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Research Article

RESVERATROL MODULATES lncRNA EXPRESSION PROFILES IN LEUKEMIA STEM CELL LINE

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ABSTRACT

Objective: Leukemia stem cells (LSCs) are central to therapy resistance and disease relapse. Long non-coding RNAs (lncRNAs) are critical epigenetic regulators whose dysregulation sustains leukemic stemness. This study evaluated the capacity of resveratrol to selectively modulate the lncRNA expression landscape in LSCs compared with healthy hematopoietic stem cells (HSCs).

Materials and Methods: Human LSC and healthy HSC lines were treated with 16.7 μM resveratrol for 72 hours. Differential expression of 90 lncRNAs was assessed using quantitative real-time PCR. Integrated RNA–protein interaction network and functional enrichment analyses were performed using the RAIN database integrated with the STRING consortium to identify molecular hubs targeted by resveratrol.

Results: Resveratrol markedly reprogrammed the LSC transcriptome, resulting in the upregulation of nine and downregulation of nineteen lncRNAs. Notably, the expression of the tumor suppressor anti-NOS2A was restored (5.70-fold), a molecule previously identified as strongly suppressed in LSCs. Significant induction was also observed for PTENP1 (6.15-fold) and LincRNA-SFMBT2 (8.30-fold), while oncogenic lncRNAs HOTTIP (−11.34-fold), SNHG5 (−8.99-fold), and MALAT1 (−7.61-fold) were strongly inhibited. In contrast, healthy HSCs exhibited a substantially attenuated transcriptional response, indicating a more pronounced transcriptional response in LSCs compared with HSCs, although measurable lncRNA alterations were also observed in the healthy cell population. Integrated network analysis further associated upregulated lncRNAs with Jak–STAT signaling and apoptotic regulation (Caspase-3/7), whereas downregulated networks were linked to epigenetic maintenance and cell cycle progression.

Conclusion: Resveratrol acts as a selective modulator in LSCs by restoring tumor-suppressive signatures and suppressing oncogenic drivers through lncRNA alterations. These findings support the potential of resveratrol as a complementary strategy to target LSC-mediated resistance while sparing normal hematopoiesis.

Keywords: Leukemia stem cells; long non-coding RNA; resveratrol

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INTRODUCTION

Leukemia remains a significant global oncological challenge; according to 2022 GLOBOCAN data, it ranks 13th in cancer incidence and 10th in cancer-related mortality. With 487,294 newly diagnosed cases and an estimated 305,405 deaths globally, leukemia accounts for approximately 3.1% of total cancer-related mortality (1). Although the development of subtype-specific targeted therapies has led to marked improvements in treatment response rates and prolonged patient survival (2), disease relapse remains a significant clinical challenge during long-term follow-up. Leukemia stem cells (LSCs), which can exhibit intrinsic resistance to conventional chemotherapy and certain targeted therapies, are thought to play a central role in disease relapse (3).

LSCs are defined as malignant cell populations arising from normal hematopoietic stem cells (HSCs) following the accumulation of genetic and/or epigenetic alterations (4). In addition to maintaining their self-renewal capacity, these cells display a therapy-resistant phenotype that contributes to disease persistence and relapse. In particular, it has been reported that oncogenic signaling pathways activated by mutations, together with accompanying genetic or epigenetic alterations, play a critical role in the intrinsic chemoresistance of LSCs through cellular adaptive mechanisms that reduce drug responsiveness (5).

In recent years, long non-coding RNAs (lncRNAs) have gained increasing attention as key regulatory elements in leukemia research. These molecules are characterized as non–protein-coding RNA transcripts exceeding 200 nucleotides in length and are commonly categorized into functional groups including signaling, decoy, guide, and scaffold lncRNAs (6-9). Accumulating evidence indicates that alterations in lncRNA expression are associated with various malignancies, including lymphoma and leukemia (7, 8). Furthermore, several lncRNAs have been reported to be associated with the biology of different leukemia subtypes (8-13). In this context, lncRNAs are considered to be closely linked to leukemia progression and myelopoiesis. In our previous study, we demonstrated that the lncRNA expression profile of LSCs was markedly different from that of healthy HSCs (14).

