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FORUM REVIEW ARTICLE

Thioredoxin-Interacting Protein in Cancer and Diabetes

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Abstract

Significance: Thioredoxin-interacting protein (Txnip) is an α-arrestin protein that acts as a cancer suppressor. Txnip is simultaneously a critical regulator of energy metabolism. Other alpha-arrestin proteins also play key roles in cell biology and cancer.
Recent Advances: Txnip expression is regulated by multilayered mechanisms, including transcriptional regulation, microRNA, messenger RNA (mRNA) stabilization, and protein degradation. The Txnip-based connection between cancer and metabolism has been widely recognized. Meanwhile, new aspects are proposed for the mechanism of action of Txnip, including the regulation of RNA expression and autophagy. Arrestin domain containing 3 (ARRDC3), another α-arrestin protein, regulates endocytosis and signaling, whereas ARRDC1 and ARRDC4 regulate extracellular vesicle formation.
Critical Issues: The mechanism of action of Txnip is yet to be elucidated. The regulation of intracellular protein trafficking by arrestin family proteins has opened an emerging field of biology and medical research, which needs to be examined further.
Future Directions: A fundamental understanding of the mechanism of action of Txnip and other arrestin family members needs to be explored in the future to combat diseases such as cancer and diabetes. *Antioxid. Redox Signal*. 36, 1001–1022.

Keywords: thioredoxin-interacting protein (Txnip, thioredoxin-binding protein-2, TBP-2), α-arrestin, cancer, RNA, autophagy, ARRDC3, thioredoxin

Introduction

METABOLISM IS RECOGNIZED as a new hallmark of cancer (52). Warburg has described enhanced, accelerated conversion of glucose to lactate in malignant tumors even in the presence of abundant oxygen (163). This phenomenon has been confirmed by metabolomics approaches in colon and stomach cancer (54). The extent of the Warburg phenotype is different in different tumor cells, while even in single cells within a single tumor. Accelerated aerobic glycolysis is not a primary consequence of dysfunctional or impaired mitochondria, but for many tumor types, oxidative phosphorylation or at least certain segments of mitochondrial metabolism are essentially required by cancer cells. In most tumors, the Warburg effect is an essential part of a metabolic reprogramming, and includes many changes, including acceleration of glycolytic fluxes, adequate ATP generation, and biosynthesis of nucleotides, nonessential amino acids, lipids, and hexosamines (9, 156, 157). Since the metabolic regulation in cancer is a new therapeutic target against cancer, the mechanism interconnecting cancer and metabolism is a key issue to be investigated (52, 103, 156). Among several metabolic changes exploited by cancer, glucose metabolism seems most important. It is well known that cancer cells have augmented tendency to uptake glucose, largely mediated by enhanced activity of glucose transporters (GLUTs). Function

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of GLUTs is considered largely by their recruitment to the cellular membrane in normal cells. However, the precise molecular mechanism how glucose metabolism is altered in cancer is not completely elucidated.

We identified thioredoxin-binding protein-2 (TBP-2) (108) as a protein that interacts with thioredoxin, which is an important regulator of the cellular oxidation/reduction (redox) system (36, 55, 146). The redox-regulating activity of thioredoxin-interacting protein (Txnip) is one aspect of its function (108, 182). TBP-2 is identical to vitamin D_3 upregulated protein-1 (VDUP1) (27) and is also referred to as *Txnip* (12). The gene name for *TBP-2/VDUP1/Txnip* was registered as Txnip in the National Center for Biotechnology Information (NCBI) database. In this review, the gene is referred to as *Txnip*.

Txnip is a multifunctional protein that plays a regulatory role in immunity and a pathophysiological role in cardiovascular (159) and neurodegenerative diseases (153). Txnip regulates various aspects of metabolism, especially glucose uptake (25, 32, 118, 120, 181), presumably through the regulation of GLUTs (99, 169). It is worth noting that *Txnip* is proven to be one of the most susceptible genes for glucose-induced transactivation (20, 69, 97, 141).

Txnip simultaneously acts as a tumor suppressor (4, 30, 92, 149, 164, 180, 189, 190). Txnip demonstrates growth-suppressive activity (50, 106–108), and its augmented expression is associated with apoptosis (14, 25, 31, 93, 97, 162). A common feature of Txnip in many cancer types is the suppression of Txnip expression associated with disease progression. Txnip messenger RNA (mRNA) expression is downregulated in colorectal cancer (147), primary breast and colon tumors (14, 60), breast, lung, and stomach cancers (50), human T-cell leukemia virus type 1 (HTLV-I)-infected interleukin (IL)-2–independent T cells (107), cutaneous T-cell lymphoma (140), and prostate cancer cells (171). In many types of cancer, the lower the expression, the grade of cancer is more advanced.

Several pieces of evidence demonstrate that *Txnip* deficiency augments glucose uptake, as written above. Thus, Txnip are considered to explain the deterioration of glucose metabolism in cancer cells. We here emphasize the role of Txnip in cancer, especially in the interconnection between cancer and metabolism. Meanwhile, the precise molecular mechanism of action of Txnip is not fully elucidated. Here, we review the 10 years of advances of Txnip research, including newly identified modes of the regulation of Txnip. Approaches against diseases facilitated by Txnip research are briefly summarized. Txnip has arrestin domains and belongs to α-arrestin family, including Txnip, arrestin domain containing 1 (ARRDC1), ARRDC2, ARRDC3 (114), ARRDC4 (174), and ARRDC5 (5). We also introduce some topics of other α-arrestin members in association with cancer and metabolism. The key outline of this review is summarized in Table 1.

Table 1. Key Notes of This Review

(1) *Txnip* is the gene to protect from starvation.
(2) *Txnip* is the most representative gene induced by glucose.
(3) Txnip suppresses glucose uptake.
(4) Txnip accumulation worsens diabetes.
(5) Txnip acts as a tumor suppressor largely through the control of glucose utilization.
(6) Txnip expression is regulated in multilayered mechanisms such as transcription, microRNA, mRNA stabilization, and protein degradation.
(7) Txnip promotes autophagy.
(8) Txnip may regulate mRNA and long noncoding RNA expression.
(9) Alpha arrestin family proteins regulate intracellular trafficking, including endocytosis and microvesicular formation.

mRNA, messenger RNA; Txnip, thioredoxin-interacting protein.

Txnip as a Critical Regulator of Metabolism and as the Frugality Gene

Many features of Txnip are consolidated into three important functions: fasting response, metabolic control, and cancer suppression. A drawing that can briefly explain Txnip functions is shown in Figure 1.

Fasting response

Txnip was identified as a causative gene for the familial combined hyperlipidemia (FCHL) HcB-19 mouse model with a nonsense mutation in the *Txnip* gene and lacking *Txnip* expression (12). However, mutation of *Txnip* was not detected in human families with hyperlipidemia (33, 117, 154). Curiously, the gene mutation was identified in a family with lactic acidosis (72). *Txnip*$^{-/-}$ mice are predisposed to death from hyperlipidemia, hypoglycemia, bleeding tendency, and hepatorenal insufficiency on fasting (113). Gene chip analyses of the liver from *Txnip*$^{-/-}$ mice showed that considerable numbers of Txnip-regulated genes are fasting-response genes. *Txnip* itself is one of the genes most upregulated during fasting. Fasted HcB-19 mice are also hypoglycemic and hypertriacylglyceridemic, possessing higher levels of ketone bodies (57, 136). These results show that Txnip is a critical regulator of fasting responses.

Glucose uptake

Txnip expression is induced by glucose, and the *Txnip* gene is considered the most representative model for glucose response (20, 69, 97, 141). *Txnip* plays a regulatory role in insulin sensitivity (58, 115). Knockdown of Txnip expression was found to enhance glucose uptake in cultured adipocytes and primary human skeletal muscle myocytes, whereas Txnip overexpression inhibited glucose uptake (118). HcB-19 mice or *Txnip*$^{-/-}$ mice crossed with ob/ob mice showed improved glucose tolerance (25, 181). Augmented glucose transport was identified in the adipose tissue and skeletal muscle of *Txnip*$^{-/-}$ mice (32). Skeletal muscle glucose uptake was increased in *Txnip*$^{-/-}$ mice (57). The suppression of Txnip expression is reported to increase GLUT1 function (169) and GLUT1 plasma membrane distribution (99). Furthermore, Txnip functions as an adaptor for the basal endocytosis of GLUT4 *in vivo*, its absence allows excess glucose uptake in muscle and adipose tissues, causing hypoglycemia during fasting (158). Thus, Txnip upregulation undoubtedly suppresses glucose uptake (118, 120). These results collectively provide an idea that Txnip is an important sensor and regulator of glucose metabolism. When individual intakes enough amount of food, upregulated Txnip seems to serve as a sensor to suppress to uptake glucose in muscle and adipose

