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ORIGINAL RESEARCH

Identification of Key Genes Involved in the Occurrence and Development of Endometrial Cancer

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Object: Endometrial cancer (EC) is one of the most common gynecologic malignancies, for which endometrial hyperplasia (EH) and type 2 diabetes are established high-risk factors. However, the common molecular mechanisms underlying this association remain poorly understood. This study therefore aimed to identify and validate hub genes linking EH, type 2 diabetes, and EC, and to assess their prognostic value.

Methods: Intersection genes among EH and EC DEGs (GSE106191) and type 2 diabetes-related genes (GeneCards) were screened. A prognostic model was constructed via Lasso-Cox regression in TCGA-UCEC. Functional enrichment (GO and KEGG) analyzed the prognostic model. The PPI network identified hub genes within the prognostic model. Subsequent prognostic analysis in TCGA-UCEC validated key hub genes. Their expression was further analyzed across GSE106191 and TCGA-UCEC datasets and confirmed via immunohistochemistry. Correlations with clinical features (age, stage, grade, TP53 mutation, weight) in EC were assessed using UALCAN.

Results: One hundred and sixty-two intersection genes were identified. The 16-gene prognostic model stratified EC patients into high/low-risk groups with significantly distinct overall survival (HR = 3.475, P = 2.51e-7; 1/3/5-year AUCs: 0.740/0.749/0.783). Functional enrichment linked genes to TGF-beta signaling and estrogen pathways. Combined PPI network analysis and prognostic validation identified *PGR* and *VIM* as key hub genes, both significantly downregulated in EC versus normal tissues across TCGA-UCEC and GSE106191 datasets ($P < 0.05$; IHC confirmed). Notably, within tumor samples, PGR and VIM expression was significantly higher in EC patients with diabetes compared to those without diabetes. Immunohistochemistry confirmed the downregulation of PGR and VIM protein expression in EC tissues compared to normal and EH tissues. Their expression correlated with clinical characteristics (age, stage, histology, TP53 mutation, weight) and was elevated in diabetic EC patients ($P < 0.05$).

Conclusion: *PGR* and *VIM* were identified as DEGs of EH, type 2 diabetes, and EC. Their reduced expression in EC correlated with poorer prognosis, underscoring their potential as prognostic biomarkers and therapeutic targets, especially in diabetic EC patients. In this study, we offer a new genetic biomarker for the prediction of EC patients' prognosis.

Keywords: endometrial hyperplasia, endometrial cancer, type 2 diabetes, prognostic

Introduction

Endometrial hyperplasia (EH) is a precancerous condition of the uterine lining that is at least three times more common than endometrial cancer (EC).[1] EC itself is a frequent gynecological malignancy.[2,3] According to the National Cancer Center in China's 2019 analysis of malignant tumor prevalence in 2015, there were approximately 69,000 endometrial cancer patients in that year, with 16,000 deaths. The incidence rate was 10.28/100,000 women, accounting for 3.88% of all female malignant tumors.[4]

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Both EH and EC can cause irregular vaginal bleeding, particularly during perimenopause.[5] Common high-risk factors for both EH and EC conditions include obesity, diabetes mellitus, long-term application of estrogen or tamoxifen without progesterone antagonism, and hereditary endometrial cancer such as Lynch syndrome.[6–9] The 2020 World Health Organization (WHO) Classification System categorizes EH into two types: endometrial hyperplasia without atypia and atypical endometrial hyperplasia (AEH).[4] AEH has a yearly progression risk to endometrial cancer of approximately 8%.[10] Definitive diagnosis relies on endometrial histopathological examination.[11] Diagnostic curettage and hysteroscopic biopsy are the main methods for obtaining endometrial tissue samples.[11]

Growing evidence suggests a strong association between type 2 diabetes and an elevated risk of multiple cancers, including pancreatic, breast, endometrial, colorectal, prostate, and liver cancers.[12–18] The underlying mechanisms are thought to involve hyperglycemia, hyperinsulinemia, insulin resistance, chronic inflammation, and obesity.[12] In particular, obesity, hypertension, and diabetes are collectively described as the "triad of endometrial cancer".[19] Epidemiological studies indicate that patients with diabetes face a 2.12-fold increased risk of endometrial cancer compared to non-diabetic individuals. This risk is further compounded by body weight: overweight patients (BMI $\geq$ 25 kg/m^2) exhibit a 2.45-fold higher risk, which rises to 3.5-fold among those with both obesity and hypertension.[2]

Previous genomic studies using TCGA and GEO datasets have revealed molecular subtypes and prognostic signatures in EC.[20] However, the common genetic basis linking EH, diabetes and EC progression remains less explored. In particular, progesterone receptor (PGR) and vimentin (VIM) have been implicated in endometrial carcinogenesis, with PGR maintaining endometrial homeostasis and VIM facilitating epithelial-mesenchymal transition.[21,22] Their specific roles in diabetes-associated EC merit further investigation.

Identifying genes commonly associated with both EH and type 2 diabetes, which are known risk factors for EC, could be valuable for preventing EC occurrence. This study aimed to identify the intersection genes in EH and EC samples from GSE106191 dataset and type 2 diabetes-related genes from GeenCareds database. Key genes were then identified using Lasso-cox regression analysis. The study further investigated the expression and prognostic values of these key genes within the TCGA-UCEC dataset. Finally, a nomogram was constructed to visualize a predictive model based on these hub genes and EC risk.

