Role of microRNA/IncRNA Intertwined With the Wnt/β-Catenin Axis in Regulating the Pathogenesis of Triple-Negative Breast Cancer

Xue Hu¹, Qiang Zhang², Wanying Xing¹ and Wan Wang¹*

¹Department of Breast Surgery, China-Japan Union Hospital of Jilin University, Changchun, China, ²Department of Breast Surgery, Cancer Hospital of China Medical University, Liaoning Cancer Hospital & Institute, Shenyang, China

Objective (s): In this mini-review, we aimed to discuss the Wnt/β-catenin signaling pathway modulation in triple-negative breast cancer, particularly the contribution of lncRNAs and miRNAs in its regulation and their possible entwining role in breast cancer pathogenesis, proliferation, migration, or malignancy.

Background: Malignant tumor formation is very high for breast cancer in women and is a leading cause of death all over the globe. Among breast cancer subtypes, triple-negative breast cancer is rife in premenopausal women, most invasive, and prone to metastasis. Complex pathways are involved in this cancer’s pathogenesis, advancement, and malignancy, including the Wnt/β-catenin signaling pathway. This pathway is conserved among vertebrates and is necessary for sustaining cell homeostasis. It is regulated by several elements such as transcription factors, enhancers, non-coding RNAs (lncRNAs and miRNAs), etc.

Methods: We evaluated lncRNAs and miRNAs differentially expressed in triple-negative breast cancer (TNBC) from the cDNA microarray data set literature survey. Using in silico analyses combined with a review of the current literature, we anticipated identifying lncRNAs and miRNAs that might modulate the Wnt/β-catenin signaling pathway.

Result: The miRNAs and lncRNAs specific to triple-negative breast cancer have been identified based on literature and database searches. Tumorogenesis, metastasis, and EMT were all given special attention. Apart from cross-talk being essential for TNBC tumorigenesis and treatment outcomes, our results indicated eight upregulated and seven downregulated miRNAs and 19 upregulated and three downregulated lncRNAs that can be used as predictive or diagnostic markers. This consolidated information could be useful in the clinic and provide a combined literature resource for TNBC researchers working on the Wnt/β-catenin miRNA/IncRNA axis.

Conclusion: In conclusion, because the Wnt pathway and miRNAs/lncRNAs can modulate TNBC, their entwinement results in a cascade of complex reactions that affect TNBC and related processes. Their function in TNBC pathogenesis has been highlighted in molecular processes underlying the disease progression.

Keywords: breast cancer, IncRNA, microRNA, wnt/β-catenin, pathogenesis
INTRODUCTION

Breast cancer represents the most common type of cancer worldwide, with high morbidity and mortality rates (Agustsson et al., 2020). Breast cancer shows high heterogeneity, which impacts the clinical course of the disease. Differential expression profiles among patients lead to tumor tissue heterogeneity, resulting in variations in malignant behavior, prognosis, and responsiveness to standard therapies (Padmanaban et al., 2019). This cancer is prevalent in women and is the first leading cause of cancerous death in women. Breast cancer has been progressively increasing in most nations (Ferlay et al., 2015). According to WHO data (https://www.who.int/news-room/fact-sheets/detail/breast-cancer), 2.3 million women were diagnosed with breast cancer in 2020, with about 685,000 fatalities. This year, in the United States alone, around 281,550 cases of invasive and 49,290 cases of non-invasive breast cancer cases were diagnosed in women, according to the American Cancer Society. Most deaths occur due to metastasis instead of the primary tumor in breast cancer (Geng et al., 2014). Metastasis is linked with stem cells, which have characteristics such as self-renewal, differentiation ability, drug resistance, etc. (Phi et al., 2018). These properties favor aggressive behavior in breast cancer stem cells, leading to recurrent and aggressive tumors on and away from the primary site. Upregulation of Wnt/β-catenin signaling has been observed in triple-negative breast cancer (TNBC)/basal-like cancer when collated with other breast cancer subtypes (luminal A, B, and HER2 positive) or normal tissues (Gangrade et al., 2018).

TNBC can be classified into at least six distinct subtypes with differences in clinical behavior and treatment response. TNBC is highly invasive and, due to the non-expression of estrogen receptor, progesterone receptor, or HER-2, it has poor prognosis, high metastatic potential, and is disposed to relapse (Yin et al., 2020). TNBCs are more common in younger and obese women, with premenopausal African American women having the highest prevalence. BRCA1 and BRCA2 gene mutations are identified in approximately 20% of TNBC patients. P53 and Rb1 mutations are also quite common in TNBC tumors (van Barele et al., 2021). Differentially expressed ncRNAs have been found in a variety of human cancers, including breast cancer. Several IncRNA molecules have been linked to tumorigenesis, and their differential expression could constitute a potential new category of biomarkers. The IncRNA HOTAIR (HOX transcript antisense intergenic RNA) was associated with the polycomb repressive complex 2 (PRC2) and the histone demethylation enzyme LSD1 (lysine-specific demethylase 1) in cancer cells, resulting in epigenetic changes that promote tumor development and metastasis (Rodrigues de Bastos and Nagai, 2020). Other circulating IncRNAs, including MALAT1, GASS, H19, and MEG3, have also been linked to survival and treatment response. IncRNAs have opened up a new field of study for researchers all over the world, and these molecules have been assigned major roles that may have a direct impact on patient survival and therapeutic responsiveness (Gupta et al., 2010). The SPARC gene (secreted protein acidic and rich in cysteine, also known as osteonectin or basement-membrane protein 40) encodes a 32-kDa matricellular glycoprotein involved in a variety of biological activities, including differentiation, proliferation, migration, and adhesion (Zhang et al., 2019).

