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Original Research

Epithelial Membrane Protein 1 is a Potential Prognostic Biomarker for Ovarian Cancer

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Abstract

Background: Epithelial membrane protein 1 (EMP1) is a cell junction protein located in the plasma membrane. The function of EMP1 in cancer cells varies in different tumour types. In the present study we investigated the expression of EMP1 and its clinical significance in ovarian cancer. **Methods**: Sequencing data from the Cancer Genome Atlas (TCGA) and from several other public databases was used to study the expression of EMP1 and its gene regulation networks in ovarian cancer patients. Oncomine and Gene Expression Profiling Interactive Analysis tools (GEPIA) were used to evaluate EMP1 expression. EMP1 alterations were identified using cBioPortal and the prognostic value of EMP1 was assessed using Kaplan-Meier analysis and OncoLnc online tools. Genes that were co-expressed with EMP1 were identified using LinkedOmics and the Link-Interpreter module was used to analyse pathway enrichment and the possible functions of co-expressed genes. **Results**: EMP1 was highly expressed in ovarian cancer and was associated with advanced tumour stage and poor overall survival (OS). Amplification of the EMP1 gene was also common in ovarian cancer. EMP1 participates mainly in the biological processes of epidermal development, cell adhesion, peptidyl tyrosine modification and angiogenesis. Functional network analysis suggests that EMP1 regulates tumorigenesis and progression of ovarian cancer through different signalling pathways that include several kinases, microRNAs (miRNAs) and transcription factors related to tumorigenesis. **Conclusions**: This study confirmed the expression of EMP1 in ovarian cancer and elucidated its regulatory networks, thus providing a theoretical basis for further studies into its functions. EMP1 could potentially serve as a diagnostic and prognostic biomarker in ovarian cancer patients. However, owing to the limited sample size and range of experimental work, further validation studies are needed to confirm the role of EMP1 in ovarian cancer.

Keywords: Epithelial membrane protein 1 (EMP1); ovarian cancer; prognostic value; overall survival (OS)

1. Introduction

Ovarian cancer is the most common tumour type of the female reproductive system and has a high mortality rate [1,2] due to the usually advanced stage at diagnosis [3]. Conventional treatment of ovarian cancer involves surgery followed by chemotherapy with platinum and paclitaxel. Despite improvements in surgery and in targeted therapeutic drugs, many ovarian cancer patients still experience only short progression-free survival [4]. It is therefore of great clinical significance to find new biomarkers or drug targets for ovarian cancer.

Epithelial membrane protein 1 (EMP1) is a plasma membrane hydrophobic glycoprotein composed of hundreds of amino acids and four transmembrane domains. It was first described in 1995 and is known to function as a cell junction protein [5,6]. EMP1 is expressed in numerous tissues and plays a key role in tumorigenesis and progression [7,8]. However, the significance of EMP1 in cancer seems to vary in different tumour types. EMP1 expression is up-regulated in leiomyoma uteri, lung cancer, leukaemia and brain glioma, but down-regulated in oesophageal carcinoma, gastric cancer, prostate cancer, oral squamous cell carcinoma, breast cancer, nasopharyngeal carcinoma, and head and neck carcinomas [9]. Activation of EMP1 was shown to prevent tumour cell proliferation, suggesting that EMP1 could be a promising new target for tumour therapy [10]. The expression level of EMP1 was shown to correlate with tumour grade, prognosis, and with gefitinib resistance in lung cancer and glioma patients [11]. Despite considerable research effort aimed at identifying the role of EMP1 in tumorigenesis and development, the functions of this gene in ovarian cancer are still not clear.

In the present study, Oncomine and GEPIA were employed to assess EMP1 mRNA expression and genomic alterations in ovarian cancer patients using data from the TCGA. We analysed the prognostic value, biological func-

