Identification of potential key genes in gastric cancer using bioinformatics analysis

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Abstract. Gastric cancer (GC) is one of the most common types of cancer worldwide. Patients must be identified at an early stage of tumor progression for treatment to be effective. The aim of the present study was to identify potential biomarkers with diagnostic value in patients with GC. To examine potential therapeutic targets for GC, four Gene Expression Omnibus (GEO) datasets were downloaded and screened for differentially expressed genes (DEGs). Gene Ontology and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were subsequently performed to study the function and pathway enrichment of the identified DEGs. A protein-protein interaction (PPI) network was constructed. The CytoHubba plugin of Cytoscape was used to calculate the degree of connectivity of proteins in the PPI network, and the two genes with the highest degree of connectivity were selected for further analysis. Additionally, the two DEGs with the largest and smallest log Fold Change values were selected. These six key genes were further examined using Oncomine and the Kaplan-Meier plotter platform. A total of 99 upregulated and 172 downregulated genes common to all four GEO datasets were screened. The DEGs were primarily enriched in the Biological Process terms: ‘extracellular matrix organization’, ‘collagen catabolic process’ and ‘cell adhesion’. These three KEGG pathways were significantly enriched in the categories: ‘ECM-receptor interaction’, ‘protein digestion and absorption’, and ‘focal adhesion’. Based on Oncomine, expression of ATP4A and ATP4B were downregulated in GC, whereas expression of the other genes were all upregulated. The Kaplan-Meier plotter platform confirmed that upregulated expression of the identified key genes was significantly associated with worse overall survival of patients with GC. The results of the present study suggest that FN1, COL1A1, INHBA and CST1 may be potential biomarkers and therapeutic targets for GC. Additional studies are required to explore the potential value of ATP4A and ATP4B in the treatment of GC.

Introduction

Gastric cancer (GC) is a malignant tumor that originates in the epithelium of the gastric mucosa and is one of the most common types of malignant tumors in the world (1). According to GLOBOCAN 2018, there were >1,000,000 new cases of GC and ~783,000 deaths in 2018, thus making it the cancer type with the fifth highest incidence rate and the third highest mortality in the world (2). The poor five-year survival rate of GC is primarily due the advanced stage of gastric tumors at the initial diagnosis in the majority of patients, and thus limits treatment opportunities (3). According to the Cancer Staging Manual, 8th edition, of the American Joint Committee on Cancer, only 30% of GC cases are diagnosed prior to metastasis, and the five-year survival for pathological Tumor-Node-Metastasis stage groups are between 68-80% for stage I, 46-60% for stage II, 8-30% for stage III and 5% for stage IV (4). Therefore, identifying potential biomarkers for patients with early GC is critical for improving patient outcomes.

In recent years, a variety of bioinformatics methods have contributed greatly to the discovery of biomarkers associated with tumor development, diagnosis and prognosis (5-8). The combined use of multiple databases of biological information for the analysis of cancer has also yielded certain breakthroughs. Yong et al (9) used Gene Expression Omnibus (GEO), Oncomine, Search Tool for Recurring Instances of Neighbouring Genes (STRING) and other databases for bioinformatic analysis, and concluded that PPP2CA may function as an oncogene and a prognostic biomarker or therapeutic target in the progression of colorectal cancer. Troiano et al (10) used the GEO database and Oncomine to examine the expression of BIRC5/Survivin in oral squamous cell carcinoma and showed that Survivin expression was upregulated compared with non-cancerous tissue. In addition, immunohistochemistry staining showed that cytoplasmic expression of Survivin was associated with poor overall survival in patients with oral squamous cell carcinoma. It may
be beneficial to use multiple datasets and analysis tools to determine the potential mechanisms underlying development and progression of GC, and to identify potentially novel and specific diagnostic biomarkers for early detection of GC to improve the survival of patients.

In the present study, the expression profiles from four datasets (GSE13911, GSE19826, GSE54129 and GSE118916) in human GC and normal gastric tissue samples were obtained from the GEO database and analyzed to identify differentially expressed genes (DEGs). Gene Ontology (GO) and pathway enrichment analysis were performed to identify the biological functions and pathways of the DEGs. STRING and Cytoscape were used to construct a protein-protein interaction (PPI) network, and a total of six key genes were selected from the PPI network and DEGs. The value of the key genes was validated using the Oncomine and Kaplan-Meier platforms to further increase the reliability of the results and confirm the prognostic value of the key genes.

