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The Potential of Neuregulin 4 as a Novel Biomarker and Therapeutic Agent for Vascular Complications in Type 2 Diabetes Mellitus

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Abstract: Neuregulin 4 (Nrg4), a novel adipokine produced primarily by brown adipose tissue (BAT), has been functionally characterized to exert beneficial effects on modulating energy homeostasis and glucolipid metabolism, and is closely associated with the development and progression of obesity and obesity-associated metabolic diseases, such as type 2 diabetes mellitus (T2DM) and cardiovascular diseases. Recently, there has been a growing focus on the relationship between circulating Nrg4 levels and T2DM-related vascular complications. In this review, we discussed the known and potential roles of Nrg4 in various physiological and pathological processes, and its association with vascular complications in T2DM, in the aim of finding a potential biomarker recommended for the clinical diagnosis, prognosis and follow-up of T2DM patients at high risk of developing vascular complications as well as providing new therapeutic approaches.

Keywords: neuregulin 4, adipokine, diabetes, type 2, vascular complications

Introduction

Type 2 diabetes mellitus (T2DM) is a systemic metabolic disease that seriously affects human health, accounting for approximately 90% of all types of diabetes mellitus, and its prevalence is continually rising worldwide.[1] T2DM is linked to both chronic microvascular (diabetic cardiomyopathy, nephropathy, retinopathy, and neuropathy) and macrovascular [coronary artery disease (CAD), peripheral arterial disease (PAD) and stroke] complications, which are the main causes of death and disability in diabetic patients. Considering the morbidity and mortality caused by vascular complications in such population, there is an urgent need to find a reliable and convenient indicator to predict and treat diabetic vascular complications.

Adipose tissue, as a key endocrine organ, is closely related to the pathophysiology of diabetic vascular complications by releasing multiple bioactive substances, known as adipokines. Neuregulin 4 (Nrg4), a recently discovered adipokine, is highly expressed and secreted in brown adipose tissue (BAT) and white adipose tissue (WAT). Numerous studies have showed that Nrg4 plays an important role in regulating neurobiogenesis, glucose and lipid metabolism, insulin sensitivity, inflammation and angiogenesis.[2–9] Current research suggests that Nrg4 is significantly decreased in adipose tissue and serums during aging, indicating that Nrg4 may be a potential therapeutic target for the treatment of age-related metabolic diseases such as obesity, T2DM and their vascular complications.[6]

Recently, Nrg4 as a modulating adipokine, has gained increasing attention for its possibility of application in the treatment of diabetic vascular complications. In this review, we summarize the possible mechanisms underlying the actions of Nrg4 in diabetic vascular complications, hoping to find a potential biomarker of diabetic vascular complications and provide a new therapy strategy for future clinical applications.

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Nrg4: An Overview

Nrg4, a newly described adipokine, belongs to the neuregulin family of EGF. Nrg4 contains an EGF-like domain that is released in the circulation after proteolysis and acts via autocrine, paracrine, or endocrine mechanisms.[10,11] Nrg4 activates intracellular signaling mainly through binding with the erb-b2 receptor tyrosine kinase 4 (ErbB4), thereby exerting its important physiological functions in stimulating cell proliferation, inhibiting cell apoptosis, and regulating glucose and lipid metabolism through phosphatidylinositol-3 kinase/protein kinase B (PI3K/Akt), mitogen-activated protein kinases (MAPK), signal transducer and activator of transcription 5 (STAT5) and other downstream signaling pathways (Figure 1).[3,8,12] In liver tissue, Nrg4 inhibits hepatic lipogenesis and stress-induced hepatocyte apoptosis, thus resulting in the prevention of diet-induced nonalcoholic fatty liver disease (NAFLD).[13]

Nrg4 is highly expressed and secreted in adipose tissue, with the highest level in BAT, followed by WAT, and a relatively low level in other tissues such as liver, heart, brain and skeletal muscle.[2,3] Although Nrg4 has the highest expression level in the BAT, its content in BAT is relatively small or even undetectable due to the significant degeneration of BAT in adults. Since white fat is abundant in human, white fat may be an important source of Nrg4 in the human circulation.

Nrg4 expression was significantly induced during adipocytes differentiation, and could be induced by norepinephrine in differentiated brown adipocytes.[3] Meanwhile, Nrg4 expression was regulated by cold stimulation, increased only in brown fat tissue after short-term rapid cold exposure, but increased in both brown fat tissue and inguinal white fat tissue after cold acclimation induced by long-term cold exposure.[3] The possible reason may be that the sympathetic innervation of BAT is denser and more sensitive to cold stimulation.