Materials and Methods

Data Collection and Workflow

Gene expression profiles for endometrial hyperplasia and endometrial cancer were obtained from the GSE106191 dataset in the GEO database (https://www.ncbi.nlm.nih.gov/geo/). Type 2 diabetes-related genes were retrieved from the GeneCards database (https://www.genecards.org/). Clinical and transcriptome data for endometrioid carcinoma (UCEC) patients were collected from the TCGA-UCEC project (https://portal.gdc.cancer.gov/). The overall workflow is illustrated in Figure 1.

Identified the DEGs and Screened the Intersection Genes

Differential expression analysis between endometrial hyperplasia and carcinoma samples from the GSE106191 dataset was performed using the "limma" package in R, with significance thresholds set at FDR < 0.01 and $|\log_2 FC| \geq 1.5$. The "Venn" package was then used to identify common genes between the DEGs and the type 2 diabetes-related gene set.

Lasso-Cox Regression

Lasso-Cox regression analysis was performed using the "glmnet" package in R to identify genes significantly associated with overall survival in the TCGA-UCEC cohort.[23,24] A risk score was calculated for each patient based on the expression levels of selected genes and their regression coefficients: risk score = Σ (gene expression $\times$ coefficient). Patients were stratified into high- and low-risk groups based on their risk scores. Survival differences between groups were analyzed using Kaplan-Meier curves ("survminer" package), and predictive accuracy was evaluated by time-dependent ROC analysis ("timeROC" package). Principal component analysis (PCA) and t-SNE were performed for

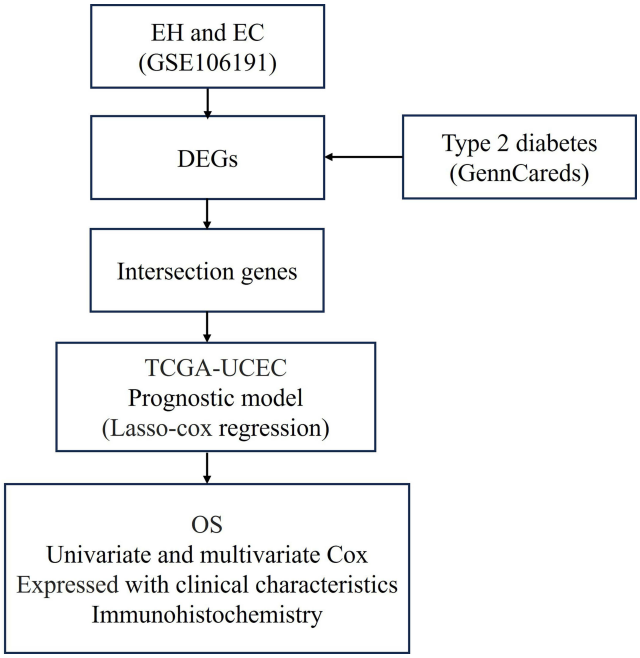

Figure 1 The workflow is illustrated in Figure 1.

dimensionality reduction and visualization. Both univariate and multivariate Cox regression analyses were conducted to identify independent prognostic factors, and a nomogram was constructed using the "rms" package.

Gene Ontology and Kyoto Encyclopedia of Genes and Genomes Pathway Analysis

Gene ontology (GO) analysis involves functional enrichment analysis, encompassing biological process (BP), molecular function (MF), and cellular component (CC). KEGG analysis delves deeper into advanced functions and mechanisms within the biological system at the molecular level. The DAVID online tool (http://david.ncifcrf.gov/) was used to perform both analyses, with enrichment results downloaded and visualized using R software. A significance threshold of P <0.05 and FDR <0.25 was applied.

PPI Network

The PPI network for the intersecting genes was constructed using the STRING database (http://string-db.org/). Cytoscape v. 3.6.1 (http://www.cytoscape.org/) was employed for network analysis and visualization. Using Cytoscape's built-in Network Analyzer tool, the degree value of each gene was calculated, with hub genes identified based on betweenness centrality (BC) values.

Analysis of mRNA Expression Profile of Hub Gene Using UALCAN

UALCAN (http://ualcan.path.uab.edu) is an online resource designed for analyzing relative mRNA expression patterns of potential genes (TCGA and MET500 transcriptome sequencing) and their relationship with various tumor subtypes. UALCAN was utilized to investigate the mRNA expression profile of hub genes identified within TCGA-UCEC tissue samples and assess their potential association with clinical characteristics.

Tissue Collection and IHC

Paraffin-embedded tissues from normal endometrium (NE), endometrial hyperplasia (EH), EH with diabetes (EHD), endometrial carcinoma (EC), and EC with diabetes (ECD) (n = 5 per group) were subjected to antigen retrieval and immunostaining using antibodies against PGR (Abcam, ab184337, 1:200) and VIM (Proteintech, 60330-1-Ig, 1:500). Detection was performed with DAB chromogenic development.

Statistical Analysis

Student's *t*-test (R function *t*-test) was performed to determine statistically significant differences between the two groups. A *P*-value < 0.05 was considered significant. The ggplot package was used to generate the corresponding graphs for data visualization.