Materials and methods

Microarray data. The key word ‘gastric cancer’ was searched in the GEO database (ncbi.nlm.nih.gov/geo/), and a total of 9,224 datasets on human GC were retrieved. In the present study, four gene expression profiles from the GEO database were used, as they have not been studied together previously. The four datasets were: GSE13911 (11), GSE19826 (12), GSE54129 and GSE118916 (13). Among these, GSE13911, GSE19826 and GSE54129 were based on the GPL570 platform [(HG-U133_Plus_2) Affymetrix Human Genome U133 Plus 2.0 Array]. GSE118916 was based on the GPL15207 platform [(PrimeView) Affymetrix Human Gene Expression Array].

Identification of DEGs. DEGs between GC samples and normal controls were identified using the GEO2R online analysis tool (ncbi.nlm.nih.gov/geo/geo2r); llogFC≥1.0 and corrected P<0.05 were used as the cutoff criteria. The common DEGs of the four gene expression profiles were screened using Wayne analysis in Funrich (funrich.org/).

GO and KEGG enrichment analyses of DEGs. After obtaining the common DEGs, GO (14,15) and KEGG (16) analyses of the DEGs were performed using the Database for Annotation Visualization and Integrated Discovery (DAVID) online tool (17,18), with P<0.01 used as the threshold for significance. GO was used to identify the enrichment functions of three independent categories of genes: biological process (BP), cellular component (CC) and molecular function (MF). KEGG was used to search for the pathways associated with the identified genes (19). Only the top 10 BP, CC and MF terms, and the KEGG pathway with the smallest P-value were selected for further examination in the present study. The figures were generated using the OmicShare tools (omicshare.com/tools), a free online platform for data analysis.

PPI network construction. To explore the interaction between DEGs, the DEGs were analyzed using STRING (20) to generate a PPI network. PPI pairs with a combined score >0.4 were extracted, and disconnected nodes in the network were hidden. Subsequently, the PPI network was visualized using Cytoscape (21) and the degree of each protein node was calculated using the cytoHubba (22) plug-in in Cytoscape.

Identification of key genes. The two genes with the highest degree of connectivity in the PPI network, the two genes with the largest logFC values and the two genes with the smallest logFC among the shared DEGs were selected and considered key genes.

Analysis of key genes in Oncomine. The Oncomine database (oncomine.org/) was used to explore the mRNA expression differences of six key genes between GC and normal gastric tissue. Oncomine is a chip-based gene database and integrated data mining online cancer microarray database designed to facilitate the discovery of novel biomarkers from genome-wide expression analysis (23).

Survival analysis of key genes. The Kaplan-Meier plotter (24) is an online tool that can assess the effect of 54,000 genes on survival in 21 types of cancer. The largest datasets include breast (n=6,234), ovarian (n=2,190), lung (n=3,452) and gastric cancer (n=1,440) cancer. The primary purpose of the tool is to discover and validate biomarkers for survival. Online survival analysis of the selected key genes based on the GC database was performed using Kaplan-Meier Plotter. The hazard ratio (HR) with 95% confidence intervals (CIs) and log-rank P-values were calculated.

Results

Identification of DEGs. GSE13911 includes 38 GC samples and 31 normal samples, GSE19826 contains 12 GC samples and 15 normal samples, GSE54129 contains 111 GC samples and 21 normal samples, and GSE118916 contains 15 GC samples and 15 normal samples (Table I). In GSE13911, there are 26 intestinal, 4 mixed, 6 diffuse and 2 unclassified gastric carcinoma tissues, as well as 31 normal adjacent tissues. Unfortunately, information on the histological subtypes were not available in the other datasets. In the datasets, 1,001 upregulated and 2,304 downregulated DEGs were identified in GSE13911, 407 upregulated and 753 downregulated DEGs were identified in GSE19826, 1,852 upregulated and 2,083 downregulated DEGs were identified in GSE54129, and 977 upregulated and 903 downregulated DEGs were identified in GSE118916. Wayne analysis identified 99 common upregulated genes and 172 common downregulated genes were obtained from the 4 datasets (Table II; Fig. 1).

| Dataset ID     | Gastric cancer | Normal | Total | Number | Platform |
|----------------|----------------|--------|-------|--------|----------|
| GSE13911       | 38             | 31     | 69    |        | GPL570   |
| GSE19826       | 12             | 15     | 27    |        | GPL570   |
| GSE54129       | 111            | 21     | 132   |        | GPL570   |
| GSE118916      | 15             | 15     | 30    |        | GPL15207 |
GO and KEGG pathway enrichment analyses of DEGs. GO and KEGG pathway enrichment analyses of the DEGs was performed using the online tool DAVID, and the results are presented in Table III. GO analysis showed that in BP, the DEGs were primarily enriched for the GO terms: ‘extracellular matrix organization’, ‘collagen catabolic process’, ‘cell adhesion’, ‘collagen fibril organization’ and ‘digestion’ (Table III; Fig. 2A). CC analysis revealed that the DEGs were significantly enriched for the terms: ‘extracellular space’, ‘extracellular matrix’, ‘extracellular exosome’, ‘extracellular region’ and…

