Identification of genes and long non-coding RNAs associated with the pathogenesis of gastric cancer

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Abstract. Gastric cancer is a lethal disease characterized by high diffusivity and mortality. To examine the mechanisms involved in gastric cancer, we analyzed the microarray of GSE41476. GSE41476 was downloaded from the Gene Expression Omnibus and included 3 primary cell culture samples from gastric cancer tissues, 3 gastric cancer cell lines and 2 normal tissue samples. Long non-coding RNAs (lncRNAs) and differentially expressed genes (DEGs) were screened by Cuffdiff software. Functions of the DEGs were predicted by functional and pathway enrichment analyses. The interaction relationships of the proteins encoded by DEGs that were obtained from the STRING database and protein-protein interaction (PPI) network were visualized using Cytoscape. Modules analysis of PPI network was performed using CFinder. Moreover, lncRNA analysis was performed. A total of 86 lncRNAs, and 1,088 up- and 1,537 downregulated transcriptions were screened. For DEGs in module A of the PPI network for upregulated genes, the enriched pathways included ECM-receptor interaction and focal adhesion, both of which involved *COL* and *ITG* genes. The *COL* genes interacted with the *ITG* genes (e.g., *COL1A1-ITGA5* and *COL1A2-ITGB1*). For DEGs in module B of the PPI network for downregulated genes, the enriched pathways for DEGs included the T-cell receptor signaling pathway, which involved *PIK3CG* and *PIK3R5*. *PIK3CG* had an interaction relationship with *PIK3R5*. In addition, *IL7* was co-expressed with *TCONS-00068220*. In summary, the results showed that *COL* and *ITG* genes, *PIK3CG*, *PIK3R5*, *IL7* and *lncRNA TCONS-00068220* may play a role in gastric cancer.

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Abbreviations: ANXA1, Annexin A1; BP, biological process; CA IX, carbonic anhydrase IX; DEGs, differentially expressed genes; GKN2, gastrokine 2; GO, Gene Ontology; hg19, human genome 19; HOTAIR, HOX transcript antisense RNA; IL8, interleukin-8; lncRNAs, long non-coding RNAs; KEGG, Kyoto Encyclopedia of Genes and Genomes; MEG3, maternally expressed 3; PI3K, phosphatidylinositol 3-kinase; PPI, protein-protein interaction; PSCA, prostate stem cell antigen; suPAR, soluble urokinase plasminogen activator receptor

Key words: gastric cancer, differentially expressed genes, long non-coding RNAs, protein-protein interaction network, module analysis

Introduction

As a type of malignant epithelial tumor, gastric cancer is derived from the glandular epithelium of the gastric mucosa (1). Gastric cancer has high diffusivity, such as spread to lungs, liver and bones (2). This cancer type is prevalent in men of developing countries (3,4), and ~8.5% of cancer cases in men is gastric cancer (5). In 2012, gastric cancer ranked third after lung and liver cancer, with 700,000 mortalities (6,7). Thus, it is necessary to examine the molecular mechanisms of gastric cancer and develop therapeutic schedules.

The molecular mechanisms of gastric cancer have been previously investigated. For example, as a member of the *BRICHO* family, the full-length gene gastrokine 2 (*GKN2*) is downregulated and associated with gastric cancer (8). The expression of *GKN1* and *GKN2* decreased in gastric adenocarcinomas, and their loss is associated with shorter survival in the intestinal subtype of gastric adenocarcinomas (9). Expression of soluble urokinase plasminogen activator receptor (*suPAR*) and carbonic anhydrase IX (*CA IX*) is associated with the stage and presence of gastric cancer, and the overexpression of *suPAR* indicates a poorer prognosis in patients with gastric cancer (10). Differentially expressed microseminoprotein (*MSMB*), Annexin A10 (*ANXA10*), Annexin A1 (*ANXA1*) and prostate stem cell antigen (*PSCA*) have been identified in normal and cancer gastric tissues, and may be used as biomarkers for the diagnosis and treatment of gastric cancer (11).

Long non-coding RNAs (lncRNAs), having a length >200 nucleotides, can regulate gene expression during transport, RNA maturation and protein synthesis (12). Dysregulation of lncRNAs is associated with many types of human cancer (13). Many differentially expressed lncRNAs, such as *LINC00152* and *LINC00261*, have been identified and may act as therapeutic targets and biomarkers in gastric cancer (12). The downregulation of lncRNA maternally

Table I. The top 10 enriched GO functions and KEGG pathways for the DEGs.

