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ORIGINAL ARTICLE

Long Non-Coding RNAs Associated with Breast Cancer Cell Apoptosis Following Resveratrol Treatment: An *In Silico* Analysis

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Running Title

Novel Long Non-Coding RNAs Involved in Breast Cancer

Abstract

Phytochemicals such as resveratrol accomplish their pleiotropic anti-tumor activities by modulating the expression of non-coding RNAs. This study examined the role of resveratrol in modulating long non-coding RNAs (lncRNAs) for apoptosis of breast cancer cells. An RNA-Seq dataset available in the NCBI, in which resveratrol-induced apoptosis in a breast cancer cell line (MDA-MB-231), was analyzed to explore the differential expression of lncRNAs. In the resveratrol-treated group, 335 lncRNAs with differential expression were identified between the control and treatment groups, of which 167 and 168 lncRNAs were upregulated and downregulated, respectively. Among the upregulated putative lncRNAs, the maximum fold change was ~34, belonging to LINC00261. Among the downregulated putative lncRNAs, the maximum fold change was -191.3, which belongs to DLEU2L. The main upregulated novel lncRNAs, with a ~50-fold increase in the content, belonged to lnc-KLF-1. Our study predicted overexpression of novel lnc-KLF-1 and LINC00261 as a signature of the response of breast cancer cells to resveratrol treatment. Furthermore, a network of interactions between the lncRNAs and miRNAs was constructed, and key-lncRNA in this network was highlighted. Our study's comparative analysis of the lncRNA transcriptional landscape discovered several novel lncRNA candidates that may regulate the response of breast cancer cells to resveratrol treatment. This may pave the way for developing new molecular biomarkers with diagnostic, prognostic, and potential therapeutic values.

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Introduction

Non-coding RNAs, which all share null translation capability into protein, are divided into two major categories based on the arbitrary length of 200 nucleotides (nt): small non-coding RNAs (sncRNAs) and long non-coding RNAs (lncRNAs) (1). MicroRNAs (miRNAs), a subtype of sncRNAs with a length of ~22 nt, have regulatory effects on their mRNA target typically by binding to the 3′ untranslated region (3′UTR) and inducing mRNA degradation (2). Besides miRNAs, rapidly growing evidence reveals that long non-coding RNAs (lncRNAs) modulate epigenetic modification via direct regulation of gene expression or indirect post-translational mode as miRNAs-regulating factors or miRNAs sponges (1,3). Interactions between lncRNAs and miRNAs can regulate both oncogenic and tumor suppressor drivers such as MYC or p53; therefore, dysregulation of lncRNAs in response to various pathophysiological states such as cancer gained a lot of interest in modern oncology (4,5).

Breast cancer is a commonly diagnosed female malignancy with thousands of deaths annually (6). Although chemotherapy remains the primary line of medication for breast cancer treatment, the adverse health effects and chemoresistance pose two significant challenges (7). To minimize the side effects of chemical anti-cancer drugs, researchers have been investigating effective natural alternatives such as phytochemicals, including polyphenols, carotenoids, and terpenoids (8–13). Resveratrol (a natural phenol) has attracted a lot of attention because of its potential to inhibit tumorigenesis at multiple levels, such as initiation, promotion, and progression, as well as restoring cancer cells' drug sensitization in a variety of human and animal models (12,14,15).

Resveratrol inhibits the progression of the human breast cancer cell line (MCF-7) by targeting the wide range of miRNAs and transcription factors involved in the cell cycle and apoptosis pathways, such as E2F2, JUN, FOS, BRCA1, CDK1, CDKN1A, TNF, and the hsa-miR34a-5p (16,17). The anti-cancer effects of resveratrol are mediated by controlling epigenetics, including modulating the expression profile of ncRNAs and their downstream targets (17,18). Although the induction of apoptosis in breast cancer cell lines by resveratrol has been proven by RNA-Seq analysis, the molecular mechanisms through which resveratrol can contribute to apoptosis are not completely understood (17). As cumulative studies have described the miRNA-regulating nature of lncRNAs (19), discovering lncRNAs induced by resveratrol helps us better understand the molecular mechanism underpinning their anti-cancer effects for therapeutic application.