Table II. The differentially expressed genes identified from the four gene expression profiles, between gastric cancer and normal tissues.

| Differentially expressed genes | Gene terms |
|-------------------------------|------------|
| Upregulated                   | INHBA CST1 COL1A1 FAP COL10A1 FNDC1 COL8A1 SERPINH1 CDH3 THBS2 CLDN1 TNFRSF11B SPP1 COL1A2 SFRP4 SULF1 CPXM1 BMP1 MFAP2 COL1A1 CTHRC1 BGN RARRES1 IGF2BP3 THBS4 COL6A3 SRRX2 OSR2 HOXB7 TIMP1 ASPI THY1 FKBP10 PRRX1 SDS APOE PMEP A1 COL12A1 GPNMB FBNI ADAM12 C3 APOC1 COL5A1 SPARC EPHB2 NID2 CMTM3 PLEKH01 TNFRSF1B EHD2 FN1 MMP11 COCH AMIG02 COL5A2 OLFML2B KLHL23 SPOCK1 CDH11 TWIST1 RAB31 SULF2 FGDF6 VCAN ITGB1 PECOLCE HAVCR2 THBS1 DNM1 IGFBP7 PLAU TMEM158 COL3A1 FLNA EDNRN LEF1 LIPF FZD2 GXYLT2 S100A10 LGALS1 NRP2 SIRPA ANTXR1 CD9 LIF COL4A2 TGM2 COL6A1 PDNP KCNJ8 ACTN1 GPR161 ZAK RCN3 BAG2 BHLHE40 COL4A1 |
| Downregulated                 | ATP4A ATP4B KCNE2 AQP4 GIF LIPF GKN1 GKN2 DPCR1 PGC SOSTDC1 ESR3 RGC MUC6 S 1ST FBP2 CPA2 VSIG1 CXCL17 PIA2 CCKBR TMED6 CHGA TFF2 PSCA FUT9 CA9 SCNN1G GUCA2B C16orf89 SLC26A9 KLK11 CWHH3 DNER PSAP1 CLN13 ALDH3A1 GATA5 SCGB2A1 UGT2B15 RHD12 CLIC6 NRG4 CLDN18 CAPN9 SLC16A7 SSTR1 FBXL13 TCN1 VSIG2 AKB10 B3GNT6 FOLR1 MUM11 CHGB MAL TRIM50 AKR7A3 KIAA1324 PAIP2B SULT2A1 PTPRZ1 ARX LIFR ALDH1A1 HYAL1 BEX5 CA2 CYP2C18 ME1 SCNN1B ADH7 GCTN2 ACER2 FMO5 HPGD RASSF6 TFF1 TMEM171 CA4 KCNJ16 LDHD KCNJ15 GABRB3 HOMER2 TMPSRSS2 LYPD6B KLHDCA7A ARHGAP42 PLAC8 IGFBP2 CAPN13 SYTL5 PDGFD RNASE1 RORC CYP2C9 EP3 PBLD METTL7A ZBTB7C UBL3 SH3RF2 RNASE4 ARHGEC37 ALDH6A1 RAB27B SULT1B1 PKIB PXMP2 GPRC5C RIMBP2 ATP8A1 FAM20A PIGR GOLM1 CYP3A5 FAM46C C9orf152 COBLL1 FA2H SORB2 DGKD SGK2 TMEM220 ANG PLLP MYCN C1orf116 FGD4 SLC4A12 ADAM28 MAGI1 GRAMD1C IQGAP2 GULP1 SYT2L DHR57 OASL RNFI128 DBT ELL2 RAB27A NOSTRIN NEDD4L PPFIB2 AKR1C3 PEL2 SMPD3 PTPRZ2 RASEF TMEM92 ABCC5 GALTNT1 LMO4 NTN4 TMEM116 ID4 ELOVL6 ALDOB EPP4L1B CD36 GALNT5 SH3BGR1L2 MAGI3 MICAL1 HIPK2 MAOA WWC1 SLC7A8 CDC14B FABM107B SUCLG2 |

Upregulated genes are listed from largest to smallest fold change values. Downregulated genes are listed from smallest to largest fold change values.

