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Full Length Research Paper

Identifying genes related with non-small cell lung cancer via transcription factors-target genes relationship

Wei-Dong Zang[1], Jian Liu[2], Li-Shan Wang[1] and Tie-Wen Pan[3]*

[1]Shanghai Jiaotong University, 800 Road, Shanghai 200241, China.
[2]Department of Molecular and Cellular Biology, Baylor College of Medicine, One Baylor Plaza, Houston TX 77030, USA.
[3]Changzheng Hospital of Second Military Medical University, Shanghai 200003, China.

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The developments of gene expression profiling technology have deeply influenced the understanding of lung cancer biology. By microarray data, we constructed a regulation network to identify potential genes that are highly correlated to non-small cell lung cancer. Of the network, some transcription factors and target genes, including perturbation factors (PPARG), ETV4, TGFBR2 and ATP2A2, have been proved to be related to non-small cell lung cancer in previous study. We also found some new transcription factors and target genes may be related to non-small cell lung cancer, including SPI-1/PU.1, ETS2, and EGR1 and so on; these genes may be potential markers for non-small cell lung cancer.

Key words: Non-small cell lung cancer, transcription factors, regulation network.

INTRODUCTION

Lung cancer is the wordwide diagnosed form of cancer and the leading cause of cancer death (Alberg et al., 2003). Only 15% of all lung cancer patients are alive 5 years or more after diagnosis (http://seer.cancer.gov/statfacts/html/lungb.html). The two major forms of lung cancer are non-small cell lung cancer (NSCLC, approximately 85% of all lung cancers) and small-cell lung cancer (SCLC, approximately15% of all lung cancers). NSCLC can be divided into three major histological subtypes: Squamous-cell carcinoma, adeno-carcinoma and large-cell lung cancer (Jemal et al., 2009). Several biomarkers have emerged as prognostic and predictive markers for NSCLC. Among these biomarkers, evidence is strongest for epidermal growth factor receptor (EGFR), the 5′ endonuclease of the nucleotide excision repair complex (ERCC1), K-ras oncogene, and the regulatory subunit of ribonucleotide reductase (RRM1) (Ettinger et al., 2010). In patients with completely resected NSCLC who did not undergo perioperative chemotherapy or radiation, ERCC1 mRNA levels were prognostic of survival. Patients whose tumors had high levels (N = 26; relative ERCC1 expression above the cohort median of 50) lived significantly longer than patients whose tumors had low levels (N = 25, relative expression below 50) (Simon et al., 2005).

The development of reliable gene expression profiling technology (Alberg and Samet, 2003) is having an increasing impact on our understanding of lung cancer biology (Sanchez-Palencia et al., 2010). The differentially expressed genes found through the expression profiles may play important roles in lung tumor genesis and may potentially serve as biomarkers in both diagnosis and prognosis of human lung cancer (McDoniels-Silvers et al., 2002).

The purpose of this paper is to develop a transcription regulation network including a set of transcription factors and differently expressed target genes to identify the

*Corresponding author. E-mail: pan.tie.wen@gmail.com. Tel: +86-(0)13601616543.

Abbreviations: SCLC, Small-cell lung cancer: **TRED,** transcriptional regulatory element database; **DEGs,** differentially expressed genes; **GO,** gene ontology; **IF,** impact factor; **PFs,** perturbation factors; **PPARG,** PPARgamma; **NSCLC,** non-small cell lung cancer; **VEGF-A,** vascular endothelial growth factor-A; **VWF,** von Willebrand factor; **ABC,** ATP-binding cassette.

potential genes in the progress of NSCLC.

MATERIALS AND METHODS

Expression profile data

The transcription profile of non-small cell lung cancer GSE18842 (Sanchez-Palencia et al., 2010) were obtained from a public functional genomics data repository GEO (http://www.ncbi.nlm.nih.gov/geo/). This data set includes 91 NSCLC samples of different disease stages with 46 tumors and 45 controls.

