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Diabetes pathogenic mechanisms and potential new therapies based upon a novel target called TXNIP

Lance Thielen and Anath Shalev

Comprehensive Diabetes Center and Department of Medicine, Division of Endocrinology, Diabetes, and Metabolism, University of Alabama at Birmingham, Birmingham, Alabama

Abstract

Purpose of review—Thioredoxin-interacting protein (TXNIP) has emerged as a major factor regulating pancreatic beta cell dysfunction and death, key processes in the pathogenesis of type 1 and type 2 diabetes. Accumulating evidence based on basic, pre-clinical and retrospective epidemiological research suggests that TXNIP represents a promising therapeutic target for diabetes. The present review is aimed at providing an update regarding these developments.

Recent findings—TXNIP has been shown to be induced by glucose and increased in diabetes and to promote beta cell apoptosis, whereas TXNIP deletion protected against diabetes. More recently, TXNIP inhibition has also been found to promote insulin production and glucagon-like peptide 1 signaling via regulation of a microRNA. Beta cell TXNIP expression itself was found to be regulated by hypoglycemic agents, carbohydrate-response-element-binding protein and cytosolic calcium or the calcium channel blocker, verapamil. Retrospective studies now further suggest that verapamil use might be associated with a lower incidence of type 2 diabetes in humans.

Summary—TXNIP has emerged as a key factor in the regulation of functional beta cell mass and TXNIP inhibition has shown beneficial effects in a variety of studies. Thus, the inhibition of TXNIP may provide a novel approach to the treatment of diabetes.

Keywords

TXNIP; diabetes; functional beta cell mass; therapeutic target; microRNA

Introduction

Loss of functional beta cell mass is a hallmark of both type 1 and type 2 diabetes (1-6). Thus, an attractive treatment for diabetes would be to promote functional beta cell mass by decreasing the elevated levels of beta cell apoptosis associated with this disease. A promising target that has recently emerged in this area of research is thioredoxin-interacting protein (TXNIP) (7, 8). In this review, we discuss the physiological role of TXNIP and

Address Correspondence to: Anath Shalev, M.D. Professor and Director, Comprehensive Diabetes Center, University of Alabama at Birmingham, 1825 University Blvd, SHELBY Bldg 1206, Birmingham, AL 35294-2182, Phone: (205) 996-9546, Fax: (205) 996-5220, shalev@uab.edu.

Conflicts of interest

There are no conflicts of interest.

recent studies regarding the impact of TXNIP on beta cell biology and as a therapeutic target in diabetes.

Physiological Role and Regulation of TXNIP

In 1994, the gene encoding what is most commonly known as TXNIP was first cloned from HL-60 cells stimulated with 1,25-dihydroxyvitamin D-3, thus earning it the name Vitamin-D upregulated protein 1 (VDUP1) (9-11). However, subsequent TXNIP promoter analysis did not uncover a consensus vitamin D response element (10) and vitamin D-induced TXNIP transcription has not been shown in other cell types. Currently, TXNIP is most commonly known as a 50kDa ubiquitously expressed protein that is highly conserved across species (10) and plays a vital role in regulating cellular redox status through binding and negatively regulating thioredoxin (Trx) (11-15). Because of its ability to act as a cellular redox regulator, TXNIP has been thought to be localized in the cytoplasm (13, 16, 17); although, it has been shown that TXNIP can translocate between cellular compartments (18).

In 2002, TXNIP was identified in human pancreatic islets as the highest glucose-induced gene in a gene expression microarray (19). TXNIP's upregulation by glucose was later confirmed by quantitative real-time RT-PCR as well as immunoblotting in both INS-1 beta cells and primary human islets (20-22). This glucose-induced TXNIP response was found to be mediated by a cis-acting element consisting of a well-conserved E-box repeat contained in the TXNIP promoter and carbohydrate response element-binding protein (ChREBP) was identified as the trans-acting factor (20). In response to glucose, ChREBP becomes dephosphorylated allowing it to translocate from the cytosol into the nucleus and bind to this E-box repeat (23). Furthermore, TXNIP is able to stimulate its own expression via a positive feedback loop involving activation of ChREBP (24). Moreover, type 1 diabetes associated inflammatory cytokines also promote beta cell TXNIP expression primarily via ChREBP (25). On the other hand, mammalian target of rapamycin (mTOR) has recently been observed to decrease TXNIP by regulating ChREBP expression (26). While ChREBP is predominantly expressed in beta cells (23), liver (27, 28), and adipose tissue (28, 29), its paralog, MondoA, is predominantly expressed and responsible for TXNIP induction in skeletal muscle and heart (30). Interestingly, this year TXNIP was also identified by genome-wide gene expression profiling in skeletal muscle to be downregulated by exercise, an effect that seems to be mediated by hypoxia-inducible factor 1a (31).