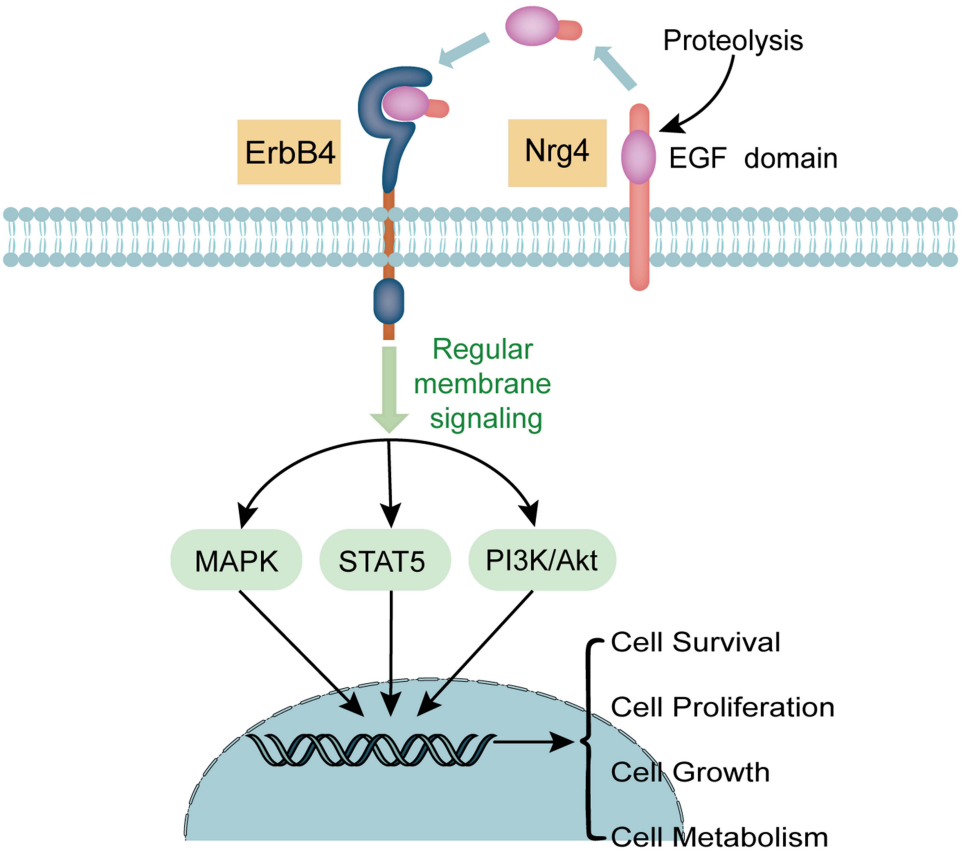

Figure 1 The regular neuregulin 4 (Nrg4)-erb-b2 receptor tyrosine kinase 4 (ErbB4) signaling pathway. The EGF-like domain of Nrg4 can be released after cleavage, and then recognizes and binds with ErbB4, which in turn triggers the signal transduction process. Nrg4-mediated activation of ErbB4 can activate downstream MAPK, STAT5 and PI3K/Akt signaling pathways, and further regulate cell survival, proliferation, growth and metabolism by regulating the expression of target genes.

Nrg4 and Diabetic Vascular Complications

Although it is well known that Nrg4 plays crucial roles in regulating insulin sensitivity, inflammation, and glucose and metabolism, the relationship between Nrg4 levels and diabetic vascular complications is less clear. In recent years, accumulating evidence shows elevated Nrg4 levels in patients with one or more type 2 diabetic vascular complications [Table 1].

Nrg4 and Cardiovascular Disease (CVD)

CVD is the leading cause of death and disability among people with diabetes. In recent years, understanding the role of Nrg4 in the cardiovascular system and how it responds to physiological and pathological stress is rapidly evolving. Previous studies have showed that Nrg4 levels were inversely associated with carotid intima-media thickness (CIMT),[19] a biomarker of atherosclerosis that could predict cardiovascular events in the general population.[20,21] In another study, Nrg4 levels were found to be remarkably decreased in patients with CAD.[22] Similarly, Rahimzadeh et al revealed a negative correlation between circulating Nrg4 levels and risk of acute coronary syndrome (ACS).[23] Additionally, Nrg4 was identified as a cardioprotective protein since administration of Nrg4 could significantly alleviate experimental myocardial ischemia in mouse model.[24] In the study of yang et al, upregulation of Nrg4 gene expression levels could inhibit the proliferation and apoptosis of cardiomyocytes in spontaneous hypertension rats (SHR), and reverse myocardial fibrosis.[25] Recently, a case-control study has tested circulating Nrg4 levels in 80 T2DM patients with coronary heart disease (CHD) group versus 77 T2DM patients without CHD controls, and reported that Nrg4 was an independent protective factor for T2DM complicated with CHD.[14] Based on the aforementioned researches, we can speculate that circulating Nrg4 might be a new protective adipokine with protective properties against the progression of CAD in T2DM. Indeed, animal studies have showed a vital role of Nrg4/erb-b2 receptor tyrosine kinase 4 (ErbB4) signaling pathway in controlling cardiomyocytes survival, growth, differentiation, and migration.[25] However, as a newly discovered adipokine, the exact role of Nrg4 in cardiovascular system is not completely clear, and still needs to be further studied.

