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ORIGINAL RESEARCH

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ERG expression as a potential biomarker for endometrial carcinoma prognosis

Jianglei Ma[1,2,†], Huijie Zhang[3,†], Chenfang Zhang[4], Xueyan Luo[5], Fuhui Duan[5], Yuanyuan Zhang[1,*], Guangming Wang[1,5,*]

[1]School of Clinical Medicine, Dali University, 671000 Dali, Yunnan, China
[2]Department of Infectious Diseases, Yantai Qishan Hospital, 264000 Yantai, Shandong, China
[3]Department of Obstetrics, The Affiliated Yantai Yuhuangding Hospital of Qingdao University, 264000 Yantai, Shandong, China
[4]Department of Neurology, The Affiliated Yantai Yuhuangding Hospital of Qingdao University, 264000 Yantai, Shandong, China
[5]Genetic Testing Center, The First Affiliated Hospital of Dali University, 671000 Dali, Yunnan, China

***Correspondence**
zhyy@dali.edu.cn
(Yuanyuan Zhang);
wgm1991@dali.edu.cn
(Guangming Wang)

† These authors contributed equally.

Abstract

Background: The protein encoded by the erythroblast transformation-specific-related gene (*ERG*) plays an important role in the occurrence and development of various human cancers. However, its biological importance in endometrial carcinoma (EC) remains unclear. Here, we aimed to assess *ERG* expression in EC and determine its prognostic value via bioinformatic analyses. **Methods**: Data from public databases were used to evaluate *ERG* expression in patients with pan-cancer or EC and elucidate its influence on tumour immune cell infiltration. *ERG* mutation types and clinical characteristics of patients were analysed. The Kaplan-Meier method was employed to evaluate the EC overall survival rate and its correlation with *ERG* expression levels. Moreover, receiver operating characteristic curves were generated to assess the specificity and accuracy of *ERG* expression in diagnosing EC. Finally, pathway enrichment analyses were performed to elucidate gene function. **Results**: *ERG* is differentially expressed in various cancers and is downregulated in EC. Moreover, copy number variation is the most common *ERG* mutation type in EC. Low *ERG* expression correlates with the clinical stage of cancer ($p = 0.011$), histological type ($p = 1.6734 \times 10^{-5}$), histological grade ($p = 2.2165 \times 10^{-8}$), and degree of invasion ($p = 0.019$). It is also associated with a relatively poor prognosis. Low *ERG* expression is also associated with immune cell infiltration and several pathways relevant to the development and progression of EC. In particular, *ERG* contributes to EC occurrence and development by regulating various transcriptional processes and carcinogenic signalling pathways. Furthermore, *ERG* expression is related to immune invasion and ET diagnosis and prognosis. Hence, *ERG* expression can be used as a prognostic biomarker for EC. **Conclusions**: Our findings can serve as a reference for identifying targets of molecular biological therapy and immunotherapy for EC.

Keywords

Cellular immune response; Gene targeting; Prognosis; Transcriptional regulator

1. Introduction

Endometrial carcinoma (EC) is the sixth most common cancer among women and the most common malignant tumour of the female reproductive tract, with 417,000 new cases reported worldwide in 2020 [1]. The lifetime risk of EC in women is approximately 3%, and the median age at diagnosis is 61 years [2]. Although current treatments have improved clinical outcomes for patients with EC, the associated prognosis remains poor as evidenced by the high incidence rate (21.9–86.6/100,000) and low patient survival rate. In other words, patients diagnosed with International Federation of Gynecology and Obstetrics stage III or IV EC have 5-year overall survival rates of 57%–65% and 20%–26%, respectively [3, 4]. Hence, more effective biomarkers and new targets for the treatment of EC are needed.

The protein encoded by the erythroblast transformation-specific-related gene (*ERG*) has important roles in cell proliferation, angiogenesis, apoptosis and vascular cell remodelling [5]. Meanwhile, genome rearrangements and chromosome translocations cause overexpression and increased ERG activity in several cancers, including sarcomas, acute myeloid leukaemia, and prostate cancer [6]. In fact, genomic rearrangement in *ERG* occurs in approximately 50% of patients with primary prostate cancer [7]. Upregulated *ERG* expression is associated with low survival rates among patients with prostate [8] and central nervous system tumours, including glioblastoma and haemangioblastoma [9]. In contrast, downregulated *ERG* expression is associated with a short survival period in renal cancer [10]. However, its role in EC progression and prognosis remains unclear.

Therefore, in this study, we performed bioinformatic analyses of *ERG* expression in EC to evaluate its influence on tumour immune cell infiltration, and its prognostic and diag-

nostic value. Furthermore, we aimed to characterise the most common *ERG* mutation types associated with EC and identify the signalling pathways related to tumour development.

2. Materials and methods

2.1 Patient dataset and *ERG* expression analysis

ERG expression levels in different cancer types were determined based on mRNA expression data from The Cancer Genome Atlas (TCGA) database, using TIMER2.0 (http://timer.cistrome.org/) [11]. Gene Expression Profiling Interactive Analysis (GEPIA) (http://gepia.cancer-pku.cn/) was used to analyse *ERG* expression in EC, RNA-sequencing data for 174 EC tissues and 91 normal adjacent tissues from TCGA were analysed [12]. The Human Protein Atlas (http://www.proteinatlas.org/) was employed to verify immunohistochemical staining results for ERG protein abundance in EC based on average optical density (AOD) values [13]. AOD refers to the concentration of reactants per unit area and is the sum of the optical density values for each point in the image divided by the target distribution area. The data and information used in this study were obtained from public databases.

2.2 *ERG* mutation type and frequency analysis

Data obtained from the cBioPortal database (http://cbioportal.org) were used to analyse different types and frequencies of *ERG* alterations in EC, including mutations, deletions and copy number variations [14].

2.3 Analysis of clinical characteristics

After arranging the TCGA data, including those on clinical and histological indicators, patients were divided into high- and low-expression groups according to the median *ERG* expression level. Correlations between *ERG* expression and clinical and histological indicators were analysed using chi-square tests.

2.4 Survival and receiver operating characteristic curve analysis

The Kaplan-Meier (KM) plotter (http://kmplot.com/analysis/) was used to predict the correlations between *ERG* expression and overall survival (OS) in patients with EC [15]. The KM plotter software was used to determine the survival period of patients stratified according to clinical characteristics and to calculate the hazard ratio (HR), log-rank *p*-value, and associated 95% confidence interval. We used the pROC package in R (v4.1.0; The R Project for Statistical Computing, Vienna, Austria) to plot a receiver operating characteristic (ROC) curve from RNA-sequencing data of patients with EC and healthy individuals. The area under the curve (AUC) was calculated to assess the sensitivity and specificity of *ERG* expression in diagnosing EC.