Figure 1. Venn diagram of shared differentially expressed genes. (A) Upregulated and (B) downregulated genes from four gene expression profiles.
Table III. GO term and KEGG pathway enrichment analyses of the 271 differentially expressed genes.

| Category | Term Description                          | Count | P-Value          |
|----------|-------------------------------------------|-------|-----------------|
| **BP term** | go:0030198 Extracellular matrix organization | 23    | 1.28x10^{-13}   |
| BP term | go:0030574 Collagen catabolic process | 14 | 7.06x10^{-12}   |
| BP term | go:0007155 cell adhesion | 30 | 3.59x10^{-11}   |
| BP term | go:0030199 Collagen fibril organization | 9 | 7.87x10^{-10}   |
| BP term | go:0007586 Digestion | 10 | 3.19x10^{-07}   |
| BP term | go:0035987 Endodermal cell differentiation | 7 | 2.13x10^{-06}   |
| BP term | go:0001501 Skeletal system development | 11 | 3.42x10^{-05}   |
| BP term | go:0008202 Steroid metabolic process | 7 | 3.60x10^{-05}   |
| BP term | go:0071230 Cellular response to amino acid stimulus | 7 | 6.04x10^{-05}   |
| BP term | go:0006805 Xenobiotic metabolic process | 8 | 1.45x10^{-04}   |
| BP term | go:0042060 Wound healing | 8 | 1.70x10^{-04}   |
| BP term | go:0006081 Cellular aldehyde metabolic process | 4 | 4.70x10^{-04}   |
| BP term | go:0030277 Maintenance of gastrointestinal epithelium | 4 | 6.20x10^{-04}   |
| BP term | go:0010107 Potassium ion import | 5 | 6.98x10^{-04}   |
| BP term | go:0007584 Response to nutrient | 7 | 7.50x10^{-04}   |
| BP term | go:0002576 Platelet degranulation | 8 | 7.99x10^{-04}   |
| BP term | go:0060021 Palate development | 7 | 8.64x10^{-04}   |
| BP term | go:0010812 Negative regulation of cell-substrate adhesion | 4 | 0.001003 |
| BP term | go:0001503 Ossification | 7 | 0.001131 |
| BP term | go:0030168 Platelet activation | 8 | 0.001523 |
| BP term | go:0051216 Cartilage development | 6 | 0.001703 |
| BP term | go:0010628 Positive regulation of gene expression | 12 | 0.001721 |
| BP term | go:0001523 Retinoid metabolic process | 6 | 0.001977 |
| BP term | go:0016525 Negative regulation of angiogenesis | 6 | 0.002125 |
| BP term | go:0055114 Oxidation-reduction process | 19 | 0.002857 |
| BP term | go:0032964 Collagen biosynthetic process | 3 | 0.003084 |
| BP term | go:0008284 Positive regulation of cell proliferation | 16 | 0.003752 |
| BP term | go:0001649 Osteoblast differentiation | 7 | 0.004274 |
| BP term | go:0022617 Extracellular matrix disassembly | 6 | 0.005144 |
| BP term | go:0071711 Basement membrane organization | 3 | 0.005647 |
| BP term | go:0050891 Multicellular organismal water homeostasis | 3 | 0.005647 |
| BP term | go:001525 Angiogenesis | 10 | 0.005716 |
| BP term | go:0042476 Odontogenesis | 4 | 0.007007 |
| BP term | go:0010575 Positive regulation of vascular endothelial growth factor production | 4 | 0.007007 |
| BP term | go:0050909 Sensory perception of taste | 4 | 0.008568 |
| BP term | go:0001937 Negative regulation of endothelial cell proliferation | 4 | 0.008568 |
| BP term | go:0040037 Negative regulation of fibroblast growth factor receptor signaling pathway | 3 | 0.008901 |
| BP term | go:0042572 Retinol metabolic process | 4 | 0.009418 |
| CC term | go:0005615 Extracellular space | 63 | 9.65x10^{-17} |
| CC term | go:0031012 Extracellular matrix | 28 | 2.46x10^{-14} |
| CC term | go:0070062 Extracellular exosome | 87 | 1.68x10^{-12} |
| CC term | go:0005576 Extracellular region | 61 | 4.86x10^{-12} |
| CC term | go:0005788 Endoplasmic reticulum lumen | 20 | 4.73x10^{-11} |
| CC term | go:0005581 Collagen trimer | 15 | 5.56x10^{-11} |
| CC term | go:0005604 Basement membrane | 9 | 1.82x10^{-09} |
| CC term | go:0005578 Proteinaceous extracellular matrix | 22 | 3.57x10^{-10} |
| CC term | go:0016324 Apical plasma membrane | 16 | 2.29x10^{-09} |
| CC term | go:0009986 Cell surface | 20 | 3.51x10^{-09} |
| CC term | go:0005887 Integral component of plasma membrane | 34 | 0.004256 |
| CC term | go:0005886 Plasma membrane | 79 | 0.004569 |
‘endoplasmic reticulum lumen’ (Table III; Fig. 2B). For MF, the DEGs were enriched for the GO terms: ‘platelet-derived growth factor binding’, ‘collagen binding’, ‘extracellular matrix binding’, ‘inward rectifier potassium channel activity’ and ‘SMAD binding’ (Table III; Fig. 2C). According to KEGG pathway analysis, the DEGs were primarily enriched for the pathway terms: ‘ECM-receptor interaction’, ‘protein digestion and absorption’, ‘focal adhesion’, ‘amoebiasis’ and ‘gastric acid secretion’ (Table III; Fig. 2D).

