The expression and prognostic role of Peroxiredoxins in lung cancer

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ABSTRACT

Background: Peroxiredoxins (Prxs) comprise antioxidant factors that are widely found in prokaryotes and eukaryotes. Abnormal expression of Prxs is closely related to tumorigenesis.

Methods: This study examined the prognostic value and expression of Prxs in lung cancer by Human Protein Atlas (HPA), Gene Expression Profiling Interactive Analysis (GEPIA), UALCAN, Kaplan-Meier Plotter, cBioPortal and Functional Enrichment Analysis Tool (FunRich) databases.

Results: We found that Prx1/2/3/4/5 were overexpressed in both lung squamous cell carcinoma (LUSC) and lung adenocarcinoma (LUAD) relative to normal lung cells. However, the expression level of Prx6 was lower in LUAD and higher in LUSC than normal lung cells. The level of Prx3 and Prx6 were associated with pathological stage. Prognostic

analysis showed that elevated Prx1 and Prx2 expression were correlated with low Overall Survival (OS), whereas high Prx5 and Prx6 expression level predicted high OS.

Conclusions: Our results effectively revealed the level of Prxs in lung cancer and its influence on the prognosis of lung carcinoma, contributing to the study of the role of Prxs in tumorigenesis.

Keywords: Peroxiredoxins, lung cancer, prognostic

INTRODUCTION

Lung cancer ranks highly among the leading causes of deaths globally (18.4% of total cancer deaths) [1]. Non-small cell lung cancer (NSCLC) is the predominant form, constituting > 80% of all lung cancer cases [2]. Despite the development of treatments in the past decade, the disease progress of lung cancer is poor [3]. Therefore, it is crucial to examine the processes of lung cancer formation and development in order to improve patient outcomes and develop individualized treatment options.

Prxs is a family of antioxidant proteins that have recently received much attention and are widely found in prokaryotes and eukaryotes [4]. In mammals, Prxs family comprise 6 proteins (Prx1-6), which are classified

to 3 subclasses: 1-cysteine Prxs (Prx6), atypical 2-cysteine Prxs (Prx5) and typical 2-cysteine Prxs (Prx1-4) [5]. Prxs can regulate intracellular signal transduction and cellular metabolism by scavenging intracellular reactive oxygen species [6], and it also regulates cell proliferation, apoptosis and gene expression [7]. Prxs are differentially expressed in various tumors, including pancreatic, liver, colorectal, gastric, and lung cancers [8-13].

Previous studies have shown that Prx1/2/4/6 are elevated in lung cancer [14], and overexpression of Prx1 or Prx4 promotes the progression of lung cancer [15]. By opposing the ERK/cyclin D1 pathway, Prx1 inhibits K-ras-driven lung tumorigenesis [16]. Prx4 overexpression was markedly correlated with shorter DFS and recurrence in lung cancer patients [17]. However, the underlying mechanisms of Prxs in the progression and development of lung cancer and the effects of their expression on the prognosis of lung cancer have not been fully elucidated.

Therefore, we used bioinformatics analysis to examine the prognostic value of Prxs and its expression in lung cancer patients in various public databases. Our analysis can expand the research on the biological function of lung cancer and reveal strategies for lung cancer prevention and treatment.

MATERIALS AND METHODS

GEPIA dataset

GEPIA is a recent database for cancer used in normal interactive analyses and gene expression profiles. In addition to the analysis of the expression, staging, prognosis and correlation of multiple tumors of TCGA, the genetic isomer information, pan-cancerous research and three-dimensional scattergram of TCGA data were further improved [18].

The Human Protein Atlas (HPA)

The HPA is designed to utilize a variety of omics techniques, such as transcriptomics and systems biology, mass spectrometry-based proteomics, antibody-based imaging, integrate all human proteins in cells, tissues and organs. Tissue specimens fixed in formalin and embedded in paraffin were obtained from the Department of Pathology at Uppsala University Hospital, followed by tissue microarray (TMA) production, immunohistochemical analysis using standardized procedures, and approval using a 20x objective scan Slides were immunostained to produce high resolution digital images. Images are imported into internally built software for subsequent manual scoring of images. All procedures follow strict guidelines and include quality control [19].

UALCAN analysis

UALCAN is an interactive online platform that analyses cancer OMICS data. It is designed on PERL-CGI and has provide high-quality graphics using CSS and javascript. A key advantages of the database is that it enables gene expression analysis and the relationship between gene expression and prognosis [20].

Kaplan-Meier Plotter

The Kaplan Meier plotter program allows examination of the effect of the 54k gene on the survival of 21 cancers. The primary aim of the tool is to discover and validate biomarkers based on meta-analysis. The database contains gene expression and survival data for 3,452 clinical lung cancer patients. Gene expression data, recurrence-free and total survival data were downloaded from TCGA EGA and GEO, all specimens were assigned into two based on the quantitation expression of the candidate markers, and two groups were compared by Kaplan-Meier survival map. Group and calculate the hazard ratio with 95% confidence interval and logrank P value [21].

cBioPortal analysis

The cBioPortal for Cancer Genomics is an open-source reservoir, open-access platform for interactive examination of multidimensional cancer genomics datasets [22]. We used cBioPortal to analyze changes in Prxs in TCGA lung cancer samples, including mutations, CNV and mRNA expression. The bio-interaction network of Prxs was calculated according to the online instructions of cBioPortal.

