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Research article

KLHL14, an ovarian and endometrial-specific gene, is over-expressed in ovarian and endometrial cancer

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Abstract: Ovarian cancer (OC) and endometrial cancer (EC) are two types of the most frequent gynecological malignancies worldwide. However, the prognosis of OC and EC patients remained gloomy. Therefore, there was still an urgent need to identify new biomarkers for early diagnosis and treatment of OC and EC. TCGA datasets were used to screen the KLHL14 expression levels in 18 different types of human cancers. TCGA datasets were also used to analyze the association between KLHL14 expression levels and OS/PFS in OC and EC. Human Protein Atlas was used to detected the KLHL14 protein levels in OC and EC. Kaplan-Meier plotter was used to evaluate the prognostic values of KLHL14 in Ovarian cancer. MAS 3.0 was used to perform GO and KEGG pathway analysis. STRING was used to perform PPI network. KLHL14 was specially expressed in OC and EC samples. Moreover, KLHL14 was found to be up-regulated in all stage of OC and EC samples. By analyzing Kaplan-Meier plotter and TCGA datasets, we found higher KLHL14 expression level was associated with shorter overall and progression-free survival in both OC and EC patients. Furthermore, GO and KEGG analysis of KLHL14 co-expressing genes indicated it played important roles in OC and EC progression. We for the first time reported KLHL14 was specially over-expressed in ovarian and endometrial cancer, up-regulation of KLHL14 was positively associated with worse outcome. Finally, we found knockdown of KLHL14 suppressed OC cell proliferation. KLHL14 could be a potential biomarker and therapy target for OC and EC.

Keywords: ovarian cancer; endometrial cancer; KLHL 14; prognosis; early diagnostic target; gynecologic

Abbreviations: OC: Ovarian cancer; EC: Endometrial cancer; BLCA: Bladder urothelial carcinoma; BRCA: Breast cancer; CESC: Cervical squamous cell carcinoma and endocervical adenocarcinoma; COAD: Colon adenocarcinoma; GBM: Glioblastoma multiforme; HNSC: Head and neck squamous cell carcinoma; KIRC: Kidney renal clear cell carcinoma; KIRP: Kidney renal papillary cell carcinoma; LIHC: Liver hepatocellular carcinoma; LUAD: Lung adenocarcinoma; LUSC: Lung squamous cell carcinoma; PAAD: Pancreatic adenocarcinoma; PRAD: Prostate adenocarcinoma; SKCM: Skin cutaneous melanoma; TGCT: Testicular germ cell tumors; THCA: Thyroid carcinoma; UCEC: Uterine corpus endometrial carcinoma; OV: Ovarian serous cystadenocarcinoma; OS: Overall survival; PFS: Progression-free survival; KM plotter: Kaplan-Meier plotter

1. Introduction

Ovarian cancer (OC) and endometrial cancer (EC) are two types of the most frequent gynecological malignancies worldwide. More than 200,000 new cases of OC and about 142,000 cases of EC were detected worldwide per year [1]. One of the biggest challenges in OC treatment was lacking of early diagnostic biomarkers, which resulted in two-thirds of OC cases being diagnosed at advanced stages. According to the reports of Rodriguez et al., the 5-year survival rate of OC was less than 50% and that of high-grade OC patients was below 30% [2]. Most of the EC patients were diagnosed as early stage EC. Of note, about 20% of EC cases were diagnosed as the advanced stage EC, with less than 30% 5 years survival rate. Over the past decades, great efforts were paid to identify accurate biomarkers [3–9], however, the prognosis of OC and EC patients remained gloomy. Therefore, there was still an urgent need to identify new biomarkers for early diagnosis and treatment of OC and EC.

KLHL14 was a member of the Kelch-like gene family. The Kelch-like gene family contains a BTB/POZ domain, a BACK domain, and five to six Kelch motifs [10,11]. Previous reports had indicated KLHL genes were associated with cancer progression. For example, HIF1A-induced KLHL20 promoted prostate cancer progression by degrading PML [12]. Meanwhile, downregulation of KLHL19 could increase the transcriptional activity of NRF2 and promote lung cancer cells proliferation [13]. KLHL14 is highly conserved during evolution, with mouse and human KLHL14 sharing 99.4% identity. KLHL14 was reported to interact with Torsin A and disruption of the KLHL14-Torsin A interaction was shown to contribute to the pathophysiology of Torsion dystonia, an autosomal dominant disorder characterized by painful muscle contractions. Furthermore, KLHL14 is mainly expressed in the spleen and thyroid gland in humans based on the Genotype-Tissue Expression (GTEx) project and is preferentially and highly expressed in B cells. A recent study showed Kelch-like protein 14 promoted B-1a but suppressed B-1b cell development. Moreover, Wu et al. found KLHL14 was hypomethylated in endometrial cancer [14]. These findings suggested KLHL14 may serve as an important diagnostic biomarker for cancers. However, the functions of KLHL14 in human cancers, especially in gynecological malignancies, remained largely unclear.

In this study, we identified KLHL14 as an ovarian and endometrial-specific gene. We also evaluated the expression pattern of KLHL14 in OC and EC tissues by using public datasets. We

found KLHL14 was associated with clinical features and could act as a biomarker for OC and EC. To further explore the potential roles of KLHL14, we performed GO and KEGG analysis of KLHL14 co-expressed genes. This study will investigate whether KLHL14 may be served as a prognostic biomarker for ovarian and endometrial cancer.

2. Materials and methods

2.1. Patients and clinicopathological data

The level-3 expression data (RNA-seqV2) for cancer patients were downloaded from the TCGA data portal (http://cancergenome.nih.gov/). A total of 18 types of human cancers were analyzed, including bladder urothelial carcinoma (BLCA), breast cancer (BRCA), cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), colon adenocarcinoma (COAD), glioblastoma multiforme (GBM), head and neck squamous cell carcinoma (HNSC), kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), pancreatic adenocarcinoma (PAAD), prostate adenocarcinoma (PRAD), skin cutaneous melanoma (SKCM), testicular germ cell tumors (TGCT), thyroid carcinoma (THCA), uterine corpus endometrial carcinoma (UCEC), and ovarian serous cystadenocarcinoma (OV). This manuscript includes the clinical characteristics of the patient as follows: The age at diagnosis, days to last follow-up, the pathology T stage and pathology N stage. All the patients were staged using the 2009 TNM classification. Overall survival (OS) and progression-free survival (PFS) were calculated in months from the date of diagnosis to the time of death and to the time of tumor progression or recurrence, or death of the patient from OC and EC, respectively.

