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ORIGINAL ARTICLE

Transcriptional Regulatory Network Analysis for Gastric Cancer Based on mRNA Microarray

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Abstract We aimed to screen the differential expressed genes (DEGs) and transcriptional factors (TFs) related to gastric cancer. GSE19826 microarray data downloaded from Gene Expression Omnibus was used to identify the differentially expressed genes (DEGs) and PPI network of DEGs were constructed by the Retrieval of Interacting Genes database. Pathway enrichment analysis of DEGs were performed by Gene Set Enrichment Analysis. Then, the transcriptional regulatory network was constructed based on TRANSFAC database. Finally, regulatory impact factor (RIF) of TF was calculated. We identified 446 DEGs including 209 up- and 237 down-regulated genes. These DEGs were mainly significantly enriched in 5 pathways including ECM receptor interaction (p = 0.013899), spliceosome (p = 0.025591), bladder cancer (p = 0.026316), focal adhesion (p = 0.047809) and WNT signaling pathway (p = 0.048077). PPI network with 247 nodes and 913 edges were constructed and COL5A2 was the hub node. Transcriptional regulatory network with 6 differently expressed TFs, 58 non-differently expressed TFs, 44 DEGs and 735 non-DEGs was constructed. Finally, top 5 TFs including *CRX, TFAP4, NKX2–1, MYB* and *RARG* with higher Z_{RIF} were screened. The identified DEGs such as *COL5A2* and *TOP2A*, and TFs including *EGR2, FOXM1, NKX2–1* and *TFAP4* might be the critical genes and TFs for gastric cancer.

Keywords Gastric cancer · Transcriptional regulatory network · Transcription factor

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Introduction

Gastric cancer, a common digestive cancer developed from the lining of the stomach, mostly strike mid-life men with different stages [1]. Early symptoms include nausea, heartburn and loss of appetite, while later symptoms are vomiting, blood in the stool and weight loss [2]. The main causes of gastric cancer contain genetic syndromes, infection by bacteria helicobacter pylori and poor dietary habits [3, 4]. Treatment strategies for gastric cancer mainly include surgery, chemotherapy and radiation therapy [5]. However, this disease is difficult to cure with a high recurrence rate [6]. Thereby, new approaches such as molecular biological therapy are being studied in clinical trials.

Runt-related transcription factor 3 (*RUNX3*) is a tumor suppressor gene which could inhibit occurrence of gastric cancer [7]. In gastric cancer cell, the expression of *RUNX3* is down-regulated because the loss of heterozygosity and methylation of promoter [8]. *RUNX3* also could improve the transcription of tissue inhibitor of metallo proteinases 1 (*TIMP1*) and further reduce the enzyme activities of matrix metallo proteinase 9 [9]. In addition, *RUNX3* also could inhibit the Akt signaling pathway, further induce β-catenin protein degradation and cyclinD2 down-regulated, finally inhibit cell growth and hinder the cell cycle of G1 [10]. Moreover, tumor necrosis factor-α (*TNF-α*) and transforming growth factor-β (*TGF-β*) are confirmed to be the main signal molecules in antitumor mechanism [11]. *TNF-α* could induce a series of cellular reactions including inflammation, cell proliferation and apoptosis, while *TGF-β* regulated basic cell functions including cell growth, differentiation, movement, adhesion and apoptosis [12]. In gastric cancer cells, *TNF-α* and *TGF-β* could synergistically induce *PARP* degradation and activation of caspase signaling pathway to improve cell apoptosis [11]. Besides, *Tipα* and *PTEN* were also confirmed to improve

the development of gastric cancer by inducing *NF-Kb* and Akt-p53-miR-365-cyclinD1/cdc25A signaling pathway, respectively [13, 14]. Much progress of molecular mechanism research on gastric cancer has been made, but this disease is still difficult to cure. Thereby, it needs to be further researched.

