Identification and Roles of miR-29b-1-3p and miR29a-3p-Regulated and Non-Regulated lncRNAs in Endocrine-Sensitive and Resistant Breast Cancer Cells

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Abstract: Despite improvements in the treatment of endocrine-resistant metastatic disease using combination therapies in patients with estrogen receptor α (ERα) primary tumors, the mechanisms underlying endocrine resistance remain to be elucidated. Non-coding RNAs (ncRNAs), including microRNAs (miRNA) and long non-coding RNAs (lncRNA), are targets and regulators of cell signaling pathways and their exosomal transport may contribute to metastasis. Previous studies have shown that a low expression of miR-29a-3p and miR-29b-3p is associated with lower overall breast cancer survival before 150 mos. Transient, modest overexpression of miR-29b-1-3p or miR-29a-3p inhibited MCF-7 tamoxifen-sensitive and LCC9 tamoxifen-resistant cell proliferation. Here, we identify miR-29b-1/a-regulated and non-regulated differentially expressed lncRNAs in MCF-7 and LCC9 cells using next-generation RNA seq. More lncRNAs were miR-29b-1/a-regulated in LCC9 cells than in MCF-7 cells, including DANCR, GAS5, DSCAM-AS1, SNHG5, and CRND. We examined the roles of miR-29-regulated and differentially expressed lncRNAs in endocrine-resistant breast cancer, including putative and proven targets and expression patterns in survival analysis using the KM Plotter and TCGA databases. This study provides new insights into lncRNAs in endocrine-resistant breast cancer.

Keywords: miR-29; lncRNA; tamoxifen; endocrine resistance; breast cancer
have metastatic disease [3,4]. The five-year survival rate for women diagnosed with metastatic breast cancer (mBC) varies between 7.2% and 29% [5]. Survival among women with mBC from ERα-expressing (ER+) primary tumors has increased over time with better therapies—including cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors (palbociclib/ribociclib/abemaciclib), an mTORC1 (MTOR, mechanistic target of rapamycin kinase) inhibitor (everolimus), and an alpha isoform-specific PI3K inhibitor (alpelisib)—which are used in combination with endocrine therapy (fulvestrant) for ER+ mBC [6–8]. Acquired endocrine resistance is the result of multiple mechanisms, including the amplification of growth signaling pathways [9]. Approximately 25–40% of metastatic tumors in AI-treated breast cancer (BC) patients have been reported to have ESR1 (ERα) mutations within the ligand binding domain (LBD) [10]. These mutations result in ligand-independent activation of the mutant ERα protein and reduce the efficacy of SERMs and selective ER downregulators (SERDs) fulvestrant, GDC-0810, RU-58688, and AZD9496 [11].

Alterations in the expression of noncoding RNAs (ncRNAs), including circular RNA (circRNA) [12–14], microRNA (miRNA) [15,16], and long noncoding RNAs (lncRNAs) [17,18] have been reported in breast tumors and in circulation in BC patients, with specific alterations in endocrine resistance [19–22]. miRNAs and lncRNAs are epigenetic regulators of human cancers [23]. Pre-miRNAs and lncRNAs are post-transcriptionally modified, e.g., by methylation on N6 of adenosine (m6A), which alters the processing and interaction with RNA binding proteins; thus, epitranscriptomic modification regulates cellular events in BC and in other cancers [24–26]. miRNAs regulate mRNA translation and RNA stability by base-pairing between the seed sequences at 5′ positions 2–7 or 2–8 of the miRNA, with ~7 bp miRNA recognition elements (MREs) in the 3′ UTR of their target miRNAs within the RNA-induced silencing complex (RISC) [27]. The current miRBase database (release 22.1) contains 2654 mature human miRNAs http://www.mirbase.org/ (accessed on 25 April 2021) [28]. Depending on the tissue, miR-29 family members (miR-29a (MI0000087), miR-29b-1 (MI0000105), miR-29b-2 (MI0000107), and miR-29c (MI0000735) act as oncomiRs or as tumor suppressor miRNAs [29–34]. We previously reported that a low expression of miR-29a-3p and miR-29b-3p is associated with lower overall BC survival before 150 mos and that transient, modest overexpression of miR-29b1-3p or miR-29a-3p inhibited MCF-7 tamoxifen (TAM)-sensitive and LCC9 TAM-resistant BC cell proliferation [35]. The TAM- and fulvestrant-resistant LCC9 cell line was derived from MCF-7 tumor xenografts in TAM-treated mice and is ER+ [36,37]. We attributed this observation in part to the repression of the transcription of ATP synthase subunit genes ATP5G1 and ATPIF1 by miR-29b-1-3p and miR-29a-3p [35], miR-29b1-3p and miR-29a-3p are derived from the same precursor-miRNA (pre-miRNA) from chromosome 7, whereas miR-29b-2 and miR-29c are located on chromosome 1 [34]. A recent study confirmed reduced miR-29a-3p to be a disease-specific survival prognostic indicator in BC [38]. miR-29 family members (miR-29a, b-1, b-2, and c) also target additional genes, i.e., ADAM12, ANGPTL4, ARPIBI, Dicer1, TTP, Pten, KL4, Myp, Lox, Mmp, Pdgfc, Serpinh1, and Vegfa (reviewed in [20,39]).

The current GENCODE (version 384) of the human genome includes 60,649 genes, 16,888 long noncoding RNAs (lncRNAs), and 1879 miRNAs https://www.gencodegenes.org/human/stats.html (accessed on 25 April 2021). The function of most lncRNAs remains to be characterized. By definition, lncRNAs are ncRNAs > 200 nucleotides in length [40]. lncRNAs are transcribed by RNA pol II from intergenic (lincRNA), intronic, antisense (AS), and regions overlapping mRNAs from loci marked with H3K4me3 at the promoter and H3K36me throughout the transcript body (reviewed in [41,42]). lncRNAs include enhancer RNAs (eRNAs), promoter upstream transcripts (PROMPTs), and small nucleolar RNA (snoRNA)-ended lncRNAs (sno-lncRNAs) [43]. lncRNAs are found in a low abundance in part due to their rapid degradation by the RNA exosome [44]. Most lncRNAs are nuclear, but lncRNAs have functional roles in the cytoplasm, tethered to cell membranes, in mitochondria, and are sorted into exosomes for systemic distribution, which contributes to metastasis (reviewed in [41]). In the cytoplasm, lncRNAs bind RNA-
binding proteins (RBPs) and can positively or negatively affect translation through their interaction with translation factors and ribosomes [43]. LncRNAs can act in trans to regulate genes or other transcripts at a distance or in cis to regulate neighboring genes [42]. Photoactivatable-ribonucleoside-enhanced crosslinking and immunoprecipitation (PAR-CLIP) studies identified miRNA–lncRNA interactions clustering in the mid-regions and 3′ ends of lncRNAs [45]. LncRNAs act as ‘sponges’ for miRNA by acting as competing endogenous RNA (ceRNA), thus blocking the repressive activity of miRNAs, i.e., blocking miRNA binding to the 3′ UTR of their target transcripts [21]. The loss of repression leads to increased target mRNA translation and protein abundance. miRNA–lncRNA interaction also regulates lncRNA stability [46]. A network analysis of ncRNAs in cancer drug resistance associated lncRNAs, miRNAs, and TAM resistance, including lncRNAs MA-LATI and CCAT2; miR-221, miR-222, miR-26a, miR-29a, and miR-29b (of which the isoform was not specified), has been described [47]. LncRNAs can also act as intracellular scaffolds, e.g., HOTAIR provides a platform for PRC2 and LSD1 histone-modifying complexes to promote H3K27 methylation and H3K4 demethylation to silence genes and promote metastasis in BC [48].

Transcriptomic regulation of endocrine resistance in BC cells involves regulatory networks of lncRNAs, miRNAs, circRNAs, and mRNAs [49]. In this study, we identified the lncRNAs regulated by miR-29b-1-3p and miR-29a-3p in MCF-7 and LCC9 breast cancer cells. In addition, we identified the lncRNAs that are differentially expressed in the two cell lines independently of miR-29b-1 or miR-29a regulation. We review the roles of these lncRNAs and their targets in BC progression, endocrine therapy responses, and metastasis.

2. Materials and Methods

2.1. RNA Sequencing

RNA sequencing was previously described in [35]. In brief, single read sequencing (75–76 cycles) was performed using the 500 High-Output v2 (75 cycle) sequencing kit (Illumina, Foster City, CA, USA) on an Illumina NextSeq500 instrument. Obtained read sequences were mapped to the human reference genome version GRCh37.1 using the mapping algorithm Tophat version 2.0.2 (Toronto, ONT, Canada) Using Cufflinks version 2.2.1 (Seattle, WA, USA) and annotations found at ENSEMBL, Homo sapiens GRCh37.73.gtf expression levels at loci were quantified. Data are from the GEO database: accession number GSE81620.

2.2. In Silico Pathway and Network Analysis

Data from RNA-seq were analyzed such that transcripts selected had a log 2 fold-change greater than 0.34 (or −0.34 for repressed transcripts) and a statistically significant threshold q-value less than 0.05. LncRNA–miR-29 interactions were checked against those verified and predicted using DIANA-LncBase v3 [50] (Athens, Greece). Network and pathway enrichment analysis for the lncRNAs was evaluated using a fee-based site license for the web-based software MetaCore version 21.1 (Cortellis, Philadelphia, PA, USA) https://portal.geneego.com/ (accessed on 25 April 2021). MetaCore is a manually curated database of experimental findings and interactions [35,51,52].

3. Results and Discussion

3.1. Identification of miR-29b-1/a-Downregulated lncRNAs and Their Roles in Breast Cancer

To identify miR-29b-1-3p- and miR-29a-3p-regulated transcripts in MCF-7 TAM-sensitive and LCC9 TAM-resistant BC cells and their possible roles in endocrine-resistant BC progression and metastasis, we previously transfected each cell line with either pre-miR™ negative control, pre-miR-29b-1-3p, pre-miR-29a-3p, anti-miR negative control, or anti-miR-29 individually or in combination. By carrying out the co-transfection of each cell line with pre-miR-29b-1-3p + anti-miR-29 and pre-miR-29a-3p + anti-miR-29 and comparing
the resulting transcriptomes to those with controls and those transfected with pre-miR-29b-1-3p or pre-miR-29a-3p, we identified miR-29b-1-3p- and miR-29b-1-3p-regulated transcripts, respectively (Figure 1). For example, for an lncRNA downregulated by miR-29b-1-3p, we expect a decrease in the fragments per kilobase of transcript per million mapped reads (FPKM) value of that lncRNA in cells transfected with pre-miR-29b-1-3p and an increase in the FPKM of that lncRNA in cells transfected with pre-miR-29b-1-3p + anti-miR-29 (Table 1). Conversely, for an lncRNA upregulated by miR-29b-1-3p, we expect an increase in the FPKM of that lncRNA in cells transfected with pre-miR-29b-1-3p and a decrease in the FPKM of that lncRNA in cells transfected with pre-miR-29b-1-3p + anti-miR-29 (Table 2).