The high toxicity profiles and long-term adverse effects of conventional chemotherapeutic agents used in leukemia have increased interest in safer and complementary therapeutic approaches (15). Accordingly, nutrition-derived natural compounds and bioactive products have been proposed as potential supportive agents in hematological malignancies due to their regulatory effects on cancer biology. In particular, polyphenolic compounds have been highlighted as promising agents in various cancers, including leukemia. Among these natural compounds, the phytochemical resveratrol has recently gained considerable attention in leukemia research.

Resveratrol (3,4′,5-trihydroxystilbene) is a polyphenolic stilbene derivative found primarily in grapes and red wine (16, 17). Numerous studies have demonstrated that resveratrol exerts antioxidant, anti-inflammatory, and cellular regulatory effects in multiple cancer types, including prostate, lung, pancreatic, liver, breast, colorectal cancers, and leukemias (18-20).

In line with the need for low-toxicity, natural, and innovative therapeutic strategies targeting leukemia stem cells, the present study aimed to identify lncRNAs involved in anti-proliferative and apoptotic processes in LSCs in response to resveratrol treatment and to evaluate the effects of the same resveratrol dose on lncRNA expression in healthy hematopoietic stem cells.

MATERIALS AND METHODS

In this study, Human Leukemia Cancer Stem Cell Line (LSC; #36111-38, Celprogen) was utilized as the experimental model. These cells were verified to be positive for the expression of Oct4, CD44, CD133, SSEA3, SSEA4, telomerase, alkaline phosphatase, and aldehyde dehydrogenase. Human Embryonic Hematopoietic Stem Cell Line (HSC; #36092-19, Celprogen) expressing CD34, CD117, SSEA3, SSEA4, and alkaline phosphatase was used as a non-malignant control.

Both cell populations were maintained in cell-type–specific complete growth media in matrix-coated flasks and incubated at 37 °C under humidified conditions containing 5% CO_2 and 95% relative humidity. To ensure biological consistency, all experiments were performed using cells between passages four and six. Cell cultures were routinely screened for mycoplasma contamination by DAPI staining, and phenotypic integrity was confirmed by flow cytometric analysis of characteristic surface markers, including CD38, CD133, and CD44 (21).

Chemicals

Resveratrol (Catalog No: R5010) was purchased from Sigma-Aldrich. The compound was dissolved in dimethyl sulfoxide to prepare stock solutions and stored at −86 °C.

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Working concentrations were freshly prepared on the day of the experiment by dilution with cell culture medium.

Total RNA Isolation

The selected resveratrol concentration (16.7 μM) and treatment duration (72 h) were based on our previous dose–response and viability screening experiments (unpublished data), as well as prior studies demonstrating effective transcriptomic modulation at comparable concentrations without inducing excessive cytotoxicity. LSC and healthy HSC cell lines were treated with 16.7 μM resveratrol. Untreated cells were used as the control group. Following a 72-hour exposure period, total cellular RNA, including the small RNA fraction, was purified using the RNeasy Mini Kit (Qiagen). The yield and qualitative integrity of the isolated RNA were quantified through UV spectrophotometric profiling. Samples exhibiting optimal spectral purity, defined by A260/A280 and A260/A230 absorbance ratios of ~2.0, were deemed suitable for subsequent molecular analysis.

Real-Time Quantitative Reverse Transcription PCR (qRT-PCR) Analysis

For the conversion of RNA to cDNA, ~1.5 μg of total RNA was utilized with the RNAQuant cDNA Synthesis Kit (System Biosciences) as per the manufacturer's directions. Transcriptional profiling of 90 distinct lncRNAs was conducted using the Human lncRNA Profiler qPCR Array Kit (System Biosciences). The qRT-PCR reactions were performed on a LightCycler 480 II PCR platform (Roche) employing Maxima SYBR Green qPCR Master Mix (Thermo Fisher Scientific). To ensure accurate normalization, a panel of internal controls was used, including two reference genes (GAPDH and LAMIN A/C) and three small RNA markers (18S rRNA, RNU43, and U6 snRNA). A negative control lacking reverse transcriptase (NC-RT) was also integrated into the experimental design. All qRT-PCR experiments were performed using three independent replicates.