This study was aimed to screen the differential expressed genes (DEGs) and transcriptional factors (TFs) related to gastric cancer. In this present study, the gene expression profile of GSE19826 was downloaded to screen DEGs. Then Protein-Protein interaction (PPI) network was constructed, followed by pathway enrichment analysis. In addition, transcriptional regulatory network was constructed. Finally, TFs related to gastric cancer was screened.

Materials and Methods

Microarray Data

The gene expression profile of GSE19826 was obtained from Gene Expression Omnibus database (GEO, http://www.ncbi.nlm.nih.gov/geo/) [15] with the platform of GPL570 Affymetrix Human Genome U133 Plus 2.0 Array. The gene expression profiling contained 12 adjacent normal / tumor-matched gastric tissues.

Data Preprocessing and differentially Expressed Genes (DEGs) Screening

The raw data were read by Affy package of R-based software and processed by background correction and normalization processing by Robust Multi-array Analysis (RMA) method and then the expression values were evaluated [16]. Multiple Linear Regression package limma was used for the calculation and analysis of DEGs, and further rectification was conducted by the method of Bayes [17]. The threshold of DEGs were $P < 0.05$ and $|\log (\text{fold change})| > 1$.

Protein-Protein Interaction (PPI) Network Construction

The Retrieval of Interacting Genes (STRING) database was a search tool for providing integrated the knowledge and predicted associations for protein network [18]. PPI network of DEGs was constructed by using this method.

Pathway Enrichment Analysis

Gene Set Enrichment Analysis (GSEA) is an enrichment analysis tool for extracting biological meaning of large number of genes based on gene set of the whole genome expression profiling [19]. It was used for Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways enrichment analysis of DEGs. Pathway with $p < 0.05$ were screened.

Construction of Transcriptional Regulatory Network

Transcription factors (TF) with $p < 0.05$ were screened in expression profile. TRANSFAC, a transcriptional regulatory database, was used for screening the target genes of TF [20]. Then, the transcriptional regulatory network was constructed.

Calculation Regulatory Impact Factor (RIF) of TF

The regulatory impact factor (RIF) of TF was calculated by the following formulas:

$$RIF1_i = \frac{1}{n_{DE}} \sum_{j=1}^{j=n_{DE}} \frac{1}{2} \left(e1_j^2 - e2_j^2 \right) \left(r1_{ij} - r2_{ij} \right)^2$$

$$RIF2_i = \frac{1}{n_{DE}} \sum_{j=1}^{j=n_{DE}} \left[\left(e1_j \times r1_{ij} \right)^2 - \left(e2_j \times r2_{ij} \right)^2 \right]$$

where nDE is the number of DE genes that candidate gene i interacted; e1j and e2j are the average expression of gene j in compared samples, respectively; r1ij and r2ij are Pearson Coefficient between gene i and j in compared samples, respectively.

Then the Z values of RIF1 and RIF2 were converted according to the following formula:

$$Z = \frac{RIF - \overline{RIF}}{SD}$$

The converted values were combined by the following formula:

$$Z_{RIF} = Z_{RIF1} + Z_{RIF2}$$

Finally, top 5 TFs with higher Z_{RIF} were screened.

Results

DEGs Screening

Based on differential expression analysis for GSE19286, a total of 446 DEGs including 209 up- and 237 down-regulated DEGs were screened (Table 1). Among these DEGs, *OLFM4, THBS2* and *FNDC1* were the up-regulated DEGs with higher logFC, while *GKN1, GKN2 and LIPF* were screened as down-regulated DEGs with lower logFC.