High glucose has been observed to confer beta cell dysfunction and apoptosis, and TXNIP plays a pivotal role in mediating these detrimental effects of glucose toxicity primarily via the mitochondrial death pathway (18). In fact, TXNIP was found to translocate to the mitochondria, where it competes with ASK1 (apoptosis signaling-regulating kinase 1) for binding of Trx2. The subsequent release and activation of ASK1 initiates a downstream apoptotic cascade, thus leading to the death of the beta cell (18). TXNIP has also been found to lead to NLRP3 inflammasome activation, resulting in caspase-1 activation and IL-1beta production (32, 33). IL-1beta, in turn, has been shown to play an important role in the pathogenesis of both type 1 and type 2 diabetes (32-35). While initially thought to be produced in the beta cell (36), NLRP3 expression and IL-1beta production are primarily observed in innate immune cells (37-39). It is conceivable though that TXNIP-induced

IL-1 β production and inflammasome activation is present in resident macrophages of the intact islet, but it is less likely this event is taking place in the beta cells themselves.

Recently, additional TXNIP-dependent mechanisms of beta cell dysfunction and death have been identified, several of which have been linked to microRNAs. Insulin production was shown to be downregulated by TXNIP as TXNIP induces expression of miR-204, which in turn targets and decreases expression of MafA, the main insulin transcription factor (40). Most recently, miR-204 has also been discovered to target and downregulate glucagon-like peptide 1 receptor (GLP1R) expression and by doing so to inhibit GLP-1 agonist mediated insulin secretion (41). Islet amyloid polypeptide, which promotes beta cell inflammation and toxicity and is found in type 2 diabetic islets (42-44), is upregulated by TXNIP through miR-124a and FoxA2 (45). Also, TXNIP has been shown to increase miR-200 leading to beta cell apoptosis (46). On the other hand, TXNIP is a target of miR-17. Activation of inositol-requiring enzyme 1 α (IRE1 α) in the context of endoplasmic reticulum (ER) stress and unfolded protein response leads to destabilization of miR-17, which results in upregulation of TXNIP (32). In non-beta cells, similar effects have been observed with miR-20a, a member of the miR-17-92 cluster (47).

Beta cell TXNIP expression is increased in diabetes (20, 40, 48-50) and overexpression of TXNIP has been shown to result in apoptosis, especially in beta cells (20, 51), which is consistent with their particular susceptibility to oxidative stress (52). Elevated TXNIP levels are therefore thought to be an important factor in the pathogenesis of diabetic beta cell loss and the development of diabetic complications. Indeed, mutation or genetic deletion of TXNIP has been shown to prevent diabetes in a variety of mouse models including type 1 and type 2 diabetes (49). TXNIP-deficient HcB-19 mice as well as beta cell-specific TXNIP knockout mice have increased beta cell mass, decreased beta cell apoptosis, elevated insulin levels, and are protected against STZ-induced diabetes (49). In addition, beta cell-specific overexpression of thioredoxin in non-obese diabetic (NOD) mice has also been shown to protect against autoimmune diabetes (53). TXNIP deletion has also been observed to reduce beta cell apoptosis and diabetes in Akita mice, whose diabetes is due to insulin misfolding and ER-stress (32). Even in the stringent, leptin-deficient type 2 diabetic BTBRob/ob mouse model, characterized by severe obesity, insulin resistance and hyperglycemia (54), TXNIP deficiency led to a decrease in beta cell apoptosis, increase in beta cell mass and protection against diabetes (49).