Genes	ID	Name	Gene no.	Gene symbol	P-value
GO functions					
Upregulated	GO:0030198	Extracellular matrix organization	71	*ACTN1*, *ADAM17*...	0
	GO:0043062	Extracellular structure organization	71	*ADAM9*, *ADAMTS2*...	0
	GO:0016477	Cell migration	110	*AJUBA*, *AMOTL1*...	8.97E-14
	GO:0031012	Extracellular matrix	422	*ADAMTS1*, *CD248*...	3.06E-14
	GO:0005515	Protein binding	521	*ABL2*, *ABLIM3*...	3.37E-11
Downregulated	GO:0048584	Positive regulation of response to stimulus	189	*A2M*, *ADA*...	6.66E-16
	GO:0044699	Single-organism process	1017	*EPHX2*, *EPN1*...	1.33E-15
	GO:0002694	Regulation of leukocyte activation	76	*AIF1*, *BCR*...	1.89E-15
	GO:0031224	Intrinsic to membrane	565	*A4GNT*, *AADAC*...	1.11E-15
	GO:0005102	Receptor binding	146	*APLP1*, *APOE*...	4.68E-08
KEGG pathways					
Upregulated	KEGG:4512	ECM-receptor interaction	20	*CD44*, *COL1A1*...	1.18E-06
	KEGG:4510	Focal adhesion	29	*ACTN1*, *COL1A1*...	0.000143
	KEGG:5146	Amoebiasis	18	*RKCA*, *SHC3*...	0.000392
	KEGG:5144	Malaria	11	*CCL2*, *CSF3*...	0.000695
	KEGG:1040	Biosynthesis of unsaturated fatty acids	6	*PTPLA*, *SCD*...	0.00262
Downregulated	KEGG:4514	Cell adhesion molecules (CAMs)	46	*CD2*, *CD22*...	1.33E-15
	KEGG:5150	*Staphylococcus aureus* infection	23	*DQA1*, *HLA-DQA2*...	2.53E-10
	KEGG:4672	Intestinal immune network for IgA production	19	*ICAM2*, *ICAM3*...	2.80E-08
	KEGG:5340	Primary immunodeficiency	15	*ADA*, *BLNK*...	2.40E-07
	KEGG:5416	Viral myocarditis	22	*BID*, *CD28*...	2.86E-07

GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; DEGs, differentially expressed genes.

expressed 3 (*MEG3*) is involved with cell proliferation and can be regarded as a poor prognostic biomarker in gastric cancer (14). Knockdown of lncRNA HOX transcript antisense RNA (*HOTAIR*) results in suppression of tumor invasion and reversal of epithelial-mesenchymal transition process in gastric cancer cells, suggesting that *HOTAIR* affects diagnostics and therapeutics of gastric cancer (15).

In the present study, to examine the molecular mechanisms of gastric cancer, the expression profile of GSE41476 was downloaded, which involved 3 primary cell culture samples from gastric cancer tissues, 3 gastric cancer cell lines and 2 normal tissue samples. The lncRNAs were predicted and differentially expressed genes (DEGs) were screened. The functions of the DEGs were analysed using Gene Ontology (GO) and pathway enrichment analyses. In addition, a search was conducted to determine the interaction relationships between the DEGs using protein-protein interaction (PPI) network and modules of the PPI network. Additionally, lncRNA-DEG pairs were screened, and pathway enrichment analysis was performed for DEGs co-expressed with each lncRNA.

Materials and methods

Microarray data. The expression profile of GSE41476 was downloaded from the Gene Expression Omnibus (GEO, http:/ www.ncbi.nlm.nih.gov/geo/), which was based on the platform of the GPL9115 Illumina Genome Analyzer II (*Homo sapiens*). GSE41476 included a collective of 3 primary cell culture samples from gastric cancer tissues, 3 gastric cancer cell lines and 2 normal tissue samples.

Sequence alignment. After GSE41476 was downloaded, the SRA format sequences were translated into FASTQ format, and microarray data were preprocessed by NGSQC software (16). The ratio of bases with base sequencing quality <20 was required to be <0.1. The remaining high quality sequences were compared to human genome 19 (hg19) using TopHat2 (17). The parameter was set to - no-discordant - phred64-quals, and the remaining parameters were set to the default values.

lncRNA prediction. The alignment results were obtained via transcriptome assembly using Cufflinks software (18).

Subsequently, the assembly results were integrated using Cuffmerge software (19). According to the gene annotation information of the genome in the UCSC, assembly results that did not overlap with the extracted arbitrary genes were extracted. Transcriptions with a length of >200 nt and with ≥2 exons were screened. According to information obtained from the 29 mammalian genome alignment, transcriptions with scores <100 were screened using PhyloCSF software (20). Moreover, HMMER software was used to compare transcriptions to Pfam database (21). E-value <1e-5 was used as the cut-off criterion.

DEGs screening. A search through the RefSeq annotation files in UCSC website identified known lncRNA comments (LNCipedia1.0 database) and the predicted lncRNA transcription document, DEGs and lncRNAs, which were screened from the alignment results using Cuffdiff software (22). The adjusted p-value of <0.05 and |log fold-change (FC)| >1 were used as the cut-off criteria.