WNT/β-CATENIN SIGNALING IN TNBC

The Wnt pathway is tangled with low-density lipoprotein receptor-related protein5/6 (LRP5/6) and frizzled (FZD) receptors for its activation (King et al., 2012). If Wnts are insufficient or non-functional, β-catenin pools with a tetrad of...
proteins (axin, casein kinase 1 (CK1), adenomatous polyposis coli (APC) tumor suppressor, and glycogen synthase kinase-3b (GSK3b). Phosphorylation (by CK1 and GSK3b) is followed by ubiquitination and ultimate degradation of β-catenin (26S proteasome). Conversely, in the presence of the Wnt signal, β-catenin attaches to FZD and LRPs receptors, leading to inhibition of GSK3b and stabilization of cytosolic β-catenin. This β-catenin is then shifted to the nucleus. It associates with T-cell factor/lymphoid-enhancing factor (TCF/LEF) to initiate the downstream expression of cell development and cell cycle control genes (MacDonald et al., 2009). Secreted proteins regulate this signaling at the cell surface, where the central modulators are Wnt and R-spondin (Rspo). Inhibitors include Wnt Inhibitory Factor 1 (WIF1), Dickkopf (Dkk), soluble Frizzled-related protein (sFRP), and sclerostin (SOST) (Yao et al., 2011; Danieau et al., 2019). Abnormal Wnt signaling has been implicated in TNBC tumorigenesis (Xu et al., 2015; Mohammadi Yeganeh et al., 2017), stemness, metastasis, and prognosis (Ryu et al., 2020). Dey et al. (2013) identified that patients with dysregulated Wnt/β-catenin signaling had a higher chance of lung and brain metastases. Dysregulation of the canonical pathway is responsible for metastasis in more than half of breast cancer patients as the nuclear β-catenin level is elevated. However, mutations in the relevant genes are uncommon (Yu et al., 2019). It implies that the role of the β-catenin is indispensable to the Wnt signaling in TNBC advancement, with the dissemination of non-phosphorylated cytoplasmic β-catenin to the nucleus having an imperative role in TNBC metastasis (Breuer et al., 2019; Satriyo et al., 2019).

Green et al. (2013) discovered that Wnt ligands caused enhanced transcription in the majority of TNBC cell lines, while Xu et al. (2015) reported that nuclear accumulation of β-catenin is linked with TNBC characteristics. The role of the key modulators of this pathway in TNBC includes the action of FZD receptors, LRPs, Receptor Tyrosine Kinase-Like Orphan Receptors (ROs), and Dead Box Proteins (DDX3 and DDX5) (Pohl et al., 2017). DLRP is crucial in mammary development and is allied with tumorigenesis (Goel et al., 2012). Overexpression of LRPs/6 has been seen in TNBC (Maubant et al., 2018). LRP6 has also been linked with migration and invasion of cells (Ma et al., 2017). Elevated FZD7 expression in TNBC also promotes tumorigenesis (Yang et al., 2011) via transformation-related protein 63 (p63) (Chakrabarti et al., 2014), while FZD8-driven Wnt signaling mediated by β-Myc overexpression drives chemoresistance (Yin et al., 2013). Dead box proteins DDX3 and DDX5 have shown increased EMT in TNBC. DDX3 is associated with increased motility and invasiveness. In comparison, DDX5 is linked with tumorigenesis and cancer cell progression (Moore et al., 2010; Wang et al., 2012; Gutti et al., 2014; Pohl et al., 2017).

### Wnt/β-Catenin Signaling in TNBC Stem Cells

Cancer stem cells (CSCs) or cancer stem-like cells within the tumor, being less responsive to environmental stop signals, are responsible for cancer progression, metastasis, chemoresistance, and hence, cancer relapse (Clarke, 2019). They differ from other cancer cells as they use mitochondrial reactive oxygen species (ROS) for respiration, which means higher oxygen consumption, increased mitochondrial mass, and high resistance to DNA damage (Petris-Pagès et al., 2018; Scatena et al., 2018). Abnormal Wnt/β-catenin signaling is linked with CSC formation and, hence, tumorigenesis, stemness, migration, and chemoresistance in TNBC (Alraouji et al., 2020). Upregulation of β-catenin triggers the CSC phenotype of TNBC, and repression by cadherin leads to suppression of this phenotype (Satriyo et al., 2019). Jang et al. (2015) observed that Wnt/β-catenin pathway genes (WNT1, FZD1, TCF4, and LEF1) are upregulated in CSC-enriched mammospheres in breast cancer, while signaling proteins (LEF1, TCF4, and β-catenin) were increased in high CSC activity, depicting cell fraction, compared to that with low CSC activity. However, recently, Brilliant et al. (2019) reported 11% of Wnt signaling expression in high vs. 33% in the low content of cancer stem cells. In contrast, some researchers have reported inhibiting TNBC CSCs by drugs targeting the Wnt/β-catenin pathway (like hydroxytyrosol) (Cruz-Lozano et al., 2019). Others have reported that β-catenin is also responsible for drug resistance (e.g., doxorubicin resistance) in TNBC CSCs (Xu et al., 2015).