Given these beneficial effects of TXNIP deletion and the many detrimental effects associated with elevated TXNIP, the question arises as to what the physiological role of this protein might be and why we even express it. However, in prehistoric times TXNIP may have provided an evolutionary advantage by contributing to the host's protective shield. TXNIP-induced oxidative stress could be viewed as a protective cellular defense mechanism against microbes and keeping beta cell mass and insulin production in check would be beneficial during periods of food scarcity and famine to prevent hypoglycemia and assure survival. Consistent with this notion, TXNIP deficient mice are more sensitive to starvation (55). Also, TXNIP has been found to be upregulated in multiple tissues during torpor and prolonged fasting and plays an important role in fuel partitioning and regulation of energy expenditure especially in the hypometabolic state (56-59). In contrast, in more recent times

of excess energy- and glucose-rich foods and sedentary life-style, TXNIP expression may easily surpass the very low, if at all present, need for TXNIP under these conditions and start contributing to the metabolic risk and the development of diabetes by promoting beta cell dysfunction and impairing glucose homeostasis. On the other hand, having recognized at least some of the implications that elevated TXNIP has for the pathogenesis of diabetes, may allow us to use TXNIP as a novel drug target for diabetes going forward (Figure 1).

Pharmacological Regulation of TXNIP

A number of hypoglycemic agents have been shown to decrease TXNIP. In fact, insulin has been reported to decrease TXNIP mRNA and protein levels in vitro (50); although, hyperglycemia seems to supersede insulin's effect on TXNIP in beta cells, as TXNIP continues to remain elevated in diabetes even in the context of in vivo hyperinsulinemia (48, 49). The biguanide metformin, a first-line oral agent to treat type 2 diabetes, has been shown to decrease glucose-induced TXNIP mRNA and protein levels in beta cells through its ability to activate AMPK (60, 61). Furthermore, it has been shown in various cell types that metformin decreases glucose-induced nuclear entry and binding of the TXNIP transcription factor ChREBP (or its paralog MondoA) to the TXNIP promoter, which is thought to be at least partially due to the effects of metformin on AMPK activation (60, 62).

Very recent work has shown that TXNIP downregulation promotes GLP1R signaling in the beta cell (41). Furthermore, GLP-1 agonists, such as exendin-4, have been shown to reduce TXNIP levels and protect against beta cell death (63, 64). Exendin-4 activates cAMP signaling, as well as protein kinase A, resulting in TXNIP ubiquitination and proteasomal degradation (64). This reduction of TXNIP results in decreased susceptibility of beta cells to glucotoxicity (64). Dipeptidyl-4 inhibitors, such as sitagliptin have also recently been reported to decrease cytokine-induced TXNIP and caspase 3/7 activity in INS-1E cells by preserving sarco-endoplasmic reticulum calcium ATPase (SERCA) activity and decreasing cytosolic calcium levels (65).

Interestingly, TXNIP had previously been found to be downregulated in response to a decrease in cytosolic calcium levels and by calcium channel blockers such as the widely used blood pressure medication, verapamil (66). These effects were not agent or class specific, were not restricted to L-type calcium channel blockers such as verapamil, and could be mimicked by calcium chelators. As such, verapamil is believed to decrease beta cell TXNIP expression by reducing cytosolic calcium, which in turn controls calcineurin/calcium-dependent protein phosphatase 2B signaling and leads to increased phosphorylation and nuclear exclusion of ChREBP and results in decreased ChREBP mediated TXNIP transcription. Indeed, the calcineurin inhibitor, cyclosporine A effectively mimicked the effects of verapamil on TXNIP transcription and ChREBP nuclear exclusion. In vivo, verapamil was found to not only prevent multiple low-dose STZ-induced diabetes, but also to rescue overtly diabetic mice by decreasing beta cell apoptosis, increasing beta cell mass and elevating insulin levels. Similar effects were also observed when verapamil was administered to BTBRob/ob mice as a model of type 2 diabetes (66).

