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LYN, a Key Gene From Bioinformatics Analysis, Contributes to Development and Progression of Esophageal Adenocarcinoma

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: Esophageal adenocarcinoma is a lethal malignancy whose incidence is rapidly growing in recent years. Previous reports suggested that Barrett's esophagus (BE), which is represented by metaplasia-dysplasia-carcinoma transition, is regarded as the premalignant lesion of esophageal neoplasm. However, our knowledge about the development of esophageal adenocarcinoma is still very limited.

Material/Methods: In order to acquire better understanding about the pathological mechanisms in this field, we obtained gene profiling data on BE, esophageal adenocarcinoma patients, and normal controls from the Gene Expression Omnibus (GEO) database. Bioinformatics analyses, including Gene Ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis, were conducted.

Results: Our results revealed that several pathways, such as the wound healing, complement, and coagulation pathways, were closely correlated with cancer development and progression. The mitogen-activated protein kinase (MAPK) pathway was discovered to be responsible for the predisposition stage of cancer; while response to stress, cytokine-cytokine receptor interaction, nod-like receptor signaling pathway, and ECM-receptor interaction were chief contributors of cancer progression. More importantly, we discovered in this study that LYN was a critical gene. It was found to be the key nodule of several significant biological networks, which suggests its close correlation with cancer initiation and progression.

Conclusions: These results provided more information on the mechanisms of esophageal adenocarcinoma, which enlightened our way to the clinical discovery of novel therapeutic makers for conquering esophageal cancer. Keywords: esophageal adenocarcinoma; LYN; Go analysis; KEGG pathway.

MeSH Keywords: **Esophageal Neoplasms • Genes, abl • Genetic Linkage • Signal Transduction**

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Background

Esophageal cancer is the eighth most prevalent cancers worldwide [1,2]. The incidence of esophageal adenocarcinoma has increased tremendously over the past several decades, much more than any other malignancies [3].

The understanding of the pathogenesis of esophageal cancer at the molecular level has not led to the development of clinical drugs that have potent anticancer effects in treatment of this disease. Specifically, researchers have shown great interest in the use of agents targeting cell surface receptors, such as epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF). Well-known gene mutations that generally occur in carcinoma, such as P53, P16, E-cadherin, and Cyclin D, were also found in esophageal adenocarcinoma, which could also be regarded as potential medication targets [3]. Although there have been great improvements in surgical techniques, reduced preoperative mortality, and the introduction of multimodal therapies, this malignancy remains difficult to cure [4]. Better prognosis of esophageal cancer can be only achieved by diagnosis in the very early stage [4]; therefore, more and more attention has been focused on finding potential diagnostic and therapeutic markers of esophageal cancer. However, much work remains in defining the molecular mechanisms underlying the development and progression of esophageal neoplasm.

Barrett's esophagus (BE) is characterized by the replacement of normal stratified squamous epithelium lining of the upper part of esophagus by simple columnar epithelium with goblet cells [5,6]. Barrett's esophagus can be potential risk factor of esophageal adenocarcinoma, which is the established predisposition to esophageal adenocarcinoma that progresses through a metaplasia-dysplasia-carcinoma transition. The close association with esophageal adenocarcinoma gives its diagnosis great importance in cancer prevention [7]. The molecular mechanism underlying the formation of Barrett's esophagus has been partially elucidated. Gene polymorphisms that play important roles in the inflammatory response, DNA repair, and chemical detoxification have been associated with progression of the lesion [8]. Multiple biomarkers have been identified that are involved in extensive biological pathways, such as cell cycle control, DNA abnormality, genomic instability, and cell proliferation regulation [9]. However, validation of these markers is still necessary and will benefit the estimation of risk of malignant transformation, early diagnosis of disease, and prognosis prediction [9].