We attempted to analyze the changes in lncRNA expression in human breast cancer cell lines treated with resveratrol. We also introduced novel lncRNAs and their miRNA targets, which are of great value for further functional studies.

Materials and Methods

The workflow illustrates the process of using RNA-Seq data from human breast cancer cell line to analyze the lncRNA expression in response to resveratrol treatment. RNA-Seq data of breast cancer cell line (MDA-MB-231) treated with resveratrol were downloaded from the National Center for Biotechnology Information (NCBI) Sequence Read Archive (SRA) database under Bioproject number PRJNA680177.

The RNA-Seq raw data, including the untreated and treated groups, were imported into QIAGEN CLC Genomics Workbench (version 20) and trimmed to remove both low-quality sequences and adaptors based on the following parameters (i) quality scores limit: 0.05; (ii) removal of the short reads: 50 nt cut-off value, and (iii) maximum number of ambiguities: 2.

Mapping RNA-Seq Reads to the Human Reference Genome

The trimmed reads were mapped to the human reference genome GRCh38 (NCBI annotation release 110). Mapped reads were filtered based on all annotations on the reference genome: Ref_mRNA, Ref_CDs, Ref_Exon, Ref_rRNA, Ref_tRNA, Ref_Centromer, Ref_Mobile elements, Ref_Gene, Ref_Precursor RNA, and Ref_Replication using the default parameters: mismatch cost: 2; insertion cost: 3; deletion cost: 3; length fraction: 0.8; and similarity fraction: 0.8. The unmapped read collections were assembled using the *de novo* assembly option with a minimum contig length of 250 for further analysis.

Identification of Putative and Novel lncRNAs

To eliminate transcripts with protein-coding potential, a series of rigorous filtering steps was performed. First, obtained contigs from the previous step were blasted against all human protein sequences downloaded from NCBI and UniProt using BLASTX with the following parameters: Query genetic code: standard; the number of threats: 20; P-Value: 0.0001; word size: 3; Maximum number of hit sequences: 10. The detected protein-coding transcripts were discarded and non-coding transcripts were imported into Coding Potential Calculator (CPC) tool to assess the protein-coding potential of transcripts based on six biologically meaningful sequence features (20). Transcripts with CPC score < 0 were defined as non-coding RNAs and

then were blasted against the Pfam database to discard transcripts with high similarity to known protein domains: E-value < 0.001. A total of 3590 transcripts were predicted as lncRNAs and used for further analysis. For detection of novel lncRNAs, 3590 predicted lncRNAs from the previous step were blasted (BLASTn) against the ncRNAs (>250 nt long) downloaded from Ensembl using the following parameters: the number of threats: 50; P-Value: 0.0001; word size: 11; Maximum number of hit sequences: 1. Our identified lncRNAs were selected as novel lncRNAs and the rest transcripts were putative lncRNAs.

Analysis of lncRNAs Expression

The final list of lncRNAs was used as a reference for the RNA-seq analysis tool using QIAGEN CLC Genomics Workbench (version 20). All trimmed reads from our original RNA-seq data (accession number: PRJNA680177) were mapped to the final list of detected lncRNAs by RNA-seq analysis method: mismatch cost: 2; insertion cost: 3; deletion cost: 3; length fraction: 0.8; similarity fraction: 0.8; the maximum number of hits for a read: 10. The lncRNA expression of the control group compared to resveratrol-treated groups was analyzed by selecting the GE results of all samples and setting up experiments. Baggerley's test was used to detect statistically significant differences in lncRNA expression between groups, and then transcripts with fold change values greater than 2 and less than -2 were highlighted. An FDR (False Discovery Rate) p-value of < 0.01 was considered statistically significant. Expression values were estimated as RPKM and normalized against the overall set based on the number of reads per 1,000,000. These expression values were used to create a heat map using the web-enabled Heatmapper tool (http://www.heatmapper.ca/) (Figure 3).