PPI Network Construction

PPI network with 247 nodes and 913 edges were constructed. In this network, *COL5A2, TOP2A, KIF20A, FN1* and *PRC1*

Table 1 The list of differently expressed genes

Gene	logFC	p.value	adj.p	Gene	logFC	p.value	adj.p
OLFM4	3.404428	0.027499	0.128416	*GKN1*	-5.17282	0.002375	0.044512
THBS2	2.812421	2.21E-05	0.010577	*GKN2*	-5.15696	0.001569	0.039486
FNDC1	2.714419	0.000307	0.026002	*LIPF*	-5.04922	0.003268	0.049435
CEACAM6	2.543344	0.006605	0.065169	*GIF*	-4.66881	0.005602	0.061419
SFRP4	2.409819	0.000666	0.032507	*ATP4A*	-4.36849	0.002536	0.045769
SULF1	2.409399	3.74E-05	0.011763	*PGA4*	-4.19593	0.019763	0.108608
CLRN3	2.399689	0.006557	0.064952	*PGA5*	-4.19593	0.019763	0.108608
MFAP2	2.384621	7.73E-07	0.002011	*PGC*	-4.11714	0.001143	0.036242
INHBA	2.374274	1.60E-05	0.008741	*DPCR1*	-3.95581	5.70E-05	0.014167
FAP	2.343024	5.96E-05	0.014253	*KCNE2*	-3.80495	0.000951	0.034711

were screened as the hub nodes with the degree of 27, 25, 24, 23 and 23, respectively (Fig. 1).

Pathway Enrichment Analysis

As shown in Table 2, the screened DEGs were mainly significantly enriched in 5 pathways including ECM receptor interaction (p = 0.013899), spliceosome (p = 0.025591), bladder cancer (p = 0.026316), focal adhesion (p = 0.047809) and WNT signaling pathway (p = 0.048077).

Transcriptional Regulatory Network Construction

Transcriptional regulatory network with 843 nodes and 1237 edges were constructed. In the network, the nodes contained 6 differentially expressed TFs, 58 non-differentially expressed TFs, 44 DEGs and 735 non-DEGs. The 6 differentially expressed TFs were *EGR2, FOXA1, HOXA1, HOXA10, PLAU* and *TFF3* (Fig. 2).

Regulatory Impact Factor (RIF) of TF

After calculation, top 5 TFs with higher Z_{RIF} were screened and showed in Table 3. The top 5 TFs were *CRX, TFAP4, NKX2–1, MYB* and *RARG* with Z_{RIF} of 4.697, 3.747, 3.744, 2.630 and 2.402, respectively.

Discussion

Gastric cancer is a common digestive cancer which creates such a stressful burden on the home caregivers as well as the whole society [21]. In this study, GSE19826 was downloaded from GEO to research the molecular mechanisms of gastric cancer. We have screened some gastric cancer related-TFs such as *EGR2, FOXM1, NKX2–1* and *TFAP4*, and some gastric cancer related-DEGs including *COL5A2* and *TOP2A*.

EGR2 (early growth response 2) is a transcription factor with three tandem C2H2-type zinc fingers [22]. It was found to enriched in the process of negative regulation of cell differentiation as a potential biomarker of gastric cancer metastasis [23]. The overexpression of miR-150 directly targets *EGR2*, and further promotes proliferation and growth of cancer cells in gastric cancer [24]. In addition, overexpressed *EGR2* could attenuate the oncogenic effect of miR-20a which regulates the *EGR2* signaling pathway in the carcinogenesis of gastric cancer [25]. In this study, it was screened as differentially expressed TFs in transcriptional regulatory network. Besides, *FOXM1* was also screened to regulate DEGs such as *COLA1*. *FOXM1* (forkhead box M1) encodes a protein which is a transcriptional activator involved in cell proliferation [26]. Moreover, it was confirmed to be an important molecule for chemoresistance to a microtubule stabilizing anticancer agent such as docetaxel via up-regulating stathmin [27, 28]. Qi et al. [29] revealed that Her-2 regulated the expression of FOXM1 at the promoter level in gastric cancer by treatment with trastuzumab. In addition, *FOXM1* could also be down-regulated by miR-194, then inhibited the acquisition of the EMT phenotype, and further inhibited cell migration and invasion [30].

