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Investigation of molecular biomarkers in BRCA1 mutated ovarian cancer using ceRNA network and survival analysis

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Abstract

Aim: One of the most deadly gynecological malignancies that affects women is ovarian cancer. Due to a genetic propensity, patients with breast cancer (BRCA)1 mutations are especially vulnerable. The crucial role that long noncoding RNA (lncRNA)- microRNAs (miRNA)- messenger RNA (mRNA) interactions play in controlling gene expression has become clear in recent years through the competing endogenous RNA (ceRNA) hypothesis. Understanding tumor biology and finding new biomarkers are two benefits of studying ceRNA networks. In this study, we employed survival analysis and differential expression to investigate the ceRNA network structure in patients with BRCA1 mutations within the The Cancer Genome Atlas ovarian cancer cohort (TCGA-OV) cohort.

Methods: This study was conducted at the Selçuk Faculty of Medicine, and two primary analyses were performed. First, a ceRNA network analysis was performed, using the ceRNA_network_edges.csv and ceRNA_hubs.csv files.

Results: The ceRNA network analysis identified 45,737 nodes and 23,017 edges, with lncRNAs being the dominant component. PCED1B antisense RNA 1(PCED1B-AS1) was the central hub with the highest connectivity. Survival analysis revealed protective effects for T-cell receptor beta variable 6-1 (TRBV6-1), T-cell receptor gamma constant 1 (TRGC1), ENSG00000162654.9, and ENSG00000228013.1, while keratin 16 (KRT16) expression was associated with poor prognosis. These findings highlight key regulatory genes with potential prognostic value.

Conclusion: In patients with ovarian cancer who had BRCA1 mutations, this study illustrated the connection between ceRNA network topology, gene expression, and survival. The biological significance of Hub lncRNAs within the ceRNA network was emphasized. According to survival analyses, several genes are crucial for determining a patient's prognosis. These facts might influence future developments of individualized treatment plans.

Keywords

ovarian cancer, BRCA 1, biomarker, ceRNA

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Introduction

Ovarian cancer is the second most common gynecological malignancy in women worldwide and has the highest mortality rate. Because it is usually diagnosed in advanced stages, with specific symptoms present, and screening methods are limited, patient survival rates are pretty low.[1] Therefore, understanding the molecular mechanisms of the disease and identifying new biomarkers is crucial. In addition to environmental factors, genetic predisposition also plays a critical role in the development of the disease. Germline mutations in the breast cancer (BRCA)1 and BRCA2 genes, in particular, are considered the primary cause of hereditary breast and ovarian cancers. The BRCA1 gene is a tumor suppressor gene that functions to repair DNA double-strand breaks through homologous recombination.[2] Mutations in this gene that lead to loss of function lead to the accumulation of DNA damage and, consequently, genomic instability. This significantly increases the risk of developing ovarian cancer in individuals carrying a BRCA1 mutation.[3] Furthermore, studies have shown that these mutations not only influence cancer development but also affect prognosis and response to treatment.[4] Recent advances in molecular biology have revealed that protein-coding genes do not solely regulate gene expression. Noncoding RNAs, including long noncoding RNAs (lncRNAs) and microRNAs (miRNAs), have been demonstrated to play crucial regulatory roles in cancer biology. The competing endogenous RNA (ceRNA) hypothesis, proposed in this context, suggests that different RNA types interact with one another to regulate gene expression.[5] In this study, examining the ceRNA network structure in ovarian cancer patients carrying BRCA1 mutations is critical for determining its molecular basis. Such an approach will pave the way for the development of personalized treatment strategies and the introduction of new prognostic markers into clinical practice.

Materials and Methods

The study was conducted using RNA-seq expression data, mutation information, and clinical survival data from the The Cancer Genome Atlas ovarian cancer cohort (TCGA-OV) cohort. The analysis was based explicitly on comparing patients carrying BRCA1 mutations with those who are BRCA1 wild-type. The ceRNA_network_edges and ceRNA_hubs tables were used to construct the ceRNA network. lncRNA: Transcripts with no gene symbol and no ENSG ID, messenger RNA (mRNA): Genes starting with ENSG ID, miRNA: Transcripts with the "hsa-miR" tag. The total number of nodes and edges was calculated; degree distributions were extracted. The highest-degree genes were identified. Network visualizations were created in a simplified format. The Cancer Genome Atlas (TCGA) data were downloaded using TCGAbiolinks, and BRCA1-mutant and wild-type groups were compared using DESeq2. Differential expression criteria of padj < 0.05 and | log2 fold change (log2FC)| > 1 were applied. Overall Survival (OS) was calculated using patients' days to death, days to last follow-up, and vital status information. Hazard ratio (HR), p-value, and false discovery rate (FDR) were calculated using Cox proportional hazards regression. High- and low-expression groups were compared using Kaplan–Meier analyses (median cutoff). Software/Packages: survival, survminer, and biomaRt were used.

