Current Trends in OMICS (CTO)
Volume 4 Issue 2, Fall 2024
ISSN$_{(P)}$: 2790-8283, ISSN$_{(E)}$: 2790-8291
Homepage: https://journals.umt.edu.pk/index.php/cto

Article QR

Title: **Decoding Breast Cancer Progression: Influence of miR-155-3p as Modulator of Molecular Signaling Pathways and Genetic Targets**

Author (s): Faiza Arshad[1], Muhammad Bilal[2], Zeeshan Mutahir[1], Muhammad Khurshid[1], Saima Suleman[3], and Naeem Mahmood Ahsraf[1]

Affiliation (s): [1]University of the Punjab, Lahore, Pakistan.
[2]Nawaz Sharif Medical College, Gujrat, Pakistan
[3]King Saud University, Riyadh, Saudi Arabia.

DOI: https://doi.org/.10.32350/cto.42.04

History: Received: July 03, 2024, Revised: August 12, 2024, Accepted: October 01, 2024, Published: November 10, 2024

Citation: Arshad F, Bilal M, Mutahir Z, Khurshid M, Suleman S, Ahsraf NM. Decoding breast cancer progression: influence of miR-155-3p as modulator of molecular signaling pathways and genetic targets. *Curr Trend OMICS*. 2024;4(2):60–76. https://doi.org/.10.32350/cto.42.04

Conflict of Interest: Author(s) declared no conflict of interest

A publication of
The Department of Life Sciences, School of Science
University of Management and Technology, Lahore, Pakistan

Decoding Breast Cancer Progression: Influence of miR-155-3p as Modulator of Molecular Signaling Pathways and Genetic Targets

Faiza Arshad[1], Muhammad Bilal[2], Zeeshan Mutahir[1], Muhammad Khurshid[1], Saima Suleman[3], and Naeem Mahmood Ahsraf[1]*

[1]School of Biochemistry and Biotechnology, University of the Punjab, Lahore, Pakistan
[2]Nawaz Sharif Medical College, Gujrat, Pakistan
[3]Department of Community Health Sciences, College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia

ABSTRACT

Breast cancer is an eminent cause of fatality in women, worldwide. It is predominantly propelled by aberrant gene expression. A pivotal element in this mechanism is the disrupted regulation of microRNAs, particularly miR-155-3p. This investigation delves into the impact of miR-155-3p in breast cancer by employing advance methodologies, such as KEGG, DIANA, and Reactome Database, in order to unveil its genetic targets and molecular repercussions. It identifies six genes targeted and downregulated by miR-155-3p in breast cancer cells. This downregulation disrupts multiple vital biological pathways, including MAPK, AKT, STAT3, NFkB, and NOTCH signaling. These pathways play a crucial role in cellular processes, such as angiogenesis, apoptosis, DNA damage response, cell cycle control, and oncogene expression. Modifying these pathways by miR-155-3p underscores its substantial influence on the progression of breast cancer. The findings exemplify that the upregulation of miR-155-3p is a major contributing factor in the advancement of breast cancer. This upregulation initiates a series of molecular events that intensify the disease. Comprehending this mechanism is imperative for the development of targeted therapies. The implications of this research extend beyond the scientific community, presenting the potential for groundbreaking clinical applications. Furthermore, it establishes that miR-155-3p can be used as a diagnostic marker for breast cancer. This could significantly transform the landscape of breast cancer management, instilling hope both for improved outcomes and preventive strategies.

*Corresponding Author: Naeem.sbb@pu.edu.pk

Keywords: breast cancer, diagnostic marker, miR-155-3p, Reactome Database, signaling pathways, targeted therapies

1. INTRODUCTION

Breast cancer is the second major cause of death in women. According to the World Health Organization (WHO), mortality rates vary significantly between regions. In high-income countries, five-year survival rates exceed 90%. Whereas, in low-income countries, they can be as low as 40%. Different factors affect breast cancer but the dysregulation of gene expression is more prominent, which has a connection with the suppression or overexpression of microRNAs (miRNA) [1]. miRNA is responsible for controlling target genes as non-coding RNAs by targeting their transcripts of messenger RNA or causing protein synthesis inhibition. miRNA binds to target genes in regulatory regions. These regions are mostly available on 3'UTR (3'untranslated region) for binding. Different studies show that miRNAs regulate about 30% of eukaryotic genes [2].

About 29 miRNAs are involved in breast cancer. All these miRNAs are downregulated in this cancer, except miRNA 155-3p which is upregulated in breast cancer [3]. The expression of miRNA-155 extensively increase in breast cancer and has a strong association with progressing stage, tumor grade, and lymph node. Interestingly, this miRNA is also associated with cancer [4].

Usually, tumors activate a genomic pathway to respond to hypoxia. So, most miRNAs are dependent on the hypoxia-induced pathway and HIF-1a (oxygen homeostasis regulator). Recent studies revealed that miRNA 155-3p plays a key role in HIF1 alpha induced-angiogenesis and the expression of this miRNA is considerably regulated in breast cancer. The relative expression of miRNA 155-3p is considerably greater in breast cancer tissues, as compared to normal tissues [5]. Moreover, the levels of miRNA 155-3p are adversely linked to VHL protein which plays an important role in cell division and inhibits the HIF1 family [6].