NKX2–1 and *TFAP4* are found to be the critical TFs with highest Z_{RIF}. *NKX2–1* (NK2 homeobox 1), a thyroid-specific transcription factor, binds to the thyroglobulin promoter and regulates the expression of thyroid-specific genes. What's more, claudin-18 which is a novel downstream target gene for *T/EBP/NKX2–1*, has been confirmed to encode stomach- and lung-specific isoforms by participating the pathway of spliceosome [31]. Furthermore, down-regulation of claudin-18 might participate in the development of gastric cancer with an intestinal phenotype, and might even be a good marker in the early of gastric carcinogenesis [32]. Besides, *TFAP4* (transcription factor AP-4 (activating enhancer binding protein 4)), which has been found to elevate in gastric carcinoma, activate cellular genes by binding to the symmetrical DNA sequence CAGCTG [33]. This gene could control target gene expression by participating various biology processes including altering signal transduction, regulating growth and cell apoptosis [34]. In addition, it was found to be targeted for proteasome-

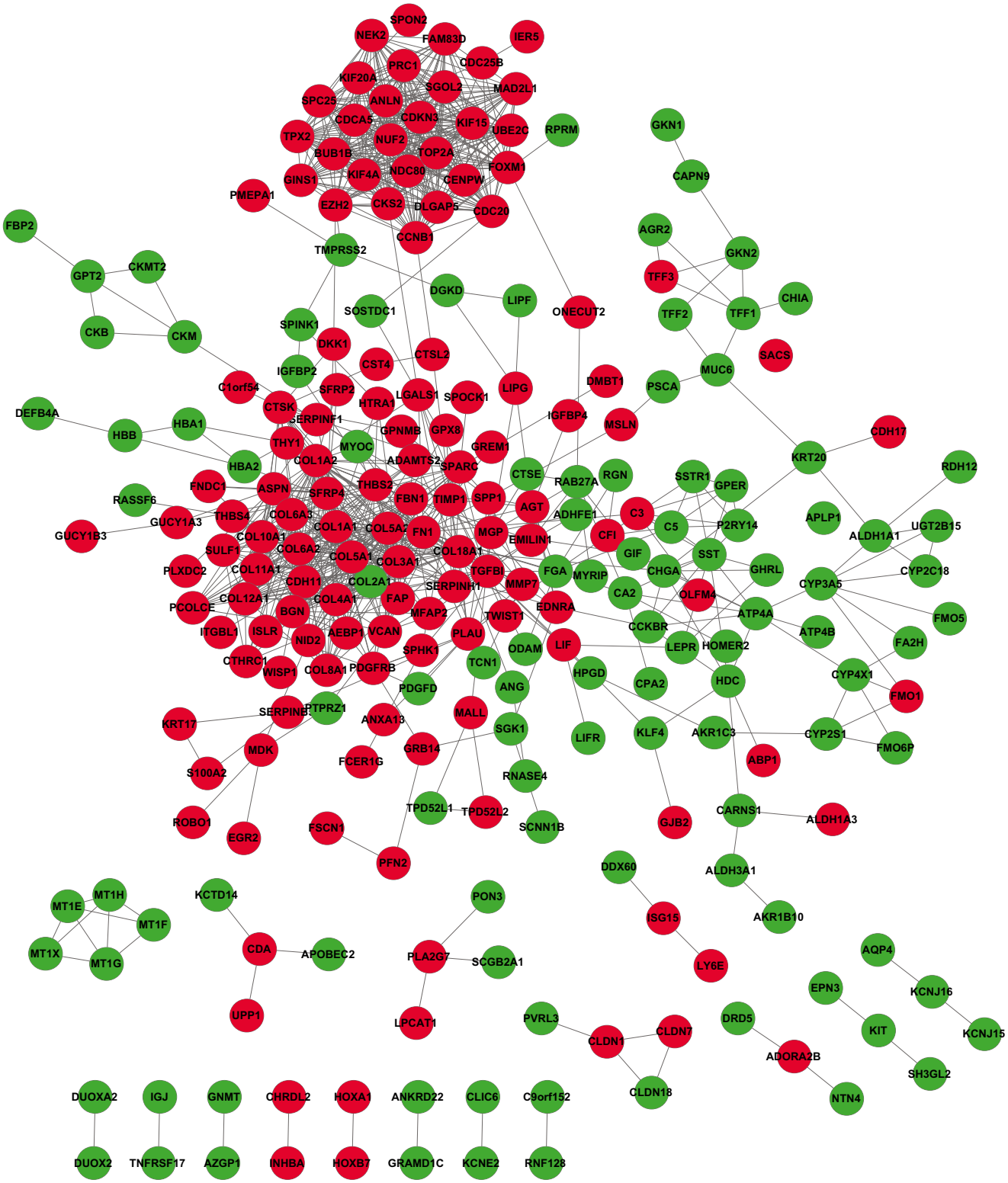

Fig. 1 Protein-Protein interaction network of DEGs. Note: The red and green nodes represent up- and down-regulated DEGs, respectively