Pathway data

Kyoto encyclopedia of genes and genomes (KEGG) is a collection of online databases dealing with genomes, enzymatic pathways, and biological chemicals (Kanehisa, 2002). The pathway database records networks of molecular interactions in the cells, and variants of them specific to particular organisms (http://www.genome.jp/kegg/). Total 130 human pathways, involving 2287 genes, were collected from KEGG.

Regulationship data

There are approximately 2600 proteins in human genome that contain DNA-binding domains, most of which are presumed to function as transcription factors (Wachi et al., 2005). The TRANSFAC database (http://www.gene-regulation.com) on eukaryotic transcriptional regulation, comprising data on transcription factors, their target genes and regulatory binding sites, has been extended and further developed (Wingender, 2008).

Transcriptional regulatory element database (TRED) has been built in response to increasing needs of an integrated repository for both cis- and trans- regulatory elements in mammals (Jiang et al., 2007). TRED provides a unique resource for both cis- and trans-regulatory elements, and provide easy access of the correlation between promoter sequences and transcription factor binding information.

Combining the two regulation datasets, we collected a total of 6328 pairs of regulatory relationships between 276 TFs and 3002 target genes (Table 1).

Differentially expressed genes (DEGs) analysis

We took the LIMMA software package of Bioconductor (Smyth, 2004) to identify the DEGs. The original expression dataset from all conditions were normalized to fit a linear model, and then the gene with absolute fold change value larger than 0.5 was selected as DEGs.

Co-expression analysis

To demonstrate the potential regulatory relationship, the Pearson correlation coefficient (PCC) was calculated from all pair-wise comparisons of gene-expression values between TFs and DEGs. The regulatory relationships whose absolute PCC are larger than 0.6 were considered as significant and taken as coexpression.

Gene ontology analysis

Ontology is the philosophical study of the nature of being, existence or reality as such, as well as the basic categories of being and their relations. BiNGO is a Java-based tool to determine which gene ontolog (GO) categories are statistically overrepresented in a set of genes or a subgraph of a biological network. We used BiNGO (Maere et al., 2005) to identify over-represented GO categories in biological process.

Table 1. Collected regulation data form, TRANSFAC and TRED.

Source	Regulationships	TFs	Target genes
TRANSFAC	774	219	265
TRED	5722	102	2920
Total	6328	276	3002

Regulation network construction

Using the regulation data that have been collected from TRANSFAC database and TRED database, we matched the relationships between differentially expressed TFs and its differentially expressed target genes.

Base on the aforementioned two regulation datasets and the pathway relationships, we build the regulation networks by Cytoscape (Shannon et al., 2003). Using the significant relationships (PCC > 0.6 or PCC < -0.6) between TFs and its target genes, 81 putative regulatory relationships were predicted between 19 TFs and 64 target genes.

Significance analysis of pathway

We adopted an impact analysis that includes the statistical significance of the set of pathway genes but also considers other crucial factors such as the magnitude of each gene's expression change, the topology of the signaling pathway, their interactions etc (Draghici et al., 2007). In this model, the impact factor (IF) of a pathway Pi is calculated as the sum of two terms:

$$IF(Pi) = \log(\frac{1}{pi}) + \frac{\sum_{g \in Pi} |PF(g)|}{|\triangle E| \cdot N_{de}(Pi)}$$

The first term is a probabilistic term that captures the significance of the given pathway P_i from the perspective of the set of genes contained in it.

It is obtained by using the hyper geometric model in which p_i is the probability of obtaining at least the observed number of differentially expressed gene, N_{de}, just by chance (Tavazoie et al., 1999; Draghici et al., 2003).

The second term is a functional term that depends on the identity of the specific genes that are differentially expressed as well as on the interactions described by the pathway (that is, its topology).

The second term sums up the absolute values of the perturbation factors (PFs) for all genes *g* on the given pathway P_i.

