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Review Article

Taurine upregulated 1: Prognostic biomarker in breast cancer

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Abstract

The most common kind of cancer and the second leading cause of cancer mortality in women is breast cancer (BC). The most proven cause of mortality in BC patients comprises tumor metastasis and invasive development. Long noncoding RNAs are endangered by many crucial mechanisms involved in BC metastasis (lncRNAs). RNAs that are classified as lncRNAs are thought to be longer than 200 nucleotides in length. Literature has long shown that lncRNAs are promising therapeutic targets in BC as well as diagnostic and prognostic indicators. Only a few studies have, to our knowledge, described the bioenergetics of taurine upregulated 1 (TUG1). Human cancer has been linked to a new lncRNA called TUG1. TUG1 has drawn increasing interest in recent years and has been shown to express abnormality in several forms of cancer. Numerous research suggested that the development of tumefaction and cell metabolism may be favorably correlated with TUG1. As a result, we aimed to concentrate on recent developments in the primary molecular processes of TUG1 in cancer in this review. This includes its role in drug resistance, invasion, cell migration, apoptosis, and proliferation. Most recent investigations asserted that TUG was overexpressed in BC tissues and cell lines as compared to their normal counterparts. To better understand the critical impact of tamoxifen (TMX) resistance and improve quality of life (QOL), researchers are looking for an early diagnostic marker.

Keywords: *Breast cancer, long noncoding RNAs, Taurine upregulated 1, Tamoxifen*.

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1. Cancer

1.1. Cancer occurrence and incidence

The United States is expected to experience 609,820 cancer deaths and 1,958,310 new cancer cases in 2023 **[1]**. Breast cancer (BC) is considered to be the second cause of death among women. The second leading cause of mortality for females is thought to be BC. GLOBOCAN reports that 2.1 million new cases of BC were discovered in the world in 2018 **[2]**. With a total of 278,165 cancer cases in Egypt in

December 2020, the most common malignancies are breast (61,160 cases), liver (28,977), bladder (26,986), non-Hodgkin lymphoma (19,096), leukemia (14,274), brain and central nervous system (11,470), and prostate (10,523) **[3]**.

One of the most important causes of the cancer catastrophe was population aging. Additionally, the increasing incidence of risk factors including obesity, inactivity, smoking and changed reproductive strategies connected to urbanization and economic growth contributed to the rise of cancer. While this is happening, the burden of cancer has subtly moved to less developed nations, which account for around 57% of cases and 65% of cancer deaths globally **[4]**.

Prostate, lung, and bronchus (hereafter lung), and colorectal cancers account for over half (48%) of all incident cases in males, with prostate cancer alone accounting for 29% of diagnoses, according to the most prevalent malignancies diagnosed in men and women in 2023. BC alone accounts for 31% of female malignancies, whereas lung cancer, colorectal cancer, and BC together account for 52% of all new diagnoses in women. In 2023, it is predicted that 609,820 Americans would pass away from cancer, or 1670 people a day. Men's lung, prostate, and colorectal cancers as well as women's lung, breast, and colorectal cancers account for the majority of fatalities **[1]**.

1.2. Cancer Complications

As the disease advances, challenges associated with cancer and its treatment become more frequent, more severe, and more pronounced. Over 75% of individuals have bone metastases, while 15% to 20% of patients experience central nervous system involvement. Hepatic illnesses and gastrointestinal (GI) issues may be a factor in the unusual morbidity **[5]**. Cancer treatment frequently results in cardiotoxicity **[6-8]**.

A special collection of physiological, anatomical, and therapy-related circumstances is presented to cancer patients. This may result in infections such as orbital cellulitis as a consequence. Due to immunosuppression brought on either by the illness itself or by the cancer therapies these sufferers are receiving, they are more vulnerable to infections **[9]**.

A common cancer symptom, fatigue is linked to noteworthy morbidity, functional impairments, and a poorer quality of life (QOL). Accordingly, effective tiredness management would significantly reduce the illness burden related to cancer and its therapies **[10]**.

While still treating cancer-related problems may not necessarily increase a patient's life expectancy, it can greatly enhance QOL. As a corollary, healthcare professionals who treat cancer patients should be aware of these issues and act quickly to address them whenever they arise **[11]**.

