Narrative Review

Integration of dietary nutrition and TRIB3 action into diabetes mellitus

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Despite intensive studies for decades, the common mechanistic correlations among the underlying pathology of diabetes mellitus (DM), its complications, and effective clinical treatments remain poorly characterized. High-quality diets and nutrition therapy have played an indispensable role in the management of DM. More importantly, tribbles homolog 3 (TRIB3), a nutrient-sensing and glucose-responsive regulator, might be an important stress-regulatory switch, linking glucose homeostasis and insulin resistance. Therefore, this review aimed to introduce the latest research progress on the crosstalk between dietary nutrition intervention and TRIB3 in the development and treatment of DM. This study also summarized the possible mechanisms involved in the signaling pathways of TRIB3 action in DM, in order to gain an in-depth understanding of dietary nutrition intervention and TRIB3 in the pathogenesis of DM at the organism level.

Key words: *diabetic complications, diabetes mellitus, dietary nutrition, mechanisms, TRIB3.*

INTRODUCTION

Diabetes mellitus (DM) is a progressive and chronic metabolic disease, which is characterized by persistent hyperglycemia and deficiencies in the production or action of insulin. It is caused by numerous genetic and environmental factors and various comorbidities, including obesity, cardiovascular diseases, microangiopathy and renal failure, and has emerged as a major epidemic in this century.[1–3] Insulin resistance (IR), a major hallmark of type 2 DM (T2DM), poses a major threat to human health.[4] Although patients with type 1 DM (T1DM) and T2DM exhibit a genetic predisposition to promote disease onset, high-quality diets and nutrition therapy can play a pivotal role in DM management. Especially after initial clinical diagnosis, nutrition therapy can be used to efficaciously reduce or delay DM-associated complications. In this regard, natural products from fruits and vegetables are gaining popularity worldwide. Sharma et al[5] demonstrated that kaempferol, a fruit flavonol, could reduce oxidative stress and levels of proinflammatory cytokines in rat and human renal tubular epithelial cells, which cause the inhibition of the hyperglycemia-induced activity of RhoA kinase, thereby significantly improving diabetic nephropathy (DN).

Moreover, the recent discovery of the integration of dietary nutrition and gene action provides a unique opportunity for the treatment of T1DM and T2DM. Numerous lines of evidence suggested that nutrients might target multiple genes, such as ovarian-tumor-domain–containing deubiquitinases 3, AMP-activated protein kinase (*Ampk*), vascular endothelial growth factor, and tribbles homolog 3 (*Trib3*).[6–8] Noticeably,

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TRIB3, a nutrient-sensing and glucose-responsive regulator, is widely expressed in insulin target tissues and plays an integral role in regulating glucose homeostasis and mediating IR in DM. A previous study showed that, due to nutrient deficiencies, TRIB3 could inhibit the induction of fibroblast growth factor 21 (FGF21) in vivo and in vitro by inhibiting the CCAAT/enhancer binding protein (C/EBP)–activating transcription factor response elements in the promoter region of *Fgf21*.[8] *Antrodia cinnamomea*, a rare mushroom, extract could significantly inhibit HCT116 tumor growth in nude mice through the C/EBP homologous protein (CHOP)/TRIB3/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway.[9] Therefore, for DM treatment, targeting the role of TRIB3 in dietary nutrition intervention might be a promising therapeutic strategy. The current review attempted to summarize the latest studies on dietary nutrition intervention and the role of TRIB3 in the progression and treatment of DM as well as the possible mechanisms and signaling pathways involved in TRIB3 action, which might provide a basis for follow-up research.

METHODS

Literature search strategy

The online literature search was conducted using the PubMed, Google Scholar, and Web of Science databases. The following keywords were used: "dietary nutrition," "diabetes mellitus," "TRIB3," "diabetic complications," "mechanisms," "insulin resistance," "high-fat diet," "diabetic cardiomyopathy," "diabetic nephropathy," "diabetic retinopathy," "apoptosis," "oxidative stress," "inflammation," "autophagy," "dietary fats," "nutrient excess," "overnutrition," "alcohol consumption," "signaling pathways," and "natural products." The selected literature was first evaluated by 4 investigators working independently. Any differences were settled by consensus. Only articles published in English were short-listed; all articles deemed likely to meet the criteria were retrieved for full-text review. In addition, the reference lists and citations of the identified studies were examined to identify further relevant research papers.

Role of TRIB3 in diabetes mellitus and its complications

TRIB3, an intracellular pseudo-kinase, is a contributing factor in glucose homeostasis and IR, and has been verified to act as a stress sensor in response to a diverse range of stressors,[10] including hypoxia,[11] fasting,[12] high glucose (HG),[13] and advanced glycation end-products (AGEs).[14] Numerous studies suggested that TRIB3 played a key role in a variety of organs, such as the heart, kidney, liver, and skeletal muscle, in the complex networks of glucose homeostasis; TRIB3 might trigger IR and inhibit cell survival by promoting endoplasmic reticulum (ER) stress, apoptosis, oxidative stress, inflammatory response, and autophagy.[15–19] More importantly, as a nutrient sensor, TRIB3 exhibits a crucial involvement in governing energy metabolism by interacting with intracellular signals, such as TRIB3-Akt signaling pathways, TRIB3–mitogen-activated protein kinase (MAPK) signaling pathways, and β-cell apoptosis–related signaling pathways, which are involved in mediating cell stress responses under conditions of excessive nutrient intake, IR, and hyperglycemia.[13,20–23] A previous study reported that TRIB3 might be closely related to the modification of O-linked N-acetylglucosamine (O-GlcNAc), because proteins could enhance O-GlcNAc modification under glucose deprivation and HG conditions.[24,25] A recent study found the involvement of TRIB3 expression in a nutrient-sensing mechanism, functioning both under the conditions of hyperglycemia and glucose deprivation.[25] More importantly, Sun et al[26] used high-fat diet and low-dose streptozotocin-induced T2DM rats models and observed that the TRIB3-AMPK signaling pathway was associated with IR in adipose tissues, and silencing the *Trib3* gene could effectively ameliorate glucose and lipid metabolism and further mitigate IR.