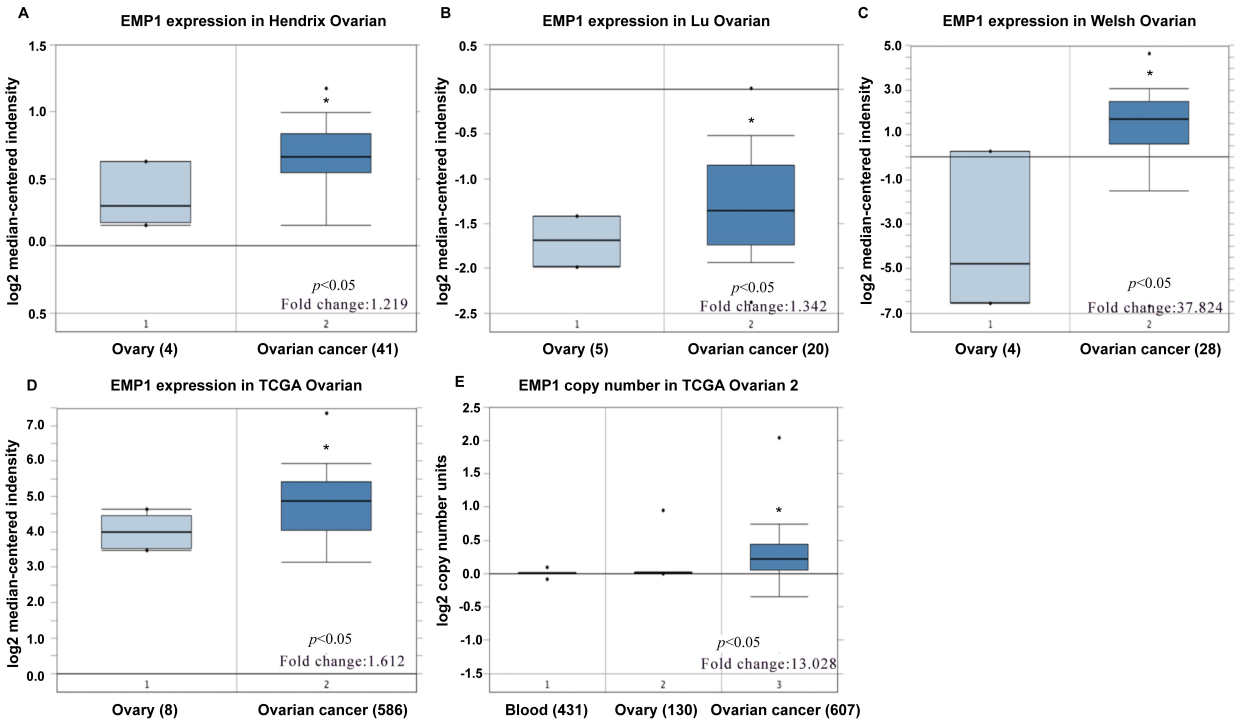

Fig. 1. EMP1 transcript levels in ovarian cancer (from Oncomine). The levels of EMP1 mRNA expression and copy number were significantly higher in ovarian cancer compared to normal ovary. (A–D) boxplots show the EMP1 mRNA level in the Hendrix, Lu, Welsh and The Cancer Genome Atlas (TCGA) ovarian cancer datasets, respectively. (E) boxplot shows EMP1 copy number in the TCGA dataset. *$p < 0.05$.

tions and relevant pathways of EMP1 in ovarian cancer using Kaplan-Meier plots, OncoLnc online tools and Gene Set Enrichment Analysis (GSEA) The aim of this study was to determine whether EMP1 can serve as a potential biomarker for the early diagnosis of ovarian cancer and as a target for therapy.

2. Materials and Methods

2.1 Oncomine Analysis

The Oncomine database (www.oncomine.org) is the largest oncogene chip database and includes 715 gene data sets from 86,733 cancer and normal tissue samples. Several ovarian cancer studies were analysed in the present work, including the Hendrix, Lu, Welsh and the Cancer Genome Atlas (TCGA) ovarian cancer studies. The mRNA expression level for EMP1 in ovarian cancer was determined in relation to the normal tissues ($p < 0.01$).

2.2 UALCAN Analysis

The UALCAN database (http://ualcan.path.uab.edu) includes RNA-seq and clinical data for 31 cancer types from the TCGA. It allows EMP1 expression in ovarian cancer to be correlated with cancer stage, age, grade, race, *etc*.

2.3 cBioPortal Analysis

The cBioPortal open-access resource (https://www.cbioportal.org) contains cancer genomics data from 225 studies. This was used to investigate EMP1 alterations in the TCGA ovarian cancer samples, including mutations, copy number variations and mRNA level.

2.4 Oncolnc Analysis

The Oncolnc database (http://www.oncolnc.org) is an excellent resource that provides the results of Cox analysis, including survival and expression data, for any gene of interest in up to 21 cancer types. In this study, multivariate cox regressions were performed for EMP1 using Kaplan–Meier analysis.

2.5 LinkedOmics Analysis

The LinkedOmics database (http://www.linkedomics.org/login.php) platform contains 32 cancer-associated datasets from the TCGA. Differentially expressed genes that correlated with EMP1 expression in ovarian cancer patients (n = 303) were identified using the LinkFinder module in LinkedOmics. Statistical analysis was performed to determine Pearson's correlation coefficient. LinkFinder also provides statistical plots, heat maps, volcano plots and scatter plots for all results. This module was used to perform pathway and network analysis of EMP1-related genes. The results were ranked and subjected to gene ontology (GO) performance analysis, including cellular component, biological process and molecule function, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways, enrich-

