CFHR1 is a potentially downregulated gene in lung adenocarcinoma

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Abstract. There is increasing evidence that human complement factor H-related protein 1 (*CFHR1*) plays a crucial role in the development of malignant diseases. However, few studies have identified the roles of *CFHR1* in the occurrence and prognosis of lung adenocarcinoma (LADC). In the present study, comprehensive bioinformatic analyses of data obtained from the Oncomine platform, UALCAN and Gene Expression Profiling Interactive Analysis (GEPIA) demonstrated that *CFHR1* expression is significantly reduced in both LADC tissues and cancer cells. The patients presenting with downregulation of *CFHR1* had significantly lower overall survival (OS) and post progression survival (PPS) times. Through analysis of the datasets from Gene Expression Omnibus database, we found that the compound actinomycin D promoted *CFHR1* expression, further displaying the cytotoxic effect in the LADC cell line A549. In addition, the expression level of *CFHR1* in the cisplatin-resistant LADC cell line CDDP-R (derived from H460) was also significantly reduced. Our research demonstrated that low levels of *CFHR1* are specifically found in LADC samples, and *CFHR1* could serve as a potential therapeutic target for this subset of lung cancers. Determination of the detailed roles of *CFHR1* in LADC biology could provide insightful information for further investigations.

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Introduction

Lung cancer, as is well known, is the most common cause of cancer-related deaths all over the world. As a malignant tumor, lung cancer kills countless patients worldwide (1,2). Every year, 1.8 million individuals are diagnosed with lung cancer, and 1.6 million patients die as a result of the disease. In addition, the incidence rate of lung adenocarcinoma (LADC), the most common histologic subtype of lung cancer, has continued to increase in men and women (3). However, due to the delay in diagnosis, the treatment results for LADC remain unsatisfactory; 5-year survival rates vary from 4 to 17% depending on the stage and on regional differences (4). Moreover, the treatment and prognosis of LADC are still public health issues characterized by no progress in advanced diagnosis and treatment (1,5,6). Therefore, there is an urgent need to discover new molecular biomarkers for the early diagnosis and treatment of LADC.

The human complement factor H (CFH)-related protein (*CFHR*) family is composed of five members: *CFHR1*, *CFHR2, CFHR3*, *CFHR4* and *CFHR5*, and each member of this group can bind to the central complement component C3b. Mutations, genetic deletions, duplications or rearrangements in the individual *CFHR* genes are associated with many diseases, including cancer (7,8). Recent research shows that CFH-related genes (*CFHR1-5*) are associated with age-related macular degeneration (AMD) (9). At the same time, large international genome-wide association studies have shown that deletion of *CFHR1* is associated with a reduced risk of developing IgA nephropathy (10). Fratelli *et al* (11) found that the germinal homozygous deletion of the *CFHR1* gene could act as a promising risk factor for acute myelogenous leukemia. Another report also indicated that *CFHR1* was homozygously deleted in the cisplatin-resistance glioma cell lines U251 and CP2 (12). However, few studies have reported the relationship between the *CFHR* family and LADC, and the influence of *CFHR1* on the pathological process of LADC remains unexplored.

The aim of the present study was to evaluate the function of *CFHR1* and its relationship with clinical treatment and prognosis in human LADC. Our data indicate that *CFHR1* functions as a potential tumor suppressor in LADC tissues and

cell lines. Kaplan-Meier analysis suggests that *CFHR1* is an independent prognostic factor for LADC patients.

Materials and methods

Data collection and reanalysis using different bioinformatic methods. The expression levels of *CFHR1* in LADC tissues and cell lines are evidenced by a variety of bioinformatic network resources (Table S1).

Oncomine, a bioinformatics project that analyzes cancer transcriptome data to make it available to the biomedical research community, contains 65 gene expression datasets (13). UALCAN provides a silicon-based platform for validation of target genes and identification of tumor subpopulation-specific candidate biomarkers (14). GEPIA is a web server for gene expression profiling and interactive analyses in human cancers. It provides several key interactive customization features, such as differential expression analysis, patient survival analysis, and similarity gene detection (15). Through these public bioinformatics platforms, we clearly defined the expression profile of *CFHR1* in human LADC tissues and cell lines.

Kaplan-Meier plotter is a web-based tool for assessing the impact of 54,675 genes on the survival of 10,461 cancer samples and quickly determining the prognosis of the diseases (16), such as overall survival (OS) and post progressive survival (PPS) (17).