Results

Differential Gene Expression in Endometrial Hyperplasia, Carcinogenesis, and Type 2 Diabetes

DEGs in EH and EC in were identified using the GSE106191 dataset from the GEO database. The analysis revealed 52 upregulated genes and 225 downregulated genes (Figure 2A and B). A Venn diagram demonstrated 162 intersection genes between DEGs and type 2 diabetes-related genes (Figure 2C).

Construction and Verification of the Stability of the Prognostic Model

Lasso-Cox regression analysis with the TCGA-UCEC dataset identified 162 genes that potentially influence patient prognosis based on the best value of log λ (Figure 3A and B). We calculated the risk score as follows: Risk score = (−0.0046) *MMP9+(−0.0855) *TRPC6+(−0.0355) *VIM+(−0.1128) *PGR+(−0.0333) *NOG+(0.0116) *CDH3 +(0.0014) *PXDN+(−0.1093) *PEG3+(0.0579) *ASPM+(0.0154) *KCTD15+(0.0087) *NLGN1+(−0.1086) *KCNK6 +(0.3321) *RAPGEF4+(−0.0619) *GNLY+(−0.0044) *ID3+(0.082) *PRDM6. Patients were then divided into high- and low-risk groups based on the median risk score (Figure 3C). The OS and prognosis were significantly better in the low-risk group than in the high-risk group (*P* = 2.51e-7, *HR*(High group) = 3.475, *95% CI*(2.16–5.58), Figure 3D). The AUC for the ROC curves indicated good performance in predicting 1-, 3-, and 5-year survival rates of 0.740, 0.749, and 0.783, respectively (Figure 3E).

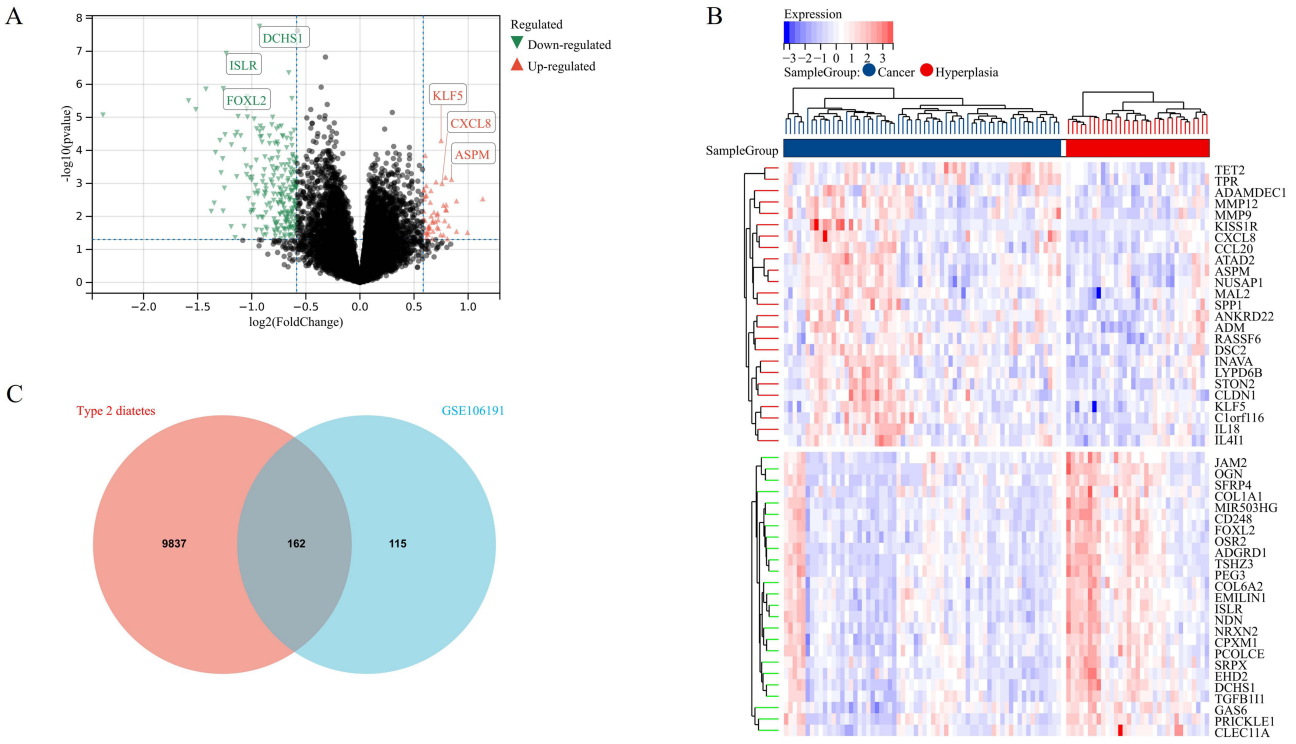

Figure 2 Differentially expressed genes were identified of EH and EC in GSE10691 from GEO database. (**A** and **B**) Volcano map and heat map of differentially expressed genes. (**C**) The intersection genes of type 2 diabetes related genes and DEGs were analyzed by Venn map.