2. Breast cancer

2.1 Etiology and risk factors

Numerous risk factors have been implicated in influencing both the prognosis and risk of acquiring BC in a person. Age, gender, family history, estrogen (ER) exposure, hormone replacement therapy, age at menarche, first full-term pregnancy, and menopause are non-modifiable variables. On the other hand, environmental and lifestyle variables are among the elements that can be modified **[12]**.

Age directly affects the incidence rate of BC, which becomes vital before the age of 50 **[13]**. Egypt experiences BC at a significantly younger age. The average age of the BC population in Egypt is 46 compared to other populations **[14]**.

2.2 Treatment and associated complications

A significant portion of women with BC may experience difficulties that change how they function as well as how their QOL is treated. Few of these women are referred for therapy, and the majority of these issues go unnoticed **[15]**.

After advancements in treatment and earlier diagnosis and staging of BC, survival rates and life expectancy improved. Surgery, radiation, and systemic therapy are used as treatment options. Breast-conserving surgery and mastectomy are two surgical treatments for BC. The scope of surgery is mostly determined by the number of lumps present in the breast tissue, the stage and grade of the disease, and the preferences of the patient. After cancer has been exposed to high-intensity ionizing radiation, there is cellular damage, including deoxyribonucleic acid (DNA) strand breakage in the targeted cancer cells and alteration of the DNA template. Apoptosis then results from the inability of proliferating cells to heal the damage. Systemic therapy for BC has considerably improved long-term survival. Systemic treatments for BC include chemotherapy, biological response modifiers, and hormone therapy. The type of therapy to be used depends on the patient's features, the characteristics of the disease, and whether or not certain cellular indicators are present **[16]**.

Since the early 1980s, incremental progress has primarily been achieved by systematic and aggressive therapy escalation, which involves using longer-term treatment plans, additional medications, or a bigger number of agents. Long-term endocrine therapy (5–10 years on tamoxifen and/or an aromatase inhibitor) also grew extremely prevalent. New therapeutic medications (such as taxanes, anthracyclines, aromatase inhibitors, and trastuzumab) were also developed. Systemic medication may routinely be given to women with early-stage BC for well over 10 years **[17]**.

Approximately 70% of BC cases are ER-positive, and it is thought that exposure to the hormone has a causal effect on malignancy. Resistance developed during hormonal endocrine therapy may be acquired during the length of the whole course of therapy or intrinsic, meaning that it exists before the initiation of any treatment **[18]**.

2.3 Tamoxifen and breast cancer

The most well-known hormonal treatment for BC patients across all settings is tamoxifen (TMX), a triphenylethylene compound that can lengthen both recurrence-free intervals and overall survival **[19]**.

Different medications are being employed in the treatment of cancer. TMX is the medicine that creates the most concern out of all of these. As an anti-ER medication, TMX works in breast tissues by blocking ER receptors and suppressing ER activities. In contrast, TMX also activates ER receptors in several human tissues, including the endometrium, liver, and bone, leading experts to believe that it is a selective ER receptor modulator. This thus makes it possible for it to be used often in both BC and prophylaxis, especially in high-risk women **[20]**.

The majority of instances of BC are ER-positive, and since this boosts breast epithelial cell proliferation, it makes it a target for anti-hormonal cancer therapy. TMX was identified as one of the most extensively studied ER antagonists in the past 50 years, helping millions of women. In addition to its direct and indirect effects on cellular lipid metabolism, TMX has been asserted to decrease blood cholesterol levels and guard against cardiovascular illnesses **[21]**.

As a selective ER receptor modulator, TMX has reduced BC-related mortality by 25–30%. Due to the development of late resistance after extended exposure to the medication, especially in the metastatic setting, about one-third of

women treated with TMX had a heightened risk of recurrence in the next ten years **[18]**.

Mechanisms of TMX resistance in BC include but are not limited to the following **[22]**;

1. Modifications in TMX availability or metabolism.
2. Changes in ER receptor and signaling.
3. Alteration in metabolism.
4. Alteration in mitochondrial bioenergetics.