Previous studies in this field have been relatively small-scale, with only a few genes examined. Due to the complexity of cancer evolution, multiple genes and pathways deviated from normal condition should have been involved. An overall study would be more helpful to understand the pathogenesis and progression of esophageal adenocarcinoma. Therefore, in this study we compared the global expression profile of the samples from Barrett's esophagus-associated cancer patients, and found that LYN gene could play an important role in mediating the pathogenesis and progression of esophageal cancer.

Material and Methods

Data extraction

Microarray expression data (accession number GSE1420) submitted by Kimchi et al. [10], which was deposited in the Gene Expression Omnibus (GEO) database, were downloaded and analyzed. Samples for gene profile analysis were acquired from 8 patients with Barrett's-associated adenocarcinoma after esophagectomy. The dataset included samples representative of the normal esophageal epithelium (normal), Barrett's esophagus (BE), and esophageal adenocarcinomas from every patient. All microarray data were obtained by use of the Affymetrix Human Genome U133A Array GeneChip.

Identification and analysis of DEGs

We set up 2 comparisons to identify differentially expressed genes (DEGs). Comparison 1 was between the Barrett's esophagus and the normal esophageal epithelium samples. Comparison 2 was between the esophageal adenocarcinoma and the normal esophageal epithelium samples. We first normalized the microarray expression data with the robust multi-array average (RMA) algorithm [11] method with background correction, quantile normalization, and log transformation.

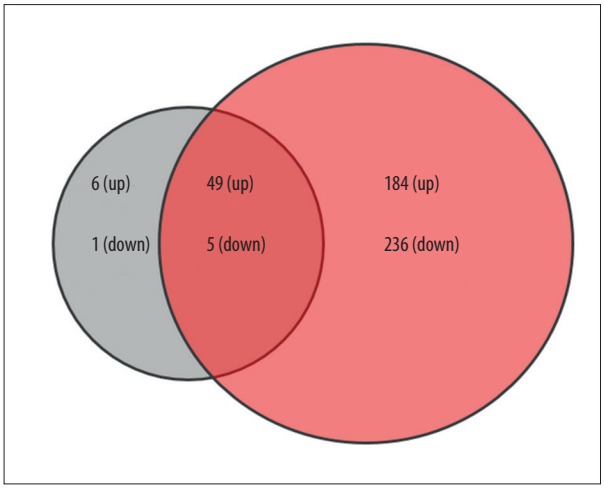

Figure 1. Venn diagram of different expressed genes of Comparison 1 and Comparison 2. Green color represents DEGs of Comparison 1 and red represents Comparison 2.

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Table 1. Up-regulated genes among commonly changed DEGs of both comparison (log2(FC) >2 and adjusted p<0.01).