Table 1 Clinical Studies Measuring Circulating Nrg4 Levels in Association with Type 2 Diabetic Vascular Complications

Author, Year	Country	Study Populations	Study Design	Sample	Assay	Results
Zhong et al 2023[14]	China	157 T2DM patients (77 with CHD, 80 without CHD)	Cross-sectional	Serum	ELISA	Nrg4 levels decreased in T2DM patients with CHD.
Yan et al 2020[15]	China	164 nT2DM patients (76 with DPN, 88 without DPN)	Cross-sectional	Plasm	ELISA	Nrg4 levels were significantly lower in nT2DM patients with DPN; Nrg4 was negatively correlated with the risk of DPN, but not related to the prevalence of DN, DR, and PAD.
Yan et al 2019[16]	China	132 nT2DM patients (66 with DPN, 66 without DPN) and 41 normal controls	Cross-sectional	Plasm	ELISA	Nrg4 levels were negatively associated with DPN in nT2DM patients.
Kocak et al 2020[17]	Turkey	89 T2DM patients (50 with DMC, 39 without DMC)	Cross-sectional	Plasm	ELISA	Nrg4 decreased by 0.1 unit, the risk of presence of DMC was 1.9 times higher; Nrg4 was a predictive marker for diabetic neuropathy and DN, but it was not significant for DR.
Ding et al 2023[18]	China	140 diabetes patients (55 with T2DM, 85 with DKD) and 43 healthy people	Prospective cohort	Serum	ELISA	Nrg4 level was significantly decreased in DM and DKD compared with the control group.

Abbreviations: T2DM, type 2 diabetes mellitus; CHD, coronary heart disease; ELISA, enzyme-linked immunosorbent assay; nT2DM, newly diagnosed T2DM; DPN, diabetic peripheral neuropathy; DN, diabetic nephropathy; DKD, diabetic kidney disease; DR, diabetic retinopathy; PAD, peripheral arterial disease; DMC, diabetic microvascular complications; DM, diabetes mellitus.

Nrg4 and PAD

PAD has been defined as a chronic arterial occlusive disease of the lower extremities due to atherosclerosis.[26] The ankle-brachial index (ABI) is a reasonably accurate measurement for the detection of PAD and has been widely used to diagnose lower extremity PAD.[27,28] An observational prospective cohort study including 3004 subjects in japan has demonstrated that low ABI is an independent predictor of all-cause death and cardiovascular events both in diabetic and non-diabetic patients.[29] Diabetic patients have higher risks for developing PAD, and the prevalence of PAD was significantly higher in elderly diabetics compared with non-diabetics.[30] However, to date, only one study consisting of 164 newly diagnosed T2DM patients explored the relationship between Nrg4 and PAD, and reported that circulating Nrg4 levels were neither related to ABI values nor to prevalence of PAD.[15] Nevertheless, this study still has some limitations due to its cross-sectional study design, small sample size and different ethnicity restriction. Thus, more well-designed prospective research are urgently needed to confirm this finding.

Nrg4 and Cerebrovascular Disease

Cerebrovascular disease comprises mainly stroke, which is one of the major macrovascular complications of T2DM. It was reported that patients with diabetes had higher risks of developing both ischemic stroke and hemorrhagic stroke compared to those without diabetes.[31] Atherosclerosis and thrombosis are the main risk factors for stroke, and patients with carotid atherosclerosis may be more likely to have a stroke due to plaque shedding and vascular stenosis. As we mentioned before, Nrg4 displays the inhibitory effect on inflammation and atherosclerosis,[9,12,23] which may provide a link between Nrg4 and cerebrovascular disease. However, up to now, no study has analyzed the association between Nrg4 and cerebrovascular diseases, thus more studies are required to elucidate the exact relationship between Nrg4 and cerebrovascular disease.