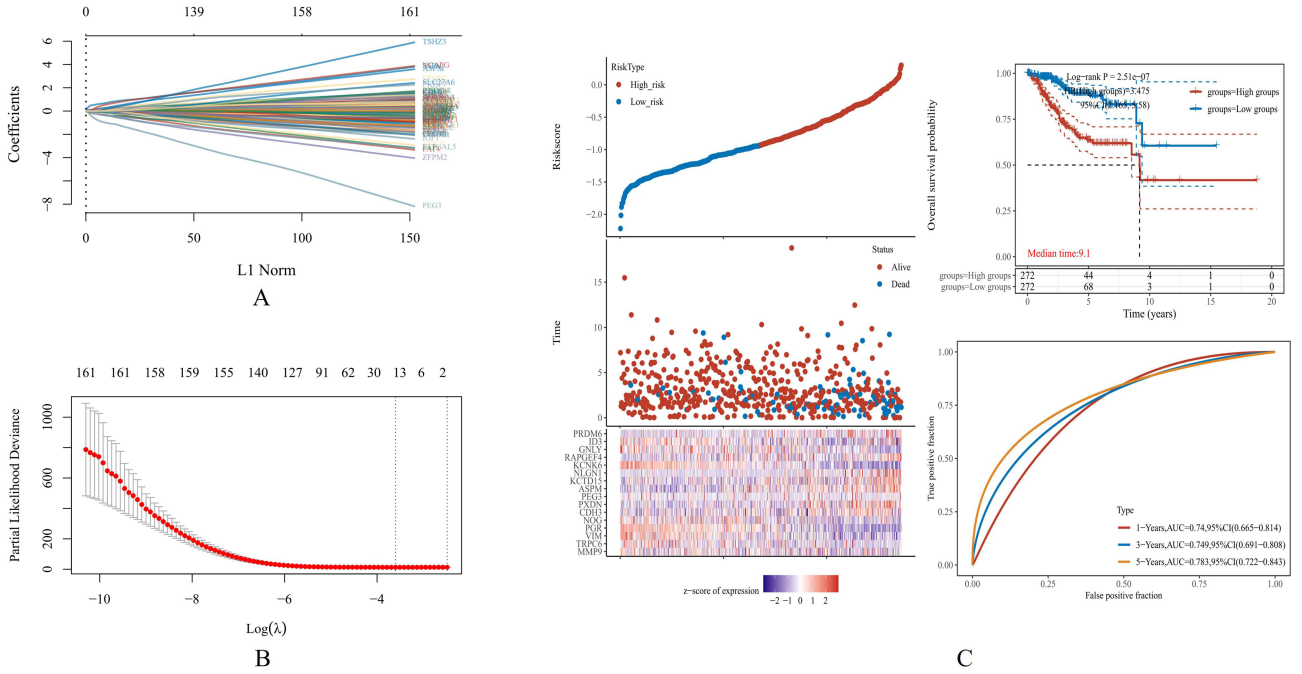

Figure 3 Established a prognostic gene model in the TCGA-UCEC dataset. (**A**) LASSO coefficients profiles of 162 prognostic genes in EC. (**B**) LASSO regression with tenfold cross-validation obtained 16 prognostic genes using minimum lambda value. (**C**) 543 patients with EC were divided equally into low-risk group and high-risk group on the basis of the median score calculated by the risk score formula. Lower OS time was observed in the high-risk group of EC patients, in comparison with the low-risk group of EC patients by Kaplan-Meier Plotter analysis. Time-dependent receiver operating characteristic (ROC) analysis to assess the sensitivity and specificity of the prognostic model.

Notes: 16 prognostic model genes including *MMP9, TRPC6, VIM, PGR, NOG, CDH3, PXDN, PEG3, ASPM, KCTD15, NLGN1, KCNK6, RAPGEF4, GNLY, ID3*, and *PRDM6*.

Gene Ontology and Kyoto Encyclopedia of Genes and Genomes Pathway Analyses of Key Genes

The GO enrichment and KEGG pathway analyses were performed using the DAVID software to explore the biological functions of the 16 key genes. Enriched GO terms included cell differentiation, cellular developmental process, regulation of multicellular organismal process, phagocytic vesicle, ion channel complex, transmembrane transporter complex, transporter complex, and dimerization activity (Figure 4A–C). Enriched KEGG pathways included the TGF-beta signaling pathway, leukocyte transendothelial migration, estrogen signaling pathway, and cell adhesion molecules (CAMs) (Figure 4D).

PPI Network Identification and Prognostic Analysis of Hub Genes in EC

The protein interaction network for the 16 key genes was constructed using the STRING online database. Cytoscape software, with its cytohubba plugin, was then employed to calculate node degree values and identify hub genes within this prognostic model. This analysis pinpointed *PGR, VIM, MMP9, CDH3*, and *PXDN* as hub genes (Figure 5A). Subsequently, the prognostic significance of these candidates was assessed in the TCGA-UCEC dataset. Prognostic analysis revealed that *PGR* and *VIM* exhibited significant associations with survival outcomes, while *MMP9, CDH3*, and *PXDN* showed no differential impact (Figure 5B and C). Therefore, based on the PPI network and prognostic results, we identified *PGR* and *VIM* as the key hub genes.