Statistical Analysis

Relative quantification of lncRNA expression levels was performed using the $2^{-}\Delta\Delta Ct$ method. Expression changes observed in resveratrol-treated groups were evaluated relative to untreated control groups. For comparative analyses, expression values were subjected to Log_2 transformation. Statistical significance of differential expression was assessed using independent Student's t-tests. LncRNAs exhibiting a fold change of $\geqslant \pm 2$ together with a p value < 0.05 were considered significantly modulated. Heat map visualizations illustrating differential lncRNA expression patterns were generated using GraphPad Prism software (Version 9.0.0).

RNA–Protein Interaction Network Mapping

To investigate potential molecular interactions between significantly altered lncRNAs and leukemia-associated proteins, the RAIN (RNA–protein Association and Interaction Networks, v10.5) platform was utilized in integration with the STRING Consortium 2020 database (22). Interaction networks were constructed using a medium-confidence threshold, defined by a minimum interaction score of 0.4. To control for false-positive findings arising from multiple comparisons, the False Discovery Rate (FDR) correction method was applied.
Proteins included in the resulting interaction networks were further analyzed through functional enrichment approaches, including Gene Ontology (GO) analyses categorized under Biological Process, Molecular Function, and Cellular Component, as well as Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis. These analyses were conducted to elucidate the biological relevance, functional roles, and subcellular localization associated with the lncRNAs of interest.

RESULTS

Effects of Resveratrol on lncRNA Expression Profiles in LSC and HSC Cell Line

In our earlier work, we characterized aberrant lncRNA expression patterns in LSCs through comparative analysis with normal HSC (14). Building on these findings, the current study aimed to evaluate the impact of resveratrol treatment on the altered lncRNA landscape of LSC relative to untreated controls.

Table 1. Up-regulated lncRNAs in LSC after resveratrol treatment

	Fold Change (Log2)	P Value
LincRNA-SFMBT2	8.30	0.000144
PTENP1	6.15	0.000236
antiPeg11	6.03	0.000049
NTT	5.93	0.000050
anti-NOS2A	5.70	0.000216
p53 mRNA	3.68	0.000312
TMEVPG1	3.10	0.000111
DHFR upstream transcripts	2.43	0.000095
GAS5	2.10	0.000279

The qRT-PCR profiling revealed that resveratrol exposure led to a significant increase in the expression of nine lncRNAs (Table 1), while nineteen lncRNAs exhibited reduced expression levels in LSC (Table 2). Notably, LincRNA-SFMBT2, PTENP1, and antiPeg11 showed robust induction, whereas MALAT1, PCGEM1, CAR

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Table 2. Down-regulated lncRNAs in LSC after resveratrol treatment

	Fold Change (Log2)	P Value
H19	-2.13	0.000095
NEAT1	-2.13	0.000234
SCA8	-2.44	0.00038
HOTAIR	-2.54	0.000451
HULC	-2.59	0.000120
UCA1	-3.09	0.000003
LIT	-3.61	0.000145
HOTAIRM1	-4.16	0.000023
Zfhx2as	-4.24	0.000138
Alpha 250	-4.77	0.000144
DLG2AS	-4.85	0.000627
PSF inhibiting RNA	-6.69	0.000423
MALAT1	-7.61	0.000355
PCGEM1	-7.65	0.000352
CAR Intergenic 10	-8.27	0.000313
Alpha 280	-8.31	0.000311
SNHG5	-8.99	0.000273
HOTTIP	-11.34	0.000170
L1PA16	-12.70	0.000126

Intergenic 10, Alpha 280, SNHG5, HOTTIP, and L1PA16 were markedly suppressed, changes that were predominantly observed in the LSC compartment. Collectively, these data demonstrate that resveratrol treatment reshapes the characteristic lncRNA expression signature of LSC.

