Identification of potential therapeutic targets for lung cancer by bioinformatics analysis

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Abstract. The aim of the present study was to identify potential therapeutic targets for lung cancer and explore underlying molecular mechanisms of its development and progression. The gene expression profile datasets no. GSE3268 and GSE19804, which included five and 60 pairs of tumor and normal lung tissue specimens, respectively, were downloaded from the Gene Expression Omnibus. Differentially expressed genes (DEGs) between lung cancer and normal tissues were identified, and gene ontology and Kyoto Encyclopedia of Genes and Genomes pathway analysis of the DEGs was performed. Furthermore, protein–protein interaction (PPI) networks and a transcription factor (TF) regulatory network were constructed and key target genes were screened. A total of 466 DEGs were identified, and the PPI network indicated that IL-6 and MMP9 had key roles in lung cancer. A PPI module containing 34 nodes and 547 edges was obtained, including PTTG1. The TF regulatory network indicated that TFs of FOSB and LMO2 had a key role. Furthermore, MMP9 was indicated to be the target of FOSB, while PTTG1 was the target of LMO2. In conclusion, the bioinformatics analysis of the present study indicated that IL-6, MMP9 and PTTG1 may have key roles in the progression and development of lung cancer and may potentially be used as biomarkers or specific therapeutic targets for lung cancer.

Introduction

Lung cancer is one of the most common malignancies and has a significant socioeconomic impact on patients and their families (1). In western countries, the mortality rate of lung cancer is 15% and the worldwide mortality rate for patients with lung cancer is 86% (2). The high mortality of lung cancer is mainly attributable to the lack of effective therapeutic methods and the difficulty of obtaining an early diagnosis. Thus, the development of effective therapeutic targets is urgently required.

Differentially expressed genes (DEGs) have been reported to have important roles in lung cancer, and their identification may aid in the elucidation of its underlying molecular mechanisms as well as the discovery of novel biomarkers and treatments (3). Numerous genes, including p53 (3,4), EGFR (5,6), kRAS (7), PIK3CA (8) and EML4 (9), are known to be associated with lung cancer, while others have remained elusive. Furthermore, SEMA5A and -6A were identified as potential therapeutic targets for lung cancer (10-12). Although tremendous efforts have been made to discover novel targets for lung cancer treatments, the current knowledge is insufficient and requires expansion.

In the present study, DEGs between lung cancer and normal lung tissues were identified. Protein–protein interaction (PPI) and transcription factor (TF) regulatory networks were constructed and key target genes were screened. Through the identification of key genes, the possible underlying molecular mechanisms as well as potential candidate biomarkers and treatment targets for lung cancer were explored.

Materials and methods

Affymetrix microarray data. The gene expression profile dataset no. GSE3268 deposited in the Gene Expression Omnibus (GEO) database (http://www.ncbi.nlm.nih.gov/geo/) by Wachi et al (13) based on the GPL96 platform (HG-U133A; Affymetrix Human Genome U133A Array), was subjected to bioinformatics analysis in the present study. The dataset contained a total of 10 chips, including five squamous cell lung cancer tissues and five paired adjacent normal lung tissues obtained from patients with squamous cell lung cancer.

Furthermore, the gene expression profile dataset GSE19804 based on the platform GPL570 (HG-U133_Plus_2; Affymetrix Human Genome U133 Plus 2.0 Array), which was deposited in the GEO database by Lu et al (14), was used. The dataset contained 120 chips, including 60 samples of non-small cell lung cancer tissues and 60 samples of paired normal lung tissues from female Taiwanese patients.

Identification of DEGs. The raw data were pre-processed using the Affy package (15) in R language. DEGs of GSE3268 (DEG1) and GSE19804 (DEG2) between normal groups and
was shown to be downregulated in squamous cell and wounding, immune response, defense response and inflammation significantly enriched in biological processes, including response to division (Table I); the downregulated DEGs were significantly enriched in organismal macromolecule metabolic processes and nuclear division (Table I); the downregulated DEGs were significantly enriched in biological processes, including response to cell cycle, extracellular matrix-receptor interaction and the p53 signaling pathway (Table I); the downregulated DEGs were significantly enriched in cytokine receptor interaction, complement and coagulation cascades as well as chemokine signaling pathways (Table I).

Construction of PPI network and screening of module. The PPI network was constructed based on the predicted interactions of the identified DEGs (Fig. 2). Genes of IL-6, FOSB, CDK1, MMP9 and ICAM1 were found to have a high degree of interaction in lung cancer. A sub-network containing 34 nodes and 547 edges was screened from the PPI network, such as PTTG1 (Fig. 3). The DEGs in the sub-net were significantly enriched in biological processes, such as the cell cycle, and pathway analysis showed that they were significantly enriched in cell cycle and oocyte meiosis (Table II).