**PPI network construction.** Based on the STRING prediction results, a PPI network with 211 nodes and 741 sides was constructed in Cytoscape (Fig. 3), and the number of segments connected to each gene in the figure represents its degree.

**Identification of six key genes.** The two genes with the most nodes were FN1 and COL1A1. In the PPI network, FN1 was the most prominent, with the highest degree of connectivity at 52. The degree of connectivity of COL1A1 is 43 (Table IV). Expression of these two genes is upregulated in GC tissues. Additionally, of those DEGs shared among the four gene expression profiles, the two DEGs with the largest logFC and the two DEGs with the smallest logFC values were selected. The higher the logFC in the upregulated DEGs, the greater the increase in expression of the gene. Similarly, the lower the logFC values in the downregulated DEGs, the greater the decrease in expression of the gene. When sorting DEGs according to logFC, the logFC of GSE19826 was used as the standard, as chip GSE19826 represented a homogenous cancer

| Category       | Term                          | Description                   | Count | P-Value |
|----------------|-------------------------------|-------------------------------|-------|---------|
| CC term        | GO:0030141                    | Secretory granule             | 6     | 0.004319|
| CC term        | GO:0031093                    | Platelet alpha granule lumen  | 5     | 0.008125|
| CC term        | GO:0031090                    | Organelle membrane            | 6     | 0.008522|
| MF term        | GO:0048407                    | Platelet-derived growth factor binding | 6 | 2.55x10^{-07} |
| MF term        | GO:0005518                    | Collagen binding              | 8     | 2.37x10^{-05} |
| MF term        | GO:0050840                    | Extracellular matrix binding  | 6     | 3.05x10^{-05} |
| MF term        | GO:0005242                    | Inward rectifier potassium channel activity | 4 | 0.002802 |
| MF term        | GO:0046332                    | SMAD binding                  | 5     | 0.003328 |
| MF term        | GO:0005201                    | Extracellular matrix structural constituent | 12 | 2.77x10^{-09} |
| MF term        | GO:0001758                    | Retinal dehydrogenase activity | 3    | 0.001432 |
| MF term        | GO:0005178                    | Integrin binding              | 11    | 2.77x10^{-06} |
| MF term        | GO:0005509                    | Calcium ion binding           | 27    | 1.47x10^{-05} |
| MF term        | GO:0008201                    | Heparin binding               | 12    | 2.07x10^{-05} |
| MF term        | GO:0016491                    | Oxidoreductase activity       | 9     | 0.008547 |
| KEGG pathway   | hsa04512                      | ECM-receptor interaction      | 16    | 5.16x10^{-01} |
| KEGG pathway   | hsa04974                      | Protein digestion and absorption | 14 | 7.73x10^{-09} |
| KEGG pathway   | hsa04510                      | Focal adhesion                | 18    | 2.67x10^{-07} |
| KEGG pathway   | hsa05146                      | Amoebiasis                    | 10    | 1.63x10^{-04} |
| KEGG pathway   | hsa04971                      | Gastric acid secretion        | 8     | 4.23x10^{-04} |
| KEGG pathway   | hsa04151                      | PI3K-Akt signaling pathway    | 17    | 7.35x10^{-04} |
| KEGG pathway   | hsa00830                      | Retinol metabolism            | 7     | 0.00124 |
| KEGG pathway   | hsa00982                      | Drug metabolism-cytochrome P450 | 7  | 0.001703 |
| KEGG pathway   | hsa00980                      | Metabolism of xenobiotics by cytochrome P450 | 7 | 0.002628 |
| KEGG pathway   | hsa05204                      | Chemical carcinogenesis       | 7     | 0.003889 |

PPI network construction. Based on the STRING prediction results, a PPI network with 211 nodes and 741 sides was constructed in Cytoscape (Fig. 3), and the number of segments connected to each gene in the figure represents its degree.