The lncRNA-miRNA Interaction

All human miRNAs were downloaded from the miRBase 22 database (http://www.mirbase.org/), and all differentially expressed lncRNAs were used for the prediction of target mimicry by psRNATarget (https://www.zhaolab.org/psRNATarget/). Top 10 differentially expressed lncRNAs and their miRNA targets were used for interactive networks using Cytoscape.

Gene Ontology and Pathway Analysis of Transcriptomic Data

Differentially expressed lncRNAs were annotated to the reference genome (maximum evaluation: 0.0001 and maximum identity: 95) to find the location of lncRNAs on each chromosome. The nearest neighboring genes to lncRNAs (located 10 kbp upstream) were extracted using *Homo sapiens* (assembly GRCh38.p14) in https://www.ensembl.org/index.html, and their expression values were calculated by QIAGEN CLC Genomic Workbench (version 20). The gene ontology (GO) enrichment was extracted for all the neighboring protein-coding genes, and then more abundant terms were computed for each category of molecular function, biological process, and cellular components using https://string-db.org/.

Results

Identification of Putative and Novel lncRNAs

RNA-Seq data from human breast cancer cell lines was used for analyzing lncRNAs expression in response to resveratrol treatment. The reads were retrieved from previously deposited data in the NCBI under accession number PRJNA680177.

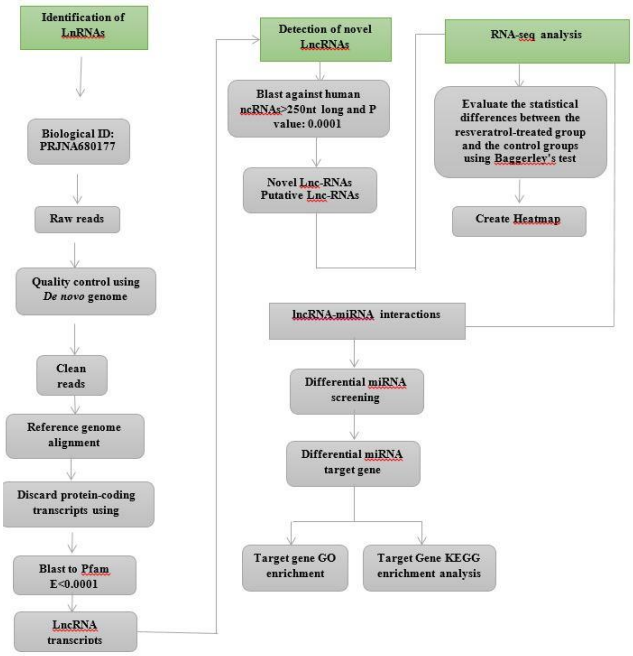

Figure 1: Flowchart for the process of bioinformatics analysis.

Differentially Expressed lncRNAs in Resveratrol-treated Cells

In the resveratrol-treated group, 335 lncRNAs with differential expression were identified between the control and treatment groups, of which 167 and 168 lncRNAs were upregulated and downregulated, respectively. The top 10 differentially expressed lncRNAs in each group are listed in Table 1. Among the upregulated putative lncRNAs, the maximum fold change was ~34, belonging to LINC00261. Among the downregulated putative lncRNAs, the maximum fold change was -191.3, which belongs to DLEU2L. The main upregulated novel lncRNAs, with a ~50-fold increase in the content, belonged to lnc-KLF-1 (Table 1).

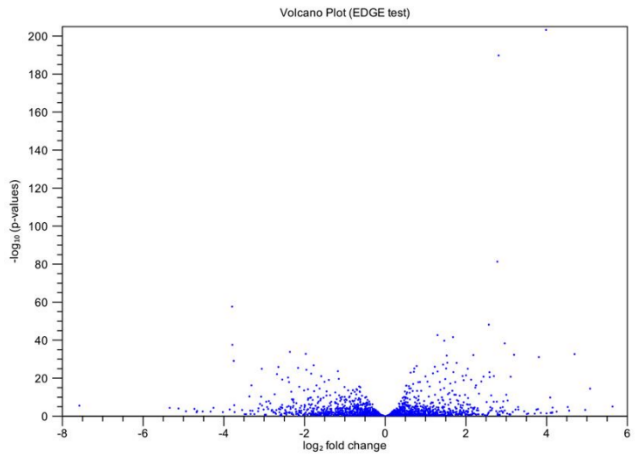

Figure 2: Volcano plots showing the distribution of the gene expression fold changes in the MDA cell line treated with resveratrol.

