Revista Científica en Ciencias de la Salud
ISSN (Digital):

ARTÍCULO DE REVISIÓN

EPIGENETIC REGULATION OF THE POTENTIAL TUMOR SUPPRESSOR TXNIP

REGULACIÓN EPIGENÉTICA DEL POTENCIAL SUPRESOR TUMORAL TXNIP

Jorge Gutiérrez-Pajares[1]

[1]Universidad Le Cordon Bleu, Perú.

Conflicto de Interés
Los autores declaran no tener conflicto de interés.

Recibido: mayo 2022

Arbitrado por pares

Aceptado: julio 2022

Para citar este articulo:
Gutiérrez-Pajares J. Epigenetic regulation of the potential tumor suppressor TXNIP. Rev. Cient. Cienc. Salud 1(1):

Correspondencia:
Dr. Jorge Gutiérrez-Pajares
jorge.gutierrez@ulcb.edu.pe

ABSTRACT

Cancer cells acquire important features that allow them to adapt to different microenvironments and proliferate endlessly. To achieve that, important changes in the expression of a variety of gene sets are orchestrated, one oncogenic gene set is upregulated while another tumor suppressing gene set is down-regulated. The thioredoxin interacting protein or TXNIP was initially described as a vitamin D3-upregulated gene. Later, several biological functions have been experimentally assigned to TXNIP that highlight its relevant role as a tumor suppressor gene. Here, the cancer-related roles of TXNIP are described as well as the scientific evidence that supports the epigenetic control towards its down-regulation in cancer.

Keywords: cancer cells, epigenetic, oncogenic, tumor.

RESUMEN

Las células cancerosas adquieren importantes características que les permiten adaptarse a diferentes microambientes y proliferar indefinidamente. Con esa finalidad, se orquestan cambios importantes en una variedad de genes, un grupo de oncogenes es incrementado mientras que otro grupo que suprime el crecimiento tumoral es disminuido. La proteína que interactúa con tioredoxina (o TXNIP) fue inicialmente descrita como un gen que incrementa sus niveles en respuesta a la vitamina D3. Posteriormente, varias funciones biológicas han sido asignadas experimentalmente a TXNIP que resaltan su papel clave como gen supresor de tumores. En este artículo, se describen las actividades de TXNIP relacionadas al cáncer así como la evidencia científica que apoya la regulación epigenética que dirige su disminución en cáncer.

Palabras clave: células cancerosas, epigenéticas, oncogénicas, tumor.

INTRODUCTION

Cancer development involves a series of modifications in gene expression that favors the acquisition of essential features to adapt, survive and progress its malignancy. Currently, fourteen key features have been acknowledged as hallmarks of cancer: sustaining proliferative signaling, evading growth suppressors, non-mutational epigenetic reprogramming, avoiding immune destruction, enabling replicative immortality, tumor-promoting inflammation, polymorphic microbiomes, activating invasion and metastasis, inducing/accessing vasculature, senescent cells, genome instability and mutation, resisting cell death, deregulating cellular metabolism, and unlocking phenotypic plasticity (1). Most of these features are consequences of stable modifications in regulators of gene expression, also known as epigenetic mechanisms (2). To be highlighted, it has been observed that several tumor suppressor genes are downregulated by epigenetic modifications.

In cancer biology, epigenetic regulators mainly include DNA methylation, histone acetylation, non-coding RNA and protein degradation. Methylation of cytosines in gene promoters containing regions of DNA with a high ratio of cytosine and guanine (CpG islands) is one of the most important ways to silence gene expression (3). It is important to consider that all cells within an individual possess identical genomes. Therefore, in order to establish and maintain cellular lineage-specific expression profiles, the genome has to be programmed to express corresponding sets of genes.

Cytosine methylation consists of nucleotide biochemical conversion to 5-methylcytosine catalyzed by DNA methyltransferases (DNMT) (3). These chemical modifications of cytosines, CpG islands, are frequently observed in tumor suppressor genes in several types of tumors (4).

Similar to DNA methylation, histone deacetylation is another way to suppress gene expression since this latter mechanism also prevents the binding of the DNA polymerase machinery to start gene transcription (5). Histones are the core protein scaffolds for the double stranded DNA, forming the nucleosome (6). When the lysines of the N-terminal histones are chemically deacetylated, the affinity of these histone tails for DNA binding increases to the point it impedes DNA transcription (7). Thus, several inhibitors of histone deacetylases have been developed and studied in clinical trials (5).