Each miRNA has a wide range of target sites. So, this study emphasizes checking different genes targeted by miR-155-3p during breast cancer to understand the cancerous behavior of the breast. Further, the study provides insights regarding the different pathways and mediators involved in cancer progression.

2. METHOD

2.1. Selection of miRNA

A meta-analysis conducted by Liu et al. [7] revealed that miRNA155-3p is upregulated in breast cancer tissues, suggesting a significant role in the disease's progression. Based on this finding, the current study further explores the role of miRNA155-3p in cancer progression, employing various bioinformatics tools. The detailed methodology is shown below in Figure 1.

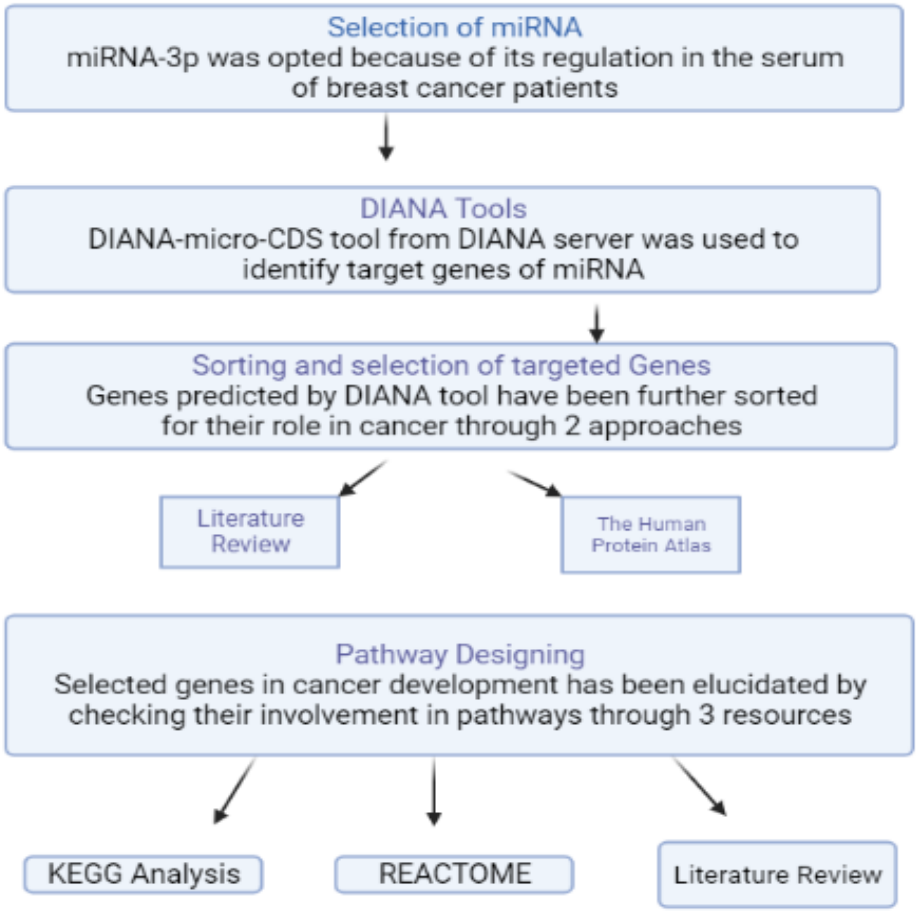

Figure 1. The Flowsheet of Methodology Including All the Tools and Databases Utilized

2.2. DIANA Tools

DIANA TOOLS (diana.imis.athena-innovation.gr/) was used for the identification of genes targeted by miR-155-3p. DIANA-microT-CDS (http://www.microrna.gr/microT-CDS) was also used to increase the predicted power for making specific predictions in human beings [8]. Moreover, this software is specialized for MREs (miRNA recognition elements) on CDS and 3' UTR regions. A threshold of 0.7 was applied to minimize false positives and negatives. miTG score, calculated by using DIANA, is the output that consists of two different values including distinct scores and a common score.

2.3 Selection and Sorting Out of Targeted Genes

Different genes were selected by microT-CDS Tools. Then, they were arranged on the basis of their carcinogenic nature. Gene selection was refined through extensive literature review. Human Protein Atlas Database (http://www.proteinatlas.org/) was also used for their sortation [9]. Genes that were directly engaged with metastasis, progression, and biochemical pathways of breast cancer were extracted through literature review. Afterwards, pure sorting was done by using the Human Protein Atlas Database. Other irrelevant genes were ignored.

2.4. Designing Pathways

Complete pathways were designed for selected genes obtained from the above sources. To design pathways or get information regarding the pathways of the selected genes, different pathway databases were used, such as KEGG and Reactome. An extensive literature review was also conducted to get information related to genes involved in breast cancer.

2.4.1. KEGG. KEGG (Kyoto Encyclopedia of Genes and Genomes) is an openly accessible pathway database used to trace different signaling pathways (http://www.genome.jp/kegg/). This pathway database stores all information of cellular processes in pictorial form, including signal transduction, membrane transport, and metabolism. It is used to identify practicable utilities represented in biological systems. Pathway databases maintain their specificity level by adding separate prefixes for each organism. Furthermore, they provide information regarding how genes and relevant molecules interact with each other by representing molecular and biological complex pathways [10].

2.4.2. Reactome. This database is considered a peer-reviewed database. It is used to trace all general pathways involving genes at the molecular level. It comprises a database of different reactions, biological processes, and pathways. Pathways from the Reactome also represent information on major diseases, even at the molecular level [11].