Discussion

Lung cancer is the leading cause of cancer-associated mortality; however, the underlying molecular mechanisms of its development and progression have remained to be fully elucidated (1). The present study used a bioinformatics approach to predict the potential therapeutic targets and explore the possible molecular mechanisms for lung cancer. A total of 466 DEGs between tumorous and normal tissues was identified, among which 310 genes were downregulated and 156 were upregulated. By constructing a PPI network and a TF regulatory network, key genes, including IL6, MMP9 and PTTG1, were identified.

IL-6 is a multifunctional cytokine that was characterized as a regulator of immune and inflammatory responses (27,28). It is involved in the regulation of cell proliferation, survival and metabolism, and IL-6 signaling has an important role in tumorigenesis (29). Chung et al (30) found that IL-6 activated PI3K, which promoted apoptosis in human prostate cancer cell lines. Furthermore, studies have shown that IL-6 inhibited the growth of numerous types of cancer, including lung (31), breast (32) and prostate cancer (33). In the present study, IL-6 was shown to be downregulated in squamous cell and non-small cell lung cancer, and GO analysis showed that IL-6 was significantly enriched in biological processes, including defense response, inflammatory response, immune response and regulation of cell proliferation, which was consistent with a previous study (29). Combined with the above studies, it is indicated that IL-6 may be a diagnostic biomarker and therapeutic target in lung cancer.

MMP9 has a key role in cell migration, proliferation, differentiation, angiogenesis, apoptosis and host defense (34). Dysregulation of MMPs has been implicated in numerous diseases, including chronic ulcers and cancer (35-37).
Figure 1. Boxplot of normalized expression values for the datasets. The dotted lines in the middle of each box represent the median of each sample, and its distribution among samples indicates the level of normalization of the data, with a nearly straight line indicating a fair normalization level. Gene expression omnibus datasets: 1, GSE3268; 2, GSE19804.
Downregulation of MMPs has been shown to inhibit metastasis, while upregulation of MMPs led to enhanced cancer cell invasion (37). In the present study, MMP9 was overexpressed and regulated by FOSB in lung cancer tissues. Kim et al (38) found that FOSB was downregulated in pancreatic cancer and promoted tumor progression. Kataoka et al (39) found that FOSB gene expression in cancer stroma is a independent prognostic indicator for patients with epithelial ovarian cancer receiving standard therapy. Combined with the above studies, the present study indicated that MMP9 may have important roles in the progression of lung cancer, and that it may be utilized as a therapeutic target.