### IncRNA and miRNAs Entangled With the Wnt/β-Catenin Pathway in TNBC

According to recent research, more than 90% of the transcripts in the human genome may not be able to code for proteins (Wilusz et al., 2009) but regulate the expression of nearby genes (He and Hannon, 2004; Trzybulska et al., 2018). They are categorized according to their size and function (Trzybulska et al., 2018), with microRNAs (miRNAs) being 19–24 nucleotides long and long non-coding RNAs (lncRNAs) being >200 nucleotides in length. There are other non-coding RNAs such as piwiRNAs, free circulating RNAs, and snRNAs, but our focus will be on miRNAs and lncRNAs in this review. Long non-coding RNAs are abundant in human cells and play critical roles in a range of biological processes, including cell cycle regulation (Lu et al., 2016), genomic expression (Ballantyne et al., 2016), and cell differentiation (Chen et al., 2016). Increasing evidence has recently indicated that abnormal lncRNA expression is linked with various tumor forms (Mendell, 2016). Researchers have proved that miRNA dysregulation also leads to human cancer via different mechanisms (Karimzadeh et al., 2021), including altered epigenetics (Arif et al., 2020) and abnormal transcriptional control (Müller et al., 2019; Ali Syeda et al., 2020). Apart from performing as oncogenes, where they support proliferative signaling (Miao et al., 2020) and abnormal transcriptional control (Müller et al., 2019; Ali Syeda et al., 2020). Apart from performing as oncogenes, where they support proliferative signaling (Miao et al., 2020), invasion (Chen et al., 2017), repelling cell death, eluding progression suppressors, and metastasis, they act as tumor suppressors too (Hong et al., 2019). This has led to their demarcation as potential biomarkers of cancer (Gai et al., 2018; Dai et al., 2019).

miRNA expression in BCSCs and cancer cells signals that they are crucial for promoting characteristics such as stemness and tumorigenesis. Piauseka et al. (2018) reviewed 121 articles demonstrating the role of miRNAs in TNBC. After scanning a
Table 1

| S. No. | MiRNA | Upregulation or downregulation | Cell line | References |
|--------|-------|-------------------------------|-----------|------------|
| 1      | miR-142 | Upregulated | HEK293T, MCF7, and MDA-MB-231 | Isobe et al. (2014) |
| 2      | miR-221 | Upregulated | MDA-MB-231, MCF7, MDA-MB-468, Hs 578T, HCC1937, and MDA-MB-231, SKBR3, T47D, BT-474, 4T1 | Liu et al. (2018) |
| 3      | miR-124 | Upregulated | BT20, HCC70, 293T | Yang et al. (2020) |
| 4      | miR-125b | Upregulated | MDA-MB-468, MDA-MB-231, MCF-10A, and MCF-7 | Nie et al. (2019) |
| 5      | miR-137 | Downregulated | HCC38, MDA-MB-231, and MDA-MB-468 | Cheng et al. (2019) |
| 6      | miR-290-1 | Downregulated | MB-231, MDA-MB-468, BT20, and HCC-1395 | Drago-Ferrante et al. (2017) |
| 7      | miR-105 | Upregulated | MB-361, MCF-7, BT-483, AU565, SkBr3, MCF-10A, MB-231 (MDA-MB-231), Hs 578T, HCC1959, HCC1806, HCC1937, BT-549, DU4475, and HCC70 | Li et al. (2017) |
| 8      | miR-93 | Upregulated | MB-361, MCF-7, BT-483, AU565, SkBr3, MCF-10A, MB-231 (MDA-MB-231), Hs 578T, HCC1959, HCC1806, HCC1937, BT-549, DU4475, and HCC70 | Li et al. (2017) |
| 9      | miR-27a | Upregulated | BT-549, MDA-MB-231, MDA-MB-468, MDA-MB-453, MCF-10A, and DU4475 | Wu et al. (2020) |
| 10     | miR-130a | Downregulated | MDA-MB-468, MDA-MB-231, and MCF-10A | Poccinine et al. (2020) |
| 11     | miR-384 | Downregulated | MCF-7, MDA-MB-231 | Wang et al. (2018a) |
| 12     | miR-34a | Downregulated | SUL159PT, mammospheres and Comma-Dj cells | Bonetti et al. (2019) |
| 13     | miR-37a | Downregulated | MCF7, T47D, BT474, MDA-MB-231, MDA-MB-435, MDA-MB-468, and 4T1 | Cai et al. (2013) |
| 14     | miR-340 | Downregulated | MCF-10A, MDA-MB-231, and HEK 293T | Mohammadi Yeganeh et al. (2017) |
| 15     | miR-218 | Upregulated | MCF-10A, MCF-7, and MDA-MB-231 | Taipaleermäki et al. (2016) |

plethora of literature, it was revealed that the miRNAs not only serve as predictive markers of TNBC but also have prognostic clinical utility. They assist in attaining CSC properties in TNBC and EMT. Since these properties are conditions for metastasis, miRNAs play an essential role in TNBC and are intertwined with the pathway gene regulation, making them essential players in miRNAs. Previously reported miRNAs with a role in TNBC and Wnt-mediated TNBC progression, prognosis, and other outcomes. Here, we review lncRNA intertwined with the Wnt pathway and TNBC progression, pathogenesis, prognosis, or invasion. LncRNA Lung Cancer–Associated Transcript 1 (LUCAT1) is interlinked with miR-5582 and regulates breast cancer stemness via the Wnt/β-catenin pathway (Zheng et al., 2019). UCA1 promotes EMT (Xiao et al., 2016), while actin filament-associated protein 1 antisense RNA1 (AFAP1-AS1) promotes EMT and tumorigenesis (Zhang et al., 2018) and differentiation antagonizing non-protein coding RNA (DANCR) negatively regulates the Wnt pathway (Li and Zhou, 2018) to uplift tumorigenesis (Tao et al., 2019), EMT, and stemness in TNBC (Zhang and Wang, 2020). HOX Antisense Intergenic RNA (HOTAIR) modulates the Wnt pathway (Li et al., 2016) and leads to metastasis (Collina et al., 2019) and poor prognosis in TNBC via upregulation by miR-146a (Liang et al., 2019). Jiang et al. (2020) reported that DiGeorge Syndrome Critical Region Gene 5 (DGC5) induces tumorigenesis in TNBC. LncRNA associated with poor prognosis of hepatocellular carcinoma (AWPPH) promotes TNBC growth by upregulating the frizzled homolog 7 (FZD7) ligand of the Wnt pathway (Wang et al., 2018b) and decreased manifestation of lncRNA has been reported to increase the malignant spread of TNBCs (Liu et al., 2017). Long intergenic non-protein coding RNA 1234 (LINC01234) modulates TNBC cell growth, invasion, and EMT positively (Xiao et al., 2021). We also mined lncRNAs with a role in TNBC and impacted by Wnt pathway genes (Table 2) from the lnc2Cancer 3.0 database (Gao et al., 2021). In addition, lncRNA–miRNA interactions entwining the Wnt pathway have also been noted in TNBC (Volovat et al., 2020). Among these, intranuclear Metastasis-Related Lung...
Adenocarcinoma Transcript 1 (MALAT1) acts as a sponge of miR-129-5p (Dong et al., 2015), and silencing of this non-coding gene causes a decline in cell propagation and movement, illustrating its role in TNBC pathology (Zuo et al., 2017). AWPPH stimulates cell proliferation and contributes to drug therapy resistance when combined with miRNA-21 and is being