Functional and pathway enrichment analyses. As a functional study method, GO analysis is used to assess large-scale transcriptomic or genomic data (23). The Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway database shows how molecules or genes act (24). The GO and KEGG pathway enrichment analyses were conducted for DEGs. The GO functional enrichment analysis was mainly focused on the biological process (BP). P<0.05 was used and ≥2 genes were used as the cut-off criteria.

PPI network and module analysis. The STRING online software (25) was used to examine the interaction relationships of the proteins encoded by DEGs, and the combined score >0.7 was used as the cut-off criterion. The Cytoscape software (26) was used to visualize the PPI network. The CFinder software (27) was used to screen modules of the PPI network, and the parameter k was set to 8.

lncRNA analysis. According to the expression matrix of the differentially expressed lncRNA and the DEGs, the relationship between lncRNA and the DEGs was calculated and lncRNA-DEG pairs were screened. Pearson's correlation of >0.99 was used as the cut-off criterion.

Results

lncRNA prediction and DEGs analysis. A total of 86 lncRNA transcriptions were obtained, including 37 transcriptions with an overlap of >50% when compared with known lncRNAs.

Compared to normal tissue samples, 1,088 upregulated transcriptions (including 16 known lncRNAs, 1 predicted lncRNAs and 1,071 mRNAs) and 1,537 downregulated transcriptions (including 18 known lncRNAs, 4 predicted lncRNAs and 1,515 mRNAs) were identified in the gastric cancer samples.

Functional and pathway enrichment analyses. The enriched GO functions for the DEGs are provided in Table I, including cell migration (P=8.97E-14), extracellular matrix (P=3.06E-14), positive regulation of response to stimulus (P=6.66E-16) and single-organism process (P=1.33E-15).

The enriched KEGG pathways for the DEGs are shown in Table I, including ECM-receptor interaction (P=1.18E-06), focal adhesion (P=0.000143), cell adhesion molecules (CAMs, P=1.33E-15) and *Staphylococcus aureus* infection (P=2.53E-10).

PPI network and module analysis. The PPI network of the upregulated genes had 568 nodes and 1,522 interactions (Fig. 1). Module A (Fig. 2A) and module B (Fig. 2B) were obtained from the PPI network. Module A had 13 nodes and 65 interactions. The enriched GO functions for DEGs in module A are provided in Table II, including collagen catabolic process (P=2.22E-16), multicellular organismal catabolic process (P=6.66E-16) and extracellular matrix disassembly (P=1.33E-15). The enriched KEGG pathways for DEGs in module A are also listed in Table II, including ECM-receptor interaction [P=0, which involved proteins encoded by collagen (*COL*) genes such as collagen, type I, α 1 (*COL1A1*)], collagen, type I, α 2 (*COL1A2*) and collagen, type IV, α 4 (*COL4A4*), as well as proteins encoded by integrin (*ITG*) genes such as integrin, α 1 (*ITGA1*), integrin, α 5 (*ITGA5*) and integrin, β 1 (*ITGB1*), focal adhesion (P=1.05E-13, which also involved proteins encoded by the *COL* and *ITG* genes) and protein digestion and absorption (P=5.49E-11). Proteins encoded by *COL* genes interacted with those of the *ITG* genes, such as COL1A1-ITGA5 and COL1A2-ITGB1. Module B had 27 nodes and 261 interactions. The enriched GO functions for DEGs in module B are provided in Table II, including ribonucleoprotein complex biogenesis (P=2.22E-16), rRNA processing (P=1.17E-11) and cellular component biogenesis (P=2.36E-07). The enriched KEGG pathway for DEGs in module B was ribosome biogenesis in eukaryotes (P=5.55E-16) (Table II).

The PPI network of the downregulated genes had 734 nodes and 2345 interactions (Fig. 3). In addition, 6 modules (module A-F) were obtained from the PPI network (Fig. 4). Module A had 8 nodes and 28 interactions. The enriched GO functions for DEGs in module A included transcription initiation from RNA polymerase II promoter (P=8.88E-16) and DNA-dependent transcription, initiation (P=2.66E-15). The enriched KEGG pathways for DEGs in module A included maturity onset diabetes of the young (P=0.000173) and bile secretion (P=0.001409). Module B had 20 nodes and 122 interactions. The enriched GO functions for DEGs in module B included activation of immune response (P=2.22E-16) and leukocyte activation (P=4.44E-16). The enriched KEGG pathways for DEGs in module B included T-cell receptor signaling pathway [P=0, which involved phosphoinositide-3-kinase, catalytic, γ polypeptide (PIK3CG) and phosphoinositide-3-kinase, regulatory subunit 5 (PIK3R5)] and primary immunodeficiency (P=7.35E-10). Specifically, PIK3CG had an interaction relationship with PIK3R5. Module C had 8 nodes and 28 interactions. The enriched GO functions for DEGs in module C included cytokine-mediated signaling pathway (P=6.98E-14) and cell response to cytokine stimulus (P=5.20E-13). The enriched KEGG pathways for DEGs in module C included antigen processing and presentation (P=0.001613) and hepatitis C (P=0.004944). Module D had 10 nodes and 44 interactions. The enriched GO functions for DEGs in module D included single-organism carbohydrate metabolic process (P=8.44E-15) and keratan