Table IV. The 10 genes with the largest degree of connectivity in the protein-protein-interaction network.

| Rank | Gene | Degree |
|------|------|--------|
| 1    | FN1  | 52     |
| 2    | COL1A1 | 43    |
| 3    | COL1A2 | 38    |
| 4    | COL3A1 | 37    |
| 5    | FBN1  | 35     |
| 6    | BGN   | 32     |
| 6    | COL5A2 | 32    |
| 8    | TIMP1 | 31     |
| 9    | SPARC | 30     |
| 10   | THBS2 | 28     |
tissue population at each Tumor-Node-Metastasis stage (25), which increases the accuracy of the expression profile (Table V). The two DEGs with the largest logFC values were INHBA (logFC=4.35) and CST1 (logFC=4.18) (Table VI). The two DEGs with the smallest logFC values were ATP4A (logFC=-6.46) and ATP4B (logFC=-5.91) (Table VII). Therefore, these six genes were selected as key genes.

Analysis of the six key genes in Oncomine. The Oncomine database was used to confirm the expression of the six key genes in 20 different types of cancer. The results showed that there were statistically significant differences in their expression. In the Oncomine database, there were no studies showing low expression of FN1, COL1A1, INHBA or CST1 in GC, but there were six, eight, seven and four studies showing increased expression, respectively. For ATP4A and ATP4B, the reverse was observed with no studies showing high expression, but seven and six studies, respectively, showing decreased expression (Fig. 4).

After comparing the expression levels of these six genes in cancerous and normal gastric tissue, the expression levels of FN1, COL1A1, INHBA and CST1 in GC tissues were significantly higher compared with the control group, and the expression levels of ATP4A and ATP4B in GC tissues were significantly lower compared with the control group (Table VIII; Fig. 5).

In addition, meta-analyses of the six key genes in GC in the Oncomine database also supported the findings that expression of FN1, COL1A1, INHBA and CST1 is upregulated in GC, whereas expression of ATP4A and ATP4B is downregulated in GC (11,12,26-28). The studies and references involved are
shown in Fig. 6. In the meta-analyses, P ≤-0.000, FC ≥2.0 and gene rank ≤300 were selected as the cutoff criteria.

Survival analysis of the six key genes. To identify the prognostic value of the six potential key genes, overall survival curves based on differential expression of the six key genes were plotted using Kaplan-Meier plotter (Fig. 7). There were 1,440 patients with GC on the Kaplan-Meier plotter platform who were suitable for the analysis of overall survival. The curves indicate that overexpression of the six key genes is significantly associated with decreased overall survival times of patients with GC. However, it is worth noting that ATP4A and ATP4B were significantly downregulated in GC samples in the present study.

Discussion

GC is a complex heterogeneous disease with high incidence and mortality rates, and poses a serious threat to afflicted patients. Therefore, it is important to identify biomarkers that are meaningful for both diagnostic and prognostic assessment (29).

In the present study, 271 DEGs were screened, including 99 upregulated and 172 downregulated genes, by analyzing four gene expression profiles containing a combined 176 GC tissue samples and 82 normal gastric tissue samples. Of the causes of cancer-associated deaths, 90% are the result of metastasis (30). In the present study, GO enrichment results showed that the occurrence and development of GC was closely associated with metastasis. GO analysis indicated that DEGs were primarily associated with extracellular matrix organization, collagen catabolic process and cell adhesion. Collagen is the primary component of the extracellular matrix and of the interstitial microenvironment. Collagen can provide a scaffold for tumor cell growth and induce migration of tumor cells (31,32). There is evidence that collagen synthesis increases in the presence of a gastric tumor (33). Zhou et al (32) reported that collagen components are quantitatively and qualitatively reorganized in the tumor microenvironment of GC, and collagen width was identified
as a useful prognostic indicator for GC (32). In addition, studies have shown that changes in cell-cell adhesion and cell-matrix adhesion can promote cancer cell metastasis (34). MF analysis showed that the DEGs were significantly enriched in platelet-derived growth factor binding. It has been demonstrated that inhibition of platelet-derived growth factor receptor-a can reduce the proliferation of gastrointestinal stromal tumor cells with mutant v-kit Hardy-Zuckerman 4
gene silencing reduced CST1 and INHBA. The largest and smallest logFC values, were all selected as key genes most closely associated with disease mechanisms. The degree of connectivity in the PPI network, and the two DEGs with the highest logFC values, was the gene with the highest degree of connectivity. It is expressed in a wide range of healthy plasmalemmas, lamina propria mucosae and smooth-muscle cell layers, and it is involved in a variety of cellular processes including embryogenesis, blood coagulation, wound healing, host defense and metastasis (44). As a glycoprotein involved in cell adhesion and migratory processes, FN1 is hypothesized to be involved in several types of cancer (36-38). The interaction between membrane receptors of tumor cells and ECM proteins serves an important role in tumor invasion and metastasis (39), and ECM-receptor interaction serves a crucial role in the process of tumor shedding, adhesion, degradation, movement and hyperplasia (38). In addition, the non-steroidal anti-inflammatory drug celecoxib may exhibit anti-GC effects by inhibiting the expression of various proteins and inhibiting leukocyte transendothelial migration and focal adhesion (40), which provides a possible mechanism for future investigations of the role of focal adhesion in GC and developing new anti-GC drugs.