We downloaded the therapeutic transcriptome microarray dataset from the Gene Expression Omnibus (GEO) database under the login numbers GSE6400 (18) and GSE21656 (19). Then, we re-analyzed the original data in these datasets to further understand the impact of *CFHR1* expression on the chemotherapy response of LADC patients.

The web resource cBioPortal of cancer genomics provides a desired strategy for the exploration, visualization and analysis of multidimensional cancer genomics data (20). We used it to screen the coexpressed genes of *CFHR1* in LADC tissues. Protein-protein interaction (PPI) networks of these coexpressed genes were constructed using the STRING database (21). Then, Cytoscape software (version 3.0) was used to perform detailed visualization (22).

Next, we used the web-based Gene SeT AnaLysis Toolkit (WebGestalt) to perform Gene Ontology (GO) enrichment analysis (23). Meanwhile, the Pathview algorithm was used to analyze the relevant KEGG pathways (24).

Statistical analyses. The Student's t-test and the statistical software package SPSS (SPSS12.0, IBM Analytics) were used to analyze the differentially expressed mRNAs between cancer tissues and noncancer tissues. Meanwhile, the relationship between *CFHR1* expression and clinicopathological features of LADC patients was analyzed using a Chi-square test. The variants with statistical significance in single-factor analysis were further examined by multiple-factor analysis using the COX regression model. Pearson correlation coefficient was used to evaluate the correlation between genes. If $P \leq 0.05$, then the result was considered statistically significant.

Results

CFHR1 is downregulated in LADC tissues. To detect changes in *CFHR1* expression between LADC and adjacent nontumor tissues, the expression profiles of *CFHR1* were analyzed using three independent bioinformatic databases. First, as shown in Fig. 1A, it was found that *CFHR1* transcription levels were significantly reduced in tumor tissues based on two microarray datasets from the Oncomine platform (25,26). Furthermore, the downregulation of *CFHR1* transcription was confirmed in LADC tissues by using the UALCAN tool (Fig. 1B). Finally, to further confirm this result, the expression of *CFHR1* was re-analyzed in the GEPIA database and the same above-mentioned trend was verified (Fig. 1C). This observation confirmed that *CFHR1* is downregulated in LADC tissues.

CFHR1 as a presumed prognostic factor for adenocarcinoma. To date, almost no literature has reported the relationship between the expression of *CFHR1* and the clinical prognosis of human LADC. Thus, we conducted a clinical follow-up survey with the most commonly used monitoring indicators, OS and PPS (17,27). By using the Kaplan-Meier plotter platform, it was found that patients with downregulated *CFHR1* expression had a significantly shorter OS ($P<0.01$) (Fig. 2A). Moreover, patients with high levels of *CFHR1* tended to have a longer PPS, although this difference was not significant ($P>0.05$) (Fig. 2B). The reasons may be due to the sample size, and future evaluations with larger datasets are warranted. Furthermore, associations between *CFHR1* expression and *KRAS* mutation or T stage were observed to be statistically significant ($P=0.013$ and $P=0.002$, respectively) (Table I). No correlation was observed between *CFHR1* expression and sex, age, race, *EGFR* mutation, *EML4-ALK* translocation, lymph node metastasis, distant metastasis, pathologic stage, smoking history and Karnofsky performance score (Table I). The multiple-factor analysis using the COX regression model indicated that pathological T stage was independently associated with *CFHR1* transcription levels in LUAD samples (Table II). In summary, decreased *CFHR1* expression in patients with LADC is likely to be a valuable prognostic factor.

Role of CFHR1 in the treatment of adenocarcinoma. Next, from the GEO database, we screened two microarray datasets related to chemotherapy to further determine the effect of *CFHR1* in the treatment of LADC patients. From the data of GSE6400 (18), it was found that treatment with the anticancer agent actinomycin D obviously upregulated the expression of *CFHR1*, further exerting this anti-proliferative activity in cultured A549 LADC cells ($P=0.017$) (Fig. 3A). Meanwhile, data from GSE21656 (19) indicated that the expression of CFHR1 in a cisplatin-resistant LADC cell line (CDDP-R) was significantly downregulated when compared with the parental cell line H460 ($P=0.03$) (Fig. 3B). These findings showed that changes in *CFHR1* expression levels may be involved in the therapeutic response to cancer.