Nrg4 and Diabetic Cardiomyopathy

Diabetic cardiomyopathy, a serious and underrecognized diabetic complication, is identified as myocardial structural or functional abnormalities in the absence of CAD, valvular disease, and hypertension.[32] Clinically, diabetic cardiomyopathy is characterized initially by myocardial fibrosis, dysfunctional cardiac remodeling, and advancing diastolic dysfunction, later by systolic dysfunction, and ultimately by clinical heart failure.[33] Numerous studies have shown that autophagy is essential for maintaining normal cardiac morpholsogy and function.[34] In view of this finding, Wang et al proposed that autophagy levels were reduced in mice with type 1 diabetes, and Nrg4 intervention could reactivate autophagy, suggesting that Nrg4 may prevent diabetic cardiomyopathy by regulating autophagy levels through the AMPK/mechanistic target of rapamycin (mTOR) signalling pathway in type 1 diabetic mice.[35] In addittion, Nrg4 has been proved to have an direct anti-apoptotic effect on cardiomyocytes through activation of PI3K/Akt signaling pathway.[36] However, there is no direct experimental evidence to test the relationship between Nrg4 and diabetic cardiomyopathy in T2DM.

Nrg4 and Diabetic Nephropathy (DN)

DN, also kown as diabetic kidney disease (DKD), is one of the most common diabetic microvascular complications and has become the main cause of end-stage renal disease worldwide. Several mechanisms of DN have been postulated, such as excessive generation of advanced glycosylation end products (AGEs), inflammatory cytokines and oxidative stress.[37–39] Among these, oxidative stress is considered as a unifying pathogenic mechanism of diabetic vascular complications. Additionally, tubulointerstitial fibrosis (TIF), characterized by excessive deposition of extracellular matrix (ECM) components,[40] always occurs in the early stage of DN. Furthermore, a previous research has indicated that Nrg4 attenuated tubulointerstitial fibrosis and AGEs accumulation through tumor necrosis factor-receptor 1 (TNF-R1) signaling pathway in rat model of DN, suggesting that Nrg4 possessed a therapeutic effect on TIF in DN.[41] Kocak et al demonstrated that Nrg4 levels in patients with DN were significantly lower than those with non-DN.[17] A similar finding that the levels of Nrg4 in patients with DKD were significantly decreased than that in the healthy control group was also reported in another study.[18] Consistent with the above findings, Kralisch et al showed that Nrg4 gene expression levels were decreased in mice with DKD and were independently related to a preserved renal function.[42] Recently, Deng et al have found that Nrg4 intervention

could attenuate podocyte injury in DN mice, partly by activating the AMPK/mTOR-mediated autophagy signaling pathway.[43] However, a cross-sectional study conducted by Yan et al showed no association between circulating Nrg4 and DN.[15] These discrepant findings may be partially explained by different study designs, sample size, diabetes duration, medication use and statistical power. Thus, more well-designed studies are required to further validate these fndings.

Nrg4 and Diabetic Peripheral Neuropathy (DPN)

DPN is the main cause of foot ulcer and non-traumatic amputation, which seriously affects diabetic patients's quality of life and leads to a huge economic burden.[16,44] It has been reported that 30% of diabetic patients are complicated with DPN.[45] However, the pathogenesis of DPN remains poorly understood. While some studies have demonstrated that IR, dyslipidemia, oxidative stress, inflammation, mitochondrial dysfunction, and microangiopathy may all participate in the occurrence and development of DPN,[46–49] its pathogenesis remains to be fully understood. As a member of the neuregulins, Nrg4 may have an important effect in neuronal survival, neurite outgrowth and myelin protection like Nrg1.[2,50] Moreover, Nrg4 has been reported to possess neuroprotective and neurotrophic effects, and can promote the outgrowth of neurite and the development of neuronal progenitor stem cells.[51–53] A preliminary in vivo study performed by Yan et al has demonstrated decreased Nrg4 levels in newly diagnosed T2DM patients with DPN.[16] Similarly, Kocak et al also found that Nrg4 levels in DPN patients were significantly decreased by subgroup analysis and Nrg4 may be a predictive marker of DPN.[17] A later study conducted by Yan et al showed a negative association between Nrg4 and vibratory perception threshold (VPT), a reliable marker for early detection of DPN.[15] Moreover, they further proposed that decreased circulating Nrg4 levels might result in DPN through a close interaction with 25-hydroxyvitamin D.[15] All the above findings consistently suggest that circulating Nrg4 might be a protective factor against DPN.