MicroRNAs (miRNA) are short non-coding single-stranded RNA that target specific coding-RNA to block its translation (8). Depending on the RNA targets, miRNAs could be tumor suppressing or oncogenic miRNAs (9). Thus, miR-21 was shown to promote pancreatic ductal carcinogenesis by targeting RhoB and inducing tumor angiogenesis (10). Similarly, miR-10b decreases the effect of the antineoplastic drug cisplatin by targeting the tumor suppressor protein P53 (11) and has been suggested as a marker for predicting breast cancer metastasis and angiogenesis (12).
In this review, the importance of thioredoxin interacting protein, TXNIP, and the epigenetic mechanisms of its expression silencing will be addressed in relation to cancer.

Biological functions of TXNIP

TXNIP, also known as Thioredoxin Binding Protein 2 or TBP-2, and Vitamin D3 Up-Regulated Protein 1 or VDU-1, was discovered to be upregulated by vitamin D3 in in vitro experiments (13). Later, it was shown that TXNIP has an oxidant effect since it binds to the cysteine residues of the antioxidant protein thioredoxin and inhibits thioredoxin activity (14). Although it has been postulated that reactive oxygen species (ROS) contribute to accumulation of DNA damages promoting malignant progression (15), excessive ROS can cause cancer cell death (16,17). Therefore, it has been proposed that TXNIP promotes apoptosis of cancer cells by inhibiting the antioxidant effect of thioredoxin (18–20). In addition, the apoptosis signal-regulated kinase 1 (ASK1), that triggers cell death, is bound and inhibited by thioredoxin (21–23) while it is activated by TXNIP (24,25).

TXNIP also has the ability to regulate cell cycle progression. It has been demonstrated that TXNIP enters the nucleus as a part of a repressor system to inhibit the expression of the mitotic-promoter cyclin A causing cell-cycle arrest (26). In a recent study, it was demonstrated that the upregulation of TXNIP mediated by a specific double-stranded RNA strategy promoted the cell cycle arrest of the A549 human lung cancer cell line (27).

In addition, TXNIP regulates cellular glucose metabolism. It has been demonstrated that TXNIP binds to the glucose transporter 1 (GLUT1) and triggers the downregulation of GLUT1, decreasing glucose uptake in non-transformed (28) and cancer cells (29).

Importantly, this metabolic regulation is mediated by its arrestin domains and is independent of its binding to thioredoxin (30). In cancer cells, the oncogenic activation of the PI3K/AKT signaling pathway decreases TXNIP levels that in turn allow the expression and activity of GLUT1 for glucose metabolism (29).

Altogether, the evidence supports a tumor suppressor role of TXNIP involving a pro-oxidant, inhibition of cell-cycle progression activities and blockage of glucose metabolism as depicted in Figure 1.