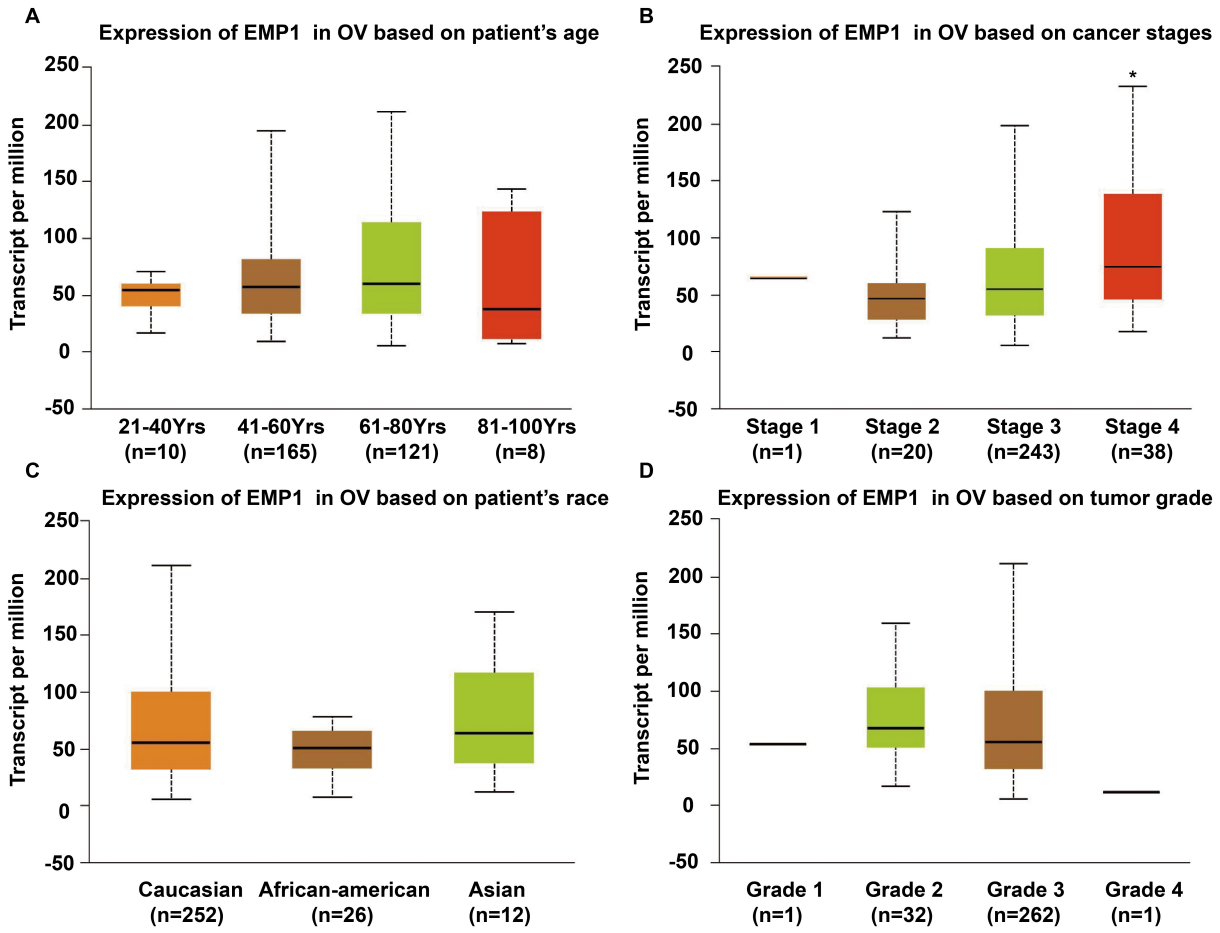

Fig. 2. EMP1 transcript levels according to age, stage, race and grade in ovarian cancer patients (from UALCAN). Boxplots show the relative EMP1 expression based on: (A) age ($p > 0.05$); (B) stage ($p = 0.0137$); (C) race ($p > 0.05$); and (D) grade ($p > 0.05$). *$p < 0.05$.

ment of kinase targets, miRNA targets and transcription targets. A false discovery rate (FDR) of $p < 0.05$ was used as the rank criterion, with 500 simulations performed.

2.6 Statistical Analysis

EMP1 expression in ovarian cancer patients from the TCGA datasets was evaluated using the student *t*-test. Overall survival (OS) was compared between EMP1 high- and low-expression patient groups using Kaplan-Meier analysis, with *p*-values calculated by the log-rank test. The Pearson correlation test was used to identify genes whose expression correlated with that of EMP1 expression, with $p < 0.05$ considered statistically significant.

3. Results

3.1 EMP1 Expression in Ovarian Cancer

We evaluated EMP1 transcript levels in ovarian cancer studies from the TCGA. Analysis of the Oncomine database revealed that EMP1 mRNA expression and DNA copy number variation (CNV) were significantly higher in ovarian cancer tissues compared to paired normal ovarian tissues ($p < 0.05$). The fold-difference in mRNA expression ranged from 1.2 to 37.8, and the CNV from 1.6 to 13.0 (Fig. 1). We next used the UALCAN database to evaluate the relationship between the EMP1 transcript level in ovarian cancer and patient age and race, as well as cancer stage and grade. EMP1 mRNA expression was significantly correlated with advanced cancer stage (Fig. 2B), but not with patient age or race, or with cancer grade (Fig. 2A,C,D, respectively). This result suggests that EMP1 expression could be a promising diagnostic biomarker for ovarian cancer.