Nrg4 and Diabetic Retinopathy (DR)

DR is the most common cause of vision loss in working-age adults.[54] Recently, DR was defined as a neurovascular disease associated with tissue-specific neurovascular impairment of the retina in diabetic patients. DR, as a common diabetic microvascular complication, may have similarities with other diabetic microvascular complications as we mentioned above in pathogenesis. Hyperglycemic toxicity, inflammation, oxidative stress, and endothelial damage can all cause microvascular injury, if the injury occurs in the retina, it presents as DR. Indeed, several biochemical mechanisms have been proposed to elucidate the pathogenesis of DR, including AGEs accumulation, inflammation, oxidative stress, protein kinase C (PKC) activation, and vascular endothelial growth factor (VEGF).[55] Additionally, neuronal abnormalities including neuronal cell death have been demonstrated to be irreversible changes preceding vascular abnormalities in the early stages of DR.[56–58] As we previously noted, Nrg4 has neuroprotective and neurotrophic effects,[51–53] suggesting that Nrg4 may also have protective effects on DR. However, Kocak et al showed that Nrg4 levels were decreased in patients with DR than non-DR patients, but there was no statistically significant difference.[17] Similarly, a later study conducted by Yan et al also showed no statistically significant difference in Nrg4 levels between T2DM patients with and without DR.[15] Since the current studies on the relationship between Nrg4 and DR are quite scare and the sample size is limited, the association between Nrg4 and DR is still unclear. Therefore, more evidence is urgently needed to validate these findings.

Mechanisms of Nrg4 in Vascular Complications of T2DM

Endothelial dysfunction is a critical and initiating factor in the occurrence and development of diabetic vascular complications,[59,60] eventually leading to vascular endothelial injury. The pathogenesis of vascular complications in T2DM is associated with many factors, among which the most important factors are IR and hyperglycaemia (Figure 2). Currently, the precise pathophysiological mechanism of Nrg4 in diabetic vascular complications still remains unclear. Nevertheless, several pathophysiologic mechanisms have been postulated for the role of Nrg4 in diabetic vascular diseases. Here we focus on the description of several known mechanisms that have been demonstrated in various experimental models.

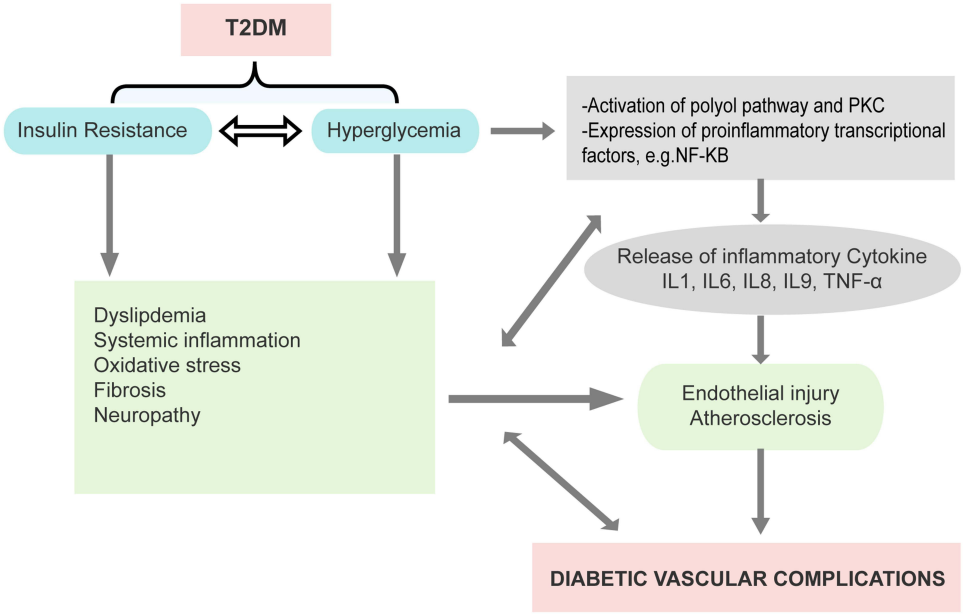

Figure 2 Some of the most important known factors in the pathophysiology of vascular complications in T2DM. Hyperglycemia, dyslipidemia, insulin resistance (IR) and other metabolic disorders existing in T2DM can affect vascular wall by a series of events including oxidative stress, inflammation and endothelial dysfunction, which ultimately leading to the development of endothelial injury and atherosclerosis.

Role of Nrg4 in IR

IR plays a pivotal role in the development and progression of T2DM and its vascular complications. It is generally believed that IR is closely related to chronic inflammation, which requires the activation of the transcription factor nuclear transcription factor-kappa B (NF-kB).[61] Insulin stimulates the production of the potent vasodilator nitric oxide (NO) from endothelium by binding to insulin receptors on vascular endothelial cells.[62] In IR states, the vasodilator actions of insulin dependent insulin signaling pathways in endothelium are impaired, leading to endothelial dysfunction. Also, the IR state reflects the existence of low-grade inflammation, which may affect vascular endothelium function through inflammatory response, thus jointly leading to angiopathy in T2DM.