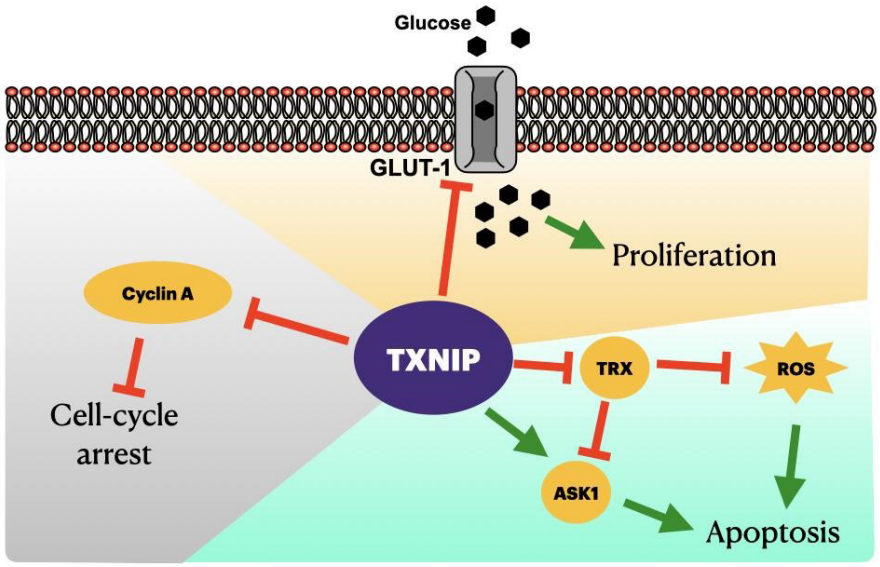

Figure 1.
Functions of TXNIP in cancer. TXNIP regulates important aspects of cancer biology: 1) TXNIP promotes apoptosis by decreasing the antioxidant protein thioredoxin (TRX) and therefore increasing intracellular reactive oxygen species (ROS). Moreover, TXNIP activates the apoptosis signal-regulating kinase 1 (ASK1) to induce apoptosis via direct interaction or by blocking the inhibition of TRX. 2) TXNIP causes cell-cycle arrest by decreasing the expression of cyclin A. Cyclin A is a key protein to conduct the transition of the cycle towards the mitosis phase. 3) TXNIP decreases GLUT1 membrane localization and promotes its degradation affecting glucose metabolism and cell proliferation.

Genomic organization of TXNIP

According to the Human Genome browser (HGB) at UCSC (hg38/Human), TXNIP gene is located in chromosome 1: q21.1 and contains 4,145 base pairs (bp) (including its untranslated region) and is orientated in the minus strand. The coding region of TXNIP has 2,416 bp distributed in 8 exons (31). A 203 bp CpG island has been predicted to be located 112 bp upstream of the start site of TXNIP transcription in the HGB (31) according to in silico prediction (G. Miklem and L. Hillier, unpublished).

An experimentally proven and published regulatory region analysis performed by the Open Regulatory Annotation (ORegAnno) (32) within the HGB (31) shows that STAT1, RB1, RBL2, MITF, FOXA1, FOS, FOXP1, NFYA, NFYB are the main transcription factors that have response elements in the promoter of TXNIP, in close proximity to the aforementioned CpG island. Moreover, ORegAnno analysis delineates a 23 bp miRNA binding site for miR-373 in the 5'-untranslated region of the TXNIP mRNA.

Epigenetic silencing of TXNIP in cancer

It has been described that the expression of TXNIP is frequently down-regulated in cancer tissues compared to non-neoplastic tissues (33), suggesting a potential role as a tumor suppressor protein. The following mechanisms, depicted in Figure 2, have been identified in cancer cells to explain TXNIP down-regulation:

a) Promoter CpG methylation

Further studies demonstrated that cytosine methylation was responsible for the

down-regulation of TXNIP at the epigenetic level (Table 1). In support of this mechanism, in vitro treatment with an inhibitor of DNMT (5'-aza-cytidine) increased the expression of TXNIP in head and neck squamous cell carcinoma (34), cutaneous T-cell lymphoma (35) and cervical cancer (36) cell lines. Moreover, this in vitro results have been confirmed in human tumor samples by using methyl specific sequencing methods (34,36) and in an in vivo model of rat kidney carcinoma (37).

b) Histone deacetylation

The relevance of histone deacetylation in the regulation of TXNIP expression is mainly supported by the use of inhibitor drugs in cell cultures. Thus, adding the pharmacological inhibitor of histone deacetylases, Trichostatin A, to the DNMT inhibitor 5'-aza-cytidine strongly improved the TXNIP protein level in HeLa cervical cancer cell line (36). Also, the in vitro exposure to the inhibitor of histone deacetylase SAHA caused the increase in gene expression of TXNIP in human cancer cell lines from prostate, bladder, myeloma, and breast (38). Interestingly, it was reported that the epigenetic regulator UHRF1 recruited the histone deacetylase HDAC1 to TXNIP promoter to decrease TXNIP expression in renal cell carcinoma (39).

c) miRNA

A few reports have indicated that the mRNA of TXNIP possess miRNA target sequences that regulate its translation. According to the Human Genome Browser (31), the ectopic expression of miR-373 caused the down-regulation of TXNIP in the MCF-7 breast cancer cell line (40,41) (Table 2). Further analysis showed that miR-373 reduced TXNIP protein level without affecting its mRNA levels, suggesting that miR-373 regulates TXNIP expression by a translational inhibition instead of mRNA degradation (42). Although no specific miR-152-5p binding sequence was detailed in TXNIP mRNA, it was recently reported that the over-expression of miR-152-5p in melanoma cells decreased TXNIP (43).

