Dong *et al. Cell Communication and Signaling* (2024) 22:389
https://doi.org/10.1186/s12964-024-01767-8

Cell Communication and Signaling

REVIEW Open Access

Metrnl: a promising biomarker and therapeutic target for cardiovascular and metabolic diseases

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Abstract
Modern human society is burdened with the pandemic of cardiovascular and metabolic diseases. Metrnl is a widely distributed secreted protein in the body, involved in regulating glucose and lipid metabolism and maintaining cardiovascular system homeostasis. In this review, we present the predictive and therapeutic roles of Metrnl in various cardiovascular and metabolic diseases, including atherosclerosis, ischemic heart disease, cardiac remodeling, heart failure, hypertension, chemotherapy-induced myocardial injury, diabetes mellitus, and obesity.

Keywords Metrnl, Biological function, Biomarker, Therapeutic target, Cardiovascular and metabolic diseases

Introduction

The prevalence of cardiovascular and metabolic diseases (CVMD) is on the rise, which burdens modern human society. Mainly caused by abnormal metabolic processes, CVMD is one of the most common causes of morbidity and mortality globally, which imposes enormous social and economic burden on the healthcare system and individuals [1, 2]. In spite of recent advances in medical care and scientific research, there is still a need to improve the prognosis of cardiometabolic patients.

Metrnl is a novel secreted protein first reported in 2009 [3]. It is encoded by the Metrnl gene, which can be found on mouse chromosome 11 and human chromosome 17 (17q25.3). It consists of a coding sequence of 311 amino acids, including a 266-amino acid mature protein and a 45-amino acid signal peptide [4]. It shares 40% homology with the neurotrophic factor Meteorin, hence initially named Meteorin-like [5]. Although Metrnl and Meteorin share structural similarities, their expression levels and distribution differ. Meteorin is predominantly expressed in the central nervous system, while Metrnl has a relatively broader distribution, with high expression in adipocytes, endothelial cells, activated monocytes and myocytes [6]. A high level of expression is also found in barrier tissues such as skin and mucosal tissues of the digestive and respiratory tracts [4], while its expression in the central nervous system is comparatively lower.

Research has found that circulating Metrnl is secreted mainly by the endothelium, and endothelial-specific knockout of Metrnl leads to approximately a 75% decline in circulating Metrnl levels in mouse serum [7]. Decline of circulating Metrnl levels is closely related to the occurrence of diseases. Reboll et al. [8]. identified the stem cell

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factor receptor KIT on endothelial cells as a high-affinity receptor for Metrnl, but the specific receptor of Metrnl is currently unclear. Research utilizing bioinformatics methods reported that Metrnl contains two structural domains, called CUB and NTR, and regions involved in its function are determined by protein-receptor docking and analysis of protein-protein interaction regions [9]. As the first research to identify the region binding to the receptor of Metrnl, it will aid in the discovery of its specific receptors and characterization of the function of each domain.

Initially, Metrnl was considered an adipokine, garnering significant attention from researchers due to its crucial roles in regulating glucose metabolism homeostasis, enhancing insulin sensitivity, promoting browning of adipose tissue, and boosting energy expenditure in metabolic diseases [6, 10]. The application of omics technology plays a significant role in gaining a deeper understanding of the physiological function of Metrnl. Using transcriptome analysis of muscle tissues from aged mice, David et al. found that intramuscular injection of Metrnl reversed the pathway up-regulated in aged muscle, including ECM development, ECM component organization and collagen formation, thereby restoring muscle cell viability [11]. By RNA-seq technology, researchers also found that overexpression of Metrnl reduced the mRNA levels of various chemokines and upregulated the Wnt/β-catenin pathway, thereby inhibiting the excessive infiltration of immune cells [12, 13]. Microarray protein profiling assay also showed overexpression of Metrnl promoted the expression and phosphorylation of AMPK, helping to activate cell autophagy [14]. Especially, the protective effect of Metrnl on cardiovascular diseases and other inflammatory immune diseases has been suggested in recent research. For instance, one indicated that Metrnl promoted myocardial infarction repair in a mouse model by stimulating the proliferation of endothelial cell clusters expressing KIT at the border of infarct zones, which further elucidated the positive role of Metrnl in cardiac repair [8]. What's more, increasing proof has demonstrated that Metrnl regulates the occurrence and development of many CVMDs. In this review, alterations and functions of Metrnl in various cardiovascular and metabolic diseases will be summarized to determine its predictive role and therapeutic value in cardiovascular and metabolic diseases (Fig. 1).