2.4.3. Literature Review. Some selected genes were not present in the designed pathways retrieved from KEGG and Reactome. So, the solution to this problem was to make pathways based on the literature review.

3. RESULTS

DIANA-MicroT-CDS predicted 316 genes linked with miR-155-3p. Out of these 316 genes, 15 play an important role in breast cancer. Through literature review and data mining, a total of 6 genes that were downregulated due to the upregulation of miR-155-3p in the case of breast cancer were collected (Table 1).

Table 1. Genes Downregulated by miRNA-155-3p in Breast Cancer

Sr #	Ensemble Gene ID	Gene Description	Chromosomes	Biological Process	Annotation Source	Expression
1	ENSG00000017427 (IGF-1)	Insulin-like growth factor	12	Cell growth, differentiation	KEGG, hsa:5224	All tissues and cell types during embryogenesis
2	ENSG00000118689 (FOXO3a)	Forkhead boxO3-transcriptional factor	6	Involve in Apoptosis, Proliferation, DNA damage	KEGG; has:04917	Breast, lymphoid organs. Brain, liver, prostate.
3	ENSG00000143507 (DUSP1)	Dual Specificity Phosphatase 1	5	Cell cycle, stress response	KEGG; hsa:04010	Stomach, breast
4	ENSG00000198740 (ZNF652)	Zinc Finger Protein 652	17	Transcription regulation, apoptosis	Uniprot KB; Q9Y2D9 MIM;613907	Skin, testis, spleen, brain, breast
5	ENS00000172216 (CEBPβ)	CCAAT enhancer binding protein β	20	Differentiation, transcription Regulation	Uniprot KB; P17676 MIM;189965	Breast, Kidney, ovary, prostate
6	ENSG00000182985 (CADM1)	Cell Adhesion Molecule 1	11	Apoptosis, cell adhesion, differentiation, immunity,	Reactome; R-HAS-420589	Glandular cells, CNS, islets of Langerhans

These targeted genes are considered to be downregulated in the case of breast cancer due to the upregulation of miR-155-3p. The downregulation of the targeted genes causes metastasis. The progression of tumor in the case of breast cancer occurs via different biological pathways. The summary of the results is given below.

3.1. IGF1

IGF1 (insulin-like growth factor 1) is an important mediator of HGH (human growth hormone). It promotes cell differentiation and cell growth in childhood and has an anabolic effect in adulthood. It is associated with different receptors, growth factors, proteins for apoptosis, cell proliferation, and differentiation as a mediator [12].

The IGF1 gene is also a well-known oncogene because it plays an important role in the progression of breast cancer. The miRNA 155-3p targets the 3'UTR of the mRNA of IGF1 and inhibits its translation, protein formation, and downstream regulation in breast cancer cells [13]. The dysregulation of IGF1 or upregulation of miRNA155-3p enables the miRNA to inhibit IRS1(insulin receptor substrate 1) which acts as a mediator of IGF1 signaling. Due to this inhibition, the IGF1 level is decreased. Further, the downstream regulation of IGF1, such as the activation of MAPK, is dysregulated which leads to invasion and metastasis of breast cancer (Figure 2).

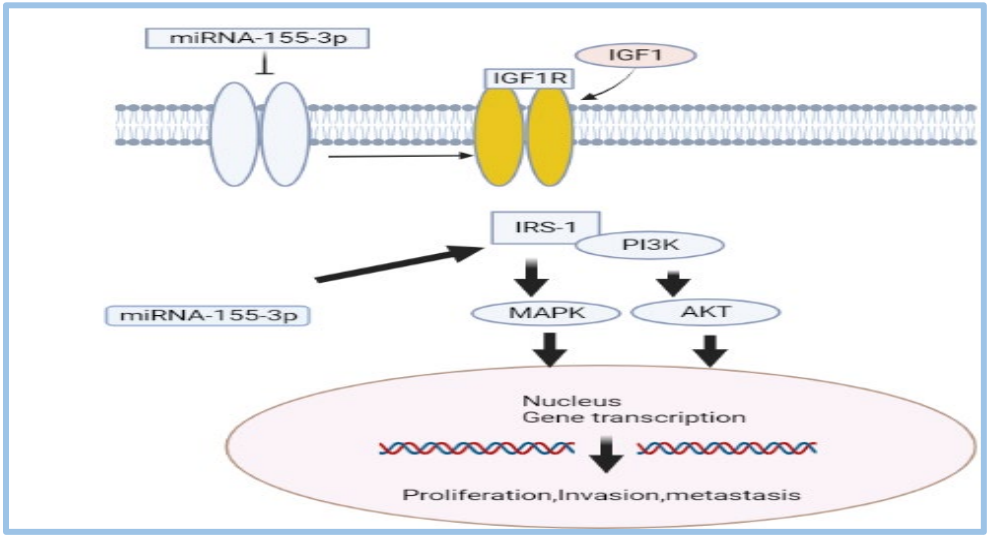

Figure 2. Illustration of IGF1 Signaling Pathway

3.2. FOXO3a

FOXO3a (forkhead box O3) protein is present in human beings and is encoded by the FOXO3 gene. Another name of FOXO3a is FKHRL1. This protein is considered as the main member of the family of forkhead transcription factors. MEK or Akt/PI3K negatively regulates the special forkhead DNA binding domain present in the members of this family. FOXO3a is also known as a tumor suppressor gene. It remains active when present in an unphosphorylated form in the nucleus and increases the apoptotic activity. Over-expression of this gene promotes apoptosis [14].