It was revealed that Nrg4 gene transfer improved insulin sensitivity by inhibiting chronic inflammation of white adipose tissue in high-fat diet (HFD)-induced obese mice (Figure 3).[9] Additionally, a previous research in mouse models has confirmed that Nrg4 can improve diet-induced IR through activating the STAT5 pathway to prevent de novo lipogenesis in liver.[3] In a subsequent study, Chen et al showed that the insulin sensitivity was increased in Nrg4 transgenic mice by promoting the utilization of glucose in peripheral tissues, thereby regulating systemic energy metabolism.[63] Consistently, it has been demonstrated that downregulation of Nrg4 expression triggered IR in mice adipocytes, which was likely the result of reduced insulin receptor expression and glucose transporter four (GLUT4) protein levels.[64] Moreover, Nrg4 could inhibit inflammation and restore insulin receptor and GLUT4 protein expression.[64] In addition, the authors further verified that Nrg4 could reduce autophagy in GLUT4 storage vesicle (GSV) protein to improve glucose metabolism and IR.[64] Of note, South et al indicated that Nrg4-ErbB4 signaling could promote insulin secretion by activating PI3K signaling pathway.[65] In view of these findings, Nrg4 can improve insulin sensitivity in different ways, raising the possibility that Nrg4 may play a crucial role in diabetic vascular complications due to impaired insulin sensitivity.

Despite Nrg4's beneficial effects on IR in experimental animal models, it appears that Nrg4 has also adverse effects in human studies. Martínez et al has found a negative correlation between Nrg4 levels and insulin sensitivity in humans,[66] contrary to another human study that Nrg4 gene expression was positively associated with insulin sensitivity.[67] In addition, they proposed that Nrg4 could attenuate mitochondrial respiration in the human HepG2 cell line but had no effect on the expression of genes related to lipid metabolism.[66] These inconsistent findings suggest that there may be other factors influencing Nrg4 level in human. In fact, the authors noted that the lack of protein-based data may lead to the conflicting conclusions.[66] To explain these contradictory results, more well-designed research is urgently needed in the future.

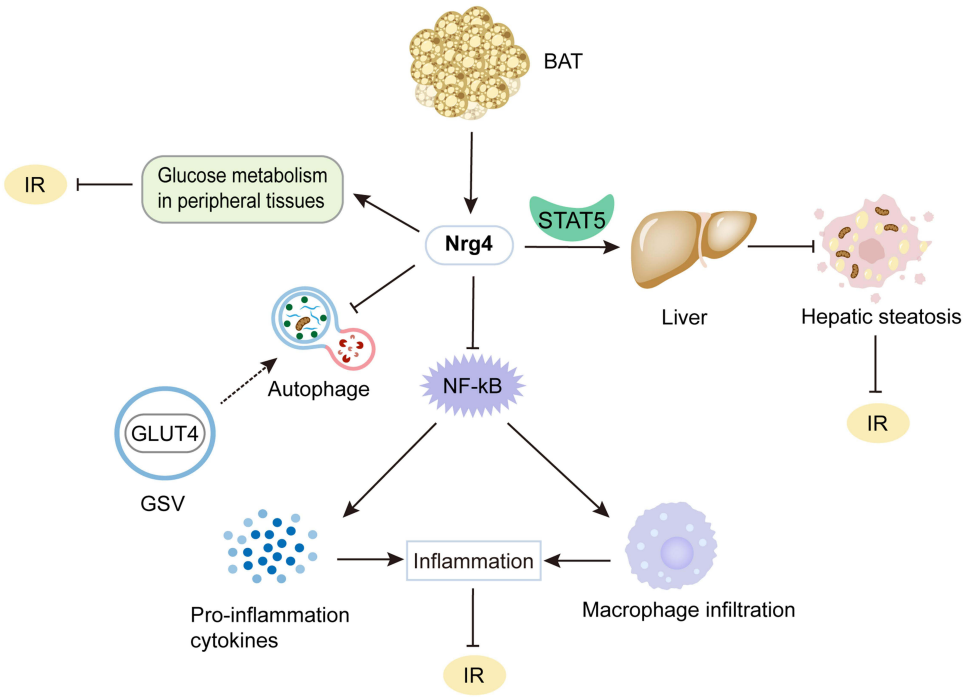

Figure 3 Nrg4 improves IR in different ways. Nrg4 inhibits inflammatory response by reducing macrophage infiltration and pro-inflammatory cytokines levels in adipose tissue. Nrg4 inhibits STAT5 pathway to improve hepatic steatosis. Nrg4 regulates systemic energy metabolism by promoting the utilization of glucose in peripheral tissues. Also, Nrg4 improves IR by inhibiting autophagic degradation in GLUT4 storage vesicle (GSV) protein.