Metrnl has a broad distribution, with high expression in adipocytes, endothelial cells, activated monocytes, and myocytes. Metrnl has been shown to have a beneficial impact on enhancing insulin sensitivity, inhibiting

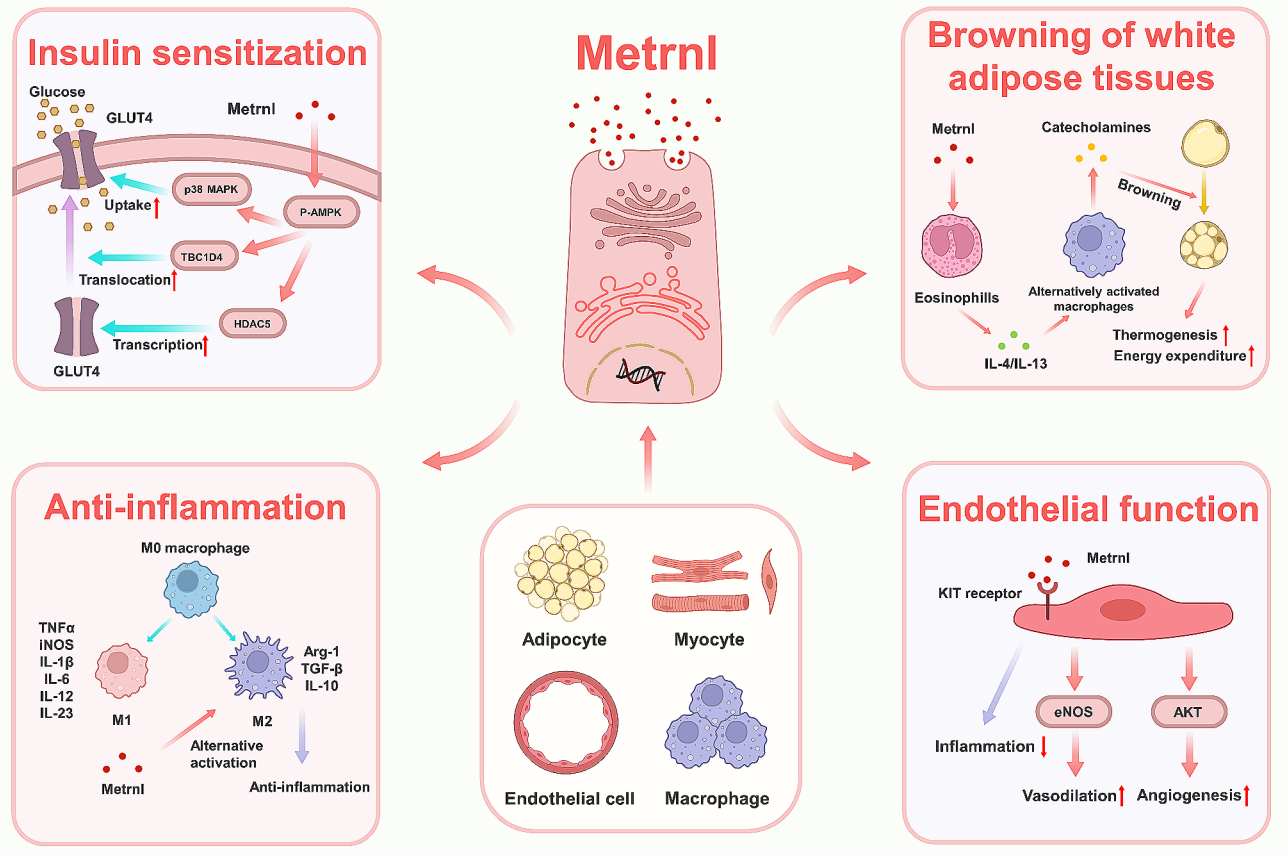

Fig. 1 Sources and main functions of Metrnl

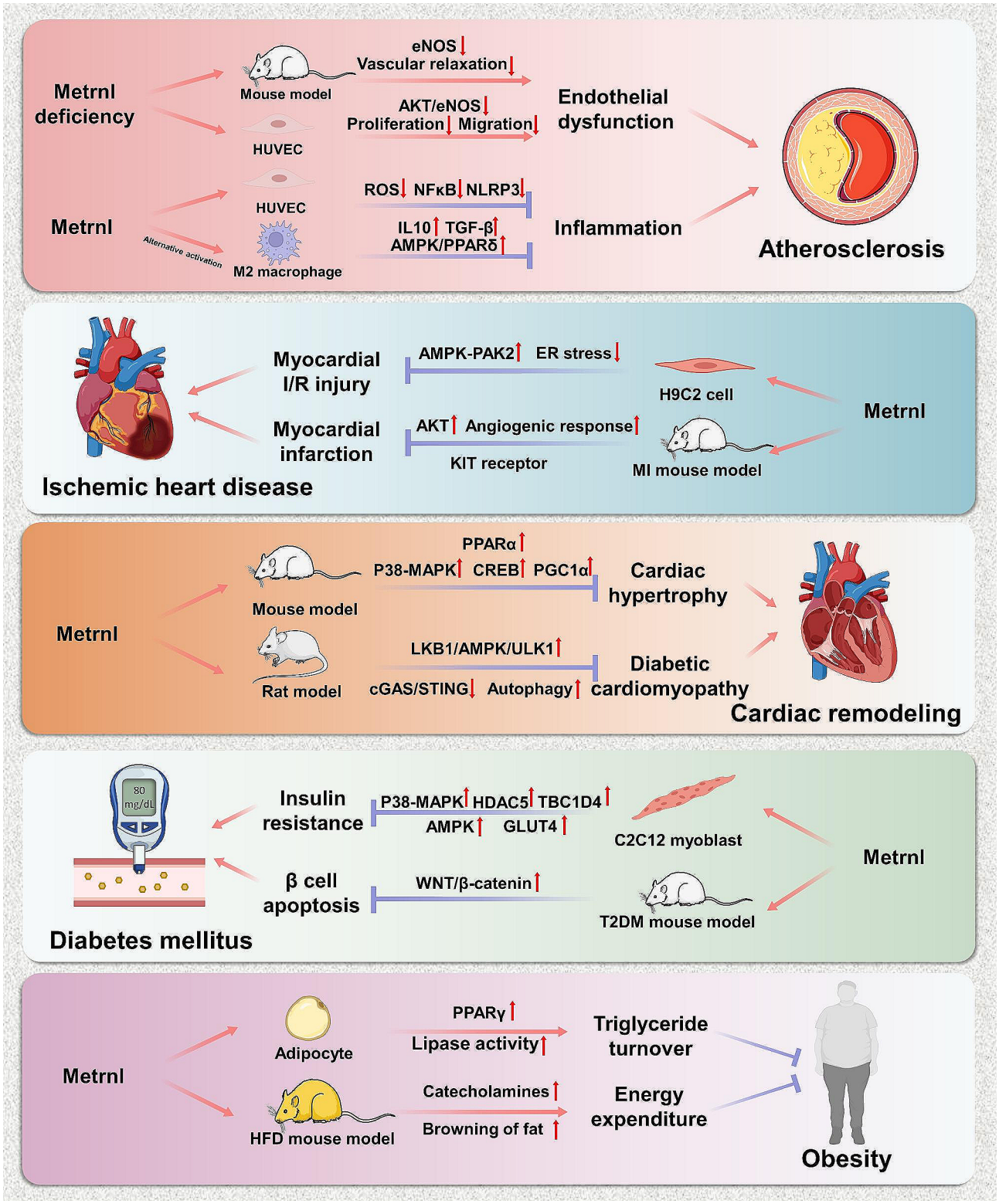

Fig. 2 Metrnl protects against various CVMDs

inflammation, preserving endothelial function, and facilitating the processes of browning in white adipose tissue.

Metrnl and cardiovascular diseases

Metrnl and atherosclerosis

Atherosclerosis is a chronic inflammatory pathological change with complex mechanism in the large and medium-sized arteries involving multiple cell types, including macrophages, adventitial fibroblasts, vascular smooth muscle cells, endothelial cells and other immune cells [15]. Key factors including endothelial dysfunction, leukocyte adhesion, foam cell formation, and phenotypic transformation of vascular smooth muscle cells contribute to the development of atherosclerosis [15]. As an early marker of atherosclerosis, a symptom of endothelial dysfunction is decreased endothelium-dependent vasodilation [16]. Zheng et al. [7]. found that in ApoE knockout atherosclerotic mice, levels of endothelial and circulating Metrnl were reduced. Moreover, Metrnl knockout accelerated atherosclerosis in mice. In molecular mechanism, by decreasing eNOS phosphorylation at Ser1177, endothelial Metrnl deficiency impairs endothelium-dependent vascular relaxation, rescued by exogenous Metrnl [7]. Xu et al. [17]. also found that knocking down Metrnl could inhibit the migration, proliferation and tube-forming ability of HUVECs. It also abolished the endothelial cell proliferation stimulated by recombinant VEGFA, which was rescued by the addition of recombinant Metrnl. The mechanism is related to impaired stimulation of the VEGFA downstream Akt/eNOS pathway due to Metrnl deficiency. Song et al. [18]. discovered that Metrnl promotes endothelial cell proliferation and angiogenesis through the KIT receptor and the PI3K/Akt pathway.