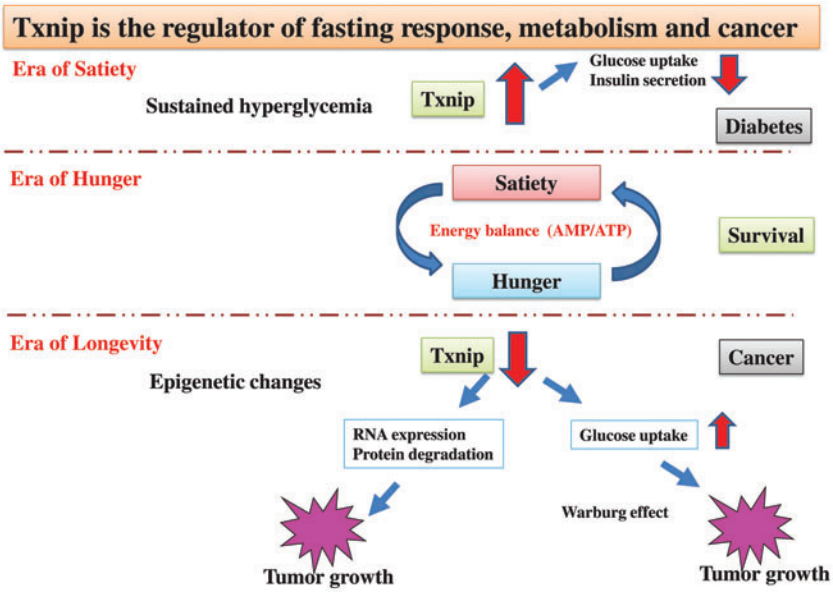

FIG. 1. Txnip is a regulator of fasting responses, metabolism, and cancer. In the era of hunger, *Txnip* is a critical survival gene to protect against fasting, and acts as a feedback regulator to utilize glucose within an appropriate range and maintain energy balance (AMP/ATP ratio). In the era of satiety, sustained hyperglycemia, which is not expected in the era of hunger, may cause Txnip to exert unanticipated effects in metabolism. In periods of satiety, sustained hyperglycemia induces augmented Txnip expression, causing suppression of glucose uptake of muscle and adipose tissues and insulin secretion from pancreatic β-cells, leading to an increased risk of diabetes. Here, we are in the era of longevity. The *Txnip* gene is downregulated mainly by epigenetic mechanisms in cancer cells, resulting in augmented glucose uptake, thus favoring tumor growth. Decreased expression of Txnip also changes the RNA and protein expression pattern to promote tumor growth. Txnip, thioredoxin-interacting protein. Color images are available online.

tissue. The meaning of the phenomenon is only to be speculated and may be explained to avoid excess decrease of blood glucose levels.

Insulin secretion

Pancreatic β-cells are also important sites of action of Txnip, regulating insulin secretion to control glucose utilization. HcB-19 and *Txnip*$^{-/-}$ mice showed enhanced insulin secretion *in vivo* (58, 115). Serum insulin levels after glucose loading *in vivo* were enhanced in ob/ob *Txnip*$^{-/-}$ mice compared with those in ob/ob mice. In isolated pancreatic islets, *Txnip* deficiency enhanced glucose-stimulated insulin secretion in wild-type and ob/ob mice. Further, silencing of Txnip enhanced glucose-stimulated insulin secretion in INS-1 cells, whereas Txnip overexpression suppressed glucose-stimulated insulin secretion (181). In summary, Txnip suppresses glucose-induced insulin secretion. If we speculate the meaning of the regulation of Txnip in the suppression of glucose-induced insulin secretion, Txnip may serve as a feedback regulator of insulin secretion, possibly avoiding excess decrease of blood glucose levels.

Physiological role of Txnip in metabolism

As shown above, in a family with lactic acidosis, Txnip expression is abrogated by nonsense mutation in the *Txnip* gene (72), demonstrating that its deficiency is evidently nonlethal, and the major clinical symptoms are lactic acidosis and low serum methionine. Lack of *Txnip* yields a rather specific deficiency in glucose or pyruvate fueled respiration, and not in mitochondrial function *per se*, at least in the myoblasts studied. A pronounced basal activation of Nrf2 in patient myoblasts lacking *Txnip* has also been observed (72). Since the role of Txnip has been studied mostly under sustained hyperglycemia or in genetically abnormal or engineered mouse models, this work opens up a new perspective regarding the physiological role(s) of Txnip in human metabolism. Moreover, since the metabolic pathways affected by a lack of *Txnip* may be different in other tissues, the physiological role of Txnip in other tissues such as liver or pancreas needs to be further investigated. Feeding induced a physiological increase in the number of peritoneal macrophages that secreted IL-1β mediated by inflammasome, in a glucose-dependent manner. Subsequently, IL-1β contributed to the postprandial stimulation of insulin secretion (41). This study reveals a role of inflammasome in metabolic regulation in physiological settings. As discussed later, Txnip is reported to be involved in redox homeostasis, and to interact with thioredoxin and the inflammasome. The physiological role of Txnip in redox homeostasis in pancreatic beta cells appears to be an important issue for further metabolism research.

β-*Cell apoptosis*

Txnip is an important regulator of β-cell apoptosis (34). Txnip is induced by glucose to induce β-cell apoptosis (97). HcB-19 mouse islets were protected against glucose-induced apoptosis (25). Lack of *Txnip* inhibits the mitochondrial death pathway underlying β-cell glucotoxicity (24). HcB-19 mice crossed with ob/ob mice were protected from diabetes and β-cell apoptosis, resulting in an increased β-cell

mass. β-cell–specific *Txnip* knockout mice also showed an enhanced β-cell mass and revealed ~50-fold reduction in β-cell apoptosis after streptozotocin treatment (25). *Txnip*$^{-/-}$ mice also showed suppressed β-cell apoptosis (181). Many recent studies have also shown that Txnip expression in β-cells causes apoptosis. Lack of *Txnip* protects against diabetes and glucotoxicity-induced β-cell apoptosis (24, 129, 132, 181). Txnip upregulation under chronic hyperglycemia is critically involved in cellular oxidative stress, DNA damage, and retinal pericyte apoptosis (39). Collectively, *Txnip* deficiency augments glucose uptake in skeletal muscles and insulin secretion from pancreatic β-cells, and protects against β-cell apoptosis. Conversely, induced Txnip suppresses glucose uptake and insulin secretion, and augments β-cell apoptosis. In the era of hunger, *Txnip* is a critical gene to protect against fasting, acting as a feedback regulator to utilize glucose within an appropriate range. In the era of satiety, sustained hyperglycemia, which is not expected in the era of hunger, may cause Txnip to exert unanticipated effects in metabolism; that is, diabetes. As discussed later, these physiological metabolic regulatory functions of Txnip seem to be exploited by cancer cells (Fig. 1).

Txnip in Cancer Suppression

In addition to the previous accumulated reports concerning the downregulation of Txnip in various cancers (14, 50, 60, 107, 140, 147, 171), several recent reports show the decrease of Txnip expression in tumors. Txnip expression decreased in colorectal and gastric cancer, and is significantly lower in stage III and IV tumors than in stage II tumors (60). Suppression of Txnip is frequently observed in patients with hepatocellular carcinoma demonstrating C-terminal truncated hepatitis B virus X protein (Ct-HBx) expression, and is significantly correlated with a poor prognosis. Reintroduction of Txnip attenuated the metabolic reprogramming induced by Ct-HBx and inhibited tumor growth in a mouse model. Ct-HBx could downregulate Txnip *via* the transcriptional repressor, nuclear factor of activated T cells 2 (NFACT2) (187). Mutations in the Txnip gene are also detected in 7% of patients with bladder cancer (19), although the role of the mutation in carcinogenesis is not elucidated.

Previously, a report showed that a decrease in Txnip expression correlates with poor prognosis in patients with diffuse large B-cell lymphoma (152). Many recent reports support the notion that downregulated Txnip expression in cancer is related to poor prognosis. Gene expression microarray data for 65 human gastric cancer tissues showed that the high thioredoxin and low Txnip expression group exhibited poor prognosis. More than half of the patients simultaneously showing high thioredoxin and low Txnip expression experienced recurrence within 1 year after curative surgery, and the 5-year survival rate of the patients in this group was 29%, compared with 89% in patients with low thioredoxin and high Txnip expression. The thioredoxin protein was overexpressed in 65% of gastric cancer tissues, whereas the Txnip protein was downregulated in 85% of cancer cells (85). In gastroesophageal adenocarcinoma, high Txnip expression is associated with a lack of lymph node involvement, no perineural invasion, and well/moderate tumor differentiation in primary surgery cases, whereas in neoadjuvant tumors high Txnip expression is an independent marker for improved disease-specific survival, especially in cases with anthracycline-based regimens (168). In an analysis of the association of Txnip RNA expression with metastasis-free interval in 788 patients with node-negative breast cancer, Txnip was found to be associated with better prognosis (16). Txnip expression was associated with better overall survival in 150 patients with breast cancer, and Txnip and Her-2 expression status showed significant inverse correlation (105). Loss of Txnip expression in ductal breast carcinoma *in situ* is not only associated with parameters characteristic of poor prognosis but is also an independent predictor of recurrence (96). Txnip expression was also shown to be associated with the overall survival of patients with breast carcinoma (185). Decreased expression of Txnip predicts poor prognosis in patients with clear renal cell carcinoma (49). In contrast, high Txnip expression was associated with improved overall survival in pediatric patients with low-grade glioma (178). Further, high expression of Txnip indicates a lower pathological grade of meningioma and is also associated with longer recurrence-free time (18). These results collectively show that decrease of Txnip is associated with poor prognosis in various cancers, providing an idea that level of Txnip in cancer can be taken into consideration to choose the intensity of therapy.