2.5 Analysis of immune cell infiltration

We used Gene Set Cancer Analysis (GSCA; http://bioinfo.life.hust.edu.cn/GSCA/#/), an online tool for immune genomics analysis based on the ImmuCellAI algorithm [16], to analyse the correlation between *ERG* expression and tumour infiltration by 24 types of immune cells in EC [17]. It was also used to determine the correlation coefficient and false discovery rate (FDR)-adjusted *p*-value (p_{FDR}).

2.6 Gene ontology term, biological process, and Kyoto Encyclopedia of genes and genomes pathway enrichment analyses

The LinkedOmics portal (http://www.linkedomics.org/) was used to identify *ERG*-related genes in EC [18]. The Pearson method was used for correlation analysis, with p_{FDR} of < 0.01 as the selection criterion. Gene Ontology (GO) term, biological process (BP), and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed using the DAVID v6.8 bioinformatics tool (https://david.ncifcrf.gov) [19]. The top 10 enriched pathways ($p < 0.01$) were selected and visualised in dot plots.

2.7 Prediction of sensitivity to therapeutic drugs

Half-maximal inhibitory concentration (IC_{50}) of 138 therapeutic drugs [20] (including chemotherapeutic drugs and targeted inhibitors, with efficacy information) in EC was calculated using the pRRophetic package in R.

2.8 Statistical analysis

Data are presented as mean $\pm$ standard deviation and were statistically evaluated using SPSS (v26.0; SPSS Inc., Chicago, IL, USA). Statistical analyses were performed using R software v4.1.0 (64-bit). The chi-square test was used to analyse intergroup differences. The KM plotter and a Cox regression model were used for survival analysis. Pearson's correlation analysis assessed correlations between *ERG* expression and tumour-infiltrating immune cells. Results with a two-sided *p*-value of < 0.05 were considered statistically significant.

3. Results

3.1 *ERG* expression in EC

TIMER2.0 analysis of pan-cancer *ERG* expression indicated that *ERG* is differentially expressed in various human tumours, including EC (Fig. 1A). GEPIA showed that *ERG* expression was lower in EC tissues than in normal adjacent tissues (Fig. 1B). Similarly, immunohistochemical staining data from the Human Protein Atlas showed that ERG protein expression was lower in EC (AOD = 0.150) than in normal adjacent tissues (AOD = 0.282; Fig. 1C). These results suggest that low *ERG* expression is associated with EC.

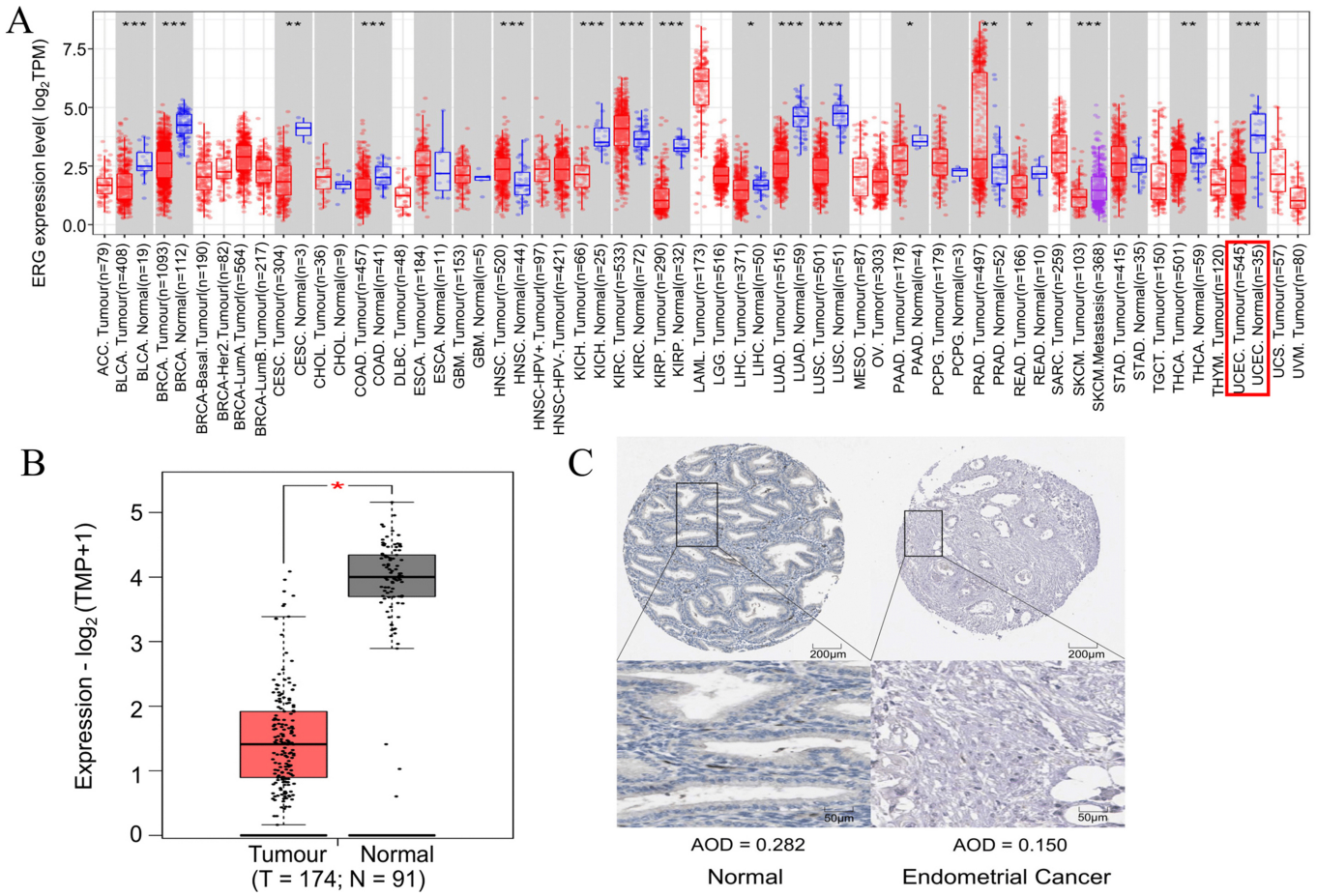

FIGURE 1. ***ERG* expression in various cancers and endometrial carcinoma (EC).** (A) *ERG* expression in various carcinomas determined using The Cancer Genome Atlas data and TIMER2.0. (B) *ERG* expression in EC determined using GEPIA. Tumour and normal tissue are indicated by red and grey, respectively. (C) Immunohistochemical staining results, retrieved from the Human Protein Atlas, for erythroblast transformation-specific-related gene (*ERG*) protein expression in EC and normal adjacent tissues. The rectangles are zoomed in portions of normal and endometrial cancer tissue. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. AOD: average optical density.