Gene symbol	Comparison 1			Comparison 2		
	Log_2 (FC)	P value	Adjusted P value	Log_2 (FC)	P value	Adjusted P value
AGMAT	4.17	7.45E-05	9.40E-03	5.26	3.25E-06	4.90E-04
AGR2	7.28	7.78E-07	5.93E-04	7.86	2.27E-07	1.68E-04
ANXA10	6.49	2.05E-05	4.40E-03	5.15	3.25E-04	4.94E-03
ARPC1B	2.19	6.36E-06	2.08E-03	3.07	2.99E-08	8.03E-05
ATP2A3	3.97	3.93E-07	4.46E-04	2.25	1.06E-04	2.67E-03
C1orf115	3.30	1.27E-05	3.14E-03	3.00	4.59E-05	1.76E-03
CASP7	2.66	3.47E-05	6.12E-03	2.24	2.68E-04	4.43E-03
CD97	3.12	4.57E-06	1.70E-03	3.46	9.78E-07	2.94E-04
CFB	3.13	1.23E-05	3.14E-03	3.88	5.03E-07	2.33E-04
CREB3L1	4.50	3.27E-06	1.53E-03	5.24	3.12E-07	1.91E-04
CTSE	7.34	6.51E-07	5.56E-04	7.84	2.23E-07	1.68E-04
EFNB2	2.20	1.10E-05	2.90E-03	2.10	2.12E-05	1.21E-03
EPCAM	4.78	4.95E-05	7.53E-03	5.80	3.60E-06	5.02E-04
FAM46A	3.05	1.57E-05	3.62E-03	3.10	1.26E-05	9.94E-04
FAT1	2.56	3.58E-07	4.46E-04	2.24	2.85E-06	4.72E-04
GALNT6	5.40	2.21E-08	2.45E-04	4.10	2.06E-06	4.15E-04
GLRX	3.26	4.71E-05	7.41E-03	2.45	1.94E-05	1.16E-03
GOLM1	5.70	1.60E-05	3.62E-03	6.57	2.13E-06	4.19E-04
GPRC5A	4.06	1.51E-06	8.09E-04	4.77	1.15E-07	1.28E-04
HOXB7	3.11	2.61E-05	5.18E-03	4.06	1.43E-07	1.44E-04
ITPR3	2.54	4.02E-05	6.66E-03	2.74	1.52E-05	1.02E-03
KDELR3	3.92	1.28E-06	7.49E-04	4.28	3.16E-07	1.91E-04
KIF3B	2.16	6.62E-05	8.65E-03	3.10	3.94E-07	1.91E-04
KRT8	3.94	5.27E-05	7.80E-03	4.68	5.24E-06	6.33E-04
LAMC2	2.10	5.08E-05	7.62E-03	2.89	5.58E-07	2.39E-04
LGALS4	7.97	1.10E-07	4.46E-04	8.37	4.77E-08	8.03E-05
LYN	3.99	3.48E-06	1.53E-03	3.72	9.22E-06	8.47E-04
LYZ	4.11	2.06E-05	4.40E-03	4.49	6.26E-06	6.66E-04
MARCKSL1	3.95	4.90E-07	4.94E-04	4.63	3.41E-08	8.03E-05
MET	2.68	5.97E-05	8.19E-03	3.72	5.80E-07	2.39E-04
MISP	2.97	6.25E-05	8.37E-03	3.33	1.40E-05	1.02E-03
MLPH	4.31	4.80E-06	1.72E-03	4.61	1.79E-06	3.97E-04
ODC1	3.53	4.73E-05	7.41E-03	2.69	9.17E-04	8.83E-03
PIP5K1B	3.73	8.02E-05	9.90E-03	4.22	1.63E-05	1.04E-03

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Table 1 continued. Up-regulated genes among commonly changed DEGs of both comparison (log2(FC) >2 and adjusted p<0.01).

Gene symbol	Comparison 1			Comparison 2		
	Log_2 (FC)	P value	Adjusted P value	Log_2 (FC)	P value	Adjusted P value
PLAUR	4.22	8.55E-07	5.93E-04	4.47	3.42E-07	1.91E-04
PLVAP	2.68	5.56E-05	8.13E-03	2.59	8.38E-05	2.39E-03
SEL1L3	4.32	2.79E-07	4.46E-04	4.87	3.76E-08	8.03E-05
SERPINA1	6.28	1.53E-06	8.09E-04	6.30	1.46E-06	3.51E-04
SLC20A1	2.28	5.83E-06	2.02E-03	2.43	2.26E-06	4.26E-04
SLC39A14	4.60	3.32E-06	1.53E-03	5.29	3.74E-07	1.91E-04
SLC44A4	4.99	3.00E-05	5.55E-03	6.20	1.41E-06	3.47E-04
SPINK1	6.86	2.84E-05	5.35E-03	8.57	1.20E-06	3.22E-04
SULT1A1	2.69	4.83E-05	7.45E-03	2.63	6.47E-05	2.10E-03
TFF1	8.35	2.75E-07	4.46E-04	7.76	8.84E-07	2.80E-04
TFF2	6.63	1.50E-05	3.54E-03	5.84	7.66E-05	2.25E-03
TMEM2	3.51	1.48E-07	4.46E-04	3.58	1.04E-07	1.28E-04
TNFRSF10B	2.19	8.38E-07	5.93E-04	2.70	2.55E-08	8.03E-05
TSPAN1	4.77	1.43E-05	3.45E-03	4.01	1.28E-04	2.99E-03
TSPAN8	8.28	1.96E-07	4.46E-04	9.02	4.59E-08	8.03E-05
TSPAN8	8.28	1.96E-07	4.46E-04	9.02	4.59E-08	8.03E-05