Regulation of Txnip Expression

Transcriptional regulation

Txnip is regulated by many transcriptional factors and the regulatory elements (30, 92, 132, 180) (Fig. 2A). The *Txnip* gene is regulated through regulatory elements, including E-box, peroxisome proliferator response element (PPRE), and heat shock element (HSE). Txnip expression was upregulated by 1α, 25-dihydroxyvitamin D_3, (27, 108), peroxisome proliferator-activated receptor (PPAR)-α ligand, and PPAR-γ agonists (114), a histone deacetylase (HDAC) inhibitor suberoylanilide hydroxamic acid (SAHA) (14), heat shock, (68), and so on. Glucose is the most important inducer of Txnip. Txnip expression induced by glucose is mediated by carbohydrate-response elements (ChoREs) (97) and the associated transcription factors, Max-like protein X (Mlx) and Mondo (MondoA or ChoRE-binding protein [ChREBP; also known as MondoB]) (20, 69, 141). Both MondoA and ChREBP are broadly expressed in most tissues (BioGPS). Multiple experiments have illustrated that Txnip is a direct and glucose-induced target of MondoA. The nuclear accumulation of MondoA/Mlx and its regulation of Txnip are immediate early responses to changes in the glucose flux into the glycolytic pathway. A growth/tumor-suppressive role for the MondoA-Txnip circuit has been reviewed previously (112). Glucose-stimulated Txnip expression is also regulated by forkhead box O1 transcription factor (FOXO1) and p38 mitogen-activated protein kinase (MAPK) (80). Meanwhile, insulin is a potent repressor of Txnip expression (131). Calcium channel blockers suppress the cardiac expression of Txnip, which may enhance cardiomyocyte survival (23). The translation initiation inhibitor, rocaglamide A, is cytotoxic to triple-negative breast cancer cell lines and induces Txnip in a MondoA-dependent manner (166). Modulatory signals also regulate Txnip gene transcription. Glutamine inhibits transcriptional activation

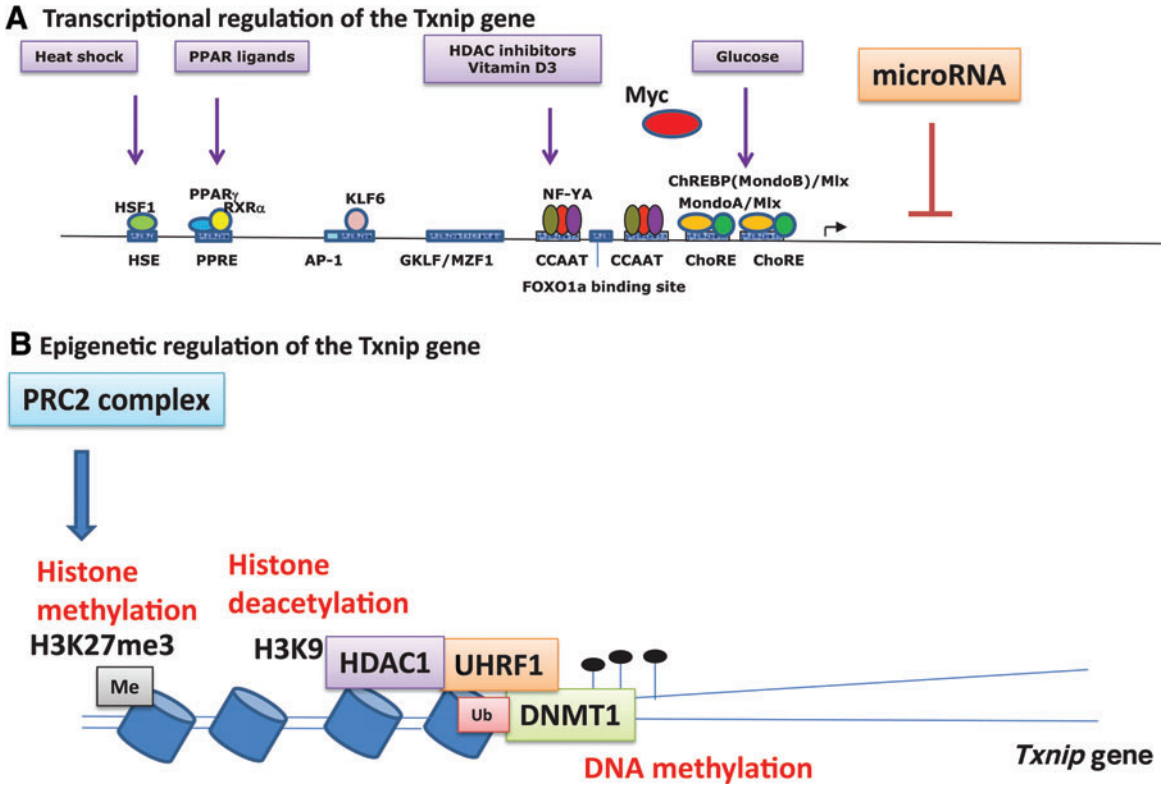

FIG. 2. Regulation of Txnip expression. Txnip expression is regulated in a multifaceted manner. **(A)** Transcriptional regulation of the Txnip gene. Txnip expression is regulated by multiple regulatory elements and transcription factors. Among them, glucose response through ChREBP/Mlx or MondoA/Mlx through ChoRE is most important. Myc may exert metabolic regulating effects and tumor promoting function by competitively binding to the ChoRE elements. MicroRNAs also play important regulatory roles of Txnip expression. **(B)** Epigenetic regulation of the Txnip gene. Txnip is regulated by multiple epigenetic mechanisms, including histone methylation, histone deacetylation, and DNA methylation. UHRF1 recruits HDAC1 and mediated histone deacetylation at H3K9 (66). UHRF1 is reported to ubiquitinate histone H3, recruiting DNMT1 to induce DNA methylation (109). ChoRE, carbohydrate-response element; ChREBP, carbohydrate response element-binding protein; DNMT1, DNA methyltransferase 1; HDAC, histone deacetylase; Mlx, Max-like protein X; RING, really interesting new gene; UHRF1, ubiquitin-like protein containing PHD and RING finger domains 1. Color images are available online.

of Txnip by triggering the recruitment of an HDAC-dependent corepressor to the amino terminus of MondoA (69). Further, Txnip and ARRDC4 expression is upregulated under acidosis (26, 167).

The human Txnip promoter contains a ChoRE consisting two E-box-like motifs. Myc/Max heterodimers are known to bind to E-box (38). Based on these findings, a novel idea about counteractive control by Myc and MondoA in the regulation of metabolism and tumorigenesis is proposed. In triple-negative breast cancer, c-Myc drives glucose metabolism by blocking MondoA-dependent activation of Txnip to stimulate aerobic glycolysis. A Myc high/Txnip low gene signature correlates with decreased overall survival and decreased metastasis-free survival in breast cancer (134). Myc_{high}, epidermal growth factor receptor $(EGFR)_{high}$, and $Txnip_{low}$ expression signature in triple-negative breast cancer showed decreased disease-specific survival and metastasis-free survival (61). F-box and WD repeat domain-containing 7 (FBW7) functions as a tumor suppressor and significantly suppressed glucose metabolism in pancreatic cancer cells *in vitro* in a xenograft model. Gene expression profiling data revealed that Txnip is a downstream target of FBW7 in a c-Myc-dependent manner. FBW7 suppressed c-Myc expression and augmented Txnip expression. Low Txnip expression worsens overall survival in pancreatic cancer (64).

MicroRNAs and circular RNAs

A mechanism attracting attention these days is the control of Txnip expression by microRNAs. Many studies have demonstrated the regulation of Txnip and its biological functions by microRNAs (30). mRNA and microRNA array datasets of breast cancer have revealed Txnip as one of the differentially expressed genes. Txnip is significantly negatively correlated with differentially expressed microRNAs (185). MiR-204/211 directly targets Txnip in MCF-7 cells (76), while miR-371 directly targets Txnip (176). MiR-373 suppresses Txnip by binding the 3′-untranslated region (UTR) of Txnip, which in turn induces cancer cell epithelial mesenchymal transition (EMT) and metastasis. miR-373 upregulates and activates the hypoxia-inducible factor 1α (HIF1α)-Twist-related protein (TWIST) signaling axis *via*

the Txnip pathway, which is correlated with a poor outcome in patients with breast cancer (22). In pancreatic ductal adenocarcinoma, miR-224 inversely regulates Txnip by binding directly to its 3′-UTR, which results in the activation of HIF1α (193). In MCF-7 cells, the protein expression level of Txnip was found to be negatively correlated with the miR-373 level (160). In nonsmall cell lung cancer tissues and cell line cells, Txnip is shown to be a direct target of miR-411-5p, which promotes tumor growth in a severe combined immunodeficiency (SCID) mouse xenograft model (184). The regulation of Txnip expression by miR-17 also seems important. Txnip expression is increased in senescent cells. FOXO3A transcriptionally upregulates Txnip expression in senescent cells. miR-17-5p, whose expression is decreased in senescent cells, directly interacts with the 3′-UTR of Txnip transcripts, and destabilizes Txnip mRNA in young cells. Knockdown of FOXO3A and/or overexpression of miR-17-5p delay cellular senescence (194). This regulation seems to indicate a link between Txnip and senescence induction. In MIN6 β-cells, cigarette smoke extract increased the levels of Txnip and the long noncoding RNA (lncRNA), metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), and downregulated the level of miR-17. An miR-17 mimic inhibited Txnip and enhanced insulin production. Knockdown of MALAT1 induced an increase in miR-17, which suppressed Txnip and promoted insulin production. Overall, this study showed a link among lncRNA, microRNA, and Txnip (145). Hyperactivated inositol-requiring enzyme (IRE) 1 alpha, an important component of the unfolded protein response pathway, increases Txnip mRNA stability by reducing the levels of miR-17 (77). Treatment with the PPAR-β/δ agonist, GW0742, increased miR-17-5p levels, reduced Txnip in the ipsilateral hemisphere after hypoxia-ischemia, and attenuated neuronal apoptosis at least partly, *via* the PPAR-β/δ/miR-17/Txnip pathway (46). Myc was also suggested to repress Txnip expression through the miR-17-92 cluster (192). The miR-224/miR-452 cluster is significantly increased in advanced melanoma and invasive/metastatic cell lines that express high levels of E2F1. Txnip is a target of miR-224/miR-452, and miR-224/452-mediated downregulation of Txnip is essential for E2F1-induced EMT and invasion (73). Txnip acts as a regulatory target of miR-20a (28, 81). Inhibition of miR-20b had a tumor-suppressive role in gastric cancer. miR-20b directly regulates the expression of phosphatase and tensin homolog deleted from chromosome 10 (PTEN), and suppresses expression of Txnip in MKN28 gastric adenocarcinoma cells (142). MiR-146a suppresses Txnip expression. Txnip could inhibit the activation of cancer-associated fibroblasts in breast cancer cells (177). Thus, Txnip expression is undoubtedly regulated by microRNAs and associated with tumor suppression. However, the weight and significance of each microRNA in the regulation of Txnip should be clarified.