Table 3. Up-regulated lncRNAs in HSC after resveratrol treatment

	Fold Change (Log2)	P Value
PTENP1	16.45	0.000079
LincRNA-SFMBT2	8.30	0.000064
antiPeg11	4.23	0.000028
E2F4 antisense	3.32	0.000257
mascRNA	3.24	0.000089
WT1-AS	3.01	0.000126
MEG9	2.67	0.000119
SRA	2.60	0.000207
p53 mRNA	2.42	0.000592
ROR	2.34	0.000088
PSF inhibiting RNA	2.12	0.000107
HAR1B	2.03	0.000025
NTT	2.01	0.000383

By comparison, the healthy HSC cell line exhibited a more limited transcriptional response to resveratrol, with the exception of PTENP1, which showed a notable upregulation in expression (Figure 1). In this cell population, thirteen lncRNAs were upregulated (Table 3) and eleven lncRNAs were downregulated (Table 4) following treatment. Taken together, these findings indicate that resveratrol exerts a more pronounced modulatory effect on lncRNA expression in leukemia stem cells than in normal hematopoietic stem cells.

Table 4. Down-regulated lncRNAs in HSC after resveratrol treatment

	Fold Change (Log2)	P Value
CAR Intergenic 10	-2.34	0.000393
AK023948	-2.40	0.000001
Zfas1	-2.47	0.000347
IPW	-2.47	0.000143
Xist	-2.54	0.000044
UCA1	-2.73	0.000278
TEA ncRNAs	-2.97	0.000171
MALAT1	-5.24	0.000212
Alpha 280	-5.58	0.000568
PCGEM1	-8.08	0.000351
L1PA16	-15.28	0.000074

The lncRNA–protein Interaction Networks

To delineate the functional consequences of the observed transcriptomic shifts and identify the specific molecular hubs targeted by resveratrol, we conducted integrated RNA–protein interaction network mapping using the RAIN database (22), prioritizing the analysis of upregulated molecules linked to tumor-suppressive and immune-modulatory signaling. Among the upregulated lncRNAs after resveratrol treatment in LSC, the network of TMEVPG (IFNG-AS1, 3.1-fold upregulation) contained IFNG, IFNA2, IFNA17, IFNGR1, STAT1, IL18, IL23A and IL2 (Figure 2a). This network has been predicted to be involved in regulation of cytokine-mediated signaling pathway (GO:0001959, FDR= 7.6e-06), leukocyte differentiation (GO:0002521, FDR= 1.4e-05), hemopoiesis (GO:0030097, FDR= 0.000187) and Jak-STAT signaling pathway (KEGG:04630, FDR= 1.85e-09). The network of GAS5 (2.1-fold upregulation) contained CASP3 and CASP7 (Figure 2b). This network has been predicted to be involved in cysteine-type endopeptidase activity involved

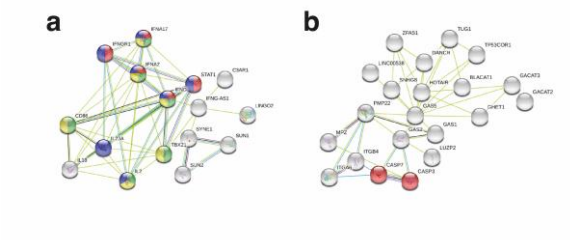

Figure 2. lncRNA–Protein interaction network for upregulated lncRNAs in LSC after resveratrol treatment (a) *TMEVPG (IFNG-AS1)*, (b) *GAS5* interactions with RNAs and proteins. In the networks of the molecular relationships between lncRNA-protein, RNAs and proteins were symbolized as nodes and the biological relationship between two nodes was represented as a line. In panel (a), the molecules indicated as red play role in regulation of cytokine-mediated signaling pathway, green in leukocyte differentiation, navy-blue in Jak-STAT signaling pathway, yellow in hemopoiesis. Red circles in (b) are the molecules that play role **in** cysteine-type endopeptidase activity involved in execution phase of apoptosis.