Network analysis of coexpressed genes of CFHR1. To further understand the biological function of *CFHR1*, we performed functional enrichment annotation analysis of its coexpressed genes. We downloaded the coexpressed genes of *CFHR1* from the cBioPortal database and screened 243 coexpressed genes with criteria of $P \leq 0.05$ and $|\text{LogFC}| \geq 0.7$ (Table SII). Then, the PPI network of 243 differentially coexpressed genes was

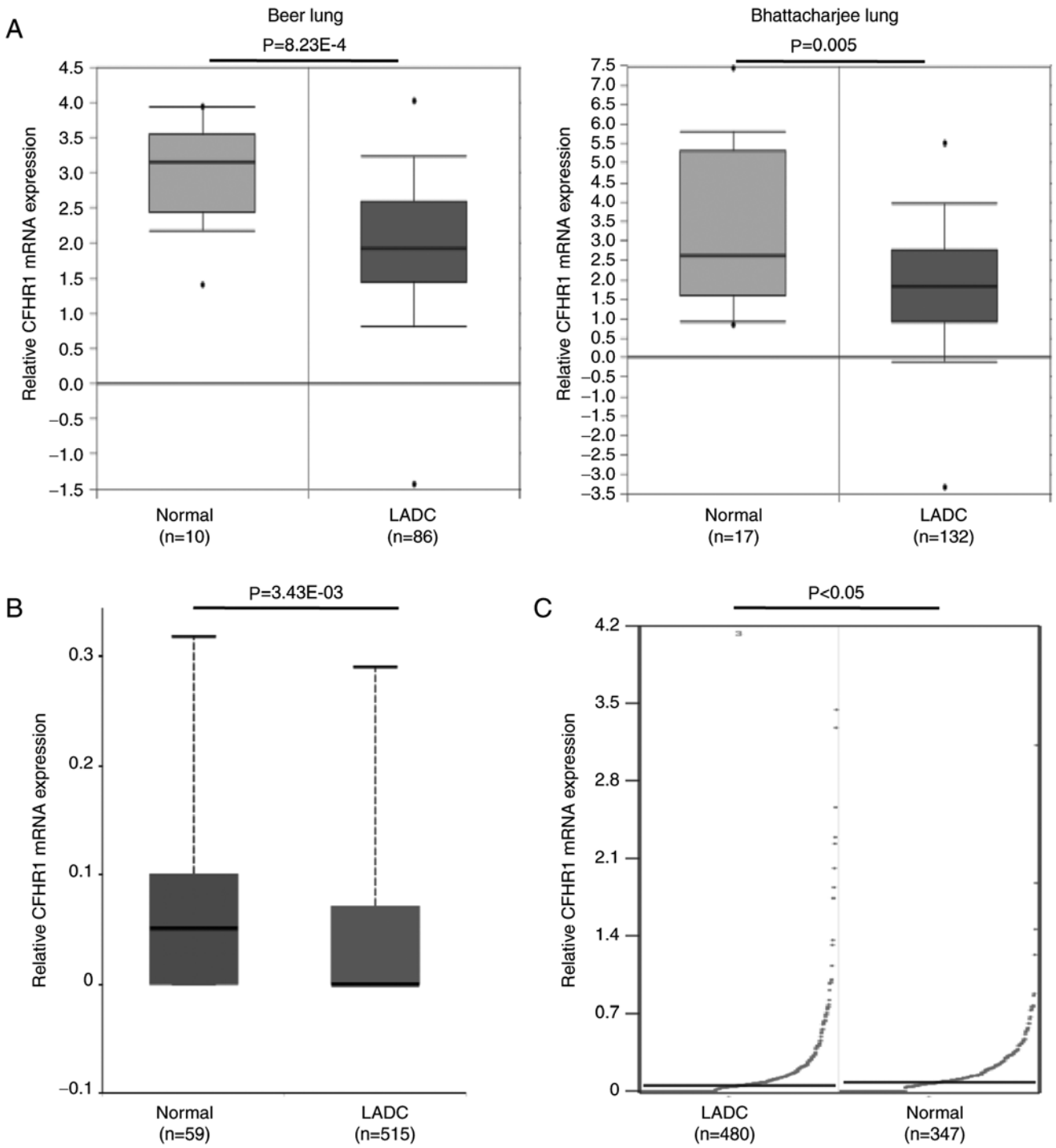

Figure 1. Analysis of *CFHR1* expression levels in LADC tissues. (A) The expression of *CFHR1* messenger RNA (mRNA) in Beer Lung and Bhattacharjee Lung was grouped by surrounding normal lung tissues and LADC. (B and C) The mRNA expression of *CFHR1* was detected from the UALCAN and GEPIA public databases, respectively. *CFHR1*, human complement factor H-related protein 1; LADC, lung adenocarcinoma.