dependent degradation by the SCFβTrCP ubiquitin ligase, and then improve the process of mitosis [33]. Thereby, the screened TFs such as *EGR2, FOXM1, NKX2–1* and *TFAP4* might be the potential key TFs in the development of gastric cancer.

We also screened some DEGs such as *COL5A2* and *TOP2A* with the highest degree in the PPI network of gastric cancer. Among of these DEGs, *COL5A2* (collagen, type V, alpha 2), encoded an alpha chain for one of the low abundance

Table 2 KEGG pathways enriched by DEGs

NAME	SIZE	ES	NES	p-val
KEGG_ECM_RECEPTOR_INTERACTION	84	0.592696	1.529564	0.013889
KEGG_SPLICEOSOME	125	0.539708	1.679218	0.025591
KEGG_BLADDER_CANCER	42	0.541169	1.493822	0.026316
KEGG_FOCAL_ADHESION	199	0.459984	1.487164	0.047809
KEGG_WNT_SIGNALING_PATHWAY	147	0.341524	1.377488	0.048077

fibrillar collagens, was found to be significantly increased in gastric cancer [35]. By the technology of microarray, *COL5A2* and other collagen genes have been proved to be elevated in gastric cancer endothelium by participating the pathways including cell adhesion, migration and ECM [36]. In this study, it was also confirmed to enriched in the pathway of ECM-