It is worth noting that clinical data showed that 30–40% of patients with T1DM and T2DM develop at least 1 complication after approximately 10 years of disease onset,[27] and TRIB3 is considered a potential target for diabetic complications, such as DN, diabetic cardiomyopathy (DCM), diabetic retinopathy, and atherosclerosis. DN, a main complication of DM, is a chronic progressive diabetic microangiopathy and is characterized by proteinuria, mesangial matrix overproduction, renal hypertrophy, and fibrosis.[28] Renal dysfunctions and nephropathy are observed at a high rate in patients with T2DM, accounting for approximately 30% of DM-related deaths.[29] A previous study showed that TRIB3 expression was enhanced through CHOP-mediated transcriptional regulation in the kidneys and podocytes of diabetic mice.[16] Silencing the *Trib3* gene could ameliorate DM-elicited accumulation of serum creatinine and urinary albumin by activating the phosphorylation of phosphatidylinositol 3-kinase (PI3K) and Akt in the rat kidneys.[1] Ample evidence has already elucidated that interstitial fibrosis and glomerular sclerosis were the main pathologic features in DN. TRIB3 might be involved in DN-associated renal fibrosis by upregulating the expression levels of transforming growth factor β1 (TGF-β1) and collagen type IV via extracellular

signal-regulated kinase 1/2 (ERK1/2)–MAPK signaling.[17] Additionally, the overexpression of TRIB3 has also been observed in proximal renal tubules of DM rats, resulting in the accumulation of extracellular matrix. Albumin accumulation could induce the overexpression of TRIB3, the synthesis of collagen type I, and fibronectin secretion, suggesting that TRIB3 is involved in DN-associated fibrogenesis.[18] As described previously, TRIB3 might exhibit a threatening role in the DN environment. However, a contradictory study suggested that TRIB3 could reduce proteinuria and expression levels of inflammatory genes in patients with DN by inhibiting the mTOR complex 2 (mTORC2)/Akt pathway.[30] Therefore, due to these controversial results, the exact regulatory mechanism of TRIB3 in DN remains unclear and requires further exploration.

Moreover, DCM is one of the leading causes of increased morbidity and mortality in patients with DM. TRIB3 has been found to be involved in the AGE-induced decrease in collagen type I and increase in collagen type III in cardiac fibroblasts by activating the ERK1/2 and p38-MAPK signaling pathways. Inhibiting the expression of the *Trib3* gene might be a therapeutic approach for regulating collagen expression and DCM.[15] Ti et al[31] suggested that silencing *Trib3* could improve cardiac function, myocardial remodeling, lipid accumulation, and cardiac inflammation. Furthermore, our and other previous studies have confirmed that TRIB3 can promote Akt-inactivating glycogen synthase kinase (GSK) 3β (GSK-3β), thereby modulating the major molecular events under diabetic and IR conditions, while the inhibition of the *Trib3* gene could attenuate IR, metabolic disorders, and cardiomyopathy.[32,33]

Besides DCM, vascular complications are also the main causes of morbidity, hospitalization, and death in diabetic patients; in the past decades, patients with DM have shown an increased risk of vascular complications.[34] According to the World Health Organization, diabetic retinopathy is on a priority list of eye diseases, and one-third of people with DM have the disease.[35] Pitale et al[36] demonstrated that TRIB3 was a major regulatory factor of diabetic retinal pathophysiology, which might accelerate the occurrence and progression of diabetic retinopathy in humans; the inhibition of *Trib3* resulted in a significant increase in survival and functional recovery of the retinal ganglion cells, along with a significant reduction in pericyte loss and acellular capillary formation.

Additionally, the clinical correlation between DM and accelerated atherosclerosis has been increasingly investigated. Atherosclerosis is another major complication of DM, and hyperglycemia and hyperlipidemia are related factors in its accelerated development.[37] The formation of macrophage foam cells is the initial event, leading to the formation of atherosclerotic lesions; TRIB3 could accelerate the formation of foam cells and the accumulation of cholesterol.[38] Reportedly, *Trib3*-silenced diabetic mice showed a significant increase in atherosclerotic plaque stability and a reduction in atherosclerotic lesion load.[39] Although the effects of TRIB3 on DM and diabetic complications have been extensively studied, the specific mechanisms and pathways remain to be further explored.

Mechanisms of TRIB3 in diabetes mellitus and its complications

TRIB3 is involved in the crosstalk of endoplasmic reticulum stress and apoptosis. Endoplasmic reticulum is widely present in eukaryotic cells and serves as a cell sensor to monitor and maintain cellular homeostasis.[40] Adverse environmental conditions can cause ER stress, resulting in the accumulation of unfolded or misfolded proteins.[41,42] Increasing evidence suggested that ER stress was an important mechanism of DM, and thus contributes to its worsening.[43,44] As an ER stress–associated protein, TRIB3 might play a crucial regulatory role in the pathological process of DM.[30] A previous study indicated that an increased level of TRIB3 in aged rat liver was correlated with increased ER stress and hepatic glucose production, suggesting that inhibiting TRIB3 might be a key event in antagonizing ER stress and glucose metabolism.[45]

Under physiological conditions, in response to the occurrence of ER stress, the adaptive unfolded protein response (UPR) is activated to maintain protein homeostasis and promote cell survival. Importantly, if ER stress is not reduced by activating the UPR pathway, it might exceed the ER functional tolerance capacity, thereby causing the imbalance of ER homeostasis and eventually leading to cell apoptosis.[40,42] In DM, ER stress is stimulated by various factors, including hyperglycemia, palmitate, and proinflammatory cytokines, which can worsen the sensitivity of pancreatic β cells, thereby resulting in apoptosis and dysfunction and further promoting the development of DM. A previous study illustrated that palmitate and HG concentrations could induce UPR-dependent apoptosis in pancreatic β cells and concomitantly increase TRIB3 expression.[46] Fang et al[47] demonstrated that ER stress could induce TRIB3 expression, which resulted in a proapoptotic function in rat insulinoma (INS-1) β cells by activating the nuclear factor-κB (NF-κB) signaling pathway. This indicated that TRIB3 was essential for promoting the ER stress–induced apoptosis of β cells. Moreover, a study demonstrated that the HG treatment elicited ER stress and further increased the expression levels of

TRIB3 in rat INS-1 cells, and overexpression of *Trib3* also synergistically enhanced the HG-induced apoptosis.[48] However, in contrast to these studies, TRIB3 has been reported to also have antiapoptotic effects.[49–51] These discrepancies might be due to using specific species, cell types, and different stressors; however, further studies are needed to explore the reasons behind these differences.