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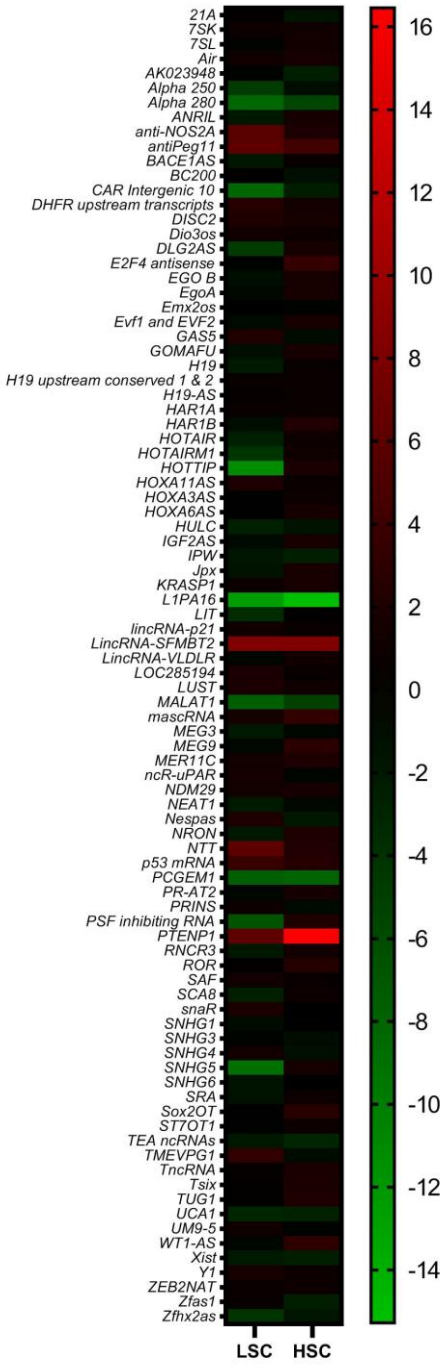

Figure 1. Heatmap representation of differentially expressed lncRNAs in LSC and healthy HSC cell lines following resveratrol treatment. Relative expression levels of lncRNAs were determined by qRT-PCR and calculated using the $2^{-}\Delta\Delta Ct$ method. Data are presented as $\log_2$ fold change values relative to untreated control cells. Red and green color intensities indicate upregulation and downregulation, respectively, as shown in the color scale. Resveratrol treatment induced a distinct lncRNA expression signature in LSC, whereas HSC exhibited a comparatively attenuated transcriptional response.

in execution phase of apoptosis (GO:0097200, FDR= 0.0124).

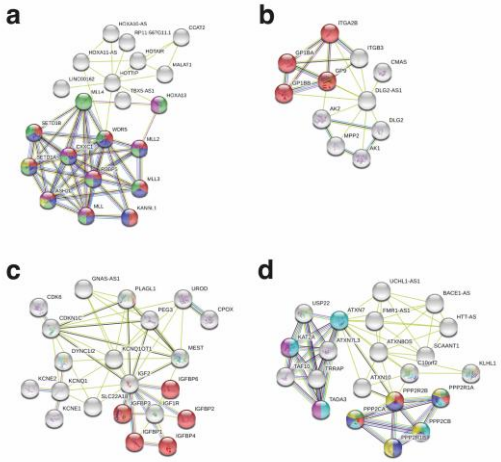

Figure 3. lncRNA–Protein interaction network for downregulated lncRNAs in LSC after resveratrol treatment, which revealed a coordinated suppression of molecular axes governing epigenetic maintenance, transcriptional fidelity, and cell cycle progression. (a) HOTTIP, (b) DLG2AS, (c) LIT (KCNQ1OT1), (d) SCA8 (ATXN8OS) interactions with RNAs and proteins. In the networks of the molecular relationships between lncRNA-protein, RNAs and proteins were symbolized as nodes and the biological relationship between two nodes was represented as a line. In panel (a), the molecules indicated as red play role in histone modification, navy-blue in chromosome organization, green in transcription, DNA-templated, yellow in euchromatin binding, pink in transcription regulatory region DNA binding.. Red circles in (b) are the molecules that play role in hematopoietic cell lineage. Red circles in (c) are the molecules that play role in regulation of cell growth. In panel (d), the molecules indicated as green play role in negative regulation of tyrosine phosphorylation of Stat3 protein, red in protein phosphatase type 2A complex, turquoise in microtubule cytoskeleton, pink in mitotic spindle, purple in AMPK signaling pathway, yellow in PI3K-Akt signaling pathway.

