https://doi.org/10.48047/AFJBS.6.2.2024.2780-2783

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Use of Long Non-coding RNAs as Novel biomarkers For breast cancer Patients

Randa H. Mohamed [a,*], Mohamed M. Alkilany [b], Hoda K. El-feky [a], Bassel T. Abdelmoeim [c], Amal F Abd-Elmageed [a]

[a] Medical Biochemistry Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt
[b] General Surgery Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt
[c] Faculty of Medicine, Ain Shams University, Cairo, Egypt

Corresponding author: Randa H. Mohamed
Email: randahussiny@yahoo.com

Article History

Volume 6, Issue 2, Apr-Aug 2024

Received: 10 August 2024

Accepted: 20 August 2024

Published: 20 August 2024

doi: 10.48047/AFJBS.6.2.2024.2780-2783

Abstract: Background: Breast cancer (BC) has been considered as the commonest malignant tumour in females and represents the main etiology of cancer morbimortality among females all over the world. Novel biomarkers are needed for rapid diagnosis and treatment. Long non-coding RNAs (lncRNAs) are broadly expressed and have main roles in terms of gene regulation. lncRNAs have exhibited oncogenic or tumor-suppressive functions with regard to BC pathogenesis. Of note, LncRNAs are downregulated in BC. In brief, owing to the tissue-specialized expressions of lncRNAs, they may be utilized as molecular biomarkers in breast cancer.

Keywords: *breast cancer; lncRNA; molecular biomarker*

Introduction

Breast cancer (BC) has been considered as the commonest malignant tumour in females. In addition recent studies have displayed that; its incidence rate is increasing annually **[1].** Based on the author's prediction, by 2050, the number of affected cases will reach 3.2 million. Most remarkably, in recent years, younger females tend to be affected, which is contrary to the previous years being predominantly developed in older females **[2].**

In 2020 breast cancer mortality-to-incidence ratio (MIR) in locations with developed health care, 5-year survival was 89.6% and in less developed nations the survival rates were 76% **[3]**. With regard to Egypt, BC has been considered the commonest malignant tumour among females representing about 40% of females all malignant tumours and the main etiology of death representing 30% of cancer-associated death **[4].**

Many risk factors have been accompanied by BC pathogenesis including, female sex, older age, early menarche, and late menopause, positive family history, diabetes, exogenous estrogen, lifestyle factors including (Dietary fat, Alcohol intake, cigarette smoking) and radiation to the Chest **[5].**

Different radiological modalities and biochemical biomarkers are utilized for the determination and monitoring of BC cases and emphasized that it is useful to manage cases with BC**.** Molecular biotechnological examination could diagnose BC earlier than radiological modalities. On the other hand, it could not substitute the radiological approaches and become a secondary approach for BC diagnosis. Such approaches aid us in analyzing BC at the level of cells, proteins, and nucleic acids **[6]**.

Definition and Classification of Long non-coding RNA (lncRNAs)

Approximately fifty two percent of the human genome is transcribed; however, 1.2% of the transcripts codify for proteins. Of note, most of the transcripts are represented by ncRNAs **[7]**.

LncRNAs are classified as RNA molecules of longer than two hundred nucleotides that don't appear to code for any proteins. The human transcriptome has annotations for over 10,000 lncRNAs, and the genes corresponding to these transcripts have been identified as intergenes or intragenes. Till now, a limited number of them are totally characterized **[8]**.

lncRNAs play an essential role with regard to gene expression tuning through a direct affection of chromatin remodeling, serving as scaffolds to adjust the activities of proteins and RNAs, controlling mRNA stability, and splicing, and affecting mRNA translations **[9].**

lncRNAs and breast cancer

Long ncRNAs have a main role in different malignant tumour types such as BC. Dysregulation of lncRNA expression is demonstrated to participate in BC development. In addition, the great majority of lncRNAs are concerned with metastatic processes **[10]**. LncRNAs have possible utilization as a new tumour therapeutic target and biomarker due to their role in the initiation, progression, and metastasis of BC **[11]**.

HOX transcript antisense intergenic lncRNA **(**HOTAIR) is a transacting lncRNA, transcribed from the HOXC locus on chromosome 12q13.13, that directs silencing complexes to particular locations across the genome.