![Image of a downregulated and an upregulated lncRNA detected in both MCF-7 and LCC9 cells from Tables 1 and 2 is shown.](image)

We identified 19 lncRNAs that were upregulated by anti-miR-29 in LCC9 cells and/or MCF-7 cells with pre-miR-29b-1/a + anti-miR-29 transfection (Table 1), suggesting miR-29 regulation. As described previously in our identification of differentially expressed genes (DEGs, i.e., mRNAs) regulated by miR-29b-1-3p and miR29a-3p (miR-29b-1/a) [35], we observed more lncRNAs downregulated by miR-29b-1/a in LCC9 than in MCF-7 cells (18 and two, respectively) with only TUG1 being downregulated by miR-29b-1/a in both cell lines. Fourteen miR-29b-1/a-downregulated lncRNAs were more highly expressed in MCF-7 cells than in LCC9 cells: SOX2-OT, LINC00473, MIR17HG, FIRRE, DLEU1, OIP5-AS1, JPX, DANCER, CYTOR, TUG1, SNHG8, SNHG5, DSCAM-AS1, and GAS5 (Table 1). Two miR-29b-1/a-downregulated lncRNAs were more highly expressed in LCC9 than in MCF-7 cells: LINC00221 and MIR99HG (Table 1). We used DIANA-LncBase v3.0 (Athens, Greece) [50] to examine lncRNA-miR-29b-1/a interaction and found that 10 of the 19 putative interactions identified in MCF-7 and/or LCC9 cells have been experimentally validated (Table 1). MetaCore enrichment analysis identified gene ontology (GO) processes, which are shown in Supplementary Table S1, but these only included the lncRNA TUG1. MetaCore network analysis is shown in Supplementary Table S2 and selected networks are shown in Figures 2–4.
| Ensembl   | Name       | Alias       | MCF-7 Pre-miR-29b-1-3p | MCF-7 Pre-miR-29a-3p | MCF-7 AS miR-Signif. Pre-miR-29b-1-3p | LCC9 Pre-miR-29b-1-3p | LCC9 Pre-miR-29a-3p | LCC9 AS-miR-29a-3p | Signific. Different between MCF-7 vs. LCC9 | Role in Breast Cancer | Network Supp. Table 2, Figures 2–4 | miR-29-IncRNA Interaction from DIANA-LncBase v.3 |
|-----------|------------|-------------|------------------------|---------------------|---------------------------------------|----------------------|------------------|------------------|---------------------------------------------|----------------------|----------------------------------------|-----------------------------------------------|
| ENSG00000270816 | LINC00221 | ND          | ND                     | ND                  | 4.05                                 | 4.26                 | 5.76             | yes              | LCC9 > MCF-7                                   | no results found             |                                        |
| ENSG00000242808 | SOX2-OT   | 0.14        | 0.40                   | 0.37                | yes                                   | 0.23                 | 0.29             | 0.15             | no                                           | MCF-7 > LCC9                          | 3                                      |
| ENSG00000224314 | LINC00473 | 0.17        | 0.24                   | 0.11                | no                                    | 0.04                 | 0.02             | 0.79             | yes                                         | MCF-7 > LCC9                          | no results found                     |
| ENSG00000215417 | MIR17HG   | 1.58        | 1.69                   | 8.16                | yes                                   | 1.11                 | 0.87             | 1.82             | no                                          | MCF-7 > LCC9                          | 7                                      |
| ENSG00000213468 | FIRRE     | 1.92        | 1.84                   | 1.55                | no                                    | 0.51                 | 0.68             | 0.77             | yes                                         | MCF-7 > LCC9                          | yes, high confidence                |
| ENSG00000215386 | MIR9AHG   | 3.61        | 3.62                   | 5.09                | no                                    | 6.68                 | 5.91             | 10.77            | yes                                         | LCC9 > MCF-7                          | yes, high confidence                |
| ENSG00000227036 | LINC00511 | 5.48        | 5.17                   | 7.83                | no                                    | 0.20                 | 0.33             | 1.01             | yes                                         | LCC9 > MCF-7                          | yes, high confidence                |
| ENSG000000176124 | DLEU1     | 15          | 15                     | 18                  | yes                                   | 9.83                 | 11.96            | 21.06            | yes                                         | MCF-7 > LCC9                          | 4                                      |
| ENSG00000214293 | APTR      | 22          | 22                     | 19                  | no                                    | 22.87                | 20.50            | 27.18            | yes                                         | MCF-7 > LCC9                          | oncogenic                            |
| ENSG00000247556 | OIPS-AS1  | 26          | 28                     | 33                  | no                                    | 20.10                | 22.11            | 74.54            | yes                                         | MCF-7 > LCC9                          | oncogenic                            |
| ENSG00000225470 | JFX       | 29          | 35                     | 39                  | no                                    | 22.40                | 20.37            | 38.48            | yes                                         | MCF-7 > LCC9                          | oncogenic                            |
| ENSG00000226950 | DANCR     | 29          | 28                     | 29                  | no                                    | 23.93                | 17.90            | 75.62            | yes                                         | MCF-7 > LCC9                          | oncogenic                            |
| ENSG00000222041 | CYTOR     | 37          | 36                     | 47                  | no                                    | 18.53                | 15.90            | 28.57            | yes                                         | MCF-7 > LCC9                          | oncogenic                            |
| ENSG00000245694 | CRNDE     | 44          | 49                     | 56                  | no                                    | 43.36                | 41.71            | 58.03            | yes                                         | MCF-7 > LCC9                          | 2                                      |
| ENSG00000253352 | TUG1      | 114         | 126                    | 173                 | yes                                   | 50.84                | 58.46            | 79.56            | yes                                         | MCF-7 > LCC9                          | oncogenic                            |
| ENSG00000269893 | SNHG8     | 282         | 293                    | 245                 | no                                    | 249.11               | 202.91           | 340.90           | yes                                         | MCF-7 > LCC9                          | no results found                     |
| ENSG00000203875 | SNHG5     | 391         | 411                    | 439                 | no                                    | 218.59               | 184.31           | 324.41           | yes                                         | MCF-7 > LCC9                          | oncogenic                            |
| ENSG00000235123 | DSCAM-AS1 | 1213        | 1444                   | 1280                | no                                    | 140.59               | 153.88           | 483.25           | yes                                         | MCF-7 > LCC9                          | oncogenic                            |
| ENSG00000234741 | GASS      | 2052        | 2000                   | 1822                | no                                    | 836.63               | 827.36           | 1239.31          | yes                                         | MCF-7 > LCC9                          | tumor suppressor                    |

Table 1. IncRNAs downregulated by miR-29b-1/a in MCF-7 and/or LCC9 breast cancer cells. MCF-7 or LCC9 cells were transfected with pre-miR-control, pre-miR-29b-1-3p, pre-miR-29a-3p, anti-miR-29a (which targets miR-29b-1/a), or anti-miR negative control for a 48 h prior to RNA isolation and RNA sequencing [35]. Values are fragments per kilobase of transcript per million mapped reads (FPKM) and are the average of five replicate samples (GSE81620). Significance was q ≤ 0.05. ND = not detected.
Table 2. lncRNAs upregulated by miR-29b-1-3p and miR-29a-3p in MCF-7 and/or LCC9 breast cancer cells. MCF-7 or LCC9 cells were transfected with pre-miR-control, pre-miR-29b-1-3p, pre-miR-29a-3p, anti-miR-29a (which targets miR-29b-1/a), or anti-miR negative control for a 48 h prior to RNA isolation and RNA sequencing [35]. Values (FPKM) are the average of five replicate samples (GSE81620). Significance was q ≤ 0.05. ND = not detected.

| Ensembl | Name | Alias | MCF-7 Pre-miR-29b-1-3p | MCF-7 Pre-miR-29a-3p | MCF-7 AS miR-29a-3p | LCC9 Pre-miR-29b-1-3p | LCC9 Pre-miR-29a-3p | LCC9 AS miR-29a-3p | Signific. Different between MCF-7 vs. LCC9 | Role in Breast Cancer | Network Supp. Table | miR-29-IncRNA Interaction from DIANA-LncBase v.3 |
|---------|------|-------|------------------------|----------------------|---------------------|----------------------|---------------------|---------------------|---------------------------------|----------------------|-----------------------------|-------------------------------|
| ENSG00000237517 | DGCR5 | NCRNA00037, LINC00037 | 0.60 | 0.42 | 0.38 | no | 0.69 | 0.70 | 0.32 | yes | oncogene | yes, high confidence |
| ENSG00000236824 | BCYRN1 | BC200a, LINC00004 | 0.79 | 0.70 | 0.30 | yes | 1.76 | 2.36 | 2.93 | yes | LCC9 > MCF-7 | oncogene | no results |
| ENSG00000214049 | UCA1 | LINC00035 | 1.32 | 1.41 | 0.33 | yes | 2.06 | 1.56 | 1.03 | no | LCC9 > MCF-7 | oncogene | 1,3 | no results |
| ENSG00000225969 | ABHD11-AS1 | LINC00035 | 2.57 | 1.57 | 1.14 | yes | 0.78 | 0.79 | 0.37 | no | MCF-7 > LCC9 | unknown | 2 | no results |
| ENSG00000237886 | NALT1 | RP11-611D20.2 | 7.77 | 5.20 | 3.88 | yes | 4.51 | 4.78 | 2.66 | yes | MCF-7 > LCC9 | unknown | no results |
| ENSG00000223573 | TINCR | LINC00036 | 17 | 17 | 17 | no | 2.74 | 2.88 | 1.77 | yes | MCF-7 > LCC9 | oncogene | no results |
| ENSG00000253716 | MINCR | RP13-582O9.5, LINC01604 | 30 | 27 | 18 | yes | 20 | 13 | 17 | no | MCF-7 > LCC9 | unknown | yes, high confidence |
| ENSG00000245532 | NEAT1 | NEAT2, LINC00047 | 395 | 372 | 186 | yes | 147 | 143 | 59 | yes | MCF-7 > LCC9 | oncogene | 1,3 | no results |
| ENSG00000251562 | MALAT1 | NEAT2, LINC000047 | 496 | 442 | 469 | no | 76 | 87 | 54 | yes | MCF-7 > LCC9 | oncogene | 1,3 | yes, high confidence |
Figure 2. Network 2: TUG1, CRNDE, APTR, DANC, and SNHG5, identified in lncRNAs downregulated by miR-29b-1-3p and miR-29a-3p in MCF-7 and/or LCC9 cells by MetaCore analysis. Green lines with arrows = stimulation; red lines with arrows = inhibition.