The lncRNA-miRNA Interactions

The lncRNA-miRNA interaction network of upregulated and downregulated lncRNAs in the resveratrol-treated MDA cell line was shown in Figures 4 and 5, respectively. Major lncRNA as key node within the networks was ENST00000371086.3, which exhibited ~192-fold decrease in expression during the course of experimental study.

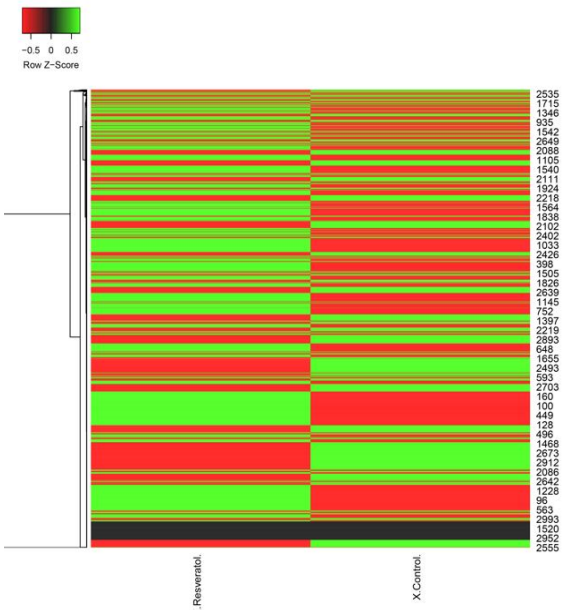

Figure 3: Heat map plot displaying the differentially expressed lncRNAs in the resveratrol-treated cell line.

The lncRNA-miRNA Interactions

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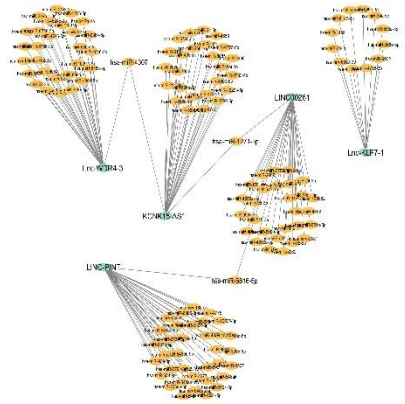

Figure 4: The top 5 upregulated lncRNAs-miRNAs interactions analyzed from an excising RNA-seq database under accession number PRJNA680177 (Resveratrol-treated breast cancer cell lines). The network was created using Cytoscape 3.8. Blue spectrum node: hub nodes that showed a higher degree in the lncRNAs-miRNAs interaction network.

Expression of lncRNAs Neighboring Protein-Coding Genes

To determine the functions of the identified putative and novel lncRNAs, we extracted the GO enrichment of protein-coding genes located in 10 kb upstream loci of our discovered lncRNAs. The essential functions of the differentially expressed genes were classified by GO analysis. The top 10 most enriched molecular functions, biological processes, and KEGG (Kyoto Encyclopedia of Genes and Genomes) pathways associated with lncRNA target genes in each group were shown in Figure 6.

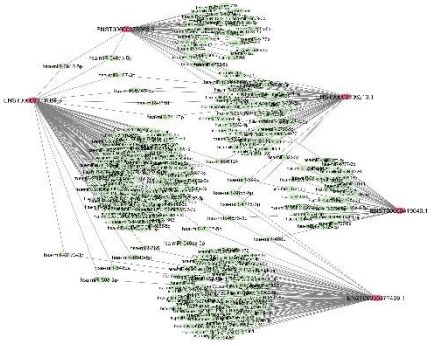

Figure 5: The top 5 downregulated lncRNAs-miRNAs interactions analyzed from an existing RNA-seq database under accession number PRJNA680177 (Resveratrol-treated breast cancer cell lines). The network was created using Cytoscape 3.8. Red spectrum node: hub nodes that showed a higher degree in the lncRNAs-miRNAs interaction network.