Table 2. Down regulated genes in commonly changed DEGs of both comparisons (log2(FC) <–2 and adjusted p<0.01).

Gene symbol	Comparison 1			Comparison 2		
	Log_2 (FC)	P value	Adjusted P value	Log_2 (FC)	P value	Adjusted P value
AGFG2	–3.39	2.83E-05	5.35E-03	–3.25	4.72E-05	1.78E-03
CD207	–3.78	3.83E-07	4.46E-04	–3.58	9.14E-07	2.82E-04
HLA-DQB2	–3.11	3.79E-06	1.56E-03	–2.64	3.53E-05	1.58E-03
TP53AIP1	–2.70	1.08E-06	6.65E-04	–2.55	2.62E-06	4.42E-04
WNT4	–2.75	3.59E-05	6.14E-03	–2.53	1.01E-04	2.60E-03

Then we identified DEGs by R Limma package (v.2.13.0) [12] for each comparison. Results with |log Fold Change| (|log FC|) >2 and P<0.05 were considered significant. To acquire more profound information on these DEGs, we performed hierarchical clustering and statistical analysis [13]. The annotation of DEGs was conducted by online DAVID [14,15] and ingenuity pathway analysis (IPA) [16].

GO and KEGG pathway enrichment analysis for DEGs

To evaluate the pathways of the DEGs between each comparison, we performed Gene Ontology analysis (GO) analysis. We also conducted pathway enrichment analysis using the KEGG database (Kyoto Encyclopedia of Genes and Genomes, *http://www.genome.jp/kegg/*, Last updated: Dec 1, 2014) and online DAVID tools [14,15] for data Annotation, Visualization, and Integrated Discovery [17].