Human Protein Atlas (https://www.proteinatlas.org) is a website that contains immunohistochemistry-based expression data, which collects approximately 20 common types of cancers, and each tumor type includes 12 individual tumors. Users can identify tumor-type specific proteins expression patterns that are differentially expressed in a given tumor. KLHL14 protein expression in ovarian and endometrial cancer tissues and in normal tissues were reviewed in the Human Protein Atlas (http://www.proteinatlas.org/) [15].

2.2. Survival analysis

Kaplan-Meier plotter (KM plotter) is a web tool that predicts the effect of genes on survival (http://kmplot.com/analysis/index.php?p=background) [16]. In this study, we discussed the prognostic values of KLHL14 in ovarian cancer by using this dataset which contained 1287 patients.

Meanwhile, we also analyzed TCGA dataset to explore the association between KLHL14 expression levels and OS/PFS in ovarian and endometrial cancer patients. The upper 25 percent KLHL14 mRNA expression in all ovarian or endometrial cancer tissues was selected as the cutoff point to divide all cases into KLHL14-low and -high groups.

2.3. *GO and KEGG pathway analysis*

Molecule Annotation System (MAS 3.0, http://mas.capitalbiotech.com/mas3/) was used to

perform the GO function enrichment analysis of KLHL14 related proteins in OC and EC. DAVID Tools (https://david.ncifcrf.gov/home.jsp) [17,18] was used to perform KEGG pathway enrichment analysis of KLHL14 related pathways in OC and EC. $P < 0.05$ was considered as significant.

2.4. Co-expression network construction and analysis

In the present study, we performed a co-expression analysis of candidate genes by calculating the Pearson correlation coefficient of paired genes. The genes that were co-expressed with KLHL14 in the ovarian and endometrial cancer patients in the TCGA database were identified using cBioportal (http://cbioportal.org) [19,20]. The co-expressed gene pairs with the |Pearson correlation coefficient ≥ 0.3 were selected for further study [21].

2.5. PPI network construction

We used STRING to analyze the interactions between DEGs and we also constructed a PPI network. STRING (https://string-db.org/) is a database of known and predicted protein-protein interactions [22]. The interaction stem from computational prediction, from knowledge transfer between organisms, and from interactions aggregated from other (primary) databases. In this study, we have only selected experimentally validated interactions. The interactions combined score ≥ 0.4 were selected as significant. The Mcode plugin (degree cut-off ≥ 2 and the nodes with edges ≥ 2-core) was used to perform a module analysis of the network. The Network Analyzer was used to compute the basic properties of the PPI network. The Cytoscape software was used to perform PPI networks.

2.6. Cell culture

Human ovarian cancer cell lines SKOV3 and HO8910 were purchased from ATCC. Cells were cultured in DMEM containing 10% FBS, 1 units/mL penicillin and 100 μg/mL streptomycin at 37 °C in a 5% CO_2 incubator.

2.7. Transfection of cells

Cells were seeded into 6-well plates one day prior to transfection. Until 60–80% of cell confluency, small interfering RNA and Lipofectamine 2000 were diluted in opti-MEM for 5 min. Diluted reagents were gently mixed and maintained for another 20 min. After that cells were added with the mixture and incubated for 4–6 hours. Cells were harvested for further analyses 24–48 hours after transfection. Sequences of siRNAs were listed below: si-KLHL14-1: CCAGCAGAATTCGCTCTAA; si-KLHL14-2: GCAGAATTCGCTCTAACAA.

2.8. RT-qPCR

TRIzol reagent (Invitrogen; Thermo Fisher Scientific) was used to extract total RNA according to kit protocols. Then, cDNAs were synthesized according to protocols of Prime-Script RT-PCR kit (Takara Biotechnology Co., Ltd., Dalian, China). PCR was conducted on an ABI PRISM 7700 Sequence Detection System (Applied Biosystems; Thermo Fisher Scientific, Inc.). The sequences for

KLHL14 primers were as follows: forward, 5′-CAGCCGATATGATCCTCGAT-3′, and reverse, 5′-TCCAACCGACATGCATAGAA-3′. GAPDH was used as an internal control for mRNAs with primers as follows: forward, 5′-GAAGGTGAAGGTCGGAGTC-3′ and reverse, 5′-GAAGATGGTGATGGGATTTC-3′. Analysis of gene expressions was measured using the ΔΔCq method.

2.9. Cell proliferation assay

CCK-8 reagent (Biotechwell, Shanghai, China) was used to measure the ability of cell proliferation. Totally, 8000 cells (logarithmic growth phase) were seeded into 96-well plates at 37 °C. RPMI-1640 without HyClone was added after cells adherent grew, and 10 μL CCK-8 was added to each well. The absorbance at 12, 24, 48 and 72 hours were, respectively, measured at 450 nm through the enzyme-linked immune detector (Biotek, Winooski, Vermont) after 4 hours of incubation.

2.10. Statistical analysis

The data was shown as the mean ± standard deviation. The Student's t-test or Mann-Whitney U-test was used to perform statistical comparisons between two groups according to the test condition. The one-way ANOVA was used to perform statistical comparisons between multiple groups. The Kaplan-Meier analyze was used to perform survival analysis. $P < 0.05$ was selected as significant.

3. Results

3.1. KLHL14 was specially expressed in OC and EC samples

In this study, we focused on exploring potential biomarkers for OC and EC. Thus, we screened KLHL14 expression levels in 18 different types of human cancers (including BLCA, BRCA, CESC, COAD, GBM, HNSC, KIRC, KIRP, LIHC, LUAD, LUSC, PAAD, PRAD, SKCM, TGCT, THCA, UCEC, and OV) by using TCGA datasets. We observed KLHL14 was significantly specially up-regulated in OC (FC = 15.47) and EC (FC = 10.32) compared to the average expression level of other kinds of human cancers (Figure 1A). Interestingly, we found KLHL14 was also up-regulated in THCA (Figure 1A), which indicated the potential prognostic roles of KLHL14 in OC and EC.