Functional Enrichment Analysis Tool

FunRich is a software that is utilized to perform interaction network analysis and functional enrichment of proteins and genes. Moreover, the findings obtained from this platform can be displayed graphically in the form of Doughnut, Column and Pie charts, Venn, and Bar graphs [23]. We analyzed the molecular functions, biological processes, and biological pathways in Prxs-related genes through Erichment analysis.

RESULTS

Prxs expression in lung cancer

We initially used the GEPIA database to analyze the mRNA levels of Prxs in LUAD and LUSC. The results showed that Prx1/2/3/4/5 were

overexpressed in both LUAD and LUSC matched with that of normal lung samples. However, the mRNA level of Prx6 was lower in LUAD and higher in LUSC than normal lung tissue (Figure 1). Then we used the Tissue and Pathology sections of the HPA database to further analyze the protein quantity of Prxs in lung cancer patients and normal lung samples. The results of immunohistochemistry indicated that Prx1/2/4/5/6 were higher in lung cancer tissues than normal lung specimen, while the level of Prx3 was lower in the latter than normal lung tissues (Figure 2).
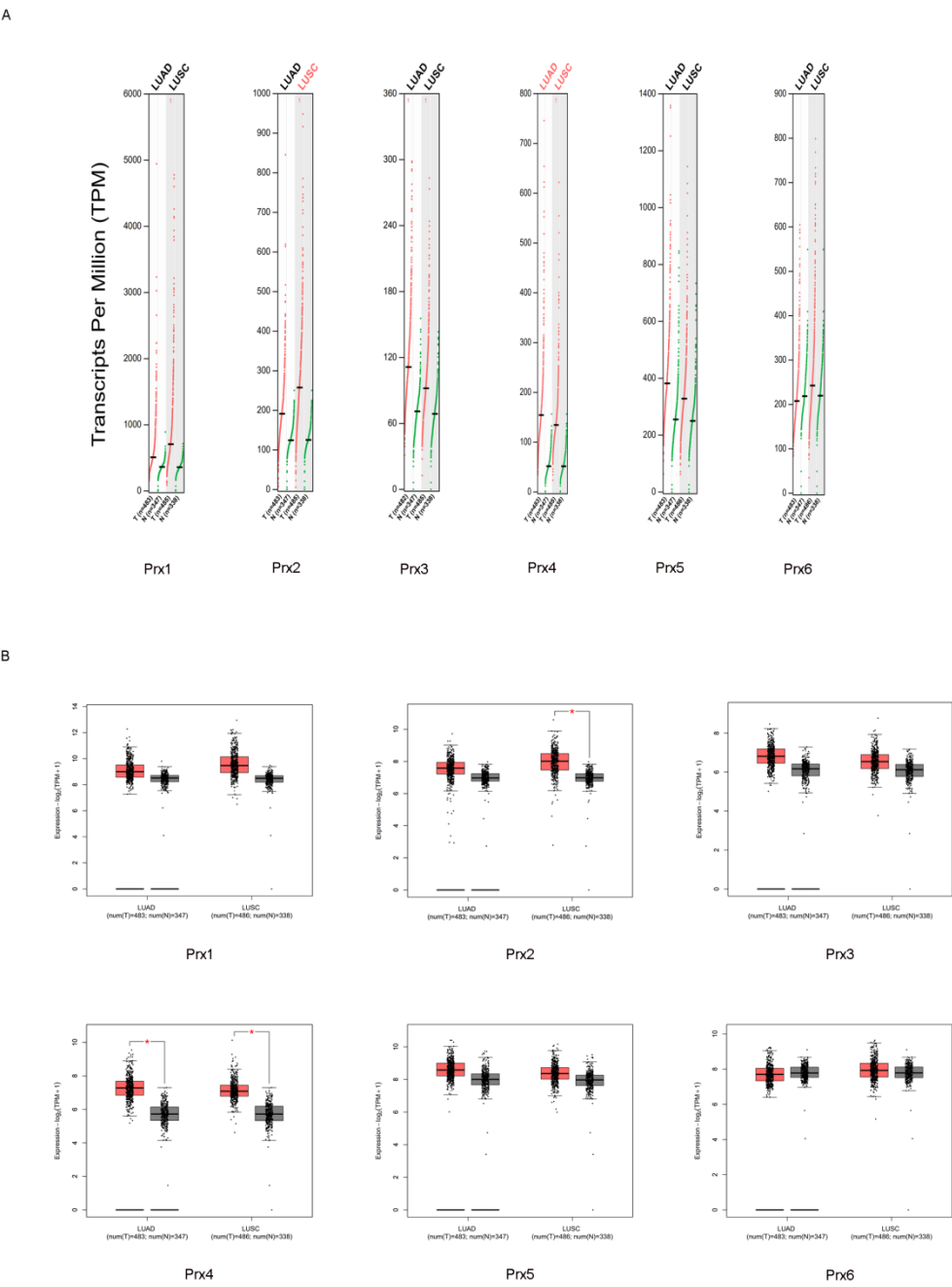
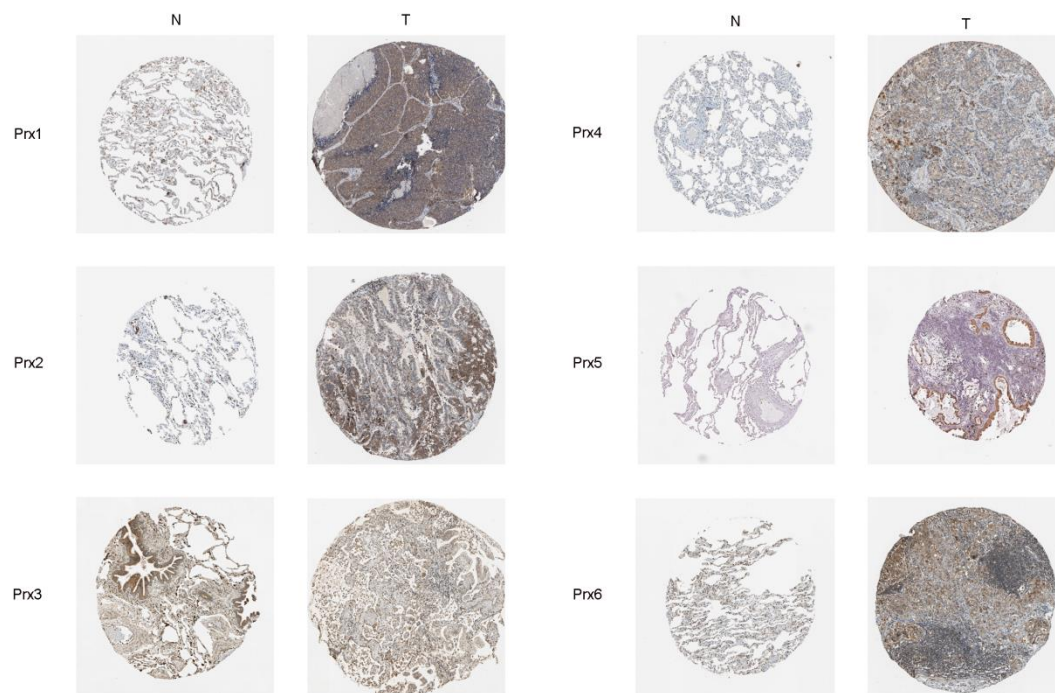Figure 1. Prxs expression in lung cancer (GEPIA).