---

**FIGURE 2** | LncRNA–miRNA gene expression regulation in normal vs. cancer phenotype.

---

**TABLE 2** | LncRNAs impacting TNBC via the Wnt/β-Catenin axis mined from the Inc2 Cancer database.

| S. No. | Name     | Method of identification                     | Expression pattern | References          |
|--------|----------|----------------------------------------------|--------------------|---------------------|
| 1      | ANRIL    | qPCR, luciferase reporter assay, RIP.         | Upregulated        | Xu et al. (2017)    |
| 2      | AFAP1-AS1| qPCR, Western blot, in vitro knockdown etc.   | Upregulated        | Zhang et al. (2018) |
| 3      | AWPPH    | qRT-PCR etc.                                 | Upregulated        | Liu et al. (2019)   |
| 4      | CCAT1    | qPCR, luciferase reporter assay, Western blot| Upregulated        | Han et al. (2019)   |
| 5      | DANCR    | qPCR, Western blot, in vitro knockdown, RIP etc.| Upregulated        | Tang et al. (2018a) |
| 6      | FAM83H-AS1| qRT-PCR, Western blot                        | Upregulated        | Han et al. (2020)   |
| 7      | GAS5     | qPCR, Western blot, luciferase reporter assay| Downregulated      | Li et al. (2018)    |
| 8      | H19      | qPCR, Western blot, other                     | Upregulated        | Han et al. (2018)   |
| 9      | HOTAIR   | Microarray, qPCR etc.                        | Upregulated        | Chen et al. (2015)  |
| 10     | LINC00052| Microarray, qPCR etc.                        | Downregulated      | Lv et al. (2016)    |
| 11     | LINC00115| qRT-PCR, Western blot                        | Upregulated        | Yuan et al. (2020)  |
| 12     | LINC00152| qPCR, Western blot                           | Upregulated        | Wu et al. (2018)    |
| 13     | LINC00173| qPCR                                          | Upregulated        | Fan et al. (2020)   |
| 14     | LINC01133| qPCR, Western blot                           | Upregulated        | Tu et al. (2019)    |
| 15     | LUCAT1   | qPCR, Western blot, a luciferase reporter assay, in vitro knockdown, RIP | Upregulated        | Mou and Wang, (2019) |
| 16     | MALAT1   | Microarray, qPCR etc.                        | Upregulated        | Chen et al. (2015)  |
| 17     | NEAT1    | qPCR, Western blot                           | Upregulated        | Shin et al. (2019)  |
| 18     | PCAT1    | qPCR, Western blot, luciferase reporter assay, in vitro knockdown etc.| Upregulated        | Shi et al. (2020)   |
| 19     | PVT1     | qPCR, Western blot, RNAi; other              | Upregulated        | Wang et al. (2018c) |
| 20     | SOX21-AS1| qPCR, Western blot, luciferase reporter assay etc.| Uregulated        | Liu et al. (2020)   |
| 21     | XIST     | qRT-PCR, Western blot                        | Upregulated        | Li et al. (2020)    |
| 22     | ZEB1-AS1 | qRT-PCR, RIP, dual luciferase reporter assay | Uregulated        | Luo et al. (2020)   |
exploited as a diagnostic biomarker (Cascione et al., 2013; Liu et al., 2019). At the same time, TUG1 impacts miR-197, prompts NLK expression, and incapacitates the Wnt signaling pathway, making the TNBC cells susceptible to cisplatin therapy (Tang et al., 2018b). AFAP1-AS1 controls miRNA-2110, leading to tumorigenesis and cell invasion (Zuo et al., 2017). The diminished NEF and boosted miRNA-155 levels segregate TNBC patients from controls, suggesting an interlinked modulation prompting enhanced invasion and cell migration in the case of increased miRNA-155 (Song et al., 2019).

CONCLUSION

This narrative review was centered on TNBC association with the Wnt/β-catenin pathway. Moreover, miRNAs and lncRNAs shown to be specific to triple-negative breast carcinoma were listed, both from literature and database searches. Since the Wnt pathway and miRNAs/lncRNAs can modulate TNBC and their interwoven forms a cascade of complex reactions that impact TNBC and associated processes, their role in TNBC pathology was highlighted concerning molecular processes underlying disease progression. Particular emphasis was put on tumorigenesis, metastasis, and EMT. Apart from cross-talk critical for TNBC tumorigenesis and treatment outcomes, miRNA and lncRNA can serve as predictive or diagnostic markers, so this consolidated information might be of clinical use and offer a consolidated literature resource to scientists working on the Wnt/β-catenin and miRNA/lncRNA axis of TNBC. They also have a role in chemotherapy resistance. However, information on detailed analyses of Wnt/miRNA/lncRNA axis mechanisms in TNBC is still scant, and more work needs to be carried out to infer the pivotal role of these moieties in TNBC. Owing to the heterogeneity of TNBC, recognition of subgroups or their pathologies based on the varied signatures of this axis could be interesting to explore. Furthermore, knock-out or knock-in functional studies in model organisms could be beneficial to understanding the comprehensive role of this axis in TNBC.