Lipid abnormalities are one of the most crucial precipitating factors for vascular injury and atherosclerosis, characterized by elevated levels of circulating LDL-C, sdLDL and TG, and declined levels of HDL-C [19]. Studies have found that overweight or obese individuals have greatly lower circulating Metrnl levels than the normal group. In addition, their circulating Metrnl levels are positively correlated with HDL-C, and negatively correlated with LDL-C, sdLDL, TG and TC [20].

It has been identified that inflammation plays a critical role in the development of atherosclerosis. Inflammation begins with the inflammasome, a complex in innate immune signaling. IL-1 family cytokine production is regulated by the inflammasome, leading to vascular inflammatory responses and driving atherosclerosis progression [21]. Studies have found that Metrnl can counteract palmatic acid-induced glucose metabolism dysfunction in HUVECs by reducing ROS production, thereby decreasing NLRP3 inflammasome expression, and alleviating vascular endothelial inflammation and dysfunction [22].

Macrophages in the subendothelial layer of the arterial wall engulf oxidized lipids, forming foam cells, which are the primary inflammatory cells in the development of atherosclerosis [23]. Metrnl is strongly induced in M2 and M2-like macrophages [4]. Metrnl may also activate M2 macrophages, which in turn stimulates anti-inflammatory cytokines like TGF-β and IL-10 and inhibits pro-inflammatory cytokines like TNF-α, IFN-γ, and IL-1β [10]. The anti-inflammation effects of M2 macrophages may contribute to preventing atherosclerosis by stabilizing plaques [24]. In terms of specific anti-inflammatory mechanisms, research has reported that Metrnl reduces LPS-induced inflammation and THP-1 monocyte adhesion to HUVECs via activating the AMPK or PPARδ-dependent signaling pathway [25]. Other studies have reported that the NF-κB pathway regulates the inflammatory response of oxLDL stimulated Metrnl-deficient HUVECs [7].