3.2 Identification of *ERG* mutations in EC

We used the cBioPortal database to determine the frequency of *ERG–TMPRSS2* fusions and other *ERG* alterations in EC. The analysis showed that 3% of all EC samples (n = 1954) had genetic alterations, and copy number variations (amplifications) as well as splicing, truncating, and missense mutations were the most common mutation types (Fig. 2); gene fusions were not detected in the EC samples.

3.3 Correlations between *ERG* expression and clinical features in EC

The chi-square test was performed to determine the clinical features of patients with EC associated with *ERG* expression. There was a significant difference between low and high *ERG* expression in terms of clinical stage ($p = 0.011$), histological type ($p < 0.001$), histological grade ($p < 0.001$), tumour invasion degree ($p = 0.019$), and menopause status ($p = 0.008$). The endometrioid type was identified as the main histological type (Table 1). No significant differences were observed between the tumour *ERG* expression level with age and body mass index (BMI). These results indicate that low *ERG* expression may be related to EC invasion and poor patient prognosis.

3.4 Prognostic and diagnostic significance of *ERG* in EC

Patients were divided into high- and low-expression groups according to the median tumour *ERG* expression level, and the KM plotter was used to assess survival rate. The OS period was shorter (indicative of poor prognosis) in the low-expression group than in the high-expression group (HR = 0.60, $p = 0.015$; Fig. 3A). Low *ERG* expression correlated with poor survival metrics in patients with BMI >30 kg/m^2 (HR = 0.51, $p = 0.023$; Fig. 3B), and tumour invasion <50% (HR = 0.41, $p = 0.043$; Fig. 3C), or age ≤60 years (HR = 0.40, $p = 0.043$; Fig. 3D). The ROC curve had an AUC value of 0.964 (0.938–0.990; Fig. 3E), which could be used to distinguish healthy individuals from patients with EC. There was no significant difference between *ERG* expression and prognosis in clinical staging, histological type, histological grade, and menopause status (**Supplementary Figs. 1–12**). The ROC curve analysis results also indicated that *ERG* expression has diagnostic value in EC.

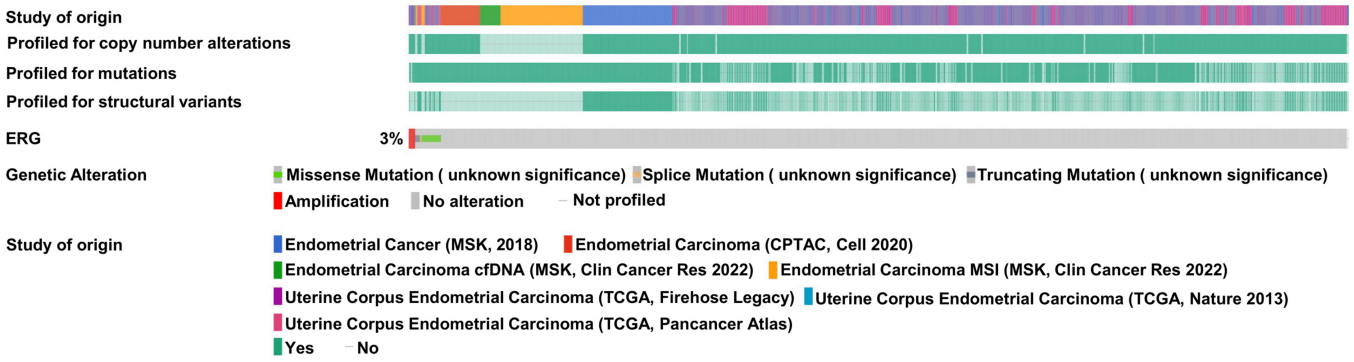

FIGURE 2. Frequency of *ERG* mutations in patients with endometrial carcinoma determined using the cBioPortal database. The different colours of the modules represent the types of mutations and the research related to ERG in endometrial cancer. *ERG*: erythroblast transformation-specific-related gene; TCGA: The Cancer Genome Atlas.

TABLE 1. Correlation between *ERG* expression and clinical characteristics of patients with endometrial carcinoma.

Characteristic	Low *ERG* expression	High *ERG* expression	*p*-value	χ^2
n	277	277		
Clinical stage, n (%)				
Stage I	154 (27.8%)	189 (34.1%)	0.011	11.128
Stage II	28 (5.1%)	24 (4.3%)		
Stage III	75 (13.5%)	55 (9.9%)		
Stage IV	20 (3.6%)	9 (1.6%)		
Age, n (%)				
≤60 yr	101 (18.3%)	106 (19.2%)	0.684	0.165
>60 yr	174 (31.6%)	170 (30.9%)		
BMI, n (%)				
≤30 kg/m^2	109 (20.9%)	103 (19.8%)	0.280	1.166
>30 kg/m^2	144 (27.6%)	165 (31.7%)		
Histological type, n (%)				
Endometrioid	182 (32.9%)	230 (41.5%)	<0.001	21.996
Mixed	17 (3.1%)	7 (1.3%)		
Serous	78 (14.1%)	40 (7.2%)		
Histologic grade, n (%)				
G1	29 (5.3%)	70 (12.9%)	<0.001	35.249
G2	47 (8.7%)	74 (13.6%)		
G3	193 (35.5%)	130 (23.9%)		
Tumour invasion, n (%)				
<50	114 (23.9%)	147 (30.9%)	0.019	5.444
≥50	117 (24.6%)	98 (20.6%)		
Menopause status, n (%)				
Pre	18 (3.6%)	17 (3.4%)	0.008	9.644
Peri	2 (0.4%)	15 (3.0%)		
Post	227 (44.8%)	228 (45.0%)		

G: histopathological cancer grading (G1: well differentiated; G2: moderately differentiated; G3: poorly differentiated); ERG: erythroblast transformation-specific related gene; BMI: body mass index.