d) Ubiquitination

Earlier, a discrepancy between mRNA and protein levels of TXNIP was described in an induced model of rat kidney carcinoma (37). While TXNIP protein levels remained diminished after 12-48 h of ferric nitrate enneahydrate treatment, no decrease was observed in its mRNA level at the 1-96 h period of evaluation (37). Similarly, the pharmacological inhibition of the proteasome strongly up-regulates the TXNIP protein in the MyLa1850 cutaneous T-cell lymphoma cell line (35). These observations suggest a post-translational mechanism that regulates TXNIP protein levels.

It has been reported that upon energy stress, the AMP-dependent protein kinase phosphorylates TXNIP leading to its degradation and allowing glucose entry via GLUT1 in mouse embryonic fibroblasts (28). Further studies pointed to the Itchy E3 ubiquitin protein ligase (ITCH) as the principal regulator of TXNIP protein stability in non-neoplastic epithelial kidney and osteosarcoma cells (44). This mechanism has also been confirmed in lung cancer cells (45).

Table 1. Research studies on TXNIP promoter methylation in cancer

Disease	Studied sample	Main observations	Reference
Renal carcinoma	Chemically induced rat kidney carcinoma.	Ferric nitrate enneahydrate induced the methylation of the promoter TXNIP analyzed by methylation-specific PCR. TXNIP protein levels diminished in tumor samples compared to normal tissue.	(37)
Head and neck squamous cell carcinoma (HNSCC)	Tumors compared to normal mucosa. JHU-012 and JHU-011 cell lines.	Bisulfite sequencing analysis showed methylation of the TXNIP promoter in tumor samples but no in normal mucosa. Cell line exposure to 5'-aza-cytidine increased the expression of TXNIP by microarray analysis.	(34)
Cutaneous T-Cell Lymphoma (CTCL)	Human CTCL cell lines.	Methylation of the promoter of TXNIP was confirmed by bisulphite sequencing in 2 out of 7 cell lines. No methylation of the TXNIP promoter was observed in lymphocytes of healthy donors while different levels of methylation were observed in cancer samples.	(35)
Cervical cancer	Tumors compared to normal tissue. HeLa, SiHa and Caski cell lines.	Increased levels of CpG methylation of TXNIP promoter in cervical cancer samples and cell lines compared to control tissue. Advance stages of cervical cancer showed higher levels of TXNIP promoter methylation UHRF1 was identified as the mediator of TXNIP promoter methylation.	(36)

Table 2. Research studies on miRNAs regulation of TXNIP expression in cancer

Disease	Main observations	Reference
Breast cancer	Ectopic expression of miR-373 decreased TXNIP in the MCF-7 cell line.	(40)
Breast cancer	Transfection of pre-miR-373 to MCF-7 cells diminished TXNIP and increased migration and invasion of cancer cells. No change in proliferation was observed.	(42)
Melanoma	miR-152-5p targets TXNIP to promote its downregulation in cancer cell lines.	(43)