To further delineate the mechanistic underpinnings of resveratrol's therapeutic effect, we conducted an integrated network and pathway enrichment analysis of the most significantly downregulated lncRNAs in LSCs, which revealed a coordinated suppression of molecular axes governing epigenetic maintenance, transcriptional fidelity, and cell cycle progression. Among the downregulated lncRNAs after resveratrol treatment in LSC, the network of one of the most altered lncRNAs; HOTTIP (11.34-fold downregulation) contained MLL, MLL2, MLL3, SETD1A, and SETD1B (Figure 3a). This network has been predicted to be involved in histone modification (GO:0016570, FDR= 2.5e-10), chromosome organization (GO:0051276, FDR= 1.98e-06), transcription, DNA-templated (GO:0006351, FDR= 0.00583), euchromatin binding (GO:1990188, FDR= 0.00113),

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transcription regulatory region DNA binding (GO:0044212, FDR= 0.00716). The network of DLG2AS (4.85-fold downregulation) contained GP1BA, GP1BB, and GP9 (Figure 3b). This network has been predicted to be involved in hematopoietic cell lineage (KEGG:04640, FDR= 1.29e-05). The network of LIT (KCNQ1OT1, 3.61-fold downregulation) contained CDKN1C, CDK6, IGF1R, IGFBP1, IGFBP2, IGFBP3, IGFBP4, and IGFBP6 (Figure3c). This network has been predicted to be involved in regulation of cell growth (GO:0001558, FDR= 0.0161). The network of SCA8 (ATXN8OS, 2.44-fold downregulation) contained ATXN7, TADA3, PPP2R2B, PPP2R1B, PPP2P1A, PPP2CB, and PPP2CA (Figure 4d). This network has been predicted to be involved in negative regulation of tyrosine phosphorylation of Stat3 protein (GO:0042518, FDR= 0.00863), protein phosphatase type 2A complex (GO:0000159, FDR= 8.61e-05), microtubule cytoskeleton (GO:0015630, FDR= 0.0173), mitotic spindle (GO:0072686, FDR= 0.0431), AMPK signaling pathway (KEGG:04152, FDR= 7.96e-06), PI3K-Akt signaling pathway (KEGG:04151, FDR= 0.000455).

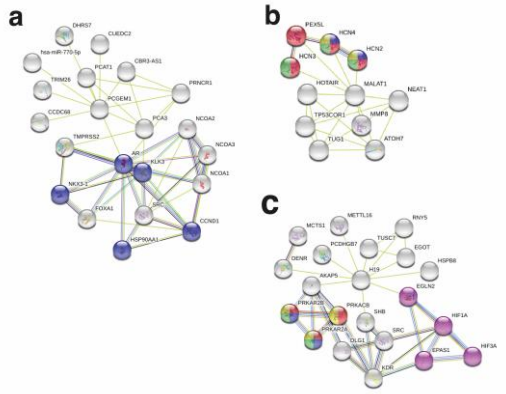

Figure 4. lncRNA–Protein interaction network for downregulated lncRNAs in LSC after resveratrol treatment, which intimately linked to the suppression of oncogenic signatures and the active induction of apoptotic execution phases. **(a)** *PCGEM1*, **(b)** *MALAT1*, **(c)** *H19* interactions with RNAs and proteins. In the networks of the molecular relationships between lncRNA-protein, RNAs and proteins were symbolized as nodes and the biological relationship between two nodes was represented as a line. Navy-blue circles in **(a)** are the molecules that play role in pathways in cancer. In panel **(b)**, the molecules indicated as navy-blue play role in cellular response to cGMP, red in regulation of membrane potential, green in cAMP binding, yellow in intracellular cAMP activated cation channel activity. In panel **(c)**, the molecules indicated as pink play role in regulation of transcription from RNA polymerase II promoter in response to hypoxia, red in activation of protein kinase A activity, navy-blue in cAMP-dependent protein kinase inhibitor activity, green in cAMP-dependent protein kinase regulator activity, yellow in apoptosis.