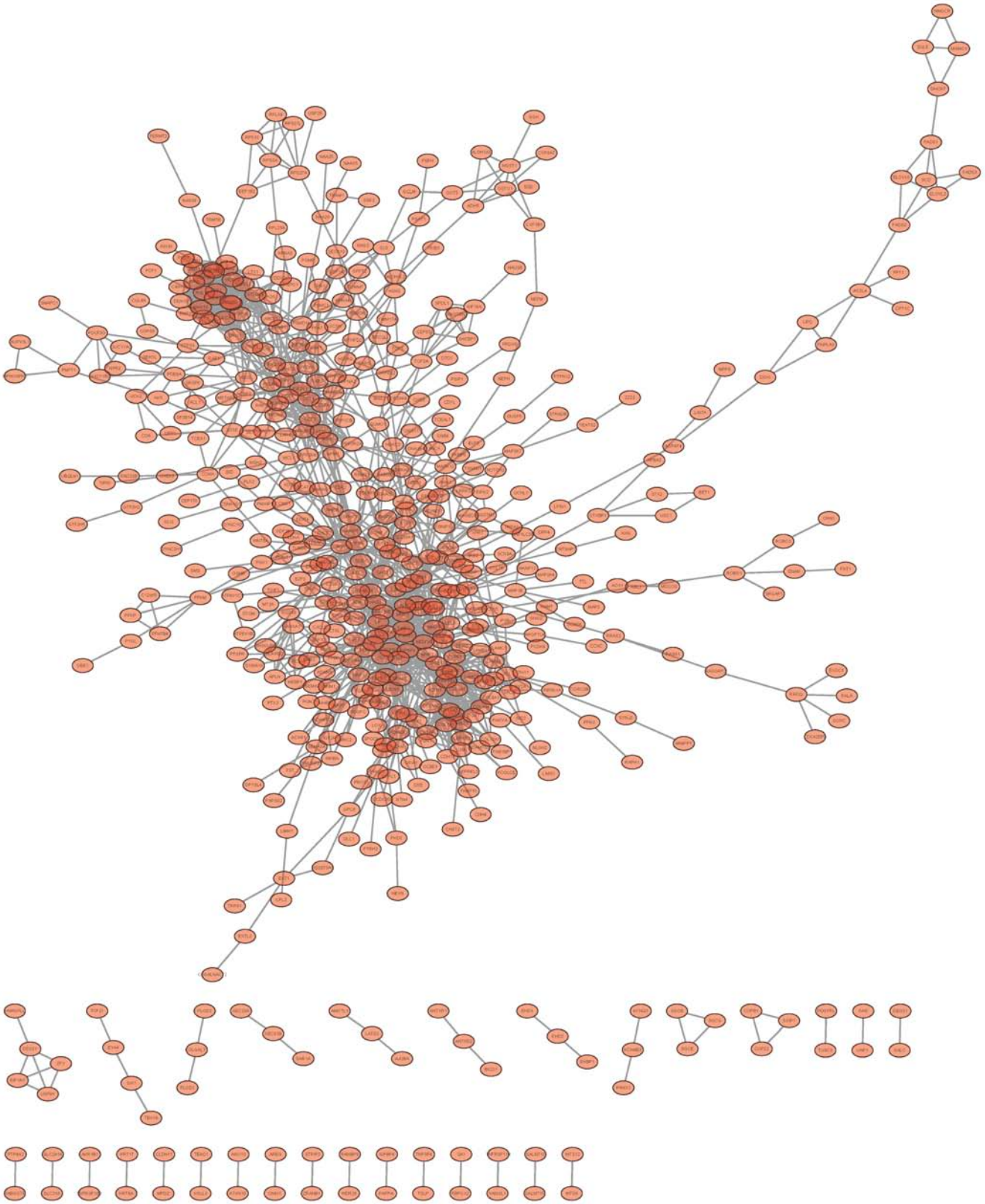

Figure 1. Protein-protein interaction network of the upregulated genes.

sulfate biosynthetic process (P=0.000153). The enriched KEGG pathways for DEGs in module D included mucin-type O-glycan biosynthesis (P=2.39E-06) and metabolic pathways (P=0.014715). Module E had 8 nodes and 28 interactions. The enriched GO functions for DEGs in module E included T-cell costimulation (P=1.20E-10). The enriched KEGG pathways for DEGs in module E included T-cell receptor signaling pathway (P=3.92E-08). Module F had 24 nodes and 273 interactions. The enriched GO functions for DEGs in module F included signal transduction (P=1.46E-13). The enriched

Table II. The top 10 enriched GO functions and KEGG pathways for DEGs in module A and B of the PPI network for the upregulated DEGs.