Figure 3. Network 3: DLEU7-AS1, GAS5, SOX2OT, LINC00152, and TUG1, identified in lncRNAs downregulated by miR-29b-1-3p and miR-29a-3p in MCF-7 and/or LCC9 cells by MetaCore analysis. Green lines with arrows = stimulation; red lines with arrows = inhibition.
3.2. Identification and Functional Roles of lncRNAs Downregulated by miR-29b-1/a

The abundance of LINC00511 and TUG1 was increased by anti-miR-29 in both MCF-7 and LCC9 cell lines transfected with either pre-miR-29a-3p or pre-miR-29b-1-3p, suggesting the downregulation of these lncRNAs by miR-29b-1/a in these cells (Table 1). The abundance of SOX2-OT and MIR17HG was increased by anti-miR-29 only in MCF-7 cells transfected with either pre-miR-29a-3p or pre-miR-29b-1-3p, suggesting the selective downregulation of these lncRNAs by miR-29b-1/a in MCF-7 cells (Table 1). The abundance of LINC00221, LINC00473, FIRRE, MIR99AHG, DLEU1, APTR, OIP5-AS1, JPX, DANCRI, CYTOR, CRNDE, SNHG8, SNHG5, DSCAM-AS1, and GAS5 was increased by anti-miR-29 only in LCC9 cells transfected with either pre-miR-29a-3p or pre-miR-29b-1-3p, suggesting the selective downregulation of these lncRNAs by miR-29b-1/a in LCC9 TAM-resistant BC cells (Table 1).

LINC00221 was not detected in MCF-7 cells but was increased by the anti-miR-29 transfection of LCC9 cells transfected with pre-miR-29b-1-3p or pre-miR-29a-3p, suggesting that miR-29b-1-3p and miR-29a-3p selectively downregulate LINC00221 in LCC9 TAM-resistant BC cells. In contrast to our findings, a previous study observed higher LINC00221 in MCF-7 compared to another TAM-resistant cell line derived from MCF-7 cells (LCC2) and reported that the higher expression of LINC00221 in ER+ BC patients was associated with a higher probability of survival [49]. The reason for this difference may be methodological: the previous study used the Agilent human lncRNA + mRNA Array V4.0 for the profiling of lncRNAs and mRNAs in MCF-7, LCC2, and LCC9 cells [49], whereas we used direct RNA seqs [35].

A report profiling Ago2:RNA interactions using HITS-CLIP in human post-mortem brain tissue identified an SOX2-OT–miR-29b-1-3p interaction [53]. An analysis of TCGA breast tumor cells identified the amplification of SOX2-OT as a putative lncRNA driver of BC [54]. SOX2-OT was identified in network 3 with DLEU1, CYTOR (LINC00152), and TUB1 (Figure 3). The reduction of the SOX2-OT abundance by miR-29b-1-3p in MCF-7 cells fits with its ‘anti-tumorigenic’ activity in BC [55].

LINC00473 was higher in breast tumors and BC cell lines compared to normal breast tissue and breast epithelial cells [56]. High LINC00473 expression was correlated with lymph node (LN) metastasis, clinical stage, and poor outcomes in BC patients [56]. In MCF-7 and MDA-MB-231 cells, LINC00473 is a ceRNA for miR-497 [56] and for miR-198 [57]. LINC00473 increases CCND1 transcription in MCF-7 cells by increasing the recruitment of pCREB and H3K27ac to activate the promoter, thus increasing cell proliferation [58]. The reduction of the LINC00473 abundance by miR-29a-3p and miR-29b-1-3p fits with their ‘anti-tumorigenic’ activity in BC (reviewed in [30]).

MIR17HG (miR-17-92a-1 cluster host gene) encodes six miRNAs: MIR17, MIR18A, MIR19A, MIR20A, MIR19B1, and MIR92A1, which are members of four seed families (miR-7, miR-18, miR-19, and miR-92) [59]. The miR-17-92a cluster is considered oncogenic (reviewed in [60]). miR-18a directly targets ESR1 and reduces ERα in MCF-7 and BT-474 cells [61], miR-17-5p targets pro-metastatic genes involved in transforming growth factor β (TGFβ) and hypoxia signaling in basal-like BC [62]. MIR17HG was included in network 7 with β-catenin (Supplementary Table S2). The reduction of MIR17HG abundance by miR-29a-3p and miR-29b-1-3p fits with their ‘anti-tumorigenic’ activity in BC (reviewed in [30]).

FIRRE forms “RNA clouds” in the nucleus, binds the nuclear matrix protein HNRNPU (heterogeneous nuclear ribonucleoprotein U), and serves as a platform for trans-chromosomal associations [63]. FIRRE is transcribed from the active X chromosome and acts in trans and cis to maintain X chromosome inactivation [64]. No reports of FIRRE/LINC01200 in BC were located in PubMed.
**Figure 4.** Network 4: DLEU1, MIR99AHG, FOXP3, KCNMB4, and nAChR delta, identified in lncRNAs downregulated by miR-29b-1-3p and miR-29a-3p in MCF-7 and/or LCC9 cells by MetaCore analysis. Green lines with arrows = stimulation; red lines with arrows = inhibition. nAChR = nicotinic acetylcholine receptor delta (CHRND). nAChRs are present in breast tumors (reviewed in [65]).

*DLEU1* abundance was significantly increased in LCC9 cells transfected with anti-miR-29 and either pre-miR-29a-3p or pre-miR-29b-1-3p (Table 1), suggesting the downregulation of DLEU1 by miR-29b-1/a, a result confirmed by DIANA-LncBase v3 (Athens, Greece) [50]. DLEU1 expression was higher in breast tumors than in normal breast tissue [74]. *DLEU1* was identified in network 4 (Supplementary Table S2) with MIR99AHG (Figure 4). The network shows the interaction of FOXP3 with DLEU1 and MIR99AHG. FOXP3

**MIR99AHG** (LINC00478, miR-99a-Let-7c cluster host gene) abundance was higher in LCC9 cells compared to MCF-7 cells and its abundance was significantly increased by anti-miR-29 in LCC9 cells transfected with pre-miR-29a-3p or pre-miR-29b-1-3p (Table 1). *MIR99AHG* (chromosome 21q21.1) is transcribed as a polycistronic primary transcript that produces a spliced lncRNA and three intronic miRNAs: miR-99a, miR-125b, and Let-7c [66]. The miRNA miR-99a/let-7c/miR-125b cluster is upregulated in luminal A compared with luminal B human breast tumors [67]. *MIR99AHG* was identified in network 4 (Supplementary Table S2) with DLEU1 (Figure 4) to be regulated by FOXP3, but no publications were identified on the role of FOXP3 in PubMed.

**LINC00511** was demonstrated to directly bind miR-29c-3p, reducing its expression in MCF-7 cells, and relieving its repression of CDK6 [68]. Previous studies demonstrated an oncogenic role for *LINC00511* that was highly upregulated in breast tumors and BC cell lines, notably in TNBC [69]. *LINC00511* acts as a ceRNA for miR-185-3p [70] and for miR-150 [71] in BC cells. ERα deficiency was reported to increase LINC00511 in breast tumors and RNA IP experiments demonstrated that LINC00511 interacts with EZH2 in UACC-812 and MDA-MB-231 TNBC cells [72]. A recent study reported that blocking LINC00511 using cell-penetrating peptide (CPP)-loaded nanobubbles (CNBs) loaded with siLINC00511 was shown to inhibit MDA-MB-231 cell growth and to enhance sensitivity to cisplatin in vitro [73]. The reduction of LINC00511 abundance by miR-29a-3p and miR-29b-1-3p fits with their ‘anti-tumorigenic’ activity in BC (reviewed in [30]).

**DLEU1** abundance was significantly increased in LCC9 cells transfected with anti-miR-29 and either pre-miR-29a-3p or pre-miR-29b-1-3p (Table 1), suggesting the downregulation of DLEU1 by miR-29b-1/a, a result confirmed by DIANA-LncBase v3 (Athens, Greece) [50]. DLEU1 expression was higher in breast tumors than in normal breast tissue [74]. *DLEU1* was identified in network 4 (Supplementary Table S2) with MIR99AHG (Figure 4). The network shows the interaction of FOXP3 with DLEU1 and MIR99AHG. FOXP3...
functions as a tumor suppressor in BC [75]. Further studies are needed to explore the role of **DLEU1** in TAM-resistant BC.

Bioinformatic analysis identified ten miRNAs as putative **APRT** interactors, but miR-29 was not included [76]. **APTR** was demonstrated to repress **CDKN1A** transcription by binding to the promoter and recruiting the **PRC2** complex [77]. **APTR** was recently reported to be increased in breast tumors compared to normal adjacent breast tissue and to be higher in larger tumors, suggesting an oncogenic function [76]. Another recent study reported that **APTR** directly interacts with **ERα** in HUt-6LM human leiomyoma cells [78]. **APTR** was identified in network 2 (Supplementary Table S2) with **TUG1**, **CRNDE**, **DANCR**, and **SNHG5** (Figure 2). The network shows the interaction of **APRT**, **SNHG5**, and **TUG1** with miR-132-3p. miR-132 was identified as a tumor suppressor in BC [79]. Additional studies are needed to explore the role of **APTR** in BC.

**RNA immunoprecipitation (RIP)** and small RNA-seq identified miR-29a, b, and c as interacting directly with **OIP5-AS1** in HeLa cells [80]. The authors demonstrated that **OIP5-AS1** functions to decrease target mRNA abundance while increasing target miRNA levels [80]. **OIP5-AS1** was higher in breast tumors compared with normal breast tissue and high **OIP5-AS1** correlated with tumor size, LN metastasis, and tumor grade [81]. Another study found that **OIP5-AS1** expression correlates with a high risk of worse outcomes for luminal BC patients [82]. Knockdown of **OIP5-AS1** in MDA-MB-231 cells inhibited xenograft tumor growth in BALB/c nude mice, validating its oncogenic activity in vivo [81]. **OIP5-AS1** acts as ‘sponge’ for RNA-binding protein HuR in HeLa cells, keeping HuR from interacting with mRNAs [83]. HuR is elevated in breast tumors compared to normal breast and increases the stability of a number of regulatory transcripts including **ESR1**, **STAT3**, **ERBB2**, and **FOXO1** to stimulate cell proliferation, invasion, and migration [84]. **OIP5-AS1** triggers target-directed miRNA degradation (TDMD) of miR-7 in human cell line K562 [85]. Other studies have demonstrated that **OIP5-AS1** acts as a ceRNA for miR-340-5p, which normally targets and downregulates **ZEB2** [86] and for miR-216a-5p [87] in BC cells. The reduction of **OIP5-AS1** abundance by miR-29a-3p and miR-29b-1-3p fits with their ‘anti-tumorigenic’ activity in BC [reviewed in (30)].

