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MINIREVIEWS

Real role of growth factor receptor-binding protein 10: Linking lipid metabolism to diabetes cardiovascular complications

Yang Yang, Hua-Jie Yao, Wei-Jie Lin, Si-Chao Huang, Xiao-Dong Li, Fa-Zhong He

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Abstract

Cardiovascular complications of patients with type 2 diabetes mellitus (T2DM) threaten the health and life of numerous individuals. Recently, growth factor receptor-binding protein 10 (GRB10) was found to play a pivotal role in vascular complications of T2DM, which participates in the regulation of lipid metabolism of T2DM patients. The genetic variation of *GRB10* rs1800504 is closely related to the risk of coronary heart disease in patients with T2DM. The development of GRB10 as a key mediator in the association of lipid metabolism with cardiovascular complications in T2DM is detailed in and may provide new potential concerns for the study of cardiovascular complications in T2DM patients.

Key Words: Type 2 diabetes mellitus; Growth factor receptor-binding protein 10; Vascular complications; Lipid metabolism

Core Tip: Growth factor receptor-binding protein 10 (GRB10) performs a vital role in vascular complications of type 2 diabetes mellitus (T2DM). GRB10 variant may be associated with the blood lipids and then may also related to the risk of coronary heart disease in patients with T2DM. GRB10 is expected to be a potential target for the prevention and treatment of vascular complications in patients with T2DM.

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INTRODUCTION

Growth factor receptor-binding (GRB) proteins belong to a class of multi-structural domain adaptor proteins with various cellular functions. Among all GRB proteins, GRB7, GRB10, and GRB14 have similar overall structure, including an N-terminal proline-rich domain, a central pleckstrin-homologous PH domain, a C-terminal SH2 domain, and a family-specific BPS domain (between PH and SH2 domains)[1-3]. GRB10 is an adaptor protein in the GRB7/GRB10/GRB14 protein family. It has three subtypes, GRB10α, GRB10β and GRB10γ, of which GRB10γ subtype has the longest amino acid chain in length, while GRB10α subtype has the shortest amino acid chain in length[4,5]. Molecular biology studies have confirmed that GRB10 can interact with multiple tyrosine kinase receptors and affect a variety of intracellular signaling pathways. In addition, GRB10 plays a key regulatory role in myriad cellular functions such as proliferation, apoptosis and metabolism[6-8]. Besides, Di Paola *et al*[9] found that the minor allele variant of *GRB10* rs4947710 was associated with the low risk of type 2 diabetes mellitus (T2DM) in Caucasian subjects from Italy, while *GRB10* rs2237457 gene variant was related to the development of T2DM in the Amish population. A recent study found the *GRB10* rs1800504 gene variant was associated with coronary heart disease (CHD) susceptibility in T2DM patients. Relative to the TT genotype, the CC + CT genotype may contribute to a significant increase of CHD incidence in T2DM and the mechanism may be achieved by regulating the levels of circulating blood lipids. In vitro experiments further confirmed that GRB10 rs1800504 genetic variation is related to lipid metabolism in hepatocytes[10]. Therefore, this article will focus on the role and mechanism of GRB10 in regulating vascular endothelial function and lipid metabolism, aiming to clarify the important role of GRB10 in the occurrence and development of vascular complications of T2DM.

GRB10 AND T2DM-RELATED CARDIOVASCULAR COMPLICATIONS

Vascular complications of diabetes are the leading reason for death of patients with T2DM, which include macrovascular and microvascular complications (Figure 1). Diabetic macroangiopathy includes cardiovascular disease, cerebrovascular disease and peripheral arterial disease, among which cardiovascular disease is the most common cause of death in diabetic patients[11,12]. One of the major hallmarks of diabetic macrovascular disease is the imbalance of vascular homeostasis caused by dysfunction of endothelial cells and smooth muscle cells, which eventually leads to atherosclerosis and thrombosis[13,14]. Reddy *et al*[15] discovered that GRB10 a critical downstream mediator of miR-504 in vascular smooth muscle cell (VSMC), and miR-504 was closely associated with VSMC dysfunction in mice with T2DM. Furthermore, as a key regulator of angiogenesis, vascular endothelial growth factor (VEGF) is widely known to be involved in the development of numerous angiogenesis-related disorders. Activation of VEGF receptor leads to recruitment of SH2 containing protein, so VEGF stimulation can increase the expression level of GRB10, while the overexpression of GRB10 leads to the increase of VEGFR2 and tyrosine phosphorylation[16,17]. It is revealed that GRB10 might participate in the positive feedback loop of the VEGF signaling pathway. Therefore, GRB10 may be a key gene in the process of VEGF regulating diabetic vascular complications.