Figure 2. Expression levels of Prxs in lung cancer (HPA).

Relationship between expression levels of Prxs and clinicopathological parameters

First, we analyzed the correlation between the level of Prxs and tumor stage in lung cancer through the GEPIA database. We found that Prx3/6 protein expression were closely related to tumor stage, while Prx1/2/4/5 were not significantly different (Figure 3). We then used the UALCAN database to analyze the association of Prxs expression with age, gender, lymph node metastasis status, ethnicity, and smoking habits. Compared with normal individuals of any age, Prx1/2/3 were not significantly

differentially expressed in LUAD patients aged 21-40 years, but significantly increased in other age groups. In contrast to the no statistical difference in Prx5, the difference in Prx4 was statistically significant in any age group. Not only that, Prx6 showed high expression levels in the 41-60 and 61-80 age groups. For gender, the expression of Prx1/2/3/4/6 in male and female LUAD patients were higher than normal individuals. Lymph node metastasis status was associated with higher protein expression levels of Prx1/2/3/4/6. Prx1/2/3/4 showed higher expression levels in Caucasian, African-American or Asian LUAD patients compared to normal individuals of any race. The expression levels of Prx1/2/3/4/6 in LUAD patients with smoking were higher and the differences were statistically significant (Figure 4, Table 1).
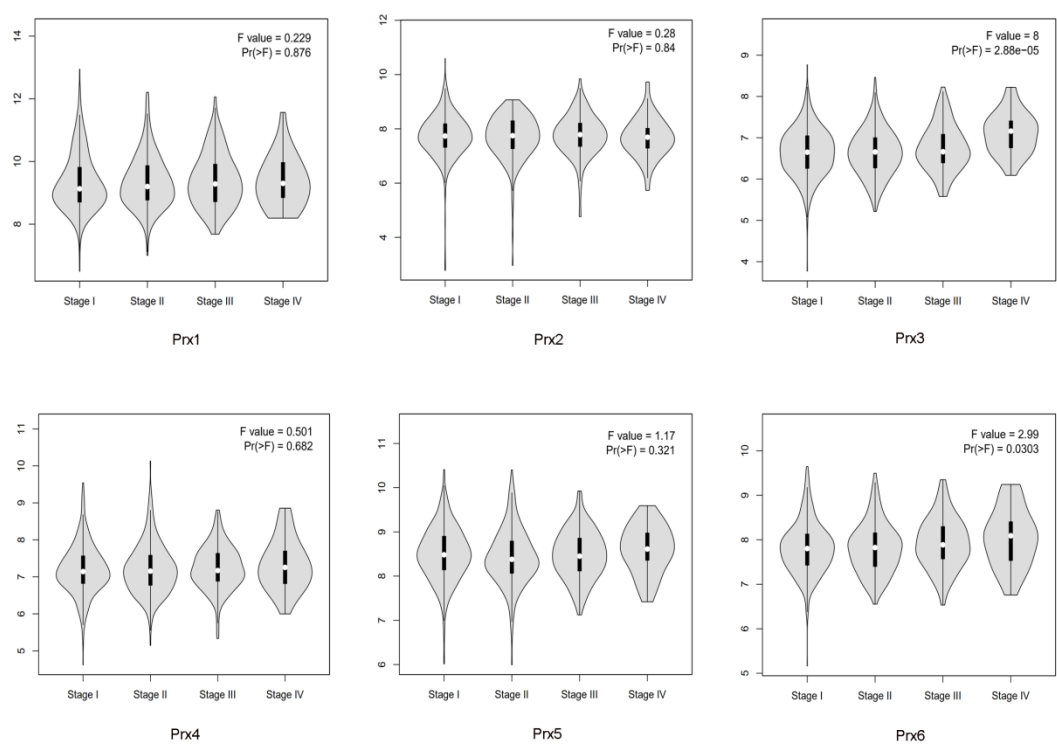
Figure 3. Relationship between expression of Prxs and clinical stage of lung cancer (GEPIA).
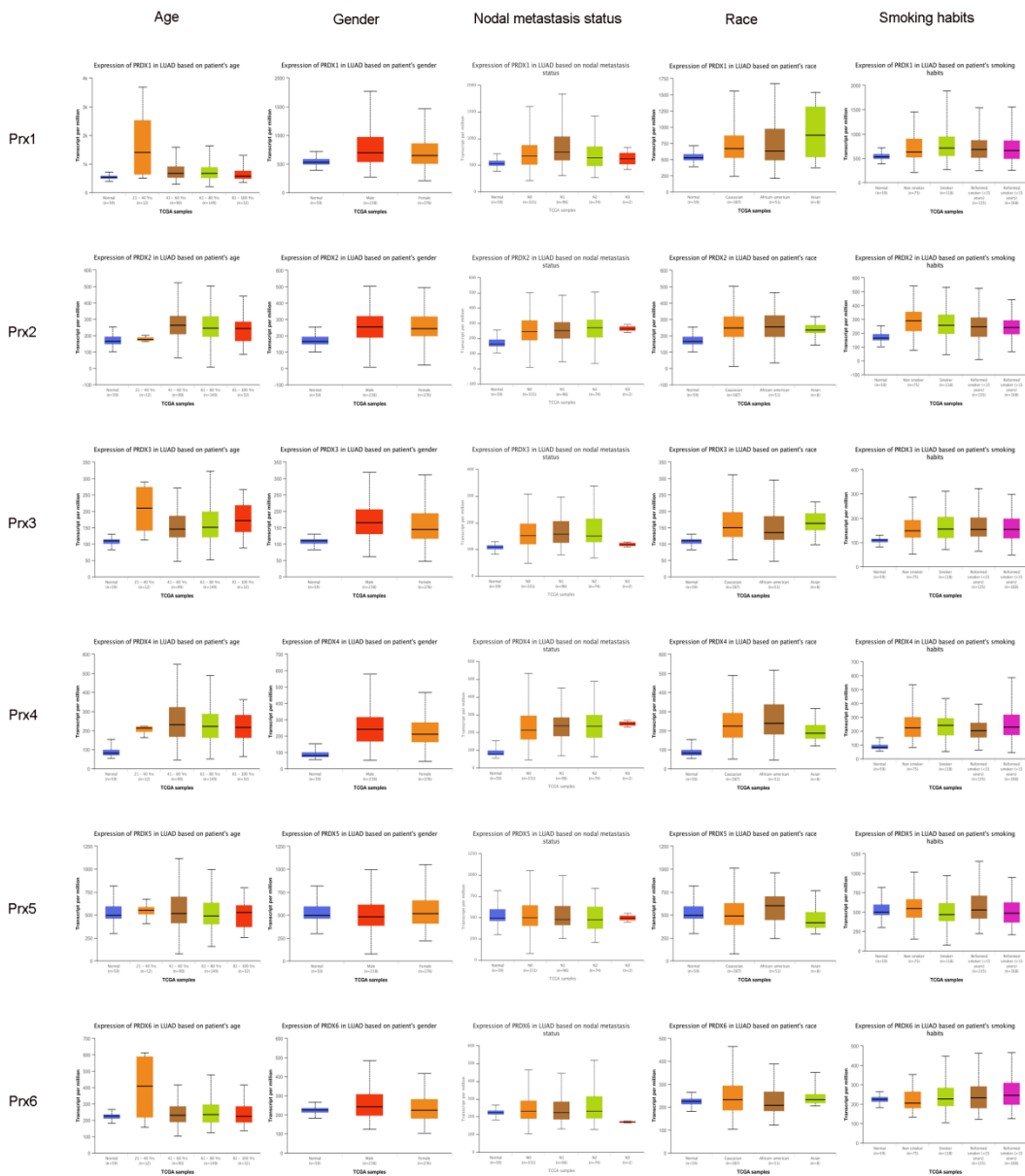
Figure 4. Relationship between expression levels of Prxs and clinicopathological parameters (UALCAN).

