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Integrative Analysis of *IGFL2-AS1* and *BRCA1* Expression in Esophageal Cancer: An Experimental and Bioinformatics-Based Study

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ABSTRACT

Background: Esophageal cancer (EC) is a leading cause of cancer-related death worldwide. The long non-coding RNA *IGFL2-AS1* is implicated in malignancies, but its role in EC remains unclear. This study evaluated the expression of *IGFL2-AS1* and *BRCA1* in EC.

Methods: Sixteen paired EC and adjacent non-tumorous tissues were collected. The expression levels of *IGFL2-AS1* and *BRCA1* were quantified using RT-qPCR, and BRCA1 protein levels were determined using Western blotting. GEPIA, STRING, and g:Profiler were used for bioinformatic analyses. Receiver-operating characteristic (ROC) curves and correlation tests were performed for statistical evaluation.

Results: Both *IGFL2-AS1* and *BRCA1* were significantly downregulated in EC tissues compared to adjacent normal controls ($p < 0.05$). A positive correlation was observed between their expression levels. ROC analysis indicated diagnostic potential for both genes (AUC>0.75), with *BRCA1* showing superior accuracy. Western blotting confirmed decreased BRCA1 protein levels in tumor samples. Interestingly, GEPIA data suggested an upregulation of both genes in EC. Functional enrichment analysis linked BRCA1-associated genes to ephrin receptor signaling and axon guidance pathways.

Conclusion: Concurrent downregulation of IGFL2-AS1 and BRCA1 at transcript and protein levels was observed in EC tissues, with a positive correlation between their expression levels. ROC curve analysis suggested their potential as candidate biomarkers. However, these findings are preliminary and require further validation. ***DOI: 10.22034/IBJ.30.4.262***

Keywords: BRCA1, Diagnosis, Esophageal Neoplasm

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1. INTRODUCTION

Esophageal cancer (EC) ranks as the seventh most frequently diagnosed malignancy worldwide and constitutes the sixth primary contributor to cancer-related mortality. Emerging evidence indicates that long non-coding RNAs (lncRNAs) play important roles in the tumorigenesis and progression of EC[1]. Approximately half of the patients with EC are diagnosed at advanced stages and often present with metastatic disease. Therefore, elucidating the signaling cascades and molecular determinants implicated in EC pathogenesis may facilitate earlier detection and improve diagnostic precision during the initial stages of disease progression[2,3].

lncRNAs are transcripts longer than 200 nucleotides that lack protein-coding capacity and regulate gene expression via diverse molecular mechanisms[4]. Recent research has revealed that alterations in lncRNA expression profiles within EC are associated with both oncogenic functions and tumor-suppressive activities[5].

IGFL2-AS1 is a lncRNA recently implicated in several cancer types. Evidence suggests that it can affect tumor cell proliferation and migration through various signaling pathways, including the Wnt/β-catenin signaling pathway[6,7].

Breast cancer type 1 (*BRCA1*) is a critical gene implicated in the pathogenesis of breast and ovarian cancers. While initial studies proposed its function as a transcription factor, subsequent research has clarified its central role in maintaining genomic integrity[8]. Germline *BRCA1* variants have been reported in some familial cases of EC. *BRCA1* expression level has been associated with treatment response, with low mRNA linked to better outcomes under cisplatin and worse prognosis with docetaxel[9].

IGFL2-AS1 is a newly characterized lncRNA implicated in tumorigenesis across multiple cancers, yet its expression in esophageal EC remains unexplored. Given the potential miRNA-mediated interplay between *IGFL2-AS1* and *BRCA1*, we hypothesized their co-expression in EC and investigated their expression patterns experimentally and bioinformatically.

2. MATERIALS AND METHODS

2.1. Sample collection

A total of sixteen EC specimens, along with adjacent non-tumorous tissues, were collected from the Cancer Center of Imam Khomeini Hospital in Tehran, Iran. Histopathological evaluation by a certified pathologist confirmed the malignant and non-malignant status of all samples. The sample size was determined based on 80% power and the mean expression levels of *IGFL2-AS1* reported in previous studies, yielding a minimum of 15 patients per group.