3.2. KLHL14 was up-regulated in all stages of OC and EC

To further evaluate possible prognostic value of KLHL14 in OC and EC, we firstly download TCGA microarray data of OC, which contained 8 normal samples, 16 stage I OC samples, 30 stage II OC samples, 450 stage III OC samples, and 85 stage IV OC samples. As shown in Figure 1B, KLHL14 was overexpressed in all stages of OC compared to normal tissues (stage I, $p < 0.05$; stage II, $p < 0.01$; stage III, $p < 0.001$; and stage IV, $p < 0.001$).

We next analyzed KLHL14 expression pattern in EC patients by using TCGA RNA-seq. A total of 35 normal samples, 342 stage I EC samples, 52 stage II EC samples, 123 stage III EC samples, and 29 stage IV EC samples were included in the present study. Significantly higher expression of

KLHL14 was found in stage I ($p < 0.001$), stage II ($p < 0.05$), stage III ($p < 0.0001$) and stage IV ($p < 0.0001$) EC patients compared to the normal controls (Figure 1C). These results suggested KLHL14 was associated with OC and EC initiation and could acted as an early diagnostic biomarker.

To further compare KLHL14 expression in OC, EC, and normal tissues, we examined KLHL14 protein expression in Human Protein Atlas. In the analysis of OC, we observed that among 12 cancer tissues examined, there were 2 cases of high and 8 cases of medium staining (Figure 2A,C). In comparison, the normal ovarian stromal cells had low KLHL14 expression levels. As shown in Figure 2B, we also found KLHL14 was overexpressed in EC samples, however, KLHL14 was not detected in normal endometrial stroma cells (Figure 2B,D).

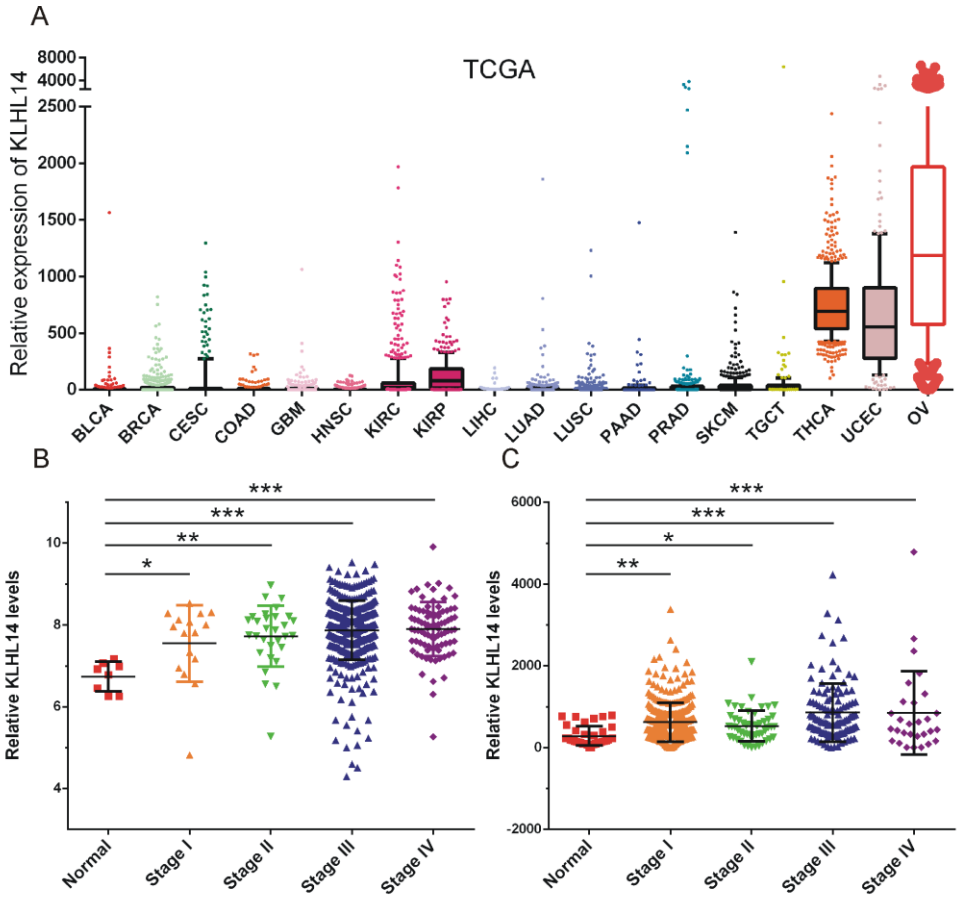

Figure 1. KLHL14 was specially expressed in OC and EC samples.(A) KLHL14 was significantly specially up-regulated in OC and EC compared to the average expression level of other kinds of human cancers (including BLCA, BRCA, CESC, COAD, GBM, HNSC, KIRC, KIRP, LIHC, LUAD, LUSC, PAAD, PRAD, SKCM, TGCT, and THCA). (B) KLHL14 expression level was up-regulated in stage I, stage II, stage III, and stage IV OC samples compared to normal samples by analyzing the TCGA dataset. (C) KLHL14 expression level was up-regulated in stage I, stage II, stage III, and stage IV EC samples compared to normal samples by analyzing the TCGA dataset. Significance was defined as $p < 0.05$ (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$).