Of note, healthy mammary epithelia have been associated with minimal HOTAIR expression; on the other hand, in BC, HOTAIR expression has a progressive course. In the context of primary tumours, high HOTAIR expression seemed to have a strong correlation with reduced metastasis-free survival and overall survival **[10]**.

The non-homologous end joining pathway 1 (LINP-1) has been considered as another lncRNA which is classified as an oncogenic lncRNA in multiple malignant tumours. Its chromosomal site is 10p14. A lot of records reinforce LINP1 over-expression role in BC cases with various types. Likewise, in *HOTAIR,* it has been recorded that blockade of LINP1 in BC cells is of great importance to raise cancer cell sensitivity to radiotherapy **[12]**.

The human PNUTS (protein phosphatase 1 nuclear targeting subunit) gene encodes 2 variants, the PNUTS mRNA and the lncRNA-PNUTS, which are generated owing to alternative splicing site utilization. Differential processing of the PNUTS preRNA has been demonstrated to be accompanied by upregulation of lncRNA-PNUTS expression in breast tumours in comparison to their non-tumour counterparts, and increased expression of lncRNA-PNUTS correlates with that of mesenchymal markers **[13]**.

Metastasis-associated lung adenocarcinoma transcript 1 *(MALAT1)* is an oncogenic lncRNA which suppress its tumour-promoting actions in multiple malignant tumours such as BC. Its chromosomal site is 11q13. MALAT1 is a nuclear lncRNA which is greatly conserved among mammals. It is repeatedly recorded that MALAT1 encourages proliferation, tumour development, and metastasis of BC. Additionally, the expression level of MALAT1 was recorded to have a great prognostic value as it has a negative correlation with the survival of ER-negative, and TNBC molecular subtypes. Together, such researches suggest MALAT1 as a core signaling molecule encouraging BC development and as a result a possible therapeutic target for a lot of BC types **[12]**.

Long intergenic nonprotein coding RNA 1638 (LINC01638) has been regarded as a further lncRNA comprised in keeping the mesenchymal features of TNBC cells and was demonstrated overexpressed in HER2-positive BC tissues relative to healthy breast tissues, also strongly correlated with BC progression of TNBC cases **[14]**.
In addition, Liu ad his colleagues recognized a NF-κB interacting lncRNA (NKILA), encoded by a gene at chromosome 20q13, that serves as a tumour suppressor in the context of BC. In fact, NKILA decreases the invasive capability of BC cell lines **[15]**. NKILA serves as a negative regulator to inhibit the basal and cytokine-stimulated NF-κB activities in BC cells by inhibiting IκB Phosphorylation through interaction with the NF-κB:IκB Complex **[15].** Moreover, Nuclear factor-κB (NF-κB) is an essential correlation between inflammation and malignant tumour which underlies the tumor microenvironment. As a result, NKILA could be comprised in the pathogenesis of a broad range of malignant tumours. Much research has reported the roles of NKILA in the blockade of tumour growth and subsequent inhibition of metastatic tumours **[16].**
Long non-coding RNA 00993 (LINC00993) maps on chromosome 10p11.21 **[17].** LINC00993 can suppress BC growth by inducing G0/G1 arrest and regulating key cell cycle-related genes **[18]**. LINC00993 expression levels were significantly greater in Luminal (ER+/PR+/Her2±) BC tissues in comparison with the HER2 subtype **[19].** In the same line, LINC00993 expression could be detected in circulating tumour cells of metastatic BC cases. As a result, its expression state might be useful to recognize the breast origin of circulating tumour cells **[20]**. In addition, Chen and his colleagues revealed that the high LINC00993 expression was accompanied by a better prognosis of BC **[19]**.

Conclusion

It has been concluded that; lncRNAs may have a considerable role in the context of BC diagnosis, and therapeutic development. In addition, they may act as talented diagnostic and prognostic biomarkers in BC.