Role of Nrg4 in Inflammation

Chronic low-grade inflammation has a strong association with IR in obese objects,[68] which could significantly lead to T2DM and its vascular complications. Researchers have reported that the expression of mRNA genes related to hepatic inflammation, including Tnfa, Il1b, Il12b, Nos2, Ccl2, Ccl5, and Adgre1 (F4/80), was significantly upregulated in Nrg4-deficient mice.[13] Additionally, a cross-sectional study revealed a negative association between circulating Nrg4 and high-sensitivity C-reactive protein (hs-CRP).[69] Consistently, the expression of proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), IL-1β, IL-6, IL-8 and IL-9, was also revealed to be negatively associated with Nrg4 levels.[64,67,70] Moreover, Ma et al found that Nrg4 overexpression could inhibit chronic inflammation by reducing the expression of macrophage marker monocyte chemotactic protein 1 (MCP-1) gene and increasing the expression of M2 macrophage marker gene Cd163,[9] which was in accordance with a subsequent study showing that Nrg4-ErbB4 signaling pathway could stimulate the apoptosis of pro-inflammatory macrophages (M1 macrophage) to ameliorate inflammation in Crohn's disease.[71] In fact, this is probably not the only mechanism by which Nrg4 regulates inflammation. For instance, evidence showed that Nrg4 could enhance adipose tissue angiogenesis to alleviate hypoxia and inflammation in obesity.[72] Indeed, Nrg4 gene transfer in mice has been demonstrated to stimulate VEGF expression.[63] These findings indicate that Nrg4 might play important roles in protecting against inflammation.

Role of Nrg4 in Oxidative Stress

Oxidative stress often occurs when the concentration of reactive oxygen species (ROS) exceeds that of antioxidant neutralizing species.[73] It is generally recognized that increased oxidative stress may be a unifying pathogenic mechanism of diabetic vascular complications. Many of biochemical pathways activated by hyperglycemia, including glucose oxidation, formation of AGEs, and polyol pathways activation, are related to the production of ROS, eventually resulting in the increase of oxidative stress.[74,75] Nrg4 gene expression levels were revealed to be negatively regulated by oxidative stress.[76] Furthermore, Yan et al found that Nrg4 levels in newly-diagnosed T2DM patients were negatively correlated with 8-iso-prostaglandin F2α (8-iso-PGF2α) and gamma-glutamyl transferase (GGT), two markers of oxidative stress.[16]