**Table I. GO and pathway analysis of the differentially expressed genes.**

| Expression       | Category          | Term/gene and function                                      | Count | P-value       |
|------------------|-------------------|------------------------------------------------------------|-------|---------------|
| Upregulated      | KEGG_PATHWAY      | hsa04110 - Cell cycle                                       | 12    | 6.94x10^-7   |
|                  | KEGG_PATHWAY      | hsa04512 - ECM-receptor interaction                         | 10    | 1.50x10^-6   |
|                  | KEGG_PATHWAY      | hsa04510 - Focal adhesion                                   | 10    | 1.42x10^-3   |
|                  | KEGG_PATHWAY      | hsa04115 - p53 signaling pathway                            | 6     | 2.14x10^-3   |
|                  | KEGG_PATHWAY      | hsa00240 - Pyrimidine metabolism                            | 5     | 3.93x10^-2   |
|                  | GOTERM_BP_FAT     | GO:0032963 - Collagen metabolic process                     | 9     | 2.10x10^-10  |
|                  | GOTERM_BP_FAT     | GO:0044259 - Multicellular organismal macromolecule metabolic process | 9     | 5.19x10^-10  |
|                  |                   |                                                            |       |               |
|                  | GOTERM_BP_FAT     | GO:0002280 - Nuclear division                               | 17    | 5.79x10^-10  |
|                  |                   |                                                            |       |               |
|                  | GOTERM_BP_FAT     | GO:0000767 - Mitosis                                        | 17    | 5.79x10^-10  |
|                  |                   |                                                            |       |               |
|                  | GOTERM_BP_FAT     | GO:0000278 - Mitotic cell cycle                              | 21    | 7.04x10^-10  |
|                  |                   |                                                            |       |               |
|                  | GOTERM_BP_FAT     | GO:0000087 - M phase of mitotic cell cycle                   | 17    | 7.55x10^-10  |
|                  |                   |                                                            |       |               |
|                  | GOTERM_CC_FAT     | GO:0005756 - Extracellular region                           | 53    | 1.41x10^-10  |
|                  |                   |                                                            |       |               |
|                  | GOTERM_CC_FAT     | GO:0005758 - Proteinaceous extracellular matrix              | 19    | 7.80x10^-9   |
|                  |                   |                                                            |       |               |
|                  | GOTERM_CC_FAT     | GO:0031012 - Extracellular matrix                            | 19    | 2.50x10^-4   |
|                  |                   |                                                            |       |               |
|                  | GOTERM_CC_FAT     | GO:0044421 - Extracellular region part                      | 30    | 2.27x10^-7   |
|                  |                   |                                                            |       |               |
|                  | GOTERM_CC_FAT     | GO:0005819 - Spindle                                        | 12    | 4.55x10^-7   |
|                  |                   |                                                            |       |               |
|                  | GOTERM_MF_FAT     | GO:004222 - Metalloendopeptidase activity                    | 9     | 9.37x10^-10  |
|                  |                   |                                                            |       |               |
|                  | GOTERM_MF_FAT     | GO:0048407 - Platelet-derived growth factor binding         | 4     | 1.53x10^-4   |
|                  |                   |                                                            |       |               |
|                  | GOTERM_MF_FAT     | GO:004175 - Endopeptidase activity                           | 13    | 3.80x10^-4   |
|                  |                   |                                                            |       |               |
|                  | GOTERM_MF_FAT     | GO:0004857 - Enzyme inhibitor activity                      | 11    | 3.81x10^-4   |
|                  |                   |                                                            |       |               |
| Downregulated    | KEGG_PATHWAY      | hsa04060 - Cytokine-cytokine receptor interaction            | 20    | 6.99x10^-5   |
|                  | KEGG_PATHWAY      | hsa04610 - Complement and coagulation cascades              | 8     | 2.47x10^-3   |
|                  | KEGG_PATHWAY      | hsa04620 - Chemokine signaling pathway                      | 13    | 4.53x10^-3   |
|                  | KEGG_PATHWAY      | hsa04650 - Natural killer cell mediated cytotoxicity        | 10    | 9.69x10^-3   |
|                  | KEGG_PATHWAY      | hsa04614 - Renin-angiotensin system                         | 4     | 1.01x10^-2   |
|                  | GOTERM_BP_FAT     | GO:0009611 - Response to wounding                           | 48    | 2.23x10^-17  |
|                  | GOTERM_BP_FAT     | GO:0006952 - Defense response                               | 46    | 1.66x10^-13  |
|                  | GOTERM_BP_FAT     | GO:0006954 - Inflammatory response                          | 33    | 2.92x10^-13  |
|                  | GOTERM_BP_FAT     | GO:0006955 - Immune response                                | 43    | 4.20x10^-10  |
|                  | GOTERM_BP_FAT     | GO:0048545 - Response to steroid hormone stimulus           | 21    | 3.81x10^-9   |
|                  | GOTERM_CC_FAT     | GO:0005615 - Extracellular space                            | 55    | 2.36x10^-18  |
|                  | GOTERM_CC_FAT     | GO:004421 - Extracellular region part                      | 64    | 2.03x10^-17  |
|                  | GOTERM_CC_FAT     | GO:0005576 - Extracellular region                           | 93    | 3.37x10^-15  |
|                  | GOTERM_CC_FAT     | GO:0005886 - Plasma membrane                                | 131   | 2.25x10^-12  |
|                  | GOTERM_CC_FAT     | GO:0005887 - Integral to plasma membrane                   | 61    | 1.99x10^-11  |
|                  | GOTERM_MF_FAT     | GO:0019838 - Growth factor binding                         | 16    | 2.01x10^-9   |
|                  | GOTERM_MF_FAT     | GO:0030246 - Carbohydrate binding                          | 27    | 7.86x10^-9   |
|                  | GOTERM_MF_FAT     | GO:0019955 - Cytokine binding                               | 13    | 1.54x10^-6   |
|                  | GOTERM_MF_FAT     | GO:0005509 - Calcium ion binding                            | 39    | 1.04x10^-3   |
|                  | GOTERM_MF_FAT     | GO:0030247 - Polysaccharide binding                         | 14    | 1.11x10^-5   |