References

1. DeSantis, C. E., Ma, J., Gaudet, M. M., Newman, L. A., Miller, K. D., Goding Sauer, A., et al. Breast cancer statistics, 2019. CA: a cancer journal for clinicians,2019. 69(6), 438-451.
2. Feng, R. M., Zong, Y. N., Cao, S. M., & Xu, R. H. Current cancer situation in China: good or bad news from the 2018 Global Cancer Statistics?. Cancer communications,2019. 39(1), 1-12.
3. Łukasiewicz S, Czeczelewski M, Forma A, Baj J, Sitarz R, Stanisławek A. Breast Cancer-Epidemiology, Risk Factors, Classification, Prognostic Markers, and Current Treatment Strategies-An Updated Review. Cancers (Basel). 2021 25;13(17):4287.
4. Ahmed, R. A., & Yussif, S. M. Immunohistochemical detection of human cytomegalovirus, Epstein-Barr virus and human papillomavirus in invasive breast carcinoma in Egyptian women: A tissue microarray study. J Solid Tumors,2016. 6(2), 8-16.
5. Tao, Z., Shi, A., Lu, C., Song, T., Zhang, Z., & Zhao, J. Breast cancer: epidemiology and etiology. Cell biochemistry and biophysics,2015. 72(2), 333-338.
6. Jafari, S. H., Saadatpour, Z., Salmaninejad, A., Momeni, F., Mokhtari, M., Nahand, J. S., et al. Breast cancer diagnosis: Imaging techniques and biochemical markers. Journal of cellular physiology,2018. 233(7), 5200-5213.
7. Fatica A, Bozzoni I. Long non-coding RNAs: new players in cell differentiation and development. Nat Rev Genet. 2014;15: 7-21.
8. Ransohoff JD, Wei Y, Khavari PA. The functions and unique features of long intergenic noncoding RNA. Nat Rev Mol Cell Biol. 2018;19: 143-157.
9. Amelio I, Melino G. Context is everything: extrinsic signalling and gain-of-function p53 mutants. Cell Death Discov. 2020;6: 16.
10. Sørensen, K. P., Thomassen, M., Tan, Q., Bak, M., Cold, S., Burton, M., et al. Long non-coding RNA HOTAIR is an independent prognostic marker of metastasis in estrogen receptor-positive primary breast cancer. Breast Cancer Res Treat. 2013;142: 529-536.
11. Liang, D., Liu, H., Yang, Q., He, Y., Yan, Y., Li, N., et al. Long noncoding RNA RHPN1-AS1, induced by KDM5B, is involved in breast cancer via sponging miR-6884-5p. J Cell Biochem. 2020.
12. Youness RA, Gad MZ. Long non-coding RNAs: Functional regulatory players in breast cancer. Noncoding RNA Res. 2019 Feb 5;4(1):36-44.
13. Grelet, S., Link, L. A., Howley, B., Obellianne, C., Palanisamy, V., Gangaraju, V. K., et al. A regulated PNUTS mRNA to lncRNA splice switch mediates EMT and tumour progression. Nat Cell Biol. 2017;19: 1105-1115.

14. Liu, P., Tang, H., Wu, J., Qiu, X., Kong, Y., Zhang, L., et al. Linc01638 Promotes Tumorigenesis in HER2+ Breast Cancer. Curr Cancer Drug Targets. 2019;19: 74-80.
15. Liu, B., Sun, L., Liu, Q., Gong, C., Yao, Y., Lv, X., et al. A cytoplasmic NF-kappaB interacting long noncoding RNA blocks IkappaB phosphorylation and suppresses breast cancer metastasis. Cancer Cell. 2015;27: 370-381.

16. Hussen, B. M., Azimi, T., Hidayat, H. J., Taheri, M., & Ghafouri-Fard, S. NF-KappaB interacting LncRNA: Review of its roles in neoplastic and non-neoplastic conditions. Biomedicine & Pharmacotherapy,2021: 139, 111604.
17. Guo, S., Jian, L., Tao, K., Chen, C., Yu, H., & Liu, S. Novel breast-specific long non-coding RNA LINC00993 acts as a tumor suppressor in triple-negative breast cancer. Frontiers in oncology,2019. 9, 1325.
18. Zangouei AS, Zangoue M, Taghehchian N, Zangooie A, Reza Rahimi H, Saburi E., et al. Cell cycle related long non-coding RNAs as the critical regulators of breast cancer progression and metastasis. Biological Research. 2023;56.
19. Chen, C., Yang, L., Rivandi, M., Franken, A., Fehm, T., & Neubauer, H. Bioinformatic Identification of a Breast-Specific Transcript Profile. PROTEOMICS–Clinical Applications,2020. 14(6), 2000007.
20. Gallo, M., De Luca, A., Maiello, M. R., D'Alessio, A., Esposito, C., Chicchinelli, N., et al. Clinical utility of circulating tumor cells in patients with non-small-cell lung cancer. Translational lung cancer research,2017. 6(4), 486.