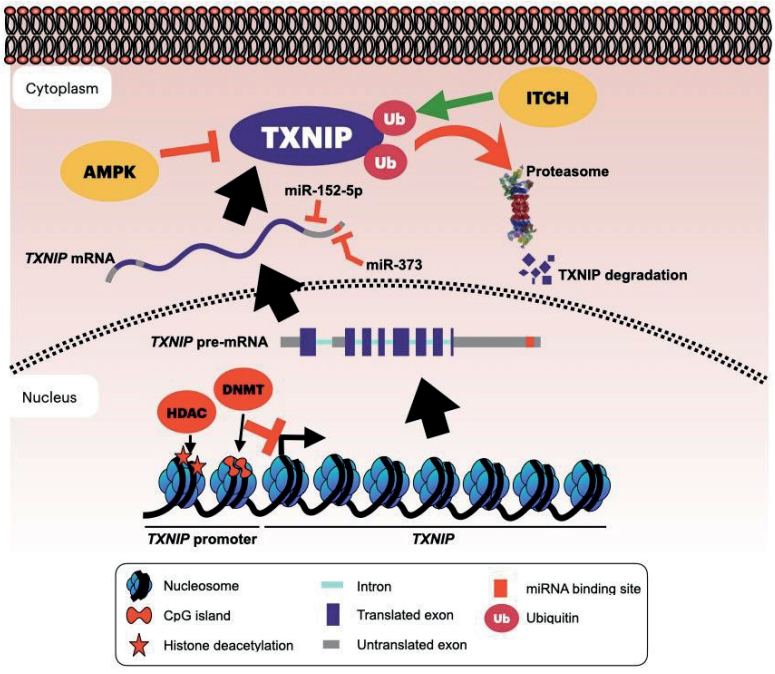

Figure 2.
Epigenetic silencing of TXNIP in cancer. The TXNIP promoter contains a CpG island susceptible for methylation by DNMT. Furthermore, histone deacetylation by HDAC also contributes to the inhibition of TXNIP transcription. After transcription, the TXNIP mRNA can be targeted by two miRNAs to block its translation. Finally, TXNIP half-life can be reduced by an AMPK-dependent phosphorylation or ITCH-directed pathways. AMPK = AMP-dependent protein kinase, DNMT = DNA methylase, HDAC = histone deacetylase, ITCH = Itchy E3 ubiquitin protein ligase.

CONCLUSION

The Thioredoxin-Interacting Protein or TXNIP negatively regulates proliferation, cell cycle progression and apoptosis, which are relevant hallmarks of cancer cells. In that sense, it has been shown that TXNIP is down-regulated in several types of cancer. Altogether, the data point to a tumor suppressor role of TXNIP. The reduced expression of TXNIP in cancer cells is mediated by well-established epigenetic mechanisms. Scientific evidence reports that promoter DNA methylation and histone deacetylation, miRNA inhibition of mRNA translation and proteasome-regulated protein degradation are key mechanisms to inhibit TXNIP expression, and as consequence, its cellular functions.

BIBLIOGRAPHIC REFERENCES

1. Hanahan D. Hallmarks of Cancer: New Dimensions. Cancer Discov. 2022; 12(1): 31 – 46. https://aacrjournals.org/cancerdiscovery/article/12/1/31/675608/Hallmarks-of-Cancer-New-DimensionsHallmarks-of

2. Darwiche N. Epigenetic mechanisms and the hallmarks of cancer: an intimate affair. Am J Cancer Res. 2020; 10(7): 1954 – 1978. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7407342/

3. Li S, Peng Y, Panchenko A. DNA methylation: Precise modulation of chromatin structure and dynamics. Curr Opin Struct Biol. 2022; 75: 102430. https://linkinghub.elsevier.com/retrieve/pii/S0959440X22001099

4. Kazanets A, Shorstova T, Hilmi K, Marques M, Witcher M. Epigenetic silencing of tumor suppressor genes: Paradigms, puzzles, and potential. Biochim Biophys Acta. 2016; 1865(2): 275 – 288. https://linkinghub.elsevier.com/retrieve/pii/S0304419X16300294

5. Dushanan R, Weerasinghe S, Dissanayake D, Senthilinithy R. Cracking a cancer code histone deacetylation in epigenetic: the implication from molecular dynamics simulations on efficacy assessment of histone deacetylase inhibitors. J Biomol Struct Dyn. 2022; 40(5): 2352 – 2368. https://www.tandfonline.com/doi/full/10.1080/07391102.2020.1838328

6. Gursoy-Yuzugullu O, House N, Price B. Patching Broken DNA: Nucleosome Dynamics and the Repair of DNA Breaks. J Mol Biol. 201; 428(9 Pt B): 1846 – 1860. https://linkinghub.elsevier.com/retrieve/pii/S002228361500683X

7. Hai R, He L, Shu G, Yin G. Characterization of Histone Deacetylase Mechanisms in Cancer Development. Front Oncol. 2021; 11. https://www.frontiersin.org/articles/10.3389/fonc.2021.700947/full

8. Lin Y, Chen T, Huang Y, Wei P, Lin J. Involvement of microRNA in Solid Cancer: Role and Regulatory Mechanisms. Biomedicines. 2021; 9(4): 343. https://www.mdpi.com/2227-9059/9/4/343