Expressions of PGR and VIM with Clinical Characteristics and Immunohistochemistry of EC

PGR and *VIM* expression was assessed across TCGA-UCEC and GSE106191 datasets. Both genes were significantly downregulated in EC compared to normal tissues (Figure 6A and B). Notably, while EH tissues showed expression levels comparable to normal endometrium, both *PGR* and *VIM* were markedly reduced in EC (Figure 6C and D). Analysis

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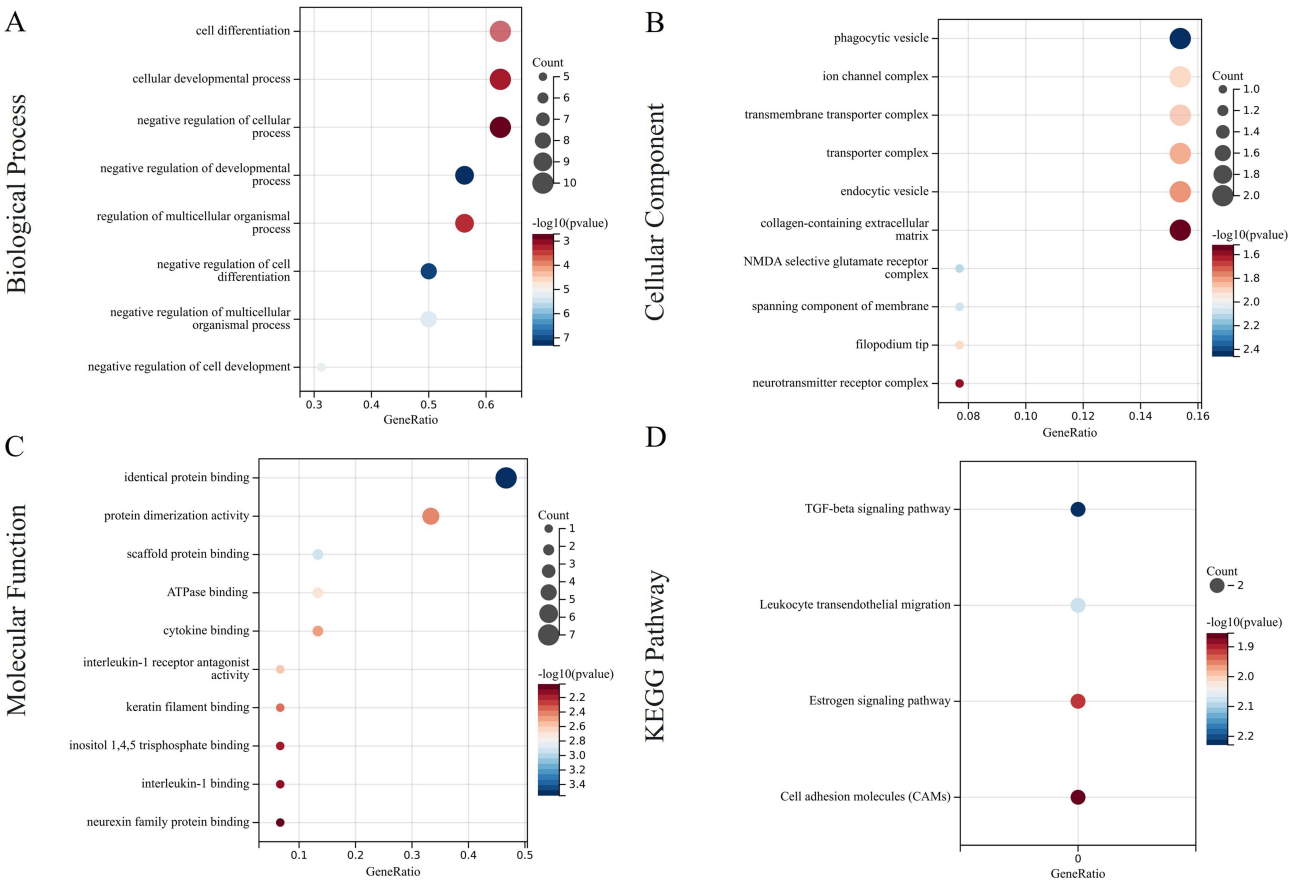

Figure 4 Gene ontology and Kyoto Encyclopedia of Genes and Genomes pathway analyses of 16 prognostic model genes. (**A**–**C**) Enriched GO terms (**D**) Enriched KEGG pathways.