In resveratrol-treated cells, in terms of biological process, our detected lncRNA target genes were enriched in the "Cellular process." The most activated molecular functions were "Binding" and "Protein binding," and the

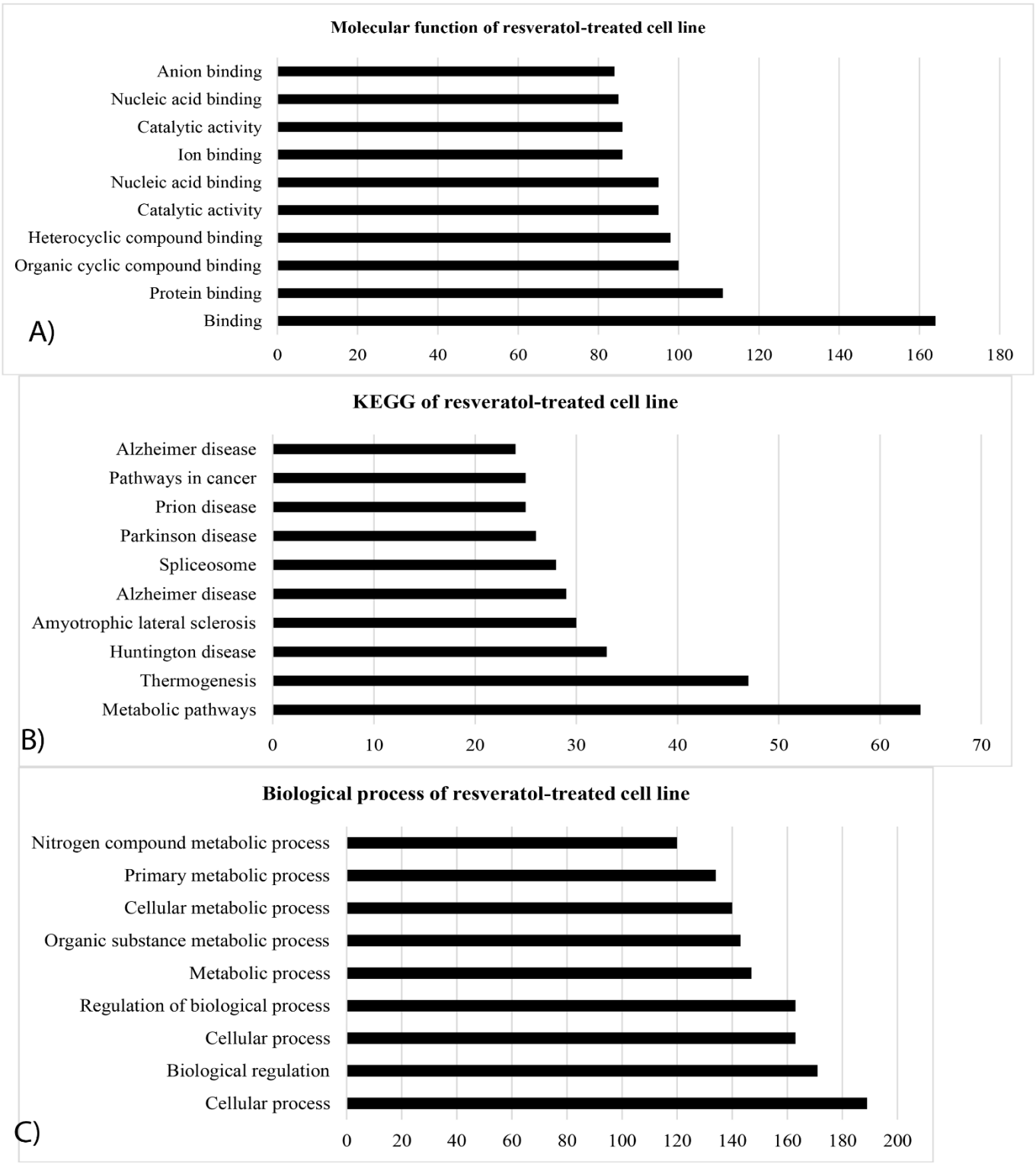

Figure 6: Gene ontology categories were performed on the up and downregulated lncRNAs transcripts in breast cancer cell lines affected by resveratrol. GO-terms for biological processes were obtained from the STRING database for analysis in the BiNGO tool: a Cytoscape plugin. Significant GO terms (5% FDR) were identified and further refined to select non-redundant terms. A: The top 10 molecular functions annotated by GO analysis with a comparison of RNA-Seq from resveratrol-treated cell lines versus untreated cell lines. B: Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways analysis. The CytoKEGG plugin was used to import the pathways into the Cytoscape 3.8 software. C: The top-10 biological processes annotated by GO analysis with comparison of RNA-Seq from resveratrol-treated cell lines versus untreated cell lines.

Table 1. The top-10 up and down-regulated lncRNAs in the MDA-MB-231 breast cancer cell line were treated by resveratrol

Transcript No.	Ensemble Transcript ID	Ensemble Gene ID	Gene Symbol*	lncRNA Type	Log2 Fold change	Adj. P-value	Status
1	ENST00000412387.5	ENSG00000223725	Novel (Lnc-KLF7-1)	Novel	49.64	0.009619714	Up
2	ENST00000420070.1	ENSG00000259974	LINC00261	lincRNA	33.74	0.003223472	Up
3	ENST00000420273.2	ENSG00000233754	Novel (Lnc-WDR4-3)	Novel	31.04	0.002247182	Up
4	ENST00000427598.5	ENSG00000244558	KCNK15-AS1	antisense	25.87	0.005748217	Up
5	ENST00000431189.1	ENSG00000231721	LINC-PINT	lincRNA	23.56	1.33599E-10	Up
6	ENST00000371086.3	ENSG00000116652	DLEU2	Sense intronic ncRNA	-191.28	1.51864E-09	Down
7	ENST00000377469.1	ENSG00000204792	LINC01291	lincRNA	-40.51	0.000553458	Down
8	ENST00000378953.8	ENSG00000197536	IRF1-AS1	antisense	-34.81	7.83937E-09	Down