The PF of a gene *g* is calculated as follows:

$$PF(g) = \triangle E(g) + \sum_{u \in USg} \beta_{ug} \cdot \frac{PF(u)}{N_{ds}(u)}$$

In this equation, the first term $\Delta E\ (g)$ captures the quantitative information measured in the gene expression experiment. The

factor $\Delta E\ (g)$ represents the normalized measured expression change of the gene g. The first term $\Delta E\ (g)$ in the aforementioned equation is a sum of all PFs of the genes u directly upstream of the target gene g, normalized by the number of downstream genes of each such gene $N_{ds}(u)$, and weighted by a factor β_{ug}, which reflects the type of interaction: $\beta_{ug} = 1$ for induction, $\beta_{ug} = -1$ for repression (KEGG supplys this information about the type of interaction of two genes in the description of the pathway topology). US_g is a set of all such genes upstream of g. We need to normalize with respect to the size of the pathway by dividing the total perturbation by the number of differentially expressed genes on the given pathway, $N_{de}(P_i)$. In order to make the *IF*s as independent as possible from the technology, and also comparable between problems, we also divided the second term in Equation 1 by the mean absolute fold change ΔE, calculated across all differentially expressed genes. The result of the significance analysis of pathway is shown in Table 3.

Regulation network between TFs and pathways

To further investigate the regulatory relationships between TFs and pathways, we mapped DEGs to pathways and got a regulation network between TFs and pathways.

RESULTS

Regulation network construction of non-small cell lung cancer

To get pathway-related DEGs of non-small cell lung cancer, we obtained publicly available microarray data sets GSE18842 from GEO. After microarray analysis, the DEGs that absolute fold change value larger than 2 and p-value less than 0.05 were selected; total DEGs is 4277. To get the regulatory relationships, the co-expressed value (0.6) was set as threshold.

Finally, we got 81 regulatory relationships between 19 different expressed TFs and their 64 differently expressed target genes. A regulation network of non-small cell lung cancer was built between TFs and itsDEGs (Figure 1). SPI1 is the largest hub node with 24 target genes including a TF. The only two TF targets of ETV4 are both deactivated by ETV4. There are 2 TF regulation subgraphs with 7 and 2 TFs each.

GO analysis of the regulation network

Several GO categories were enriched among these genes in the regulatory network, including response to chemical stimulus, response to stress, positive regulation of biological process, and so on (Table 2).

Significant pathway

To identify the pathways affected in NSCLC, we used a statistical approach on pathway expression change.

Significance analysis at single gene level may suffer from the limited number of samples and experimental noise that can severely limit the power of statistical test. Pathway can provide an alternative way to relax the significance threshold and may lead to a better biological interpretation. So, we adopted a pathway-based impact analysis method that contained many factor: statistical significance of the set of differentially expressed genes in the pathway, the magnitude of each gene's expression change the topology of the signaling pathway, and so on. The impact analysis method yielded many significant pathways which contained complement and coagulation cascades, ECM-receptor interaction, cell cycle etc (Table 3).

Pathway regulation network

To further investigate the regulatory relationships between TFs and pathways, we mapped DEGs to pathways and constructed a pathway regulation network (Figure 2). In the network, SP1, FLI1, ERG and EGR1 were shown as hub nodes linked to NSCLC related pathways. SPI1, ERG and FLI1 together regulated cytokine-cytokine receptor interaction, Chagas disease (American trypanosomiasis) and endocytosis. ETV4, ETS2 and FLI1 may make active the downstream pathways through regulating the ERG. FLI1 also respond to NSCLC related pathways through regulating ANPEP and FOS indirectly.

DISCUSSION

According to the transcription regulation network of NSCLC, we found that many TFs and pathways closely related to NSCLC have been linked by our method. The gene SPI1 and FLI1 are shown as hub nodes in our transcription regulation network, some were proven to be related to NSCLC by previous study. Although the roles of SP1, EGR1 and ETS2 in NSCLC have not been investigated so far, some evidences also suppose that these genes may play important roles in response to NSCLC. There a few genes that are proved to be related to NSCLC.