Clinical studies on the impact of Metrnl on atherosclerosis indicate that circulating Metrnl levels are related to the progression of vascular atherosclerosis, making it considered an independent predictive factor in clinical atherosclerosis. Liu et al. [26]. conducted a study on the relationship between the severity of coronary heart disease and serum Metrnl levels. The results indicated a significant negative correlation between the number of narrowed vessels and serum Metrnl levels, suggesting an association between the severity of coronary heart disease and lower Metrnl levels. Dadmanesh et al. [27]. concluded that a lower serum Metrnl level may result in impaired endothelial function, worsened glucose tolerance and atherosclerosis. In El-Ashmawy et al. [28]. 's study, the negative correlation between serum Metrnl levels and the severity of atherosclerosis was also affirmed. In summary, these studies clarify the anti-atherosclerotic function of Metrnl and suggest that Metrnl may be a biomarker for endothelial dysfunction and atherosclerosis. Moreover, it holds promise as a therapeutic target.

Metrnl and ischemic heart disease

Myocardial ischemia damages the myocardium severely due to its acute and severe nature, which can seriously impair cell morphology, function, and metabolism [29]. Myocardial infarction is a common ischemic heart disease caused by thrombotic occlusion of coronary arteries, and it is a major cause of heart failure [2]. R Giden et al. [30]. found that circulating Metrnl levels decrease in patients with acute myocardial infarction, and Metrnl levels are negatively correlated with cardiac troponin levels. In a clinical study focused on ST-segment elevation myocardial infarction patients undergoing primary PCI treatment, it was found that circulating Metrnl levels in the first few hours are associated with disease severity

and acute complications [31]. Furthermore, it serves as a predictive indicator for adverse outcomes such as all-cause mortality and non-fatal myocardial infarction during a 3-year follow-up [31]. Neoangiogenesis after myocardial infarction can alleviate scar formation and deterioration of cardiac function, potentially serving as a therapeutic target [32]. Reboll et al. [8]. demonstrated that in mouse cardiac injury, macrophages and monocytes migrate to the heart, where they secrete Metrnl. This stimulates a subpopulation of vascular endothelial cells expressing the KIT receptor to expand, leading to a vascular regenerative response that limits damage. Their research also indicated that Metrnl is essential for the normal vascular response after myocardial infarction as a ligand for KIT. It can be utilized for therapeutic intervention, as the delivery of Metrnl protein increases vascular regeneration in mice after acute MI, improving cardiac function [8]. This study builds up new approaches for understanding the injury response in ischemic heart disease and developing therapies that promote vascular regeneration.

Early restoration of blood perfusion through percutaneous coronary intervention and thrombolysis is considered an effective method for alleviating adverse outcomes in myocardial infarction patients [33]. However, myocardial ischemia/reperfusion injury (MI/R) occurs when myocardial cells suffer further damage due to reperfusion processes [34]. A previous study suggested that myocardial ischemia can be effectively treated by blocking myocardial cell apoptosis resulted from activation of endoplasmic reticulum stress (ERS) [35]. Research has found that P21-activated kinase 2 (PAK2) is a downstream target of AMPK, and the activation of the AMPK-PAK2 signaling pathway can inhibit ERS to block cell apoptosis caused by myocardial ischemia/reperfusion [36]. Xu et al. [37]. found that overexpression of Metrnl inhibits ER stress, inflammation and cell apoptosis induced by oxygen-glucose deprivation/reoxygenation in H9C2 cells. Metrnl alleviates ER stress induced by MI/R by activating the AMPK-PAK2 signaling pathway in myocardial cells. Overall, Metrnl may be an important biomarker for evaluating myocardial ischemia, and targeting Metrnl holds therapeutic value for patients with myocardial infarction.

Metrnl and cardiac remodeling

Cardiac remodeling occurs in the heart under a variety of stimulation such as blood pressure overload, myocardial infarction and inflammation, ultimately resulting in heart failure [38]. In cardiac remodeling, cardiac structure and function are altered, resulting in pathological cardiac hypertrophy, fibrosis and cell apoptosis [39]. Cardiac hypertrophy is characterized by a shift in the metabolic energy source from fatty acids to glucose, increased protein synthesis, a more organized sarcomere tissue, and increased size of myocardial cells [40]. Celia et al. [41]. found that Metrnl- deficient mice with isoproterenol-induced aging and cardiac hypertrophy exhibit enhanced fibrosis, asymmetric cardiac hypertrophy and signs of cardiac dysfunction. In contrast, heart-specific overexpression of Metrnl mediated by adenovirus can inhibit the development of cardiac remodeling and restore normal myocardial function. Furthermore, the study also demonstrated that expression of Metrnl in the heart is controlled by the PPARα pathway, consistent with previous research indicating that the heart is protected from cardiac hypertrophy by the PPARα pathway [42]. The upstream of PGC1α transcriptional regulation consists of the CREB and p38-MAPK pathways, which are directly activated by Metrnl [41]. Targeting PGC1α helps alleviate cardiac hypertrophy [43]. Cao et al. also found that overexpression of Metrnl improves pressure overloading induced pathological cardiac hypertrophy by stimulating AMPK/SIRT1 signaling [44]. The anti-inflammatory role of Metrnl may be a key mechanism for improving cardiac remodeling, given that the pro-inflammatory state is frequently linked to cardiac hypertrophy and that Metrnl can induce anti-inflammatory M2 macrophage activation, inhibiting pro-inflammatory cytokines like TNF-α, IFN-γ and IL-1β and stimulating anti-inflammatory cytokines like IL-10 and TGF-β [10]. These studies suggest that Metrnl is a therapeutic target for cardiac remodeling.