In breast cancer, the FOXO3a gene is downregulated when targeted by miR-155-3p, which directly targets the 3'UTR of FOXO3a and inhibits the expression of FOXO3a protein. The miR-155-3p does not degrade the mRNA of the target but blocks the translation [15]. With FOXO3a, bim and p27 are important for apoptosis, but the downregulation of this gene by miR155-3p in breast cancer stops apoptotic activity and causes cell cycle arrest (Figure 3).

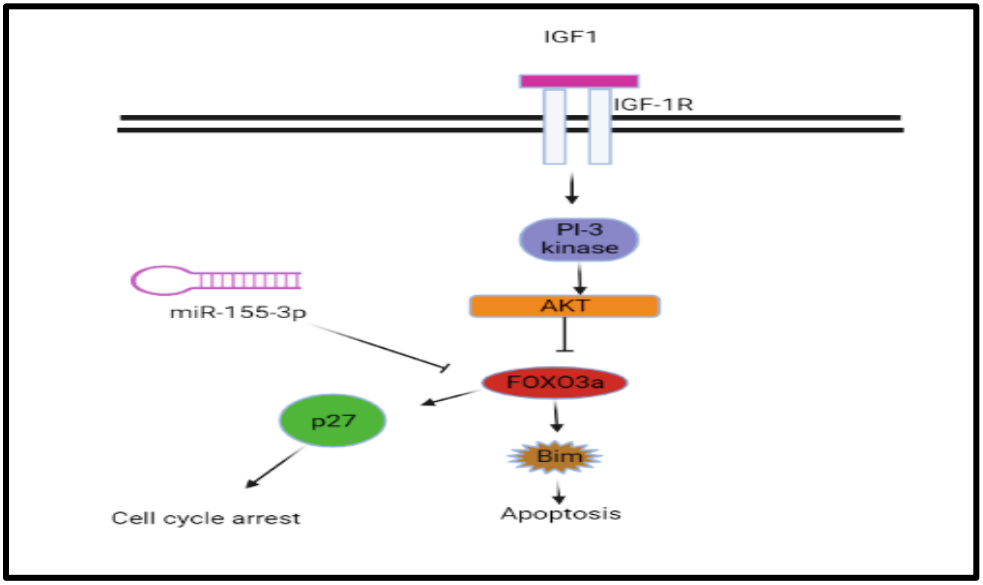

Figure 3. Illustration of FOXO3a Signaling Pathway

3.3. DUSP1 (MKP5)

This gene encodes a phosphate protein with dual specificity for threonine and tyrosine, hence it is known as dual specificity phosphatase 1

or DUSP1. The encoded protein is involved in different cellular processes by the dephosphorylation of MAPK1/ERK2. It performs a remarkable role in the negative regulation of cell proliferation. Its main function is to inhibit MAP kinases [16]. The protein encoded by DUSP1 has the ability to make solid tumors that are resistant to both radiotherapy and chemotherapy. Therefore, this is a potential therapeutic target to treat breast cancer [17].

In normal conditions, DUSP1 encodes a protein that inhibits the MAP kinase pathway to prevent cellular proliferation and inflammation and protects the body from cancer [18]. However, in the case of breast cancer, miR-155-3p is upregulated and due to its upregulation, DUSP1 mRNA does not perform translation, while protein synthesis stops leading to downregulation of DUSP1. Then, DUSP1 loses its ability to inhibit ERK1 and increases the activation of the MAPK signaling pathway, which leads to metastasis and invasion (Figure 4).

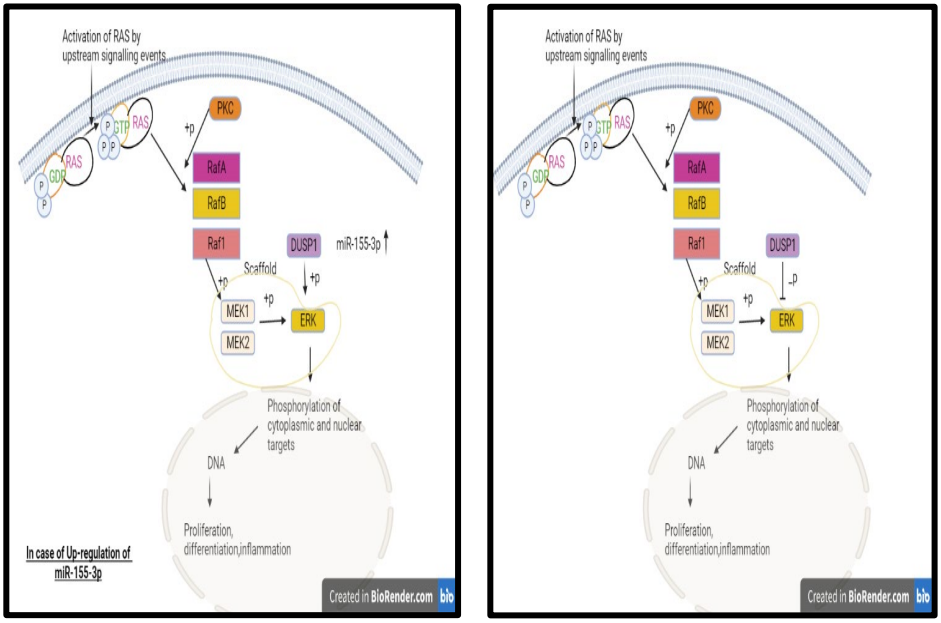

Figure 4. Illustration of DUSP1 Signaling Pathway

3.4. ZNF652

This gene encodes a protein known as zinc finger protein 652 (ZNF 652), which is present in human beings at the location of 17 chromosomes. This protein is composed of 606 amino acids and has 69,744 molecular weight.