These mechanisms are summarized in **Fig. 1.**

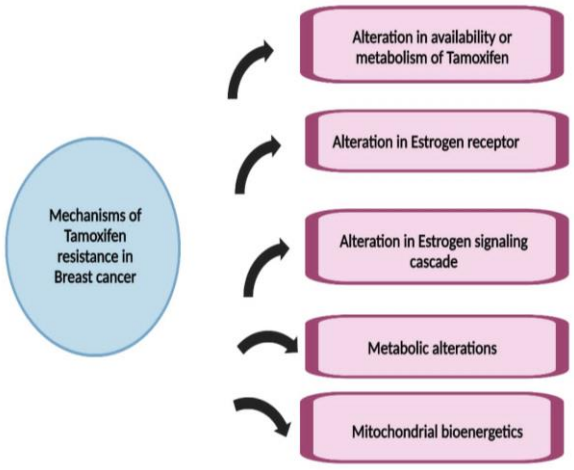

Fig. 1. Schematic diagram representing mechanisms of TMX resistance in BC

3. Taurine upregulated 1

3.1. Different functions and mechanisms

Taurine up-regulated 1 (TUG1) is a long non-coding RNA (lncRNA) with a 7,598-nucleotide sequence that is mostly located on chromosome 22q12.2. Its genesis was determined using the genes of mouse retinal cells treated with taurine **[23]**. Human cancer is closely intersected with TUG1 as a novel lncRNA **[24]**. TUG1 helped several essential regulatory tasks in several biological processes connected to cancer, which in turn gave an imagined unique therapeutic approach for the disease. A few previous meta-analyses have emphasized that increased TUG1 expression is a warning sign for human cancer. Additionally, TUG1 was deemed to be extremely well associated with expanding tumor size, an advanced clinical stage, and metastasis **[25, 26].** TUG1 is thought to regulate genes through a variety of diverse methods, including acting as a micro-RNA (miRNA) sponge, according to recent studies **[27, 28]**. TUG1 also has a crucial role in being a competing endogenous RNA (ceRNA) to target miRNA, aiming for their biological functions' suppression **[29]**. Downstream target genes' levels of expression fluctuate as a result. TUG1 recruits and binds with polycomb repressive complex 2 **[27]**, which has methyltransferase activity and is made up of the protein's retinoblastoma-associated protein 46/48, enhancer of zeste homolog 2 and suppressor of zeste 12 protein homolog. The lysine residue 27 on histone 3 is di- and tri-methylated by this combination. Epigenetic silencing results from the binding of TUG1 to polycomb repressive complex 2, which guides the associated genomic DNA to polycomb bodies **[30]**.

Zinc finger E-box binding homeobox 1, the **miR-145** target, is expressed more often as a result of TUG1's ability to insulate it. Therefore, TUG1 controls this signaling pathway to induce enhanced cell proliferation **[31]**.

TUG1 acts as an oncogene in cervical cancer by interacting with **miR138p** and neutralizing it. Sirtuin 1 is increased by TUG1 because it competes with miR138p. A high level of Sirtuin 1 expression suppresses the production of E-cadherin while promoting the expression of c-myc, -catenin, and cyclin D1. This results in the Wnt/catenin signaling pathway being activated, which then inhibits apoptosis and promotes the proliferation and invasion of cervical cancer cells **[32]**.

According to a prior study, TUG1 upregulates the expression of the astrocyte-elevated gene 1 via sponging **miR-129-5p** in human metastatic melanoma. Through phosphatidylinositol 4,5-bisphosphate 3 kinase and Wnt signaling pathways, astrocyte-elevated gene-1 plays a significant role in carcinogenesis. When this axis is active, malignant melanoma cells proliferate less and endure more apoptosis **[33]**.

It has been proven that TUG1 regulates oral squamous cell cancer through sponging **miR219** to control its expression. Additionally, by acting as an endogenous sponge of **miR-9** and influencing the expression of the miR-9 target gene, methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2, TUG1 stimulates cell proliferation and prevents apoptosis in BC cells **[34]**. TUG1 also enhances cell proliferation in gallbladder carcinoma by inhibiting **miR-300 [35]**.

TUG1 may alter gene expression by distinct mechanisms controlling different biological processes. These processes include but are not limited to the following **[36]**;