Modules	ID	Name	Gene no.	Gene symbol	P-value
GO functions					
A	GO:0030574	Collagen catabolic process	8	*COL5A2*, *COL4A4*...	2.22E-16
	GO:0044243	Multicellular organismal catabolic process	8	*COL4A4*, *COL1A2*...	6.66E-16
	GO:0022617	Extracellular matrix disassembly	8	*COL1A2*, *COL1A1*...	1.33E-15
	GO:0005581	Collagen	8	*COL5A2*, *COL4A4*	4.44E-16
	GO:0005201	Extracellular matrix structural constituent	5	*COL1A1*, *COL12A1*...	4.23E-09
B	GO:0022613	Ribonucleoprotein complex biogenesis	11	*BRIX1*, *TSR1*...	2.22E-16
	GO:0006364	rRNA processing	7	*WDR12*, *NOP58*...	1.17E-11
	GO:0044085	Cellular component biogenesis	11	*BRIX1*, *TSR1*...	2.36E-07
	GO:0031981	Nuclear lumen	21	*BRIX1*, *TSR1*...	1.33E-15
	GO:0003723	RNA binding	7	*PNO1*, *DKC1*...	4.48E-06
KEGG pathways					
A	KEGG:4512	ECM-receptor interaction	11	*COL5A2*, *COL4A4*, *COL1A2*...	0
	KEGG:4510	Focal adhesion	10	*COL5A2*, *COL4A4*, *COL1A2*...	1.05E-13
	KEGG:4974	Protein digestion and absorption	7	*COL5A2*, *COL4A4*, *COL1A2*...	5.49E-11
	KEGG:5412	Arrhythmogenic right ventricular cardiomyopathy (ARVC)	4	*ITGB1*, *ITGA1*, *ITGA5*, *ITGB5*	1.07E-05
	KEGG:5410	Hypertrophic cardiomyopathy (HCM)	4	*ITGB1*, *ITGA1*, *ITGA5*, *ITGB5*	1.69E-05
	KEGG:5414	Dilated cardiomyopathy	4	*ITGB1*, *ITGA1*, *ITGA5*, *ITGB5*	2.33E-05
	KEGG:5146	Amoebiasis	4	*COL5A2*, *COL4A4*, *COL1A2*, *COL1A1*	4.45E-05
	KEGG:5131	Shigellosis	3	*ITGB1*, *ITGA5*, *CD44*	0.000219795
	KEGG:4640	Hematopoietic cell lineage	3	*ITGB1*, *ITGA5*, *CD44*	0.000649577
B	KEGG:3008	Ribosome biogenesis in eukaryotes	9	*NOP58*, *GTPBP4*, *WDR3*, *WDR75*, *UTP15*, *WDR36*, *DKC1*, *CIRH1A*, *WDR43*	5.55E-16

GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; DEGs, differentially expressed genes; PPI, protein-protein interaction.

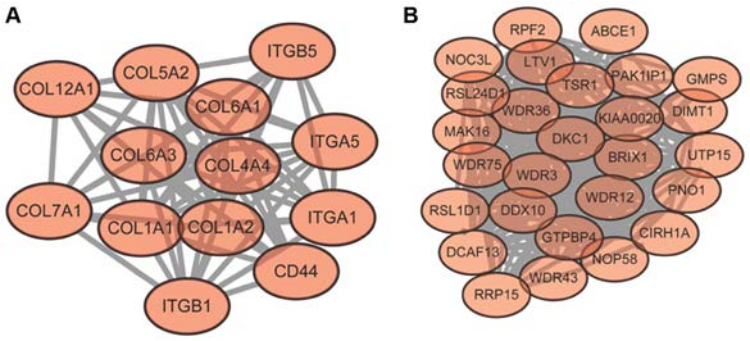

Figure 2. Module A and B obtained from the PPI network of the upregulated genes. PPI, protein-protein interaction.

Table III. The top 10 enriched GO functions and KEGG pathways for DEGs in module A, B, C, D, E and F of the PPI network for the downregulated DEGs.