ZNF652 gene acts as a tumor suppressor gene and plays an important role in transcription regulation and some other biological processes. This protein has a binding site for DNA and some metal ions such as zinc ions. Mainly, its location is the nucleus.

The upregulation of miR-155-3p leads to the downregulation of ZNF652 and causes metastasis in breast cancer cells. This is because, in normal conditions, this gene acts as a tumor suppressor and increases apoptosis. In Figure 5A, p53 is attached with P63 which blocks the tenure of its promoter let7i, which causes the downregulation of its promoter and upregulates the levels of targets, such as E2F5, MYC, and CPSF1. These targets are responsible for cellular proliferation and invasion. In Figure 5B, due to the upregulation of miR-155-3p, mutant p53 increases the metastatic potential because this microRNA blocks the mRNA of ZNF652, leading to the downregulation of ZNF652 protein and increased metastasis, invasion, and proliferation in breast cancer cells [19, 20] (Figure 5).

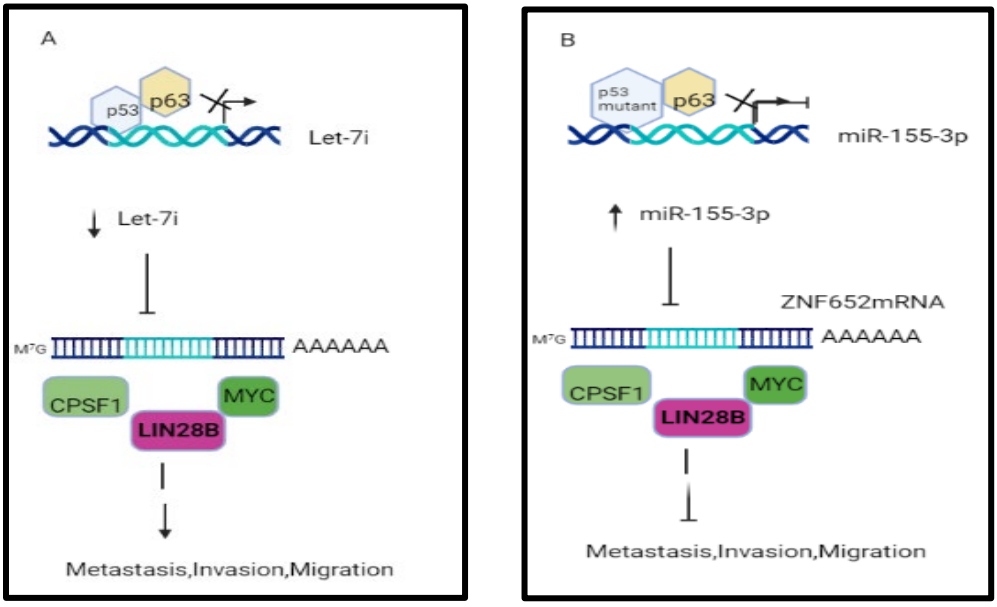

Figure 5. Illustration of ZNF652 Signaling Pathway

3.5. CEBPβ

CEBP gene encodes CCAAT enhancer-binding proteins (C/EBPs) which act as transcription factors (Leucine zipper) to regulate gene expression. CEBP consists of six members namely CEBPα, CEBPβ, CEBPδ,

CEBPϵ, CEBPγ, and CEBPζ. CEBPβ plays an important role in controlling inflammation, proliferation, and differentiation. This gene is considered an intron-less gene. It also regulates those genes that are involved in inflammatory responses, as well as the immune system [21].

In normal conditions, this gene is finely regulated and performs its role in apoptosis and cell proliferation. Its expression is controlled by different growth factors, cytokines, and some hormones. In the case of breast cancer, due to the upregulation of miR-155-3p, MAPK/ERK pathway activates and the phosphorylation of CEBPB by ERK starts to decrease. E3 ubiquitin ligases target this gene and degrade it. This degradation leads to the downregulation of CEBPB protein levels, while TGF beta or cytokines lose their growth inhibitory effect and the cells undergo EMT and metastasis [22] (Figure 6).