9. Eniafe J, Jiang S. MicroRNA-99 family in cancer and immunity. Wiley Interdiscip Rev RNA. 2021; 12(3): e1635. https://onlinelibrary.wiley.com/doi/10.1002/wrna.1635

10. Sicard F, Gayral M, Lulka H, Buscail L, Cordelier P. Targeting miR-21 for the therapy of pancreatic cancer. Mol Ther J Am Soc Gene Ther. 2013; 21(5): 986 – 994. https://linkinghub.elsevier.com/retrieve/pii/S1525001616306785

11. Lin C, Liao W, Yang T, Lu H, Hsu S, Wu C. MicroRNA-10b modulates cisplatin tolerance by targeting p53 directly in lung cancer cells. Oncol Rep. 2021; 46(2): 167. http://www.spandidos-publications.com/10.3892/or.2021.8118

12. Liu X, Guan Y, Wang L, Niu Y. MicroRNA-10b expression in node-negative breast cancer-correlation with metastasis and angiogenesis. Oncol Lett. 2017; 14(5): 5845 – 5852. http://www.spandidos-publications.com/10.3892/ol.2017.6914

13. Nishiyama A, Matsui M, Iwata S, Hirota K, Masutani H, Nakamura H, et al. Identification of thioredoxin-binding protein-2/vitamin D(3) up-regulated protein 1 as a negative regulator of thioredoxin function and expression. J Biol Chem. 1999; 274(31): 21645 – 21650. https://linkinghub.elsevier.com/retrieve/pii/S0021925819724260

14. Junn E, Han S, Im J, Yang Y, Cho E, Um H, et al. Vitamin D3 up-regulated protein 1 mediates oxidative stress via suppressing the thioredoxin function. J Immunol. 2000; 164(12): 6287 – 6295. http://www.jimmunol.org/lookup/doi/10.4049/jimmunol.164.12.6287

15. Cheung E, Vousden K. The role of ROS in tumor development and progression. Nat Rev Cancer. 2022; 22(5): 280 – 297. https://www.nature.com/articles/s41568-021-00435-0

16. Chen Q, Hou Y, Li D, Ding Z, Xu X, Hao B, et al. Berberine induces non-small cell lung cancer apoptosis via the activation of the ROS/ASK1/JNK pathway. Ann Transl Med. 2022; 10(8): 485. https://atm.amegroups.com/article/view/93813/html

17. Di S, Fan C, Ma Z, Li M, Guo K, Han D, et al. PERK/eIF-2α/CHOP Pathway Dependent ROS Generation Mediates Butein-induced Non-small-cell Lung Cancer Apoptosis and G2/M Phase Arrest. Int J Biol Sci. 2019; 15(8): 1637 – 1653. http://www.ijbs.com/v15p1637.htm

18. Gallegos A, Gasdaska J, Taylor C, Paine-Murrieta G, Goodman D, Gasdaska P, et al. Transfection with human thioredoxin increases cell proliferation and a dominant-negative mutant thioredoxin reverses the transformed phenotype of human breast cancer cells. Cancer Res. 1996; 56(24): 5765 – 5770. https://pubmed.ncbi.nlm.nih.gov/8971189/

19. Baker A, Payne C, Briehl M, Powis G. Thioredoxin, a gene found overexpressed in human cancer, inhibits apoptosis in vitro and in vivo. Cancer Res. 1997; 57(22): 5162 – 5167. https://pubmed.ncbi.nlm.nih.gov/9371519/

20. Kim Y, Kim Y, Kim M, Kim J, Lee H, Kim T. Thioredoxin-interacting Protein (TXNIP) Mediates Thioredoxin-dependent Antioxidant Mechanism in Endometrial Cancer Cells Treated With 1 α,25-dihydroxyvitamin D3. Anticancer Res. 2019; 39(9): 4795 – 4803. http://ar.iiarjournals.org/lookup/doi/10.21873/anticanres.13664

21. Saitoh M, Nishitoh H, Fujii M, Takeda K, Tobiume K, Sawada Y, et al. Mammalian thioredoxin is a direct inhibitor of apoptosis signal-regulating kinase (ASK) 1. EMBO J. 1998; 17(9): 2596 – 2606. http://emboj.embopress.org/cgi/doi/10.1093/emboj/17.9.2596