AUTHOR CONTRIBUTIONS

Conception/Design: WW, QZ. Collection and assembly of data: XH, WX. Manuscript writing: XH, WW. Final approval of manuscript: WW, QZ, WX.

FUNDING

This study was supported by the China Postdoctoral Science Foundation Grant (No. 2019M651216).

ACKNOWLEDGMENTS

We acknowledge the China Postdoctoral Science Foundation for supporting this study.
Cheng, S., Huang, Y., Lou, C., He, Y., Zhang, Y., and Zhang, Q. (2019). FSTL1 Enhances Chemoresistance and Maintains Stemness in Breast Cancer Cells via Integrin β1/Wnt Signaling under miR-137 Regulation. Cancer Biol. Ther. 20 (3), 328–337. doi:10.1080/15384024.2018.1529101

Clarke, M. F. (2019). Clinical and Therapeutic Implications of Cancer Stem Cells. N. Engl. J. Med. 380 (23), 2237–2245. doi:10.1056/NEJMr1804280

Collina, F., Aquino, G., Brogna, M., Cipolletta, S., Buonfanti, G., De Laurentiis, M., et al. (2019). Lncrna hotair up-regulation is strongly related with lymph nodes metastasis and lar subtype of triple negative breast cancer. J. Cancer 10 (9), 2018–2024. doi:10.7150/jca.29670

Cruz-Lozano, M., González-González, A., Marchal, J. A., Muñoz-Muela, E., Molina, M. P., Cara, F. E., et al. (2019). Hydroxytyrosol Inhibits Cancer Stem Cells and the Metastatic Capability of Triple-Negative Breast Cancer Cell Lines by the Simultaneous Targeting of Epithelial-To-Mesenchymal Transition, Wnt/β-Catenin and TGFβ Signaling Pathways. Eur. J. Nutr. 58 (8), 3207–3219. doi:10.1007/s00394-018-1864-1

Dai, W., He, J., Zheng, L., Bi, M., Hu, F., Chen, M., et al. (2019). miR-148b-3p, miR-190b, and miR-429 Regulate Cell Progression and Act as Potential Biomarkers for Breast Cancer. J. Breast Cancer 22 (2), 219–236. doi:10.4048/jbc.2019.22.e19

Danieu, G., Morice, S., Rédini, F., Verrecchia, F., and Royer, B. B. (2019). New Frontiers in Pharmacology | www.frontiersin.org June 2022 | Volume 13 | Article 814971

David, J. L., La, J., Yoon, K. W., Desai, P., Rodewald, L. W., Zhang, X., et al. (2013). Paracrine Wnt Signaling Both Promotes and Inhibits Human Breast Tumor Growth. Proc. Nutr. Acad. Sci. U. S. A. 110 (17), 6991–6996. doi:10.1073/pnas.1306711110

Gupta, R. A., Shah, N., Wang, K. C., Kim, J., Horlings, H. M., Wong, D. J., et al. (2010). Long non-coding RNA hotair reprograms chromatin state to promote cancer metastasis. Nature 464 (7291), 1071–1076. doi:10.1038/nature08975

Guturi, K. K., Sarkar, M., Blowmik, A., Das, N., and Ghosh, M. K. (2014). DEAD-box Protein P68 Is Regulated by β-catenin/transcription Factor 4 to Maintain a Positive Feedback Loop in Control of Breast Cancer Progression. Breast Cancer Res. 16 (6), 496. doi:10.1186/s13058-014-0496-5

Han, C., Fu, Y., Zeng, N., Yin, J., and Li, Q. (2020). LncRNA FAM83H-AS1 Promotes Triple-Negative Breast Cancer Progression by Regulating the miR-136-5p/methadherin axis. Aging (Albany NY) 12 (4), 3594–3616. doi:10.18632/aging.102832

Han, C., Li, X., Fan, Q., Liu, G., and Yin, J. (2019). CAT1 Promotes Triple-Negative Breast Cancer Progression by Suppressing miR-218/ZFX Signaling. Aging (Albany NY) 11 (14), 4858–4875. doi:10.18632/aging.102080

Han, J., Han, B., Wu, X., Hao, J., Dong, X., Shen, Q., et al. (2018). Knockdown of IncRNA H19 Restores Chemo-Sensitivity in Paclitaxel-Resistant Triple-Negative Breast Cancer through Targeting Apoptosis and Regulating Akt Signaling Pathway. Toxicol. Appl. Pharmacol. 359, 55–61. doi:10.1016/j.taap.2018.09.019

He, L., and Hannon, G. J. (2004). MicroRNAs: Small RNAs with a Big Role in Gene Regulation. Nat. Rev. Genet. 5 (7), 522–531. doi:10.1038/nrg1379

Hong, B. S., Ryu, H. S., Kim, N., Kim, J., Lee, E., Moon, H., et al. (2019). Tumor Suppressor miRNA-204-5p Regulates Growth, Metastasis, and Immune Microenvironment Remodeling in Breast Cancer. Cancer Res. 79 (7), 1520–1534. doi:10.1158/0008-5472.CAN-18-0891