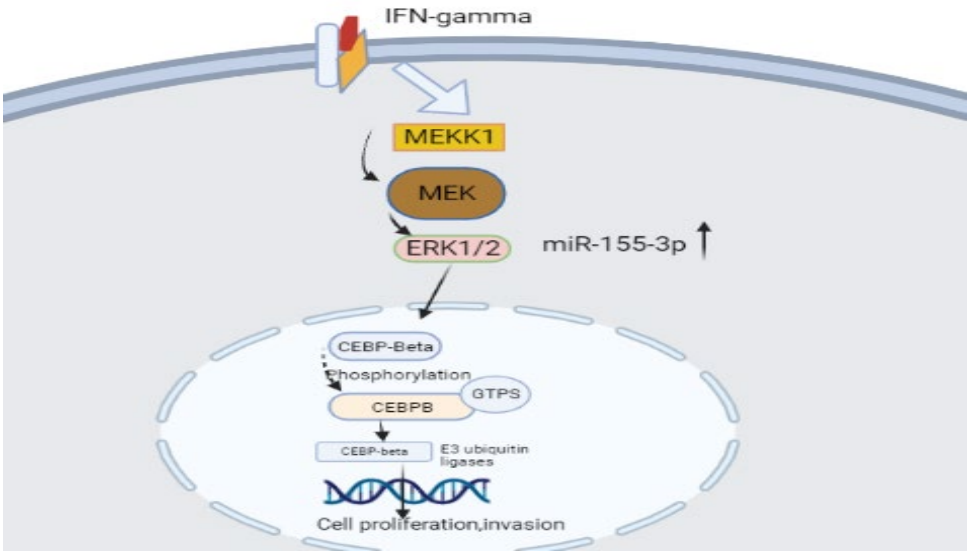

Figure 6. Illustration of CEBPβ Signaling Pathway

3.6. CADM1

CADM1 (cell adhesion molecule 1) protein is present in human beings. This protein plays an important role in signal transduction and cell adhesion. It acts as a tumor suppressor in breast cancer. The upregulation of CADM1 is responsible for apoptosis and has the ability to inhibit tumor proliferation. It actively participates in the regulation of different signaling pathways,

such as AKT, STAT3, and EMT with the help of other cell cycle-related proteins [23].

Some non-coding microRNAs, such as miR-155-3p, directly or indirectly attack CADM1 to increase the growth of tumors and cell motility. The expression of CADM1 is linked with poor prognosis [24]. The stimuli received from outside to receptors present on the membrane activate TWIST and upregulate the level of miR-155-3p with the activation of MAPK, NFkB, and STAT3 pathways. The activation of TWIST inhibits E-cadherin, which is responsible for the inhibition of EMT. Due to the upregulation of miR-155-3p, CADM1 loses the ability to inhibit MAPK, STAT3, and AKT pathways [25], which leads to the proliferation invasion of breast cancer cells (Figure 7).

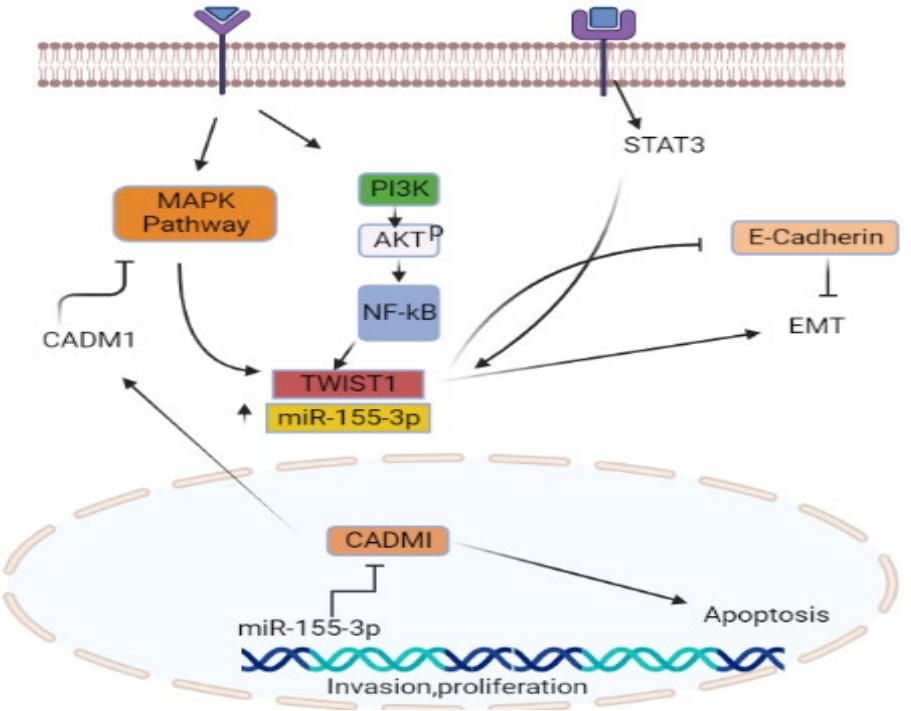

Figure 7. Illustration of CADM1 Signaling Pathway

4. DISCUSSION

Numerous studies consistently indicate that miR-155-3p functions as an oncogene in the development and progression of breast cancer. This non-

coding RNA exhibits dysregulation in breast cancer, as evidenced by its elevated levels in the serum and plasma of the affected patients. The upregulation of miR-155-3p plays a crucial role in cancer progression by inhibiting apoptosis and promoting cell proliferation, thus contributing significantly to the disease's severity [26].

This research identified several genes that are targets of miR-155-3p and also investigated the genotoxic effects of this miRNA on breast cells. The genotoxic impact of miR-155-3p disrupts the normal homeostatic environment, transforming it into a tumor microenvironment conducive to cancer development.

IGF1 is a hormone essential for childhood growth. It is primarily produced in the liver and stimulated by the growth hormone (GH) [27]. It plays a pivotal role in DNA synthesis and interacts with cellular receptors, including the insulin receptor and IGF1R. The binding of IGF1 to its receptor activates the AKT pathways. However, its role in breast cancer remains controversial, especially considering that miR-155-3p upregulation can inhibit IRS1, which is a key mediator in this pathway. This may lead to enhanced cancer progression [28].