2.2. Reverse transcription–quantitative polymerase chain reaction (RT-qPCR)

Total RNA was extracted using RNX Plus reagent (Sinaclone, Iran), and its purity and integrity were evaluated by spectrophotometry (NanoDrop, Thermo Fisher, USA) and agarose gel electrophoresis. RNA (1 µg) was reverse-transcribed into complementary DNA using a standard synthesis kit (Yektatajiz, Iran). RT-qPCR was conducted on a Roche LightCycler 96 instrument (Germany) using RealQ Plus 2× Master Mix Green (Ampliqon, Denmark). Gene expression levels were normalized to *β-actin* and quantified using the $2^{-\Delta\Delta Ct}$ method[10]. The primer sequences used for quantitative real-time PCR are as follows: for *IGF2-AS1*, forward 5′-TGTGGTTGTTCCATGACACTGA-3′ and reverse 5′-CCTGGGTTGACAGGGTAGAAT-3′; for *BRCA1*, forward 5′-TGGACACCTACCTGATA CC-3′ and reverse 5′-TAGTAGCCAGGACAGTAGA AG-3′; and for *β-actin*, forward 5′-GAGCCTCGCCT TTGCCGATCC-3′ and reverse 5′-ACATGCCGGAG CCGTTGT CG-3′, with *β-actin* serving as the internal control. All primer pairs were validated for specificity and efficiency prior to quantitative PCR analysis. Standard curves were generated using serial dilutions of cDNA. Primer efficiencies ranged from 90% to 110%, with correlation coefficients >0.99 for all targets. No primer dimers or non-specific amplification products were observed in melt curve analyses.

2.3. Western blot analysis

Total protein was extracted from tissue samples using RIPA buffer supplemented with protease inhibitors (Kiazist, Iran) and quantified using the BCA assay (DNAbiotech, Iran). After SDS-PAGE separation, proteins were transferred to nitrocellulose membranes and blocked with 5% skim milk solution. Membranes were incubated with primary antibodies against BRCA1 and β-actin (both from Santa Cruz Biotechnology, USA; sc-6954 and sc-47778, respectively), followed by horseradish peroxidase-conjugated secondary antibodies. Detection was performed using ECL reagents, and band intensities were quantified with ImageJ software. Protein expression levels were normalized to β-actin as the loading control, and relative expression was calculated as the ratio of band intensity of the target protein to β-actin for each sample.

2.4. Bioinformatic analysis using the GEPIA database

The GEPIA (version 2.0) web-based platform (http://gepia.cancer-pku.cn/) was utilized to perform a bioinformatic assessment of *IGFL2-AS1* and *BRCA1* gene expression in EC[11]. This database provided transcriptomic profiles of these genes in EC and

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included survival analyses based on overall and disease-free survival.

2.5. Bioinformatic data acquisition and functional annotation

A protein-protein interaction (PPI) network was constructed using the STRING database (version 12.0, https://string-db.org/) to explore molecular interactions among the selected genes. Functional enrichment analysis was conducted using the g:Profiler web tool (version e114_eg62_p19_27110d83, https://biit.cs.ut.ee/gprofiler/). Enrichment significance was evaluated using the g:SCS algorithm, and results were visualized according to *p* values to highlight the most relevant biological processes and pathways. Default filtering criteria, including a minimum interaction score of 0.4 for STRING and an adjusted *p* value < 0.05 for enrichment analyses, were applied.

2.6. Statistical evaluation

Statistical analyses were conducted using GraphPad Prism version 8 and SPSS version 26. Results were expressed as mean ± standard error of the mean (SEM), with *p* value <0.05 considered statistically significant. The Shapiro-Wilk test was used to assess the normality of data distribution. Depending on data distribution, either an independent-samples t-test or a nonparametric Mann–-Whitney U test was applied. Correlations between IGFL2-AS1 and BRCA1 expression were evaluated using Pearson's or Spearman's correlation coefficient, based on data distribution. Receiver-operating characteristic (ROC) curves were generated to evaluate the diagnostic performance of the selected genes in EC.

3. RESULTS

3.1. Baseline clinicopathological characteristics of EC cases

Among the 16 enrolled EC patients, 7 were male, and 9 were female. The mean age of patients was 62.05 ± 4.56 years. Histologically, the cohort comprised nine esophageal squamous cell carcinoma and seven esophageal adenocarcinoma cases. All patients were newly diagnosed with no prior treatment history. Clinical stages included II (n = 8, 50.0%), III (n = 6, 37.5%), and IV (n = 2, 12.5%). Tumor grades were distributed as grade 1 (n = 5, 31.25%), grade 2 (n = 9, 56.25%), and grade 3 (n = 2, 12.5%). Pathological T classification showed T2 (n = 5, 31.25%), T3 (n = 10, 62.5%), and T4 (n = 1, 6.25%), while lymph node metastasis was observed in N1 (n = 10, 62.5%) versus N0 (n = 6, 37.5%).