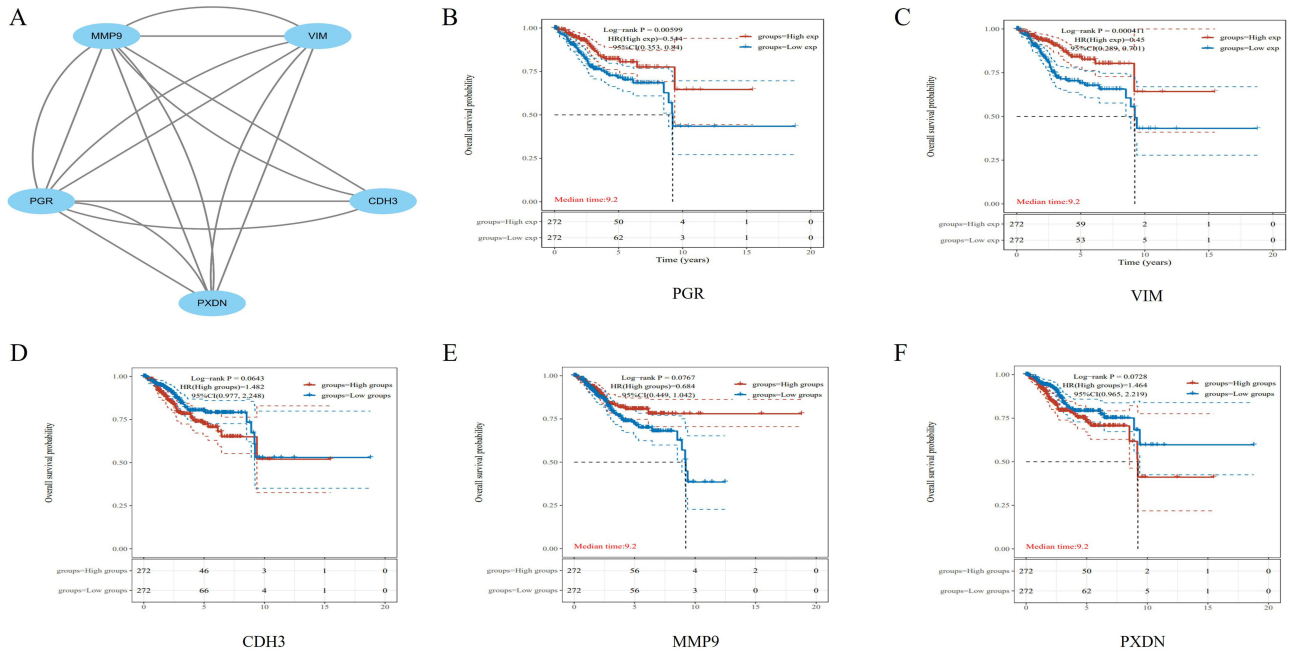

Figure 5 Prognostic analysis and PPI network of key genes in EC. (**A**) Protein-protein interaction (PPI) network identifies 5 key genes (*MMP9*, *CDH3*, *PXDN*, *VIM*, and *PGR*) in prognostic models. (**B**–**F**) Overall survival analysis of *MMP9*, *CDH3*, *PXDN*, *VIM*, and *PGR* in the TCGA-UCEC cohort.