performed by two frequently used algorithms, STRING and Cytoscape (Fig. 4A). At the same time, the Pathview database was used to analyze the KEGG pathways (Table SIII), and it was found that the most significant pathway was ribosome (Fig. 4B). Finally, to further illuminate the function among these 243 screened genes, WebGestalt was used to conduct the GO annotations and to identify the main molecular function (protein binding), biological process (response to stimulus and biological regulation) and cellular component (membrane) related to *CFHR1* biology (Fig. 4C).

Discussion

The aim of the present study was to understand the potential of human complement factor H-related protein 1 (*CFHR1*) in the development and treatment of lung adenocarcinoma (LADC). The present study is the first to use multiple public datasets to analyze the expression of *CFHR1* in LADC tissues. At the same time, the coexpressed genes of *CFHR1* were analyzed and several possible signaling pathways were identified that could determine its biological

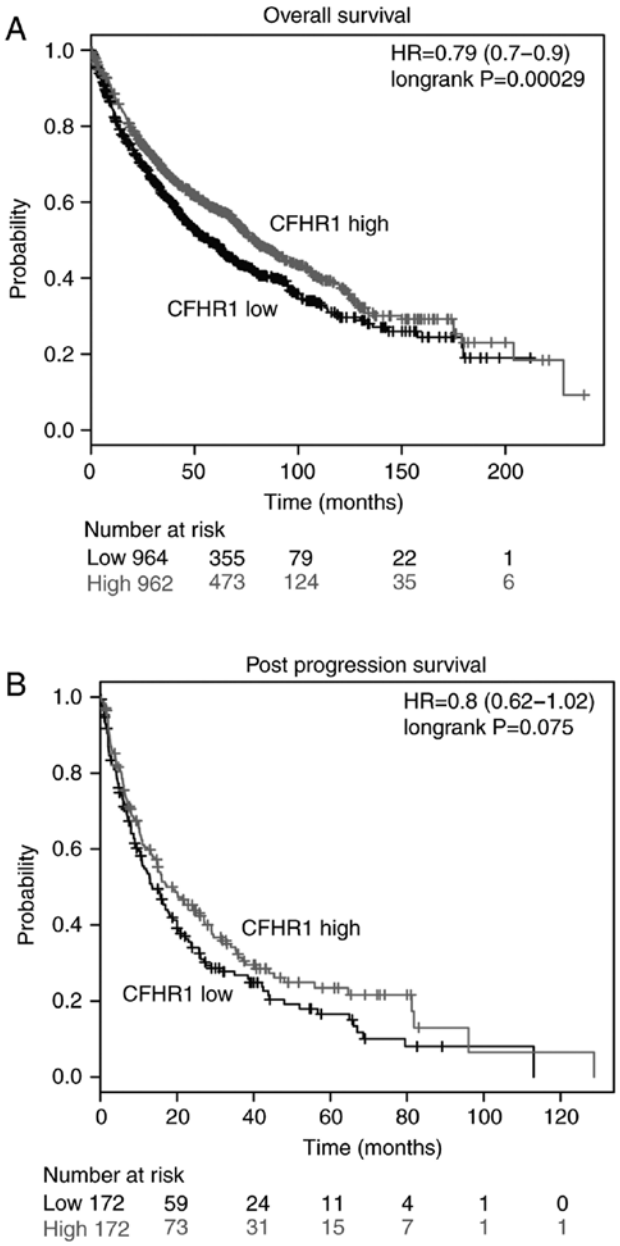

Figure 2. Relationship between *CFHR1* expression and the clinical features of patients with LADC. (A) Kaplan-Meier analysis of overall survival (OS) in LADC patients based on *CFHR1* expression. (B) Kaplan-Meier analysis of post progression survival (PPS) in LADC patients based on *CFHR1* expression. *CFHR1*, human complement factor H-related protein 1; LADC, lung adenocarcinoma.

significance in cancer development. Using the Oncomine, UALCAN and GEPIA datasets, it was demonstrated that *CFHR1* is significantly downregulated in LADC tissues. Moreover, through statistical analysis of clinical data from TCGA, it was found that the expression level of *CFHR1* was closely related to KRAS mutation and pathological T stage in LADC patients.