In addition, in many cases, TRIB3 is also directly involved in promoting apoptosis independently of ER stress. Humphrey et al,[52] utilizing *Trib3*-deficient mice, observed that the loss of *Trib3* resulted in the basal activation of Akt and resistance to the cytokine-induced apoptosis of β cells. Furthermore, TRIB3 was rapidly upregulated in free fatty acid (FFA)–induced INS-1 β cells, thereby promoting the apoptosis of INS-1 β cells through the protein kinase C (PKC) δ (PKCδ) pathway.[53] Altogether, these studies demonstrated that TRIB3, a pivotal regulator of cellular ER stress and apoptosis, might play a mediating role in the occurrence and development of T1DM and T2DM.

TRIB3 is involved in oxidative stress and inflammation. Oxidative stress is a negative effect caused by uncontrolled free radicals, which results from an imbalance between the production of free radicals and the effects of reactive metabolites in the body.[54,55] Increasing evidence suggested that changes in the expression levels of TRIB3 were correlated with oxidative stress. A study by Morse et al[16] reported that the increase in the contents of reactive oxygen species (ROS) and/or FFAs was associated with an increase in the expression levels of CHOP and TRIB3 in podocytes in DM, and TRIB3 could further inhibit the expression of monocyte chemoattractant protein 1 (MCP-1). Moreover, TRIB3 might mediate the AGE-induced oxidative damage in INS-1 cells and regulate nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity, resulting in the synthesis of ROS. ROS could induce oxidative stress by activating the PKCβ2 pathway, thereby causing cell failure.[14]

Over the past 2 decades, numerous studies demonstrated a close correlation between oxidative stress and inflammation.[56–58] Inflammation is a natural defense mechanism against pathogens, which plays an integral role in responding to changes in tissue integrity and inducing various repair mechanisms to restore tissue homeostasis.[59,60] Oxidative stress plays a critical role in the pathogenesis of inflammation and subsequently mediates numerous chronic diseases, including obesity, IR, DM, and cardiometabolic complications.[61,62] ROS has also been involved in causing chronic inflammation by increasing the production of proinflammatory cytokines through activation of the NF-κB signaling pathway.[63] An in vivo study of muscle-specific *Trib3*-overexpressing mice showed that TRIB3 could enhance inflammation by increasing the levels of proinflammatory cytokines, including NF-κB, interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), and MCP-1. In addition, the muscle-specific overexpression of *Trib3* could also significantly increase the expression levels of the ROS-producing gene NADPH oxidase-1 (NOX-1), and impair antioxidation capacity, while significantly decreasing the expression of catalase (CAT), superoxide dismutase 1 (SOD1), glutathione peroxidase 1 (GPX1), and GPX4, suggesting that TRIB3-induced IR was coupled with alterations in oxidative stress and inflammation mechanistic pathways.[64] Moreover, a study by Zhang et al[65] showed that Q84R missense polymorphism in the TRIB3 (arginine at position 84 replaced glutamine) resulted in a gain of function variant, which could attenuate the ability of TRIB3 to inhibit oxidative stress–induced inflammation in DN. Based on the above-mentioned findings, TRIB3 tightly participates in oxidative stress and inflammation under diabetic conditions; however, the specific correlation and underlying mechanisms of TRIB3 with oxidative stress and inflammation require further investigation.

Autophagy and proteasomal degradations mechanism of TRIB3. Under normal circumstances, cells must constantly remove defective proteins or damaged organelles through a process called autophagy to maintain a healthy and functional intracellular environment and achieve cellular metabolism and the renewal of certain organelles.[60] Current studies on the mechanisms of autophagy and proteasomal degradation of TRIB3 in DM showed that TRIB3 was mainly associated with cancers. Both DM and cancer are chronic diseases, which seriously threaten human health, and metabolic risk factors play a critical role in triggering various cancers. A recent study introduced that TRIB3 might bind to an autophagic receptor p62, and inhibit autophagic/proteasomal degradation, thereby enabling the accumulation of multiple tumor factors in cells and ultimately promoting tumor invasion and metastasis.[66] Furthermore, a study on the role of metabolic risk factors in cancer showed that the *Trib3* depletion could induce the clearance of an autophagic receptor, sequestosome-1 (SQSTM1), thereby activating an autophagy-dependent degradation pathway; this suggested that the stress protein TRIB3 could mediate the progression and development of autophagy-related metabolic risk factor–induced cancers in patients with T2DM.[67] According to previous studies, the dysfunction of vascular smooth muscle cells (VSMCs) might play an important role in the vascular complications of DM.[68,69] Due to the critical role of TRIB3 in the induction and maintenance of the contractile phenotype of

VSMCs, the vascular remodeling of VSMCs can be suppressed by inhibiting *Trib3* expression. A study on VSMC dysfunction showed that, during HG condition in VSMCs, the expression levels of hsa_circRNA_0008028 and TRIB3 were significantly elevated; mechanistically, hsa_circRNA_0008028 could promote autophagy by regulating TRIB3 and act as a sponge for miR-182-5p.[70] Overall, these studies suggested that there might be a balance between the levels of TRIB3-related autophagy and proteasomal degradation in DM, which is yet to be investigated. The schematic diagram of the mechanisms involved in TRIB3 in DM and its complications is shown in Fig. 1.