The relationship between Txnip and circular RNAs (circRNAs) is also reported. The circRNA RAPGEF5 (cRAPGEF5) may promote papillary thyroid cancer progression and function as a sponge of oncogenic miR-27a-3p, which targets Txnip (29). CircECE1 is overexpressed in osteosarcoma cells. Txnip was identified as a target gene of CircECE1 by RNA-seq. In osteosarcoma cell lines, Txnip protein levels decreased after CircECE1 overexpression. In contrast, Txnip could reverse the effects of CircECE1 overexpression, and is thus considered an important downstream effector of CircECE1 in regulating glucose metabolism (135). Downregulated expression of circDCUN1D4 was prevalent in lymph node metastatic tissues and served as an independent risk factor for the overall survival of patients with lung adenocarcinoma. CircDCUN1D4 acts as a scaffold to facilitate interaction between human antigen R (HuR) protein and Txnip mRNA, which enhances Txnip mRNA stability. circDCUN1D4 also suppressed the metastasis and glycolysis of lung cancer cells in a Txnip-dependent manner (84).

Epigenetic mechanisms

Downregulation of Txnip by epigenetic mechanisms is important in cancer cells (Fig. 2B). Epigenetic silencing of the Txnip gene results in loss of responsiveness to IL-2 (3). In ferric nitrilotriacetate-induced carcinogenesis in rat kidneys, Txnip is silenced by epigenetic mechanisms during tumorigenesis (42). Txnip levels are correlated with the clinical stages of cancer largely *via* epigenetic mechanisms (190). Several mechanisms of silencing Txnip expression have been reported. Recruitment of HDAC1 to the Txnip promoter was found to be mediated by a complex consisting of the RET finger protein and nuclear transcription factor Y (NF-Y). A high level of RET finger protein was correlated with downregulated Txnip expression in human colon cancers and was associated with poor clinical outcome (71). Ubiquitin-like protein containing PHD and really interesting new gene (RING) finger domains 1 (UHRF1) inhibits Txnip expression by recruiting HDAC1 to its promoter to mediate H3K9 deacetylation in human renal carcinoma cells (66). UHRF1 also regulates DNA methylation *via* ubiquitination of histone H3 (109). Ring finger protein 2 (RNF2), also known as RING1b or RING2, which is the catalytic subunit of polycomb repressive complex 1 (PRC1), has an oncogenic function in many cancer types. Txnip is one of the most significantly increased genes in Du145 prostate cancer cells with RNF2 knockdown. Simultaneously, Txnip knockdown can partially rescue the phenotype in RNF2 single knockdown DU145 cells (165). It seems important to elucidate the epigenetic regulation of Txnip to develop measures to revive Txnip expression in cancer cells.

Regulation at mRNA stability and protein level

Regulation of Txnip mRNA stability in extracellular matrix remodeling and metabolism is another intriguing mechanism (Fig. 3). In a breast cancer model, treatment of cells and xenografts with hyaluronidase triggers a robust increase in glycolysis, largely mediated through receptor tyrosine kinase-mediated induction of the mRNA decay factor zinc finger protein 36 homolog (ZFP36), targeting Txnip transcripts for degradation. This study revealed a novel mechanism of Txnip regulation and the interconnection between extracellular matrix remodeling and metabolism in tumorigenesis (144).

Txnip protein level is maintained at low levels. Upon treatment with either glucose or proteasome inhibitors or the combination, Txnip protein level is rapidly augmented for several hours. The regulation of Txnip expression at the protein levels works more rapid than its regulation at the transcriptional level. Therefore, the regulation of Txnip expression at the protein level seems important (Fig. 4). Txnip is phosphorylated by AMP-activated protein kinase

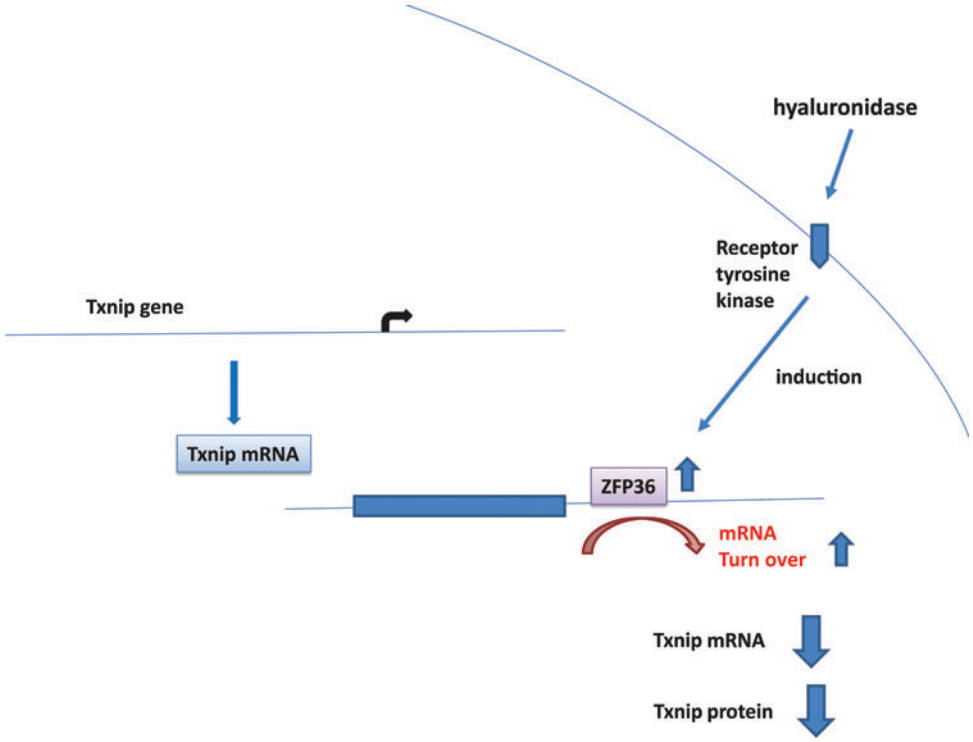

FIG. 3. Control of Txnip mRNA turnover. Txnip expression is reported at the level of mRNA turnover (144). Hyaluronidase treatment activates receptor tyrosine kinase activation, leading to the induction of ZFP36 expression. ZFP36 binds to the mRNA of Txnip to induce degradation of Txnip mRNA. mRNA, messenger RNA; ZFP36, zinc finger protein 36 homolog. Color images are available online.

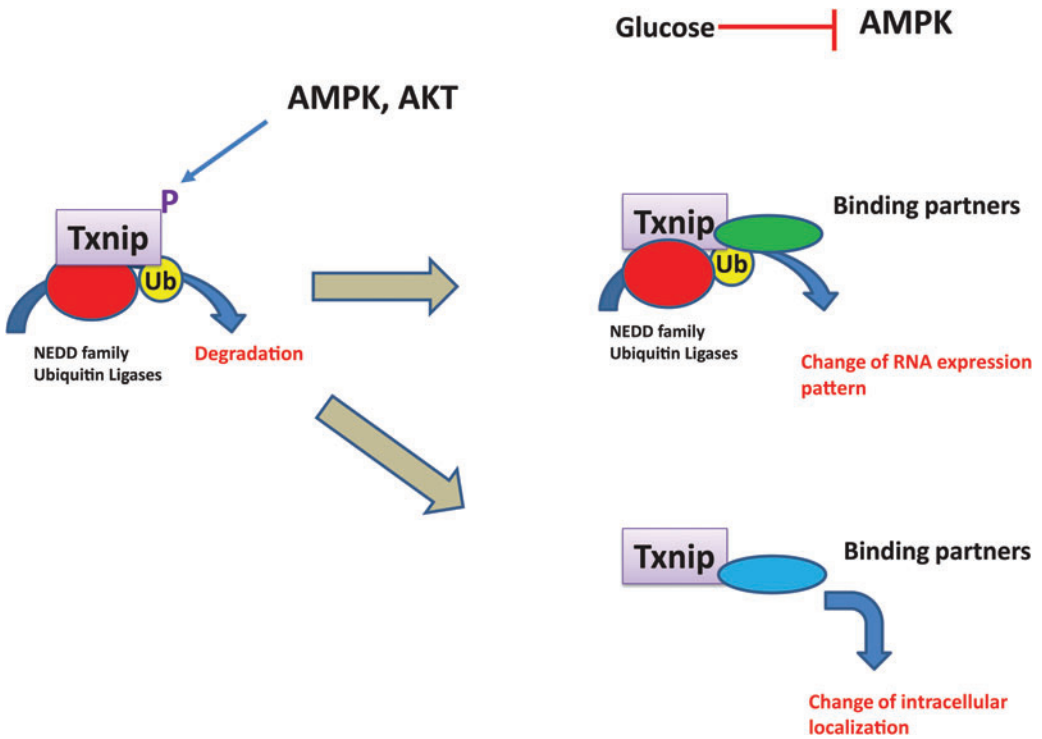

FIG. 4. Regulation of Txnip protein expression. Txnip protein is rapidly turned over by the regulation of NEDD family ubiquitin ligases such as ITCH. Txnip is phosphorylated by several kinases, including AMPK and AKT. Glucose inhibits AMPK and subsequently leads to the accumulation of Txnip protein level. Txnip interacts with yet unelucidated binding partners, which seem to change the RNA expression pattern. Txnip is also proposed to interact with binding partners such as GLUT1 and GLUT4 to change their intracellular localization. The precise regulatory mechanisms how Txnip regulates each binding partner and their fate are to be determined. AMPK, AMP-activated protein kinase; GLUT, glucose transporter; ITCH, itchy E3 ubiquitin protein ligase; NEDD, neural precursor cell expressed developmentally down-regulated protein. Color images are available online.

(AMPK), leading to its rapid degradation (169). Glucose treatment seems to suppress AMPK by changing ATP/AMP ratio. Txnip is also differentially phosphorylated at S308 by AMPK and AKT in response to glucose and insulin (158). Itchy E3 ubiquitin protein ligase (ITCH), a member of the neural precursor cell expressed developmentally down-regulated protein (NEDD) ubiquitin ligase family, targets Txnip for degradation (186).