While these findings raised the question as to why such beneficial effects of calcium channel blockers had not been described in diabetic patients before, it is important to remember that for antihypertensive medications, the primary and secondary outcomes monitored are most commonly mortality and cardiovascular complications, not metabolic regulation or diabetes. However, several intriguing retrospective epidemiological findings have recently emerged. The International Verapamil SR-Trandolapril Study (INVEST) trial found that participants in the verapamil arm had a lower risk of developing diabetes (67, 68). In an association study using the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort, it was further revealed that diabetic verapamil users had fasting blood glucose levels that were up to 37mg/dL lower as compared to diabetic subjects not on calcium channel blockers (69). Most recently, using Taiwan's National Health Insurance Research Database, it was observed that verapamil use was associated with reduced incidence of newly diagnosed type 2 diabetes especially in patients older than 65 years (70). While these observations combined with all the pre-clinical data make it tempting to speculate that verapamil may also have beneficial effects in human diabetes, only the results of properly controlled prospective studies such as the currently ongoing randomized double-blind placebo controlled phase II trial in type 1 diabetic patients will be able to determine whether verapamil also promotes functional beta cell mass and has protective effects in human diabetes. If so, this obviously would provide a completely novel, yet easily translatable and cost-effective additional approach to diabetes management.

Considerations of Targeting TXNIP as a Novel Approach to Diabetes

While verapamil provides a realistic investigational possibility for in vivo TXNIP inhibition as it is already FDA approved as an antihypertensive medication, this also might limit its use in some diabetic patient populations, such as children and adult subjects with severe ventricular dysfunction or hypotension. Also, the possibility of potential adverse effects due to inhibition of a ubiquitously expressed pro-apoptotic protein has to be considered. However, TXNIP inhibition has been shown to have beneficial effects beyond the beta cell including various extrapancreatic tissues (71-74), such as the cardiovascular system (75-80), kidney (81, 82), and retina (83, 84), making a beta cell-specific approach unnecessary and even undesirable. Furthermore, while complete whole body TXNIP deficiency has been associated with an elevated risk later in life of developing hepatocellular carcinomas in the HcB-19 mice (85), it does not seem to lead to other malignancies typically associated with inhibition of a pro-apoptotic tumor-suppressor gene such as lymphomas or leukemias. Importantly, since the goal of any pharmacological TXNIP inhibition is to normalize pathologically elevated TXNIP levels back to physiological levels, side effects from low TXNIP expression would be extremely unlikely. The most recent findings that TXNIP and/or miR-204 inhibition can specifically induce expression of GLP1R in the beta cell also raises the intriguing possibility that TXNIP inhibition could be used in combination with GLP-1 agonists to amplify their desired effects on the beta cell, reduce the necessary dose and thereby possibly avoid some of the common dose-dependent GLP-1 side effects.

Conclusion

The emergence of TXNIP as a viable therapeutic target to promote functional beta cell mass has been strongly supported by numerous studies showing its impact on beta cell biology and diabetes development. TXNIP is rapidly induced by glucose, is elevated in diabetes, and results in beta cell apoptosis, whereas normalizing TXNIP to basal levels reverses these deleterious effects. Much about TXNIP biology has been learned over the last 15 years since it was found to be induced by glucose in human pancreatic islets. TXNIP has gone from a hit in an oligonucleotide gene expression microarray, to being a recognized factor linking glucotoxicity and beta cell apoptosis, preventing and reversing diabetes in mice, regulating insulin production and secretion via microRNAs, and serving as the therapeutic target in a phase II diabetes trial. Together, these recent advances have positioned TXNIP as an exciting and promising candidate for diabetes drug discovery and development.

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Key Points

- TXNIP expression is induced by glucose and TXNIP levels are pathologically elevated in diabetes.
- TXNIP downregulation has beneficial effects on functional beta cell mass as well as on extrapancreatic tissues in the context of diabetes.
- Multiple TXNIP-dependent mechanisms of beta cell dysfunction and death are mediated by microRNAs.
- TXNIP inhibition has emerged as a viable therapeutic target for promoting functional beta cell mass in humans and is currently being evaluated in pre-clinical and clinical trials.

Fig. 1.
Schematic of the predicted changes in the role of TXNIP over time.