Modules	ID	Name	Gene no.	Gene symbol	P-value
GO functions					
A	GO:0006367	Transcription initiation from RNA polymerase II promoter	8	*ESRRG*, *ESRRB*...	8.88E-16
	GO:0006352	DNA-dependent transcription, initiation	8	*NR0B2*, *HNF4G*...	2.66E-15
B	GO:0002253	Activation of immune response	13	*CD3D*, *CD3E*...	2.22E-16
	GO:0045321	Leukocyte activation	14	*CD3D*, *CD3E*...	4.44E-16
C	GO:0019221	Cytokine-mediated signaling pathway	8	*IRF7*, *CIITA*...	6.98E-14
	GO:0071345	Cellular response to cytokine stimulus	8	*IRF7*, *CIITA*...	5.20E-13
D	GO:0044723	Single-organism carbohydrate metabolic process	10	*GALNT12*, *MUC1*...	8.44E-15
	GO:0018146	Keratan sulfate biosynthetic process	2	*B3GNT7*, *B3GNT3*	0.000153
E	GO:0031295	T-cell costimulation	5	*CD4*, *CD247*, *CD3D*, *CD3E*, *CD3G*	1.20E-10
F	GO:0007165	Signal transduction	24	*CCL5*, *ADORA3*...	1.46E-13
KEGG pathways					
A	KEGG: 04950	Maturity onset diabetes of the young	2	*HNF4G*, *HNF4A*	0.000173
	KEGG:04976	Bile secretion	2	*NR0B2*, *RXRA*	0.001409
B	KEGG:4660	T-cell receptor signaling pathway	13	*CD3D*, *CD3E*, *CD3G*...	0
	KEGG:5340	Primary immunodeficiency	6	*CD3D*, *CD3E*, *CD4*...	7.35E-10
C	KEGG:4612	Antigen processing and presentation	2	*CIITA*, *IFI30*	0.001613
	KEGG:5160	Hepatitis C	2	*IRF7*, *OAS3*	0.004944
D	KEGG:512	Mucin-type O-glycan biosynthesis	3	*COL5A2*, *COL4A4*, *COL1A2*, *COL1A1*	2.39E-06
	KEGG:1100	Metabolic pathways	4	*ITGB1*, *ITGA5*, *CD44*	0.014715
E	KEGG:4660	T-cell receptor signaling pathway	5	*CD4*, *CD247*, *CD3D*, *CD3E*, *CD3G*	3.92E-08
F	KEGG:4080	Neuroactive ligand-receptor interaction	9	*ADORA3*, *C5AR1*, *C3AR1*...	9.26E-08

GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; DEGs, differentially expressed genes; PPI, protein-protein interaction.

KEGG pathways for DEGs in module F included neuroactive ligand-receptor interaction (P=9.26E-08) (Table III).

lncRNA analysis. After lncRNA-DEG pairs, such as *TCONS-00068220-IL7*, were screened, KEGG pathway enrichment analysis was conducted for DEGs co-expressed with each lncRNA. Proteins encoded with co-expressed DEGs of *TCONS_00068220* were enriched in cancer-related pathways, such as bladder cancer, CAMs, chemokine signaling pathway and natural killer cell-mediated cytotoxicity (Table IV) (28).

Discussion

In the present study, 86 lncRNA transcriptions were obtained, including 37 transcriptions with an overlap of >50% when compared with known lncRNAs. Additionally, 1,088 upregulated and 1,537 downregulated transcriptions were screened. The functions of cell migration, positive regulation of response to stimulus and single-organism process were enriched for the DEGs.

At the tumor periphery of scirrhous gastric carcinoma, collagen biosynthesis is increased and may contribute to the invasion of tumor cells (29). Collagen IV can play a role in cell adhesion, as well as tumor metastasis and invasion (30-32). It is reported that integrin (ITG) α2β1 can be used as a candidate target molecule involved in the prevention of gastric cancer peritoneal dissemination (33). Integrin α6β4 is a suppressor and can be a biomarker for peritoneal dissemination in gastric cancer (34). In module A of the PPI network for the upregulated genes, the enriched KEGG pathways for DEGs