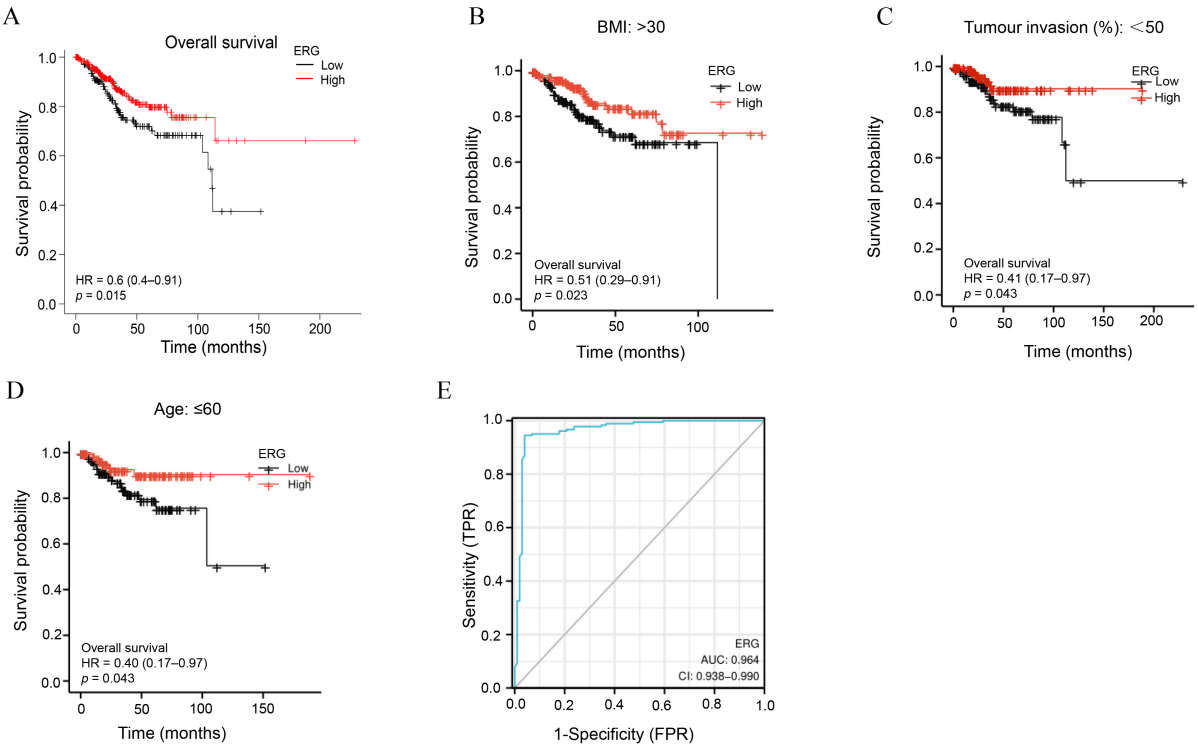

FIGURE 3. Prognostic and diagnostic values of *ERG* expression in patients with endometrial carcinoma (EC). (A–D) Kaplan-Meier plotter analysis showing the prognostic relationship between *ERG* expression in patients with EC and (A) overall survival, (B) body mass index >30 kg/m^2, (C) tumour invasion <50%, or (D) age ≤60 years. (E) Receiver operating characteristic curve showing the diagnostic value of *ERG* expression. HR: hazard ratio; *ERG*: erythroblast transformation-specific related gene; BMI: body mass index.

3.5 Correlation between *ERG* expression and tumour-infiltrating immune Cells in EC

We used the GSCA database to explore whether *ERG* expression correlates with tumour immune invasion and immunotherapy response in EC. Tumour *ERG* expression correlated positively with the presence of cluster of differentiation 4 $(CD4)^+$ T cells ($r = 0.067$, $p_{FDR} < 0.001$), central memory T cells ($r = 0.38$, $p_{FDR} < 0.001$), T follicular helper (Tfh) cells ($r = 0.33$, $p_{FDR} < 0.001$), mucosal-associated invariant T (MAIT) cells ($r = 0.27$, $p_{FDR} = 0.003$), natural killer (NK) cells ($r = 0.21$, $p_{FDR} = 0.011$), $CD8^+$ naive cells ($r = 0.20$, $p_{FDR} = 0.024$), and T helper 2 (Th2) cells ($r = 0.19$, $p_{FDR} = 0.028$). Meanwhile, negative correlations were observed with monocyte ($r = -0.38$, $p_{FDR} < 0.001$), dendritic cell (DC) ($r = -0.36$, $p_{FDR} < 0.001$), macrophage ($r = -0.35$, $p_{FDR} < 0.001$), effector memory T cell ($r = -0.32$, $p_{FDR} < 0.001$), exhausted T cell ($r = -0.28$, $p_{FDR} < 0.001$), neutrophil ($r = -0.23$, $p_{FDR} = 0.007$), and regulatory T (Treg) cell ($r = -0.20$, $p_{FDR} = 0.016$) counts and infiltration score ($r = -0.17$, $p_{FDR} = 0.048$) (Fig. 4, **Supplementary Figs. 13–27**). These results indicate that *ERG* expression may be associated with the immune invasion observed in EC.

3.6 Identification of potential pathways of *ERG* involvement in EC

To analyse the potential pathways related to *ERG* in EC, genes related to *ERG* were identified using the LinkedOmics portal. Using $p_{FDR} < 0.01$ as a selection criterion, we identified 4962 *ERG*-related genes (Fig. 5A), which were imported into the DAVID bioinformatics tool, and GO term and KEGG pathway enrichment analyses were conducted. The main enriched BPs included regulation of transcription (DNA-templated), regulation of transcription from RNA polymerase II promoters, cilium assembly, heart development, regulation of catalytic activity, cell division, protein photoluminescence, and positive regulation of endothelial cell proliferation (Fig. 5B). The main enriched KEGG pathways included Huntington's disease, proteasome, spinocerebellar ataxia, and calcium signalling pathways as well as pathways associated with cancer, neurodegeneration-multiple diseases, cortisol synthesis and secretion, Parkinson's disease, renin secretion, and gap junctions (Fig. 5C).

3.7 Prediction of drug sensitivity

The IC_{50} value is a measure of drug efficacy; a low IC_{50} value indicates that the drug is effective at low concentrations. Additionally, the IC_{50} value can be used to describe the drug resistance of cancer cells. The pRRophetic analysis of *ERG* expression in EC and the IC_{50} values of various therapeutic drugs showed that 24 drugs, including a C-Jun N-terminal kinase inhibitor (AS601245) and checkpoint kinase inhibitor (AZD7762), are expected to be significantly more effective in patients with low *ERG* expression than in patients with a high expression (Fig. 6). The prediction of drug sensitivity can provide clinical guidance for EC treatment.