Table 1 Relationship between Prxs and clinicopathological parameters

characteristic	Comparison	Prx1	Prx2	Prx3	Prx4	Prx5	Prx6
Age	Normal-vs-Age(21-40Yrs)	2.04E-01	3.15E-01	1.28E-01	1.22E-10	6.99E-01	2.40E-01
	Normal-vs-Age(41-60Yrs)	1.51E-10	<1E-12	3.77E-15	<1E-12	7.68E-01	1.21E-02
	Normal-vs-Age(61-80Yrs)	1.62E-12	<1E-12	1.62E-12	1.62E-12	1.95E-01	4.85E-08
	Normal-vs-Age(81-100Yrs)	3.13E-02	8.61E-04	1.86E-06	6.28E-07	3.02E-01	3.67E-01
Gender	Normal-vs-Male	1.63E-12	1.62E-12	1.62E-12	<1E-12	1.53E-01	7.68E-09
	Normal-vs-Female	1.64E-12	<1E-12	1.62E-12	<1E-12	7.58E-01	1.46E-03
Lymph node metastasis status	Normal-vs-N0	1.33E-15	<1E-12	<1E-12	<1E-12	4.80E-01	6.13E-07
	Normal-vs-N1	1.14E-10	1.86E-12	2.29E-12	1.62E-12	8.92E-01	8.90E-03
	Normal-vs-N2	5.74E-05	7.56E-12	1.58E-10	<1E-12	5.46E-02	4.38E-03
	Normal-vs-N3	7.96E-01	1.01E-04	8.38E-01	7.04E-11	5.04E-01	2.94E-03
Ethnicity	Normal-vs-Caucasian	1.62E-12	1.62E-12	1.62E-12	1.62E-12	2.53E-01	4.42E-08
	Normal-vs-AfricanAmerican	7.65E-04	5.80E-09	8.42E-05	3.70E-11	3.35E-01	3.63E-01
	Normal-vs-Asian	6.43E-02	4.69E-02	6.28E-02	3.18E-02	7.54E-01	1.61E-01
Smoking habits	Normal-vs-Non smoker	4.13E-06	1.66E-12	2.40E-09	<1E-12	3.91E-01	9.80E-01
	Normal-vs-Smoker	1.90E-08	1.63E-12	7.94E-14	<1E-12	2.28E-01	1.44E-03
	Normal-vs-Reformed smoker1	3.27E-11	1.65E-12	<1E-12	<1E-12	9.86E-01	4.44E-04
	Normal-vs-Reformed smoker2	1.75E-11	<1E-12	1.62E-12	<1E-12	4.16E-02	1.53E-07

Relationship of Prxs level with the prognosis of patients with lung cancer

We next wanted to explore the association of Prxs level with the prognosis of patients with lung cancer. To this end, we used Kaplan-Meier Plotter to determine the association between Prxs expression levels and survival in 3,452 lung cancer patients. Prognostic analysis showed that high Prx1 and Prx2 levels were correlated with low OS, whereas high expression levels of Prx5 and Prx6 predicted high OS (Figure 5).
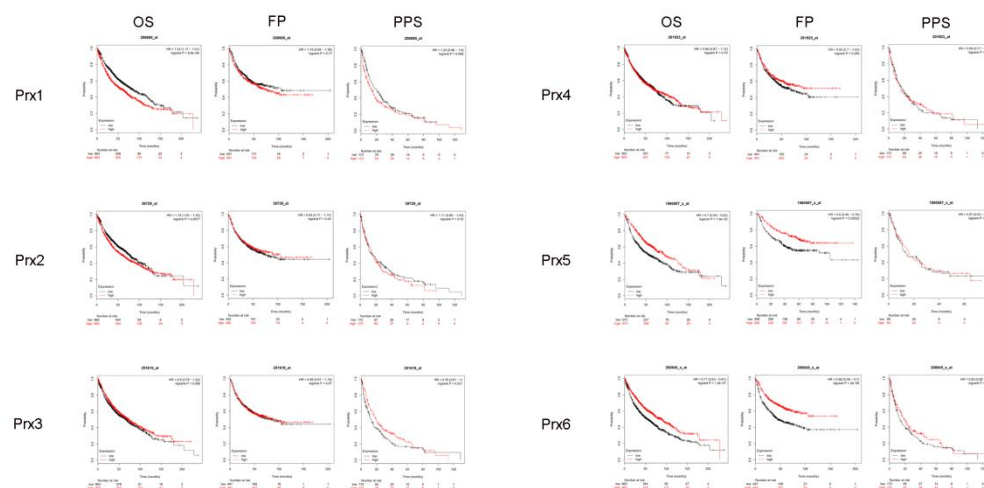