The study also highlights the downregulation of FOXO3a and CADM1 due to the upregulation of miR-155-3p. This downregulation triggers various signaling pathways including AKT/PI3K and mTOR. These pathways are known to promote cell proliferation and increase the malignancy of breast cancer cells [29]. FOXO3 is negatively regulated by kinases such as Akt, which relocates it from the nucleus to the cytoplasm, thereby inhibiting its apoptotic functions [30].

Another significant finding is the role of DUSP1. This typically inhibits MAPK pathways involved in metastasis and invasion. The downregulation of DUSP1, as influenced by miR-155-3p, impairs the cell's ability to regulate environmental stress. Therefore, it facilitates cancer proliferation. Additionally, CEBPB is also downregulated. This downregulation removes the growth-inhibitory effects of cytokines, inducing epithelial-mesenchymal transition (EMT) [31].

Moreover, ZNF652 (which works alongside the tumor suppressor gene p53) is adversely affected by miR-155-3p. Mutations in p53 or the downregulation of ZNF652 by miR-155-3p contribute to the progression of breast cancer.

Through pathway analysis of these six genes, the current study provides a clear depiction of the oncogenic role of miR-155-3p in breast cancer. It uncovers complex mechanisms and molecular pathways involved in the disease's progression and metastasis. These insights are invaluable for developing advanced therapeutic strategies for breast cancer.

4.1. Conclusion

The progression of breast cancer is an intricate mechanism that necessitates a comprehensive understanding of the underlying molecular mechanisms. Among the main regulators that have been recognized, miR-155-3p gene emerges as a critical modulator of molecular signaling pathways and genetic targets. The analysis suggests that this regulatory molecule has a significant impact on the advancement of breast cancer by controlling key genes that are intricate in cell proliferation, differentiation, and apoptosis. The upregulation of miR-155-3p is a key driver in breast cancer metastasis and the formation of a tumor microenvironment. The miR-155-3p targets several genes involved in various biological processes, including the MAP kinase, AKT/PI3K, Notch, NFkB signaling pathways, and pathways related to angiogenesis, DNA damage response, and inflammation. These findings underscore the potential of miR-155-3p as a target for therapeutic interventions in breast cancer. Thus, decoding the precise mechanism by which miR-155-3p exerts its influence on breast cancer progression can pave the way for the development of novel and effective therapeutic strategies for this disease.

CONFLICT OF INTEREST

The authors of the manuscript have no financial or non-financial conflict of interest in the subject matter or materials discussed in this manuscript.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article.

FUNDING DETAILS

The authors extend their appreciation to the Researchers Supporting project number (RSP2023R502), King Saud University, Riyadh, Saudi Arabia for funding this project.

REFERENCES

1. Kong W, He L, Coppola M, et al. MicroRNA-155 regulates cell survival, growth, and chemosensitivity by targeting FOXO3a in breast cancer. *J Biol Chem*. 2010;285(23):17869–17879. https://doi.org/10.1074/jbc.M110.101055
2. Ling H, Fabbri M, Calin GA. MicroRNAs and other non-coding RNAs as targets for anticancer drug development. *Nat Rev Drug Discov*. 2013;12(11):847–865. https://doi.org/10.1038/nrd4140
3. Hussen BM, Abdullah ST, Rasul MF, et al. MicroRNAs: important players in breast cancer angiogenesis and therapeutic targets. *Front Mol Biosci*. 2021;8:e764025. https://doi.org/10.3389/fmolb.2021.764025
4. Chen J, Wang BC, Tang JH. Clinical significance of MicoRNA-155 expression in human breast cancer. *J Surg Oncol*. 2012;106(3):260–266. https://doi.org/10.1002/jso.22153
5. Chang S, Wang RH, Akagi K, et al. Tumor suppressor BRCA1 epigenetically controls oncogenic microRNA-155. *Nat Med*. 2011;17(10):1275–1282. https://doi.org/10.1038/nm.2459
6. Kong W, He L, Richards EJ, et al. Upregulation of miRNA-155 promotes tumour angiogenesis by targeting VHL and is associated with poor prognosis and triple-negative breast cancer. *Oncogene*. 2014;33(6):679–689. https://doi.org/10.1038/onc.2012.636
7. Liu X, Chang Q, Wang H, Qian H, Jiang Y. Discovery and function exploration of microRNA-155 as a molecular biomarker for early detection of breast cancer. *Breast Cancer*. 2021;28:806–821. https://doi.org/10.1007/s12282-021-01215-2
8. Paraskevopoulou MD, Georgakilas G, Kostoulas N, et al. DIANA-microT web server v5.0: service integration into miRNA functional analysis workflows. *Nucleic Acids Res*. 2013;41(W1):W169–W173. https://doi.org/10.1093/nar/gkt393
9. Uhlen M, Oksvold P, Fagerberg L, et al. Towards a knowledge-based human protein atlas. *Nat Biotechnol*. 2010;28(12):1248–1250. https://doi.org/10.1038/nbt1210-1248
10. Kanehisa M, Goto S. KEGG: kyoto encyclopedia of genes and genomes. *Nucleic Acids Res*. 2000;28(1):27–30.