3.2 Genomic Alterations of EMP1 in Ovarian Cancer

The type and frequency of EMP1 alterations in ovarian cancer patients from the TCGA were analysed using the cBioPortal database. It was found that 19 of 201 patients (9.45%) had EMP1 gene alterations (Fig. 3A), of which 8 showed EMP1 amplification (3.98%), 10 showed EMP1 mRNA upregulation (4.98%), and one showed EMP1 deep deletion (0.5%) (Fig. 3B). These results indicate that amplification was the most common type of EMP1 genomic alteration in ovarian cancer patients.

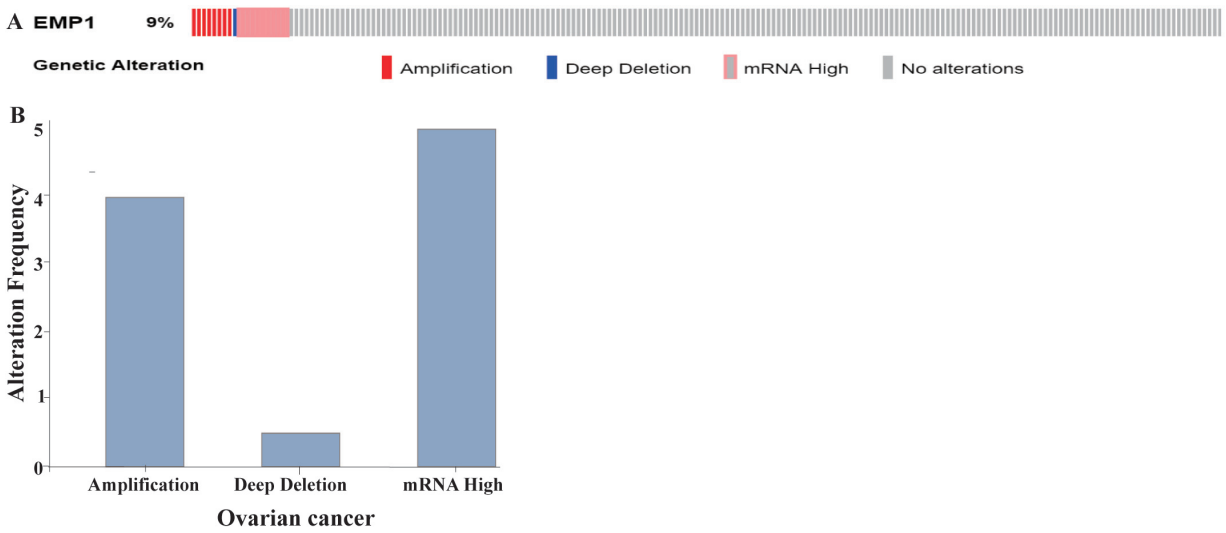

Fig. 3. Genomic alterations of EMP1 in ovarian cancer patients as observed in the cBioPortal database. (A) Overview of genomic alterations in EMP1. (B) Observed frequencies of EMP1 amplification, deep deletion and elevated mRNA level.

3.3 High Expression of EMP1 was Associated with Worse Overall Survival in Ovarian Cancer Patients

Based on data from the TCGA database, Kaplan-Meier analysis was used to evaluate the relationship between EMP1 mRNA expression and OS in ovarian cancer patients. Patients with an EMP1 expression level above the median were classified as being EMP1 high-expression. These patients had shorter OS ($p < 0.01$), indicating that high EMP1 expression was a risk factor for worse prognosis in ovarian cancer (Fig. 4).

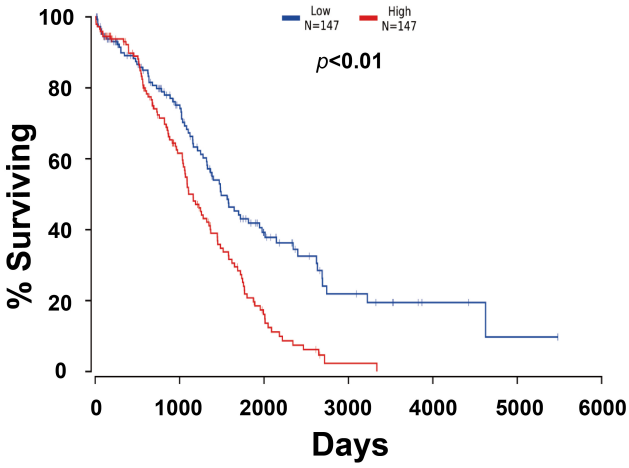

Fig. 4. High expression of EMP1 was associated with significantly worse overall survival in ovarian cancer patients.