Figure 5. Relationship between expression of Prxs and prognosis of patients with lung cancer (Kaplan-Meier Plotter).

Frequency of Prxs alterations in lung cancer and network views of adjacent genes

We then used cBioPortal to examine the frequency of changes in Prxs in lung cancer and the network of adjacent genetic organisms. In 522 patients with lung adenocarcinoma, Prxs altered in 32% of the samples, and multiple alterations were detected in 6% of the samples (Figure 6A). Next, we analyzed the correlation between Prxs. The results showed that there was a significant correlation between Prx1 and Prx6, and there was also a high correlation between Prx3 and Prx4 (Figure 6B). In addition, we studied the biological interaction network of Prxs with the most frequently altered neighboring genes. The most frequently changed neighboring genes for Prxs were PBK (11%), MYC (10.2%) and MAPK1 (10%) (Figure 6C).
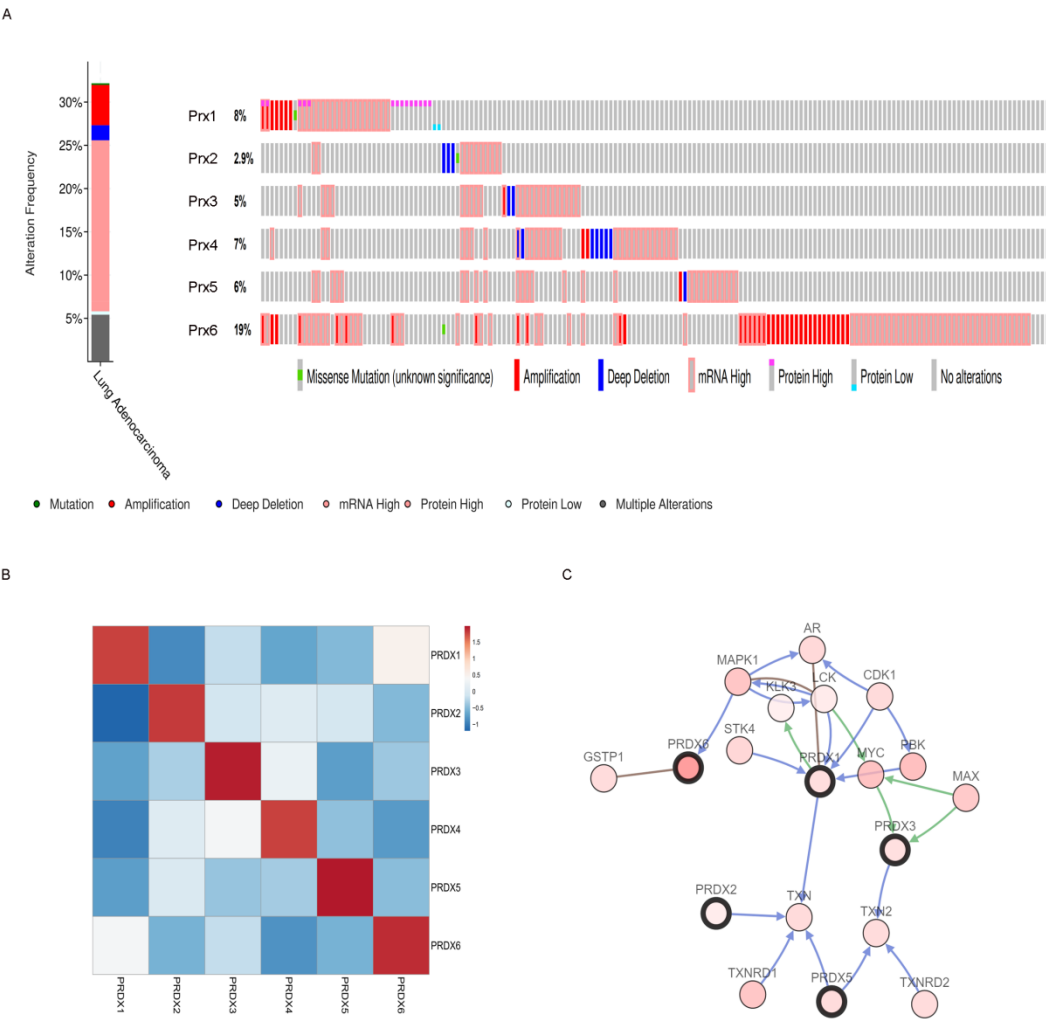
Figure 6. Frequency of Prxs alterations in lung cancer and network views of adjacent genes (cBioPortal).