PPARgamma (PPARG) encodes a member of the peroxisome proliferator-activated receptor (PPAR) subfamily of nuclear receptors. PPARgamma is a nuclear receptor involved in the regulation of many cellular processes. Compared with the normal lung tissues, PPARγ expression was much higher in the NNK-induced lung tumor tissues. However, PPARγ transcriptional activity, and the levels of two major endogenous PPARγ ligands,13-hydroxyoctadecadienoic acid and 15-hydroxyeicosatetraenoic acid, were significantly lower in the NNK-treated lung tissues. Therefore, the level of endogenous PPARγ ligands and the activities of PPARγ may be viewed as tumor markers for lung cancer (Zhang

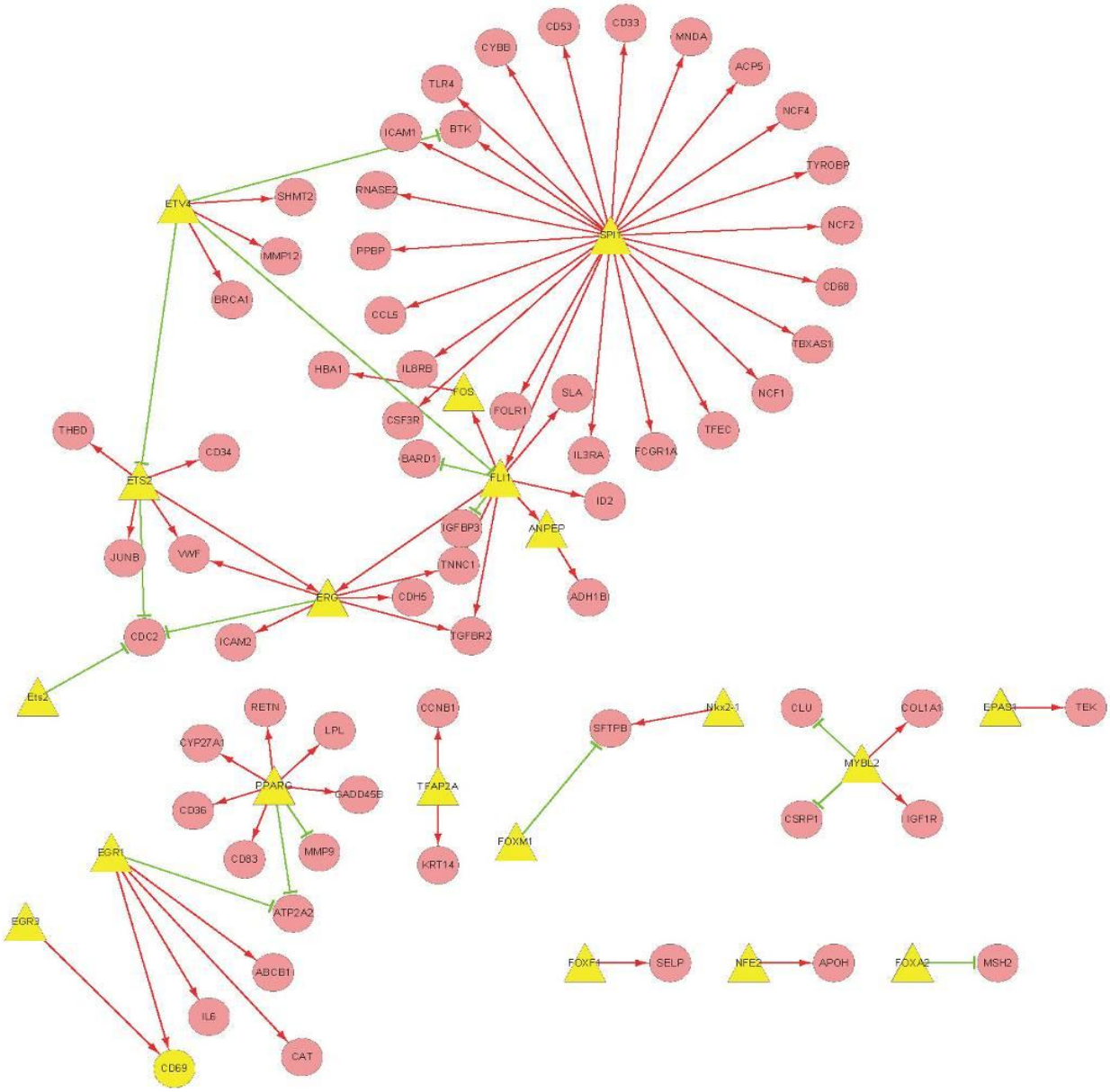

Figure 1. Regulation network of non-small cell lung cancer.

Table 2. GO enrichment analysis of biological process.

GO-ID	Description	Count	p-value	Adj p-value
42221	Response to chemical stimulus	34	1.54E-14	2.79E-11
6950	Response to stress	36	1.08E-13	9.82E-11
48518	Positive regulation of biological process	39	5.28E-13	3.19E-10
2376	Immune system process	26	1.46E-12	5.43E-10
50896	Response to stimulus	49	1.50E-12	5.43E-10
48522	Positive regulation of cellular process	36	4.60E-12	1.39E-09
10033	Response to organic substance	24	1.18E-11	3.05E-09
70887	Cellular response to chemical stimulus	16	2.89E-10	6.56E-08
51094	Positive regulation of developmental process	15	3.98E-10	8.03E-08
48513	Organ development	31	7.97E-10	1.44E-07

Table 3. Significant pathways.

Database	Pathway	Impact factor	Pathway genes in input (%)	Corrected gamma p-value
KEGG	Complement and coagulation cascades	21.288	44.928	1.27E-08
KEGG	ECM-receptor interaction	19.688	40.476	5.83E-08
KEGG	Cell cycle	19.551	36.441	6.64E-08
KEGG	Long-term depression	16.304	16	1.44E-06