3.4 Genes Co-Expressed with EMP1 in Ovarian Cancer

The function model of LinkedOmics was used to analyse mRNA sequencing data in ovarian cancer patients from the TCGA database (n = 303). The expression of 3755 genes was significantly correlated with that of EMP1. Of these, 1946 were positively correlated and 1809 were negatively correlated (FDR < 0.01) (Fig. 5A). The top 50 genes that were positively or negatively correlated with EMP1 expression are shown in heatmaps (Fig. 5B–C). Strong positive associations were observed between the expression of EMP1 and *LAMC2* (Pearson correlation = 0.5513, $p < 0.01$), *ANXA2P2* (0.5336, $p < 0.01$), *GPRC5A* (0.5178, $p < 0.01$) and *ANXA2* (0.5145, p = 7.123e-23) (Fig. 5D–G). These genes are involved in biological processes that include cellular growth and adhesion, cell migration and metastasis, calcium ion binding, calcium-dependent phospholipid binding, and signal transduction pathways.

3.5 GO and KEGG Analyses of Genes Co-Expressed with EMP1 in Ovarian Cancer

GO term analysis was performed on genes whose expression was correlated with that of EMP1. These genes underwent functional and pathway enrichment analyses using the Link-Interpreter module of LinkedOmics, as well as GSEA. Gene products that were co-expressed with EMP1 are mostly located in the extracellular matrix, cell-cell junctions, receptor complexes, endocytic vesicles, and actin cytoskeleton (Fig. 6A). These co-expressed proteins participate primarily in epidermal development, leukocyte cell-cell adhesion, peptidyl-tyrosine modification, ossification and angiogenesis (Fig. 6B). They function as structural constituents of the extracellular matrix and of guanyl-nucleotide exchange factor (Fig. 6C). KEGG pathway analysis showed that genes co-expressed with EMP1 participate mainly in the phosphatidyl-inositol 3-kinase/serine-threonine kinase (PI3K-Akt) and Rap1 pathways in cancer, as well as being involved in osteoclast differentiation (Fig. 6D).