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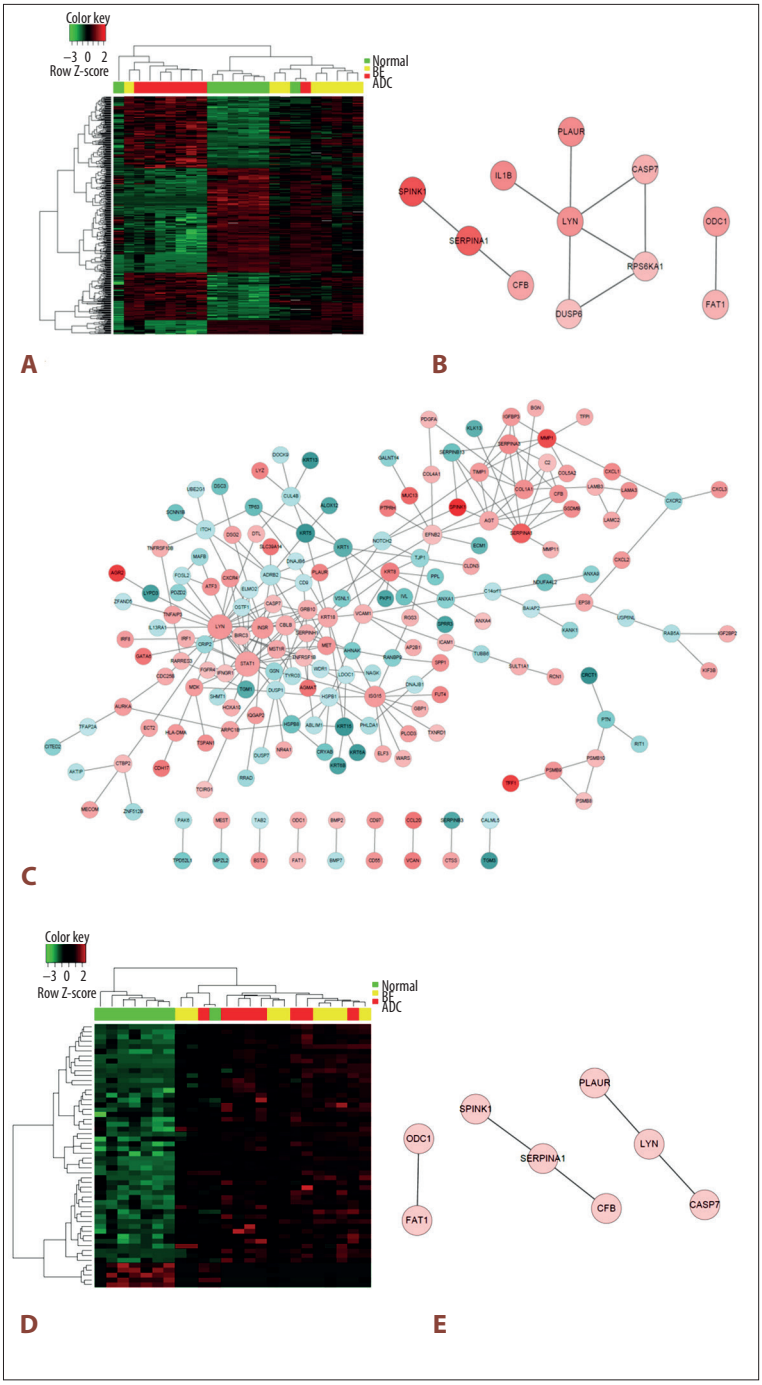

Figure 2. LYN gene was identified as the key network module in both comparisons. Red color indicates relatively high expression, and green indicates relatively low expression. (**A**) Heat map of all DEGs in both comparisons. (**B**) Biological network of Comparison 1. (**C**) Biological network of Comparison 2. (**D**) Heat map of common DEGs in both comparisons. (**E**) Biological network of commonly-changed DEGs.

Results

Identification of DEGs

We used R Limma package software to analyze which gene sets were deregulated in both comparisons with the threshold of |log FC| >2 and P<0.05. There were 55 genes up-regulated and 6 genes down-regulated in Comparison 1; accordingly, the numbers in Comparison 2 were 233 and 244. Altogether, Comparisons 1 and 2 share a DEGs pool including 49 up-regulated genes and 5 down-regulated genes (Figure 1, Tables 1, 2).

Gene ontology analysis for DEGs and biological processes

We performed Gene Ontology analysis for DEGs (Figures 2, 3, Table 3). Gene expression profiles of all DEGs is shown in Figure 2A, showing some genes were shared among groups, while some showed different expression patterns between