1. Cell migration, invasion, differentiation, and death.

2. Resistance to drugs.

3. Resistance to radiation

4. Angiogenesis

5. Mitochondrial bioenergetics.

6. Epithelial-mesenchymal transition (EMT).

7. The control of blood tumor barrier permeability.

TUG1 functions and mechanisms are summarized in **Fig. 2.**

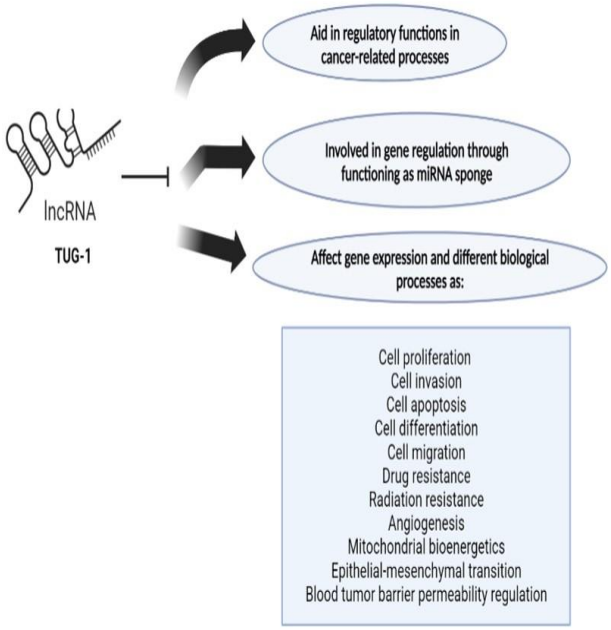

Fig. 2. Schematic diagram representing mechanisms and functions of TUG1

3.2 Expression in breast cancer therapy

In BC, it has been determined that lncRNAs play a critical part in the onset, progression, and development of anti-ER resistance. Additionally, it has been shown that a novel molecular categorization of BC based on lncRNA expression exists and that around two-thirds of the lncRNAs expressed in BC are localized in enhancer areas **[37]**.

Evidence suggests that TUG1 is increased in BC **[38]**. Recently, 100 samples of malignant breast tissue were examined for the presence of TUG1 hyperexpression, and this finding was connected to BC malignancy characteristics such as tumor size and distant metastasis **[39]**. TUG1 can also act as an oncogene or a possible tumor suppressor due to aberrant regulation of the gene during carcinogenesis **[40]**. TUG1 was overexpressed in human BC, and another investigation found that its expression was strongly correlated with tumor aggressiveness **[41]**.

Additionally, a recent study found that BC tissues and cells have significant levels of TUG1 expression. Reduced proliferation and higher apoptosis of BC cells were positively correlated with TUG1 knockdown **[42]**. Recent research identified TUG1 as an elevated lncRNA in BC tissues using comparative profiling of lncRNAs between BC tissues and peritumor tissues **[43]**.

TUG1 has a strong propensity for the virulent side effects of traditional carcinogenic medications like TMX, establishing their curative impact. Comparing the plasma levels of TUG-1 in the two groups, an innovative study found that patients resistant to TMX had significantly higher TUG-1 levels than TMX-responsive individuals **[40]**. TUG1 expression was characterized to be diminished by TMX treatment, meaning that TUG1 downregulation can be used as a hallmark of cancer treatment **[44] (Table 1)**.

Table 1. Summary of all studies showing TUG1 expression in BC

TUG1 expression	References for studies
Upregulated in BC	**[38] [43]**
Hyperexpression in 100 samples of cancerous breast tissue	**[39]**
Overexpressed in human BC	**[41]**
Highly expressed in BC tissues and cells	**[42]**

Conclusion

Non-coding RNAs (ncRNAs), which are considered to be excellent diagnostic and advantageous prognostic indicators and therapeutic targets in BC, are anticipated to possess a decisive role in the epigenetic control of target genes **[45]**. Indeed, several lncRNAs and miRNAs manifest mitochondrial and metabolic abnormalities amendments **[46]**. Information on lncRNAs' role in cancer has accumulated during the past ten years.

The discovery of effective medications and prospective targets for the treatment of BC patients has been strengthened by outstanding efforts. LncRNAs perform as oncogenes and tumor suppressors in addition to being excellent prognostic indicators for BC **[47]**.

TUG1 exerts its action as a major regulator of drug resistance by sponging miRNAs and affecting the expression of some cancer-related genes **[43]**. The recognition of TUG1 as a pivotal mediator of BC progression implies that it might serve as a biomarker for the diagnosis and treatment of BC **[41]**. Future research on TUG1 indexing processes in cancer cells may provide a number of novel therapeutic approaches for the treatment of malignancies. Current and future research must concentrate on understanding the underlying molecular processes of TUG1 **[36]**.