Finally, Txnip is reported to be regulated at the level of protein synthesis. Ras suppresses Txnip protein synthesis by reducing the rate at which ribosomes transit the coding region of Txnip mRNA. The N terminus of the growing Txnip polypeptide is a target for Ras-dependent translational repression (179).

Txnip Mechanism of Action

Mechanism of action of Txnip is to be elucidated to explain pleiotropic functions, including fasting response, the regulation of glucose uptake, insulin secretion, and growth arrest.

Txnip and thioredoxin

Txnip seems to exert its function at least partly through the negative regulation of thioredoxin. Txnip was identified as a protein that interacts with thioredoxin (108). Thioredoxin is a key molecule of oxidation/reduction (redox) system (36, 55, 146). Thioredoxin 1 localizes in cytosol and nucleus, whereas thioredoxin 2 specifically localizes in mitochondria. Thioredoxin couples with peroxiredoxin to scavenge hydrogen peroxide. Several groups also have independently reported an interaction between thioredoxin and Txnip (59, 68, 122, 175). The redox-regulating activity of Txnip is one aspect of its function (108, 182), as overexpressed Txnip inhibits thioredoxin reducing activities in some situations (107, 108). It seems reasonable to assume that glucose-induced Txnip suppress thioredoxin reducing activity, leading to augmented reactive oxygen species (ROS) level. Curiously, Txnip and thioredoxin show reciprocal expression pattern in response to some stimulation, including SAHA, vitamin D_3, and PPAR ligands (14, 108, 114). While thioredoxin augments cellular proliferation and suppresses apoptosis, Txnip suppresses cellular proliferation and induces apoptosis. In tumor cells, thioredoxin expression is rather augmented (7, 8), while Txnip expression decreases. Therefore, thioredoxin and Txnip act as mutual negative regulators. Many reports show that the augmented expression of Txnip leads to the suppression of thioredoxin, producing ROS. Txnip expression in the mitochondria is reported in some literature (42, 129) and could interact with thioredoxin 2. Thioredoxin 1 is also reported to bind to apoptosis signal-regulating kinase (ASK) 1 (128). The interplay among Txnip, thioredoxin 2, and ASK1 in the regulation of apoptosis is reported (129).

Inflammasome

Upon excessive ROS, Txnip dissociates from thioredoxin. Txnip subsequently interacts with NLR family pyrin domain containing 3 (NLRP3), leading to NLRP3 inflammasome activation. Txnip deficiency was shown to impair NLRP3 inflammasome activation and IL-1β secretion (191). Similar results have also been reported in other studies. Txnip and NLRP3 were recruited to the high molecular weight inflammasome fractions upon stimulation with homocysteine in podocytes. Inhibition of Txnip by small interfering RNA (siRNA) or verapamil prevented homocysteine-induced Txnip protein recruitment to form NLRP3 inflammasomes, and abolished homocysteine-induced increases in caspase-1 activity and IL-1β production (1). Silencing Txnip suppressed palmitate-induced IL-1β secretion in human retinal endothelial cells (98). These results suggest the regulatory role of Txnip in NLRP3 inflammasome. However, the following results favor the dispensability of Txnip in NLRP3 inflammasome activation. Bone marrow (BM)-derived macrophages from Txnip-deficient mice, compared with wild-type mice, showed no difference in IL-1β secretion in response to islet amyloid polypeptide (IAPP) or other inflammasome activators (91). Further, Txnip-deficient BM-derived macrophages did not show any defects in IL-12p40 and IL-1β secretion, compared with wild-type controls. Moreover, administration of monosodium urate, a known inflammasome activator, to Txnip-deficient and sufficient mice, elicited a comparable influx of neutrophils in the peritoneum (100). Considering all these reports, the significance of the interaction among Txnip, thioredoxin 1, thioredoxin 2, ASK1, and NLRP3 should be further revalidated.

NEDD family proteins

Txnip belongs to α-arrestin family. α-Arrestins are termed by phylogenic analysis and share some structural similarity with β-arrestins (5). The crystal structure of the N-terminal domain of Txnip has been reported (123). β-Arrestins are scaffold/adaptor proteins that interact with various signaling regulators such as MAPK and have a wide variety of functions, including regulation of endocytosis and degradation of surface receptors such as G protein-coupled receptors (GPCRs). Txnip, ARRDC1, ARRDC2, ARRDC3 (114), and ARRDC4 (174) have conserved PPXY motifs, which are features of the α-arrestin family but not of β-arrestin and are known as binding motifs for the WW domain (5, 114, 120, 122). α-Arrestin family proteins are thought to interact with the NEDD family of ubiquitin ligases, including NEDD4, NEDD4L, WW domain protein (WWP)1, WWP2, ITCH, SMAD-specific E3 ubiquitin protein ligase (SMURF)1, SMURF2, HECT, C2, and WW domain containing E3 ubiquitin protein ligase (HECW)1, and HECW2, through interaction between the PPXY motifs and WW domains. Like the yeast system and β-arrestins, human α-arrestin proteins may act as adaptors for ubiquitin ligases. Among α-arrestin family proteins, only Txnip interacts with thioredoxin (114, 122). It thus seems reasonable to assume that Txnip can exert its functions through protein–protein interaction and together with NEDD family of ubiquitin ligases in common with other α-arrestin proteins (Fig. 4). Indeed, a report shows that Txnip exerts metabolic functions in a largely redox-independent manner (120).

Other interacting molecules

Txnip is reported to interact with c-Jun activation domain-binding protein (JAB)1 (62), HDAC1, Fanconi anemia zinc finger (FAZF), promyelocytic leukemia zinc finger (PLZF) (50), von Hippel-Lindau (pVHL) (137), Dnajb5 (2), and heat shock protein (HSP)90, HSP70, and pre-mRNA-processing factor (Prp)31 (53). Txnip is reported to be associated with

the plasma membrane, in some situation, interacting with binding partners such as GLUT1 and GLUT4 to change their intracellular localization (99) (Fig. 4). Whereas Txnip expression is reported in the mitochondria (42, 129, 191) and to be associated with the plasma membrane (99), many have reported that Txnip is expressed and functions primarily in the nucleus (106, 115, 129, 137, 181). By native polyacrylamide gel electrophoresis (PAGE), we recently showed that Txnip is involved in the formation of high molecular weight complexes (1000–1300 kDa) in the nuclear fraction of cells treated with glucose and bortezomib. Dithiothreitol (DTT) treatment partly dissolved these high molecular weight complexes, suggesting that Txnip forms redox-sensitive high-order nucleoprotein complexes. RNAse treatment slightly decreased the complex, and RNA-seq showed differential expression of RNAs in the complexes between Txnip protein overexpressing and control cells. These results collectively provide a model, wherein Txnip exerts its functions through multiple binding partners, forming transient higher order complexes to regulate other signaling molecules (53), which are regulated metabolically (35). As discussed here, many interaction partners with Txnip are shown to explain Txnip function. However, it seems difficult to comprehensively understand a wide variety of biological functions of Txnip, including fasting response, glucose uptake, insulin secretion, β-cell apoptosis, and growth suppression. Therefore, the fundamental mechanism of Txnip action needs to be further pursued.

RNAs

Txnip expression is not only regulated by microRNA network but Txnip also, in turn, regulates the expression of several microRNAs, including miR-124, miR-200, and miR-204 (4). Microarray analysis showed the regulation of miR-204 by Txnip. This finding was validated in INS-1 beta cells, islets of Txnip-deficient mice, diabetic mouse models, and primary human islets. Txnip induces miR-204 by inhibiting the activity of signal transducer and activator of transcription 3 (STAT3). MAFA was also shown to be downregulated by miR-204 (173). Txnip downregulated the expression of miR-124a, which directly targets FoxA2, a transcription factor regulating IAPP precursor expression (67). Txnip induced miR-200 expression in pancreatic β-cells. MiR-200 decreased zinc finger E box-binding homeobox 1 (Zeb1), promoting β-cell apoptosis. MiR-200 also increased the expression of E-cadherin, consistent with EMT inhibition (45). As miR-200 inhibition is sufficient to induce EMT (183), the decrease in Txnip expression and EMT in cancer might be associated with miR-200 downregulation. Thus, Txnip may exert its function through the regulation of microRNA network.

lncRNAs open a novel field to explain the regulation and function of Txnip. lncRNA Gm15441 is an antisense lncRNA of *Txnip*. *Txnip* is a PPAR-α target gene whose expression in the liver is inversely regulated with that of Gm15441 after PPAR-α activation. Gm15441 regulates Txnip translation partly through internal ribosome entry site (IRES) sequences found within the 5′-UTR of *Txnip* and directly suppresses Txnip protein levels (13). *Txnip*$^{-/-}$ mice lack exons 1–4 (113), also resulting in Gm15441 ablation. The interplay between Txnip and lncRNA Gm15441 may explain the variation in the phenotypes of several mice genetically engineered for *Txnip* (92) and the reciprocal regulation of Txnip and thioredoxin (14, 108, 115).

We recently showed, by RNA-seq analysis, the differential expression of RNAs in the nucleus between Txnip overexpressing and control cells, indicating that Txnip influences the RNA component in the nucleus. Gene ontology (GO) studies have shown that mRNAs involved in metabolism are enriched in association with Txnip. Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment of mRNA target genes showed that they were involved in pathways such as cancer, Epstein-Barr virus infection, mechanistic target of rapamycin (mTOR) signaling pathway, proteoglycans in cancer, MAPK signaling pathway, and influenza A. lncRNAs were also involved in phagosomes, herpes simplex infection, allograft rejection, graft-*versus*-host disease, and type I and II diabetes mellitus. These results may explain the pleiotropic aspects of the biological roles of Txnip in cancer suppression, diabetes, and inflammation (35, 53). The molecular mechanism how Txnip regulates RNA expression pattern and the significance should be further investigated.