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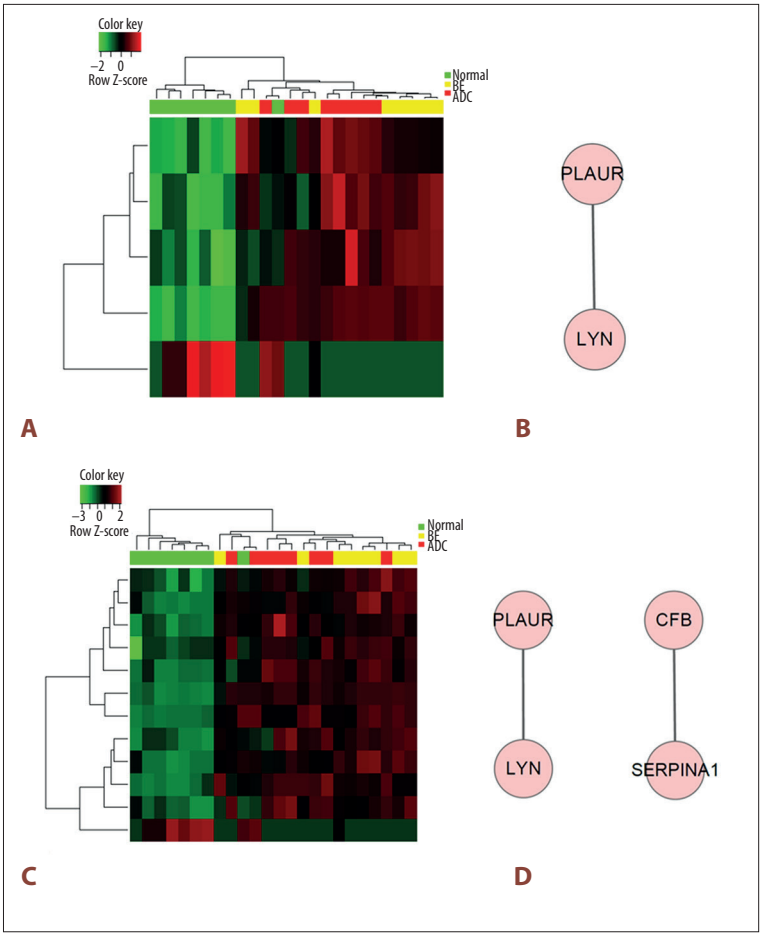

Figure 3. Regulation of wound healing process and corresponding biological network is significantly enriched in both comparisons. Red color indicates high expression and green color indicates low expression. (**A**) Heat map of hierarchical clustering of DEGs in "regulation of wound healing". (**B**) Biological network of "wound healing". (**C**) Heat map of hierarchical clustering of DEGs in "response to wounding". (**D**) Biological network of "response to wound healing".

Table 3. Significantly changed GO biological processes of DEGs in both comparisons.

GO-BP-ID	P value	Count	Term
GO: 0061041	2.26E-05	5	Regulation of wound healing
GO: 0009611	1.44E-04	11	Response to wounding

groups. Commonly-changed DEGs expression profile is shown in Figure 2D. The protein network of Comparison 2 (esophageal adenocarcinoma versus normal) (Figure 2C) showed more complexity and information compared with Comparison 1 (BE versus normal) (Figure 2B). As a result, protein network of shared and single comparisons (Figures 2, 3) all identified LYN as the key module. Additionally, this gene was over-expressed in both BE and cancer samples (Table 2). These observations indicate its important function in esophageal adenocarcinoma pathogenesis and progression. Biological processes involved in both and each single comparison are shown in Table 3, in which wound healing is shown to take part in pathological transitions from normal to BE and normal to esophageal carcinoma (Figure 3, Table 3). The mitogen-activated protein kinases (MAPK) pathway was found to be specifically associated with Comparison 1 (Supplementary Table 1), which indicated that the activation of MAPK might contribute to the formation of BE. Cell migration, proliferation, differentiation, and classical cancer-related biological events were related with the pathogenesis of esophageal adenocarcinoma in this analysis (Supplementary Table 2).

KEGG pathway enrichment for DEGs

To better clarify the pathological mechanisms, we did KEGG enrichment analysis for the DEGs. As shown in Figure 4 and Table 4, complement and coagulation pathways showed significant association with both comparisons, indicating their possible role in driving pre-malignant transformation and cancer progression. We analyzed the corresponding pathways in each single comparison. In Comparison 1, MAPK pathway

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Supplementary Table 1. Significantly changed GO biological processes for DEGs only in comparison 1.

GO-BP-ID	P Value	Count	Term
GO: 0051403	9.37E-05	3	Stress-activated MAPK cascade

Supplementary Table 2. Significantly changed GO biological processes for DEGs only in comparison 2.