9	ENST00000406213.1	ENSG00000218537	MIF-AS1	antisense	-26.49	0	Down
10	ENST00000419640.1	ENSG00000227542	MYO1B-AS1	antisense	-25.28	0.003166736	Down

*Gene symbols for novel lncRNAs were retrieved from LNCipedia, and for putative lncRNAs were retrieved from HGNC. Abbreviations: HGNC= HUGO Gene Nomenclature Committee

major KEGG signaling pathway included "Metabolic pathways" (Figure 6).

Discussion

Resveratrol modulates cancer biology, e.g., tumor cell growth, migration, and survival, by controlling the expression of ncRNAs such as miRNAs (21–24). However, there are few studies regarding the potential role of resveratrol in the modulation of lncRNA expression for inducing apoptosis in cancer cells. LncRNAs can act as competing endogenous RNAs (ceRNAs), such as miRNAs, as one of the epigenetic manipulation processes that ultimately affect gene expression. A recent bioinformatics study found that crosstalk between transcription factors–miRNA–mRNA is responsible for the inhibition of breast cancer cell proliferation by resveratrol (16). For instance, resveratrol triggers the p53 pathway for enhancing tumor-suppressive miR-34a, miR-424, and miR-503, which inhibit breast cancer cell growth (18,25). Compared to mRNAs, lncRNAs display a lower level of expression, but their expression is tissue- and condition-specific (26–28). The specific expression patterns of the functional lncRNAs in different stages of cancer biology or tumor cells' response to therapy have the potential to be used as optimal disease biomarkers and develop strategies for therapeutic purposes (29). We used an RNA-Seq dataset to find putative and novel lncRNAs associated with the response of breast cancer cells to resveratrol treatment. We identified novel lncRNAs involved in breast cancer. Focusing on the functional characteristics of these novel lncRNAs could provide valuable information for developing breast cancer therapy.