Diabetic cardiomyopathy (DCM) is a metabolic heart disease featured by myocardial apoptosis, hypertrophy, fibrosis, and other cardiac remodeling features [45]. It results in dysfunction during the systolic and diastolic phases of the heart, putting diabetes individuals at increased risk of heart failure and unexpected death [45]. Lu et al. [14]. found that in both type 1 diabetes mice induced by streptozotocin and type 2 diabetes mice with leptin receptor deficiency, the cardiac and circulating levels of Metrnl were suppressed. However, in diabetic mice, cardiac-specific overexpression of Metrnl improves cardiac dysfunction by preventing oxidative damage, fibrotic remodeling, and myocardial cell apoptosis. Autophagy is a cellular defensive mechanism during DCM that can trigger the LKB1/AMPK/ULK1 pathway [46]. Mechanistically, research indicated that Metrnl deactivates the cGAS/STING signaling pathway by activating the LKB1/AMPK/ULK1 signaling axis in DCM, leading to autophagy activation and providing protection against DCM [14]. It is evident that Metrnl, as a novel therapeutic target for DCM, holds significant promise.

Metrnl and heart failure

Heart failure (HF) refers to a syndrome of cardiac circulation disorders caused by various factors leading to impaired ventricular filling or ejection function, and it

is a common end-stage manifestation of various cardiovascular diseases. HF is a growing public health problem, significantly impacting the quality of life due to its high incidence and mortality rates [47]. As mentioned above, Metrnl significantly improves cardiac dysfunction and prevents adverse cardiac remodeling under various pathological conditions, playing a positive role in heart failure by reducing oxidative stress and decreasing myocardial cell apoptosis. Cai et al. [48]. found that, in elderly congestive heart failure patients, lower circulating Metrnl levels are linked to weight loss and the severity of heart failure. What's more, lower circulating Metrnl levels are associated with a poorer prognosis notably in patients with coronary artery disease. However, another study's conclusion contradicts this finding. Rupérez et al. [41]. observed higher plasma Metrnl levels in congestive heart failure patients, which were associated with an increased risk of mortality in these patients. The authors suggest that these discrepancies may be partially attributed to the heterogeneity of study designs, with factors such as patient age, blood sampling methods, and race potentially influencing the results. Given the relatively clear evidence of Metrnl's therapeutic role in heart failure, further well-designed clinical studies are needed to establish a reliable conclusion regarding Metrnl as a biomarker for heart failure.

Metrnl and hypertension

Hypertension is characterized by an elevation in systemic arterial pressure and is a significant risk factor for cardiovascular diseases. In the early stages of hypertension, renal arterioles experience spasms and constriction. The elevated blood pressure induces pressure and shear forces on the vascular endothelium, leading to injury in the endothelial cells of renal glomerular vessels. Endothelial injury results in a reduction in the production of vasodilatory substances such as nitric oxide (NO) and prostacyclin. Simultaneously, there is an increased production of vasoconstrictive substances (Ang II, PDGF, TGF-B, ET-1, thromboxane A2), enhancing the constriction of renal arteries, further exacerbating hypertension and ischemia in renal tissues [49]. Zheng et al. [7]. investigated the impact of Metrnl on vascular tension by conducting ex vivo experiments on thoracic aortas from mice with endothelial cell-specific Metrnl knockout and normal mice. The findings indicated that the absence of Metrnl in endothelial cells impairs endothelial function, affecting the endothelium-dependent vasodilatory response mediated by acetylcholine (ACh). Additionally, the experiment revealed mechanistic details wherein the lack of endothelial Metrnl impairs endothelial nitric oxide synthase (eNOS) activity by reducing phosphorylation at the Ser1177 site of the enzyme. This reduction in phosphorylation leads to decreased generation of NO, impacting the vasodilatory effects mediated by NO. This suggests that the deficiency of Metrnl may be associated with the pathogenesis of renal hypertension, but further research is needed to confirm this. In addition, Li et al. found that overexpression of Metrnl reduced blood pressure and ameliorated hypertension-induced cardiac hypertrophy in a spontaneously hypertensive rat model [50]. Metrnl also inhibited Ang II-induced autophagy by stimulating BRCA2/Akt/mTOR signaling pathway in H9c2 cardiomyocytes [50]. In short, Metrnl holds promise as a potential therapeutic target for hypertension.