Autophagy

Txnip has been recognized as an autophagy regulator. In islet β-cells, Txnip overexpression upregulates LC3B-I, -II, and P62, thus accentuating the increase in autophagy and organelle destruction induced by free fatty acids (37). In myocardial ischemia/reperfusion injury, Txnip overexpression significantly promoted cardiac autophagy, whereas Txnip knockdown significantly inhibited cardiac autophagy. Txnip directly interacts and stabilizes regulated in development and DNA damage response 1 (REDD1), an autophagy regulator, resulting in the inhibition of mTOR and activation of autophagy (48). Tissues lacking Txnip increase the catalytic activity of ATG4B cysteine endopeptidase, leading to enhanced LC3B delipidation and failed autophagy. REDD1/Txnip expression is sufficient to induce ROS, suppress ATG4B activity, and activate autophagy (125). Txnip directly interacts with and positively regulates p-PRKAA (catalytic subunit of AMPK), leading to inactivation of mTOR complex 1 (mTORC1) and nuclear translocation of transcription factor EB (TFEB), which in turn promotes autophagy (119). We recently showed that Txnip overexpression suppressed cell growth without significant cell cycle change and apoptosis induction in acute myelogenous leukemia (AML) cells with mixed-lineage leukemia (MLL) gene rearrangements. Txnip overexpression promoted autophagy by increasing the expression of Beclin1 and lipidation of LC3B (110). These reports collectively show that Txnip overexpression causes autophagy, although the underlying mechanism is not well determined. Controversial results have been reported concerning the role of Txnip in autophagy. Txnip was found to induce LC3-II expression, indicating that autophagosome was induced by Txnip. However, Txnip failed to degrade p62, a substrate of autophagy, suggesting that Txnip blocked autophagic flux. In addition, Txnip aggravated alpha-synuclein accumulation. Txnip decreased the expression of ATP13A2, a lysosomal membrane protein, which may lead to α-synuclein accumulation. Txnip might thus be a disease-causing protein in Parkinson's disease (143). The role

of autophagy in cancer is complicated because of its dual functions as a tumor suppressor and promoter. Overall, the role of Txnip in autophagy, especially in cancer, needs to be investigated further.

Quiescence and senescence

Txnip deficiency reduced the CXCL12- and osteopontin-mediated interaction between hematopoietic stem cells (HSCs) and the BM, and impaired homing and retention in the osteoblastic niche, resulting in HSC mobilization. This study indicates that Txnip is essential for maintaining HSC quiescence and the interaction between HSCs and the BM niche (63). BRG1, the catalytic subunit of the switch/sucrose nonfermentable (SWI/SNF) chromatin remodeling complex, plays a fundamental role in maintaining glioma-initiating cells in their stem-like state, in the drug resistance of glioma-initiating cells and glioma-initiating cell-induced tumorigenesis. BRG1 downregulates the expression of Txnip. BRG1 may maintain glucose availability in glioma-initiating cells by downregulating Txnip expression (47). Protein arginine methyltransferase 5 (PRMT5) is overexpressed in osteosarcoma, and its overexpression predicts poor clinical outcomes. PRMT5 knockdown significantly triggered pronounced senescence in osteosarcoma cells, as evidenced by the increase in senescence-associated β-galactosidase (SA-β-gal)-stained cells, induction of p21 expression, and upregulation of senescence-associated secretory phenotype (SASP) gene expression. Knockdown of PRMT5 upregulated the protein but not the mRNA expression level of Txnip in U2 osteosarcoma cells. Knockdown of Txnip significantly reduced the percentage of senescent cells and the induction of p21 resulting from PRMT5 depletion (82). Another report showed that Txnip removal largely reversed senescence upregulation in MDA-MB-231 cells (133). These results indicate that the augmented Txnip induces senescence.

Therapy

Txnip is now considered as an important target for treating diabetes and cancer.

Diabetes

Excess of Txnip expression results in augmented apoptosis of β-cells, decrease of insulin secretion from β-cells, decrease of insulin sensitivity of muscle and adipose cells, and decrease of thioredoxin antioxidative stress activity. Therefore, suppression of Txnip is a very reasonable strategy against diabetes, leading to protection of β-cells, augmentation of insulin secretion from β-cells, enhancement of insulin sensitivity of muscle and adipose cells, and preservation of thioredoxin antioxidative activity. However, inhibition of total activity of Txnip may cause untoward effects such as deterioration of fasting response and augmented susceptibility to cancer. Thus, suppression of the excess portion of augmented Txnip expression above normal level may be a reasonable strategy.

Metformin is recognized as first-line therapy for type 2 diabetes (90). Metformin suppressed the expression of Txnip and protected against intestinal ischemia–reperfusion injury (65). Metformin reduced high-glucose–induced expression of Txnip and NLRP3 in adipocytes (78). These results indicate that the effect of metformin is partly mediated by the suppression of the expression of Txnip. Verapamil, an antihypertensive calcium-channel blocker, decreases the binding of ChREBP to the E-box repeat in the *Txnip* promoter, resulting in suppression of glucose-induced Txnip expression. Verapamil promotes the survival of insulin-producing β-cells and reverses diabetes in mouse models (172). Repositioning of drugs such as Verapamil already approved by authorities for other diseases is far easier for clinical application than development of drug from the beginning. Clinical trials have been already performed. Verapamil treatment promoted endogenous β-cell function, and reduced insulin requirements and hypoglycemic episodes in adult individuals with recent onset type 1 diabetes (116). Efforts have also been undertaken to develop novel small-molecule compounds to suppress Txnip in diabetes. SRI-37330 was identified to inhibit Txnip promoter activity in β-cells. SRI-37330 treatment inhibited glucagon secretion and function, reduced hepatic glucose production, and reversed hepatic steatosis, although the molecular target of this compound still needs to be identified (150). W2476 [9-((1-(4-acetyl-phenyloxy)-ethyl)-2-) adenine] was identified as a modulator of the Txnip-regulated signaling pathway. Oral administration of W2476 rescued streptozotocin-induced diabetic mice by promoting β-cell survival and enhancing insulin secretion (79). A fluorinated derivative of curcumin (designated Shiga-Y6) was effective at reducing high-glucose–mediated induction of Txnip mRNA and protein (15). Efforts have been started to develop drugs targeting Txnip for diabetes. For clinical application, careful evaluation should be done to avoid unanticipated results such as augmented cancer risk and disordered metabolic regulation.

Cancer

As discussed above, cancer cells have depressed level of Txnip, largely through epigenetic silencing of the gene. The decrease of Txnip expression is highly associated with advanced phenotype and worsened prognosis of cancer. It is reasonable to reverse Txnip expression as a novel cancer treatment strategy (189). Several lines of approaches have been used to reverse the epigenetic downregulation of Txnip. Txnip is downregulated in AML cell lines and AML patients. 3-Deazaneplanocin A (DZNep), an S-adenosylhomocysteine hydrolase inhibitor, depletes EZH2, a core component of PRC2. DZNep induces robust apoptosis in AML cell lines, primary cells, and targets $CD34^{+}CD38^{-}$ leukemia stem cell-enriched subpopulations. DZNep was also found to dose dependently elevate Txnip protein expression in MOLM-14, MV4-11, and Kasumi-1 cells, and in two primary AML samples. In contrast, DZNep treatment failed to augment Txnip expression in KG-1 cells, which were resistant to DZNep. Induction of Txnip by DZNep thus seems to be specific to sensitive cell lines and may be important in mediating sensitivity to DZNep. Txnip overexpression showed significantly increased ROS production and cell death in MOLM-14 cells (188). In MDA157 cells, but not in MDA468 cells, combined treatment with the HDAC inhibitor SAHA and PJ34, a poly ADP-ribose polymerase (PARP) inhibitor, induced a decrease in cell viability and an increase in apoptosis. In the MDA157 cells, increased Txnip expression was associated with a decrease in cell viability and an

increase in apoptosis. In contrast, MDA468 cells were not responsive to the SAHA-PJ34 cocktail, in terms of both Txnip expression and cell proliferation parameters. These findings are consistent with the correlation between Txnip expression increment, growth inhibition, and apoptosis induction (10). Targeting bromodomain and extraterminal (BET)-containing proteins (BRD2/3/4) is effective in castration-resistant prostate cancer. BET degraders increased Txnip expression in prostate cancer cells (74). JQ1, a BET inhibitor, has been shown to suppress Myc expression by inhibiting the chromatin-binding subunit of BRD4, causing dissociation of BRD4 from the Myc promoter. JQ1 augmented Txnip expression in AML cells (192). Thus, inhibition of BET can be a therapeutic rational against cancer, possibly through augmentation of Txnip expression. Metastatic pancreatic cancers are dependent on the glucose-metabolizing enzyme phosphogluconate dehydrogenase (PGD). PGD suppressed Txnip expression. Txnip was suppressed in pancreatic ductal adenocarcinoma distant metastasis. Experimental metastasis is dependent on PGD and suppression of Txnip *in vivo*. This study highlighted the link between Txnip-mediated metabolic control and cancer metastasis, and proposed a metaboloepigenetic reprogramming intervention against metastasis (11).

Txnip was identified as a target of paired box (PAX) 5 and the Ikaros family zinc finger protein 1 (IKZF1), which are critical transcription factors for early B-cell development. Lesions of the genes encoding PAK5 and IKZF1 occur in >80% cases of pre-B-cell acute lymphoblastic leukemia (ALL). Txnip agonists 3-*O*-methylglucose and D-allose worked in synergy with glucocorticoid treatment in patient-derived pre-B ALL cells, suggesting that Txnip is a novel target of the treatment of pre-B-ALL (21).