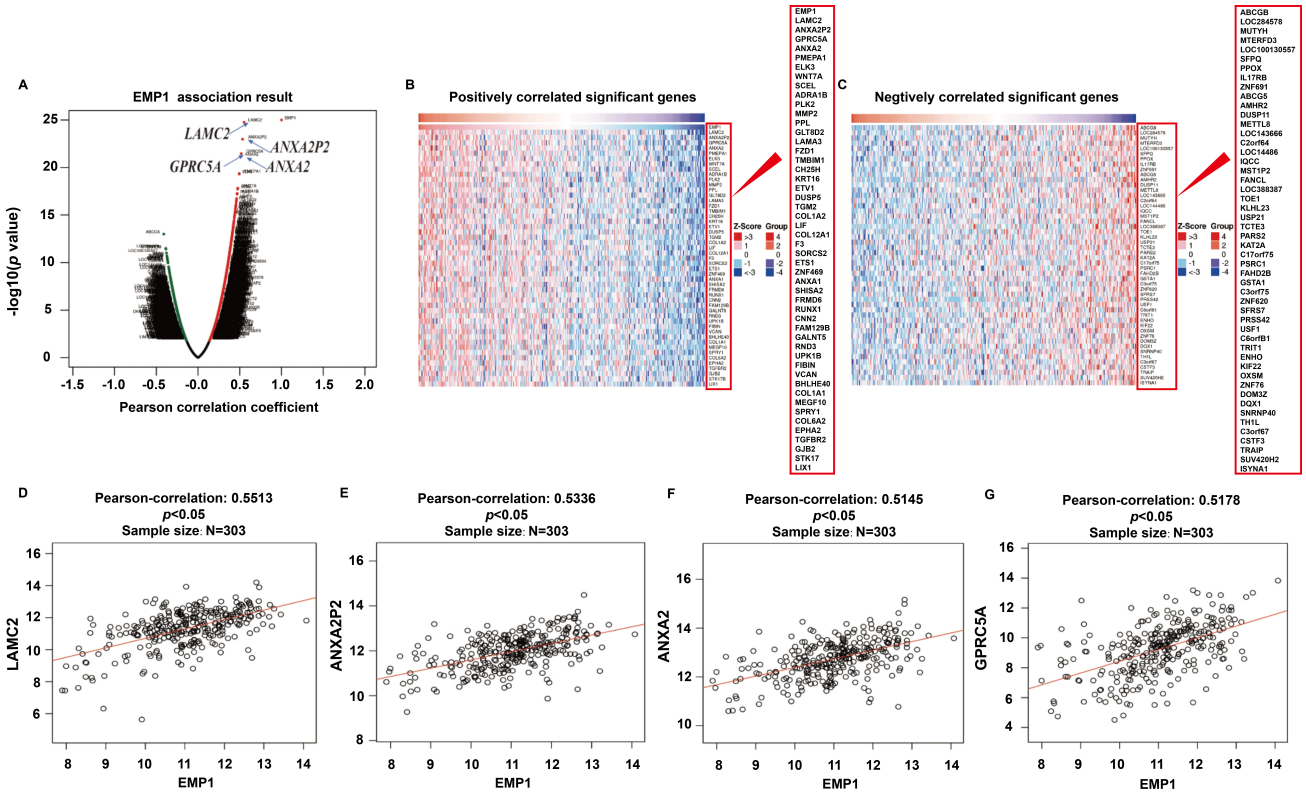

Fig. 5. Differential expression of EMP1-related genes in ovarian cancer patients (LinkedOmics). (A) Correlations between EMP1 and differentially expressed genes in ovarian cancer patients were analysed by Pearson tests. (B,C) Genes positively and negatively correlated with EMP1 in ovarian cancer are shown in heatmaps (TOP 50). Positively correlated genes are shown in red and negatively correlated genes in blue. (D–G) Pearson correlations of EMP1 expression with the expression of *LAMC2* (D), *ANXA2P2* (E), *ANXA2* (F) and *GPRC5A* (G).

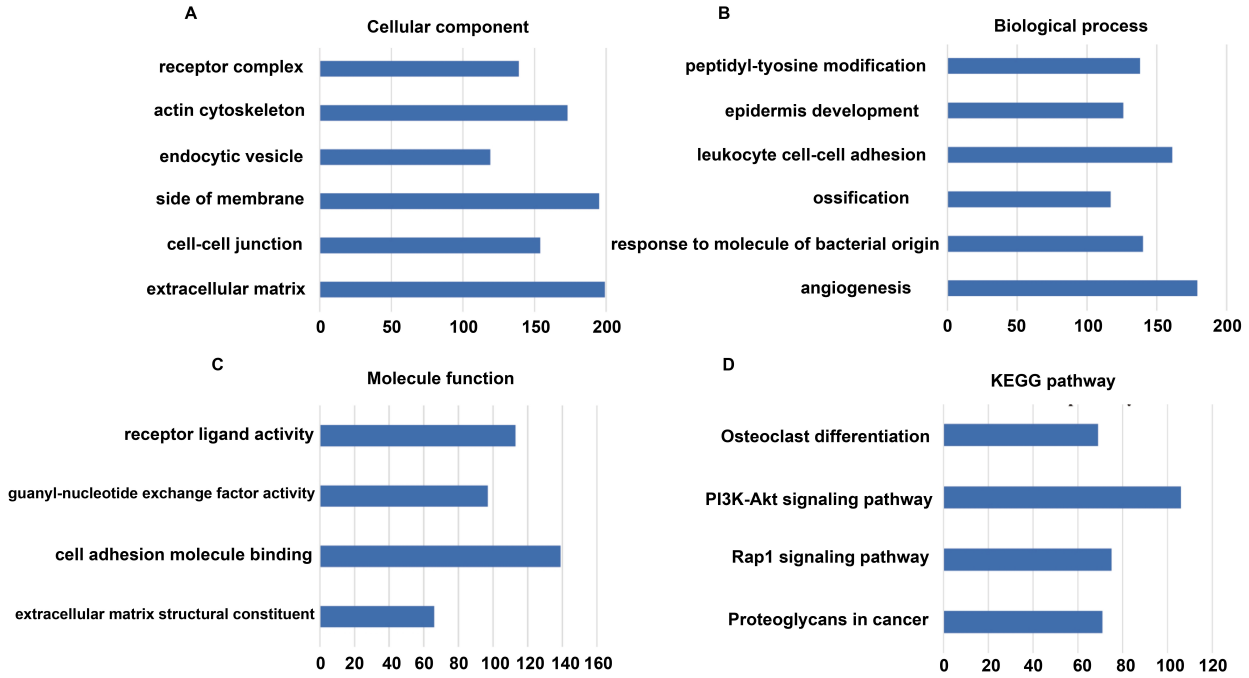

Fig. 6. GO annotations and KEGG pathways of genes co-expressed with EMP1 in ovarian cancer. (A–C) GO annotations include cellular components, biological processes and molecular functions. (D) KEGG pathway analysis enrichment.