3.2. Gene expression of *IGFL2-AS1* and *BRCA1* and protein expression of BRCA1 in EC patients

RT-qPCR analysis demonstrated a significant downregulation of *IGFL2-AS1* and *BRCA1* in EC tissues compared to adjacent normal controls (Fig. 1A and 1B). Moreover, a statistically significant positive correlation was detected between the expression levels of *IGFL2-AS1* and *BRCA1* ($p < 0.05$; Fig. 1C). ROC curve analysis indicated that both *IGFL2-AS1* and *BRCA1* have significant diagnostic potential for discriminating EC from normal tissues. The obtained AUC values and statistical significance support their potential as candidate biomarkers, with *BRCA1* exhibiting superior diagnostic accuracy ($p < 0.05$; Fig. 1D-1F). Western blot analysis revealed a significant decrease in BRCA1 protein expression in EC tissues relative to adjacent normal controls ($p < 0.05$; Fig. 1G and 1H).

3.3. Analysis of *IGFL2-AS1* and *BRCA1* expression in EC using GEPIA

In contrast to our experimental results, transcriptomic data from the GEPIA database showed significant upregulation of *IGFL2-AS1* and *BRCA1* in EC samples compared with normal tissues (Fig. 2A and 2B). Kaplan-Meier survival analysis revealed no significant association between *IGFL2-AS1* or *BRCA1* expression and overall or disease-free survival (Fig. 2C-2F).

3.4. PPI network and functional enrichment analysis

The PPI network highlights *BRCA1* as a central hub in DNA damage response, showing strong connectivity with key regulators such as *TP53*, *BRCA2*, *ATM*, and *RAD50*. These associations suggest the pivotal role of *BRCA1* in homologous recombination and checkpoint control (Fig. 3). Functional enrichment analysis using g:Profiler identified biologically relevant pathways associated with the selected genes. In the gene ontology (GO) biological process (BP) category, the most significantly enriched term was the ephrin receptor signaling pathway (GO:0038128), suggesting its potential role in cell communication and tumor progression. For the molecular function (MF) category, transmembrane ephrin receptor activity (GO:0005001) was the top enriched term, implying relevance to receptor-mediated signaling. The top cellular component (CC) term was dendrite (GO:0030425), indicating possible neuronal structural associations. Additionally, KEGG pathway analysis identified axon guidance (KEGG:04360) as the most significantly enriched pathway, supporting the involvement of neurodevelopmental mechanisms in EC (Fig. 4).

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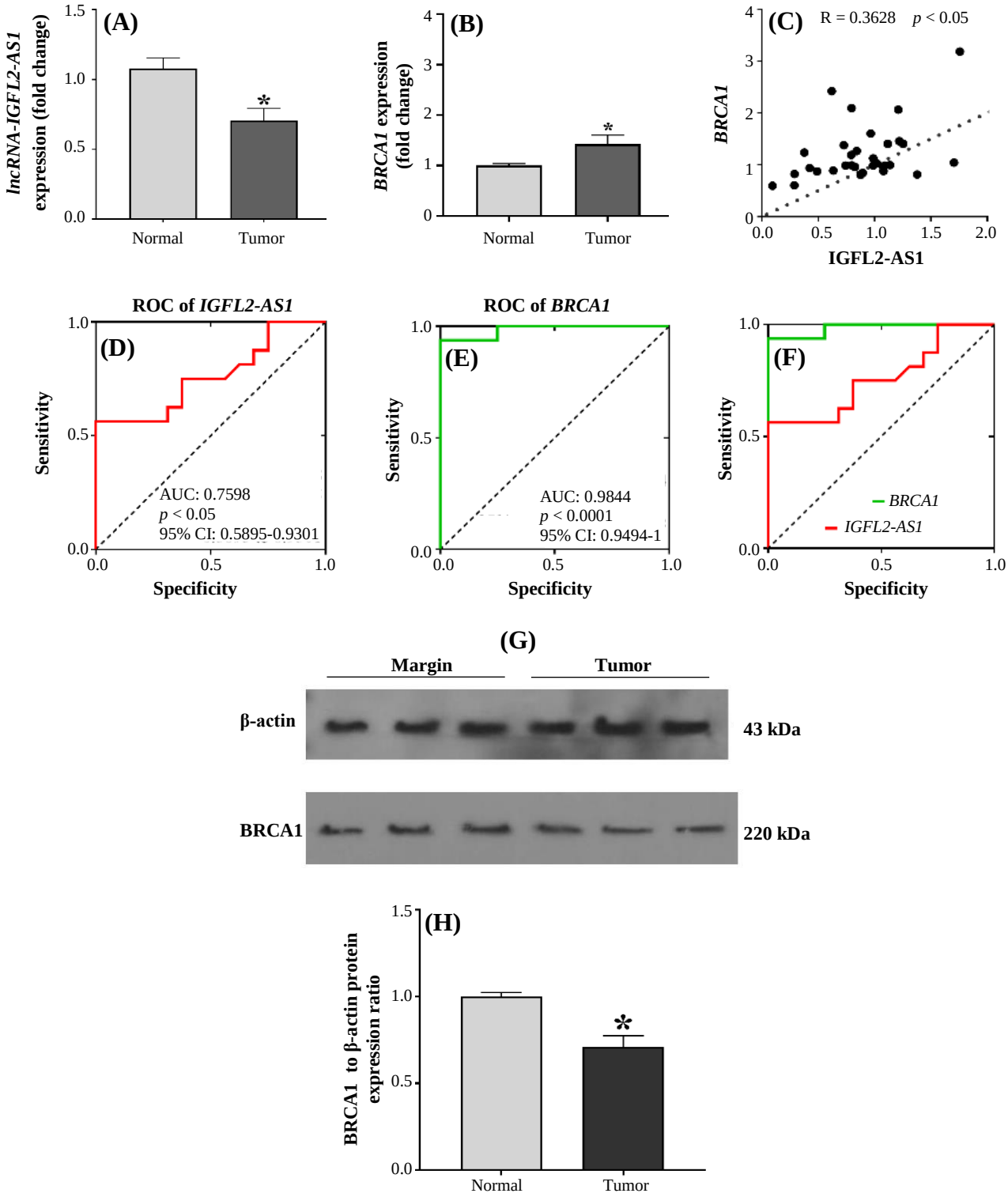