It's essential to look for TMX resistance mechanisms in BC patients. In addition, it is important to search for an effective marker for treating BC patients who are resistant to TMX. Nevertheless, even though TUG1 and TMX have a role in many malignancies, research on their relationship to BC development is still ongoing. Therefore, the purpose of this investigation was to ascertain the clinical importance and biological roles of TUG1 in BC. This review's data suggested that TUG1 is essential for BC cell proliferation and metastasis. In order to

comprehend, perceive, and forecast illness processes, it is crucial to examine the remarkable impact that TMX resistance has on BC patients.

List of Abbreviations

BC	Breast cancer
CeRNA	Competing endogenous RNA
DNA	Deoxy ribonucleic acid
EMT	Epithelial-mesenchymal transition
ER	Estrogen
GI	Gastrointestinal
lncRNA	Long non-coding RNA
miRNA	micro-RNA
ncRNAs	Non-coding RNAs
QOL	Quality of life
TMX	Tamoxifen

Declarations

Consent to publish

All authors have read and agreed to the published version of the manuscript

Ethics approval and consent to participate

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article in the main manuscript.

Competing interests

No competing interests were declared by the authors

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Authors' contributions

Hany N. Azzam: collecting literature, and writing the first draft of the review.

Marwa O. El-Derany, Sara A. Wahdan, Reham M. Faheim, Gouda K. Helal & Ebtehal El-Demerdash: organizing, editing, and reviewing the manuscript.

All authors read and approved the final manuscript.

4. References

1. Siegel, R.L., K.D. Miller, N.S. Wagle, and A. Jemal, Cancer statistics, 2023. CA Cancer J Clin, 2023. 73(1): p. 17-48.
2. Bray, F., J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, and A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin, 2018. 68(6): p. 394-424**.**
3. Ibrahim, A.H. and E. Shash, General Oncology Care in Egypt, in Cancer in the Arab World, H.O. Al-Shamsi, et al., Editors. 2022, Springer Singapore: Singapore. p. 41-61.
4. Torre, L.A., F. Bray, R.L. Siegel, J. Ferlay, J. Lortet-Tieulent, and A. Jemal, Global cancer statistics, 2012. CA: a cancer journal for clinicians, 2015. 65(2): p. 87-108.
5. Nelson, K.A., D. Walsh, O. Abdullah, F. McDonnell, J. Homsi, S. Komurcu, S.B.

LeGrand, and D.S. Zhukovsky. Common complications of advanced cancer. in Seminars in oncology. 2000.

6. Zimmer, L., S.M. Goldinger, L. Hofmann, C. Loquai, S. Ugurel, I. Thomas, M.I. Schmidgen, R. Gutzmer, J.S. Utikal, and D **.**Göppner, Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. European Journal of Cancer, 2016. 60: p. 210-225.

7. Dimos, A.K., P.N. Stougiannos, and A.G. Trikas, First, do no harm": chemotherapy or healthy heart. Hellenic J Cardiol, 2012. 53(2): p. 127-136**.**

8. Stergiopoulos, K., S. Vasu, T. Bilfinger, and M. Poon, Embolic stroke in a patient with metastatic renal cell cancer. Hellenic J Cardiol, 2011. 52(3): p. 256-58**.**

9. Thuro, B., S. Thakar, O. Sagiv, D.P. Kontoyiannis, and B. Esmaeli, Orbital Cellulitis in Cancer Patients, in Orbital Cellulitis and Periorbital Infections. 2018, Springer. p. 161-173.

10. Wagner, L. and D. Cella, Fatigue and cancer: causes, prevalence and treatment approaches. British journal of cancer, 2004. 91(5): p. 822.

11. Markman, M., Common complications and emergencies associated with cancer and its therapy. Cleveland Clinic journal of medicine, 1994. 61(2): p. 105-14; quiz 162**.**

12. McPherson, K., C.M. Steel, and J.M. Dixon, ABC of breast diseases. Breast cancer-epidemiology, risk factors, and genetics. Bmj, 2000. 321(7261): p. 624-8.

13. Colditz, G.A. and B. Rosner, Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. Am J Epidemiol, 2000. 152(10): p. 950-64.

14. Omar, S., H. Khaled, R. Gaafar, A.R. Zekry, S. Eissa, and O. el-Khatib, Breast cancer in Egypt: a review of disease presentation and detection strategies. East Mediterr Health J, 2003. 9(3): p. 448-63.

15. Cheville, A.L., A.B. Troxel, J.R. Basford, and A.B. Kornblith, Prevalence and treatment patterns of physical impairments in patients with metastatic breast cancer. J Clin Oncol, 2008. 26(16): p. 2621-9.