22. Liu H, Nishitoh H, Ichijo H, Kyriakis J. Activation of apoptosis signal-regulating kinase 1 (ASK1) by tumor necrosis factor receptor-associated factor 2 requires prior dissociation of the ASK1 inhibitor thioredoxin. Mol Cell Biol. 2000; 20(6): 2198 – 2208. https://journals.asm.org/doi/10.1128/MCB.20.6.2198-2208.2000

23. Pramanik K, Srivastava S. Apoptosis Signal-Regulating Kinase 1–Thioredoxin Complex Dissociation by Capsaicin Causes Pancreatic Tumor Growth Suppression by Inducing Apoptosis. Antioxid Redox Signal. 2012; 17(10): 1417 – 1432. http://www.liebertpub.com/doi/10.1089/ars.2011.4369

24. Wang X, Nachliely M, Harrison J, Danilenko M, Studzinski G. Participation of vitamin D-upregulated protein 1 (TXNIP)-ASK1-JNK1 signalosome in the enhancement of AML cell death by a post-cytotoxic differentiation regimen. J Steroid Biochem Mol Biol. 2019; 187: 166 – 173. https://linkinghub.elsevier.com/retrieve/pii/S0960076018304187

25. Zhou Y, Zhou J, Lu X, Tan T, Chng W. BET Bromodomain inhibition promotes De-repression of TXNIP and activation of ASK1-MAPK pathway in acute myeloid leukemia. BMC Cancer. 2018; 18(1): 731. https://bmccancer.biomedcentral.com/articles/10.1186/s12885-018-4661-6

26. Han S, Jeon J, Ju H, Jung U, Kim K, Yoo H, et al. VDUP1 upregulated by TGF-beta1 and 1,25-dihydorxyvitamin D3 inhibits tumor cell growth by blocking cell-cycle progression. Oncogene. 2003; 22(26): 4035 – 4046. https://www.nature.com/articles/1206610

27. Park K, Yang J, Kwon J, Lee H, Yoon Y, Choi B, et al. Targeted Induction of Endogenous VDUP1 by Small Activating RNA Inhibits the Growth of Lung Cancer Cells. Int J Mol Sci. 2022; 23(14): 7743. https://www.mdpi.com/1422-0067/23/14/7743

28. Wu N, Zheng B, Shaywitz A, Dagon Y, Tower C, Bellinger G, et al. AMPK-dependent degradation of TXNIP upon energy stress leads to enhanced glucose uptake via GLUT1. Mol Cell. 2013; 49(6): 1167 – 1175. https://linkinghub.elsevier.com/retrieve/pii/S1097276513000993

29. Hong S, Yu F, Luo Y, Hagen T. Oncogenic activation of the PI3K/Akt pathway promotes cellular glucose uptake by downregulating the expression of thioredoxin-interacting protein. Cell Signal. 2016; 28(5): 377 – 383. https://linkinghub.elsevier.com/retrieve/pii/S0898656816300110

30. Patwari P, Chutkow W, Cummings K, Verstraeten V, Lammerding J, Schreiter E, et al. Thioredoxin-independent regulation of metabolism by the alpha-arrestin proteins. J Biol Chem. 2009; 284(37): 24996 – 5003. https://linkinghub.elsevier.com/retrieve/pii/S0021925820305895

31. Kent W, Sugnet C, Furey T, Roskin K, Pringle T, Zahler A, et al. The Human Genome Browser at UCSC. Genome Res. 2002; 12(6): 996 – 1006. http://genome.cshlp.org/lookup/doi/10.1101/gr.229102

32. Lesurf R, Cotto K, Wang G, Griffith M, Kasaian K, Jones S, et al. ORegAnno 3.0: a community-driven resource for curated regulatory annotation. Nucleic Acids Res. 2016; 44(D1): D126 - 132. https://academic.oup.com/nar/article-lookup/doi/10.1093/nar/gkv1203

33. Chen Y, Ning J, Cao W, Wang S, Du T, Jiang J, et al. Research Progress of TXNIP as a Tumor Suppressor Gene Participating in the Metabolic Reprogramming and Oxidative Stress of Cancer Cells in Various Cancers. Front Oncol. 2020; 10. https://www.frontiersin.org/articles/10.3389/fonc.2020.568574