Fig. 1. Expression, correlation analysis, and diagnostic evaluation of *IGFL2-AS1* and *BRCA1* in EC. (A and B) RT-qPCR results showing significant downregulation of *IGFL2-AS1* and *BRCA1* in tumor tissues compared to normal samples (n = 16, $^{*}p < 0.05$); (C) positive correlation between *IGFL2-AS1* and *BRCA1* expression (n = 16); (D) ROC curve of *IGFL2-AS1* with moderate diagnostic accuracy (AUC = 0.7598, 95% CI: 0.5895–0.9301, $p < 0.05$, n = 16); (E) ROC curve of *BRCA1* with high diagnostic performance (AUC = 0.9844, 95% CI: 0.9444–1.000, $p < 0.0001$, n = 16); (F) Comparative ROC curves highlighting the superior accuracy of BRCA1; (G and H) Western blot analysis of BRCA1 protein expression normalized to β-actin (n = 3). Molecular weight markers: 43 kDa (β-actin) and 220 kDa (BRCA1); $^{*}p < 0.05$. Data are presented as mean ± SEM.

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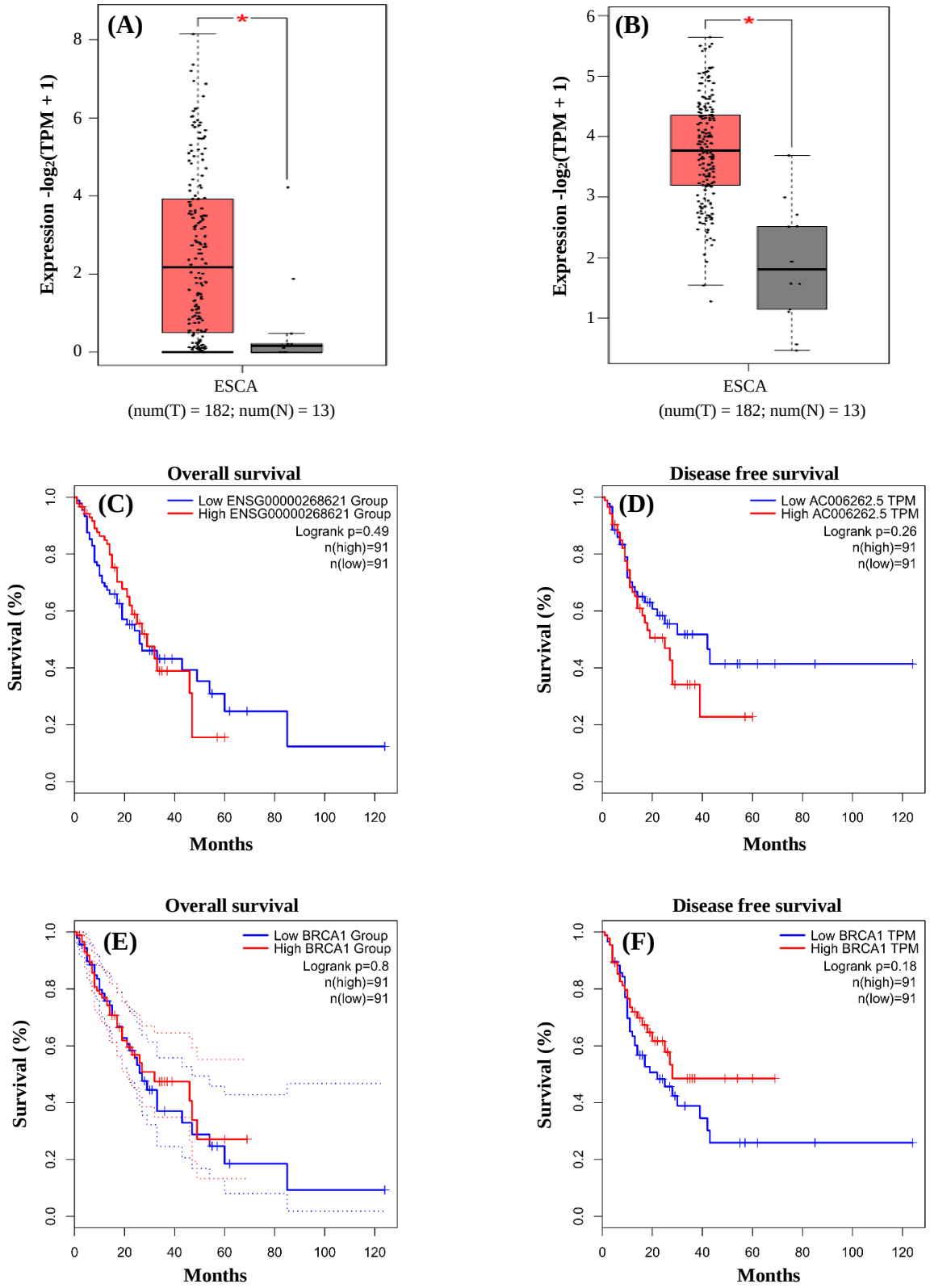