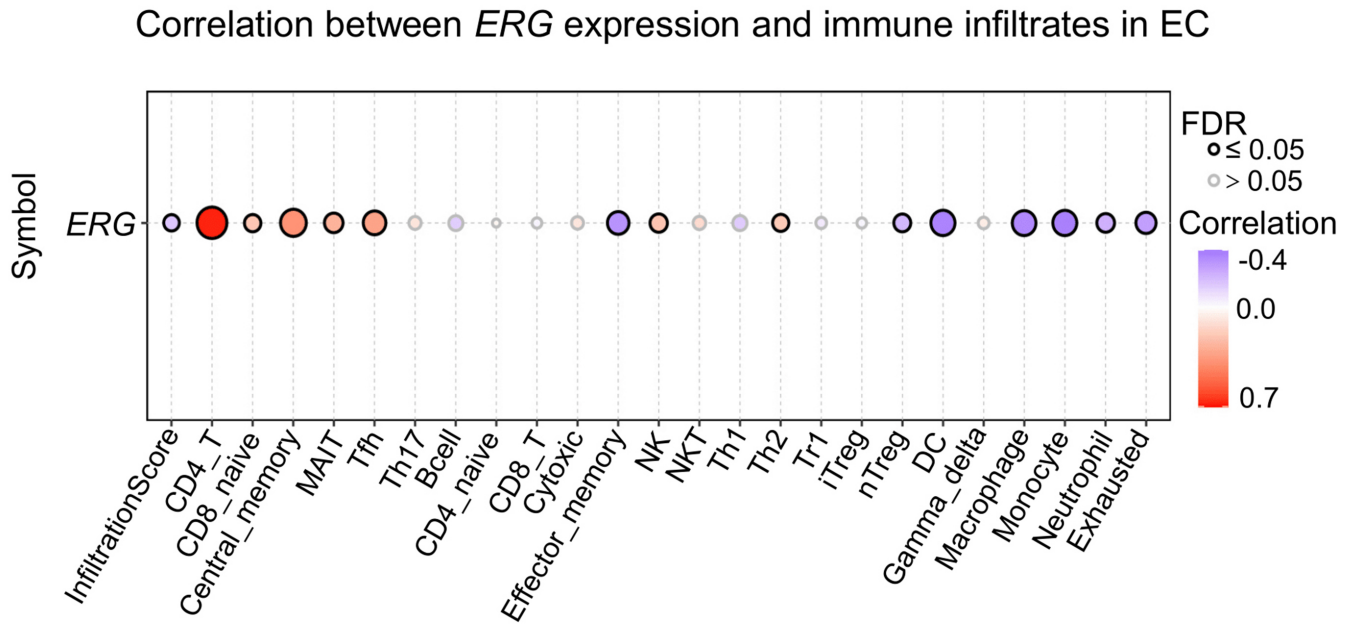

FIGURE 4. Correlation between tumour *ERG* expression and tumour immune cell infiltration. Solid red circles, significant positive correlation; solid blue circles, significant negative correlation; the circle size corresponds to the correlation strength. *ERG*: erythroblast transformation-specific related gene; FDR: false discovery rate; CD: cluster of differentiation; MAIT: mucosal-associated invariant T; NK: natural killer; DC: dendritic cell.

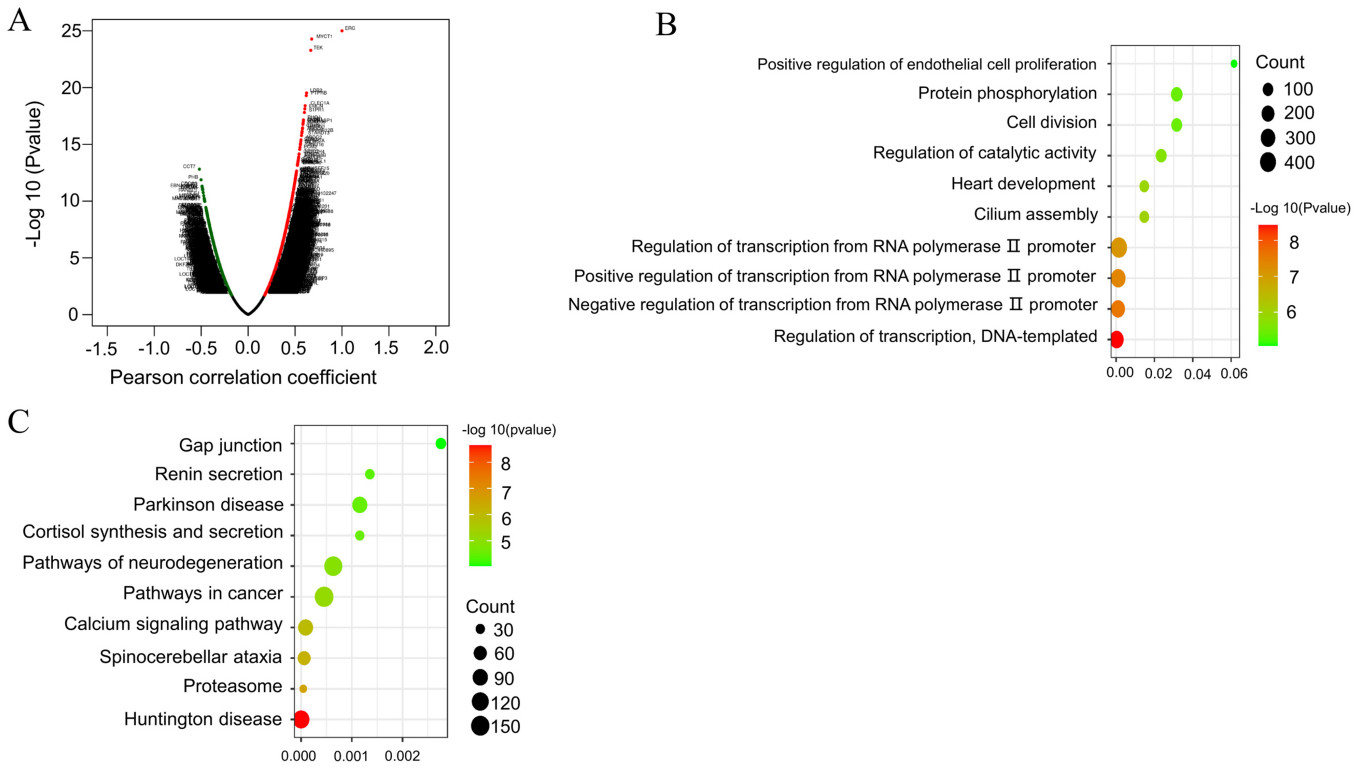

FIGURE 5. Gene Ontology (GO) term, biological process (BP), and Kyoto Encyclopedia of Genes and Genome (KEGG) pathway enrichment analyses. (A) Genes related to *ERG*. Positively associated genes are indicated in red and negatively associated genes in green. (B) Dot plot of the top 10 most significantly enriched GO BPs obtained using the DAVID v6.8 bioinformatics tool. Dot size indicates the number of genes enriched in the BP and colour indicates the *p*-value. (C) Dot plot of the top 10 most significantly enriched KEGG pathways. Dot size indicates the number of genes enriched in the BP and dot colour indicates the *p*-value.