34. Demokan S, Chuang A, Chang X, Khan T, Smith I, Pattani K, et al. Identification of guanine nucleotide-binding protein γ-7 as an epigenetically silenced gene in head and neck cancer by gene expression profiling. Int J Oncol. 2013; 42(4): 1427 – 1436. https://www.spandidos-publications.com/10.3892/ijo.2013.1808

35. Stolearenco V, Levring T, Nielsen H, Lindahl L, Fredholm S, Kongsbak-Wismann M, et al. The Thioredoxin-Interacting Protein TXNIP Is a Putative Tumor Suppressor in Cutaneous T-Cell Lymphoma. Dermatology. 2021; 237(2): 283 – 290. https://www.karger.com/Article/FullText/509159

36. Kim M, Lee H, Choi M, Kang S, Kim Y, Shin J, et al. UHRF1 Induces Methylation of the TXNIP Promoter and Down-Regulates Gene Expression in Cervical Cancer. Mol Cells. 2021; 44(3): 146 – 159. http://molcells.org/journal/view.html?doi=10.14348/molcells.2021.0001

37. Dutta K, Nishinaka Y, Masutani H, Akatsuka S, Aung T, Shirase T, et al. Two distinct mechanisms for loss of thioredoxin-binding protein-2 in oxidative stress-induced renal carcinogenesis. Lab Investig J Tech Methods Pathol. 2005; 85(6): 798 – 807. http://www.nature.com/articles/3700280

38. Butler L, Zhou X, Xu W, Scher H, Rifkind R, Marks P, et al. The histone deacetylase inhibitor SAHA arrests cancer cell growth, up-regulates thioredoxin-binding protein-2, and down-regulates thioredoxin. Proc Natl Acad Sci U S A. 2002; 99(18): 11700 – 11705. https://pnas.org/doi/full/10.1073/pnas.182372299

39. Jiao D, Huan Y, Zheng J, Wei M, Zheng G, Han D, et al. UHRF1 promotes renal cell carcinoma progression through epigenetic regulation of TXNIP. Oncogene. 2019; 38(28): 5686 – 5699. http://www.nature.com/articles/s41388-019-0822-6

40. Wang J, Zhang L, Chen Y, Zhang T, Yuan P, Liu D. Influence of mir-373 on the invasion and migration of breast cancer and the expression level of target genes TXNIP. J Biol Regul Homeost Agents. 2015; 29(2): 367 – 372. https://pubmed.ncbi.nlm.nih.gov/26122224/

41. Chen D, Dang B, Huang J, Chen M, Wu D, Xu M, et al. MiR-373 drives the epithelial-to-mesenchymal transition and metastasis via the miR-373-TXNIP-HIF1α-TWIST signaling axis in breast cancer. Oncotarget. 2015; 6(32): 32701 – 32712. https://www.oncotarget.com/lookup/doi/10.18632/oncotarget.4702

42. Yan G, Xu S, Tan Z, Liu L, He Q. Global identification of miR-373-regulated genes in breast cancer by quantitative proteomics. Proteomics. 2011; 11(5): 912 – 920. https://onlinelibrary.wiley.com/doi/10.1002/pmic.201000539

43. Li K, Tang M, Tong S, Wang C, Sun Q, Lv M, et al. BRAFi induced demethylation of miR-152-5p regulates phenotype switching by targeting TXNIP in cutaneous melanoma. Apoptosis. 2020; 25(3): 179 – 191. http://link.springer.com/10.1007/s10495-019-01586-0

44. Zhang P, Wang C, Gao K, Wang D, Mao J, An J, et al. The Ubiquitin Ligase Itch Regulates Apoptosis by Targeting Thioredoxin-interacting Protein for Ubiquitin-dependent Degradation. J Biol Chem. 2010; 285(12): 8869 – 8879. https://linkinghub.elsevier.com/retrieve/pii/S0021925820872846

45. Sun Q, Wang B, Wei W, Huang G, Liu L, Chen W, et al. ITCH facilitates proteasomal degradation of TXNIP in hypoxia-induced lung cancer cells. Thorac Cancer. 202; 13(15): 2235 – 2247. https://onlinelibrary.wiley.com/doi/10.1111/1759-7714.14552