Metrnl and chemotherapy-induced myocardial injury

Doxorubicin (DOX) is a representative anthracycline drug widely used as a first-line treatment in cancer therapy. However, the significant limitation of its clinical application is the doxorubicin-induced cardiotoxicity, with pathological mechanisms involving mitochondrial dysfunction, excessive production of ROS and cardiomyocyte apoptosis [51]. Our previous research has found that in mice treated with DOX, cardiac-specific overexpression of Metrnl dramatically reduced cardiac dysfunction, oxidative stress and cell apoptosis, thereby improving survival status [52]. In contrast, the viral injection administered intramyocardially to eliminate endogenous Metrnl made the cardiotoxicity and mortality caused by DOX worse. Mechanistically, in an autocrine manner, cardiac-derived Metrnl stimulates SIRT1 via the cAMP/PKA pathway, thereby mitigating DOX-induced oxidative stress, cardiac dysfunction and cell apoptosis [52]. This suggests that Metrnl holds promise as a therapeutic target to overcome DOX-induced cardiotoxicity.

Metrnl and metabolic diseases

Metrnl and Diabetes Mellitus

Diabetes is a clinically heterogeneous metabolic/endocrine disorder brought on by insulin resistance or insufficiency [53]. Some adipokines secreted by adipose tissue such as leptin, adiponectin and FABP4 can regulate glucose metabolism homeostasis [54]. Prolonged lack of physical activity or a long-term high-fat diet (HFD) inducing obesity may lead to glucose metabolism dysregulation, resulting in insulin resistance and the development of diabetes [55]. Metrnl, as an adipokine, is also closely associated with the conversion of glucose and fat metabolism. In skeletal muscle, PGC-1α4, an exercise-induced splice variant of PPARγ coactivator-1α, increases Metrnl secretion [10]. Following physical activity and exposure to cold, skeletal muscle and adipose tissue produce Metrnl, which subsequently enters the circulation. Elevations in circulating Metrnl levels lead to an increase in whole-body energy expenditure, browning of white adipose tissue, and improved glucose tolerance [10]. Mechanistically, this study indicates that Metrnl, as

a myokine and adipokine, activates adipose tissue macrophages (ATM) selectively in white adipose tissue via an eosinophil-dependent activation of the STAT-6 signaling pathway. This activation increases the expression of tyrosine hydroxylase and then induces the production of catecholamines to promote browning of fat tissue. Consistent with this study's findings, research by Nguyen et al. [56]. and Qiu et al. [57]. suggests that ATM induces catecholamine production in adipose tissue, leading to browning of fat tissue in mice exposed to cold. Şekerci et al. [58]. reported that peripheral hypothalamic-pituitary-thyroid axis activation can occur through UCP activation when central injection of Metrnl is administered. UCP and PGC-1α are typical thermogenic genes, highlighting the role of Metrnl in regulating energy homeostasis in the body.

Insulin resistance is often related to intertwined metabolic abnormalities and acts as the initial indications of many human diseases, including cardiovascular diseases and type 2 diabetes mellitus [59]. Upon binding to the insulin receptor, insulin triggers the phosphorylation of the insulin receptor β-subunit, which then phosphorylates insulin receptor substrate (IRS)-1 and IRS-2 [60]. Further downstream, either mitogenic signals or metabolic signals are triggered. Metabolic signal transduction is mostly conducted by phosphatidylinositol 3-kinase (PI3K), which is made up of p85 and p110 subunits [61]. PI3K facilitates the transformation of PIP_2 into PIP_3, thereby enhancing the activation of Akt [61]. Akt plays a crucial role in the insulin pathway by influencing multiple biological processes through its interaction with numerous substrates. These processes include facilitating the translocation of glucose transporter type 4 (GLUT4), regulating the production of proteins, and controlling the synthesis of glycogen. Insulin resistance is strongly associated with anomalies in the insulin signaling system. Research has demonstrated that oxidative stress can impede the phosphorylation of IRS-1 by activating the JNK signaling pathway, thereby reducing the insulin-dependent PI3K-Akt signaling [62]. Metrnl has been discovered as a critical regulator in the insulin signaling pathway, improving insulin sensitivity. Spiegelman et al. first reported that Metrnl improves glucose tolerance and boosts whole-body energy expenditure [10]. Li et al. [6]. found that mice with adipocyte-specific overexpression of Metrnl can counteract insulin resistance induced by hyperphagia (leptin knockout) or HFD, indicating that Metrnl is linked to overall insulin resistance in mice. Another study suggested that recombinant Metrnl improved impaired insulin response in C2C12 myoblasts and skeletal muscle of HFD-fed mice through signaling transduction mediated by AMPK/PPARδ [63]. Hu et al. [64]. found in T2DM mice that Metrnl can improve β cell function by inhibiting β cell apoptosis and activating β cell proliferation through the WNT/β-catenin pathway. Additionally, Lee et al. [65]. discovered that treating C2C12 myoblasts with Metrnl increases glucose uptake through calcium-dependent p38 MAPK and AMPKα2 pathways, and regulates the binding of HDAC5 to the GLUT4 promoter in an AMPKα2-dependent manner, promoting GLUT4 transcription activation. These studies suggest that Metrnl has insulin-sensitizing effects, contributing to the improvement of insulin resistance. Recently, there is also research indicating that intravenous injection of Metrnl can improve pancreatic islet lymphocyte infiltration and regulate immune cell responses in T1DM mice, suggesting that Metrnl plays a crucial role in improving type 1 diabetes caused by autoimmune destruction of pancreatic β cells [66].