**JPX** positively regulates **XIST** promoter activity by binding **CTCF** (a transcription factor) and repressing its binding to the **XIST** promoter [88]. **XIST** and **JPX** expression is reduced in breast tumors and BC cell lines due to hypermethylation [89]. The decrease in **JPX** by miR-29b-1-a in LCC9 cells may relate to miR-29b-1-a’s anti-proliferative activity in this cell line [19,20,35,39].

**DANCR** was reported to be higher in basal-like than luminal breast tumors [90]. A high **DANCR** level is associated with reduced overall survival (OS) in TNBC patients [91]. Knockdown of **DANCR** suppressed MDA-MB-231 and MDA-MB-468 TNBC cell proliferation and xenograft tumor growth in mice [91]. **DANCR** interacts directly with the retinoid X receptor alpha (**RXRA**, **RXRα**) protein and increased its serine 49/78 phosphorylation via **GSK3β**, resulting in increased **PIK3CA** transcription and activation of the PI3K/AKT pathway in TNBC [91]. **DANCR** is a ceRNA for miR-4319, upregulating VAMP-associated protein B and C (**VAPB**) [92]. **TUFT1** (tuftelin 1) increased **DANCR** expression [93]. **DANCR** is also a ceRNA for miR-874-3p, resulting in de-repression of SOX2 and stimulating epithelial–mesenchymal transition (EMT) in TNBC [93]. A recent study reported that **DANCR** promoted the binding of EZH2 to the promoter of **SOC5**3, thus repressing SOC53 to promote EMT, inflammation, and BC stem cells (BCSC) [94]. **DANCR** was identified in network 2 (Supplementary Table S2) with **TUG1**, **CRNDE**, **APTR**, and **SNHG5** (Figure 2). Figure 2 indicates that **DANCR** and **CRNDE** interact with miR-33a-5p, which is downregulated in breast tumors and acts as a tumor suppressor [95]. Indeed, **DANCR** is a ceRNA for miR-33a-5p in pancreatic beta cells [96], osteosarcoma cells [97], and other cancer cell types, but no reports were found for this interaction in breast tumors or BC cell lines. Further experiments are needed to determine whether **DANCR** is a ceRNA for miR-33a-5p in BC.
The abundance of lncRNA CYTOR (LINC00152) was higher in MCF-7 than LCC9 cells (Table 1). These findings are in contrast to a report showing higher CYTOR in two other TAM-resistant MCF-7 cell lines compared to the parental MCF-7 cells [98]. CYTOR was shown to be a ceRNA for miR-125-5p, resulting in increased serum response factor (SRF) and activated Hippo and MAPK signaling pathways in the TAM-R cell lines [98]. CYTOR was elevated in breast tumors and in plasma from BC patients compared to normal controls [99]. Higher CYTOR was associated with reduced OS in a study of 70 breast tumors [100]. This study identified an interaction between CYTOR and KLF5 in MDA-MB-231 and MCF-7 cells that stabilized KLF5 (Kruppel-like factor 5) protein and enhanced tumorigenesis. The authors also demonstrated that KLF5 binds the CYTOR promoter and increases CYTOR transcription [100]. CYTOR (LINC00152) was identified in network 3 (Supplementary Table S2) with DLEU7-AS1, GAS5, SOX2OT, and TUG1 (Figure 3). That network indicates that YY1 (YY1 transcription factor) increases CYTOR (LINC00152) expression. YY1 correlates with HER2/ERBB2 expression in breast tumors [101] and is upregulated by NFκB signaling and stimulates the expression of BC stem cell (BCSC) transcription factors OCT4, SOC2, and NANOG [102]. While there was no difference in YY1 transcript levels between MCF-7 and LCC9 cells, YY1 was downregulated by miR-29b-1/a in LCC9, but not MCF-7 cells [35]. In summary, the downregulation of CYTOR by miR-29b-1/a in LCC9 cells fits with their anti-proliferative activity in this cell line [19,20,35,39].

CRNDE expression is higher in breast tumors than in normal breast tissue and was associated with larger tumor size, advanced tumor nodes, and metastases (TNM) stage and was correlated with reduced OS [103]. CRNDE is a ceRNA for miR-136, resulting in activation of WNT/β-catenin signaling in MDA-MB-231 cells [103]. Wnt signaling stimulates BCSC adhesion, proliferation, and invasion to promote metastasis [104]. IGF/insulin signaling represses CRNDE [105]. CRNDE was identified in network 2 (Supplementary Table S2) with TUG1, APTR, DANC, and SNHG5 and was indicated, along with DANC, to interact with miR-33a-5p (Figure 2). CRNDE was reported to be a ceRNA for miR-33a-5p in hepatocellular carcinoma (HCC) [106].

In agreement with the data presented in Table 1, TUG1 directly binds and reduces the expression of miR-29b and miR-29c [107]. The expression of TUG1 is higher in breast tumors and cell lines compared to normal breast tissue [108]. TUG1 expression was higher in HER2-enriched and basal-like breast tumor subtypes compared to luminal A [109]. Knockdown of TUG1 reduced BC cell proliferation and xenograft tumor growth in vivo by increasing miR-9, resulting in a reduction of miR-9 target MTHFD2 [108]. TUG1 expression is associated with doxorubicin (Dox)-resistance in BC and TUG1 interaction with miR-9-5p increases translation factor elf5A2 [110]. TUG1 is also a ceRNA for miR-197 in TNBC cell lines MDA-MB-231 and BT549, thus increasing nemo-like kinase (NLK) expression and resulting in enhanced cisplatin resistance [111]. TUG1 was identified in networks 2 and 3 (Supplementary Table S2) with CRNDE, APTR, DANC, SNHG5, and with DLEU7-AS1, GAS5, SOX2OT, and LINC00152 (Figures 2 and 3). TUG1 was shown to interact with BRM (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 2), CRYM (cry stallin Mu), and LCE1D (late cornified envelope 1D) in network 2 (Figure 2) and with UGT2B7 (UDP glucuronosyltransferase family 2 member B7) which has unique specificity for 3,4-catechol estrogens and estriol, suggesting that TUG1 may reduce active estrogens [112]. TUG1 polymorphisms are associated with BC responses to systemic therapy and responses [112]. The reduction of TUG1 abundance by miR-29a-3p and miR-29b-1-3p fits with their 'anti-tumorigenic' activity in BC (reviewed in [30]).

SNHG8 expression was higher in breast tumors and BC cell lines compared to normal breast tissue and cell lines, respectively [113]. SNHG8 was reported to be a ceRNA for miR-634, relieving the repression of ZBTB20 [113,114] and for miR-384, relieving the repression of HDGF [115] in BC. Additional studies are needed to determine the mechanisms by which miR-29b-1/a regulate SNHG8 abundance in LCC9 cells.
SNHG5 was more highly expressed in MDA-MB-231 cells than in MCF-7 cells [116]. Another study reported high levels of SNHG5 in SK-BR3 HER2+ BC cells [117]. SNHG5 was reported to be higher in TNBC compared to luminal A or B BC cell lines and to be a ceRNA for miR-154-5p, thus relieving the repression of PCNA and upregulating cell proliferation [118]. SNHG5 was identified in network 2 (Supplementary Table S2) with TUG1, CRNDE, APTR, and DANCR and depicted as regulating miR-132-3p with APTR and TUG1 (Figure 2).

Although it is more highly expressed in MCF-7 cells, the abundance of DSCAM-AS1 was significantly increased by anti-miR-29 only in LCC9 cells transfected with either pre-miR-29a-3p or pre-miR-29b-1-3p, suggesting that DSCAM-AS1 is regulated by miR-29b-1/a selectively in LCC9 cells (Table 1). DSCAM-AS1 was identified as the lncRNA that was most upregulated by “apo-ERα” (non-ligand-occupied ERα) in a bioinformatics analysis of BC cell lines and tumor tissues [119]. That study showed that luminal A and B breast tumors had higher DSCAM-AS1 expression compared to normal breast tissue and HER2+, or basal-like breast tumors. In follow-up experiments in MCF-7 cells, knockdown of DSCAM-AS1 increased markers of EMT [119]. A bioinformatics interrogation of 947 breast tumor RNA-seq libraries identified gene sets positively correlated with DSCAM-AS1 expression as being significantly associated with clinical signatures of cancer aggression, TAM resistance, as well as a higher grade, stage and metastasis [120]. A more recent report confirmed the highest levels of DSCAM-AS1 in luminal B breast tumors and that DSCAM-AS1 expression is correlated with disease relapse [121]. Interestingly DSCAM-AS1 interacts with the RNA binding protein hnRNPL (HNRNPL, heterogeneous nuclear ribonucleoprotein) and influenced alternative splicing in MCF-7 cells [121]. Knockdown of DSCAM-AS1 resulted in decreased expression of many cell-cycle-related genes, including MYC, RET, TOP2A, and POL2A in MCF-7 cells, implicating it as a driver of cell proliferation in BC [121]. Knockdown of DSCAM-AS1 was reported to enhance the inhibitory activity of TAM in a TAM-resistant MCF-7 cell line that had higher DSCAM-AS1 expression compared to parental MCF-7 cells [122]. As indicated in Table 1, we observed a lower DSCAM-AS1 abundance in LCC9 TAM-resistant cells compared to parental MCF-7 cells. Differences in the derivation of TAM-resistant MCF-7 cells and their culture conditions likely contributed to this difference. DSCAM-AS1 was reported to be a ceRNA for miR-137, relieving the repression of EPS8 (epidermal growth factor receptor pathway substrate 8), which simulates MCF-7 growth in vitro and as tumor xenografts in vivo [122].