GO-BP-ID	P Value	Count	Term
GO: 0043588	9.95E-14	36	Skin development
GO: 0006950	8.51E-11	135	Response to stress
GO: 0060429	7.09E-09	56	Epithelium development
GO: 0030154	1.09E-08	126	Cell differentiation
GO: 0016477	2.25E-07	52	Cell migration
GO: 0008283	2.54E-07	76	Cell proliferation

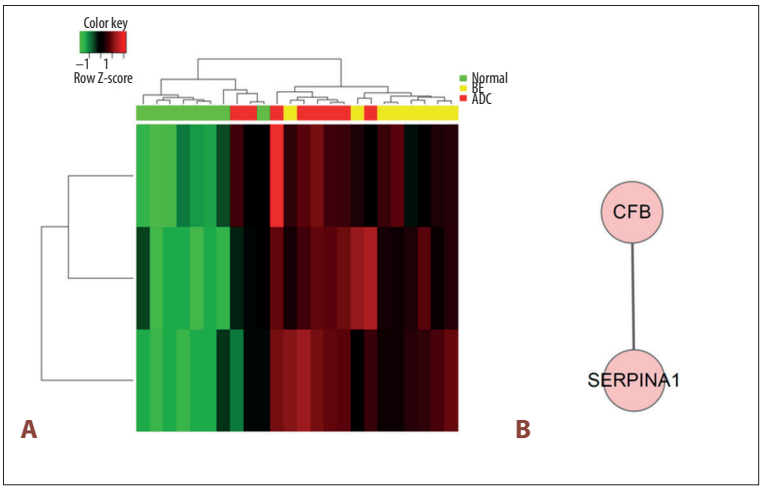

Figure 4. Complement and coagulation cascades pathway and corresponding biological network significantly enriched in both comparisons. Red indicates high expression, and green indicates low expression. (**A**) Heat map of hierarchical clustering of DEGs in "complement and coagulation cascades". (**B**) Biological network of "complement and coagulation cascades".

Supplementary Table 3. Significantly changed KEGG pathways for DEGs changed only in comparison 1.

KEGGID	P Value	Count	Term
04010	3.64E-04	3	MAPK signaling pathway

showed close significance, which is consistent with GO analysis (Figure 4A, Supplementary Table 3). Significantly changed pathways in Comparison 2 converged on immunology-related pathways as cytokine-cytokine receptor interaction, nod-like receptor signaling pathway, and ECM-receptor interaction (Supplementary Table 4).

Discussion

Esophageal adenocarcinoma has the most rapidly increasing incidence in the Western world, especially in the USA. The overall dismal 5-year survival is below 20%. During the past 4 decades, the incidence of esophageal adenocarcinoma increased at an annual rate of around 1~8% [18]. Compelling evidence demonstrated that Barrett esophagus is a precursor lesion for the development of esophageal adenocarcinoma, whose progression involves the transition from BE [18]. However, our understanding of the progression from BE to cancer is very limited. In order to fill in this gap, we performed an overall investigation by using bioinformatics analysis of BE and esophageal adenocarcinoma patients compared with normal controls, trying to clarify possible mechanisms. We discovered that multiple pathways, especially 1-gene pathways,

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Supplementary Table 4. Significantly changed KEGG pathways for DEGs changed only in comparison 2.

KEGGID	P Value	Count	Term
04060	1.50E-02	14	Cytokine-cytokine receptor interaction
04621	2.18E-02	5	Nod-like receptor signaling pathway
04512	3.02E-02	6	ECM-receptor interaction

are closely related with the pathogenesis and progression of esophageal adenocarcinoma.