Studies on the differences in circulating Metrnl levels between healthy individuals and T2DM patients have contradictory findings. Some studies suggest that blood Metrnl levels are decreased in individuals with T2DM compared to non-diabetic individuals, including studies by Lee et al. [67], Dadmanesh et al. [27], Zheng et al. [68], El-Ashmawy et al. [28], and Timurkaan et al. [69]. On the contrary, other studies draw the opposite conclusion, suggesting elevated blood Metrnl levels in individuals with T2DM, including studies by Chung et al. [70], AlKhairi et al. [71], Wang et al. [72], and Tuncer et al. [73]. Despite the controversy regarding changes in circulating Metrnl levels, the majority of studies affirm a negative correlation between circulating Metrnl levels and insulin resistance index (HOMA-IR) in T2DM patients. As for gestational diabetes, research found that mothers with gestational diabetes had higher circulating Metrnl levels, but could be controlled by proper diet [74]. The differences in these results may be attributed to compensatory increases in Metrnl or various confounding factors in clinical studies, such as patient age, weight, ethnicity, received treatments, medication use, physical activity, and the presence of other diseases. Therefore, to avoid confounding factors, well-designed and controlled clinical studies with larger sample sizes are necessary before credible conclusions can be drawn to clarify whether Metrnl has a predictive role in diabetes.

Metrnl and obesity

Obesity is a globally prevalent disease and a major health concern in modern life, considered a significant predisposing factor for cardiovascular and metabolic diseases [75]. There is some controversy regarding the changes in circulating Metrnl levels in obese patients. Some studies suggested that circulating Metrnl levels might compensatorily increase in obese or overweight individuals [71, 72, 76, 77], while others found a decrease in circulating Metrnl levels in obese patients [20, 78–80]. Another set of studies suggested no significant differences [70, 81].

Due to variations in inclusion criteria for subjects, differences in assessment methods, and the presence of numerous confounding factors in these studies, more well-controlled, large-scale, and comprehensive clinical research is needed in humans.

Obesity is associated with the dysfunction of adipocytes. Studies on the Metrnl's direct effects on adipocytes indicated that Metrnl suppresses adipocyte differentiation and promotes adipocyte proliferation, potentially resulting in hypertrophy of adipocytes [76]. This may seem unfavorable for the improvement of obesity. However, Li et al. [6], building upon the mentioned study, further pointed out that Metrnl, both in vitro and in vivo, upregulates adipogenesis and lipolysis-related genes through the PPARγ signaling pathway. Additionally, it enhances lipase activity in white adipose tissue (WAT) without causing fat deposition within cells. Instead, it increases the turnover rate of triglycerides. Additionally, improving triglyceride turnover in adipocytes could be a potential target for treating insulin resistance [82]. Other studies indicated that in HFD mice, Metrnl promotes the processes of browning in white adipose tissue, enhancing the expression of genes related to thermogenesis and fatty acid β-oxidation, contributing to the improvement of metabolic dysfunction in obese mice [57].

In some clinical studies [20, 26, 67, 70, 79] on patients with metabolic diseases, it has been observed that circulating Metrnl levels are negatively correlated with TG, TC and LDL-C, and positively correlated with HDL-C. This suggests that Metrnl also plays a crucial role in maintaining lipid homeostasis in the body. Exercise has long been considered an effective means to combat obesity, and in both preclinical [83–88] and clinical studies [89–92], it has been found that exercise can induce the expression of Metrnl and elevate circulating Metrnl levels. Mechanistically, researchers have found that Metrnl mediates crosstalk between muscle and adipose tissue during exercise, suppressing the activation and inflammation of NLRP3 inflammasomes in adipose tissue, thereby improving metabolic dysfunction in obese patients [87]. In summary, Metrnl plays a significant role in both the pathogenesis and treatment of obesity. Utilizing Metrnl as a molecular biomarker and therapeutic target for assessing obesity holds great promise (Fig. 2).

In atherosclerosis, Metrnl deficiency leads to endothelial dysfunction as evidenced by reduced eNOS activity and vascular relaxation, impaired AKT/eNOS signaling leading to decreased proliferation and migration of endothelial cells. Metrnl can inhibit inflammation through alternative activation of M2 macrophages, increasing anti-inflammatory cytokines IL-10 and TGF-β, and activating AMPK/PPARδ pathways. In ischemic heart disease, Metrnl enhances AMPK-PAK2 signaling and reduces ER stress to prevent myocardial I/R injury. Myocardial infarction is also improved by stimulated AKT signaling and angiogenic responses via the KIT receptor. In cardiac remodeling, Metrnl modulates PPARα, P38-MAPK, CREB, and PGC1α signaling pathways to reduced cardiac hypertrophy and activates the LKB1/AMPK/ULK1 and cGAS/STING pathways to enhance autophagy and prevent diabetic cardiomyopathy. In diabetes mellitus, Metrnl improves insulin sensitivity by increasing GLUT4 translocation and reduces β cell apoptosis through the WNT/β-catenin pathway. In obesity, Metrnl enhances PPARγ signaling, increases lipase activity and catecholamine levels, promoting triglyceride turnover and increasing energy expenditure.