GAS5 abundance was ~2.4-fold higher in MCF-7 than in LCC9 cells (Table 1). Others have also reported that GAS5 expression is lower in TAM-resistant MCF-7 cells compared to MCF-7 cells [123]. GAS5 levels were significantly increased by anti-miR-29 only in LCC9 cells transfected with either pre-miR-29a-3p or pre-miR-29b-1-3p, suggesting that GAS5 is downregulated by miR-29b-1/a selectively in LCC9 cells (Table 1). GAS5 is considered to be a tumor suppressor that inhibits cell proliferation and stimulates apoptosis in BC cells [124]. GAS5 transcript levels are lower in breast ductal carcinomas compared to adjacent normal breast tissue [125]. GAS5 was identified in plasma from BC patients, but due to low levels of lncRNAs, GAS5 was not considered to be prognostic in that study [126]. GAS5 is a ceRNA for oncogenic miR-21 [127]. A network analysis of ncRNAs in the trastuzumab-resistance-associated lncRNAs GAS5, miR-16, and miR-155 has been reported [47]. GAS5 expression was low in breast tumors from trastuzumab-treated patients [128]. miR-21 negatively regulates GAS5 [129]. GAS5 is a ceRNA for miR-222 in TAM-resistant BC cells, thus upregulating tumor suppressor PTEN (phosphatase And tensin homolog) [123]. GAS5 was identified in network 3 with DLEU1, SOX2-OT, CYTOR (LINC00152), and TUB1 (Figure 3) and was depicted as interacting with P53. Although a role for GAS5 in regulating P53 in BC is unknown, this association has been detected in other cancers, e.g., neuroblastoma (reviewed in [130]). The reduction of GAS5 abundance by miR-29a-3p and miR-29b-1-3p in LCC9 fits with their ‘anti-tumorigenic’ activity in BC (reviewed in [30]).
3.3. Identification of miR-29b-1/a-Upregulated IncRNAs and Their Roles in Breast Cancer

We identified nine IncRNAs that were upregulated in response to the transfection of MCF-7 and/or LCC9 cells with pre-miR-29b-1-3p or pre-miR-29a-3p and downregulated in response to the co-transfection with anti-miR-29 (Table 2), suggesting that miR-29b-1/a-mediated upregulation. The abundance of three IncRNAs—BCYRN1, MALAT1, and NEAT1—was increased by anti-miR-29 in both cell lines. Six of the miR-29b-1/a-upregulated IncRNAs were more highly expressed in MCF-7 cells than in LCC9 cells and two upregulated IncRNAs were more highly expressed in LCC9 cells than in MCF-7 cells (Table 2). MetaCore pathway analysis identified one pathway associated with IncRNA UCA1: development: YAP (YAP, yes 1-associated transcriptional regulator)/TAZ (TAFAZZIN, tafazzin, phospholipid-lysophospholipid transacylase)-mediated co-regulation of transcription (Figure 5). MetaCore enrichment analysis identified GO processes that are shown in Supplementary Table S3, but these only included the IncRNA MALAT1. The MetaCore network analysis is shown in Supplementary Table S4 and selected networks are shown in Figures 6 and 7. An increase in the abundance of an IncRNA by miRNA may result from the miRNA-mediated reduction of a transcription factor that normally increases that lncRNA’s transcription or by the reduction of a factor, e.g., an RNA binding protein, that decreases lncRNA stability. The expression of BCYRN1, UCA1, ABHD11-A51, NALT1, and NEAT1 was decreased by anti-miR-29 in both cell lines transfected with either pre-miR-29a or pre-miR-29b-1-3p, suggesting the upregulation of these IncRNAs by miR-29b-1/a in these cells (Table 2). The expression of DGCR5, TINCR, and MALAT1 was reduced by anti-miR-29a-3p only in LCC9 cells transfected with either pre-miR-29a-3p or pre-miR-29b-1-3p, suggesting the selective upregulation of these IncRNAs by miR-29b-1/a in LCC9 TAM-resistant BC cells (Table 2).

DGCR5 is upregulated in some cancers, e.g., lung and gallbladder cancers, but is low in many other cancers, including HCC, ovarian, cervical, pancreatic, and thyroid (reviewed in [131]). DGCR5 was higher in TNBC tumors compared to normal breast tissue [132]. Further experiments are needed to evaluate the role of DGCR5 in BC and endocrine resistance.

Knockdown of BCYRN1 reduced the viability and stimulated apoptosis of MCF-10A ‘normal’ breast epithelial cells and MCF-7, MDA-MB-231, SK-BR-3, and T47D BC cell lines [133]. A recent study demonstrated that BCYRN1 knockdown reduced translation, whereas stable overexpressed BCYRN1 was associated with polysomes and enhanced translation, but reduced MCF-7 cell growth [133]. These reports suggest that BCYRN1 may be oncogenic in BC, but further studies are needed to determine the role and targets of BCYRN1 in BC and the mechanism by which miR-29b-1/a increase BCYRN1 abundance in MCF-7 and LCC9 cells.

UCA1 was not predicted to interact with miR-29 in DIANA-LncBase [50]. A previous report showed higher levels of UCA1 in LCC2 and LCC9 TAM-resistant cell lines compared to MCF-7, and levels were comparable to those in BT474 HER2+ BC cells [134]. Isolated exosomes from TAM-resistant LCC2 BC cells contained ~25-fold higher UCA1 levels compared to parental MCF-7 cells and the incubation of MCF-7 cells with exosomes from LCC2 cells resulted in decreased growth inhibition by TAM [135], although no uptake of UCA1 or other IncRNAs or miRNAs was observed. UCA1 was upregulated in MCF-7 cells with TAM treatment and is a ceRNA miR-18a, resulting in increased HIF1α, which increases UCA1 expression [134]. UCA1 is also upregulated in trastuzumab and paclitaxel resistance (reviewed in [136]) and in DOX-resistant MCF-7 cells [137]. UCA1 expression was upregulated in breast tumors compared to normal breast tissue and stabilized by its interaction with hnRNP I [137]. UCA1 expression was associated with LN metastasis in breast tumors and reduced OS in BC patients [138]. On the other hand, a recent review found that reduced UCA1 was a poor prognostic biomarker of luminal BC by controlling the tumor necrosis factor (TNF) signaling and immune responses [139]. UCA1 transcription is directly upregulated by TGFβ-activated TEAD1 (TEA domain transcription factor 1) and by SMAD2/3 recruitment to the UCA1 promoter in BC cells [140]. UCA1 was iden-
ified in network 1 with NEAT1, MALAT1, TINCR, and SMAD2 (Figure 6) and, in agreement with the previous citation, was depicted as being stimulated by SMAD2. UCA1 was shown to repress miR-129-5p (Figure 6), which targets the 3’ UTR of FMR1 (fragile X mental retardation protein (FMRP)), an RNA-binding protein [141]. UCA1 is a ceRNA for miR-129, thus upregulating SOC4 in renal cell carcinoma (RCC) [142]. Likewise, UCA1 repression of miR-129 increased ABCB1 in ovarian cancer cells [143]. There are no reports on this interaction in BC cells; however, FMRP is elevated in breast tumors and its high expression correlates with lung and LN metastasis [144].

![Figure 5. Pathway Map: development: YAP/TAZ-mediated co-regulation of transcription. The lncRNA UCA1 was upregulated by miR-29b-1/a in MCF-7 and LCC9 cells. Image is from Meta-Core analysis.](image)

No information with respect to ABHD11-AS1 in BC was found in PubMed; however, ABHD11-AS1 is increased in colorectal carcinoma (CRC) [145], endometrial carcinoma [146], ovarian cancer [147], papillary thyroid cancer [148], and pancreatic cancer [149], implicating an oncogenic role for ABHD11-AS1 in these cancers. ABHD11-AS1 was identified in network 2 (Supplementary Table S4, Figure 7) and was depicted as negatively regulating miR-1254, which targets RBBP6 (RB binding protein 6, ubiquitin ligase). KM plotter [150] revealed no significant difference in OS in BC patients related to ABHD11-AS1 expression (data not shown).

Although PubMed contained no reports on NALT1 in BC, NALT1 was overexpressed in gastric cancer (GC), associated with reduced OS, and was found to promote the invasion of the normal human gastric epithelial GES-1 cell line and GC cancer cell lines in vitro.
by suppressing NOTCH signaling [151]. Further studies are needed to determine the role and expression of NALT1 in BC.

\[ TINCR \] was reported to be overexpressed and oncogenic in HER2+ breast tumors [69]. Higher \[ TINCR \] expression in breast tumors (all types) was associated with reduced OS [69]. This study showed that \[ TINCR \] expression was higher in MDA-MB-453 HER2+ BC cells compared to UACC-812 TNBC, BT549 TNBC, MDA-MB-231 TNBC, and MCF-7 Luminal A BC cells. \[ TINCR \] acted as a ceRNA for miR-125b, relieving the repression of \[ ERBB2 \] in UACC-812 cells [69]. \[ TINCR \] was identified in network 1 (Supplementary Table S4, Figure 6) and was depicted as positively regulating KRT78 (keratin 78, gene \[ KRT14 \]). \[ TINCR \] was reported to interact directly with mRNAs in human epidermal differentiation and barrier formation [152]. KRT14-expressing BC cells are invasive and metastatic, forming clusters for dissemination and colonization in metastatic niches [153,154]. The increase in \[ TINCR \] in response to miR-29b-1/a transfection appears to oppose their anti-tumorigenic activity in BC cells.

![Figure 6. Network 1: NEAT1, UCA1, MALAT1, TINCR, and SMAD2, identified in lncRNAs upregulated by miR-29b-1-3p and miR-29a-3p in MCF-7 and/or LCC9 cells by MetaCore analysis; green lines with arrows = stimulation; red lines with arrows = inhibition.](image)

![Figure 7. Network 2: ABHD11-AS1, miR-1254, and RBBP6, identified in lncRNAs upregulated by miR-29b-1-3p and miR-29a-3p in MCF-7 and/or LCC9 cells by MetaCore analysis. Red line with arrow = inhibition. The dotted gray line is a putative regulation.](image)
The MINCR level was higher in MCF-7 cells than in LCC9 cells and was decreased by anti-miR-29 in MCF-7 cells transfected with either pre-miR-29a-3p or pre-miR-29b-1-3p, suggesting the upregulation of MINCR by miR-29b-1/a in these cells (Table 2). No information with respect to MINCR in BC was found in PubMed; however, MINCR was upregulated in CRC tumors [155] and in non-small cell lung cancer (NSCLC) [156]. KM plotter [150] revealed no significant difference in OS in BC patients related to MINCR expression (data not shown).