CFHR1 is a complement modulator that regulates complement by blocking complement C5 convertase activity and interfering with C5b surface binding (28). In autoimmune atypical hemolytic uremic syndrome (aHUS), CFH is blocked by FH autoantibodies, and 90% of patients carry homozygous deletions of *CFHR1* (29). However, heterozygous *CFHR1/CFH*

Table I. Single factor clinical data analysis related to *CFHR1*.

Source	No.	Mean ± SD	P-value
Sex			0.350
Male	207	0.959±1.47	
Female	248	0.830±1.46	
Kras_mutation			**0.013**
No	34	1.22±1.84	
Yes	14	0.341±0.427	
EGFR_mutation			0.301
No	171	0.842±1.18	
Yes	64	1.09±1.78	
EML4_ALK_ translocation			0.773
No	183	0.888±1.38	
Yes	23	0.978±1.72	
Pathologic_T			**0.002**
T1/T1a/T1b	140	0.979±1.66	
T2/T2a/T2b	254	0.814±1.28	
T3	41	0.603±0.986	
T4	18	1.12±1.47	
TX	2	7.69±0.868	
Race			0.802
Caucasian	355	0.907±1.43	
Asian	7	0.544±1.01	
Black or African-American	25	0.882±1.63	
Pathologic_N			0.801
N0	290	0.877±1.48	
N1	83	0.838±1.16	
N2	70	0.990±1.63	
N3	2	0	
NX	9	1.22±2.23	
Pathologic_M			0.560
M0	311	0.886±1.50	
M1/M1a/M1b	22	0.936±1.61	
MX	118	0.915±1.38	
Pathologic_stage			0.669
Stage I/IA/IB	246	0.908±1.53	
Stage IIA/IIB	106	0.753±1.13	
Stage IIIA/IIIB	79	1.02±1.63	
Stage IV	23	0.895±1.58	
Karnofsky performance score			0.394
0-70	13	0.698±0.692	
80	19	1.10±1.67	
90	19	0.395±0.835	
100	29	0.637±1.41	
Age (years)			0.471
40-60	116	0.858±1.35	
60-80	292	0.911±1.50	
>80	27	0.562±0.637	

CFHR1, human complement factor H-related protein 1. The clinical characteristics of the patients were downloaded from the dataset (TCGA Provisional) in cBioPortal and have not been published to date. P-values denoted in bold print are significant.

Table II. Clinical multivariate data related to *CFHR1*.

Source	Type III sum of squares	df	Mean square	F	P-value
Kras_mutation_found	4.627	1	4.627	2.513	0.120
Pathologic_T	36.867	4	9.217	5.005	**0.002**

CFHR1, human complement factor H-related protein 1. P-value denoted in bold print is significant.