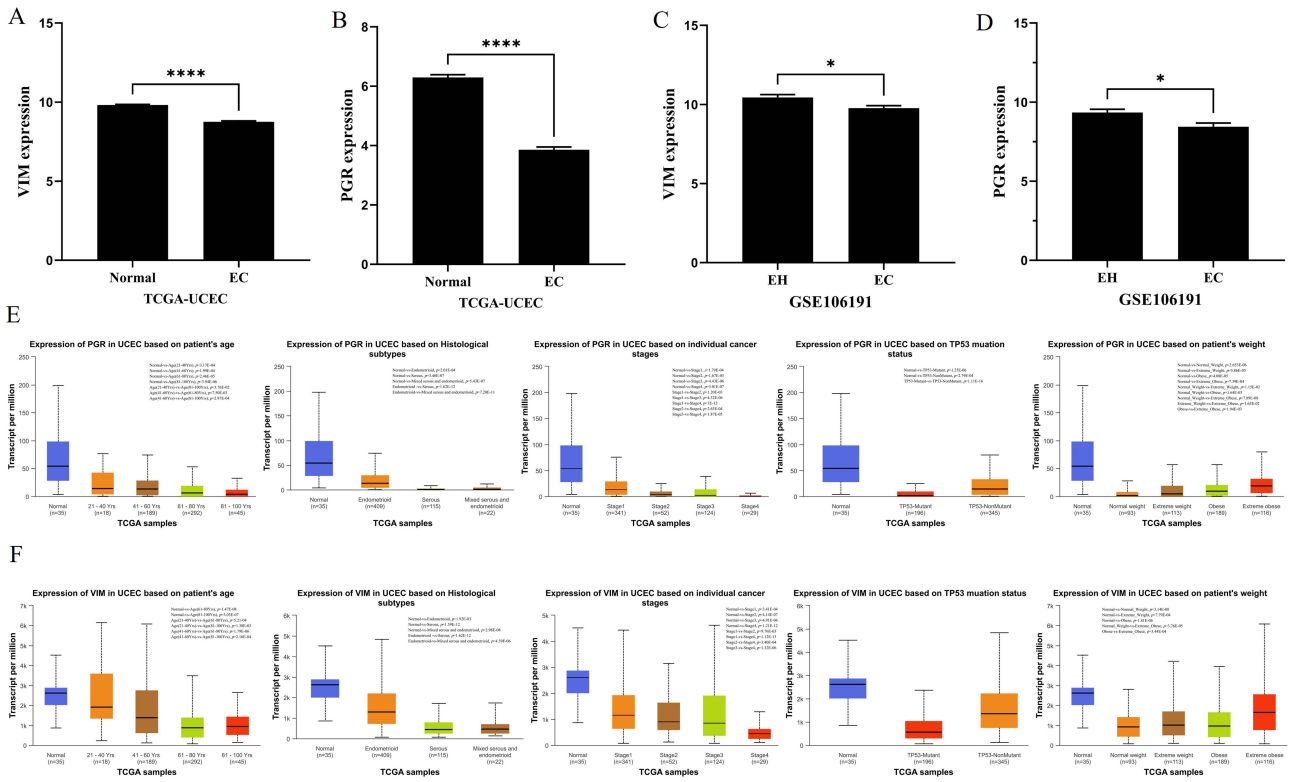

Figure 6 Expression of *PGR* and *VIM* in EC and their association with clinical characteristics. (**A** and **B**), *PGR* and *VIM* expression levels in the TCGA-UCEC dataset. (**C** and **D**), *PGR* and *VIM* expression comparison between endometrial hyperplasia (EH) and endometrial cancer (EC) tissues in GSE106191 dataset. (**E** and **F**), Association of *PGR* and *VIM* expression with clinical characteristics of EC analyzed using the UALCAN database: Age, Histological subtype, Stage, TP53 mutation status, Weight. (*p<0.05, ****p<0.0001).

using the UALCAN database explored correlations between *PGR*/*VIM* expression and key EC clinical characteristics (age, histological subtype, stage, TP53 mutation status, weight) (Figure 6E and F). Interestingly, when comparing tumor samples specifically, expression of both markers was significantly higher in EC with diabetes compared to EC without diabetes. Differences in expression between normal and tumor samples were observed across various clinical features. Furthermore, within the tumor group itself, *PGR* and *VIM* levels exhibited significant variation associated with these clinical parameters. Subsequently, immunohistochemical staining confirmed these expression patterns in normal, EH, and EC tissues for both *PGR* and *VIM* (Figure 7).

Discussion

Endometrial hyperplasia and type 2 diabetes mellitus are well-established risk factors for endometrial cancer, a disease whose incidence has been rising globally.[25–27] Epidemiological studies underscore this link, showing diabetic patients have a 2.12-fold increased risk of EC, which is further compounded by obesity and hypertension.[2] The risk of progression from EH to EC is significantly higher in atypical cases (25–33%) than in non-atypical cases (1–3%), and diabetes further elevates the risk of development and lymph node metastasis.[28,29] Although antidiabetic therapies show potential benefits in managing EC and EH, the precise molecular mechanisms connecting T2DM and EC malignant progression remain poorly defined.[30,31] This gap highlights the necessity of identifying common genetic drivers to improve prognostic prediction and personalized treatment.

In this study, we integrated transcriptomic profiles of EH and EC (GSE106191) with T2DM-associated genes from GeneCards. Through a comprehensive bioinformatics approach—including Venn analysis, Lasso-Cox regression, and nomogram construction—we identified *VIM* and *PGR* as central hub genes influencing EC prognosis.

Our findings on *VIM* align with its well-characterized role in promoting cell migration, invasion, and metastasis across various cancers.[32] For instance, in colorectal cancer, *VIM* expression correlates with malignancy grade and

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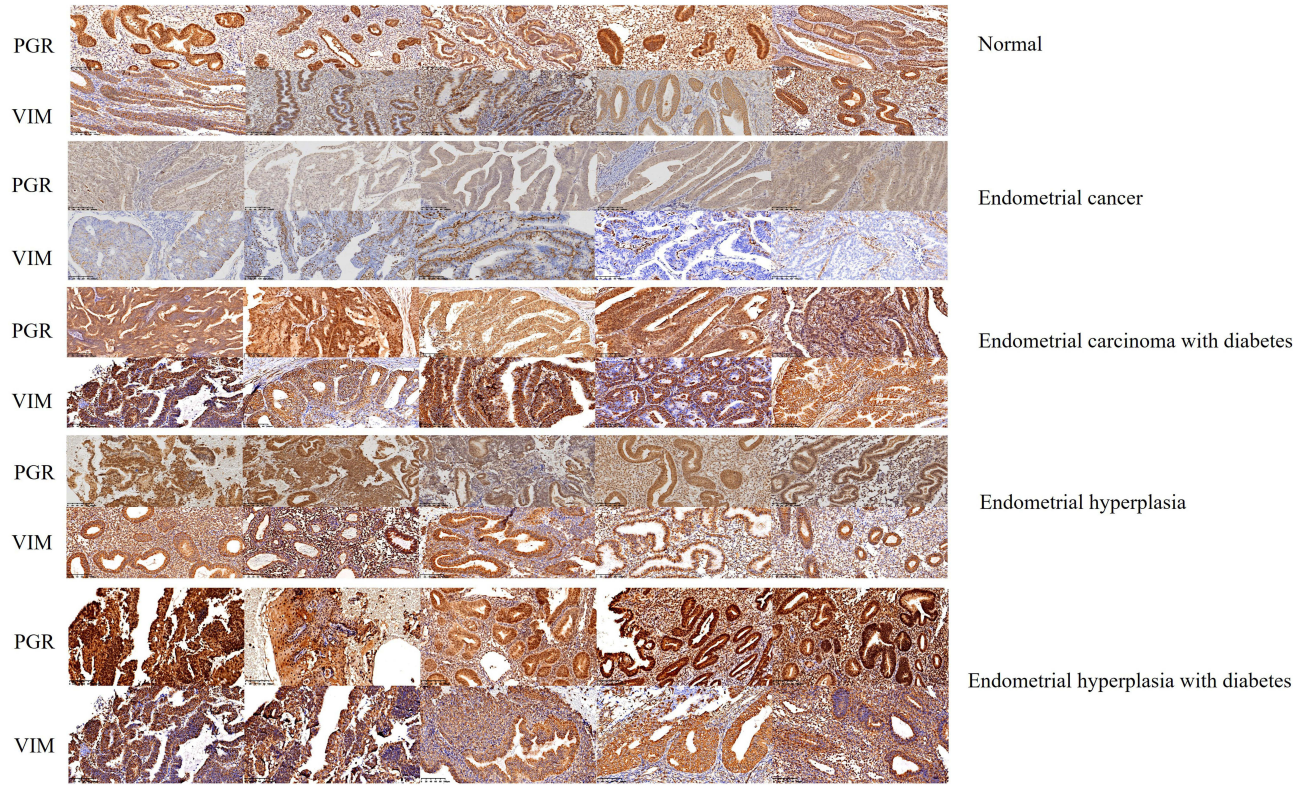