Fig. 2. Expression and survival analysis of target genes in EC. (A and B) Boxplots showing significant upregulation of target genes in EC tumor tissues (red box, n = 182) compared to normal samples (grey box, n = 13). The y-axis represents expression $-\log^2$(TPM + 1) (*indicates statistical significance); (C) Kaplan-Meier curve for overall survival based on IGFL2-AS1 expression [n(high) = 91, n(low) = 91; Logrank p = 0.49]; (D) Kaplan-Meier curve for disease free survival based on *IGFL2-AS1* expression [n(high) = 91, n(low) = 91; Logrank p = 0.26]; (E) Kaplan-Meier curves for overall Survival [n(high) = 91, n(low) = 91; Logrank p = 0.8]; (F) Kaplan-Meier curves for disease free survival (Logrank p = 0.18) based on *BRCA1* expression groups [n(high) = 91 and n(low) = 91].

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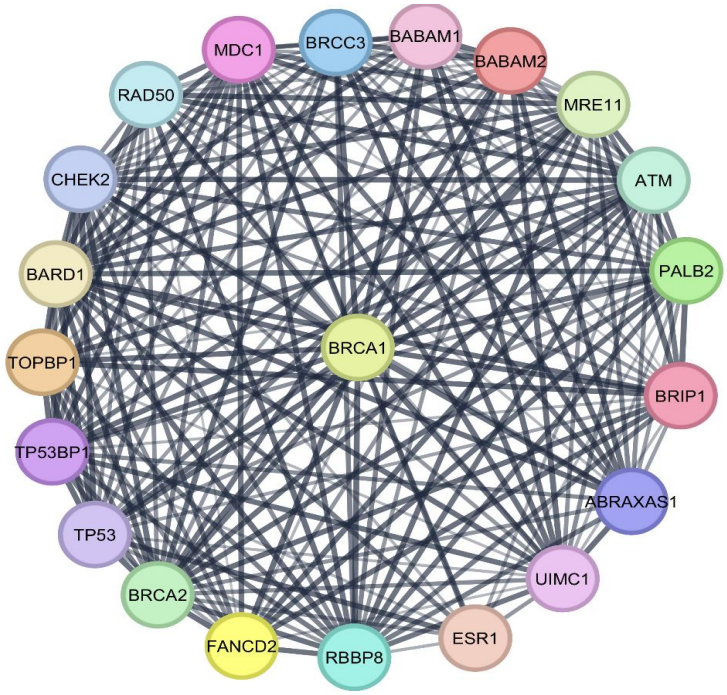