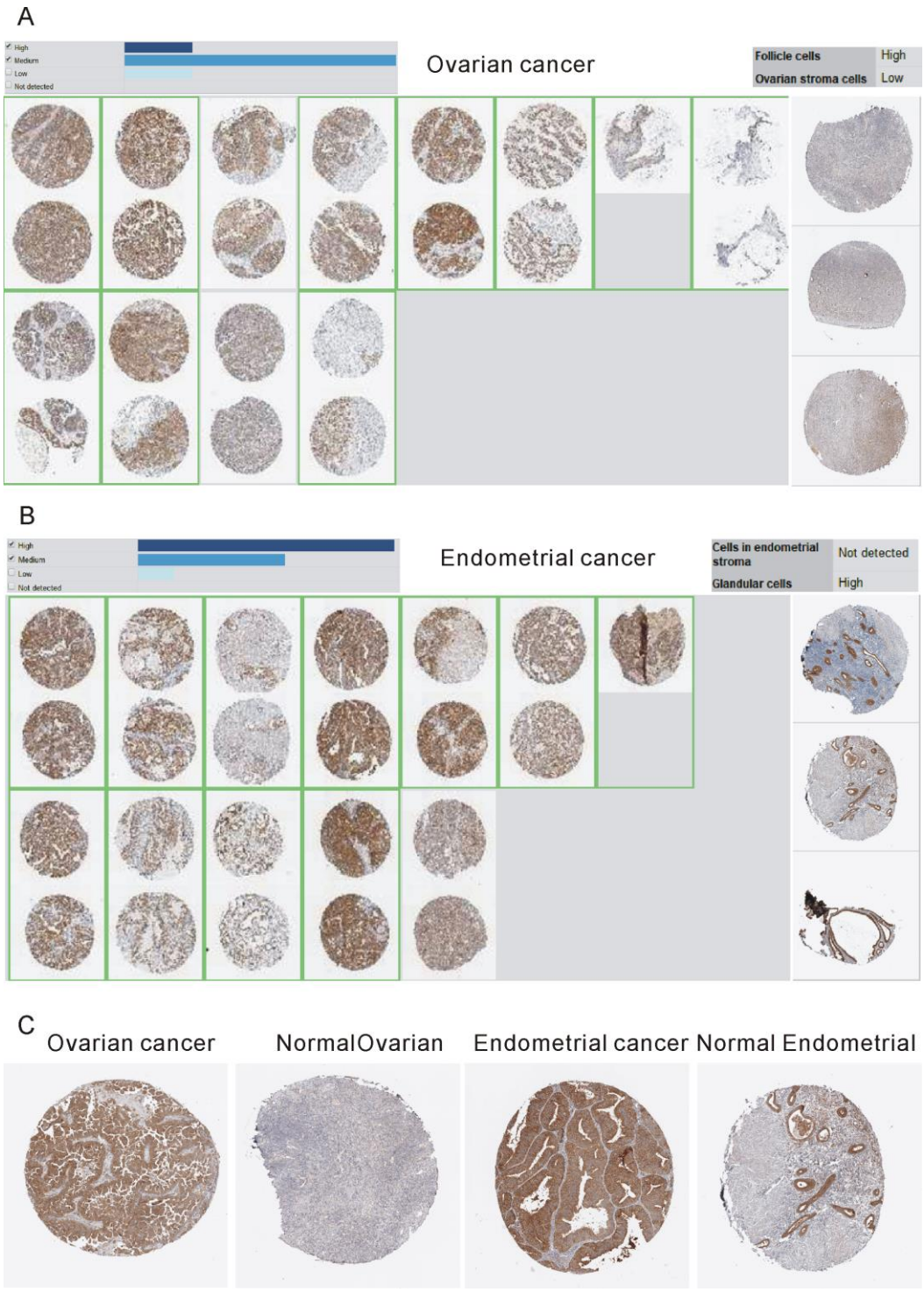

Figure 2. KLHL14 protein levels were up-regulated in OC and EC samples. (A) IHC staining of KLHL14 expression in 12 cases of ovarian cancer tissues and in normal ovarian tissues. (B) IHC staining of KLHL14 expression in 12 cases of endometrial cancer tissues and in normal endometrial tissues.

Figure 2B KLHL14 protein levels were up-regulated in OC and EC samples compared to normal samples. Images were obtained from Human Protein Atlas (https://www.proteinatlas.org/).