As shown in Table 1, lnc-KLF7-1 and LINC00261 were upregulated in resveratrol-treated breast cancer cells, which is consistent with a study by Ferrando et al. 2020 which revealed that a set of lncRNAs: lnc-KLF7-1, lnc-MAB21L2-1, and LINC00324 was informative to predict the response to chemo-radiotherapy in the individuals with locally advanced rectal adenocarcinoma (30). In the same

study, LINC00261 exhibited a 6.6-fold increase in responder patients compared to non-responders (30). Guo et al. 2020 revealed that knockdown or even lower levels of LINC00261 induce the proliferation and migration of several neoplastic disorders, such as breast cancer cells and endometrial carcinoma (31). Additional evidence shows that LINC00261 protected the nucleoside diphosphate kinase 1 (NME1) mRNA from degradation, leading to suppression of tumor metastasis outgrowth (32). Accordingly, it could be concluded that overexpression of novel lnc-KLF-1 and LINC00261 represents a meaningful candidate for the prediction of breast cancer cell response to resveratrol.

Among the downregulated putative lncRNAs, the maximum fold change was -191.3, which belongs to DLEU2L. The lncRNA Deleted in Lymphocytic Leukemia 2 Like (DLEU2L, previously known as BCMSUNL) was extremely downregulated in resveratrol-treated cells (Table 1). DLEU2L is an independently expressed homolog of DLEU2 (90.3% homology) that is considered a cancer-related lncRNA as its overexpression is associated with the proliferation and apoptosis prevention of several malignant tumors (33,34). Recent evidence showed that DLEU2L was overexpressed in hepatic cell carcinoma compared to normal tissues, and high expression of DLEU2L was associated with poor outcomes based on survival analysis (35). As shown in Fig 5, DLEU2L emerged as the most substantial hub node within the lncRNAs-miRNAs interaction network of resveratrol-treated cells.

Another downregulated lncRNA in Table 1 was IRF1-AS1, which is inconsistent within *in silico* analyses by Nazem, et al. 2023 and Huang et al. 2019, who showed that IRF1-AS1 acts as a tumor suppressor in colorectal cancer and esophageal squamous cell carcinoma, respectively (36,37). Accordingly, it seems that the downregulation of DLEU2L and IRF1-AS1 are lncRNA targets of the resveratrol for inducing apoptosis in breast cancer cells.

In resveratrol-treated cells, in terms of biological process, our detected lncRNA-related genes were enriched in the "Cellular process." The most activated molecular functions were "Binding" and "Protein binding," and the major KEGG signaling pathway included "Metabolic pathways" (Figure 6).

Conclusion

We found that lncRNAs, whose expression levels were altered after resveratrol treatment, were associated with breast cancer. We discovered several potential clinically relevant lncRNAs that may participate in breast cancer apoptotic cell death, which deserve attention for future functional analyses. Our study also predicted overexpression of novel lnc-KLF-1 and LINC00261 as a signature of the response of breast cancer cells to resveratrol treatment.

Acknowledgements

Not applicable

Author Contributions

Salome Dini contributed to the conceptualization and design of the study, data analysis, and manuscript writing. **Abozar Ghorbani** was involved in the collection of data, in silico analysis, and interpretation of results. **Neda Eskandarzade** supervised the study, provided critical revisions, and was responsible for overall project administration. **Maryam Alibeiki** assisted in data interpretation, validation, and manuscript editing. All authors have read and approved the final manuscript

Data Availability

All data generated or analyzed in this study are included within the published article and its supplementary materials or can be accessed through the mentioned public databases, ensuring transparency and reproducibility of the bioinformatics findings.

Ethical Approval

This study was conducted as an *in silico* analysis based on publicly available datasets and bioinformatics tools. Therefore, it did not involve direct experiments on human participants, animals, or clinical samples. As such, ethical approval was not required for this research. The research adhered to all applicable guidelines and regulations for the use of secondary data in biomedical research. Any data sourced from human studies were previously collected with appropriate ethical approval and informed consent by the original investigators.

Conflict of Interest

The authors declare that there are no commercial or financial relationships that could be construed as a potential conflict of interest with respect to the research, authorship, and/or publication of this article.

Consent for Publication

All authors have reviewed and approved the final version of the manuscript and consent to its publication.

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