16. Smoot, B., M. Wampler, and K.S. Topp, Breast Cancer Treatments and Complications: Implications for Rehabilitation. Rehabilitation Oncology, 2009. 27.(3)

17. Pondé, N.F., D. Zardavas, and M. Piccart, Progress in adjuvant systemic therapy for breast cancer. Nature Reviews Clinical Oncology, 2019. 16(1): p. 244.-7

18. Haque, M.M. and K.V. Desai, Pathways to Endocrine Therapy Resistance in Breast Cancer. Front Endocrinol (Lausanne), 2019. 10: p. 573.

19. Clifford, R.E., D. Bowden, E. Blower, C.C. Kirwan, and D. Vimalachandran, Does tamoxifen have a therapeutic role outside of breast cancer? A systematic review of the evidence. Surg Oncol, 2020. 33: p. 100-107.

20. Escudero, C., S. Rodríguez-Mozaz, and L. Ferrando-Climent, Tamoxifen: Occurrence, Fate, Transformation Products, and Non-Conventional Treatment Technologies. 2020. p. 71-86**.**

21. Hultsch, S., M. Kankainen, L. Paavolainen, R.M. Kovanen, E. Ikonen, S. Kangaspeska, V. Pietiäinen, and O. Kallioniemi, Association of tamoxifen resistance and lipid reprogramming in breast cancer. BMC Cancer, 2018. 18(1): p.850 .

22. Clarke, R., T.C. Skaar, K.B. Bouker, N. Davis, Y.R. Lee, J.N. Welch, and F. Leonessa, Molecular and pharmacological aspects of antiestrogen resistance. J Steroid Biochem Mol Biol, 2001. 76(1-5): p. 71-84.

23. Zhang, S., X. Liu, J. Liu, H. Guo, H .Xu, and G. Zhang, PGC-1 alpha interacts with microRNA-217 to functionally regulate breast cancer cell proliferation. Biomed Pharmacother, 2017. 85: p. 541-548.

24. Zhou, H., L. Sun, and F. Wan, Molecular mechanisms of TUG1 in the proliferation, apoptosis ,migration, and invasion of cancer cells. Oncology letters, 2019. 18(5): p. 4393-4402.

25. Li, N., K. Shi, X. Kang, and W. Li, Prognostic value of long non-coding RNA TUG1 in various tumors. Oncotarget, 2017. 8(39): p. 65659-65667.

26. Zhou, Y., Y. Lu, R .Li, N. Yan, X. Li, and T. Dai, Prognostic role of long non-coding RNA TUG1 expression in various cancers: a meta-analysis. Oncotarget, 2017. 8(59): p. 100499-100507.

27. Khalil, A.M., M. Guttman, M. Huarte, M. Garber, A. Raj, D. Rivea Morales, K. Thomas, A. Presser, B.E. Bernstein, A. van Oudenaarden, A. Regev, E.S. Lander, and J.L. Rinn, Many human large intergenic noncoding RNAs associate with chromatin-modifying complexes and affect gene expression. Proc Natl Acad Sci U S A, 2009. 106(28): p. 11667-72.

28. Lin, P.C., H.D. Huang, C.C. Chang, Y.S. Chang, J.C. Yen, C.C. Lee, W.H. Chang, T.C. Liu, and J.G. Chang, Long noncoding RNA TUG1 is downregulated in non-small cell lung cancer and can regulate CELF1 on binding to PRC2. BMC Cancer, 2016. 16: p. 583.

29. Tang, T., Y. Cheng, Q. She, Y. Jiang, Y. Chen, W. Yang, and Y. Li, Long non-coding RNA TUG1 sponges miR-197 to enhance cisplatin sensitivity in triple negative breast cancer. Biomed Pharmacother, 2018. 107: p. 338-346.

30. Wahlestedt, C., Targeting long non-coding RNA to therapeutically upregulate gene expression. Nat Rev Drug Discov, 2013. 12(6): p. 433-46.

31. Lei, H., Y. Gao, and X. Xu, LncRNA TUG1 influences papillary thyroid cancer cell proliferation, migration, and EMT formation through targeting miR-145. Acta Biochim Biophys Sin (Shanghai), 2017. 49(7): p. 588-597.