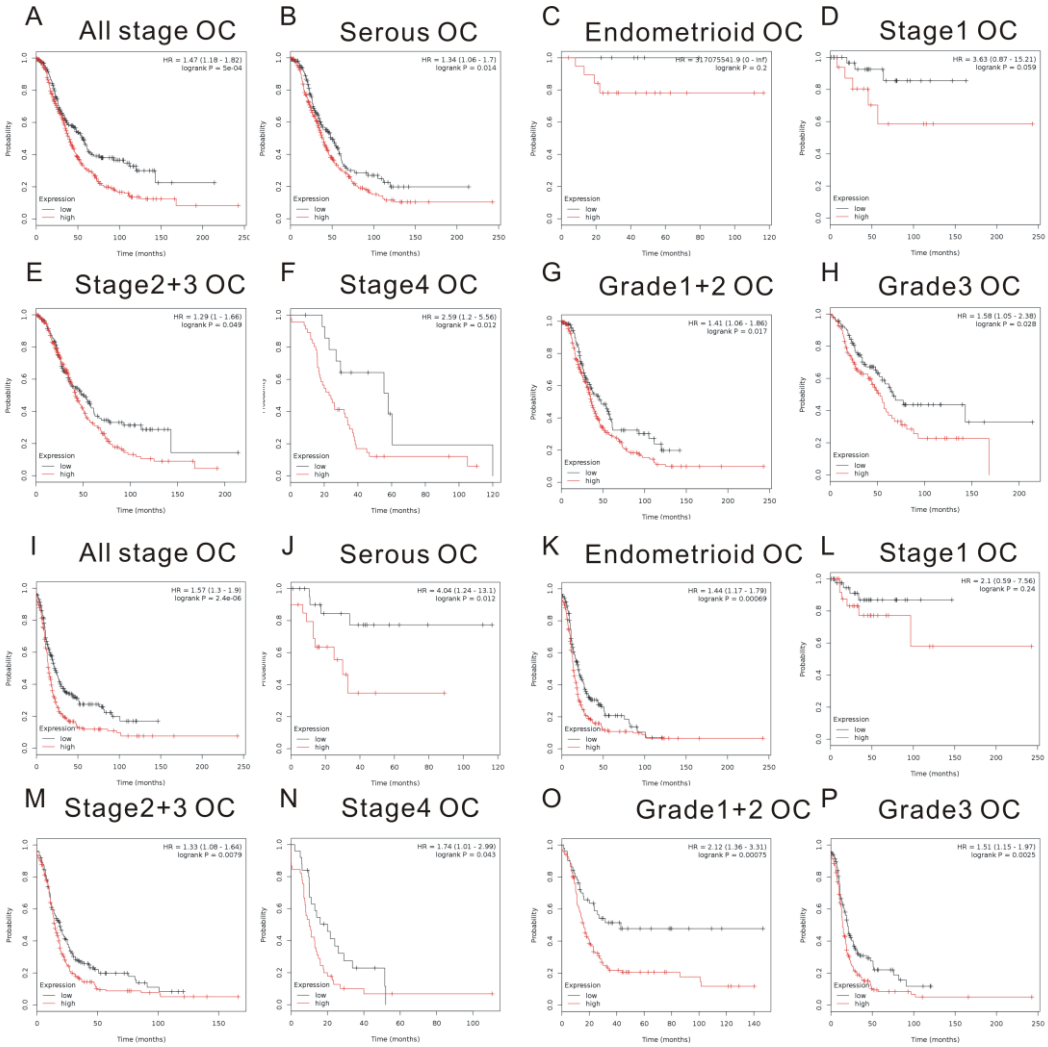

Figure 3. Higher KLHL14 expression was associated with worse overall survival and progression-free survival in OC samples.Higher KLHL14 expression was associated with worse overall survival in all stage (A), serous (B), Stage 2 + 3 (E), Stage 4 (F), Grade 1 + 2 (G), and Grade 3 OC patients (H), but not in endometrioid OC samples (C) and Stage 1 (D), based on Kaplan-Meier plotter dataset analysis. Higher KLHL14 expression was associated with worse progression-free survival in all stage(I), serous (J), endometrioid OC (K), Stage 2 + 3 (M), Stage 4 (N), Grade 1+2 (O), and Grade 3 OC patients (P), but not in Stage 1 (L), based on Kaplan-Meier plotter dataset analysis. Significance was defined as $p < 0.05$.

3.3. Higher KLHL14 expression is associated with worse survival EC

Then, Kaplan–Meier-plotter database was first applied to evaluate the prognostic values of KLHL14 in OC. As shown in Figure 3, we observed high mRNA expression of KLHL14 was significantly associated with shorter OS and PFS time in OC patients. Moreover, we found overexpression of KLHL14 is associated with worse survival in serous OC samples (Figure 3B), but not in endometrioid OC samples (Figure 3C). Based on our above results, we found KLHL14 was up-regulated in all stages of OC, suggested it could serve as an early diagnostic biomarker. Therefore,

we evaluate whether KLHL14 is associated with survival status in different stage of OC. As expected, we found the overall survival (OS) rate was lower in KLHL14-high groups compared to KLHL14-low groups in Stage 2 + 3 (Figure 3E), Stage 4 (Figure 3F), Grade 1 + 2 (Figure 3G), Grade 3 (Figure 3H), OC samples. However, we did not find the dysregulation of KLHL14 was associated with OS in Stage1 OC samples (Figure 3D). The similar tendency between KLHL14 expression and PFS were also observed in this study (Figure 3I–P).

Due to that Kaplan–Meier-plotter database did not contain EC samples, we performed Kaplan–Meier survival curve analysis to evaluate the correlation between KLHL14 expression and survival time in EC by using EC TCGA data. The upper quarter KLHL14 mRNA expression in all EC samples was used as the cutoff point to divide all cases into KLHL14 low and KLHL14 high groups. We found the overall survival rates were lower in KLHL14-high patients compared to KLHL14-low patients by using EC TCGA RNA-seq (Figure 4A).

Moreover, we also used OC TCGA dataset to validate whether Higher KLHL14 expression is associated with worse survival in OC. As shown in Figure 4C, we found the overall survival rates were lower in KLHL14-high patients compared to KLHL14-low patients by using ovarian cancer TCGA RNA-seq ($p = 0.0315$), TCGA microarray datasets ($p = 0.0026$, Figure 4E). We also examined the impact of KLHL14 expression on disease-free survival of OC and EC patients. Our analysis demonstrated that the OC and EC patients with higher KLHL14 expression had a suggestive shorter disease-free survival ($p = 0.081$, in EC RNA-seq data, Figure4B; $p = 0.051$, in OC RNA-seq microarray data, Figure 4D; $p = 0.0132$, in OC microarray data, Figure 4F).

3.4. Bioinformatics analysis of KLHL14 in OC and EC

Of note, KLHL14 was never reported in human cancers. In the present study, we conducted a series of bioinformatics analysis, including co-expression, GO, KEGG and protein-protein interaction analysis, to reveal the potential functions of KLHL14 in OC and EC. Firstly, co-expression analysis showed that about 457 genes in OC and 987 genes in EC were significantly correlated to KLHL14 with the absolute value of the Pearson correlation coefficient ≥ 0.3. Following the construction of the PPI network, a module analysis of the network was performed using the Mcode plugin (degree cut-off ≥ 2 and the nodes with edges ≥ 2-core). The top 3 positively (Figure 5A–C) and top 3 negatively (Figure 5D–F) hub-networks in OC and EC were shown in Figure 5. We then performed GO and KEGG analysis by using MAS3.0 system (Figure 6).

Our analysis revealed that KLHL14 was involved in regulating a series of biological processes in OC, including transcription, signal transduction, development, oxidation reduction, protein amino acid phosphorylation, cell adhesion, cell differentiation, ion transport, lipid metabolism, and cell cycle (Figure 6A). Meanwhile, MAPK signaling pathway, Jak-STAT signaling pathway, Wnt signaling pathway, and TGF-beta signaling pathway were also observed to be associated with KLHL14 in OC (Figure 6C). In EC, we observed KLHL14 was significantly associated with cell proliferation related pathways (such as cell cycle, cell division, mitosis, and DNA replication, Figure 6B,D). Meanwhile, we constructed a protein-protein interaction network of KLHL14 co-expressed genes in OC and EC based on the information in the STRING database (Figure 6).