Huang, Q. Y., Liu, G. F., Qian, X. L., Tang, L. B., Huang, Q. Y., and Xiong, L. X. (2019). Long Non-coding RNA: Dual Effects on Breast Cancer Metastasis and Clinical Applications. Cancers (Basel) 11 (11). doi:10.3390/cancers11111802

Isobe, T., Hisamori, S., Hogan, D. J., Zabala, M., Hendrickson, D. G., Dalerba, P., et al. (2014). miR-142 Regulates the Tumorigenicity of Human Breast Cancer Stem Cells through the Canonical WNT Signaling Pathway. Elife 3. doi:10.7554/elife.01977

Jang, G. B., Kim, J. Y., Cho, S. D., Park, K. S., Jung, J. Y., Lee, H. Y., et al. (2015). Blockade of Wnt/β-Catenin Signaling Suppresses Breast Cancer Metastasis by Inhibiting CSC-like Phenotype. Sci. Rep. 5, 12465. doi:10.1038/srep12465

Jiang, D., Wang, C., and He, J. (2020). Long Non-coding RNA DGC5R5 Inhibits Tumorigenesis of Triple-Negative Breast Cancer by Affecting Wnt/β-Catenin Pathway. J. BUON 25 (2), 702–708.

Karamzadeh, M. R., Pourdavoud, P., Ehtesham, N., Qadbeigi, M., Asl, M. M., Alani, B., et al. (2021). Regulation of DNA Methylation Machinery by Epi-miRNAs in Human Cancer: Emerging New Targets in Cancer Therapy. Cancer Gene Ther. 28 (3–4), 157–174. doi:10.1016/j.carg.2020.02.010–7

King, T. D., Suto, M. J., and Li, Y. (2012). The Wnt/β-Catenin Signaling Pathway: a Potential Therapeutic Target in the Treatment of Triple Negative Breast Cancer. J. Cell Biochem. 113 (1), 13–18. doi:10.1002/jcb.23350

Li, H. Y., Liang, J. L., Kuo, Y. L., Lee, H. H., Calkins, M. J., Chang, H. T., et al. (2017). miR-105-93-3p Promotes Chemosoresistance and Circulating miR-105-93-3p Acts as a Diagnostic Biomarker for Triple Negative Breast Cancer. Cancer Res. 79 (19), 5024–5036. doi:10.1158/0008-5472.CAN-16-3631

Liu, J., Yang, S., Su, N., Wang, Y., Yu, J., Qiu, H., et al. (2016). Overexpression of long non-coding RNA hotair leads to chemoresistance by activating the wnt/β-catenin pathway in human ovarian cancer. Tumour Biol. 37 (2), 2057–2065. doi:10.1007/s13277-015-3996-6

Li, J., and Zhou, L. (2018). Overexpression of Incrna dancr positively affects progression of glioma via activating wnt/β-catenin signaling. Biomed. Pharmacother. 102, 602–607. doi:10.1016/j.biopha.2018.03.016

Li, S., Zhou, J., Wang, Z., Wang, P., Gao, X., and Wang, Y. (2018). Long Noncoding RNA GA5S Suppresses Triple Negative Breast Cancer Progression through Inhibition of Proliferation and Invasion by Competitively Binding miR-196a-5p. Biomed. Pharmacother. 104, 451–457. doi:10.1016/j.biopha.2018.05.056

Li, X., Hou, L., Yin, L., and Zhao, S. (2020). Lncrna xist interacts with mir-454 to inhibit cells proliferation, epithelial mesenchymal transition and induces...
apoptosis in triple-negative breast cancer. *J. Biosci.* 45. doi:10.1007/s12038-020-9999-7

Li, X., Wu, Z., Fu, X., and Han, W. (2014). IncRNAs: Insights into Their Function and Mechanics in Underlying Disorders. *Mutat. Res. Rev. Mutat. Res.* 762, 1–21. doi:10.1016/j.mrrev.2014.04.002

Li, J., Wu, L., Huang, M., Zhang, Y., and Xu, F. (2021). Wnt/β-catenin axis in tumor progression. *Front. Oncol.* 11. doi:10.3389/fonc.2021.65434

Muller, S., Glaß, M., Singh, A., Hoang, N., Ferrer, S., et al. (2014). Long Non-coding RNA TUG1 Sponges miR-197 to Enhance Cisplatin Sensitivity in Triple Negative Breast Cancer Cells. *Aging Cell* 13(1), 42–54. doi:10.1111/acel.12102

Nie, J., Si, L., Chen, Y., and Li, T. (2021). Wnt/β-catenin axis regulates triple-negative breast cancer by affecting epithelial-mesenchymal transition. *Can. J. Oncol.* 11(2), 107–116. doi:10.5455/cjoc.10.2147/OTT.S237559

Peiris-Pagès, M., Bonuccelli, G., Sotgia, F., and Lisanti, M. P. (2018). Mitochondrial Fission as a Driver of Stemness in Tumor Cells: mDIVI1 Inhibits Mitochondrial Function, Cell Migration and Cancer Stem Cell (CSC) Signalling. *Oncotarget* 9(17), 13235–13247. doi:10.18632/oncotarget.24285

Pohl, S. G., and Marra, A. P. (2014). Targeting the Wnt/β-catenin pathway in triple-negative breast cancer. *Exp. Mol. Med.* 46(12), e310. doi:10.1038/ymem.2014.12

Poldineh, J., Sirati-Sabet, M., Rajabizad, M., and Mohammadi-Yeganeh, S. (2020). Wnt-130a-3p Blocks Wnt Signaling Cascade in the Triple-Negative Breast Cancer by Targeting the Key Players at Multiple Points. *Heleny* 6(11), e05434. doi:10.1007/s10346-020-0045-9