Ethical Approval

This study was approved by the Ethics Committee of Selçuk University Faculty of Medicine (Date: 2025-08-10, No: E-70632468-050.01-1103917).

Statistical Analysis

All statistical analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria). Raw RNA-seq count data were normalized, and differential gene expression analysis was conducted using the DESeq2 package. Patients carrying BRCA1 mutations were compared with BRCA1 wild-type patients. Differentially expressed genes (DEGs) were identified using an adjusted p-value (false discovery rate, FDR, Benjamini–Hochberg correction) < 0.05 and an absolute log2 fold change (|log2FC|) > 1 as the significance thresholds. OS was calculated based on days to death, days to last follow-up, and vital status information. The association between gene expression levels and survival outcomes was evaluated using univariate Cox proportional hazards regression models. Hazard ratios (HRs), 95% confidence intervals (CIs), and p-values were calculated. Multiple testing correction was applied using the FDR method where appropriate. Kaplan–Meier survival curves were generated to compare high- and low-expression groups using the median expression value as the cutoff. Differences between survival curves were assessed using the log-rank test. A two-sided p-value < 0.05 was considered statistically significant. For ceRNA network analysis, the total number of nodes and edges was calculated, and degree distributions were extracted. Genes with the highest degree values were defined as hub genes. Descriptive network topology statistics were computed, and simplified network visualizations were generated. All statistical tests were two-tailed, and the significance level was set at $\alpha = 0.05$.

Reporting Guidelines

This observational study was conducted and reported in accordance with the STROBE guidelines.

Results

The ceRNA network analysis yielded a total of 45,737 nodes and 23,017 edges. These nodes included 44,727 lncRNAs, 732 mRNAs, and 278 miRNAs. When examining the interaction types, 21,294 lncRNA–mRNA, 1,426 miRNA–mRNA, and 297 lncRNA–miRNA relationships were identified. The hub gene with the highest degree in the network was PCED1B antisense RNA 1 (PCED1B-AS1) (degree = 379), and this lncRNA was shown to interact with numerous miRNAs and mRNAs. This suggests that PCED1B-AS1 may play a critical regulatory role in the ceRNA network (Supplementary Figure 1). When comparing BRCA1-mutated and wild-type patient groups, significant differential gene expression was detected (padj < 0.05, |log2FC| > 1). Among these genes, those associated explicitly with survival were evaluated in detail. Cox regression and Kaplan–Meier analyses revealed that the expression levels of some genes had a statistically significant effect on survival: T-cell receptor beta variable 6-1 (TRBV6-1): HR = 0.5, p = 0.00058, High expression showed a protective effect and significantly prolonged survival. Keratin 16 (KRT16): HR = 1.32, p = 3.9e-05, High expression

increased the risk of death and was a predictor of poor prognosis. ENSG00000162654.9: HR = 0.8, p = 0.0045. High expression was associated with better survival. ENSG00000228013.1: HR = 0.81, p = 0.00117, showed a protective effect (borderline significance). T-cell receptor gamma constant 1 (TRGC1): HR = 0.8, p = 0.0048, high expression was associated with more prolonged survival. Consequently, hub lncRNAs in the ceRNA network, particularly PCED1B-AS1, are potential regulatory centers through numerous interactions. Survival analyses have shown that genes such as TRBV6-1, TRGC1, and ENSG00000162654.9 play a protective role, while KRT16 is associated with poor prognosis.