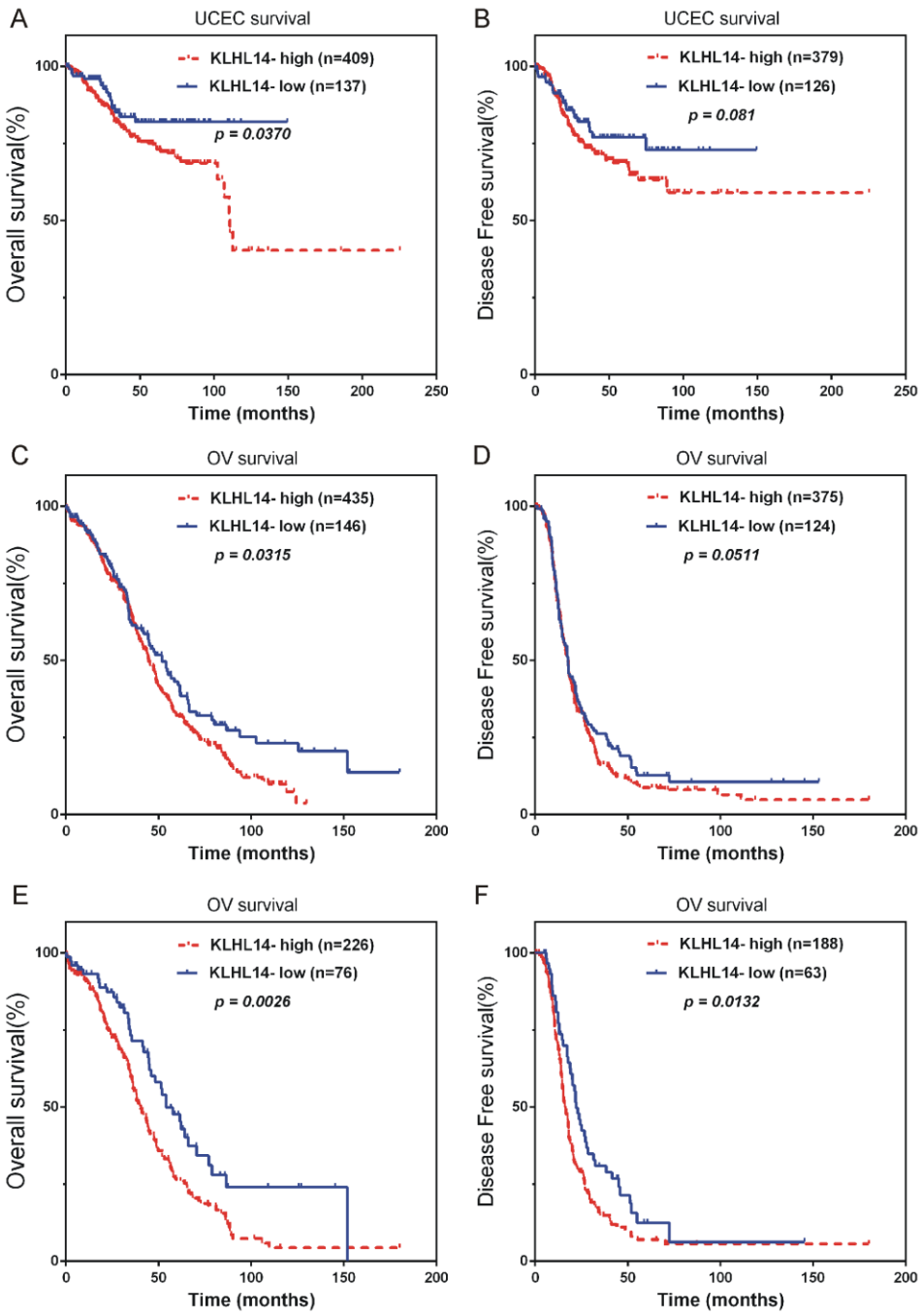

Figure 4. Higher KLHL14 expression was associated with worse overall and progression-free survival in EC samples. (A–B) Higher KLHL14 expression was associated with overall (A) and worse progression-free survival (B) in EC samples based on TCGA EC RNA-sequence dataset. (C–D) Higher KLHL14 expression was associated with overall (C) and worse progression-free survival (D) in OC samples based on TCGA OC RNA-sequence dataset. (E–F) Higher KLHL14 expression was associated with overall (E) and worse progression-free survival (F) in OC samples based on TCGA OC microarray dataset. Significance was defined as $p < 0.05$.