Enrichment analysis of Prxs neighborhood altered genes in lung cancer

Finally, we used Funrich to analyze the enrichment of Prxs neighboring genes in lung cancer. The GO enrichment analysis mainly includes three aspects: cellular composition, biological process and molecular function.

Analysis shows that most of these genes were located in mitochondria and exosomes, mainly involved in metabolism and energy pathways, and they acted as structural components of peroxidase (Figure 7A-7C). KEGG pathway analysis showed enrichment in the TRAIL signaling pathway, Integrin-linked kinase signaling, Sphingosine 1-phosphate （S1P）pathway, AP-1 transcription factor network and thioredoxin pathway .(Figure 7D).
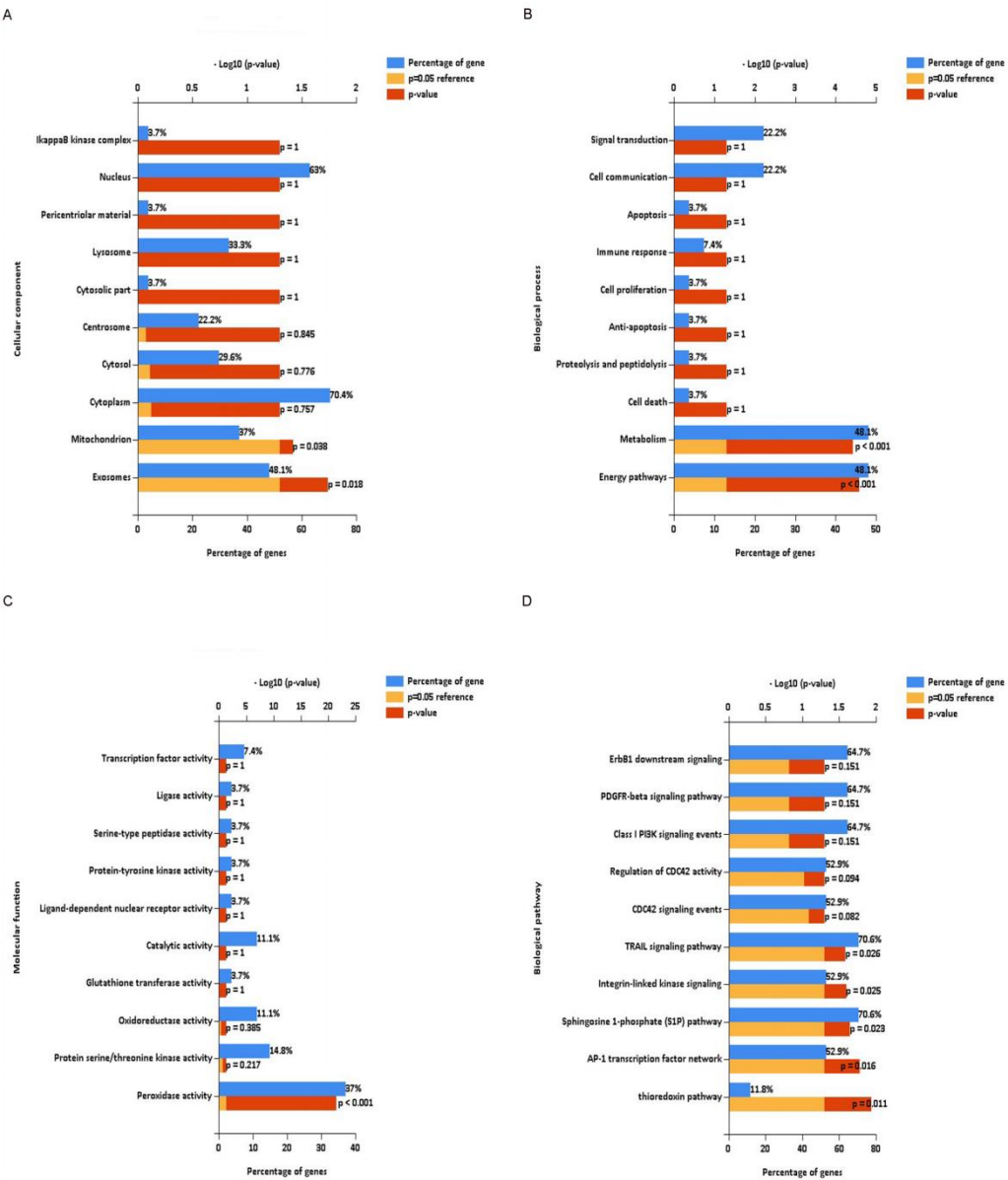
Figure 7. Enrichment analysis of Prxs neighborhood altered genes in lung cancer (FunRich).