Mutations were identified in the promoter of NEAT1 that increased its expression in BC [157]. NEAT1 was overexpressed in luminal A, luminal B, HER2+, and basal-like (TNBC) tumors [158]. Patients whose primary breast tumors showed high expression of NEAT1 had shorter OS [138]. NEAT1 was elevated in the plasma of BC patients and associated with LN positivity and TNBC tumor type [159]. NEAT1 is involved in the organization of nuclear paraspeckles for gene transcription and splicing [42]. Nuclear speckles are dynamic punctate compartments in the nucleus that contain components of the pre-mRNA spliceosome, including serine/arginine-rich splicing factors (SRSFs), small nuclear ribonucleoproteins (snRNPs), RNA polymerase (Pol) II subunits, 3’ end processing proteins, m6A writers METTL3/METTL14, m6A reader YTHDC1, and various protein kinases that regulate the pool of proteins in the speckles [160,161]. NEAT1 was identified as an essential component of the FOXN3-SIN3A repressor complex and overexpression of NEAT1 promoted EMT in MCF-7 cells and lung metastasis of MCF-7 cells when orthotopically implanted in the mammary fat pad of immunocompromised female mice, suggesting that NEAT1 has oncogenic and pro-metastatic activity [162]. NEAT1 was also identified in a gene (ESR1, DKC1)—lncRNA (TERC and TUG1) interaction network in breast tumors from The Cancer Genome Atlas (TCGA) [163]. Increased NEAT1 was detected in cisplatin- and taxol-resistant MDA-MB-231 cell lines compared to parental MDA-MB-231 cells, and knockdown of NEAT1 inhibited MDA-MB-231 xenograft tumor growth in vivo [164]. NEAT1 has been shown to be a ceRNA for a number of miRNAs, including miR-124, thus upregulating STAT3 [165]; for miR-133b, thus de-repressing TIMM17A [166]; for miR-141-3p, thus increasing KLF12 [167] in MCF-7 and MDA-MB-231 cells; for miR-107, thus upregulating CPT1A in HEK-293 cells [168]; and for miR-205-5p, thus de-repressing VEGFA in CRC cells [169]. NEAT1 was identified in network 1 (Supplementary Table S4, Figure 6) and was depicted as negatively regulating miR-1321, miR-361-5p, and miR-1246. miR-361-3p was upregulated in fulvestrant-resistant MCF-7 cells [170] and targets GLI1 (GLI family zinc finger 1, a transcription factor), which is increased in breast tumors and inversely correlates with disease-free survival (DFS) in luminal A tumors (reviewed in [22]). NEAT1 was identified in network 3 (Supplementary Table S4, Figure 8), in which it was depicted as negatively regulating miR-185-5p and miR-101-3p. miR-185-5p expression is reduced in breast tumors and miR-185-5p targets VEGFA, E2F6, and DNMT1 (reviewed in [129]). miR-101 is a tumor suppressor that targets ZEB1 and ZEB2 (reviewed in [22]). Overall, the increase in NEAT1 by miR-29b-1/a in MCF-7 and LCC9 cells seems to oppose the mechanisms of anti-tumor activity of these miRNAs.
Figure 8. Network 3: NEAT1, MALAT1, UCA1, miR-185-5p, and SMAD1, identified in lncRNAs upregulated by miR-29b-1-3p and miR-29a-3p in MCF-7 and/or LCC9 cells by MetaCore analysis. Green lines with arrows = stimulation; red lines with arrows = inhibition.

MALAT1 was ~5.5-fold higher in MCF-7 cells than in LCC9 cells and is an established miR-29 interactor (Table 2). MALAT1 is a well-studied IncRNA (1573 papers in PubMed) that is evolutionarily conserved and highly expressed across all tissues (reviewed in [171]). MALAT1 was originally identified as an oncogene in non-small cell lung cancer [172]. MALAT1 is upregulated in multiple myeloma and in many solid tumors, including breast tumors (reviewed in [173,174]). MALAT1 is oncogenic and promotes tumor progression and metastasis in various cancers, including BC (reviewed in [21,175]). Patients whose primary breast tumors showed high expression of MALAT1 had shorter OS [138]. In addition to tumor expression, one study reported higher serum levels of MALAT1 in BC patients (n = 157) compared to control women (n = 107) [176]. MALAT1 expression is associated with ERα+/PR+ breast tumors and with lower relapse-free survival (RFS) [138]. However, MALAT1 expression was associated with decreased DFS in patients with HER2+ and TNBC tumors [177]. MALAT1 increases with breast tumor stage and was 2–3 times higher in lung and brain metastases when compared to matched primary luminal breast tumor sections [175]. Other studies have reported higher MALAT1 levels in breast tumors than in normal breast tissue [178]. MALAT1 is oncogenic in BC and upregulates the WNT/β-catenin (CTNNB1) pathway [179]. MALAT1 mutations are frequent in breast
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MCF-7 and LCC9 cells that were not regulated by miR-29b-1/a. Of these, 17 had low expression levels in MCF-7 cells, i.e., FPKM ≤ 1, and ten had no published role in BC tumors or cell lines (Supplementary Table S5). The roles of seven lncRNAs (PCAT1, CAHM, HOXA-AS2, MIR2052HG, BDNF-AS, CASCL5, and HOXA11-AS) in BC are summarized in Supplementary Table S5. Thirty-five lncRNAs were expressed at FPKM ≥ 1 and their roles in BC are reviewed below. Of these, twenty-seven showed higher abundance in MCF-7 than LCC9 cells: PCGEM1, KRT7-AS1, SATB2-AS1, HAGLR, HARI1B, VLDLR-AS1, ZEB1-AS1, FTX, CDKN2B-AS1, PCAT6, HOTAIRM1, MIR22HG, LINC-PINT, NBR2, TMEM161B-AS1, HARI1A, MIR503HG, PSMD6-AS1, DHR54-AS1, MIR600HG, NORAD, XIST, PVT1, SNHG1, and ZFAS1 (Table 3). The lncRNAs FOXP4-AS1, H19, HMMR-AS1, FOXD3-AS1, PPP1R12A-AS1, LINC01116, HOTAIR, DLEU2, MIF-AS1, and TPS3TG1 were more abundant in LCC9 cells than in MCF-7 cells. GO processes and network analysis for these differentially expressed lncRNAs are summarized in Supplementary Tables S6 and S7, respectively. Selected networks are shown in Figures 9–12 and Supplementary Figure S2. Only one lncRNA, APOBEC3B-AS1, was commonly downregulated in LCC9 vs. MCF-7 cells in both our analysis and in the Agilent human lncRNA + mRNA Array V4.0 reported previously [49]. However, the avg. FPKM was 1.45 in MCF-7 and 0.033 in LCC9 cells, suggesting low abundance. There are no reports about APOBEC3B-AS1 in PubMed.
Figure 9. Network 1: LOC647979 (NORAD), NBR2, PCGEM1, LINC-PINT, and MIR600HG, identified in lncRNAs differentially expressed in MCF-7 and or LCC9 cells by MetaCore analysis. Green lines with arrows = stimulation; red lines with arrows = inhibition.
Table 3. IncRNAs differentially expressed in MCF-7 and LCC9 breast cancer cells that are not regulated by miR-29b-1/a. Values (FPKM) are the average of five replicates.

| Ensembl     | Gene       | Alias       | MCF-7 Avg | LCC9 Avg | Signific. Different between MCF-7 vs. LCC9 | Role in Breast Cancer |
|-------------|------------|-------------|-----------|----------|-------------------------------------------|-----------------------|
| ENSG00000227418 | PCGEM1     | LINC00071   | 1.18      | 0.16     | MCF-7 > LCC9                              | unknown               |
| ENSG00000234753 | FOXP4-AS1  | RP1-32BM4.2 | 1.58      | 0.14     | LCC9 > MCF-7                              | unknown               |
| ENSG00000130600 | H19        | LINC0008    | 1.28      | 0.09     | LCC9 > MCF-7                              | oncogenic             |
| ENSG00000251018 | HMMR-AS1   | RP11-80G7.1 | 1.57      | 0.09     | LCC9 > MCF-7                              | oncogenic             |
| ENSG00000230798 | FOXD3-AS1  | RP4-792G4.2 | 1.56      | 0.05     | LCC9 > MCF-7                              | oncogenic             |
| ENSG00000257671 | KRIT7-AS   | RP3-416H24.1| 1.64      | 0.17     | MCF-7 > LCC9                              | oncogenic-metastasis |
| ENSG00000257557 | PPP1R12A-AS1 | RP11-84G21.1| 1.62      | 0.23     | LCC9 > MCF-7                              | unknown               |
| ENSG00000163364 | LINC01116  | AC017048.3  | 2.55      | 0.20     | LCC9 > MCF-7                              | oncogenic             |
| ENSG00000225953 | SATB2-AS1  | RP11-80G7.1 | 2.29      | 0.20     | MCF-7 > LCC9                              | unknown               |
| ENSG00000224189 | HAGLR      | HOXD-AS1    | 3.19      | 0.13     | MCF-7 > LCC9                              | unknown               |
| ENSG00000228630 | HOTAIR     | RP3-416H24.1| 3.58      | 0.14     | LCC9 > MCF-7                              | oncogenic             |
| ENSG00000231133 | HARI1      | RP11-84G21.1| 4.31      | 0.07     | MCF-7 > LCC9                              | unknown               |
| ENSG000002236404 | VLDLR-AS1  | RP11-125B21.2| 5.85     | 0.38     | MCF-7 > LCC9                              | unknown               |
| ENSG00000237036 | ZEB1-AS1   | AC017048.3  | 4.72      | 0.52     | MCF-7 > LCC9                              | oncogenic             |
| ENSG00000225390 | FTX        | AC017048.3  | 5.75      | 0.34     | MCF-7 > LCC9                              | oncogenic             |
| ENSG00000240498 | CDKN2B-AS1 | ANRIL       | 6.15      | 0.23     | MCF-7 > LCC9                              | oncogenic             |
| ENSG00000228288 | PCAT6      | AC017048.3  | 5.80      | 0.05     | MCF-7 > LCC9                              | oncogenic             |
| ENSG00000231607 | DLEU2      | AC017048.3  | 5.71      | 0.47     | LCC9 > MCF-7                              | oncogenic             |
| ENSG00000233429 | HOTAIRM1   | AC017048.3  | 8.14      | 0.35     | MCF-7 > LCC9                              | oncogenic             |
| ENSG00000186594 | MIR22HG    | AC017048.3  | 11.59     | 1.64     | MCF-7 > LCC9                              | tumor suppressor      |
| ENSG00000218537 | MIF-AS1    | AC017048.3  | 17.53     | 3.08     | LCC9 > MCF-7                              | Oncogenic             |
|Gene Accession| Gene Symbol| Expression 1| Expression 2| Expression 3| Expression 4| Tumor Status|
|--------------|------------|-------------|-------------|-------------|-------------|--------------|
|ENSG00000197775| DHRS4-AS1| 30.69| 2.09| 15.33| 0.81| MCF-7 > LCC9| tumor suppressor|
|ENSG00000236901| MIR600HG| 38.30| 1.75| 4.64| 1.57| MCF-7 > LCC9| tumor suppressor|
|ENSG00000260032| NORAD| 65.34| 3.03| 44.08| 0.97| MCF-7 > LCC9| oncogenic|
|ENSG00000229807| XIST| 82.54| 6.05| 0.01| 0.01| MCF-7 > LCC9| tumor suppressor|
|ENSG00000249859| PVT1| 107.75| 9.24| 79.45| 6.90| MCF-7 > LCC9| oncogenic|
|ENSG00000255717| SNHG1| 581.99| 16.98| 357.14| 41.34| MCF-7 > LCC9| oncogenic|
|ENSG00000177410| ZFAS1| 928.45| 30.95| 282.98| 27.79| MCF-7 > LCC9| tumor suppressor|
3.5. lncRNAs More Highly Expressed in Endocrine-Sensitive MCF-7 versus Endocrine-Resistant LCC9 Cells and Their Roles in BC

PCGEM1 (LINC00071) is a scaffolding lncRNA that plays a role in the transcription of androgen receptor (AR) target genes in prostate cancer (PCa) cell lines (reviewed in [188]). PCGEM1 was not identified in LCC9 cells and showed low expression in MCF-7 cells (Table 3). PCGEM1 was identified in networks 1 and 3 (Figures 9 and 10). PCGEM1 was reported to physically associate to a subset of the metabolic gene promoters (CANT1, CYP11A1, DHCR24, FASN, G6PD (shown in Figure 10), GLS, GPI, GSR, HK2, IDH1, IDH2, and LDHA) [189].