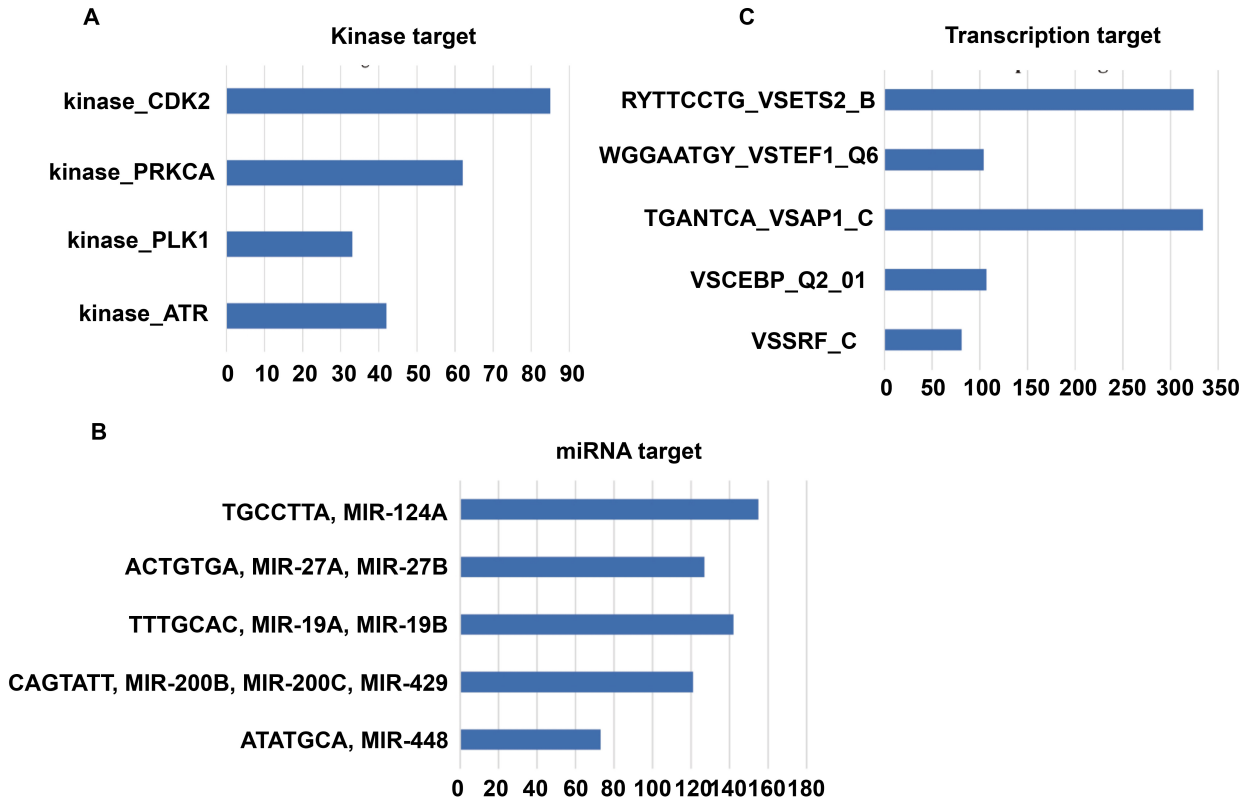

Fig. 7. The kinase, miRNA and transcription factor target networks of genes co-expressed with EMP1 in ovarian cancer. (A) Kinase target. (B) miRNA target. (C) Transcription factor target.

3.6 The Kinase, Mirna and Transcription Factor Target Networks of Genes Co-Expressed with EMP1 in Ovarian Cancer

We used GSEA to investigate the targets of genes whose expression correlated with that of EMP1 in ovarian cancer. The kinase target networks included ataxia telangiectasia-mutated and Rad3-related (ATR), polo-like kinase 1 (PLK1), protein kinase C alpha (PRKCA1), and cyclin dependent kinase 2 (CDK2) (Fig. 7A). The miRNA targets included (ATATGCA) miR-448, (CAGTATT) miR-200B/C, miR-429, (TTTGCAC) miR-19A/B, (ACTGTGA) miR-27A/B and (TGCCTTA) miR-124A (Fig. 7B). The transcription factor target networks were related to SRF_C, CEBP_Q2_01, AP1_C, TEF1_Q6 and ETS2_B (Fig. 7C).

4. Discussion

Ovarian cancer patients are rarely diagnosed at an early stage due to the lack of an effective diagnostic method. New biomarkers for ovarian cancer are therefore urgently needed. Members of the EMP family have been widely implicated in the regulation of cancer progression. EMP2 was reported to function as an oncogene in gynaecological tumours such as ovarian and endometrial cancers, but as a tumour suppressor gene in urothelial cancer [12]. EMP3 was also reported to be a tumour suppressor gene in several solid tumour types [13]. Recently, EMP1 was suggested to be a promising therapeutic target since it appears to play a role in tumour growth [14]. The significance of EMP1 seems to vary in different tumour types, and there is still very little known about its role in ovarian cancer. To further investigate the potential functions of EMP1 and its regulatory networks in ovarian cancer, we performed a bioinformatics analysis using data from publicly available databases. Our results should provide a theoretical basis for future studies of ovarian cancer.