Dietary nutritional disorder targets TRIB3 in diabetes mellitus and its complications

Dietary fats. Insulin resistance, a key trigger for T2DM, is an abnormality, which promotes the progression of T2DM.[71] Over recent years, dietary nutrition interventions have been effectively used for the prevention or treatment of IR and DM. In the past 2 decades, the health effects of individual dietary fats have been investigated, and complex dietary fats are widely considered a risk factor for DM. Epidemiological studies have shown that dietary fat composition can affect the prognosis of DM and IR.[72,73] Chronic elevation in the contents of fatty acids (FAs) is linked to increased IR and inflammation. Saturated FAs can reduce insulin sensitivity, while unsaturated FAs can prevent this from happening. Geng et al[74] demonstrated that the dietary alterations in the major saturated and unsaturated FAs could differentially regulate ER stress, TRIB3 induction, and IR; specifically, a diet with lower unsaturated fat content could induce ER stress, TRIB3, and IR as compared with the standard and widely used obesogenic diets with higher unsaturated fat contents. This, together with the findings that *Trib3* is encoded by ER stress–inducible gene,[75] suggested that ER stress–mediated induction of TRIB3 might link the dietary fat composition to IR. Therefore, dietary interventions that contain more polyunsaturated fats and fewer saturated fats might reduce circulating FAs, resulting in lower IR and reduced risk of future DM.

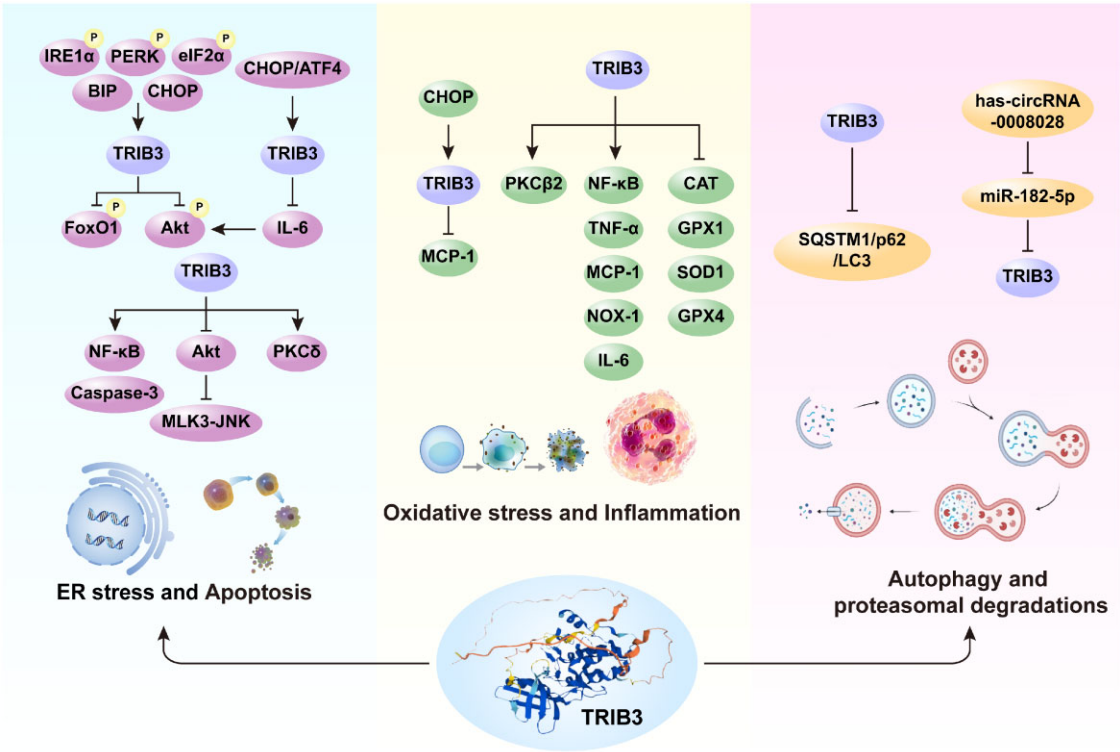

Figure 1 **The mechanisms of TRIB3 in DM and its complications.** *Abbreviations*: Akt, protein kinase B; ATF4, transcription factors 4; BIP, immunoglobulin heavy chain binding protein; CAT, catalase; CHOP, CCAAT/enhancer binding protein homologous protein; DM, diabetes mellitus; eIF2α, eukaryotic translation initiation factor 2; FoxO1, forkhead box O 1; GPX1, glutathione peroxidase 1; IL-6, interleukin 6; IRE1α, inositol-requiring enzyme 1; JNK, c-Jun N-terminal kinase; LC3, light chain 3; MCP-1, monocyte chemoattractant protein-1; MLK3, mixed lineage kinase-3; NF-κB, nuclear factor-kappa B; NOX-1, NADPH oxidase-1; P, phosphorylation; PERK, protein kinase RNA-like endoplasmic reticulum kinase; PKCβ2, protein kinase C β2; PKCδ, protein kinase C δ; SOD1, superoxide dismutase 1; SQSTM1, sequestosome-1; TNF-α, tumor necrosis factor-α; TRIB3, tribbles homolog 3.

The liver is the primary organ responsible for the endogenous production of glucose, which is tightly controlled by multiple metabolic and nutritional factors.[76] Defective insulin signaling in hepatocytes is a major cause of DM. Dietary fat composition might mediate obesity-related liver pathology, and IR due to TRIB3 is closely related to dietary exposure factors in liver IR.[74] Dietary fats have acute and persistent effects on the uptake and metabolism of glucose, which have important implications in chronic metabolic control and the acute regulation of glucose homeostasis in diabetic patients.[77,78] Moreover, FA-induced lipotoxicity plays an essential role in the pathogenesis of DM. Lipotoxicity leads to the development and progression of DM via IR and/or impaired function of pancreatic β cells.[79] Under lipotoxic conditions, TRIB3 could recruit constitutive photomorphogenic 1 (COP1) to Sirtuin 1 (SIRT1) to promote its proteasomal degradation, resulting in IR in hepatocytes.[79]