DISCUSSION

Previous studies found that Prxs are differentially expressed in various

tumors, such as gastric, colorectal, liver, breast, pancreatic and lung cancers [8-13]. However, no further bioinformatics analysis has been conducted. To gain a deeper understanding of the potential functions of Prxs in lung cancer, we examined the expression and prognosis of Prxs in lung cancer patients in various public databases. Our analysis expand the research on the biological function of lung cancer and reveal strategies for lung cancer prevention and treatment.

The expression of Prx1 in tumors is the most widely studied. Several studies have shown that Prx1 quantity is elevated in lung cancer tissues relative to normal lung tissue [15,16], these studies indicate that Prx1 may enhance the development and progression of lung cancer. Moreover, Prx1 is elevated in various tumor tissue cells including mesothelioma and liver cancer, and is associated with tumor recurrence and clinicopathological features [6, 10]. This study show that Prx1 expression is up-regulated in lung cancer patients and associated with lymph node metastasis status, gender, age, ethnicity and smoking habits. In addition, the overall survival in patients with high levels of Prx1 lung cancer was low.

The high plasma levels of Prx2 are thought to be associated with asbestos exposure or a diagnosis of asbestosis [24]. Prx2 is up-regulated in certain tumors, such as breast and liver cancer [25,26]. However, Prx2 has relatively few studies in lung cancer. In this study, we demonstrated that

Prx2 was up-regulated in lung cancer patients and related to age, gender, lymph node metastasis status, ethnicity and smoking habits. Patients with high expression of Prx2 lung cancer had a lower overall survival.

Prx3 is up-regulated in lung adenocarcinoma cells and tissues, and DACH1 can suppress the invasion and proliferation of lung adenocarcinoma by down-regulating Prx3 [27]. As a mediator of oxidative stress, high level of Prx3 in tumor cells decreases cellular ROS and apoptosis, which enhances cell proliferation in the microenvironment. Prx3 also participates in chemotherapy resistance of cancer [28]. In our report, the GEPIA database showed an increase in Prx3 level in lung cancer, and Prx3 was significantly related with tumor stage. Interestingly, immunohistochemical staining in the HPA database showed that Prx3 staining intensity was weaker in lung cancer samples than in normal lung samples. Prx3 expression was correlated with gender and smoking habits, but increased level of Prx3 was not markedly related with prognosis.

Prx4 plays an crucial role in the progression and metastasis of lung cancer. In a mouse xenograft model, interference with Prx4 expression in A549 cells decreased subcutaneous tumor metastasis and growth, and Prx4 overexpression further enhanced mouse xenografts [15]. Moreover, the expression level of Prx4 is markedly related with shorter DFS and tumor recurrence, and can be used as a prognostic marker for patients with lung squamous cell carcinoma [17].Our study revealed that the level of Prx4

was elevated in lung cancer, which was related to age, gender, lymph node metastasis status, ethnicity and smoking habits, but not to tumor stage and prognosis.

The poor prognosis of breast cancer is associated with overexpression of Prx5 in breast tissue, and Prx5 protects cells from oxidative stress-mediated apoptosis by modulating GATA1 [29]. Overall, the current functional study of Prx5 in lung cancer is still quite lacking. Our study showed that Prx5 expression was up-regulated in lung cancer tissues, but had no marked correlation with age, gender, lymph node metastasis status, ethnicity and smoking habits. High expression levels of Prx5 predicted high overall survival.

Activation of Prx6 via JAK2 / STAT3 pathway promotes the development of lung tumors [30]. In the lung cancer, the expression of peroxide toxin is increased, Prx6 has the characteristics of reducing phospholipid hydroperoxide and expressing phospholipase A2 activity, these unique properties regulate lung cell function [12]. In our study, GEPIA analysis showed that the expression level of Prx6 was lower in LUAD and higher than normal lung tissue in LUSC, but immunohistochemistry of HPA database showed that Prx6 has strong staining in lung cancer tissues. Furthermore, Prx6 was significantly associated with gender, lymph node metastasis status, smoking habits, and tumor stage. The low expression level of Prx6 indicated a poor prognosis in lung cancer patients, which

seemed to be inconsistent with the role of Prx6 as an oncogene.

We analyzed the Prxs using tumor data from a public database. Compared with traditional basic research, this method has the advantages of large tumor sample size, low research cost and simple operation. This study provides multiple levels of evidence for the expression of Prs in lung cancer and its impact on prognosis.

CONCLUSION

Our results suggest that elevated levels of Prx1/2 may play an important role in the development of lung cancer, Prx1/2/ 5/6 is a potential molecular target for improving the prognosis of lung cancer.

Author Contributions

Data curation, Ben Li; Formal analysis, Ben Li; Investigation, Bo Zhang and Qiong Wu; Writing – original draft, Ben Li; Writing – review & editing, Xinming Chen, Xiang Cao and Qun Xue.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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