KEGG	DNA replication	12.312	47.222	5.99E-05
KEGG	Systemic lupus erythematosus	11.379	24.306	1.42E-04
KEGG	Graft-versus-host disease	11.154	38.095	1.74E-04
KEGG	Ribosome	10.782	2.97	2.45E-04
KEGG	Focal adhesion	10.291	25.616	3.83E-04
KEGG	Pathways in cancer	9.922	23.333	5.36E-04

et al., 2010). Previous works have demonstrated that PPARgamma inhibits transformed growth of non-small cell lung cancer (NSCLC) cell lines *in vitro* and *in vivo*; in addition, during this process, snail family which are crucial for cell survival act as important regulators (Choudhary et al., 2010).

ETV4 is a member of the Ets-transcription factor family, which promotes metastatic progression in various types of solid cancer. ETV4 is frequently overexpressed in non-small-cell lung cancers (NSCLCs). ETV4 activates the Rho/ROCK pathway in an HGF-enhanced manner and its activation is important in ETV4-induced motility and invasion as well as tumor genesis and metastasis in NSCLC cells (Hakuma et al., 2005).

TGFBR2 encoded protein is a transmembrane protein that has a protein kinase domain, forms a heterodimer complex with another receptor protein, and binds TGF-beta. This receptor/ligand complex phosphorylates proteins, which then enter the nucleus and regulate the transcription of a subset of genes related to cell prolife-ration. Microarray analysis found that repression of type II TGF-beta receptor may act as a significant determinant of lung adenocarcinoma invasiveness, an early step in tumor progression toward metastasis (Borczuk et al., 2005). A novel homozygous microdeletion (c.492_507del) of TGFBR2 was identified in non-small cell lung cancer. The mutated TGFBR2 seems to play an important role in the abrogation of TGFB signal transduction in non-small cell lung cancer cells (Wang et al., 2007).