Rodrigues de Bastos, D., and Nagai, M. A. (2020). In silico analyses Identify IncRNAs: WDFY3-AS1, BDNF-AS and APAF1-AS1 as Potential Prognostic Factors for Patients with Triple-Negative Breast Tumors. *PLoS One* 15(5), e0232284. doi:10.1371/journal.pone.0232284

Ryu, W. J., Lee, J. D., Park, J. C., Cho, P. H., Choi, Y. H., Kim, J. Y., et al. (2020). PDCD4, a Negative Regulator of the canonical Wnt/β-catenin pathway, modulates cancer stem cell self-renewal in triple-negative breast cancer. *Oncotarget* 22604. doi:10.18632/oncotarget.22604

Satriyo, P. B., and Mamduhi, O. A., Chen, J. H., Arad, T., Haryana, S. M., Yeh, C. T., et al. (2019). Cadherin 11 Inhibition Downregulates β-catenin, Deactivates the Canonical WNT Signalling Pathway and Suppresses the Cancer Stem Cell-like Phenotype of Triple Negative Breast Cancer. *J. Clin. Med.* 8(12), 2755. doi:10.3390/jcm8122755

Shi, R., Wu, P., Liu, M., Chen, B., and Cong, L. (2020). Knockdown of IncRNA PCTA6 Enhances Radiosensitivity in Triple-Negative Breast Cancer Cells by Regulating miR-185-5p/TDP52 Axis. *Onco Targets Ther.* 13, 3025–3037. doi:10.2174/OTT.213726

Shin, Y. S., and Lim, J. H. (2013). Long Non-coding RNA NEAT1 Confers Oncogenic Role in Triple-Negative Breast Cancer. *Cancer Genet.* 202(1), 27–32. doi:10.1016/j.cancer.2013.03.012

Song, X., and Yu, Z. (2019). Lncrna nef is downregulated in triple negative breast cancer and correlated with poor prognosis. *Acta Biochim. Biophys. Sin. (Shanghai)* 51(4), 386–392. doi:10.1039/c8/bb00201e

Tapielennaki, H., Farina, N. H., van Wijnen, A. J., Stein, J. L., Hesse, E., Steindl, S., et al. (2016). Antagonizing miR-218-5p Attenuates Wnt Signaling and Reduces Metastatic Bone Disease of Triple Negative Breast Cancer Cells. *Oncotarget* 7(48), 79332–79406. doi:10.18632/oncotarget.12593

Tang, J., Zhang, G., Zhang, H., Yu, B., Wei, F., Luo, L., et al. (2018). LncRNA danzr upregulates pi3K/akt signaling through activating serine phosphorylation of rxxr. *Cell Death Dis.* 9(12), 1167. doi:10.1038/cdnd.2018-1220-7

Tang, T., Cheng, Y., Qu, X., Ji, J., Yan, Y., and Yang, W., et al. (2018). Long Non-coding RNA TUG1 Sponges miR-197 to Enhance Cisplatin Sensitivity in Triple-Negative Breast Cancer Cells. *MicroRNA-lncRNA Regarding Wnt/β-Catenin Axis in TNBC* 8, June 2022 | Volume 13 | Article 814971
Negative Breast Cancer. *Biomed. Pharmacother.* 107, 338–346. doi:10.1016/j.biopha.2018.07.076

Tao, W., Wang, C., Zhu, B., Zhang, G., and Pang, D. (2019). lncRNA dance contributes to tumor progression via targeting mir-216a-5p in breast cancer: lncRNA dance contributes to tumor progression. *BioSci. Rep.* 39 (4). doi:10.1042/BSR20181618

Taube, J. H., Malouf, G. G., Lu, E., Sphyris, N., Vijay, V., Ramachandran, P. P., et al. (2013). Epigenetic Silencing of microRNA-203 Is Required for EMT and Cancer Stem Cell Properties. *Sci. Rep.* 3, 2687. doi:10.1038/srep02687

Telenis, A. G., and Rigoutsos, I. (2018). Race Disparities in the Contribution of miRNA-146a and miRNA-21 to Systemic Lupus Erythematosus. *EJIFCC* 29 (3), 221–226.

Tu, Z., Schmöllerl, J., Cuiffo, B. G., and Karnoub, A. E. (2019). Microenvironmental Regulation of Long Noncoding RNA LINC01133 Promotes Cancer Stem Cell-like Phenotypic Traits in Triple-Negative Breast Cancers. *Stem Cells* 37 (10), 1281–1292. doi:10.1002/stem.3055

van Barele, M., Heemskerk-Gerritsen, B. A. M., Louwers, Y. V., Vaathuinder, M. B., Martens, J. W. M., Hooning, M. J., et al. (2021). Estrogens and Progestogens in Triple Negative Breast Cancer: Do They Harm? *Cancer (Basel)* 13 (11). doi:10.3390/cancers13112506

Volovat, S. R., Volovat, C., Hordila, I., Hordila, D. A., Mirestean, C. C., Miron, O. T., et al. (2020). MRNA and LncRNA as Potential Biomarkers in Triple-Negative Breast Cancer: A Review. *Front. Oncol.* 10, 526850. doi:10.3389/onc.2020.526850

Wang, D., Huang, J., and Hu, Z. (2012). RNA Helicase DDX5 Regulates microRNA Expression and Contributes to Cytoskeletal Reorganization in Basal Breast Cancer Cells. *Mol. Cell Proteomics* 11 (2), M111-M011932. doi:10.1074/mcp.M111.011932

Wang, D. Y., Gendoo, D. M. A., Ben-David, Y., Woodgett, J. R., and Zacksenhaus, E. (2019). A Subgroup of microRNAs Defines PTEN-Deficient, Triple-Negative Breast Cancer Patients with Poorest Prognosis and Alterations in RB1, MYC, and Wnt Signaling. *Breast Cancer Res.* 21 (1). doi:10.1186/s13058-019-1098-z