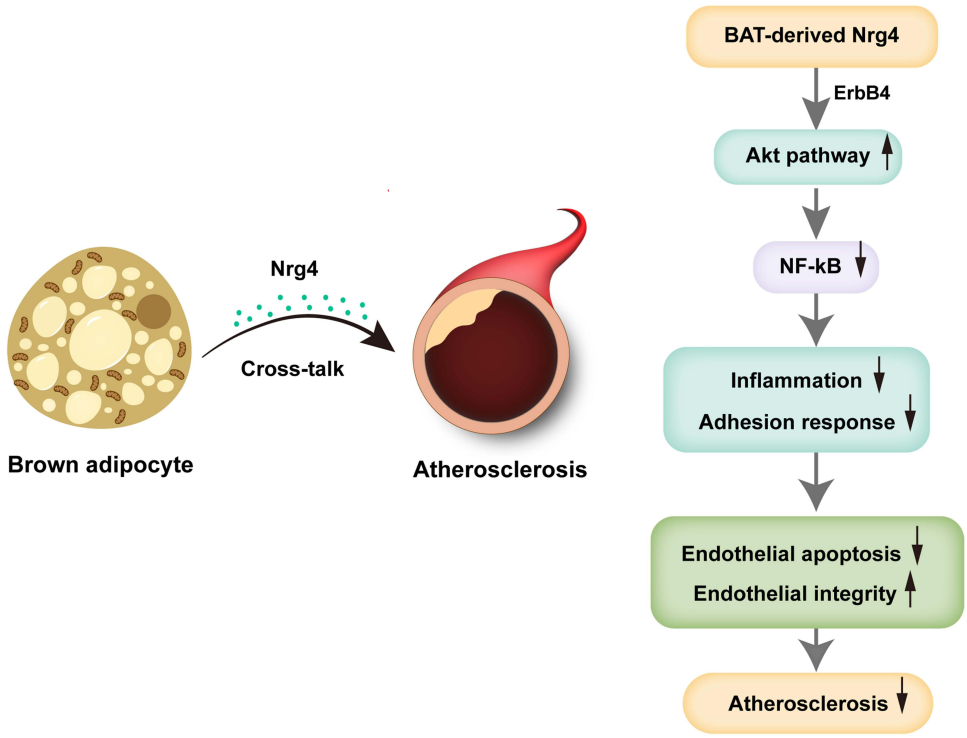

Figure 4 Schematic showing that Nrg4 protects against atherosclerosis via ErbB4/Akt/NF-kB signaling pathway. Nrg4 acts as a cross-talk factor between brown adipose tissue and arteries, and inhibits endothelial inflammation and adhesion response by ErbB4/Akt/NF-kB pathway (80), thus alleviating vascular injury and atherosclerosis.

These findings indicate that Nrg4 may be used as a potential oxidative stress marker, and Nrg4 may protect against diabetic vascular complications due to its antioxidant property.

Role of Nrg4 in Atherosclerosis

Atherosclerosis is generally considered an inflammatory response to chronic vascular injury, which is associated with perturbed vascular flow and vascular inflammation mediated by oxidized lipoprotein.[77] It is reported that inflammation is a critical risk factor in the development of atherosclerosis and requires the activation of NF-kB.[78] According to this concept, Nrg4 may protect against atherosclerotic partly mediated by its anti-inflammatory property as we mentioned above. Indeed, Nrg4 levels have been reported to be inversely associated with CIMT, a biomarker for atherosclerosis and increased angiographic severity of CAD and ACS.[22,23] Recently, Shi et al demonstrated that patients with atherosclerosis had significantly lower Nrg4 levels than controls.[79] They also observed impaired endothelial function or integrity and an increase of endothelial cells apoptosis in BAT-specific Nrg4 knockout mice.[79] Moreover, they further confirmed the important role of Nrg4 in preventing atherosclerosis by inhibiting endothelial inflammation via ErbB4/Akt/NF-κB pathway (Figure 4).[79] These findings strongly suggest that Nrg4 can protect against atherosclerosis, at least, partly by its anti-inflammatory effect.

Conclusions

In conclusion, as a novel adipocytokine, Nrg4 has been revealed to be closely related to T2DM-related vascular complications by regulating insulin sensitivity, inflammation, and glucose and lipid metabolism, and may be used as a good biomarker for the early detection of diabetic vascular complications. However, information about the relationship between Nrg4 and diabetic vascular complications is little, and further clinical and experimental studies are urgently need to determine whether Nrg4 can be used as a novel biomarker and therapeutic agent for type 2 diabetic vascular complications, thus to make it possible to develop therapeutic drugs targeting Nrg4-ErbB4 pathway. Therefore, Nrg4

may be a potential endocrine therapeutic target for type 2 diabetic vascular complications in the future. We hope this review can be helpful to researchers interested in the association between Nrg4 level and diabetic vascular complications.

Abbreviations

Nrg4, Neuregulin 4; BAT, brown adipose tissue; T2DM, type 2 diabetes mellitus; CAD, coronary artery disease; PAD, peripheral arterial disease; EGF, epidermal growth factor; WAT, white adipose tissue; PI3K/Akt, phosphatidylinositol-3 kinase/protein kinase B; ErbB4, erb-b2 receptor tyrosine kinase 4; MAPK, mitogen-activated protein kinases; STAT5, signal transducer and activator of transcription 5; NAFLD, nonalcoholic fatty liver disease; CVD, cardiovascular disease; CIMT, carotid intima-media thickness; ACS, acute coronary syndrome; SHR, spontaneous hypertension rats; CHD, coronary heart disease; ABI, ankle-brachial index; mTOR, mechanistic target of rapamycin; DN, diabetic nephropathy; DKD, diabetic kidney disease; AGEs, advanced glycosylation end products; TIF, tubulointerstitial fibrosis; ECM, extracellular matrix; TNF-R1, tumor necrosis factor-receptor 1; DPN, diabetic peripheral neuropathy; VPT, vibratory perception threshold; DR, diabetic retinopathy; PKC, protein kinase C; VEGF, vascular endothelial growth factor; NF-kB, nuclear transcription factor-kappa B; IR, insulin resistance; NO, nitric oxide; HFD, high-fat diet; GLUT4, glucose transporter four; GSV, GLUT4 storage vesicle; hs-CRP, high-sensitivity C-reactive protein; TNF-α, tumor necrosis factor alpha; MCP-1, monocyte chemotactic protein 1; 8-iso-PGF2α, 8-iso-prostaglandin F2α; GGT, gamma-glutamyl transferase.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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