Fig. 3. PPI network analysis of BRCA1 and associated DNA repair genes. The PPI network of 20 proteins surrounding BRCA1. Nodes represent individual proteins, and edges symbolize protein-protein interactions. BRCA1 is positioned centrally, exhibiting high degrees of connectivity with other known DNA damage response and repair factors, including members of the MRN complex (MRE11 and RAD50), BRCA-associated proteins (BARD1, PALB2, and BRCA2), and cell cycle checkpoint regulators (CHEK2, TP53, and ATM). Different colors represent functional sub-complexes or related pathways.

4. DISCUSSION

Despite notable advances in the diagnosis and treatment of EC, it remains one of the most prevalent gastrointestinal malignancies and a leading cause of cancer-related mortality worldwide[12]. Achieving early detection and improved therapeutic outcomes requires a comprehensive understanding of the molecular mechanisms underlying EC pathogenesis[13]. Identification of key signaling pathways and regulatory molecules involve in EC tumorigenesis is essential for improving early detection and treatment efficacy[14,15].

Recent research highlights the critical roles of lncRNAs in the development and progression of EC. Several lncRNAs have been proposed as promising diagnostic and therapeutic biomarkers; however, their precise functions in EC pathogenesis remain largely unclear[16]. In this study, we evaluated the expression of lncRNA *IGFL2-AS1* in EC tissue samples for the first time. Our experimental results revealed a significant downregulation of *IGFL2-AS1* in tumor tissues compared to adjacent non-tumorous controls. Interestingly, bioinformatic analysis revealed an upregulation of *IGFL2-AS1* in EC, suggesting a discrepancy between in silico and experimental findings.

The oncogenic potential of *IGFL2-AS1* has been documented in several malignancies, including colorectal cancer and head and neck squamous cell carcinoma[17,18]. In colorectal cancer, *IGFL2-AS1* promotes oncogenic activity by inhibiting *HIF-1α* degradation, which leads to the upregulation of carbonic anhydrase 9 and enhanced cell proliferation, migration, and invasion[17]. These findings highlight its potential as both diagnostic biomarker and therapeutic target in colorectal cancer[17]. *IGFL2-AS1* overexpression may promote tongue squamous cell carcinoma by acting as a competing endogenous RNA that sequesters tumor-suppressive miR-1224-5p, resulting in *SATB1* upregulation. Elevated *SATB1* can activate Wnt/β-catenin signaling, promoting proliferative, migratory, and invasive phenotypes and facilitating epithelial-mesenchymal transition[6].

Our study demonstrated that *BRCA1* gene and protein expressions were significantly downregulated in EC tissues, whereas bioinformatic analysis from GEPIA indicated BRCA1 mRNA upregulation in EC. This inconsistency between experimental and in silico findings may reflect differences in sample composition, analytical techniques, histological heterogeneity, or epigenetic regulation; however, the underlying reasons remain unclear and warrant systematic investigation in future studies.