Wang, K., Li, X., Song, C., and Li, M. (2018). LncRNA awphp promotes the growth of triple-negative breast cancer by up-regulating frizzled homolog 7 (fl7d). *BioSci. Rep.* 38 (6). doi:10.1042/BSR20181223

Wang, L., Wang, R., Ye, Z., Wang, Y., Li, X., Chen, W., et al. (2018). PVT1 Affects EMT and Cell Proliferation and Migration via Regulating P21 in Triple-Negative Breast Cancer Cells Cultured with Mature Adipogenic Medium. *Acta Biochim. Biophys. Sin. (Shanghai)* 50 (12), 1211–1218. doi:10.1093/abs/gmy129

Wang, Y., Zhang, W., and Wang, J. (2018). MicroRNA-384 Inhibits the Progression of Breast Cancer by Targeting ACVR1. *Oncol. Rep.* 39 (6), 2563–2574. doi:10.3892/or.2018.6385

Wilusz, J. E., Sunwoo, H., and Spector, D. L. (2009). Long Noncoding RNAs: Critical Role in Cell Proliferation in Triple Negative Breast Cancer. *Biomed. Pharmacother.* 63, 1237. doi:10.1016/j.biopha.2009.08.005

Xu, S. T., Xu, J. H., Zheng, Z. R., Zhao, Q. Q., Zeng, X. S., Cheng, S. X., et al. (2017). Long non-coding rna anril promotes carcinogenesis via sponging mir-199a in triple-negative breast cancer. *Biomed. Pharmacother.* 96, 14–21. doi:10.1016/j.biopha.2017.09.107

Yang, L., Wu, X., Wang, Y., Zhang, K., Wu, J., Yuan, Y. C., et al. (2011). Fzd7 Has a Critical Role in Cell Proliferation in Triple Negative Breast Cancer. *Oncogene* 30 (43), 4437–4446. doi:10.1038/onc.2011.145

Yang, W., Cui, G., Ding, M., Yang, M., and Dai, D. (2020). MicroRNA-124-3p-1 Promotes Cell Proliferation through Axin1-dependent Wnt Signaling Pathway and Predicts a Poor Prognosis of Triple-Negative Breast Cancer. *J. Clin. Lab. Anal.* 34 (7), e23566. doi:10.1002/jcla.23566

Yao, H., Aishihara, E., and Maskawa, T. (2011). Targeting the Wnt/β-Catenin Signaling Pathway in Human Cancers. *Expert Opin. Ther. Targets* 15 (7), 873–887. doi:10.1517/14728222.2011.577418

Yin, L., Duan, J. J., Bian, X. W., and Yu, S. C. (2020). Triple-negative Breast Cancer Molecular Subtyping and Treatment Progress. *Breast Cancer Res.* 22 (1), 61. doi:10.1186/s13058-020-01296-5

Yin, S., Xu, L., Bonfill, R. D., Banerjee, S., Sarkar, F. H., Sethi, S., et al. (2013). Tumor-initiating Cells and Fzd8 Play a Major Role in Drug Resistance in Triple-Negative Breast Cancer. *Mol. Cancer Ther.* 12 (4), 491–498. doi:10.1158/1535-7163.MCT-12-1090

Yu, L., Wang, C., Pan, F., Liu, Y., Ren, X., Zeng, H., et al. (2019). HeTTP Promotes Migration and Invasion in Triple-Negative Breast Cancer Cells via Activation of Wnt/β-Catenin Signaling. *Biomed. Pharmacother.* 118, 109361. doi:10.1016/j.biopha.2019.109361

Yuan, C., Luo, X., Duan, S., and Guo, L. (2020). Long Noncoding RNA LINC00115 Promotes Breast Cancer Metastasis by Inhibiting miR-7. *FEBS Open Bio* 10 (7), 1230–1237. doi:10.22121/febs.1218.12482

Zhang, K., Liu, P., Tang, H., Xie, X., Kong, Y., Song, C., et al. (2018). AFAP1-AS1 Promotes Epithelial-Mesenchymal Transition and Tumorigenesis through Wnt/β-Catenin Signaling Pathway in Triple-Negative Breast Cancer. *Front. Pharmacol.* 9, 1248. doi:10.3389/fphar.2018.01248

Zhang, T., Hu, H., Yan, G., Wu, T., Liu, S., Chen, W., et al. (2019). Long Non-coding RNA and Breast Cancer. *Technol. Cancer Res. Treat.* 18, 153333819438899. doi:10.1177/153333819438899

Zhang, Y., and Wang, X. (2020). Targeting the Wnt/β-Catenin Signaling Pathway in Cancer. *J. Hematol. Oncol.* 13 (1). doi:10.1186/s13045-020-00990-3

Zheng, A., Song, X., Zhang, L., Zhao, L., Mao, X., Wei, M., et al. (2019). Long Noncoding RNA LUCAT1/mir-5582-3p/TCF7L2 axis Regulates Breast Cancer Stemness via Wnt/β-Catenin Pathway. *J. Exp. Clin. Cancer Res.* 38 (1). doi:10.1186/s13046-019-1315-8

Zou, Y., Li, Y., Zhou, Z., Ma, M., and Fu, K. (2017). Long non-coding RNA MALAT1 Promotes Proliferation and Invasion via Targeting mir-129-5p in Triple-Negative Breast Cancer. *Biomed. Pharmacother.* 95, 922–928. doi:10.1016/j.biopha.2017.09.005

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors, or the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Hu, Zhang, Xing and Wang. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.