GRB10 AND LIPID METABOLISM

Insulin resistance and lipid metabolism disorder are the main causes of T2DM, and they are also crucial factors leading to diabetic vascular complications. Holt *et al*[18] found that GRB10 was highly expressed in tissues involving insulin action and glucose metabolism, such as muscle, pancreas and adipose tissue. Relevant data show that severe obesity (Body mass index > 35 kg/m^2) can increase the risk of diabetes and coronary heart disease by about two times[19]. Wang *et al*[20] demonstrated that GRB10 could interact with IGFR to negatively modulate IGF/IGFR signaling pathway. IGF overexpressed in diabetes, and may lead to insulin resistance by blocking insulin signal transduction. Insulin resistance can result in lipid metabolism disorder and obesity. On the contrary, obesity further aggravates insulin resistance. Obesity leads to heterotopic deposition of fat and insufficient insulin signal transduction, followed by insulin resistance, inhibition of hepatic glycogen synthesis and increase of hepatic gluconeogenesis, which eventually leads to abnormal lipid metabolism in peripheral tissues such as adipocytes[21,22].

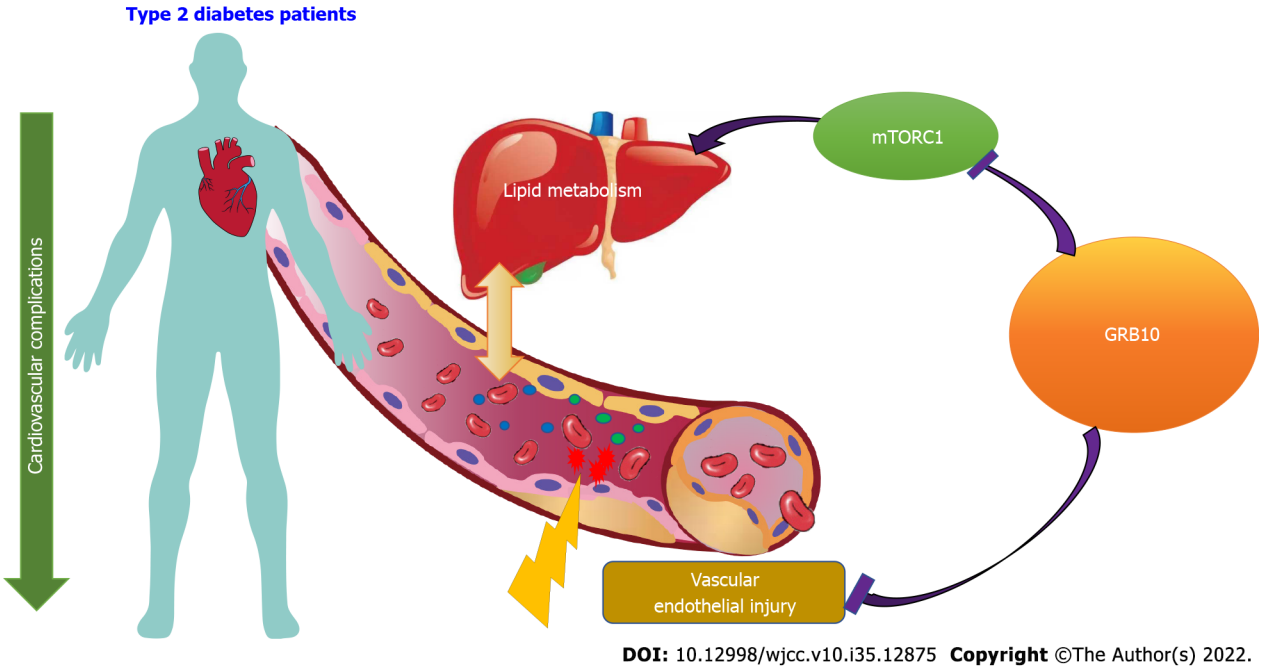

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Figure 1 Growth factor receptor-binding protein 10 is involved in the regulation of cardiovascular complications in patients with type 2 diabetes. GRB10: Growth factor receptor-binding protein 10; mTORC1: Mammalian target of rapamycin complex 1.