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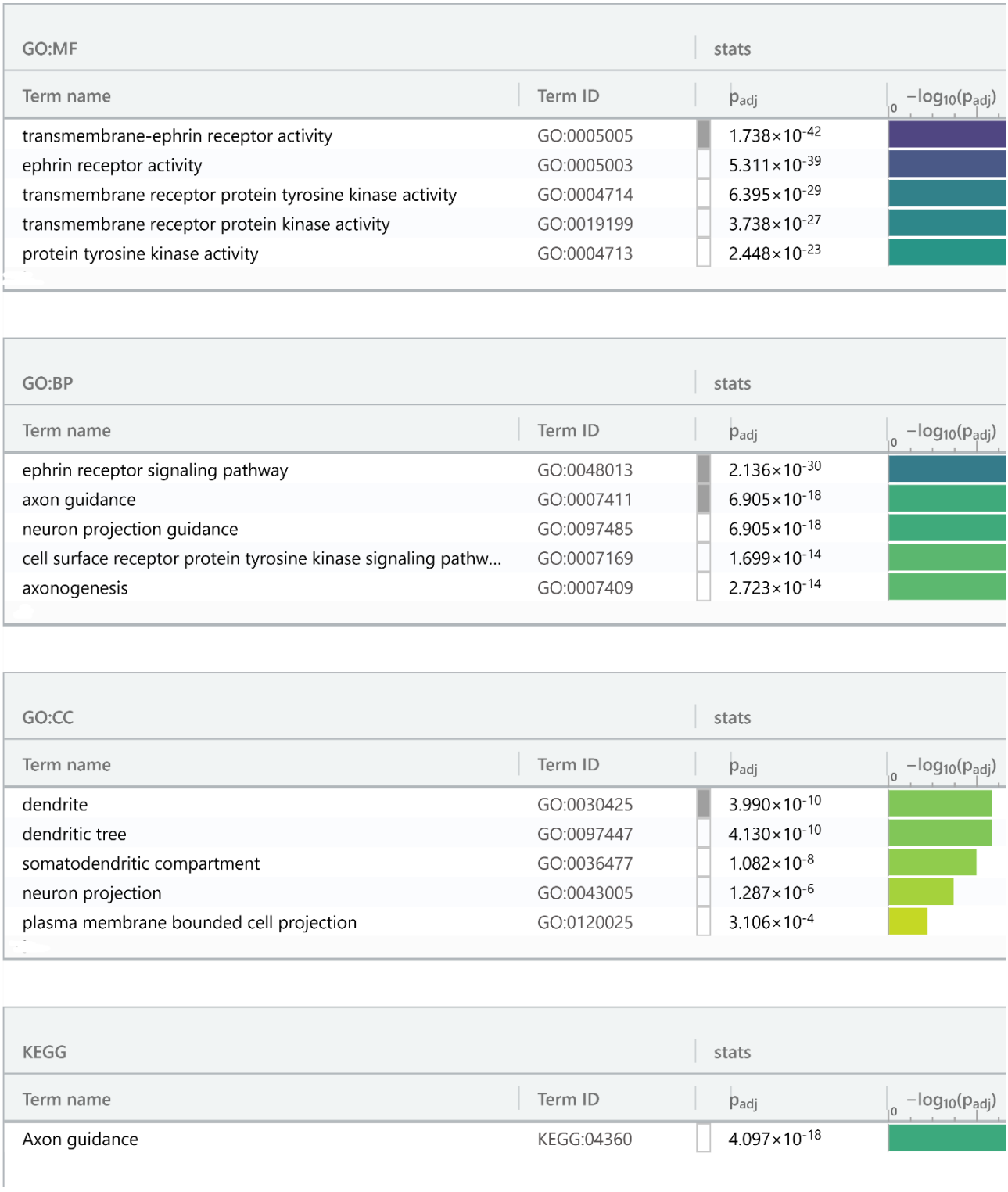

GO:MF

Term name	Term ID	p_{adj}	$-\log_{10}(p_{adj})$
transmembrane-ephrin receptor activity	GO:0005005	1.738×10^{-42}	
ephrin receptor activity	GO:0005003	5.311×10^{-39}	
transmembrane receptor protein tyrosine kinase activity	GO:0004714	6.395×10^{-29}	
transmembrane receptor protein kinase activity	GO:0019199	3.738×10^{-27}	
protein tyrosine kinase activity	GO:0004713	2.448×10^{-23}	

GO:BP

Term name	Term ID	p_{adj}	$-\log_{10}(p_{adj})$
ephrin receptor signaling pathway	GO:0048013	2.136×10^{-30}	
axon guidance	GO:0007411	6.905×10^{-18}	
neuron projection guidance	GO:0097485	6.905×10^{-18}	
cell surface receptor protein tyrosine kinase signaling pathw...	GO:0007169	1.699×10^{-14}	
axonogenesis	GO:0007409	2.723×10^{-14}	

GO:CC

Term name	Term ID	p_{adj}	$-\log_{10}(p_{adj})$
dendrite	GO:0030425	3.990×10^{-10}	
dendritic tree	GO:0097447	4.130×10^{-10}	
somatodendritic compartment	GO:0036477	1.082×10^{-8}	
neuron projection	GO:0043005	1.287×10^{-6}	
plasma membrane bounded cell projection	GO:0120025	3.106×10^{-4}	

KEGG

Term name	Term ID	p_{adj}	$-\log_{10}(p_{adj})$
Axon guidance	KEGG:04360	4.097×10^{-18}	

Fig. 4. GO and KEGG pathway enrichment analysis. The figures illustrate the top significantly enriched terms categorized into GO:MF, GO:BP, GO:CC, and KEGG pathways. For GO:MF, the most enriched terms include transmembrane-ephrin receptor activity and various protein kinase activities. In GO:BP, significant terms involve the ephrin receptor signaling pathway, axon guidance, and neuron projection guidance. For GO:CC, terms related to neuronal structures such as dendrite, dendritic tree, and somatodendritic compartment are highly enriched. The KEGG pathway analysis specifically highlights Axon guidance (KEGG:04360). Statistical significance is indicated by the adjusted *p* value (Padj) and depicted by $-\log^{10}$(Padj) bar charts, where varying color gradients represent the degree of significance.