Txnip induction induces autophagy. Although the role of autophagy in cancer is under debate, Txnip-induced autophagy may be a target of cancer therapy. mTOR pathway links to autophagy (104), and rapamycin is a specific mTOR inhibitor and induces autophagy. Rapamycin has been approved for the treatment of cancers. Metformin also interferes with the mTOR pathway. As shown above in the section of treatment of diabetes, metformin is utilized as first-line drug for diabetes (90). Metformin also appears to inhibit the proliferation and growth of certain types of cancer (70). However, metformin decreases the expression of Txnip, which may enhance the risk of tumor promotion. Therefore, the use of metformin should be carefully considered, depending on the level of Txnip in each type of cancer.

Other systems

An interesting study showing the link between Txnip and Alzheimer's disease has been published recently. Txnip is overexpressed in the hippocampus of patients with Alzheimer's disease. Amyloid beta peptide (Abeta1–42) leads to Txnip overexpression in SH-SY5Y cells, which in turn induces oxidative stress and activation of p38 MAPK, promoting tau phosphorylation at Ser202/Thr205. Silencing of Txnip abolishes Abeta1–42-induced tau phosphorylation. Further, Verapamil prevents Txnip expression and tau phosphorylation at Ser202/Thr205 in the hippocampus of 5xFAD mice (94).

α-Arrestin Proteins and Regulation of Intracellular Traffic

It seems reasonable to consider that α-arrestin proteins with a structure similar to Txnip have common features and functions with Txnip (Fig. 5).

Regulation of cancer by ARRDC3

We reported ARRDC3 as a thioredoxin-binding protein-2-like inducible membrane protein (TLIMP) expressed in the endosomes (114). ARRDC3 regulates the β_2-adrenergic receptor in collaboration with β-arrestin (102). ARRDC3 plays a role in trafficking NEDD4-β_2-adrenergic receptor complexes to a subpopulation of early endosomes (51). ARRDC3

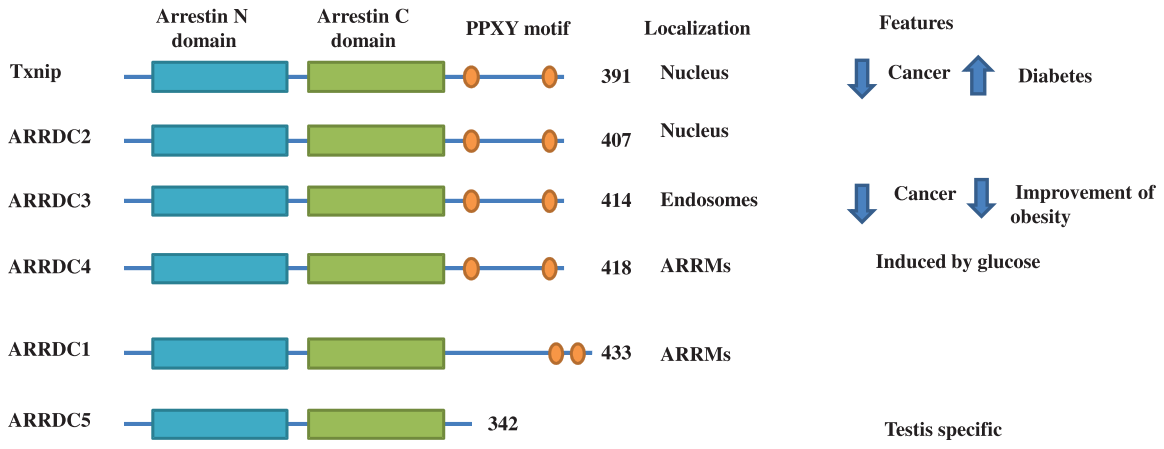

FIG. 5. Features of α-arrestin family proteins. α-Arrestin family proteins have arrestin N and C domains and conserved PPXY motifs. ARRDC5 is a testis-specific paralog and lacks the PPXY motifs. Txnip and ARRDC2 are localized mainly in the nucleus, whereas ARRDC3 is localized to the inner plasma membrane and endosomes. ARRDC1 and ARRDC4 are detected in ARMMs. Downregulation of Txnip is associated with cancer, whereas its upregulation worsens diabetes. Downregulation of ARRDC3 has also been reported in cancer, while its decrease augments energy expenditure to ameliorate obesity. ARMMs, ARRDC1-mediated microvesicles; ARRDC, arrestin domain containing. Color images are available online.

functions as a switch to modulate the endosomal residence time and subsequent intracellular signaling of the β_2-adrenergic receptor (151). ARRDC3 interacts directly with β_2-adrenergic receptors, and loss of ARRDC3 increases the response to β-adrenergic stimulation in isolated adipose tissues (121). The regulation of endolysosomal sorting of GPCRs is further discussed by Wedegaertner *et al.* (164a) in this forum series. ARRDC3 colocalizes with ALIX, a part of the endosomal sorting complexes required for transport (ESCRT) machinery and is required for protease-activated receptor-1 (PAR1), which is a GPCR for thrombin, for sorting at late endosomes, and for degradation. ARRDC3 directly binds to the phosphorylated form of β4 integrin, leading to its internalization, ubiquitination, ultimate degradation (40), and sorting into extracellular vesicles (138). ARRDC1/3 negatively regulates yes-associated protein 1 (YAP1) protein stability by facilitating E3 ubiquitin ligase Itch-mediated ubiquitination and degradation of YAP1, indicating the nature of ARRDC1/3 as tumor suppressors (170). ARRDC3 expression is epigenetically suppressed in basal-like breast cancer (139). A genome-wide association study (GWAS) showed that a single nucleotide polymorphism (SNP) upstream of the *ARRDC3* locus is potentially associated with the prognosis of early onset breast cancer (126). In a GWAS among East Asian women, a genetic locus rs10474352 at 5q14.3 near the *ARRDC3* gene was identified to be associated with breast cancer risk (17). In turn, ARRDC3 is involved in the infectious entry of the human papilloma virus (148) and promotes *Helicobacter pylori*-associated gastritis (88). ARRDC3 is thus receiving increased attention in the cancer research field. As for the localization of ARRDC3 and NEDD family proteins, we previously showed the localization of ARRDC3 in endosomes and lysosomes (114). As shown above, ARRDC3 localizes in early endosomes and regulates the endosomal residence of the β2-adrenergic receptor (151). On the contrary, there does not seem enough studies to show the existence of ARRDC3 and NEDD proteins in multivesicular endosomes and resulting secreted exosomes. The role of ARRDC3 and NEDD family proteins in exosome secretion remains to be elucidated (Fig. 5).

Regulation of extracellular vesicles by ARRDC1/4

Arrestin-related trafficking adaptors (ARTs) contain PPXY motifs that interact with Rsp5/NEDD4-like ubiquitin ligase, regulating the internalization of plasma membrane proteins (cargos) and the degradation in the lysosome in the yeast system (86). Mammalian ARRDC proteins have considerable homology around the PPXY motif with Art1. ARRDC1 is implicated in viral budding through the regulation of NEDD family ubiquitin ligases (127). By direct plasma membrane budding, ARRDC1 is discharged into ARRDC1-mediated

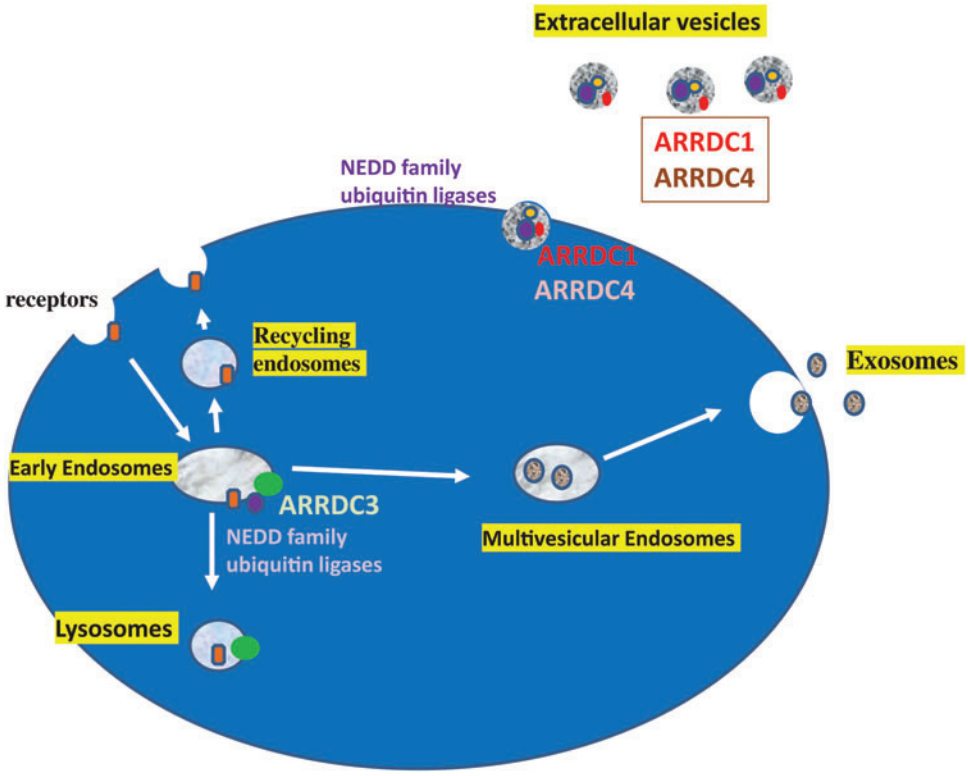

FIG. 6. α-Arrestin family proteins are regulators of intracellular and extracellular traffic. Like their counterparts in the yeast system, α-arrestin family proteins seem to play important roles in intracellular and extracellular traffic. ARRDC3 is a key regulator of endocytosis of receptors, including the β_2-adrenergic receptor, together with NEDD family ubiquitin ligases. The role of ARRDC3 in recycling endosomes and lysosomes does not seem to be determined. ARRDC1, ARRDC4, and NEDD family ubiquitin ligases are detected in ARMMs for packaging and the intracellular delivery of macromolecules. Multivesicular body contains vesicles, which are exosomes once the multivesicular body fuses with the plasma membrane. The role of α-arrestin family proteins in multivesicular endosomes and exosomes is not clear. Note that intracellular and extracellular vesicles in this figure are not drawn in the proportion to the actual size. Color images are available online.

microvesicles (ARMMs), distinct from exosomes derived from microvesicular bodies (101). A literature showed that ITCH, one of NEDD family proteins, is present in ARMMs (161). ARMMs contain tumor susceptibility gene 101 (TSG101), a component of the ESCRT machinery (130). This finding suggests a role for ARMMs in intercellular communication (75). Indeed, ARMMs contain active Notch receptors and mediate noncanonical intercellular Notch signaling (161). Further, ARRDC1 and β-arrestins are reported to heterodimerize and cooperate in the same complex to promote nonactivated Notch receptor degradation, thus acting as negative regulators of Notch signaling (124). ARRDC4, first reported to be down-regulated in advanced human hepatocellular carcinoma (DRH1) (174), is also found in extracellular vesicles (89) and may regulate the innate immune response (95). In ARRDC1-defecient mice, the content of protein cargos of exosomes and endosomes is changed, indicating the role of ARRDC1 in regulating extracellular vesicles (6). In hepatocellular carcinoma cells, ARRDC1 interacts with and regulates the ectosomal excretion of pyruvate kinase muscle isozyme (PKM2) (56). Overall, the regulation of microvesicle formation by arrestin family proteins is an emerging field of biology, and requires further investigation (Fig. 6).