![Network](image_url)

Figure 10. Network 2: PVT1, ZFAS1 RNA, XIST, SNHG1, and DLEU, identified in lncRNAs differentially expressed in MCF-7 and or LCC9 cells by MetaCore analysis. Green lines with arrows = stimulation; red lines with arrows = inhibition.

KRT7-AS is m6A modified by METTL3 and forms an RNA hybrid with KRT7 to stabilize that transcript, and KRT7-AS promotes lung metastasis from MDA-MB-231 and BT-549 cells [190]. There are no known functions of SATB2-AS1 in BC. A recent report showed that HAGLR overlaps with miR-7704, which represses HAGLR expression in MCF-7, MDA-MB-231, and MCF-10A cells [191]. High HAGLR expression was associated with lower RFS in BC patients [192].

No reports of HAR1B or VLDLR-AS1 in BC were found. Decreased HAR1B expression levels are associated with poor prognosis in HCC [193].

ZEB1-AS1 is a well-recognized cancer-related lncRNA that has been identified as an oncogene in diverse malignancies [194]. It is associated with several functional roles, including EMT, proliferation, migration, invasion, and metastasis by regulating multiple genes including miR-200s [195]. ZEB1-AS1 was upregulated in TNBC cell lines and tumors and stabilized ZEB1 mRNA by binding with ELAVL1 (ELAV1, ELAV-like RNA binding protein 1), forming a feedback loop to promote TNBC progression [196]. ZEB1-AS1 interacts with miR-505-3p (Figure 11). The opposite strand miRNA-miR-505-5p was
downregulated in the serum of BC patients compared to that of healthy controls [197]. ZEB1-AS1 is a ceRNA for miR-505-3p, thus de-repressing TRIB2 (tribbles pseudokinase 2) in pancreatic cancer [198].

FTX, a chromatin-associated lncRNA, is regulated by pathways mediating the initiation and progression of breast tumors [199]. The FTX gene harbors two miRNA clusters: miR-374b/421 and the miR-545/374a cluster, which were upregulated in HCC tissues and associated with a poor prognosis [200]. Estrogen-related receptor gamma (ERRγ, ESRRG) was reported as a target of miR-545 [200]. ERRγ is upregulated in 75% of breast tumors [201] and induces TAM resistance [202]. ESRRG transcript levels were low in both MCF-7 and LCC9 cells (FPKM < 1, data not shown).

CDKN2B-AS1 (ANRIL) is located in the 9q21.3 region with rs62560775, associated with lung adenocarcinoma and BC susceptibility [203]. CDKN2B-AS1 is upregulated in MCF10A breast epithelial cells [204] and in breast tumors [205]. CDKN2B-AS1 was identified as a member of the ceRNA network for MMP1/MMP11 [204]. PCAT6 was suggested to be a ceRNA for miR-145-5p and speculated to be involved in the development of early BC [205]. Network analysis showed CDKN2B-AS1 stimulating HDAC (histone deacetylases) (Supplementary Figure S2B).

PCAT6 is upregulated in TNBC tissues and cells [206]. PCAT6 acts as a sponge for miR-4723-5p to upregulate KDR (VEGFR2, vascular endothelial growth factor receptor 2) [206]. Knockdown of PCAT6 promotes the radiosensitivity of MDA-MB-468 and MDA-MB-231 cells by inhibiting proliferation and inducing apoptosis [207]. This occurs with PCAT6 directly targeting and negatively regulating the expression of miR-185-5p to modulate TPD52 (tumor protein D52) expression [207]. Network analysis showed E2F1 stimulating PCAT6 (Supplementary Figure S2D).

HOTAIRM1 was reported to be overexpressed in basal-like breast tumors [90] and showed higher expression in TAM-resistant MCF-7 cells [208]. These results are in contrast with our observation of ~4-fold higher expression of HOTAIRM1 in MCF-7 cells compared to LCC9 cells.

We previously reported that the expression of MIR22HG was downregulated in response to the treatment of MCF-7 BC cells with the anti-cancer phenolic lipid anacardic acid T [209]. MIR22HG is a tumor suppressor and high MIR22HG was associated with increased OS in BC samples in an analysis of data from TCGA database [210]. MIR22HG was suggested to be a ceRNA for miR-424 [211]. Network analysis showed ERRα regulating MIR22HG and LINC-PINT (Figure 9). In a pan-cancer dataset of 15 BC tissues, LINC-PINT expression was downregulated compared to normal tissue [212]. High expression of LINC-PINT was associated with favorable DFS in BC patients [212].

The lncRNA NBR2 is encoded ‘head-to-head’ with tumor suppressor BRCA1 [213]. The expression of NBR2 and BRCA1 are affected by the SNP rs9911630 [214]. Upon energy stress, i.e., glucose deprivation, NBR2 expression was increased in MDA-MB-231 TNBC cells and in other cancer cells [215]. Network analysis showed ERRα regulating NBR2 (Figure 9). NBR2 was shown to interact with AMP-activated protein kinase (AMPK; a critical sensor of cellular energy status) to potentiate the AMPK kinase activity and increase GLUT1 expression [215]. NBR2 expression, which has been associated with higher OS in BC and NBR2, acts like a tumor suppressor in MDA-MB-231 xenograft tumors in vivo [216]. It is yet to be determined whether NDR2 regulates BRCA1 but the >2-fold higher expression of NBR2 in MCF-7 cells compared to LCC9 cells suggests an altered metabolism in LCC9 cells, as reported previously [217–219].

In combination with four other lncRNAs, higher TMEM161B-AS1 was reported to be a predictor for tumor recurrence in BC patients [192]. An in silico analysis using the HGNC (HUGO Gene Nomenclature Committee) database (Bethesda, MD, USA) predicted TMEM161B-AS1 to be associated with miR-17-5p and MAPK14 [220].

HAR1A was among a signature of nine other lncRNAs identified in TCGA of which the upregulation predicted recurrence in invasive BC [221]. Network analysis showed ERRα regulating HAR1A (Figure 9). No reports on ERRα regulating HAR1A in BC were found in PubMed.
Low MIR503HG expression was detected in TNBC tissues, and in MDA-MB-231 and TB549 TNBC tissues, in which MIR503HG serves as a tumor suppressor [222,223]. Low MIR503HG expression was associated with a worse prognosis and was correlated with clinical stage, LN metastasis, and distant metastasis in TNBC patients. In vitro upregulation of MIR503HG inhibited MDA-MB-231 and MDA-MB-453 TNBC cell migration and invasion. Two pathways—the miR-103/OLFM4 axis and the miR-224-5p/HOXA9 axis [222]—have been implicated in mediating the functions of MIR503HG [223]. Network analysis showed ERRα to regulate MIR503HG (Figure 9). The lower abundance of MIR503HG in LCC9 cells is in agreement with their higher proliferative rate and greater invasion and migration abilities compared to MCF-7 cells [224].

Initially identified in an lncRNA microarray study, PSMD6-AS1 expression levels were significantly higher in ER/PR(+) versus ER/PR(-) BC patients and in postmenopausal versus premenopausal BC patients [225]; however, the functional role of PSMD6-AS1 in ER + BC is yet to be determined.

DHR54-AS1 and MIR600HG are tumor suppressors in human cancer and their higher expression in MCF-7 cells compared to LCC9 cells fits the endocrine-resistant phenotype of these cells. DHR54-AS1 was downregulated in NSCLC and mediated its effects through a TP53- and TET1-associated DHR54-AS1/miR-224-3p axis [226]. MIR600HG is downregulated in CRC and its expression has been inversely correlated with OS [227].

NORAD is oncogenic and increased in BC tissues, MCF-7, and MDA-MB-231 cells, and is correlated with reduced OS [228]. NORAD knockdown reduced proliferation, invasion, and migration of MCF-7 and MDA-MB-231 BC cells and reduced tumor growth in vivo [228]. NORAD stimulated TGF-β signaling and directly increased RUNX2 expression, resulting in BC progression and metastasis [228]. The NORAD level was higher in luminal A tumors compared to basal-like or TNBC breast tumors [229]. High expression of NORAD in basal-like cancers was associated with lower OS; however, NORAD offered no prognostic information in luminal A BC tumors [229].

XIST, which is involved in X-inactivation and genomic imprinting, has a tumor suppressive role in BC [89,230]. The abundance of XIST was negligible in LCC9 cells and high in MCF-7 cells (Table 3). Network analysis depicted XIST as downregulating miR-140-5p and interacting with miR-20a-5p (Figures 10 and 11). XIST expression was low in primary breast tumors and their metastasis [89]. Ectopic expression of XIST in MCF-7 cells reduced AKT phosphorylation and cell viability—a process that was shown to be under epigenetic regulation via the recruitment of HDAC3 to the PHLLP1 promoter [89]. The tumor suppressive role of XIST in BC occurs in part through the miR-155/CDX1 axis [230]. In contrast with these reports, other studies have reported XIST to be higher in breast tumors than in normal breast tissue [231]. XIST, a direct target of miR-7, was inversely associated with miR-7 in breast tumors [231]. Ectopic expression of miR-7 was shown to bind directly to XIST and reduce its expression and to reduce BC stem cell-driven tumor growth in vivo [231]. Consistently with its tumor suppressor role, the knockdown of XIST increased M1-to-M2 macrophage phenotype polarization and promoted the cell proliferation and migration of breast and ovarian cancer cells by competing with miR-101 and inhibiting C/EBPα and KLF6 expression [232].
PVT1 expression is upregulated in breast tumors and cell lines and associated with BC risk [90,233,234]. Serum levels were also higher in BC patients [5]. PVT1 expression is positively correlated with miR-1207-5p (a PVT1-derived miRNA) and the estrogen-treatment-induced expression of PVT1 and miR-1207-5p in T47D BC cells [235]. PVT1 expression was negatively correlated with the pathological stage and the levels of ER, HER2, and p53, and was positively correlated with PR in multiple primary neoplastic tissues [236]. Network analysis indicated that PVT1 downregulates miR-186-5p (Figure 10). Knockdown of PVT1 inhibited growth and motility, and induced apoptosis in MCF-7 and MDA-MB-436 BC cells [237]. In vivo, knockdown of PVT1 reduced tumor volume and weight [237]. Multiple mechanisms have been described in order to understand PVT1’s role in breast tumorigenesis. PVT1 suppression enhanced TRPS1 levels by negatively targeting miR-543 in BC [238]. PVT1 binds KLF5, an interaction that is enhanced by BAP1 (BRCA1-associate protein), to upregulate beta-catenin signaling and promote TNBC tumorigenesis [237]. PVT1 is a ceRNA for miR-186 in multiple cancers [239]. For example, in gastric cancer, PVT1–miR-186 interaction inhibits HIF-1α expression and promotes cell proliferation and invasion [240].