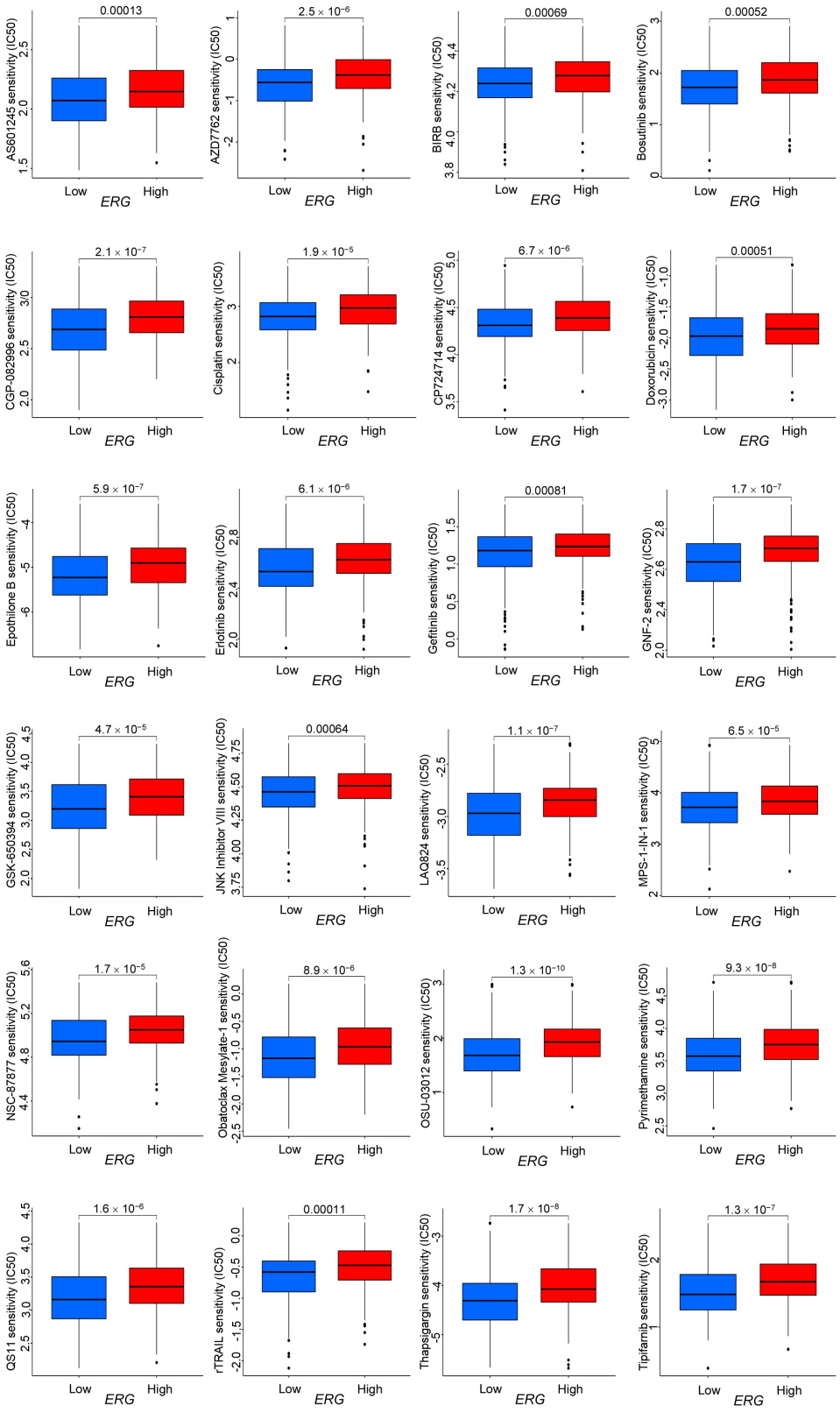

FIGURE 6. IC_{50} values of 24 drugs in the high- and low-*ERG* expression groups. High expression and low expression are indicated by red and blue, respectively ($p < 0.001$). *ERG*: erythroblast transformation-specific related gene.

4. Discussion

ERG is essential for postnatal vascular development and is expressed throughout the life cycle of endothelial cells. Moreover, it is a regulator that maintains vascular stability, growth, and participates in tumour angiogenesis and expansion [21].

The results of this study indicate that *ERG* is aberrantly expressed in numerous cancer types, suggesting it plays a central role in various human cancers. The ROC curve analysis demonstrated that *ERG* expression had a diagnostic value for EC. Additionally, *ERG* expression was related to tumour immune invasion and participates in processes and pathways associated with EC development and progression. The potential prognostic value of *ERG* expression was assessed in EC patients, and it was found that *ERG* expression was downregulated in those patients; the GEPIA database was used to verified and confirmed its universal downregulation in EC. Therefore, low *ERG* tumour expression was associated with poor prognosis. A previous study showed that ectopic *ERG* expression may upregulate hexokinase 2 and phosphoglycerate kinase 1, induce glycolysis, and promote the progression of cervical cancer [22]. However, the precise role of ERG in terms of the occurrence and development of EC had not been previously elucidated. In prostate cancer, *ERG–TMPRSS2* fusion is important in tumour development [23]. Meanwhile, although we identified copy number variations as the most common *ERG* alterations in EC, gene fusion was absent. Moreover, while the risk of EC reportedly increases with age, BMI, and menopausal status (higher risk in postmenopausal women) [3], our results revealed that *ERG* expression in EC had no significant correlation with age or BMI.