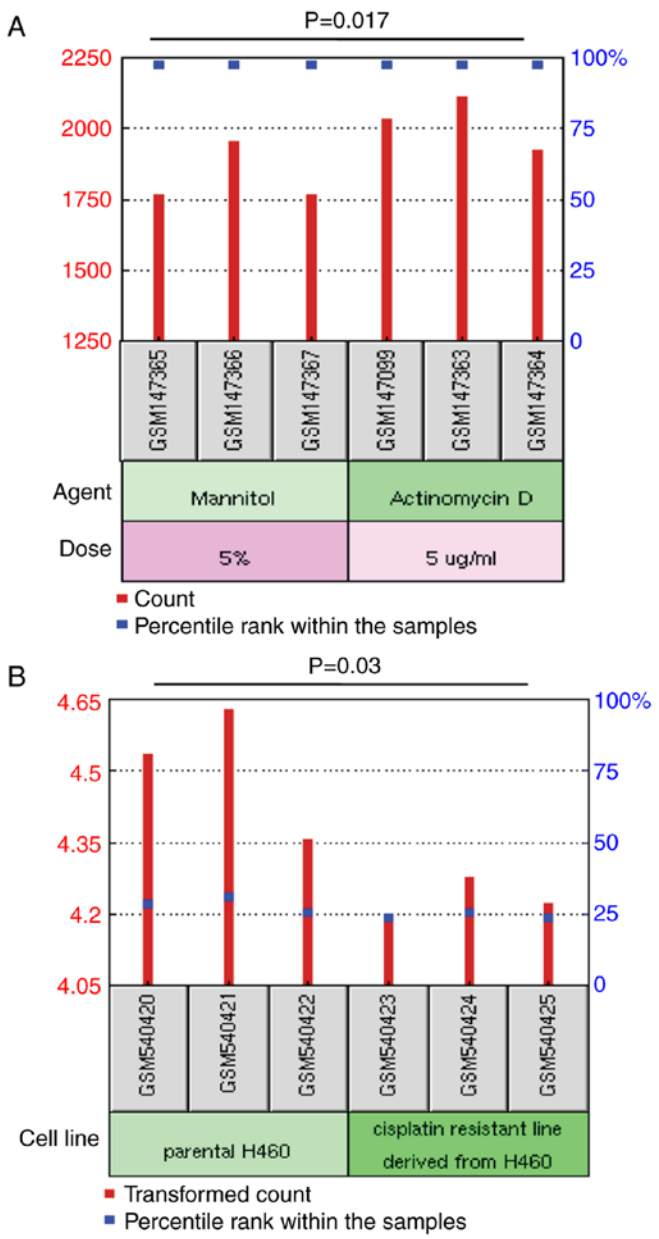

Figure 3. Effect of *CFHR1* on the therapeutic response of LADC patients. (A and B) The potential role of *CFHR1* expression in the treatment of LADC patients was evaluated using two therapeutically relevant microarray datasets (GSE6400 and GSE21656) in the Gene Expression Omnibus (GEO) database. *CFHR1*, human complement factor H-related protein 1; LADC, lung adenocarcinoma.

hybrid genes were also identified in 4.5% of patients with aHUS. These genomic rearrangements among *CFH* and *CFHR* have been proven to be associated with a high risk of posttransplant recurrence and poor clinical prognosis (30). In addition, Guo *et al* (31) found that abnormally expressed *CFHR1* could act as a promising predictive biomarker for cervical squamous cell carcinoma. Using an off-site matrix-based electrochemistry platform, Arya and Estrela further investigated CFHR1 as a bladder cancer protein marker (32). *CFHR1* gene polymorphisms also showed stronger associations with event-free survival in patients with follicular lymphoma (33). Although several studies have indicated the roles of *CFHR1* in the pathological process of human diseases, including cancers, no studies have revealed the functions of *CFHR*1 in LADC. In the present study, we demonstrated that *CFHR1* plays a potential role in tumor inhibition in LADC samples. In addition, it was also demonstrated that high expression of *CFHR1* is significantly associated with prolonged clinical OS and PPS in LADC patients. This provides an idea for further comprehensive exploration of the molecular mechanism of *CFHR1* as a promising therapeutic biomarker in LADC.

In the present study, the exact interaction between *CFHR1* and its coexpressed genes was not found; however, the PPI that was constructed benefits the identification of the function of *CFHR1* to some extent. Jullien *et al* (34) discovered that *CFHR1* is connected with a decreased level of glomerular immune deposits. Moreover, interleukin-6 (IL-6), located in the PPI network (Fig. 4A), is considered as a cytokine that essentially functions in immunoregulation via a signal transducer and activator of transcription 3 (STAT3) -dependent manner (35). Therefore, a phenomenon may exist in which *CFHR1* controls the secretion of IL-6 to influence the immunoregulation of human cancer cells. In addition, through the functional enrichment annotation analysis, the main functional pathway of the coexpressed genes of *CFHR1* has been confirmed to be the ribosome pathway. Previous research has demonstrated that the ribosome signaling pathway is significantly related to the microenvironment and metabolic changes of cancer cells (36,37). However, according to the published literature, no relevant studies have illuminated the detailed function and mechanism of *CFHR1* in the pathway modulation. Therefore, further studies are needed to clarify the roles of *CFHR1* in these KEGG pathways.

Overall, our results suggest that *CFHR1* is a candidate tumor suppressor in human LADC disease. The public database-based re-analysis methods also provide a novel research strategy for screening potential biomarkers related to the pathogenesis of malignant human diseases.

Acknowledgements

Not applicable.