Nutrient excess. Excess feeding (overnutrition) is associated with systemic and tissue-related IR and has become an epidemic problem as an underlying cause of metabolic disorders, including DM.[80,81] TRIB3 expression is induced in the liver under fasting conditions and interferes with insulin signaling by directly binding to Akt and blocking the activation of the kinase; this suggested that TRIB3 might contribute to IR in T2DM-susceptible individuals.[19] However, in the presence of overnutrition, TRIB3-induced IR is coupled with changes in various metabolic pathways, such as oxidative stress, inflammation, adiponectin action, ER stress, and insulin signaling, thereby promoting the development of DM.[64] Furthermore, accumulating evidence suggested that TRIB3 expression in skeletal muscle and liver tissues was associated with overnutrition and hyperglycemia.[25,82,83] Moreover, under the conditions of nutrient excess, Zhang et al[64] examined the effects of *Trib3* overexpression on metabolism; both the glucose-induced IR and IR due to diet-induced obesity were dependent on muscle TRIB3 levels. Under physiological conditions, muscle TRIB3 could affect energy consumption and substrate metabolism. However, under the condition of long-term nutrient excess, the expression of TRIB3 in muscle is increased, and the muscle-specific inhibition of *Trib3* showed a preventive effect on IR and improved insulin signal transduction in muscles.

More importantly, Matsushima et al[84] demonstrated that, compared with C57BL/6 mice, in hyperinsulinemic, hyperphagocytic *db/db* mice, overnutrition could induce the hepatocytes to respond to the nutrients, increasing the activity of S6 kinase 1 (S6K1). An increase in the binding of TRIB3 to constitutive S6K1 activity resulted in diminished insulin signaling in the insulin receptor substrate 1 (IRS-1)/PI3K/Akt pathway. Furthermore, studies have shown that the increased levels of TRIB3 in the adipose tissue of fructose-fed rats could directly interact with Akt and block its activation.[85] In case of overnutrition, the increased TRIB3 levels in cells might limit the excessive glucose uptake to muscle, while the decreased TRIB3 levels in adipose tissue might lead to an increase in glucose uptake required for glycerol/triglyceride synthesis. Thus, TRIB3 can inversely affect tissue glucose uptake in muscle and fat and redirect the fuel from muscle to adipose tissue for storage under overnutrition conditions.[13] As previously mentioned, TRIB3 is considered to be a critical regulator of energy metabolism in vivo and a necessary factor for the induction of IR by nutrient excess; however, the specific correlation and underlying mechanisms require further investigation.

Alcohol consumption. Modern epidemiological studies have shown that chronic and excessive alcohol consumption could reduce glucose absorption and utilization and increase IR, thereby positively correlating with the development of T2DM.[86–89] A study conducted on female adult rats, which were prenatally exposed to alcohol, revealed an increased expression of phosphatase and tensin homolog (PTEN) and TRIB3 in the liver, concomitant with an increase in gluconeogenesis and diminished insulin signaling.[90] In addition, feeding rats an ethanol-containing diet could significantly enhance the expression level of TRIB3 and inhibition of Akt activation and phosphorylation in their hepatic tissues, thereby resulting in the inhibition of insulin signaling.[91] In summary, chronic and excessive alcohol consumption can target TRIB3 and is an important and modifiable risk factor for DM. The schematic diagram in Fig. 2 summarizes the dietary nutritional disorders that target TRIB3 in DM and its complications.

Possible pathways of TRIB3 in the development of diabetes mellitus and its complications

TRIB3-Akt signaling pathways. Serine (Ser)-threonine (Thr) kinase Akt is a major target of the insulin pathway. Under physiological conditions, the binding of insulin to its receptor can trigger the activation of a phospholipid-dependent kinase cascade that culminates in the phosphorylation of Akt.[92] TRIB3 acts as an endogenous negative regulator of Akt and binds to both nonactivated and nonphosphorylated Akt, inhibiting the phosphorylation and activation of Thr308 and Ser473, thereby negatively regulating the insulin signaling pathway.[19,93]

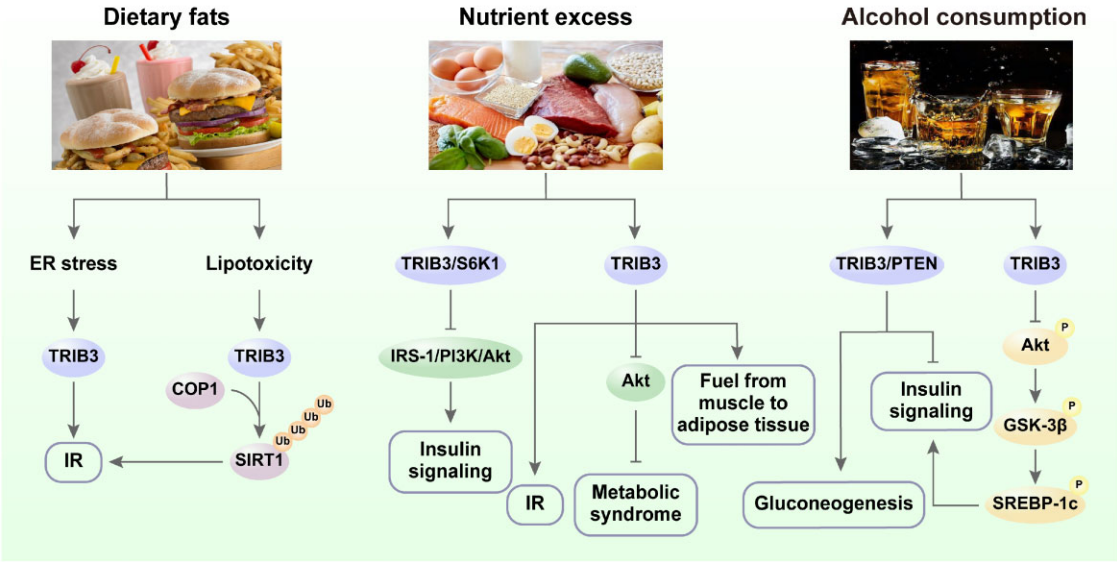

Figure 2 **Dietary nutritional disorders that target TRIB3 in DM and its complications.** *Abbreviations*: Akt, protein kinase B; COP1, constitutive photomorphogenic 1; DM, diabetes mellitus; ER, endoplasmic reticulum; GSK-3β, glycogen synthase kinase-3β; IR, insulin resistance; IRS-1, insulin receptor substrate 1; P, phosphorylation; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; SIRT1, sirtuin 1; SREBP-1c, sterol-regulatory element-binding protein-1; S6K1, S6 kinase 1; TRIB3, tribbles homolog 3; Ub, ubiquitination.