Figure 7 Immunohistochemical staining of *PGR* and *VIM* in endometrial tissues. Representative immunohistochemical staining images showing protein expression levels of *PGR* and *VIM* in normal endometrial (Normal), endometrial hyperplasia (EH), and endometrial cancer (EC) tissues. The staining results confirm the transcriptomic expression trends observed in Figure 6: Protein expression of both *PGR* and *VIM* is markedly reduced in EC tissues compared to normal and EH tissues. Scale bar: 100μm.

metastatic potential,[33] and it has even been proposed as a diagnostic biomarker in stool samples.[34] Similarly, in breast cancer, *VIM* positivity aids in distinguishing malignant from benign tumors.[35] Most notably, and directly supporting our findings, Martinez-Garcia et al (2022) recently identified *VIM* as a promising protein biomarker in cervical fluid for detecting early-stage EC, showing high specificity (81%) and sensitivity (78%).[36] We confirm that *VIM* is underexpressed in EC tissues and its expression level is a significant predictor of patient survival.

The role of *PGR* in endometrial homeostasis and carcinogenesis is equally critical. Long-term unopposed estrogen stimulation is a known driver of EH and EC, whereas progesterone-based therapy is the standard treatment for non-atypical hyperplasia, effectively reducing the risk of progression to malignancy.[37,38] The receptor's two main isoforms, PRA and PRB, mediate distinct transcriptional responses influencing cell proliferation and differentiation.[39] Clinically, progesterone is a recommended endocrine therapy for recurrent EC per NCCN guidelines, particularly for patients with positive hormone receptor status.[40,41] Our results reinforce the crucial protective role of *PGR*, demonstrating its significant downregulation in EC and strong correlation with favorable clinical outcomes.

Notably, both *VIM* and *PGR* were significantly downregulated in EC compared to normal tissues. Their expression levels were correlated with key clinicopathological variables, including age, histological subtype, disease stage, TP53 mutation status, and body weight. Most importantly, we established that their expression levels are independent predictive factors for overall survival. A prognostic model integrating these two molecular markers with clinical staging demonstrated improved predictive accuracy, highlighting their translational potential for risk stratification.

It is important to note that the IHC validation in this study was conducted on a relatively small sample size. While the results are consistent with our bioinformatic predictions and show clear trends, future studies with larger, independent cohorts are warranted to confirm the generalizability of these protein-level findings.

Looking forward, the differential expression of *PGR* and *VIM* offers promising translational implications. The incorporation of these biomarkers into existing diagnostic algorithms could improve risk stratification for patients with

EH and diabetes, potentially enabling earlier detection of malignant transformation. Furthermore, given the established role of progesterone therapy in EC management, the status of *PGR* expression could serve as a predictive biomarker for selecting patients who are most likely to benefit from endocrine-based interventions. From a therapeutic perspective, the association of *VIM* with aggressive tumor phenotypes positions it as a potential target for drugs aimed at inhibiting epithelial-mesenchymal transition and metastasis. Future studies validating these genes in larger prospective cohorts and developing standardized assays for clinical use will be essential steps toward translating these findings into practice.

In conclusion, we have identified *VIM* and *PGR* as key genes at the intersection of EH, diabetes, and EC. Their downregulation in tumor tissues and association with aggressive clinical features underscore their roles in EC progression. These findings provide novel insights into the molecular mechanisms linking metabolic disease and endometrial carcinogenesis and offer a promising biomarker signature for prognostic stratification in EC patients, which could guide more personalized treatment decisions in the future.

Conclusion

EH and DM are high-risk factors for EC. Prevention and treatment management of EC are equally important. *VIM* and *PGR* were identified as DEGs of EH, type 2 diabetes, and EC. These genes exhibited low expression in EC and played a role in influencing EC prognosis. When combined with clinical characteristics (stage), these genes contributed to an effective prognostic model for EC.

Data Sharing Statement

All data in this study can be obtained by GSE106191, TCGA-UCEC, and UALCAN databases.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare no competing interest in this work.

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