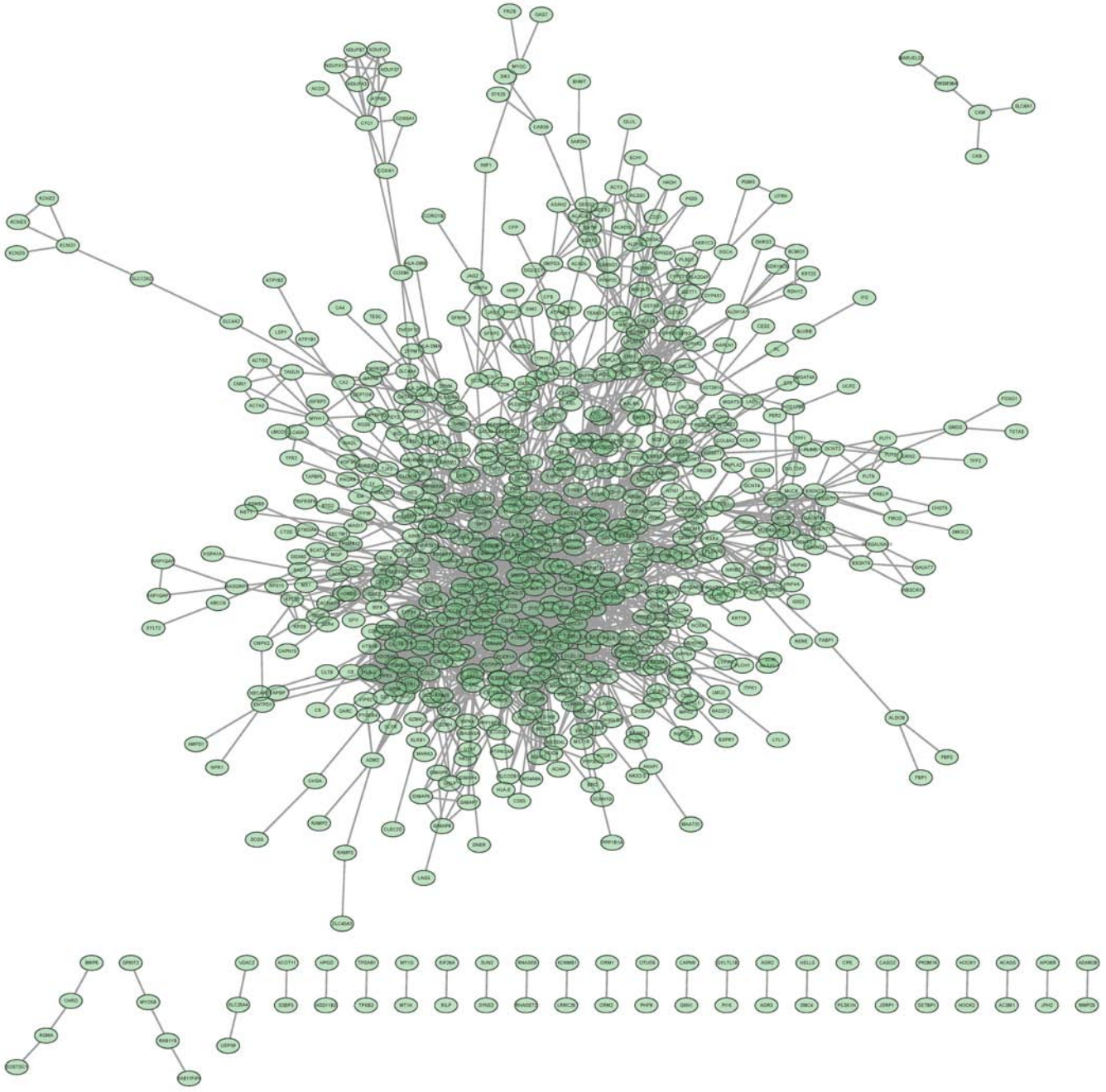

Figure 3. Protein-protein interaction network of the downregulated genes.

included ECM-receptor interaction and focal adhesion, both of which involved proteins encoded by *COL* and *ITG* genes. ECM-receptor interaction and focal adhesion are associated with cancer metastasis and aggression (35,36), and can represent some molecular differences in gastric cancer (37). These observations may indicate that the *COL* and *ITG* genes were associated with gastric cancer. In module A of the PPI network for proteins encoded by the upregulated genes, proteins encoded by *COL* genes were able to interact with those of *ITG* genes, suggesting that *COL* genes are involved in gastric cancer through the regulation of *ITG* genes.

There is a high mutation probability of phosphoinositide-3-kinase, catalytic, α (*PIK3CA*) in human cancers and it is a potential therapy target for various tumors (38). The mutations of *PIK3CA* can lead to the attenuation of apoptosis and assist tumor invasion (39). The phosphatidylinositol 3-kinase (PI3K) pathway is of great alteration frequency in gastric tumors and can be used as a therapeutic target in gastric cancer (40). In module B of the PPI network for the downregulated genes, the enriched KEGG pathways for DEGs included the T-cell receptor signaling pathway, which involved proteins encoded by *PIK3CG* and *PIK3R5*. It has been reported that the T-cell receptor signaling pathway plays a role in gastric cancer (41). The abovementioned findings showed that *PIK3CG* and *PIK3R5* may be associated with gastric cancer. In module B of the PPI network for