Beyond the disruption of fundamental cell growth and transcriptional control, our analysis further revealed that resveratrol orchestrates a profound modulation of lncRNA-protein networks intimately linked to the suppression of oncogenic signatures and the active induction of apoptotic execution phases. The network of PCGEM1 (7.65-fold downregulation) contained CCND1, KLK3, AR, and HSP90AA1 (Figure 4a). This network has been predicted to be involved in pathways in cancer (KEGG: 05200, FDR= 0.00144). The network of MALAT1 (7.61-fold downregulation) contained HOTAIR, NEAT1, PEX5L, HCN2, HCN3, and HCN4 (Figure 4b). This network has been predicted to be involved in cellular response to cGMP (GO:0071321, FDR= 0.0253), regulation of membrane potential (GO:0042391, FDR= 0.0283), cAMP binding (GO:0030552, FDR= 0.000419), intracellular cAMP activated cation channel activity (GO:0005222, FDR= 0.00738). The network of H19 (2.13-fold downregulation) contained HIF1A, HIF1B, PRKACB, PRKAR2A, and PRKAR2B (Figure 4c). This network has been predicted to be involved in regulation of transcription from RNA polymerase II promoter in response to hypoxia (GO:0061418, FDR= 0.000454), activation of protein kinase A activity (GO:0034199, FDR= 0.00257), cAMP-dependent protein kinase inhibitor activity (GO:0004862, FDR= 0.0288), cAMP-dependent protein kinase regulator activity (GO:0008603, FDR= 0.0331), apoptosis (KEEG:04210, FDR= 0.00806).

DISCUSSION

Long non-coding RNAs (lncRNAs) are defined as RNA molecules longer than 200 nucleotides that lack protein-coding potential; they exert functional roles as signaling, decoy, guide, and scaffold molecules, thereby precisely regulating gene expression at both transcriptional and post-transcriptional levels (6-9). These molecules function as critical epigenetic regulators in the maintenance of fundamental biological processes such as cell growth, apoptosis, and hematopoiesis (7, 8). Accumulating evidence in recent years has suggested that disruptions in lncRNA expression profiles are directly associated with leukemia pathogenesis and that these molecules may exhibit oncogenic or tumor suppressor properties depending on leukemia subtype (7-9).

Leukemia stem cells (LSCs), which constitute the primary focus of this study, represent malignant cell populations with self-renewal capacity that lie at the core of therapy resistance and disease relapse. In our previous work, we demonstrated that the lncRNA expression profile of LSCs markedly diverges from that of healthy hematopoietic stem cells (14). This dysregulated landscape indicates that lncRNAs may serve as both biomarkers and strategic therapeutic targets in leukemia management (6, 7, 9).

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Resveratrol, a natural polyphenol, has been reported to reduce cell viability, induce apoptosis in leukemia cells, and particularly to overcome chemoresistance by exhibiting synergistic effects with agents such as venetoclax in TP53-mutant AML cells (16-20, 23).

In the present study, we found that resveratrol triggered a far broader and more pronounced modulation of lncRNA expression in LSCs compared with healthy HSCs. Following resveratrol treatment, the expression of nine lncRNAs was significantly upregulated, whereas nineteen lncRNAs were downregulated in LSCs. A particularly noteworthy finding was the strong induction (5.70-fold) of anti-NOS2A, previously identified as one of the most markedly downregulated lncRNAs in LSCs (14). Restoration of anti-NOS2A expression suggests that resveratrol may partially reverse the LSC-specific dysregulated lncRNA landscape and shift leukemic cells toward a more stable phenotype (6, 7).