GO analysis revealed that wound healing may be crucial in both cancer initiation and progression. Wound healing in humans functions as an important tissue repair system, involving multiple processes, such as inflammation component recruitment, fibroblast proliferation, and the formation of new connective tissue [19]. Wounds and carcinomas have striking phenotypic similarities in terms of cellular behavior, signaling molecules, and gene expression. These common features were not only found in epithelial cell behaviors, but also in the stroma of wound healing and carcinomas [20]. Therefore, some researchers described cancer as a wound that would not heal [21], indicating the huge influence of wound healing on cancer.

The complement and coagulation pathways are part of the innate immune system, which serves an important purpose in maintaining physical homeostasis [22,23]. In most pathological situations, the activation of both the complement and coagulation cascades occur simultaneously [22], and cooperate during inflammation to stabilize homeostasis of the human body [24]. As important participants in the immune system, the complement and coagulation pathways sometimes could suppress tumor initiation and progression [25].

Each pathway has its own key player. The most striking finding of this study is that over-expression of the LYN gene was shared in both comparisons, suggesting its important function in both early and late stages of esophageal adenocarcinoma pathogenesis. Being identified as the key nodule of majority of the biological networks involved in cancer enhances this hypothesis. LYN is a kinase belonging to the Src family, and has been reported to be an important mediator in several signal transduction pathways in various malignancies of different cell types [26]. As a Src family kinase, LYN performs its function by regulating downstream signals, such as growth factors, cytokines, and antigen stimulation factors [26]. LYN was also found to regulate epithelial-mesenchymal transition in breast cancer [27], and mediate tumor cell motility and growth in EGFR VIII-expressing head and neck cancer [28]. Additionally, LYN can promote the proliferation of lung adenocarcinoma cells through the activation of EGFRs [29], and regulate androgen receptor expression and activity in castrate-resistant prostate cancer [30]. In our study, LYN gene was also found to be the key nodule in all of the GO networks, such as wound healing. This further strengthened the biological importance of this gene in the development and progression of esophageal cancer, which is possibly accomplished through regulating some essential biological pathways, including wound healing.

Apart from the common features of these comparisons, we also identified some specific pathways that may be associated with each individual esophageal disorder we focused on. Both GO and KEGG analysis found that MAPKs pathway was highly associated with BE. The MAPK family includes multiple extracellular signal-regulated kinases, whose activation regulates a variety of cellular activities, such as proliferation, differentiation, and cell death [31]. The MAPK signaling pathway has been implicated in the development of many human diseases [23,31]. This finding suggests that this pathway may contribute greatly to the malignant transition from BE, the precursor disorder, into esophagus cancer.

On the other hand, response to stress, cytokine-cytokine receptor interaction, nod-like receptor (NLRs) signaling pathway, and ECM-receptor interaction were found to be possible predictors of esophageal adenocarcinoma in our study. By referring to the background of these pathways, we can then explicitly understand their importance in regulating cancer progression. Human cells are constantly exposed to various stresses, such as radiation, carcinogens, oxidative stress, and oncogene activation [32], which can cause damage to the cell, and thus lead to malignant transformation [33]. Growing evidence shows that tumors can progress in a microenvironment not necessarily filled with transformed cells, which can be attributed to the crosstalk accomplished by secreted cytokines between normal and malignant cells [34]. NLRs have been implicated in various diseases caused by its involvement in promoting inflammation and immunity, and its ability to inhibit anti-tumor immunosurveillance. Therefore, nod-like receptors have been believed to contribute to the development of cancer [35]. The extracellular matrix (ECM) is a very essential intracellular component that regulates tissue development and maintains homeostasis. Its deregulation contributes to tumor progression [32]. By interacting with specific receptors, such as integrins, ECM can also regulate the availability of growth factors

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and cytokines, which also broaden its function in regulating tumor cell progression [36].

Conclusions

Our study shows that the over-expression of LYN gene is highly correlated with the development and progression of esophageal adenocarcinoma by being the key nodule of all GO networks. Although its function needs to be further confirmed, this result strongly indicates that LYN gene might be a novel and potential diagnostic and therapeutic target in clinical esophageal adenocarcinoma treatment.

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