ATP2A2 gene encodes one of the SERCA $Ca(^{2+})$-ATPases, which are intracellular pumps located in the sarcoplasmic or endoplasmic reticula of muscle cells. This enzyme catalyzes the hydrolysis of ATP coupled with the translocation of calcium from the cytosol into the sarcoplasmic reticulum lumen, and is involved in regulation of the contraction/relaxation cycle (Hovnanian, 2007). Changes in ATP2A2 were significantly more common in patients with lung cancer. Analysis of cancer patient suggests that germline alterations of ATP2A2 may predispose to lung and colon cancer and that an impaired ATP2A2 gene might be involved, directly or indirectly, as an early event in carcinogenesis (Korosec et al., 2006). Further study suggests that the ATP2A3 gene may not act as a classical tumor suppressor gene, but rather haplo-insufficiency of this gene may be enough to change the cell and tissue environment in such a way to predispose to cancer development (Korosec et al., 2009).

Both SPI-1/PU.1 and FLI-1 gene are virus related genes; SPI-1/PU.1 encodes spleen focus forming virus (SFFV) proviral integration oncogene spi1 which is an ETS-domain transcription factor that activates gene expression during myeloid and B-lymphoid cell development. FLI-1 gene encodes friend leukemia virus integration-1 protein. Friend virus insertions occur frequently adjacent to one of two cellular genes, Spi-1/PU.1 or Fli-1. At the same time, high frequency mutation of p53 happened which strongly suggests that inactivation of p53 may be an obligatory step in the development of Friend disease. Mutation of p53 may be the most common genetic abnormality detected in human cancer; p53 mutations and allele loss were observed in human breast, lung, colon and hepatocellular carcinomas (Johnson and Benchimol, 1992).

ETS2 encodes a transcriptions factor, ETS2 which regulates numerous genes and are involved in stem cell development, cell senescence and death, and tumorigenesis. ETS2 is involved in protein kinase C-induced granulocyte-macrophage colony-stimulating factor (GM-CSF) transcriptional function. Endogenous expression of GM-CSF mRNA was increased by ETS2 and the increased expression was further enhanced by PMA which is an ETS consensus-dependent manner (Lu et al., 2003). Furthermore, GM-CSF directly regulates COX-2 expression to mediate the tumor proliferation and invasion in lung cancer cells (Uemura et al., 2007).

Protein encoded by EGR1 gene belongs to the EGR family of C_2H_2-type zinc-finger proteins. It is a nuclear protein and functions as a transcriptional regulator. Studies suggest this is a cancer suppresor gene. In lung cancer cells, Egr-1 upregulate the expression of vascular