A study on the significance of *ERG* expression in renal cell carcinoma prognosis showed that the downregulation or deletion of *ERG* positively correlates with a poor prognosis [10]. Similarly, our results indicated that downregulated *ERG* expression is associated with a worse prognosis in EC. Moreover, in a previous study where EC prognosis was determined by constructing *ERG* signals, and low OS and progression-free survival rates were observed in the high-risk patient group [24]. Several factors, including tumour immune cell infiltration, affect EC prognosis, and tumour-infiltrating immune cells can form an ecosystem within the tumour microenvironment that regulates tumour progression and has potential prognostic value [25]. We found that *ERG* expression in EC is associated with immune cell infiltration. According to the specificity of major histocompatibility complex class I and II molecules, T cells are classified into $CD4^+$ and $CD8^+$ T cells, with $CD4^+$ T cells comprising Th1, Th2, Tfh and Treg cells [26]. Upon encountering antigens, naive $CD8^+$ and $CD4^+$ T cells proliferate and differentiate into various types of effector cells to fight infections or tumours. A portion of these cells survive long-term and become memory T cells. Furthermore, MAIT cells, a subset of T cells that have regulatory properties similar to NK cells in autoimmune models and diseases, can potentially kill cancer cells [27]. Our tumour immune cell infiltration analysis revealed that tumour *ERG* expression correlated positively with $CD4^+$ T, naive $CD8^+$, MAIT and NK cell infiltration and negatively with DC, monocyte, macrophage, and Treg cell infiltration. DCs are derived from macrophages or DC progenitor cells found in bone marrow and are part of the heterogeneous family of myeloid antigen-presenting cells that comprise various subsets [28, 29]. Myeloid cells have immunosuppressive characteristics and can promote the development of tumours [30]. Hence, the presence of monocytes, tumour-associated macrophages, and Treg cells indicates invasive progression and poor prognosis [31–33]. Our results suggest that tumour *ERG* expression regulates immune infiltration, which may affect EC prognosis, suggesting that immunotherapy may be effective for EC depending on the *ERG* expression status.

ERG is a specific vascular endothelial cell marker involved in regulating Wnt/β-catenin signalling, which affects the expression of vascular endothelial-cadherin—an adhesion molecule involved in endothelial cell–cell connections—and ultimately modulates vascular integrity [21]. *In vivo*, blood vessels formed in response to vascular endothelial growth factor activity are highly permeable and unstable. ERG promotes the stability of vascular endothelial growth factor-induced blood vessels *in vivo* and contributes to angiogenesis [34]. In contrast, the absence of ERG leads to angiogenesis defects in the retina and tumours by reducing blood vessel stability [21]. Meanwhile, ERG promotes tumorigenesis when expressed *in vitro*, in sharp contrast to its effect *in vivo* [35]. Our GO term enrichment analysis revealed that ERG participates in the transcriptional regulation of endothelial cell proliferation in EC. Similarly, a previous study paired thousands of RNA polymerase II-related enhancers with their target genes in prostate cancer, revealing multiple RNA polymerase II network hubs for receiving, processing, and transmitting regulatory signals. Abnormal regulation of these hubs in cancer can lead to resistance to systemic chemotherapy and molecular-targeted therapy [36]. This can guide the formulation of intervention strategies to prevent or delay cancer onset. We also found a significant correlation between *ERG* expression and RNA polymerase II transcriptional regulation in EC. We infer that the development and progression of EC and prostate cancer have similar mechanisms. Furthermore, the KEGG pathway enrichment analysis indicated that ERG is involved in calcium signalling, which plays a central role in cancer development [37].

Our study has limitation as well. This is a prospective study, the results are based solely on bioinformatic analyses. Therefore, numerous prospective clinical investigations are needed to validate the predictive value of ERG on the prognostic of EC.

5. Conclusions

ERG expression is downregulated in EC and might interfere with tumour immune cell infiltration and influence patient survival. In particular, low *ERG* expression in tumours is associated with relatively poor EC prognosis. Thus, *ERG* expression may serve as a prognostic biomarker and immunotherapy target in EC.

ABBREVIATIONS

AOD, average optical density; AUC, area under the curve; BMI, body mass index; BP, biological process; CD4, cluster of differentiation 4; DC, dendritic cell; EC, endometrial carcinoma; ERG, erythroblast transformation-specific-related gene protein; FDR, false discovery rate; GEPIA, Gene Expression Profiling Interactive Analysis; GO, Gene Ontology; GSCA, Gene Set Cancer Analysis; HR, hazard ratio; IC_{50}, half-maximal inhibitory concentration; KEGG, Kyoto Encyclopedia of Genes and Genomes; KM, Kaplan-Meier; MAIT, mucosal-associated invariant T; NK, natural killer; OS, overall survival; ROC, receiver operating characteristic; TCGA, The Cancer Genome Atlas; Tfh, T follicular helper; Th2, T helper 2; Treg, regulatory T.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated and analysed during the current study are publicly available, and details are provided in the article.

AUTHOR CONTRIBUTIONS

YYZ and GMW—conceptualised and designed the research study; reviewed and revise the manuscript. CFZ, XYL and FHD—organised the data. JLM—analysed the data. JLM and HJZ—performed software analysis; wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The data used in this study were sourced from public databases. The contributors to the database have obtained ethical approval. Our research has no ethical issues and there was no requirement for informed consent.

ACKNOWLEDGMENT

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.ejgo.net/files/article/1900459494759907328/attachment/Supplementary%20material.docx.

REFERENCES

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2021; 71: 209–249.

[2] Gu B, Shang X, Yan M, Li X, Wang W, Wang Q, *et al*. Variations in incidence and mortality rates of endometrial cancer at the global, regional, and national levels, 1990–2019. Gynecologic Oncology. 2021; 161: 573–580.

[3] Crosbie EJ, Kitson SJ, McAlpine JN, Mukhopadhyay A, Powell ME, Singh N. Endometrial cancer. The Lancet. 2022; 399: 1412–1428.

[4] Van Nyen T, Moiola CP, Colas E, Annibali D, Amant F. Modeling endometrial cancer: past, present, and future. International Journal of Molecular Sciences. 2018; 19: 2348.

[5] Mazzotta C, Marden G, Farina A, Bujor A, Trojanowski MA, Trojanowska M. FLI1 and ERG protein degradation is regulated via Cathepsin B lysosomal pathway in human dermal microvascular endothelial cells. Microcirculation. 2021; 28: e12660.

[6] Lorenzin F, Demichelis F. Past, current, and future strategies to target ERG fusion-positive prostate cancer. Cancers. 2022; 14: 1118.

[7] Mao N, Gao D, Hu W, Gadal S, Hieronymus H, Wang S, *et al*. Oncogenic ERG represses PI3K signaling through downregulation of IRS2. Cancer Research. 2020; 80: 1428–1437.

[8] Khosh Kish E, Choudhry M, Gamallat Y, Buharideen SM, Dhananyaya D, Bismar TA. The expression of proto-oncogene ETS-related gene (ERG) plays a central role in the oncogenic mechanism involved in the development and progression of prostate cancer. International Journal of Molecular Sciences. 2022; 23: 4772.