BP, biological process; CC, cellular component; MF, molecular function; Count, numbers of differentially expressed genes; ECM, extracellular matrix; GO, gene ontology; hsa, Homo sapiens; KEGG, Kyoto Encyclopedia of Genes and Genomes; FAT, functional annotation tool.
PTTG1 has tumorigenic activity and is highly expressed in various tumor types (40). Studies have shown that PTTG1 was overexpressed in esophageal cancer and associated with endocrine therapy resistance in breast cancer (41,42). Yoon et al (40) showed that the PTTG1 oncogene promoted tumor malignancy via epithelial-to-mesenchymal expansion of the cancer stem cell population. Hamid et al (43) found that PTTG1 promoted tumorigenesis in human embryonic kidney cells. A study by Li et al (44) indicated that PTTG1 promoted migration and invasion of human non-small cell lung cancer cells. Panguluri et al (45) showed that PTTG1 was an important target gene for ovarian cancer therapy. In the present study, PTTG1 was found to be overexpressed in lung cancer tissues and regulated by LMO2. LMO2 is an important regulator in determining cell fate and controlling cell growth and differentiation (46). Nakata et al (47) found that LMO2 was a novel predictive biomarker with the potential to enhance the accuracy of prognoses for pancreatic cancer. Yamada et al (48) showed that LMO2 is a key regulator of tumour angiogenesis. Combined with the above studies, the present study indicated that PTTG1 may have important roles in the progression of lung cancer and that it may represent a therapeutic target.

In conclusion, the bioinformatics analysis of the present study indicated that IL-6, MMP9 and PTTG1 may have key roles in the progression and development of lung cancer. They
Table II. GO and pathway analysis of genes in sub-network.

| Category          | Term/gene and function                        | Count | P-value       |
|-------------------|-----------------------------------------------|-------|---------------|
| KEGG_PATHWAY      | hsa04110 - Cell cycle                         | 10    | 1.09x10^{-11}|
| KEGG_PATHWAY      | hsa04114 - Oocyte meiosis                     | 6     | 1.09x10^{-3}  |
| KEGG_PATHWAY      | hsa04914 - Progesterone-mediated oocyte maturation | 4    | 1.83x10^{-1}  |
| KEGG_PATHWAY      | hsa04115 - p53 signaling pathway              | 3     | 1.65x10^{-3}  |
| KEGG_PATHWAY      | hsa00240 - Pyrimidine metabolism              | 3     | 3.10x10^{-2}  |
| GOTERM_BP_FAT     | GO:0000278 - Mitotic cell cycle               | 19    | 7.13x10^{-21} |
| GOTERM_BP_FAT     | GO:0007049 - Cell cycle                       | 22    | 1.65x10^{-19} |
| GOTERM_BP_FAT     | GO:0000280 - Nuclear division                 | 16    | 2.14x10^{-19} |
| GOTERM_BP_FAT     | GO:0007067 - Mitosis                          | 16    | 2.14x10^{-19} |
| GOTERM_BP_FAT     | GO:0000087 - M phase of mitotic cell cycle    | 16    | 2.82x10^{-19} |
| GOTERM_CC_FAT     | GO:0015630 - Microtubule cytoskeleton          | 14    | 5.31x10^{-11} |
| GOTERM_CC_FAT     | GO:0000779 - Condensed chromosome, centromeric region | 8    | 3.94x10^{-11} |
| GOTERM_CC_FAT     | GO:0015630 - Microtubule cytoskeleton          | 14    | 5.31x10^{-11} |
| GOTERM_CC_FAT     | GO:0000779 - Condensed chromosome, centromeric region | 8    | 1.01x10^{-10} |
| GOTERM_CC_FAT     | GO:000922 - Spindle pole                      | 7     | 1.01x10^{-10} |
| GOTERM_MF_FAT     | GO:0005524 - Adenosine triphosphate binding   | 15    | 4.89x10^{-7}  |
| GOTERM_MF_FAT     | GO:0032559 - Adenyl ribonucleotide binding    | 15    | 5.78x10^{-7}  |
| GOTERM_MF_FAT     | GO:0030554 - Adenyl nucleotide binding        | 15    | 1.10x10^{-6}  |
| GOTERM_MF_FAT     | GO:0001883 - Purine nucleoside binding        | 15    | 1.32x10^{-6}  |
| GOTERM_MF_FAT     | GO:0001882 - Nucleoside binding               | 15    | 1.44x10^{-6}  |

BP, biological process; CC, cellular component; MF, molecular function; Count, numbers of DEGs; GO, gene ontology; hsa, Homo sapiens; KEGG, Kyoto Encyclopedia of Genes and Genomes; FAT, functional annotation tool.

Figure 4. Transcriptional regulatory network analysis. Blue nodes represent products of upregulated DEGs and pink nodes represent products of downregulated DEGs. Triangle arrowheads indicate transcription factors and circles indicate target genes. DEG, differentially expressed gene.
may be used as prognostic biomarkers as well as specific therapeutic targets for the treatment of lung cancer. However, molecular biology experiments are required to confirm these findings.

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