Discussion

In this study, the ceRNA network structure and survival analyses were performed in ovarian cancer patients carrying BRCA1 mutations, and the findings were significant in terms of both molecular mechanisms and clinical outcomes. The ceRNA network has a largely lncRNA-dominated structure, and some lncRNAs stand out as central hub genes within these networks. PCED1B-AS1, in particular, was located at the center of the network, exhibiting a high degree of connectivity and interacting with numerous mRNAs and miRNAs. Similarly, the literature suggests that hub lncRNAs play a crucial role in regulating gene expression and are linked to tumor progression in various cancer types.[6,7] Furthermore, hub lncRNAs have been reported to contribute to cell proliferation, invasion, and metastasis processes, generally by modulating signaling pathways.[8] Therefore, elucidating the biological role of PCED1B-AS1 through functional studies increases its potential as a therapeutic target. Survival analyses have revealed that specific genes have a significant impact on patient prognosis. High expression of the TRBV6-1 and TRGC1 genes has been associated with a protective effect. These genes are involved in the T-cell receptor complex and enhance the immune system's antitumor response. Previous studies have also reported that the presence of intratumoral T cells in ovarian cancer prolongs survival and improves prognosis.[9,10] In this context, TRBV6-1 and TRGC1 may be candidate biomarkers related to the immune response. Additionally, the ENSG00000162654.9 and ENSG00000228013.1 genes have been shown to positively impact survival. Although these genes have not been described in detail in the literature, our findings suggest that these genes may be potential protective biomarkers. These new candidate genes need to be further characterized through functional analyses. On the other hand, high expression of the KRT16 gene has been linked to a poor prognosis. This gene, which belongs to the keratin family, plays a role in the cytoskeleton and epithelial cell differentiation. It has been reported in the literature that disruption of keratin expression may increase the invasive and metastatic capabilities of tumor cells and may be associated with aggressive tumor phenotypes.[11,12] Therefore, KRT16 can be considered a potential biomarker for poor prognosis. The findings demonstrate that ceRNA networks can not only elucidate molecular biological mechanisms but also be used to identify new biomarkers of clinical importance. The identification of hub lncRNAs and genes affecting survival is crucial for personalized treatment approaches. Identifying genes that enhance immune responses can guide the selection of immunotherapies, while identifying genes associated with a poor prognosis can serve as an early warning for implementing more aggressive treatment strategies. Future studies must validate the functional roles of these genes and lncRNAs in in vitro and in vivo models. Furthermore, confirmatory studies in larger patient cohorts are needed to validate the utility of these molecules as clinical biomarkers. Furthermore, examining ceRNA networks in relation to mutations in other DNA repair genes could contribute to a more comprehensive understanding of ovarian cancer biology.

Limitations

This study has several limitations that should be considered when interpreting the findings. First, the analyses were based solely on retrospective data obtained from the TCGA-OV cohort, which may introduce selection bias and limit the generalizability of the results. Second, the study relied entirely on bioinformatic and in silico analyses without experimental validation. Therefore, the biological functions of the identified hub lncRNAs and survival-associated genes, particularly PCED1B-AS1, require confirmation through in vitro and in vivo experiments. Third, the sample size of BRCA1-mutated patients within the cohort was relatively limited compared to the wild-type group, which may have affected statistical power. Additionally, potential confounding clinical variables such as treatment regimens, tumor stage, and comorbidities were not comprehensively integrated into the survival models. Future studies should focus on validating the identified ceRNA interactions and prognostic biomarkers in independent and larger patient cohorts. Functional experiments are needed to clarify the mechanistic roles of key hub lncRNAs and survival-related genes in tumor progression and immune regulation. Integrating multi-omics data, including proteomics and epigenomics, may provide a more comprehensive understanding of the regulatory landscape. Furthermore, exploring the predictive value of these biomarkers in relation to treatment response, particularly PARP inhibitors and immunotherapy, could contribute to the development of personalized therapeutic strategies for patients with BRCA1-mutated ovarian cancer.

Conclusion

In conclusion, this study demonstrates the impact of ceRNA network structure and gene expression on patient survival in ovarian cancer patients carrying BRCA1 mutations. lncRNAs interact with numerous mRNAs and miRNAs. These findings provide a valuable foundation for the development of future personalized treatment approaches and the identification of new biomarkers.

Ethics Declarations

This study was conducted using publicly available, de-identified data from The Cancer Genome Atlas (TCGA) database. Ethical approval was obtained from the Ethics Committee of Selçuk University Faculty of Medicine (Date: 2025-08-10, No: E-70632468-050.01-1103917). The study was performed in accordance with the ethical principles of the Declaration of Helsinki.

Animal and Human Rights Statement

This study did not involve experiments on humans or animals.

Informed Consent

Informed consent was waived due to the retrospective design of the study and the

use of anonymized publicly available data.

Data Availability
The datasets used and/or analyzed during the current study are not publicly available due to patient privacy reasons but are available from the corresponding author on reasonable request.

Conflict of Interest
The authors declare that there is no conflict of interest.

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Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content, including study design, data collection, analysis and interpretation, writing, and some of the main line, or all of the preparation and scientific review of the contents, and approval of the final version of the article.

AI Usage Disclosure
The authors declare that no artificial intelligence tools were used in the preparation of this manuscript.

Abbreviations
BRCA1: Breast cancer gene 1
ceRNA: Competing endogenous RNA
CI: Confidence interval
DEG: Differentially expressed gene
FDR: False discovery rate
HR: Hazard ratio
KRT16: Keratin 16
lncRNA: Long noncoding RNA
log2FC: Log2 fold change
miRNA: MicroRNA
mRNA: Messenger RNA
OS: Overall survival
PCED1B-AS1: PCED1B antisense RNA 1
TCGA: The Cancer Genome Atlas
TCGA-OV: The Cancer Genome Atlas ovarian cancer cohort
TRBV6-1: T-cell receptor beta variable 6-1
TRGC1: T-cell receptor gamma constant 1

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