The degree of connectivity of a gene in a PPI network reflects its association with GC. The higher the connectivity, the closer a gene is to the disease mechanism. The logFC values of DEGs reflects the level of up or downregulation of the gene. The higher the logFC values in the upregulated DEGs, the greater the degree of upregulation of the gene, and the lower the logFC values in the downregulated DEGs, the greater the degree of downregulation (41-43). Thus it was hypothesized that the DEGs with the highest and lowest logFC values would be the genes most closely associated with disease mechanisms.

In the present study, the two genes with the highest degree of connectivity in the PPI network, and the two DEGs with the largest and smallest logFC values, were all selected as key genes. These were FN1, COL1A1, INHBA, CST1, ATP4A and ATP4B. These six key genes were verified in the Oncomine database. Expression of FN1, COL1A1, INHBA and CST1 were upregulated in GC, and expression of ATP4A and ATP4B were downregulated, consistent with the results obtained from analysis of the GEO datasets. Furthermore, survival analysis showed that upregulation of the six key genes was significantly associated with worse overall survival, and downregulation of ATP4A and ATP4B expression predicted a more favorable prognosis for patients with GC, providing novel insights into potential GC treatment strategies.

FN1 was the gene with the highest degree of connectivity. It is expressed in a wide range of healthy plasmalemmas, lamina propria mucosae and smooth-muscle cell layers, and it is involved in a variety of cellular processes including embryogenesis, blood coagulation, wound healing, host defense and metastasis (44). As a glycoprotein involved in cell adhesion and migratory processes, FN1 is hypothesized to be involved in several types of cancer (13). Expression of FN1 is significantly increased in anti-chemotherapy osteosarcoma cell lines and tissues, and is associated with a poor prognosis (45). Knockdown of FN1 gene expression results in reduced cell proliferation, increased cellular senescence and apoptosis, and reduced migration and invasion, by blocking the activation of the PI3K/AKT signaling pathway (46). Furthermore, downregulation of FN1 inhibits proliferation, migration and invasion, and thus reduces progression of colorectal cancer (47). The results of the present study suggest that FN1 may be a potential biomarker and therapeutic target for diagnosis and treatment of GC, consistent with previous studies (13,48,49), and thus further confirming the significance of FN1 in GC.

COL1A1 is one of the most important components of the ECM, and it is highly expressed in most connective tissues and various human solid tumors (50). It is also the primary component of type I collagen, which serves a key role in tumor cell adhesion and invasion (51). A mechanistic study revealed that COL1A1 and COL1A2 affects angiogenesis in GC, and their expression is also significantly associated with progression of GC (52). In addition, Zhang et al (53) further confirmed that overexpression of COL1A1 promoted GC cell proliferation in vitro. These previous studies support the use of COL1A1 as a key potential GC biomarker in the present study.

INHBA is a member of the transforming growth factor-β (TGF-β) superfamily, which is closely associated with tumor proliferation and expression is upregulated in lung cancer (54), GC (12) and colon cancer (55), where INHBA expression is closely associated with their prognosis. In a study of GC, Chen et al (56) found that INHBA gene silencing reduced migration and invasion of GC cells by blocking the activation of the TGF-β signaling pathway. They suggested that INHBA was a potential target for GC therapy (56). Another study showed that INHBA mRNA expression in GC may be a useful prognostic biomarker for patients with stage II or III GC who receive adjuvant chemotherapy with S-1 (57). The results of the present study support the conclusions drawn in these previous studies.

Cystatin SN (CST1) is a member of the type 2 cystatin superfamily, the primary role of which is to limit the proteolytic activity of cysteine proteases (58). The dysregulated expression of CST1 is hypothesized to be involved in several types of
cancer, including cholangiocarcinoma (59), breast cancer (58), GC (60) and colorectal cancer (61). CST1 prevents cell aging and promotes cancer development by affecting the activity of cathepsin B (62). However, CST1 has not been analyzed using bioinformatics for survival prognosis in GC, to the best of our knowledge. Using multiple databases, the present study is the first to validate CST1 as a novel prognostic biomarker and a potential therapeutic target for treatment of GC.

