future. Comparing its expression with existing markers will help determine its unique or complementary use. It should be noted that since Metrnl is expressed in several bodily tissues, such as muscle, liver, and adipose tissue, and because it is crucial for metabolic regulation, more research and clinical trials are necessary to determine whether it could cause systemic side effects as a targeted medication. Adverse effects of targeted drugs are an important topic in research. For example, some targeted drugs may cause systemic reactions such as weakness and fatigue, fever and chills, joint and muscle pain, and gastrointestinal and skin reactions. These side effects suggest that even targeted drugs may have systemic side effects due to the systemic distribution and metabolism of the drug. It has been shown that the Metrnl protein is an endogenous protein in the body and is highly safe as a potential drug. This means that the risk of systemic side effects may be reduced if the drug is designed to target the specific function of Metrnl precisely and does not affect its other physiological functions. To assess the safety and effectiveness of Metrnl-targeted drugs in various patient populations, as well as the variations in their expression throughout the disease, it is also critical to consider individual differences when designing these drugs, rationally design drug dosages and dosing regimens, and carry out additional clinical trials and long-term follow-up studies. To overcome the obstacles presented by disputes and individual variations in its expression, multifaceted research must be conducted, and techniques must be developed to understand better and apply the role of Metrnl in metabolic diseases. Finally, many difficulties and challenges may be encountered in the clinical translation of Metrnl. Firstly, Metrnl recombinant protein is very expensive, and secondly, for some slow-developing diseases, such as atherosclerosis, it may be difficult to provide therapeutic effects with short-term use.

CONCLUSION

Metrnl is essential for the metabolism of glycolipids as well as the onset and advancement of associated disorders. It may potentially serve as a therapeutic target and biomarker. However, the specific mechanism of action, receptor identification, potential as a clinical biomarker, and development of targeted Metrnl drugs still need further research.

DECLARATIONS

Authors' contributions

Conceptualization, investigation, writing - original draft, writing - review and editing: Zhang J, Wang G
Supervision, data curation: Liu X, Wang X
Conceptualization, supervision, writing - original draft, writing - review and editing: Zhou X

Availability of data and materials

The datasets generated or analyzed during the current study are available from the corresponding author upon reasonable request. For any inquiries regarding the data, please contact corresponding author Zhou X.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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