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Reduced BRCA1 expression at both mRNA and protein levels may promote the initiation and progression of EC by disrupting DNA repair mechanisms, particularly homologous recombination repair[19]. *BRCA1* deficiency results in genomic instability and accumulation of mutations, facilitating the malignant transformation of esophageal epithelial cells[20]. Our GO and KEGG analyses linked *BRCA1* downregulation to ephrin receptor signaling and axon guidance pathways. For instance, the ephrin receptor signaling pathway implies that *BRCA1* downregulation may impair cell adhesion and migration control, thereby enhancing tumor progression through aberrant signaling cascades[21,22]. However, to validate these mechanisms and resolve the experimental-bioinformatics discrepancy, further studies focusing on epigenetic regulation and proteomics in larger, stage-specific cohorts are essential.

In our study, the expression of the *IGFL2-AS1* gene showed a positive correlation with the *BRCA1* gene. Ma et al. have reported that *IGFL2-AS1* functions as a ceRNA by sponging miR-802 in gastric cancer[23]. Moreover, TarBase data confirm that miR-802 directly targets the *BRCA1* gene[24]. These observations raise the hypothesis that *IGFL2-AS1* may indirectly modulate *BRCA1* expression through miR-802, which could potentially explain the positive correlation observed in our experiments. However, we acknowledge that this proposed mechanism remains speculative and requires experimental validation through functional assays, such as miRNA overexpression and knockdown studies, to establish a direct regulatory link.

ROC curve analysis showed that *IGFL2-AS1* and *BRCA1* had acceptable AUC values and significant *p* values. However, the predictive reliability of the model was limited due to wide confidence intervals, suggesting a need for refinement through larger sample sizes or adjustment for confounding variables. Kaplan-Meier survival analysis from the GEPIA database revealed no significant association between IGFL2-AS1 and BRCA1 and overall survival in EC, which may reflect tumor heterogeneity, patient comorbidities, or underlying molecular alterations[25].

Several limitations of this study should be considered. The relatively small sample size limits the statistical power, and ROC analysis requires validation in larger independent cohorts. The observed correlation between *IGFL2-AS1* and *BRCA1* expression does not imply causality, and functional studies are needed to establish a regulatory link. Despite these limitations, our study highlights the potential clinical relevance of *IGFL2-AS1* and *BRCA1* in esophageal cancer, supporting their further investigation as candidate biomarkers or therapeutic targets. Future studies should involve larger cohorts, include early-stage patients, and incorporate serum-based validation. In addition, exploring miRNAs mediating the regulatory crosstalk between these genes may yield mechanistic insights and enhance their translational relevance.

5. CONCLUSION

Our study demonstrates significant downregulation of IGFL2-AS1 and BRCA1 at both mRNA and protein levels in EC tissues, contrasting with the upregulation observed in the GEPIA database. ROC curve analysis indicated statistically significant AUC values for both genes, suggesting their potential as candidate biomarkers in EC. A positive correlation was observed between the expressions of *IGFL2-AS1* and *BRCA1*, warranting further investigation into their regulatory mechanisms, including miRNA-mediated interactions, in larger and histologically stratified cohorts. However, these findings are preliminary and require validation in independent studies with larger sample sizes.

DECLARATION

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Generative AI and AI-assisted technologies

ChatGPT was used to improve clarity and correct grammar in some sentences.

Ethical approval

All the experimental procedures in this study were approved by the Ethics Committee of Hamadan University of Medical Sciences, Hamadan, Iran (ethical code: IR.UMSHA.REC.1403.750).

Consent to participate

Written informed consent was obtained from all individuals, and their privacy and confidentiality were fully respected throughout the study.

Consent for publication

All authors reviewed the results and approved the final version of the manuscript.

Authors' contributions

ShM: writing-original draft, methodology, formal analysis, and investigation; HJ: data curation and methodology; NZ: writing-review and editing and data curation; MB: supervision, conceptualization, and methodology; RA: funding acquisition, supervision, and project administration.

Data availability

All original analytical datasets used or analyzed during

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the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare no competing interests.

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Supplementary information

The online version does not contain supplementary material.

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