Our in silico network analysis demonstrated that resveratrol-induced transcriptomic alterations are translated into functional cellular reprogramming. The interaction network of the upregulated lncRNA TMEVPG (IFNG-AS1) featured key regulatory hubs, including IFNG, STAT1, and IL2, linking this lncRNA to cytokine-mediated signaling and activation of the Jak–STAT pathway. These findings suggest that resveratrol may promote immune recognition and/or leukocyte differentiation programs in LSCs through modulation of this axis. Similarly, the induction of the tumor-suppressive lncRNA GAS5 and its predicted interactions with Caspase-3 and Caspase-7 indicate that resveratrol may facilitate direct activation of the apoptotic execution phase via lncRNA-dependent regulatory mechanisms (22).

In parallel, the upregulation of tumor suppressor–associated lncRNAs such as PTENP1 (6.15-fold) and LincRNA-SFMBT2 (8.30-fold) further supports the regulatory impact of resveratrol on leukemic stem cell survival and stemness-associated properties. PTENP1 functions as a competing endogenous RNA (ceRNA), stabilizing of PTEN protein to attenuate oncogenic PI3K/Akt signaling. The dramatic 11.34-fold suppression of HOTTIP and its network associations with histone-modifying enzymes such as MLL2, MLL3, and SETD1A/B is highly significant. This suggests that resveratrol targets the HOTTIP-mediated epigenetic maintenance of the HOXA gene cluster, which is essential for LSC identity and self-renewal (25).

Conversely, the significant suppression of oncogenic lncRNAs such as HOTTIP (−11.34-fold) and SNHG5 (−8.99-fold) following resveratrol treatment is therapeutically relevant. HOTTIP supports LSC maintenance by activating the HOXA gene cluster (12), whereas SNHG5 contributes to chemoresistance by inducing autophagy via the PTBP1/ATG5 axis (13). Suppression of these oncogenic drivers by resveratrol may enhance apoptotic sensitivity in leukemic cells. In addition, although H19 plays a crucial role in maintaining quiescence in normal HSCs, its dysregulation in LSCs may contribute to malignant progression (9, 24).

Furthermore, the suppression of oncogenic drivers such as PCGEM1, SCA8, and MALAT1 broadens the anti-leukemic spectrum of resveratrol. The downregulation of PCGEM1 targets pathways involved in cancer progression (CCND1, AR). The marked downregulation of SCA8 (ATXN8OS) and its association with the PI3K-Akt and AMPK signaling pathways further confirms that resveratrol modulates metabolic and proliferative checkpoints in LSCs. Finally, the interaction of the MALAT1/H19 network with HIF1A suggests that resveratrol may impair the survival strategies of LSCs within the hypoxic bone marrow niche.

Several limitations of this study should be acknowledged. The findings are based on an in vitro stem cell model and transcriptomic profiling, and the predicted RNA–protein interactions were generated through in silico analyses. Therefore, functional validation experiments and in vivo studies will be required to confirm the mechanistic relevance of the identified lncRNA networks.

CONCLUSION

In conclusion, our findings suggest that resveratrol is capable of reprogramming the aberrant lncRNA expression landscape in leukemia stem cells. The limited transcriptional impact of resveratrol on healthy HSCs further strengthens its clinical potential as a low-toxicity, selective epigenetic modulator (17, 19). These lncRNA-based molecular alterations offer novel and innovative strategies for overcoming resistance and preventing relapse in leukemia treatment.

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Authorship contributions
Both authors contributed to the study conception and design. Material preparation, data collection, analysis, and literature search were performed by Cagla Kayabasi. The first draft of the manuscript was written by Cagla Kayabasi. Supervision, review and editing were done by Cumhur Gunduz.

Data availibity statement
The data are available from the corresponding author upon reasonable request.

Declaration of competing interest
The authors declare no competing interests.

Ethics
The local ethics committee ruled that no formal ethics approval was required in this particular case.

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