[9] Haber MA, Iranmahboob A, Thomas C, Liu M, Najjar A, Zagzag D. ERG is a novel and reliable marker for endothelial cells in central nervous system tumors. Clinical Neuropathology. 2015; 34: 117–127.

[10] Han E, Kim J, Jung MJ, Chin S, Lee JH, Won KY, *et al*. ERG and Nestin: useful markers of immature vessels and novel prognostic markers in renal cell carcinoma. International Journal of Clinical and Experimental Pathology. 2021; 14: 116–125.

[11] Li T, Fu J, Zeng Z, Cohen D, Li J, Chen Q, *et al*. TIMER2.0 for analysis of tumor-infiltrating immune cells. Nucleic Acids Research. 2020; 48: W509–W514.

[12] Tang Z, Li C, Kang B, Gao G, Li C, Zhang Z. GEPIA: a web server for cancer and normal gene expression profiling and interactive analyses. Nucleic Acids Research. 2017; 45: W98–W102.

[13] Pontén F, Jirström K, Uhlen M. The human protein atlas—a tool for pathology. The Journal of Pathology. 2008; 216: 387–393.

[14] Zheng Q, Min S, Zhou Q. Identification of potential diagnostic and prognostic biomarkers for LUAD based on TCGA and GEO databases. Bioscience Reports. 2021; 41: BSR20204370.

[15] Nagy Á, Munkácsy G, Győrffy B. Pancancer survival analysis of cancer hallmark genes. Scientific Reports. 2021; 11: 6047.

[16] Xu J, Guo Z, Yuan S, Li H, Luo S. Upregulation of B3GNT3 is associated with immune infiltration and activation of NF-κB pathway in gynecologic cancers. Journal of Reproductive Immunology. 2022; 152: 103658.

[17] Miao Y, Zhang Q, Lei Q, Luo M, Xie G, Wang H, *et al*. ImmuCellAI: a unique method for comprehensive T-Cell subsets abundance prediction and its application in cancer immunotherapy. Advanced Science. 2020; 7: 1902880.

[18] Boron D, Zmarzly N, Wierzbik-Stronska M, Rosińczuk J, Mieszczański P, Grabarek BO. Recent multiomics approaches in endometrial cancer. International Journal of Molecular Sciences. 2022; 23: 1237.

[19] Xie R, Li B, Jia L, Li Y. Identification of core genes and pathways in melanoma metastasis via bioinformatics analysis. International Journal

of Molecular Sciences. 2022; 23: 794.

[20] Geeleher P, Cox N, Huang RS. pRRophetic: an R package for prediction of clinical chemotherapeutic response from tumor gene expression levels. PLOS ONE. 2014; 9: e107468.

[21] Birdsey G, Shah A, Dufton N, Reynolds L, Osuna Almagro L, Yang Y, *et al*. The endothelial transcription factor ERG promotes vascular stability and growth through Wnt/β-catenin signaling. Developmental Cell. 2015; 32: 82–96.

[22] Zhang Z, Chen F, Li S, Guo H, Xi H, Deng J, *et al*. ERG the modulates Warburg effect and tumor progression in cervical cancer. Biochemical and Biophysical Research Communications. 2020; 522: 191–197.

[23] Stopsack KH, Su XA, Vaselkiv JB, Graff RE, Ebot EM, Pettersson A, *et al*. Transcriptomes of prostate cancer with TMPRSS2: ERG and other ETS fusions. Molecular Cancer Research 2023; 21: 14–23.

[24] Cai L, Hu C, Yu S, Liu L, Zhao J, Zhao Y, *et al*. Identification of EMT-related gene signatures to predict the prognosis of patients with endometrial cancer. Frontiers in Genetics. 2020; 11: 582274.

[25] Zhang S, Zhang E, Long J, Hu Z, Peng J, Liu L, *et al*. Immune infiltration in renal cell carcinoma. Cancer Science. 2019; 110: 1564–1572.

[26] Yang W, Chen X, Hu H. CD4+ T-cell differentiation *in vitro*. Methods in Molecular Biology. 2020; 28: 91–99.

[27] Vorkas CK, Krishna C, Li K, Aubé J, Fitzgerald DW, Mazutis L, *et al*. Single-cell transcriptional profiling reveals signatures of helper, effector, and regulatory MAIT cells during homeostasis and activation. The Journal of Immunology. 2022; 208: 1042–1056.

[28] Geissmann F, Manz MG, Jung S, Sieweke MH, Merad M, Ley K. Development of monocytes, macrophages, and dendritic cells. Science. 2010; 327: 656–661.

[29] Waisman A, Lukas D, Clausen BE, Yogev N. Dendritic cells as gatekeepers of tolerance. Seminars in Immunopathology. 2017; 39: 153–163.

[30] Li K, Shi H, Zhang B, Ou X, Ma Q, Chen Y, *et al*. Myeloid-derived suppressor cells as immunosuppressive regulators and therapeutic targets in cancer. Signal Transduction and Targeted Therapy. 2021; 6: 362.

[31] Kübler K, Ayub TH, Weber SK, Zivanovic O, Abramian A, Keyver-Paik M, *et al*. Prognostic significance of tumor-associated macrophages in endometrial adenocarcinoma. Gynecologic Oncology. 2014; 135: 176–183.

[32] Olingy CE, Dinh HQ, Hedrick CC. Monocyte heterogeneity and functions in cancer. Journal of Leukocyte Biology. 2019; 106: 309–322.

[33] Toor SM, Sasidharan Nair V, Saleh R, Taha RZ, Murshed K, Al-Dhaheri M, *et al*. Transcriptome of tumor-infiltrating T cells in colorectal cancer patients uncovered a unique gene signature in $CD4^+$ T cells associated with poor disease-specific survival. Vaccines. 2021; 9: 334.

[34] Neal A, Nornes S, Louphrasitthiphol P, Sacilotto N, Preston MD, Fleisinger L, *et al*. ETS factors are required but not sufficient for specific patterns of enhancer activity in different endothelial subtypes. Developmental Biology. 2021; 473: 1–14.

[35] Shah AV, Birdsey GM, Randi AM. Regulation of endothelial homeostasis, vascular development and angiogenesis by the transcription factor ERG. Vascular Pharmacology. 2016; 86: 3–13.

[36] Ramanand SG, Chen Y, Yuan J, Daescu K, Lambros MBK, Houlahan KE, *et al*. The landscape of RNA polymerase II-associated chromatin interactions in prostate cancer. Journal of Clinical Investigation. 2020; 130: 3987–4005.

[37] Wu L, Lian W, Zhao L. Calcium signaling in cancer progression and therapy. The FEBS Journal. 2021; 288: 6187–6205.

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