Insulin can enhance the intake of FFA by adipocytes and the synthesis of triglycerides[23]. However, insulin resistance leads to the increase of FFA, which in turn promotes the occurrence of atherosclerosis [24]. Moreover, Trayhurn *et al*[25] found that the cytokines [such as tumor necrosis factor-α, interleukin (IL)-1β, IL-6 and plasminogen activator inhibitor-1] released by adipose tissue of T2DM patients can promote chronic inflammation and thrombosis. About 97% of T2DM patients have dyslipidemia, which is closely related to atherosclerosis[26].

GRB10 is closely related to obesity and participates in lipid metabolism. Studies have shown that specific knock-down of GRB10 in peripheral tissues leads to significant overgrowth of mice[20]. The mutation of GRB 10/14 is also related to obesity and insulin resistance[27]. The silenced GRB10 gene can be reactivated by acute ER stress, and its reactivation plays an important role in the early development of hepatic steatosis[28]. A study by Madon-Simon *et al*[29] found that GRB10 affected the fat ratio, glucose metabolism regulation and lipid storage in the liver. Besides, recent clinical study found that patients with TT genotype of *GRB10* rs1800504 had significantly lower levels of cholesterol and low-density lipoprotein cholesterol than patients with CC + CT genotype. Compared to GRB10-*WT*, the total cholesterol level was notably reduced in GRB10-*Mut* of MIHA cells[10]. Cold exposure obviously induced the expression of GRB10 in adipose tissues. In addition, fat-specific knockout of GRB10 inhibits the expression of lipogenic and thermogenic genes, reduces energy consumption, and aggravates diet-induced obesity and insulin resistance[30]. In conclusion, GRB10 plays an important role in lipid metabolism.

The mammalian target of rapamycin complex 1 (mTORC1) signaling pathway is an important regulatory pathway for cell growth and metabolism. The deletion of GRB 10 and the over-activation of mTORC1 lead to the increase of insulin over-expression, thus inhibiting the activation of PI3K/Akt signal pathway mediated by insulin. GRB10 negatively regulates insulin and mTORC1 signals in insulin target cells[31,32]. mTORC1 is highly active in tissues of rodents fed an obese and high-fat diet[33]. In vitro, activation of the mTORC1 signaling pathway has been shown to inhibit lipolysis, stimulate lipogenesis, and promote lipid accumulation in cells[34]. On the other hand, inhibition of mTORC1 promotes triacylglycerol glycolysis and the release of free fatty acids, blocking fat production and impairing the maintenance of adipocytes[35,36]. GRB10 can promote the metabolism of thermogenic brown adipose cells, inhibit lipogenesis, regulate the expression of thermogenic genes and energy consumption by negatively regulating the mTORC1 signaling pathway[30]. Therefore, GRB10 may negatively regulate lipid metabolism by inhibiting mTORC1 pathway, and then participate in the pathogenesis of diabetic vascular complications.

CONCLUSION

T2DM is a major risk factor for cardiovascular disease. In recent years, the therapeutic strategy for

T2DM has shifted from lowering blood glucose to reducing target organ damage and improving clinical outcomes for patients. The management of cardiovascular complications in patients with T2DM is widely respected for improving the quality of life for T2DM patients. Here we discussed that GRB10 is associated with the risk of cardiovascular complications in T2DM patients by affecting lipid metabolism of T2DM patients. Its potential mechanism may be mediated through the VEGF and mTORC1 pathway. However, our conclusion needs to be confirmed by more studies. In summary, GRB10 might be a new potential target for the prevention and therapy of vascular complications in T2DM patients.

FOOTNOTES

Author contributions: Yang Y performed the majority of the writing, prepared the figures; Yao HJ coordinated the writing of the paper; Lin WJ and Huang SC contributed to the design of this work, and performed overall supervision; He FZ and Li XD revised the paper, and make equal contributions; and all authors approved the final manuscript.

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