Over-expression of EMP1 was the most common type of alteration detected in ovarian cancer. The levels of EMP1 mRNA and CNVs were significantly higher in ovarian cancer than in normal ovarian tissue, which is consistent with previous results obtained using RNA sequencing technology [15]. We propose that alterations in EMP1 expression in ovarian cancer might lead to changes in chromosome structure, which then promote tumour progression. In the present study we found that high mRNA expression of EMP1 was significantly associated with advanced stage of ovarian cancer, as well as correlating with poor OS of these patients. EMP1 could therefore be useful for the clinical assessment of prognosis in ovarian cancer patients and as a diagnostic marker.

We also investigated the function of EMP1 in ovarian cancer and how it may affect tumour progression. Genes that are co-expressed with EMP1 were identified using the LinkFinder module of the LinkedOmics database and

then subjected to functional and pathway enrichment analyses by GSEA. EMP1 participates primarily in the biological processes of epidermis development, cell-cell adhesion, peptidyl-tyrosine modification and angiogenesis. This is consistent with the fact that EMP1 functions mainly at the cell junction. According to KEGG analysis, EMP1 is involved in several signalling pathways including the PI3K-Akt and Rap1 pathways. These functions could ultimately affect tumourigenesis and progression of ovarian cancer. Notably, PI3K-Akt is a key pathway in cancer development and is an important target of cancer therapy. This suggests that PI3K-Akt signalling could be a promising mechanism through which EMP1 could regulate the progression of ovarian cancer. Although these mechanisms have rarely been studied in ovarian cancer, the activation of PI3K/Akt/mTOR promoted by EMP1 has been reported as the driving force for glioma progression [6]. Deficiency of EMP1 markedly inhibited tumour growth and increased OS in an experimental animal model. EMP1 was also shown to play an inhibitory role in prostate cancer cells by regulating the protein expression of caspase-9 and vascular endothelial growth factor C (VEGFC) [10]. Therefore, we conclude that EMP1 may regulate the development and progression of ovarian cancer through different signalling pathways, suggesting it may be a promising target for ovarian cancer therapy.

We further analysed the molecular mechanisms that regulate the expression and activity of EMP1. Networks of kinases, miRNAs and transcription factor targets were identified using GSEA. We found that EMP1 expression was associated with that of ATR, PLK1, PRKCA1, and CDK2. These have been reported to regulate genomic stability, cell adhesion, cell transformation and the cell cycle checkpoint. Several miRNAs normally involved in the post-transcriptional regulation of genes were shown to potentially interact with EMP1. Amongst these, the miR-200 and miR-19 families were identified as oncogenic miRNAs [16,17]. miR-200 has a vital role in regulating tumour cell growth by inhibiting the tumour suppressor *Ras Association Domain Family Member 2* (*RASSF2*) [18]. miR-448 has been associated with many human cancer types, and its over-expression has been proposed to inhibit tumour cell growth and metastasis by down regulating *insulin receptor substrate 2* (*IRS2*) in lung cancer [19]. miR-27a is reported to be a promising biomarker and drug target for clinical application [20]. miR-124a can ameliorate inflammation in fibroblast-like synoviocytes *rheumatoid arthritis* (*RAFLS*) by targeting the PIK3/NF-κB pathway [21]. However, few studies have reported on the association between these miRNAs and EMP1 in ovarian cancer. Our results indicate that dysfunction of these miRNAs could lead to the overexpression of EMP1 in ovarian cancer. In this case, the targeting of such miRNAs leading to alteration of EMP1 expression could be a useful treatment strategy. The transcription factor target networks for EMP1 were associated with *SRF_C*, *CEBP_Q2_01*, *AP1_C*, *TEF1_Q6* and *ETS2_B*. Most of these factors regulate transcription by interacting with different co-factors and participating in cell growth and differentiation, cell cycle regulation and apoptosis [22,23]. Therefore, our results suggest that targeting of these transcription factors may influence tumour cell growth control via the regulation of EMP1 expression.

In summary, our results showed that EMP1 mRNA expression and CNVs were significantly elevated in ovarian cancer and were associated with advanced tumour stage. High expression of EMP1 mRNA also correlated with poor OS in ovarian cancer patients. EMP1 expression is regulated by various genes and miRNAs and participates in ovarian cancer progression through several signalling pathways.

5. Conclusions

The present results confirm the expression of EMP1 in ovarian cancer and identify the regulatory networks, thus providing a theoretical basis for further studies on its function in this tumour type. EMP1 could potentially serve as a diagnostic and prognostic biomarker in ovarian cancer patients. However, owing to the limited sample size and range of experimental work, further validation studies are needed to confirm the role of EMP1 in ovarian cancer.

Author Contributions

YYL designed the study, YJX and ZH performed the statistical analysis and wrote the manuscript. ZWC analyzed the data. YYL reviewed relevant literature and revised the manuscript. All authors read and approved the final version.

Ethics Approval and Consent to Participate

The study was approved by the Hospital Ethics Committee of Fujian Provincial Maternity and Children's Health Hospital, affiliated hospital of Fujian Medical University (No FPMC2021KLRD641).

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Conflict of Interest

The author declares no conflicts of interests.

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