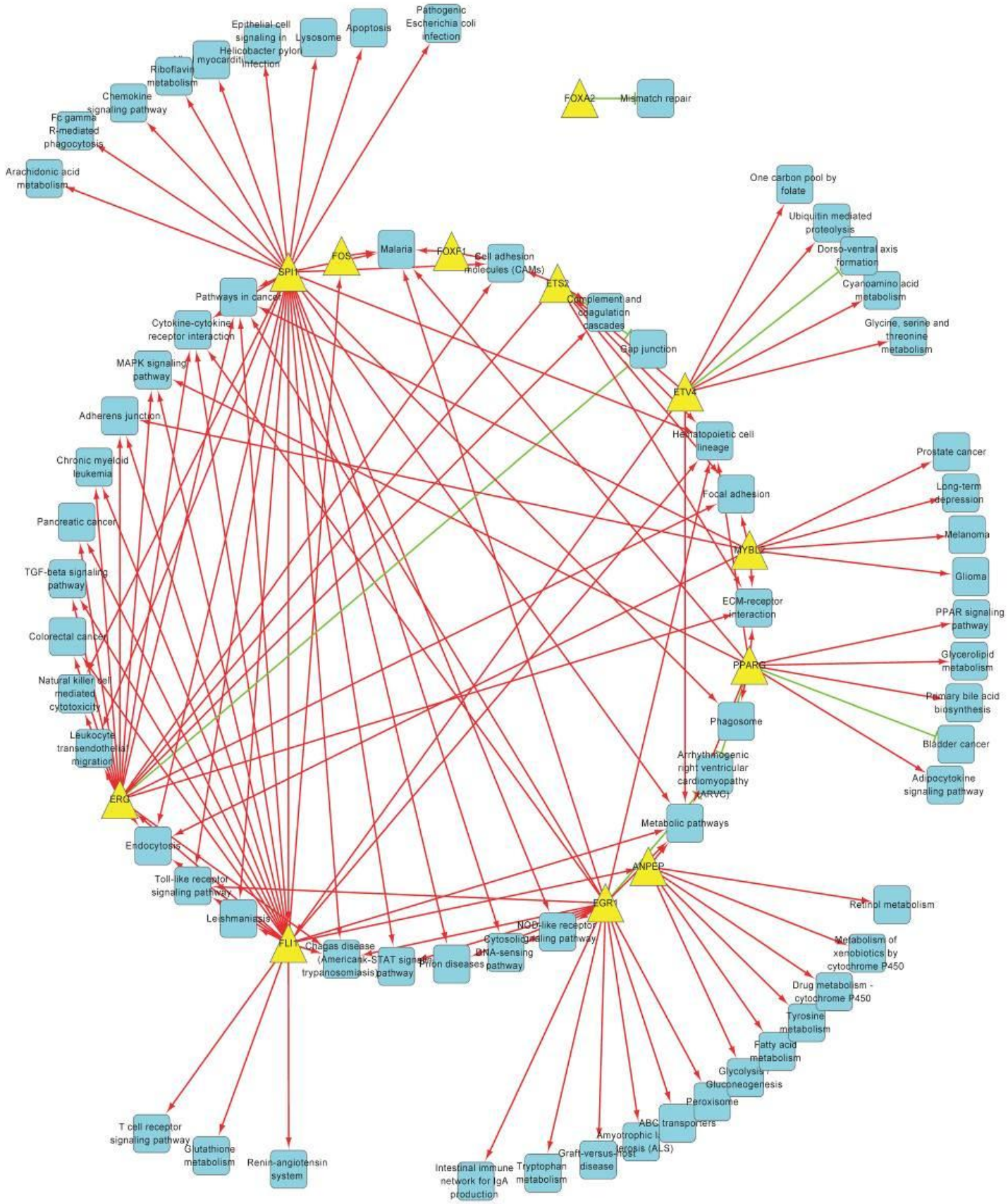

Figure 2. Pathway regulation network.

endothelial growth factor-A (VEGF-A) which is crucial for angiogenesis, vascular permeability, and metastasis during tumor development (Shimoyamada et al., 2010). Stathmin is overexpressed in a variety of assessed human malignancies and is correlated with tumor progression and poor prognosis. Both stathmin gene promoter activity and stathmin gene expression level were downregulated following the expression of Egr1 based on analysis of non-small cell lung cancer cell line-A549 (Fang et al., 2010).

Von Willebrand factor (VWF) encodes a protein functions as both an antihemophilic factor carrier and a platelet-vessel wall mediator in the blood coagulation system. It is crucial to the hemostasis process. Investigations proved significant increase in the number of pulmonary metastatic foci in VWF-null mice as compared with the wild-type mice. They also found that increased survival of the lung tumor cells during the first 24 h in the absence of VWF was the cause. These findings suggest that VWF plays a protective role against lung tumor cell dissemination *in vivo* (Terraube et al., 2006).

ABCB1 encodes a member of the superfamily of ATP-binding cassette (ABC) transporters. The protein encoded by this gene is an ATP-dependent drug efflux pump. It is responsible for decreased drug accumulation in multidrug-resistant cells and often mediates the development of resistance to anticancer drugs. Previous investigations found that gene polymorphisms in MDR1 (genes that control import/export of drugs) G2677T/A may be a predictive marker of platinum-based treatment response and of secondary effects, especially gastrointestinal toxicity for advanced NSCLC patients (Chen et al., 2010).