GSK-3β, a downstream target of Akt, is involved in insulin-regulated glycogen synthesis, and its phosphorylation requires the activation of Akt.[94,95] During DCM, upregulated TRIB3 leads to the inhibition of Akt2 function and GSK-3β activation, which ultimately causes abnormalities in the cardiac insulin signal delivery.[32] Akt is a key enzyme for the regulation of apoptosis,[96] and the activated Akt can promote cell survival in multiple cell types and prevent apoptosis by protecting the cells from a variety of apoptotic stimuli.[97,98] The insulin-mediated PI3K/Akt signaling pathway primarily regulates the synthesis and storage of proteins, carbohydrates, and lipids. As IR is an early feature of T2DM, the identification and inhibition of negative regulators of this pathway might be of great therapeutic interest.[99] Ma et al[1] observed that, during the development of DN lesions, the *Trib3* gene could suppress the phosphorylation of PI3K and Akt, thereby promoting cellular inflammation and extracellular matrix protein accumulation. Furthermore, absence of *Trib3* was associated with the enhanced phosphorylation of Akt residue Ser473; TRIB3 could reduce the gene expression levels of albuminuria and inflammation in DN through a mechanism involving inhibition of the mTORC2/Akt pathway.[30] Meanwhile, TRIB3 could also reduce glucose tolerance, decrease insulin sensitivity, increase IR, and inhibit Akt activation, thereby aggravating DCM and T2DM.[19,98] Additionally, chronic ethanol intake can also increase the expression of TRIB3, which, by binding to Akt, can prevent its plasma membrane association, Akt-Thr308 phosphorylation, and subsequent Akt-mediated signaling. This resulted in maintaining GSK-3 activation, GSK-3-induced phosphorylation of sterol-regulatory element-binding protein 1 (SREBP-1c), decreasing the abundance of nuclear SREBP-1c, thereby disinhibiting alcohol dehydrogenase gene transcription.[91] In summary, because of the decisive role it plays in the Akt pathway, TRIB3 might be an important target for DM and IR.

TRIB3-MAPK signaling pathways. Mounting evidence indicates that IR is associated with the development of both T1DM and T2DM.[100] Besides Akt, MAPK is also an important pathway involved in IR.[101] Under normal conditions, TRIB3 acts as a scaffold protein and regulates the activation of MAPK.[102] However, ERK1/2, a member of the MAPK family, can be activated in the presence of HG.[103] Ti et al[31] illustrated that the mRNA and protein expression levels of cardiac TRIB3 were upregulated in diabetic rats, and the phosphorylation levels of ERK1/2 and c-Jun N-terminal kinase (JNK) were significantly increased, while the level of p38 MAPK was significantly decreased. Therefore, it was speculated that TRIB3 activation might be involved in the development and progression of DCM through the MAPK pathway. MAPK also plays a crucial role in collagen synthesis and cardiac fibrosis, and is known as an important mediator of fibrosis.[104–108] A previous study showed that ERK activity might enhance TGF-β1–dependent responses, and TRIB3 might upregulate the expression levels of fibrosis cytokine TGF-β1 and collagen type IV via the ERK1/2-MAPK signaling pathway,

thereby participating in the renal fibrosis of DN.[17] However, inhibiting TRIB3 could partially reverse the MAPK-regulated expression levels of collagen types I and III, suggesting that the TRIB3/MAPK signaling pathway might be involved in regulating collagen types I and III via AGEs. This might provide new strategies for the treatment of DCM.[15]

β-*Cell apoptosis–related signaling pathways.* The American Diabetes Association defines T1DM as autoimmune β-cell destruction, usually leading to absolute insulin deficiency, and T2DM as progressive loss of β-cell insulin secretion, frequently occurring in the context of IR.[109] Therefore, elucidating the underlying molecular mechanism of β-cell apoptosis might help in understanding the etiology of DM. Numerous recent studies have described that the complex signaling regulatory network of ER stress, cytokines, and chronic exposure to FFAs might induce β-cell apoptosis and are involved in the progression of DM.[110–112]

Emerging evidence revealed that the prolonged ER stress in β cells could increase their sensitivity to apoptosis and contribute to DM development.[113–115] During ER stress, the NF-κB pathway plays a vital role in the apoptosis of β cells. A recent study indicated that the overexpression of *Trib3* in rat INS-1–derived cells could increase the nuclear translocation of NF-κB, playing a proapoptotic role, which was even more prominent under ER stress conditions. This suggested that TRIB3-mediated ER stress could induce β-cell apoptosis through the NF-κB pathway.[47] Accumulating evidence suggests that the cytokine-induced mixed-lineage kinase 3 (MLK3)–JNK pathway could effectively reduce the cellular defense and increase the potency of subsequent inflammatory events, resulting in impaired glucose homeostasis and reduced insulin sensitivity.[116–119] Moreover, in the absence of *Trib3*, the increased activity of Akt could rapidly induce MLK3 degradation, decreasing the total amount of MLK3 available for JNK activation. This suggested that TRIB3 was required for the activation of MLK3-JNK for optimal kinetics to enable cell death.[52] FFAs might induce the dysfunction and apoptosis of β cells in T2DM. Saturated FFAs can upregulate TRIB3 expression, which is also associated with an increase in the apoptosis of β cells. The activation and nuclear accumulation of PKCδ could also be enhanced by the upregulation of TRIB3. Inhibiting the PKCδ nuclear translocation and its selective antagonist could significantly reduce the proapoptotic effects.[53] Collectively, TRIB3-related signaling pathways, such as NF-κB, JNK, and PKCδ, might play a crucial role in the apoptosis of β cells. The possible pathways of TRIB3 action in the development of DM and its complications are shown in Fig. 3.