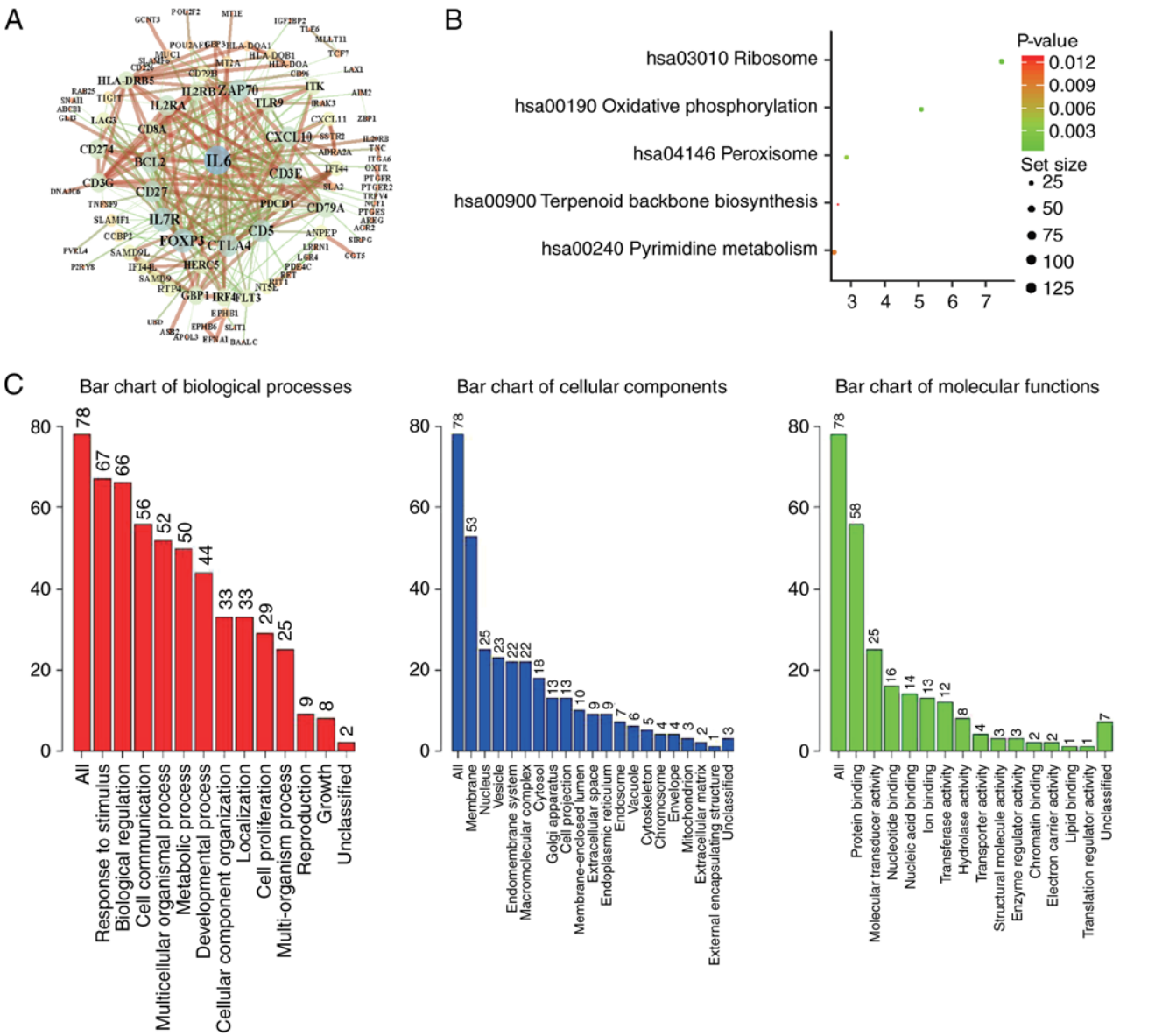

Figure 4. Coexpression network analysis of *CFHR1*. (A) The PPI network of *CFHR1*-associated genes, performed by two frequently used algorithms, STRING and Cytoscape. (B) The most significant KEGG pathway, ribosomal, was found in the Pathview database. (C) The main molecular functions, biological processes and cell components related to the biology of *CFHR1* were identified by WebGestalt. *CFHR1*, human complement factor H-related protein 1; PPI, protein-protein interaction; KEGG, Kyoto Encyclopedia of Genes and Genomes.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

GW, YY, JZ and ZX concieved and designed the study. GW, XW, XR, XC, SZ, JW, LQ, XY, CO, WL and ZG acquired and interpreted the data. GW, YY, JZ and ZX drafted the manuscript. YY and ZX revised the manuscript. All authors read and approved the final manuscript, and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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