Conclusion and Clinical Perspective

Txnip is a multifunctional protein associated with various disease conditions such as cancer and diabetes. The Txnip-mediated link between metabolism and cancer is well recognized. Txnip seems to be originally an essential molecule to regulate glucose metabolism, particularly to combat against hungry. Cancer cells abuse the metabolic regulatory function of Txnip. Down-regulation of Txnip expression caused in cancer cells is a way to increase glucose uptake to satisfy the demand of cancer cells. This phenomenon partly explains the Warburg effect of cancer. Txnip expression is most influenced by glucose levels and is tightly regulated by multifaceted mechanisms such as transcription, epigenetic regulation, microRNA, mRNA stabilization and protein degradation. Reverse of Txnip expression in cancer cells by manipulating these mechanisms, especially epigenetic regulation is a new approach against cancer. Combination of revival of Txnip expression by reversing the epigenetic silencing and conventional chemotherapeutic agents is to be considered, in a condition that metabolic aspects of Txnip is carefully taken into consideration. Novel mechanisms of action of Txnip, including autophagy and RNA regulation, have been proposed and may become new lines of target of therapy.

Txnip can be developed as a biomarker for diabetes. In an epigenome-wide association study (EWAS) of metabolic syndrome and its components, testing 1187 individuals of European ancestry for approximately 470,000 methylation sites throughout the genome, a strong association was found between glucose and the cg19693031 methylation site annotated to 3'UTR of the *Txnip* gene. Although the methylation site cg19693031 showed no association with *Txnip* gene transcript, a suggestive direct trans effect between the methylation locus and the gene transcripts of sterol regulatory element-binding factor (SREBF) as well as two separate transcripts of ATP-binding cassette sub-family G member (ABCG)1 was seen. This study suggests the methylation site cg19693031 is strong candidate linking separate components of metabolic syndrome (111). DNA methylation of *Txnip* in blood may be developed into biomarkers that predict type 2 diabetes (87). The frequency distribution of a 3' UTR single nucleotide polymorphism (SNP) in *Txnip* did not differ between groups (subjects with normal glucose tolerance, impaired glucose tolerance and Type 2 diabetes). Meanwhile, within the group of diabetic subjects, carriers of the *Txnip*-T variant had 1.6-fold higher triglyceride concentrations and a 5.5-mmHg higher diastolic blood pressure than homozygous carriers of the common C-allele, whereas in non-diabetic subjects fasting glucose was 0.26 mmol/l lower in carriers of the T-allele. Moreover, a significant interaction between plasma glucose concentrations and *Txnip* polymorphism on plasma triglycerides was observed (155). *Txnip* rs7211 T/rs7212 G haplotype (present in approximately 17% of individuals) was significantly associated to diabetes in the Brazilian general population (44). In Chinese Han population from central China, the frequencies of G allele, the CG, and CG/GG genotypes of *Txnip* rs7212 were all significantly higher in type 2 diabetes patients than the controls. G allele, CG, and CG/GG genotypes of rs7212 were associated with a higher risk of type 2 diabetes. Furthermore, the CG and CG/GG genotypes of rs7212 in type 2 diabetes patients with a longer duration of disease were more frequent compared with the CC genotype diabetes. For rs7212, type 2 diabetes patients with higher glucose level or/and HbA1c level more frequently carried G allele. Thus, the *Txnip* polymorphisms seem to be associated with the susceptibility to type 2 diabetes (83). The accumulation of such results would lead to the prediction of the predisposition of diabetes. On the other hand, as for cancer, studies have not been reported concerning the association of the cancer predisposition and genetic polymorphisms or epigenetic changes of the *Txnip* gene. Novel viewpoints are required for the application of Txnip research for cancer diagnosis and prevention.

The knowledge about mechanism of transcriptional regulation of the *Txnip* gene to stimuli, notably glucose has been much accumulated. As shown above, the excess in glucose-induced Txnip expression could be an ideal target against diabetes. Drug repositioning such as verapamil has been used for clinical trial. Other candidates of small molecules to suppress glucose-induced activation of the *Txnip* gene are reported. Since Txnip is necessary for fasting response and suppression of Txnip facilitates cancer progression, very careful caution should be taken to develop drugs to reduce Txnip expression.

As for cancer, decrease of Txnip expression worsen the malignancy. Txnip decrease causes enhancement of cellular growth and suppression of apoptosis in cancer cells. Since *Txnip* is often epigenetically silenced in cancer cells, the reverse of epigenetic suppression of *Txnip* is a promising approach. *Txnip* is silenced by DNA methylation and histone modifications. Inhibitors of polycomb recessive complex such as DZNep have been investigated to reverse Txnip expression. Combination of DZNep with other types of drugs is also under investigation. More attractive inhibitors of polycomb recessive complex have been developed (43). SAHA, an HDAC inhibitor has dual mode of action on the *Txnip* gene by specifically transactivating *Txnip* via NF-Y and suppressing histone deacetylation. UHRF1 is another intriguing target since UHRF1 regulates both HDAC and DNA methylation. The problem is, if we mention, that these epigenetic reverse approaches are currently not specific to the

Txnip gene. To develop more specific Txnip revival therapy, the more detailed mechanism of the epigenetic regulation of *Txnip* is need to be elucidated.

Targeting RNAs is a next generation approach. Txnip expression is regulated by the network of microRNA. In turn, Txnip may regulate the network and RNA expression pattern. Further elucidation of the molecular function and regulation of Txnip will provide new insights to develop against diseases such as cancer and diabetes.

Moreover, α-arrestin family proteins have been found to regulate intracellular trafficking including endocytosis and microvesicular formation, which are involved in cancer pathophysiology. Shedding light on molecular mechanism of α-arrestin proteins such as the regulation of traffic control would open new perspectives.

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Author Disclosure Statement

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Abbreviations Used

ALL = acute lymphoblastic leukemia
AML = acute myelogenous leukemia
AMPK = AMP-activated protein kinase
ARMMs = ARRDC1-mediated microvesicles
ARRDC = arrestin domain containing
ASK = apoptosis signal-regulating kinase
BET = bromodomain and extraterminal
BM = bone marrow
BRD = bromodomain and extraterminal-containing proteins
ChoRE = carbohydrate-response element
ChREBP = carbohydrate response element-binding protein
circRNA = circular RNA
Ct-HBx = C-terminal truncated hepatitis B virus X protein
DNMT1 = DNA methyltransferase 1
DZNep = 3-Deazaneplanocin A hydrochloride
EMT = epithelial mesenchymal transition
ESCRT = endosomal sorting complexes required for transport
FBW7 = F-box and WD repeat domain-containing 7
FOXO = forkhead box O transcription factor
GLUT = glucose transporter
GPCR = G protein-coupled receptor
GWAS = genome-wide association study
HDAC = histone deacetylase
HECW = HECT, C2, and WW domain containing E3 ubiquitin protein ligase
HIF1α = hypoxia-inducible factor 1α
HSC = hematopoietic stem cell
HSP = heat shock protein
IAPP = islet amyloid polypeptide
IKZF1 = Ikaros family zinc finger protein 1
IL = interleukin
ITCH = itchy E3 ubiquitin protein ligase
lncRNA = long noncoding RNA
MALAT1 = metastasis-associated lung adenocarcinoma transcript 1
MAPK = mitogen-activated protein kinase
Mlx = Max-like protein X
mRNA = messenger RNA
mTOR = mechanistic target of rapamycin
NEDD = neuronal precursor cell expressed developmentally down-regulated protein

NLRP3 = NLR family pyrin domain containing 3
PGD = phosphogluconate dehydrogenase
PPAR = peroxisome proliferator-activated receptor
PRC = polycomb repressive complex
PRKAA = AMP-activated protein kinase, catalytic alpha subunit
PRMT5 = protein arginine methyltransferase 5
REDD1 = regulated in development and DNA damage response 1
RING = really interesting new gene
RNF2 = ring finger protein 2
ROS = reactive oxygen species
SAHA = suberoylanilide hydroxamic acid
SMURF = SMAD-specific E3 ubiquitin protein ligase
SNP = single nucleotide polymorphism
TBP-2 = thioredoxin-binding protein-2
Txnip = thioredoxin-interacting protein
UHRF1 = ubiquitin-like protein containing PHD and RING finger domains 1
UTR = untranslated region
VDUP1 = vitamin D_3 upregulated protein-1
WWP = WW domain protein
YAP1 = yes-associated protein 1
ZFP36 = zinc finger protein 36 homolog