Antidiabetic effects of natural products targeting TRIB3 function

Although various drugs have been used for the treatment of T1DM and T2DM, novel antidiabetic drugs are currently emerging. In particular, natural products, such as fruits, vegetables, herbal medicines, and their active ingredients, are widely accepted as adjuncts to conventional treatments due to their antidiabetic properties with minimal toxicity and fewer adverse effects and are used worldwide.[120–122] Winiarska-Mieczan et al[123] demonstrated that the regular consumption of tea or dietary supplements containing tea polyphenols could combat oxidative stress and inflammation in the body and had a positive effect on improving DM. These compounds are widely found in vegetables, herbs, fruits, and other plant-based foods and are increasingly being applied for the treatment of DM. The underlying effects of natural products as dietary supplements against DM occur through various targets, among which TRIB3 might be an important player.

Yacon. Among the various natural products, yacon, a perennial plant with a lower caloric value and a high fiber content, has shown a wide range of therapeutic effects against DM and DM-related complications in animal studies.[124–127] In a recent study, concentrated yacon syrup, extracted and concentrated from the yacon tubers, could improve IR and reduce body weight in obese individuals.[128] Researchers suggested that yacon supplementation might effectively increase hepatic insulin sensitivity and reduce hepatic glucose production. Mechanistically, in yacon-fed rats, the phosphorylation of Akt increased uniformly, while the expression levels of TRIB3 in the liver was decreased, providing a physiological mechanism for the beneficial effects of yacon dietary supplementation on T2DM in humans.[129]

Resveratrol. Resveratrol is another naturally occurring polyphenolic compound present in grape skins as well as in various other plants and fruits, such as soybeans, peanuts, pomegranates, and aster. The mechanisms of resveratrol to regulate blood glucose levels and improve insulin sensitivity have gained great attention of researchers. Resveratrol could activate SIRT1 in vivo, which acts downstream of energy deprivation and has beneficial effects on glycemic control.[130,131] In addition, resveratrol could also stimulate glucose uptake by increasing the expression levels of glucose transporters,[132] thereby activating the Akt and AMPK signaling pathways to regulate energy expenditure.[133] Moreover, resveratrol-treated, high-fat-diet–fed mice showed reduced levels of TRIB3 and ER stress in the liver,