Conclusion and perspective

Overall, Metrnl, as a novel secreted protein widely expressed throughout the body, has garnered significant attention from researchers, and it plays a crucial role in inflammation, immunity, and metabolic diseases. Given the increasing research on Metrnl in the cardiovascular field in recent years, this review primarily summarizes the research progress of Metrnl in cardiovascular metabolic diseases. It suggests that Metrnl may be a promising biomarker and therapeutic target. However, its clinical application is still a considerable distance away because there are some pressing issues to be addressed. Firstly, although we have gained some understanding of the mechanisms through which Metrnl exerts its effects, most of these mechanisms focus on downstream pathways, with insufficient research on upstream pathways. Although KIT, the receptor for SCF, has been identified as a receptor of metrnl, the existence of a specific receptor for Metrnl is still uncertain. Identifying a specific receptor will be a crucial step in clarifying the therapeutic effects of Metrnl. What's more, due to the widespread expression of Metrnl in organs and tissues throughout the body, the circulating levels of Metrnl are influenced by numerous factors. This has led to inconsistent results in clinical studies on various cardiovascular and metabolic diseases. Therefore, more well-controlled, large-scale, and comprehensive clinical studies are needed to evaluate the use of Metrnl as a predictive biomarker or indicator of disease activity.

Abbreviations

Akt	Protein kinase B
AMPK	Adenosine monophosphate-activated protein kinase
Ang II	Angiotensin II
ApoE	Apolipoprotein E
ATM	Adipose tissue macrophage
BRCA2	Breast cancer gene 2
cAMP	Cyclic adenosine monophosphate
cGAS	Cyclic GMP-AMP synthase
CREB	Cyclic AMP response element-binding protein
CVMD	Cardiovascular and metabolic disease
DCM	Diabetic cardiomyopathy
DOX	Doxorubicin

ECM	Extracellular matrix
eNOS	Endothelial nitric oxide synthase
ERS	Endoplasmic reticulum stress
FABP4	Fatty acid binding protein 4
GLUT4	Glucose transporter type 4
HDAC5	Histone deacetylase 5
HDL	High-density lipoprotein
HF	Heart failure
HFD	High-fat diet
HUVEC	Human umbilical vein endothelial cell
IFN	Interferon
IL	Interleukin
IRS	Insulin receptor substrate
JNK	c-Jun N-terminal kinase
KIT	Receptor tyrosine kinase
LDL	Low-density lipoprotein
LKB1	Liver kinase B1
LPS	Lipopolysaccharide
MAPK	c-Jun N-terminal kinase
MI/R	Myocardial ischemia/reperfusion injury
mTOR	Mechanistic target of rapamycin kinase
NF-κB	Nuclear factor kappa B
NLRP3	NLR family pyrin domain containing 3
NO	Nitric oxide
PAK2 P21	Activated kinase 2
PCI	Percutaneous coronary intervention
PGC1α	Peroxisome proliferator-activated receptor γ coactivator-1α
PI3K	Phosphatidylinositol 3-kinase
PIP_2	Phosphatidylinositol (4,5) bisphosphate
PIP_3	Phosphatidylinositol (3,4,5) bisphosphate
PKA	Protein kinase A
PPAR	Peroxisome proliferator-activated receptor
ROS	Reactive oxygen species
SCF	Stem cell factor
Ser	Serine
SIRT1	Sirtuins1
STAT	Signal transducer and activator of transcription
STING	Cyclic GMP–AMP receptor stimulator of interferon genes
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TG	Triglyceride
TGF	Transforming growth factor
TNF	Tumor necrosis factor
UCP	Uncoupling protein
ULK1	UNC-51-like kinase 1
VEGFA	Vascular endothelial growth factor

Acknowledgements
This work was supported by grants from the Natural Science Foundation of Hubei Province (No. 2023AFB099, 2024AFB092), the Fundamental Research Funds for the Central Universities (No. 2042023kf0046), the Open Project of Hubei Key Laboratory (No. 2023KFZZ028), Undergraduate Training Programs for Innovation and Entrepreneurship of Wuhan University (202410486110, S202410486326), Clinical Medicine + Youth Talent Support Program of Wuhan University and Free Innovation Pre-Research Fund of Wuhan Union Hospital (2023XHYN034).

Author contributions
WS.D., C.H. and X.Z. contributed to the conception and design of the review. WS.D. drafted the manuscript. X .Z., C. H., M. H., YP. G., YX.H., K. L. and YJ. Y. critically reviewed the manuscript. WS. D. and C. H. revised the manuscript. All authors made intellectual contributions and agreed to the published version of the manuscript.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

Received: 12 May 2024 / Accepted: 27 July 2024
Published online: 05 August 2024

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