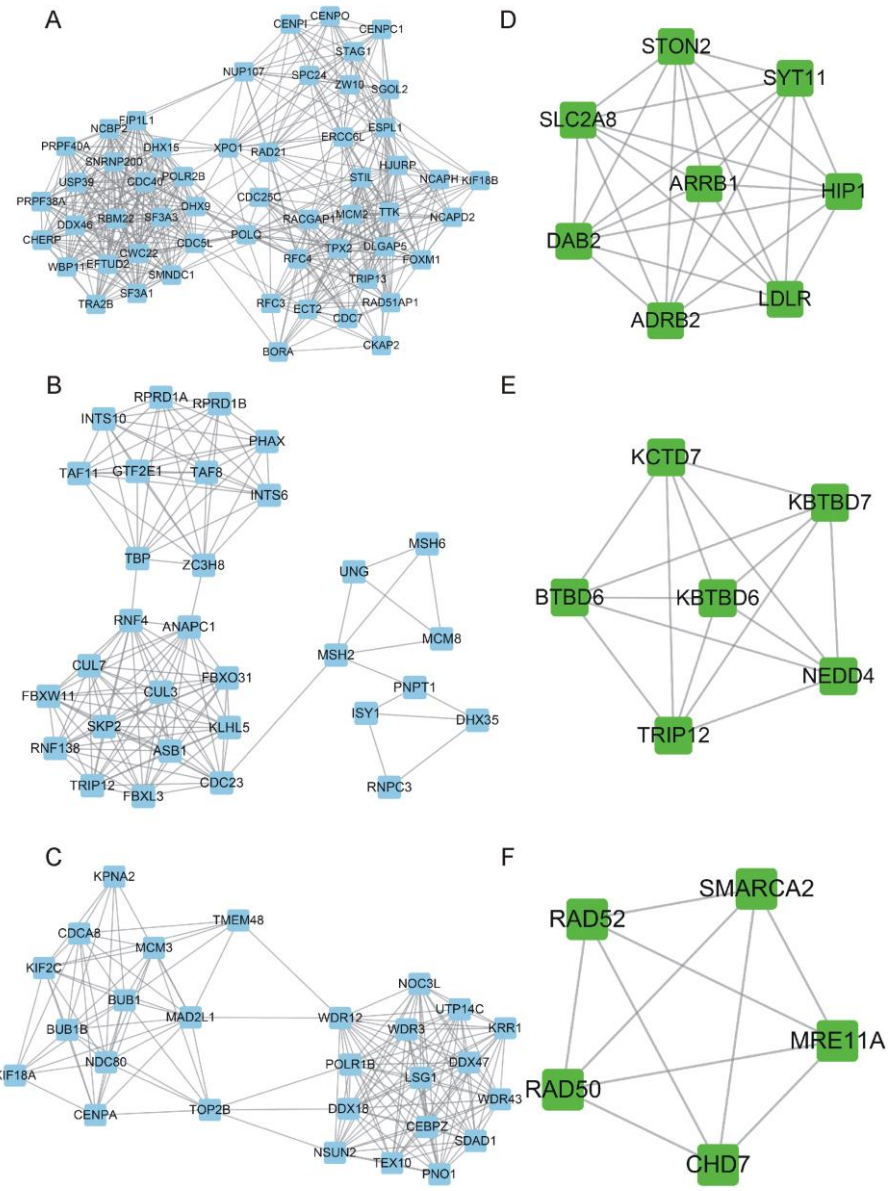

Figure 5. PPI network construction analysis for KLHL14 co-expressing genes in OC and EC. Three top hub-networks in EC (A–C) and OC (D-3) were identified. Blue nodes, KLHL14 co-expressing genes in EC; Green nodes, KLHL14 co-expressing genes in OC.

3.5. Knockdown of KLHL14 suppressed OC cell proliferation

In order to explore the potential functions of KLHL14 in OC, we designed 2 siRNAs to reduce its expression levels in SKOV3 and HO8910 cells. The results showed that the expression levels of KLHL14 were significantly suppressed following the transfection of si-KLHL14-1 and si-KLHL14-2 in SKOV3 (Figure 7A) and HO8910 cells (Figure 7C). CCK-8 assay showed that knockdown of KLHL14 significantly suppressed the cell proliferation rate compared to NC group in SKOV3 (Figure 7B) and HO8910 cells (Figure 7D).

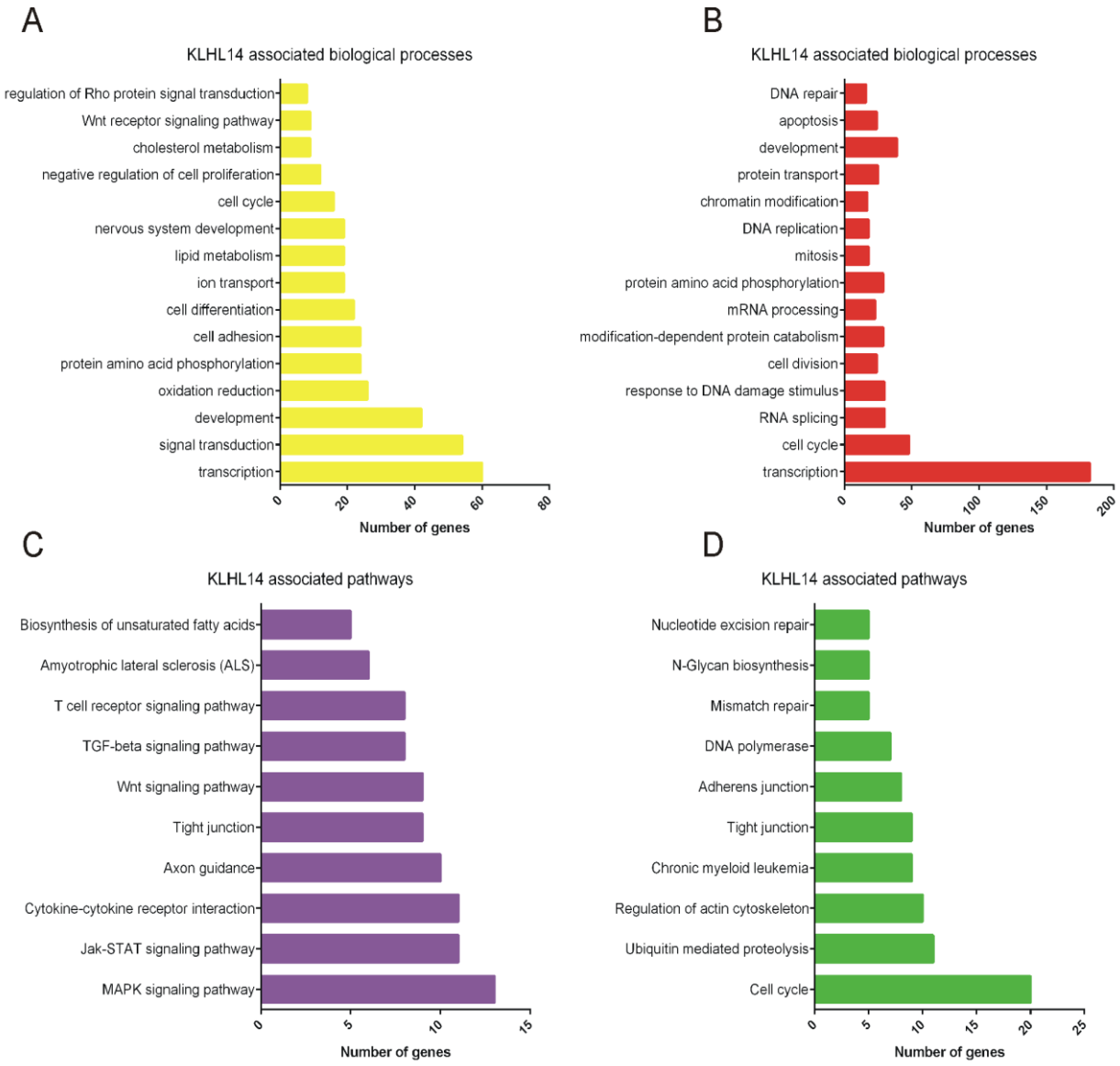

Figure 6. Bioinformatics analysis for KLHL14 in OC and EC. (A–B) GO analysis for KLHL14 co-expressing genes in OC (A) and EC (B). (C–D) GO analysis for KLHL14 co-expressing genes in OC (C) and EC (D).