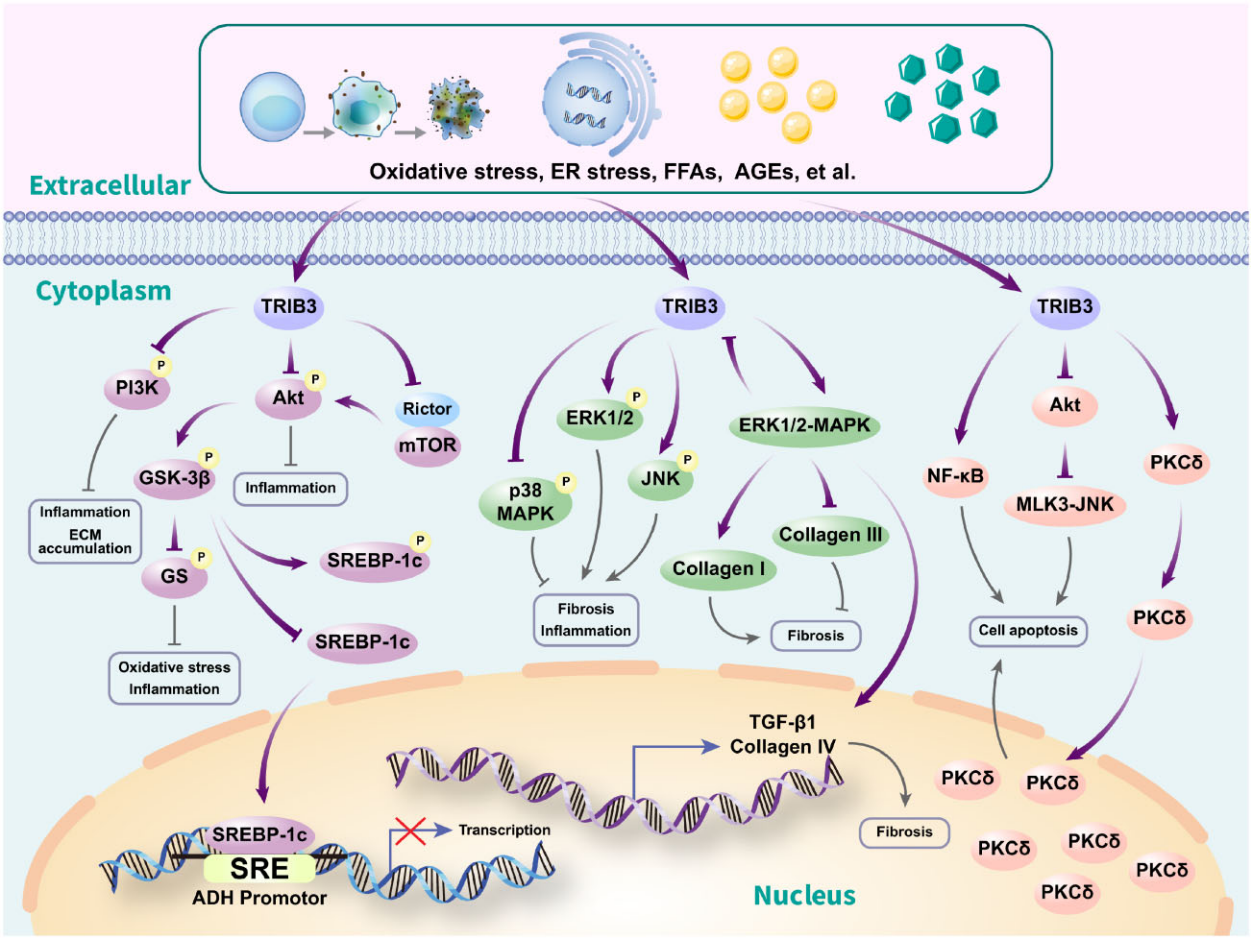

Figure 3 **The possible pathways of TRIB3 in the development of DM and its complications.** *Abbreviations*: ADH, alcohol dehydrogenase; Akt, protein kinase B; DM, diabetes mellitus; ERK1/2, extracellular signal-regulated kinase 1/2; GSK-3β, glycogen synthase kinase-3β; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MLK3, mixed lineage kinase-3; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor-kappa B; P, phosphorylation; PI3K, phosphatidylinositol 3-kinase; PKCδ, protein kinase C δ; SREBP-1c, sterol-regulatory element-binding protein-1; TGF-β1, transforming growth factor β1; TRIB3, tribbles homolog 3.

resulting in increased insulin sensitivity and glucose levels.[134]

Shengmai san. Shengmai san consists of 3 traditional Chinese herbs: *Ginseng radix*, *Ophiopogon japonicus*, and *Fructus schisandrae*. A previous study demonstrated that Shengmai san exhibited a variety of pharmacological activities, such as antioxidant and anti-inflammatory activities.[135] It could also improve myocardial fibrosis and ventricular remodeling in diabetic mice.[136] Recent studies showed that Shengmai san could ameliorate lipid metabolism. In a high-fat-diet–induced DCM rat model established by the intraperitoneal injection of high-dose streptozotocin, the expression levels of TRIB3 were significantly upregulated, while Shengmai san supplementation could significantly decrease the expression levels of TRIB3 as well as blood glucose levels, cholesterol, and triglycerides, thereby significantly delaying the development of DCM in hyperglycemic rats through multiple pathways.[137] Collectively, further investigation is needed to explore the antidiabetic activities of Shengmai san.

Micronutrient zinc. It has been shown that there is an intricate correlation between the micronutrient zinc and insulin hexamer structure.[138] The highest amount of zinc in the human body is present in pancreatic β cells, and DM has been characterized by zinc deficiency.[139] Accumulating evidence suggests that micronutrient zinc supplementation might play a significant role in preventing IR and DM.[139,140] Mechanistically, it can affect the synthesis and action of insulin by promoting proper insulin hexamerization and processing, both physiologically and in DM, which can stimulate insulin action and insulin receptor tyrosine kinase activity.[141,142] Most importantly, zinc is the major microelement that binds to metallothionein (MT) under physiological conditions.[143] A study on streptozotocin-

Table 1 **Antidiabetic effects of natural products targeted by TRIB3 in the development of DM and its complications**

Natural products	Animal species	Animal or cellular model	Natural product dose	Treatment period	Effect on expression of TRIB3	Reference
Yacon	Zucker *fa/fa* rats	6-wk-old male Zucker *fa/fa* rats display pronounced IR	6.5% of yacon incorporated in feed pellet preparation	5 wk	Inhibition	[129]
RES	C57BL/6J mice and HepG2 cells	HFD-induced IR model, PA-induced IR model	60 mg/kg, 20 μM	12 wk, 24 h	Inhibition	[134]
SMS	Male SD rats	HFD for 4 wk with intraperitoneal injection of 50 mg/kg STZ-induced DCM rat model	7.5 mL/kg	8, 11, 14 wk	Inhibition	[137]
Zinc	FVB background mice	Male *db/db* mice	10% kcal %fat plus Zn, 90 mg/4057 kcal	3 mo	Inhibition	[32]

Abbreviations: DCM, diabetic cardiomyopathy; FVB, friend virus B; HFD, high-fat diet; IR, insulin resistance; PA, palmitate; RES, resveratrol; SMS, shengmai san; STZ, streptozotocin.

induced diabetic mice observed that chronic supplementation with zinc could mediate cardiac MT induction, thereby preventing cardiac pathological changes and dysfunction, and protecting against DCM.[144] Moreover, our previous study demonstrated that the DM-inhibited cardiac Akt2 function via TRIB3 upregulation led to aberrant cardiac glucose metabolism; supplementation of zinc to induce MT significantly protected against all DM-induced cardiac structural and functional changes via the TRIB3-Akt signaling pathway, thereby alleviating DCM.[32] Although it is now well accepted that the supplementation of zinc exhibits a crucial involvement in preventing DM, the precise mechanisms and optimal dose of zinc supplementation during the process of DM treatment and its complications remain unresolved. The antidiabetic effects of natural products targeted by TRIB3 are detailed in Table 1.

It is worth noting that numerous studies on natural products have been conducted on rodents, and the findings have not been validated in humans. In particular, there is a lack of randomized, placebo-controlled human clinical trials involving the use of natural products to treat DM and its complications.

CONCLUSIONS AND FUTURE PERSPECTIVES

Diabetes mellitus has become a major global epidemic of this century. Exploring the complexity of dietary nutrition and the TRIB3 signal transduction pathway has shown their correlations and importance in DM. Although some of these questions remain to be answered, the crosstalk between dietary nutrition and TRIB3 signaling is surprising. In conclusion, in-depth studies on the regulation network of dietary nutrition and the TRIB3 signaling pathway might provide novel therapeutic strategies for the prevention and treatment of DM.

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Abbreviations: DCM, diabetic cardiomyopathy; DM, diabetes mellitus; DN, diabetic nephropathy; ER, endoplasmic reticulum; ERK1/2, extracellular signal-regulated kinase 1/2; FA, fatty acid; FFA, free fatty acid; GSK, glycogen synthase kinase; HG, high glucose; IR, insulin resistance; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; PKC, protein kinase C; ROS, reactive oxygen species; T1DM, type 1 diabetes mellitus; T2DM,

type 2 diabetes mellitus; TRIB3, tribbles homolog 3; UPR, unfolded protein response; VSMC, vascular smooth muscle cell.

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