11. Fabregat A, Sidiropoulos K, Viteri G, et al. Reactome pathway analysis: a high-performance in-memory approach. *BMC Bioinfo*. 2017;18(1):27–30. https://doi.org/10.1093/nar/28.1.27
12. Christopoulos PF, Msaouel P, Koutsilieris M. The role of the insulin-like growth factor-1 system in breast cancer. *Mol Cancer*. 2015;14:e43. https://doi.org/10.1186/s12943-015-0291-7
13. Fujita M, Takada YK, Takada Y. Insulin-like growth factor (IGF) signaling requires αvβ3-IGF1-IGF type 1 receptor (IGF1R) ternary complex formation in anchorage independence. *J Biol Chem*. 2013;288(5):3059–3069. https://doi.org/10.1074/jbc.M112.412536
14. Wang J, Wu J. Role of miR-155 in breast cancer. *Front Biosci*. 2012;17(6):2350–2355.
15. Keyse SM. Dual-specificity MAP kinase phosphatases (MKPs) and cancer. *Cancer Metastasis Rev*. 2008;27:253–261. https://doi.org/10.1007/s10555-008-9123-1
16. Liu R, Yang G, Bao M, et al. STAMBPL1 promotes breast cancer cell resistance to cisplatin partially by stabilizing MKP-1 expression. *Oncogene*. 2022;41(16):2265–2274. https://doi.org/10.1038/s41388-022-02252-7
17. Neilsen PM, Noll JE, Mattiske S, et al. Mutant p53 drives invasion in breast tumors through up-regulation of miR-155. *Oncogene*. 2013;32(24):2992–3000. https://doi.org/10.1038/onc.2012.305
18. Johansson J, Berg T, Kurzejamska E, et al. MiR-155-mediated loss of C/EBPβ shifts the TGF-β response from growth inhibition to epithelial-mesenchymal transition. *Oncogene*. 2013;32(50):5614–5624. https://doi.org/10.1038/onc.2013.322
19. Zhang Y, Yang P, Sun T, et al. miR-155 promotes breast cancer tumorigenesis by suppressing the expression of the SOCS1 gene. *Cancer Res*. 2010;70(8):3119–3127. https://doi.org/10.1158/0008-5472.CAN-09-4250
20. O'Connell RM, Rao DS, Chaudhuri AA, Baltimore D. Physiological and pathological roles for microRNAs in the immune system. *Nat Rev Immunol*. 2010;10(2):111–122. https://doi.org/10.1038/nri2708
21. Van Roosbroeck K, Calin GA. Cancer hallmarks and microRNAs: the therapeutic connection. *Adv Cancer Res*. 2017;135:119–149. https://doi.org/10.1016/bs.acr.2017.06.003

22. Zhang X, Chen X, Lin J, Liao L, Chen L, Huang W. miR-155 regulates the proliferation and apoptosis of Treg cells in patients with asthma by targeting CTLA-4. *Exp Ther Med*. 2020;20(2):1194–1202. https://doi.org/10.3892/etm.2020.8795
23. Esquela-Kerscher A, Slack FJ. Oncomirs—microRNAs with a role in cancer. *Nat Rev Cancer*. 2006;6(4):259–269. https://doi.org/10.1038/nrc1840
24. Al-Khanbashi M, Caramuta S, Alajmi AM, Al-Moundhri MS, Al-Riyami M, Lui WO. MicroRNA profiling in chemotherapy resistant breast cancer tissues reveals association of miR-155 overexpression with poor response. *PLOS ONE*. 2017;12(3):e0174118. https://doi.org/10.1371/journal.pone.0174118
25. Rottiers V, Näär AM. MicroRNAs in metabolism and metabolic disorders. *Nat Rev Mol Cell Biol*. 2012;13(4):239–250. https://doi.org/10.1038/nrm3313
26. Negrini M, Nicoloso MS, Calin GA. MicroRNAs and cancer—new paradigms in molecular oncology. *Curr Opin Cell Biol*. 2009;21(3):470–479. https://doi.org/10.1016/j.ceb.2009.04.003
27. Wang X, Cao X, Sun R, et al. Tumor microenvironment-based predictive biomarker candidates for anti-PD-1/PD-L1 immunotherapy in breast cancer. *Front Oncol*. 2021;11:e771304. https://doi.org/10.3389/fonc.2021.771304
28. Gasparini P, Cascione L, Fassan M, et al. microRNA expression profiling identifies a four-microRNA signature as a novel prognostic biomarker in triple-negative breast cancer. *Oncotarget*. 2014;5(5):1174–1184. https://doi.org/10.18632/oncotarget.1653
29. Hamam R, Ali AM, Alsaleh KA, et al. microRNA-320a downregulates multiple targets including SOX4 in breast cancer. *Oncol Lett*. 2016;12(5):3865–3870. https://doi.org/10.3892/ol.2016.5172
30. Eissa S, Matboli M, Essawy NO, Shehta MA. MicroRNA-155 and its regulatory effect on TLR-4 signaling pathway in breast cancer patients. *Mol Cell Biochem*. 2021;476(5):2043–2053. https://doi.org/10.1007/s11010-020-04027-5
31. Mar-Aguilar F, Mendoza-Ramírez JA, Malagón-Santiago I, et al. Serum circulating microRNA-155 as a potential biomarker for diagnosis and prognosis of breast cancer. *Cancer Biomark*. 2013;13(2):105–113. https://doi.org/10.3233/CBM-130330