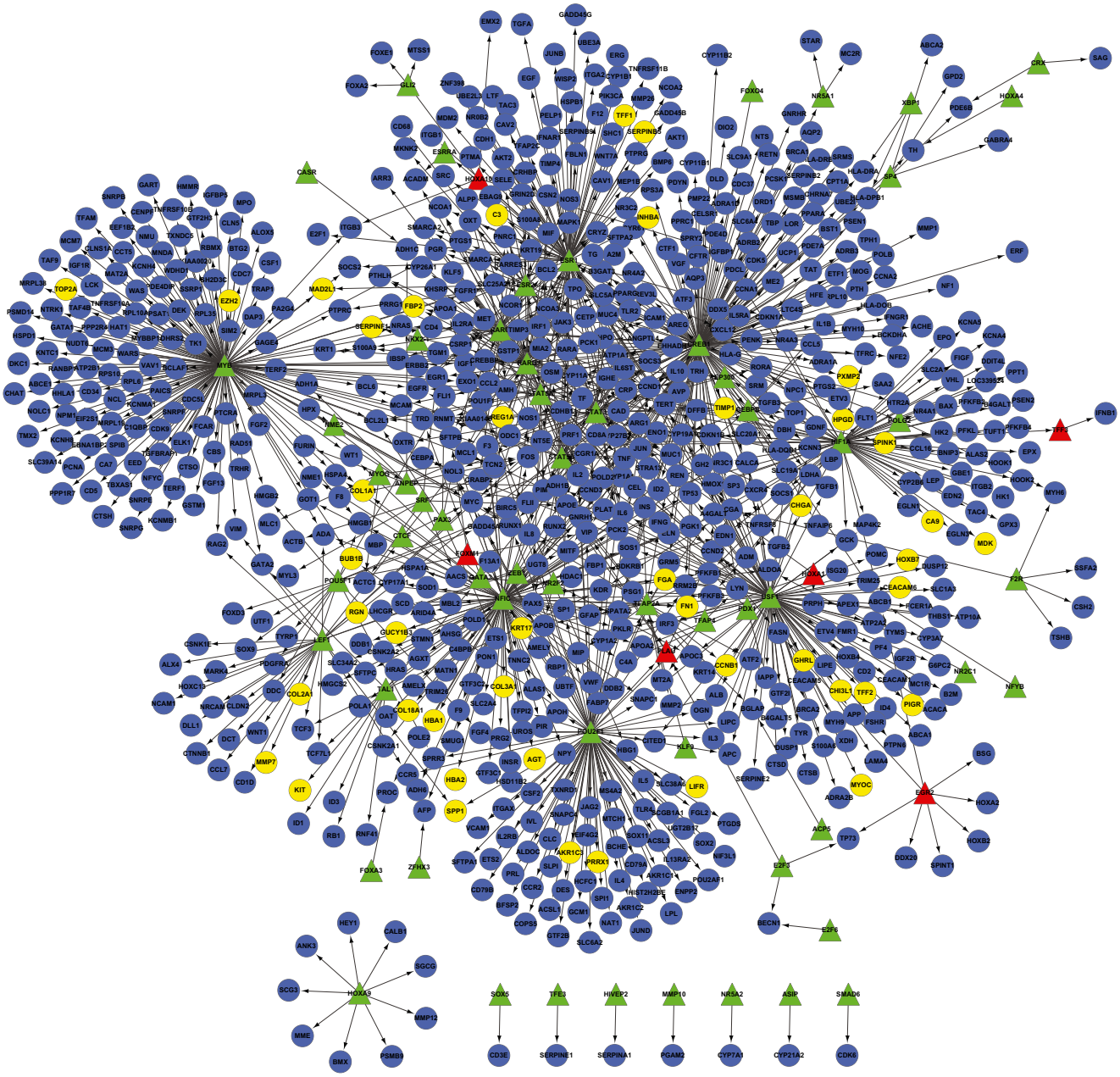

Fig. 2 Transcriptional regulatory network. Note: The red and green triangles represent differentially expressed TFs and non-differentially expressed TFs, respectively. The blue and yellow dots represent differentially expressed and non-differentially expressed target genes, respectively

Table 3 Top5 transcription factors with highest Z_{RIF}

TF	Z	Degree	FC	P-val
CRX	4.697509	2	0.866153	0.039002
TFAP4	3.747261	2	0.794519	0.003851
NKX2–1	3.744425	2	0.893976	0.023677
MYB	2.630773	155	1.451805	0.014699
RARG	2.402177	40	0.871602	0.019651

receptor-interaction. In addition, *TOP2A* was screened as a gastric cancer-related DEG, and regulated by *MYB* which is a non-differently TF in this study. The *TOP2A* gene, located near *HER2* on chromosome 17, has been verified to be a target of many chemotherapeutic agents [37]. It is also an enzyme which could catalyze ATP-dependent strand-passing reaction, and participate in DNA replication and chromosome condensation with amplification and independence [38]. Therefore, the screened DEGs including *COL5A2* and *TOP2A* were the critical targets for the treatment of gastric cancer.

In conclusion, the identified DEGs such as *COL5A2* and *TOP2A*, and TFs including *EGR2, FOXM1, NKX2–1* and *TFAP4* might be the critical genes and TFs of gastric cancer by participating the pathways such as ECM-receptor-interaction and spliceosome. However, these results need to be further confirmed by experimental study.

Compliance with Ethical Standards

Conflict of Interests The authors have not declared any conflicts of interest.

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