Table VIII. Additional information for the six key genes shown in Figure 5.

| Author, year | Gene | Normal tissue samples | Gastric cancer samples | P-value | Fold Change | Published journal | (Refs.) |
|--------------|------|-----------------------|------------------------|---------|-------------|-------------------|---------|
| Chen et al, 2003 | FN1  | 28                    | 8                      | 5.73x10^-14 | 7.441 | Molecular Biology of The Cell | (26) |
| Cui et al, 2011 | COL1A1 | 80                    | 80                     | 1.81x10^-15 | 3.201 | Nucleic Acids Research | (28) |
| Cui et al, 2011 | INHBA | 80                    | 80                     | 5.17x10^-13 | 3.043 | Nucleic Acids Research | (28) |
| Cho et al, 2011 | CST1 | 19                    | 31                     | 3.17x10^-13 | 21.525 | Clinical Cancer Research | (27) |
| Cho et al, 2011 | ATP4A | 19                    | 20                     | 4.73x10^-17 | -100.911 | Clinical Cancer Research | (27) |
| D’Errico et al, 2009 | ATP4B | 31                    | 26                     | 6.15x10^-19 | -246.630 | European Journal of Cancer | (11) |

Figure 5. Expression of six key genes in different gastric cancer gene chips in Oncomine. P<0.0001 and a |fold change|>2 were used as the threshold. Comparison of mRNA expression in cancerous vs. normal gastric tissue. (A) FN1, (B) COL1A1, (C) INHBA, (D) CST1, (E) ATP4A and (F) ATP4B.
ATP4A encodes the α subunit and ATP4B encodes the β subunit of the gastric H+, K+–ATPase, respectively. They regulate gastric acid secretion and, as a result, are targets for acid reduction (63). Fei et al (64) found that expression of ATP4A and ATP4B were significantly downregulated in patients with GC, but their expression was not significantly correlated with overall survival (64). In the present study, downregulation of ATP4A and ATP4B expression
was associated with favorable overall survival in patients with GC. Downregulation of ATP4A and ATP4B mRNA expression in GC tissue is associated with the development of GC (65). Correa's Cascade is inversely associated with gastric acid secretion rate, the downregulation of ATP4A and ATP4B mRNA expression begins in the early stages of gastric mucosal lesions, and the expression of both is gradually decreased as Correa's cascade progresses (66). In addition, Helicobacter pylori (H. pylori) inhibits parietal acid secretion by downregulating the expression of ATP4A and ATP4B in gastric parietal cells prior to the formation of GC, suggesting that H. pylori is closely associated with the development of GC (67). Thus, it was hypothesized that ATP4A and ATP4B may inhibit the formation of GC. Survival analysis showed that ATP4A and ATP4B in GC are adverse prognostic factors for patients with GC, suggesting that upregulation is associated with progression of GC. However, studies have reported that the expression of ATP4A

Figure 7. Kaplan-Meier overall survival analyses of patients with gastric cancer based on expression of the six key genes. (A) FN1, (B) COL1A1, (C) INHBA, (D) CST1, (E) ATP4A, (F) ATP4B. HR, hazard ratio.
and ATP4B is not regulated by *H. pylori* in GC (68-70). Other studies have shown significant decreases in the abundance of *Helicobacter* and *Neisseria*, and significant increases in *Achromobacter, Citrobacter, Pseudobacterium, Clostridium, Rhodococcus* and *Lactobacillus* in gastric carcinoma in comparison with chronic gastritis (71,72). Additionally, the gastric microbiota composition in patients with gastric carcinoma is significantly different compared with patients with chronic gastritis (71). Therefore, it was hypothesized that the formation of an altered gastric microbiota composition may result in the expression of ATP4A and ATP4B to be passively upregulated as GC progresses. Further research is required to more accurately determine the biological function of ATP4A and ATP4B in GC.

Although several genes were identified as promising diagnostic and prognostic biomarkers for GC, the present study has the following limitations. First, the present study lacked experimental and clinical validation. Second, the possibility that different histological types may affect the accuracy of results cannot be eliminated. Thus, future bioinformatics analysis should be designed such that samples can be stratified to reflect the wider populace. Therefore, it is necessary to use larger samples to perform bioinformatics analysis, and further experimental and clinical studies are required.

In conclusion, the present study used bioinformatics to analyze biological processes and signaling pathways closely associated with GC occurrence and development and identified *FN1, COLIA1, INHBA* and *CST1* as promising diagnostic and prognostic biomarkers for GC patients. Additionally, the results of the survival analysis of ATP4A and ATP4B were inconsistent with other international studies. Therefore, further studies are required to assess the effects of ATP4A and ATP4B on GC initiation and development. Furthermore, experimental and clinical studies are required to validate the findings of the present study and determine the potential clinical value of these potential biomarkers.

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**Availability of data and materials**

The datasets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

**Authors' contributions**

WW and YH conceived of and designed the study. YH and QZ performed the bioinformatics analysis and analyzed the data. WW and QZ wrote the manuscript. WW and ZL revised the manuscript. XZ contributed to the design of the study and revised the manuscript. All authors read and approved the final manuscript.

**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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