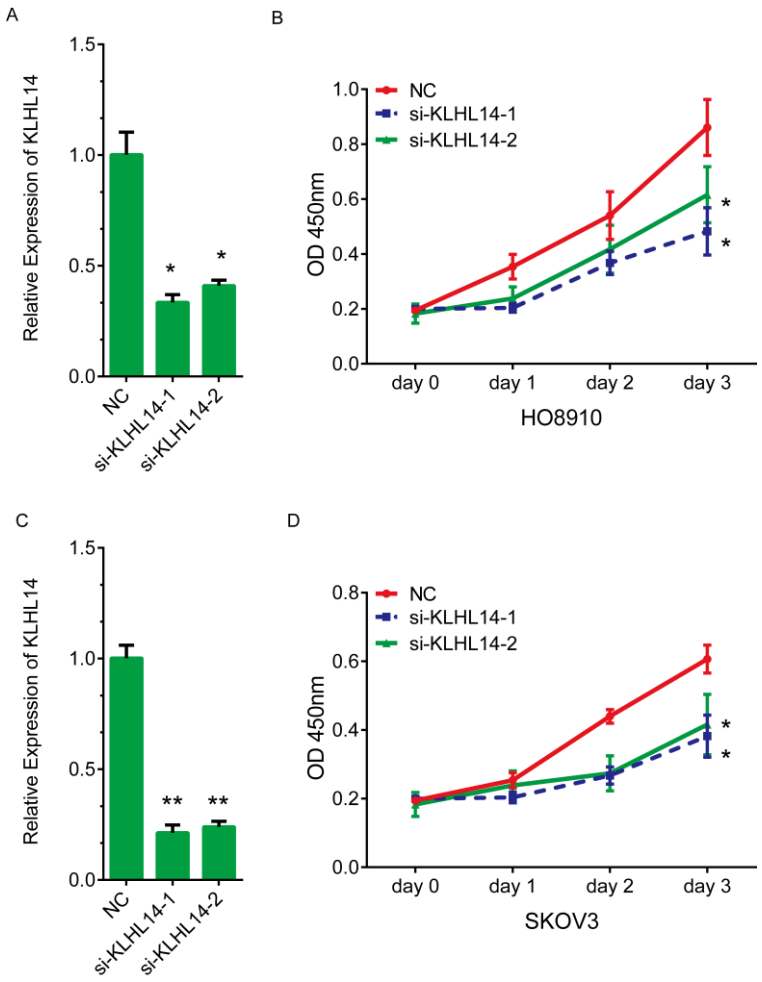

Figure 7. Knockdown of KLHL14 suppressed OC cell proliferation. (A,C) The expression levels of KLHL14 were significantly suppressed following the transfection of si-KLHL14-1 and si-KLHL14-2 in SKOV3 ($p < 0.05$) and HO8910 ($p < 0.01$) cells. (B,D) CCK-8 assay showed that knockdown of KLHL14 significantly suppressed the cell proliferation rate compared to NC group in SKOV3 and HO8910 cells ($P < 0.05$). (*, $p < 0.05$; **, $p < 0.01$).

4. Discussion

OC and EC are two of the most frequent gynecological malignancies worldwide. Over the past decades, great efforts were paid to identify accurate biomarkers for OC and EC. For example, a series of genes, including PKM2 [23], TBL1XR1 [24], LAMP3 [25], KPNA2 [26,27], and lncRNA TUBA4B [28] were dysregulated in OC. Meanwhile, the differential expression of EMP2 [29–31] and SOX2 [32] were reported to be linked to EC progression. However, the prognosis of OC and EC patients remained gloomy. The 5-year survival rate of advanced stage OC and EC was still less than 30%. In the present study, we for the first time reported KLHL14 was specially overexpressed in ovarian and endometrial cancer. By analyzing KLHL14 expression levels in 18 different types of human cancers, we observed KLHL14 was significantly specially up-regulated by more than 20 folds in OC and EC compared to other kinds of human cancers. Moreover, KLHL14 was overexpressed in

all stages of OC and EC compared to normal tissues. These results strongly suggested KLHL14 could act as an early diagnostic biomarker for OC and EC.

Previous reports had indicated KLHL genes were associated with cancer. For example, KLHL19 could inhibit lung cancer proliferation by decreasing the transcriptional activity of NRF2 [13]. KLHL14 was found to be hypomethylated in endometrial cancer. However, the functions of most members of this gene family, including KLHL14, remained largely unclear. In our present investigation, we observed KLHL14 protein level was overexpressed in OC and EC samples; however, KLHL14 was low or not detected in normal ovarian or endometrial stroma cells. Of note, Kaplan–Meier survival curve analysis demonstrated that overexpression of KLHL14 was correlated with significantly shorter overall survival and disease-free survival rate of OC and EC. These results showed KLHL14 is a prognostic marker for poor survival in OC and EC patients.

In the present study, we also explored the potential function roles of KLHL14 in OC and EC by using bioinformatics analysis. Our analysis revealed that KLHL14 was involved in regulating a series of biological processes in OC, including transcription, signal transduction, development, oxidation reduction, protein amino acid phosphorylation, cell adhesion, cell differentiation, ion transport, lipid metabolism, and cell cycle. Meanwhile, MAPK signaling pathway, Jak-STAT signaling pathway, Wnt signaling pathway, and TGF-beta signaling pathway were also observed to be associated with KLHL14 in OC. In EC, we observed KLHL14 was significantly associated with cell proliferation related pathways (such as cell cycle, cell division, mitosis, and DNA replication). Meanwhile, we constructed a protein-protein interaction network of KLHL14 co-expressed genes in OC and EC based on the information in the STRING database. Moreover, we conducted loos-of function assays. And we found that knockdown of KLHL14 suppressed OC cell proliferation.

5. Conclusion

To the best of our knowledge, this is the first study showed KLHL14 could serve as an early diagnostic target and predict a poor prognosis for OC and EC. Our findings showed KLHL14 was specially overexpressed in OC and EC. Significantly higher expression levels of KLHL14 was observed in all stages of OC and EC. Kaplan–Meier survival curve analysis demonstrated that overexpression of KLHL14 was correlated with significantly shorter overall survival and disease-free survival rate of OC and EC. Moreover, bioinformatics analysis indicated KLHL14 played an important role in OC and EC progression. Finally, we found knockdown of KLHL14 suppressed OC cell proliferation.

Acknowledgments

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Conflict of interest

The authors declare that they have no competing interests.

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