From the result of regulation network between TFs and pathways in NSCLC, we found that there are many pathways such as cell cycle, DNA repair/replication pathway, ribosome pathway closely related with lung cancer have been linked by our method.

Cell cycle protein cyclin Y (CCNY) was overexpressed in samples of NSCLC. CCNY mRNA expression associated with histologic types of NSCLC and promoted the malignant growth of lung cancer cell line *in vivo* and *in vitro* (Yue et al., 2011). Protein levels of checkpoint kinase 1 (Chk1), which has a major role in G(2) cell cycle checkpoint regulation, was markedly reduced at the protein and transcriptional levels in lung cancer cells treated with anticancer drugs. In histone deacetylase inhibitor (hdaci) treated cells Chk1 function was impaired as determined by decreased inhibitory phosphorylation of cdc25c and its downstream target cdc2 and increased expression of cdc25A and phosphorylated histone H3, a marker of mitotic entry (Brazelle et al., 2010). All these data suggest that cell cycle is involved in the non-small lung cancer.

DNA replication is regulated by an elegant network of many different protein factors to ensure the timely and accurate copying of their entire genome once per cell cycle. The replication factors include the maintenance (MCM) proteins, Cdt1, Cdc6, Cdc7, Cdc45, and geminin. All of these proteins are involved in the regulation of DNA replication at the initiation step (Knockleby and Lee, 2010). Based on examined 35 surgical-pathologic stage-I-NSCLC patients with complete follow-up in all cases for at least 49 months, the conclusion suggests that replication-error-type instability (RER)+ is common in NSCLC, and that it may provide important prognostic information in stage-I NSCLC and serve as a useful marker for relapse-risk assessment in operable NSCLC patients (Rosell et al., 1997). Evaluate differential mRNA levels of 22 DNA repair genes of five different DNA repair pathways. A significant overexpression was detected in 20 of 30 (67%) genes, mostly belonging to double-strand break (DSBR) pathways. Overall, genes belonging to DNA repair/replication pathways are overexpressed in NSCLC and are associated with a more aggressive phenotype (Saviozzi et al., 2009).

Ribosome biogenesis is a complex process comprising transcription, modification, and processing of ribosomal RNA, production of ribosomal proteins and auxiliary factors, and coordinated assembly of ribonucleoprotein particles to produce mature ribosomes (Deisenroth Zhang, 2010). Leucine zipper/EF hand-containing transmembrane-1 (LETM1) served as an anchor protein for complex formation between mitochondria and ribosome. Previous results demonstrated that adenovirus-LETM1 suppressed lung cancer cell growth *in vitro* and *in vivo* (Hwang et al., 2010). CIGB-300 is a proapoptotic peptide-based drug that abrogates the CK2-mediated phosphorylation. From the proteome analysis of the non-small lung cancer cell line, it suggests that CIGB-300 can be viewed as anticancer agent. CIGB-300 significantly modulate ribosome biogenesis, therefore, ribosome is correlated with non-small lung cancer (Rodriguez-Ulloa et al., 2010).

The understanding of the mechanisms underlying the functioning of NSCLC genes is important. A deeper understanding of transcription factors and their target genes remain an area of intense research activity in the future. Our regulation network is useful in investigating the complex interacting mechanisms of transcription factors and their regulated genes squamous lung cancer. We also found some new transcription factors and target genes related to NSCLC; besides, cell cycle pathway, DNA repair/replication pathway and ribosome pathway have been linked to NSCLC by our method.

However, further experiments are still needed to confirm the conclusion.

In order to further confirm the role of the gene SP1, EGR1 and ETS2 in NSCLC, some research about gene expression lever in animal model is necessary.

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