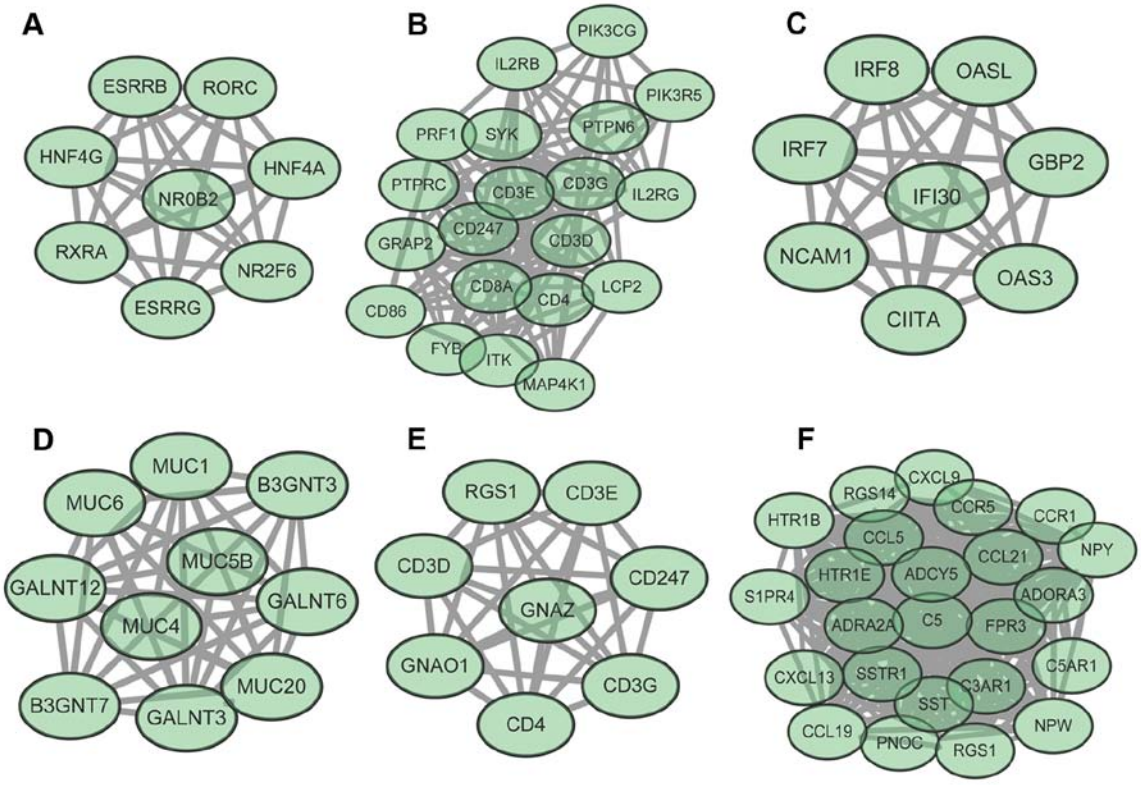

Figure 4. Module A-F obtained from the PPI network of the downregulated genes. PPI, protein-protein interaction.

Table IV. The top 10 enriched KEGG pathways for the DEGs co-expressed with lncRNA TCONS_00068220.

ID	Name	Gene no.	Gene symbol	P-value
KEGG:4514	Cell adhesion molecules	15	*CD2*, *CD28*...	3.10E-06
KEGG:4062	Chemokine signaling pathway	15	*CCL5*, *CCR1*...	0.00020233
KEGG:5219	Bladder cancer	5	*MMP9*, *MYC*...	0.005609503
KEGG:4650	Natural killer cell-mediated cytotoxicity	8	*BID*, *ICAM2*...	0.033796553
KEGG:4672	Intestinal immune network for IgA production	8	*CD28*, *ICOSLG*...	4.17E-05
KEGG:5150	*Staphylococcus aureus* infection	8	*C1QB*, *C1QC*...	0.000114261
KEGG:5140	Leishmaniasis	9	*ITGB1*, *MAPK12*...	0.000142588
KEGG:4940	Type I diabetes mellitus	7	*CD28*, *PRF1*...	0.000149447
KEGG:5330	Allograft rejection	6	*CD28*, *HLA-DMB*...	0.000460506
KEGG:5416	Viral myocarditis	8	*BID*, *CD28*...	0.000623762

KEGG, Kyoto Encyclopedia of Genes and Genomes; DEGs, differentially expressed genes.

proteins encoded by the downregulated genes, PIK3CG also had an interaction relationship with PIK3R5, indicating that *PIK3CG* may be involved in gastric cancer by mediating *PIK3R5*.

The interleukin-8 (*IL8*) promoter polymorphism plays a role in atrophic gastritis and gastric cancer (42). Serum *IL6* is correlated with the progression of gastric cancer and may be used as a biomarker for monitoring the treatment and response of patients with gastric cancer (43). Recombinant human *IL7* can retard tumor growth and induce complete regression (44). By activating p53 and inhibiting cell proliferation, lncRNA *TCONS-00090092-MEG3* may act as a putative tumor-suppressor gene (45-47). In the present study, *IL7* was co-expressed with *TCONS-00068220*. Proteins encoded with co-expressed DEGs of *TCONS_00068220* were enriched in cancer-associated pathways. Thus, the expression levels of *IL7* and *TCONS-00068220* may be associated with gastric cancer, and *IL7* may function in gastric cancer by regulating *TCONS-00068220*.

In conclusion, we have conducted a comprehensive bioinformatics analysis of genes and lncRNAs that may be associated with gastric cancer. A total of 86 lncRNA transcriptions were obtained, as well as 1,088 upregulated and 1,537 downregulated transcriptions were screened. *COL* and *ITG* genes,

PIK3CG, *PIK3R5*, *IL7* and lncRNA *TCONS-00068220* may be correlated with gastric cancer. However, investigations are to be conducted to determine the functional mechanisms of these genes in gastric cancer.

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