32. Zhu, J., H. Shi, H. Liu, X. Wang, and F. Li, Long non-coding RNA TUG1 promotes cervical cancer progression by regulating the miR-138-5p-SIRT1 axis. Oncotarget, 2017. 8(39): p. 652.65264-53

33. Long, J., Q. Menggen, Q. Wuren, Q. Shi, and X. Pi, Long Noncoding RNA Taurine-Upregulated Gene1 (TUG1) Promotes Tumor Growth and Metastasis Through TUG1/Mir-129-5p/Astrocyte-Elevated Gene-1 (AEG-1) Axis in Malignant Melanoma. Med Sci Monit :24 .2018 ,p. 1547-1559.

34. Zhao, X.B. and G.S. Ren, LncRNA Taurine-Upregulated Gene 1 Promotes Cell Proliferation by Inhibiting MicroRNA-9 in MCF-7 Cells. J Breast Cancer, 2016. 19(4): p. 349-357.

35. Ma, F., S.H. Wang, Q. Cai, L.Y. Jin, D. Zhou, J. Din and Z.W. Quan, Long non-coding RNA TUG1 promotes cell proliferation and metastasis by negatively regulating miR-300 in gallbladder carcinoma. Biomed Pharmacother, 2017. 88: p. 863-869.

36. Zhou, H., L. Sun, and F.J.O.l. Wan, Molecular mechanisms of TUG1 in the proliferation, apoptosis, migration, and invasion of cancer cells. 2019. 18(5): p. 4393-4402.

37. Rondón-Lagos, M., V.E. Villegas, N. Rangel, M.C. Sánchez, and P.G. Zaphiropoulos, Tamoxifen Resistance: Emerging Molecular Targets. Int J Mol Sci, 201 .6 .(8)17

38. Zeng, B., H. Ye, J. Chen, D. Cheng, C. Cai, G. Chen, X. Chen, H. Xin, C. Tang, and J. Zeng, LncRNA TUG1 sponges miR-145 to promote cancer progression and regulate glutamine metabolism via

Sirt3/GDH axis. Oncotarget, 2017. 8(69): p. 113650-11.3661

39. Li, T., Y. Liu, H. Xiao, and G. Xu, Long non-coding RNA TUG1 promote cell proliferation and metastasis in human breast cancer. Breast Cancer, 2017. 24(4): p. 535-543.

40. Azzam, H.N., M.O. El-Derany, S.A. Wahdan, R.M. Faheim, G.K. Helal, and E.J.S.R. El-Demerdash, Metabolic/hypoxial axis predicts tamoxifen resistance in breast cancer. 2022. 12(1): p. 1-13.

41. Li, T., Y. Liu, H. Xiao, and G.J.B.C. Xu, Long non-coding RNA TUG1 promotes cell proliferation and metastasis in human breast cancer. 20 :(4)24 .17p. 535-543.

42. Zhao, X.-b. and G.-s.J.J.o.b.c. Ren, LncRNA taurine-upregulated gene 1 promotes cell proliferation by inhibiting microRNA-9 in MCF-7 cells. 2016. 19(4): p. 349-357.

43. Wang, S., M. Cheng, X. Zheng, L. Zheng, H. Liu, J. Lu, Y. Liu, W.J.O. Chen, and therapy, Interactions between lncRNA TUG1 and miR-9-5p modulate the resistance of breast cancer cells to doxorubicin by regulating eIF5A2. 2020. 13: p. 13159.

44. Dehghan, M.H., M. Hedayati, S. Shivaee, H. Shakib, and S.J.G.R. Rajabi, Tamoxifen triggers apoptosis of papillary thyroid cancer cells by two different mechanisms. 2021. 24: p. 101266.

45. Yousefi, H., M. Maheronnaghsh, F. Molaei, L. Mashouri, A. Aref, M. Momeny, and S. Alahari, Long noncoding RNAs and exosomal lncRNAs: classification, and mechanisms in breast cancer metastasis and drug resistance. Oncogene, 2019. 39.

46. Lekka, E. and J. Hall, Noncoding RNAs in disease. FEBS Lett, 2018. 592(17): p. 2884-2900.

47. Yousefi, H., M. Maheronnaghsh, F. Molaei, L. Mashouri, A. Reza Aref, M. Momeny, and S.K.J.O. Alahari, Long noncoding RNAs and exosomal lncRNAs: classification, and mechanisms in breast cancer metastasis and drug resistance. 2020. 39(5): p. 953-974.