SNHG1 is associated with endocrine cancers, including BC [241]. SNHG1 is upregulated in breast tumors and cell lines and promotes cell migration, invasion, and proliferation in vitro, as well as MDA-MB-231 ‘metastasis’ and colonization in the lungs of immune-compromised female mice after tail-vein injection [242]. SNHG1 is a ceRNA and reduces miR-382-5p [243], miR-193a-5p [242], and miR-573 [244] in BC cells. Knockdown of SNHG1 reduced BC cell proliferation, migration, invasion colony formation, and EMT [243]. SNHG1 inhibited the differentiation of regulatory T cells (Tregs), reduced miR-448 expression, and increased IDO1 (indoleamine 2,3-dioxygenase 1), which is implicated in
the immune escape of BC cells [245]. SNHG is a ceRNA for miR-140-5p in cholangiocarcinoma [246] and glioma [247]. Whether this interaction occurs in BC cells is unknown.

ZFAS1 is a host to three C/D box snoRNAs, which target rRNAs for post-transcriptional modification [248]. ZFAS1 was identified among the highest and most differentially expressed transcripts during mouse mammary gland development, i.e., decreases 10-fold between pregnancy and lactation [249]. Network analysis showed ZFAS1 downregulating miR-186-5p and interacting with ESR1 (Figures 10 and 11). The abundance of ZFAS1 is reduced in breast tumors compared to normal breast tissue [249] and in BC cells lines compared to MCF-10A cells [250]. ZFAS1 ectopic expression significantly suppressed cell proliferation by causing cell cycle arrest and inducing apoptosis in MCF-7 and MDA-MB-436 BC cells [250]. ZFAS1 was predominantly associated with the 40S small ribosomal subunit in MDA-MB-468 TNBC cells [248]. The lower expression of ZFAS1 in LCC9 cells compared to MCF-7 cells fits with the tumor-suppressive activity of this IncRNA.

3.6. IncRNAs More Highly Expressed in Endocrine-Resistant LCC9 Cells than in MCF-7 Cells and Their Roles in BC

We observed that FOXP4-AS1 was more abundant in LCC9 cells than in MCF-7 cells (Table 3). FOX4P is also higher in LCC9 cells than in MCF-7 cells (data not shown). There are no reports of FOXP4-AS1 in BC; however, FOXP4-AS1 expression is high in prostate tumors and PCa cell lines [251]. FOXP4-AS1 acts as a ceRNA for miR-3184-5p and increases FOXP4 expression, acting in an oncogenic pathway in prostate cancer [251]. FOXP4-AS1 is also upregulated and oncogenic in HCC [252] and gastric cancer [253]. In contrast, FOXP4-AS1 upregulation in ovarian cancer is associated with higher OS, suggesting cell-type-specific regulatory roles of FOXP4-AS1 in different tumors [254].

H19 is increased and plays an oncogenic role in a variety of cancers, including BC, where it acts as a ceRNA for various miRNAs (reviewed in [255]). Fulvestrant increased H19 expression and H19 was higher in LCC2 and LCC9 cells than in MCF-7 cells [256]. H19 targets miR-29b-3p in rat cardiomyocytes [257], bladder cancer cells [258], and CRC cells [259].

HMMR-AS1 was higher in breast tumors than in normal breast tissue, with the highest levels found in basal-like tumors, followed by HER2+ tumors, which showed higher expression than luminal A or B breast tumors [260]. Knockdown of HMMR-AS1 inhibited the proliferation, migration, and invasion of MDA-MB-231 and MDA-MB-468 basal-like TNBC cell lines [260].

FOX3D-AS1 [261] and LINC01116 [262] were more highly expressed in breast tumors compared to normal breast tissue. High expression LINC01116 correlated with reduced OS, tumor size, and TNM stage. LINC01116 is a ceRNA for miR-145, resulting in increased ERα.

HOTAIR abundance was ~3 times higher in LCC9 cells than in MCF-7 cells (Table 3). HOTAIR was one of the first characterized IncRNAs with a conserved structure that interacts with over 70 proteins (reviewed in [129]). HOTAIR acts as a nuclear scaffold for the PRC2 and LSD1 histone modifying complexes to promote histone H3K27 methylation and H3K4 demethylation to silence target genes and promote BC metastasis [48]. HOTAIR is upregulated in breast tumors and is a ceRNA for miR-20a-5p [263]. In agreement with our data (Table 3), HOTAIR is upregulated in endocrine-resistant BC cells and its overexpression activates ERα transcriptional activity independently of ligands [264]. HOTAIR is also increased in TAM-resistant human breast tumors [264]. High expression of HOTAIR in exosomes in serum from BC patients was associated with lower RFS and OS [265]. ERα interacts directly with HOTAIR in MCF-7 cells [266]. Overexpression of HOTAIR in MCF-7 cells grown under hormone-free (serum-starved) medium conditions increases the number of DNA sites to which ERα binds in chromatin immunoprecipitation (ChIP) assays and increases the mRNA expression of some ERα target genes, e.g., GREB1, TFF1, PGR,
and CTSD [264]. This is depicted in network 3: PCGEM1, ZFAS1 RNA, ZEB1-AS1, HO-TAIR, and ESR1, shown in Figure 11.

DLEU2 is an oncogene in multiple malignancies [267–269]. DLEU2 expression was increased by MVLN (MCF-7-derived) BC cells and abolished by 4-hydroxytamoxifen (4-OHT, an active TAM metabolite) in a process that was independent of protein synthesis [270]. Tumor suppressor miRs miR-15a and miR-16 are transcribed from the DLEU2 locus [271]. Network analysis showed DLEU2 downregulating miR-186-5p (Figure 12).

MIF-AS1 abundance was approximately nine times higher in in LCC9 cells than in MCF-7 cells (Table 3). MIF-AS1 was upregulated in BC tissues and cells, including MCF-7, MDA-MB-231, and MDA-MB-468 cells [272]. Low MIF-AS1 expression was associated with poor OS. The repression of MIF-AS1 inhibited cell proliferation, migration, and EMT markers in MCF-7 and MDA-MB-231 BC cells [272]. By functioning as a ceRNA, MIF-AS1 modulated the miR-1249-3p/HOXB8 axis, resulting in increased HOXB8 (Homeobox B8) expression [272].

TP53TG1 (LINC00096) abundance was approximately three times higher in LCC9 cells than in MCF-7 cells (Table 3). LINC00096 was identified in a microarray screening study to be the most significantly increased LncRNA in TNBC tissues and cells [273]. Loss-of-function assays indicated that LINC00096 suppression inhibited cell proliferation and invasion through regulation of the miR-383-5p/RBM3 (RNA binding motif protein 3) pathway in BT-549 and MDA-MB-231 cells [273]. Other studies have reported TP53TG1 to be a tumor suppressor in CRC, due to epigenetic inactivation [273]. TG53TG1 expression is stimulated by DNA damage and depends on a wild-type TP53 expression in breast tumors [274]. Network analysis showed that TG53TG1 is regulated by ERRα (Figure 9).

Taken together, the lncRNAs differentially expressed in MCF-7 endocrine-sensitive and LCC9-endocrine-resistant breast cancer implicate a network of miRNAs and genes in pathways known to regulate cell proliferation, invasion, and cell signaling in breast cancer.

![Network 4](image_url)

**Figure 12.** Network 4: H19, XIST, HOTAIRM1, SNAIL1, and cyclin A2 (CCNA1), identified in lncRNAs differentially expressed in MCF-7 and or LCC9 cells by MetaCore analysis. Green lines with arrows = stimulation; red lines with arrows = inhibition.
4. Conclusions

This is the first examination of the impact of modulating the expression of miR-29b-1-3p and miR-29a-3p on lncRNA abundance in TAM- and fulvestrant-sensitive (MCF-7) versus resistant (LCC9) ER+ BC cells. Some of the miR-29b-1/a–lncRNA interactions identified here appear to be direct interactions, as indicated in the DIANA-LncBase v.3 database; however, a number of new potential interactions were detected that require further confirmation. In addition to the miR-29b-1-3p- and miR-29a-3p-regulated lncRNAs, we also identified cell-line-specific differences in lncRNA expression in MCF-7-endocrine-sensitive and LCC9-endocrine-resistant BC cells. The networks and GO processes identified in the analysis of these lncRNAs provide new insights into the contributions of lncRNAs to endocrine resistance. Further experiments are needed in order to elucidate these mechanisms in endocrine-resistant ER+ BC in vivo.

Supplementary Materials: The following are available online: www.mdpi.com/article/10.3390/cancers13143530/s1. Table S1: GO Processes for miR-29b-1-3p/miR-29a-3p-down-regulated lncRNAs in MCF-7 and LCC9 cells from Table 1 were identified by MetaCore. Table S2: Networks and GO Processes identified for miR-29b-1-3p/miR-29a-3p-down-regulated lncRNAs in MCF-7 and LCC9 cells from Table 1 were identified by MetaCore. Table S3: GO Processes for miR-29b-1-3p/miR-29a-3p-down-regulated lncRNAs in MCF-7 and LCC9 cells from Table 1 were identified by MetaCore. Table S4: Networks and GO Processes identified for miR-29b-1-3p/miR-29a-3p-down-regulated lncRNAs in MCF-7 and LCC9 cells from Table 1 were identified by MetaCore. Table S5: lncRNAs differentially expressed in MCF-7 and LCC9 cells that were not regulated by miR-29b-1-3p/miR-29a-3p-with low expression < 1 FPKM. Values are FPKM and are the average of 15 biological replicates +/- Standard deviation. Table S6: GO Processes for lncRNAs differentially expressed in MCF-7 and LCC9 cells from Table 3 were identified by MetaCore. Table S7: Networks and GO Processes identified for miR-29b-1-3p/miR-29a-3p-down-regulated lncRNAs in MCF-7 and LCC9 cells from Table 1 were identified by MetaCore. References [275–286] were cited in Supplementary Materials.

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