Risk Evaluation and Molecular Biomarkers Identification of Firefighter Suffering Lung Cancer Via the TCGA Database

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Title Page

Title:

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Abstract

To evaluate the risk of firefighters suffering lung cancer after a long-term career and identify novel molecule biomarkers for evaluation, we tested the composition of flame-resistance door combustion byproducts. The results showed that the main component of combustion byproducts was PAHs and VOCs. The ceRNAs network showed that 26 mRNAs, 18 miRNAs, and 141 lncRNAs were involved in the lung cancer process. Most of the ceRNAs in our study could be affected by PAHs and VOCs. The Kaplan-Meier plots of differentially expressed RNAs in the ceRNA network showed that 3 mRNAs, 4 miRNAs, and 13lncRNAs have a relationship with the survival time of lung cancer patients. We recommended that mRNA *COL1A1*, *CCBN1*, and *PFKP*; miRNA *hsa-miR-143*, *hsa-miR-183*, *hsa-miR-144*, *hsa-miR-372* and *hsa-miR-373*; lncRNA *UCA1*, *TTY16*, *LSAMP-AS1*, *LINC00337* and *LNK1-AS1* as a biomarker to evaluate the risk of a firefighter suffering lung cancer and other cancers.

Key words

Competing endogenous RNAs (ceRNAs); firefighters; lung cancer; biomarker; PAHs, VOCs

1 Introduction

In recent researches, numerous transcriptions of the human genome were documented. Surprisingly, less than 2% of the total human genome encodes protein-coding genes, indicating that a prominent proportion of transcriptome from the human genome may be non-coding RNAs [1]. Recent reports suggest that the human transcriptome includes not only coding-RNA but about 9,000small RNAs, 10,000-32,000 long-non-coding RNAs (lncRNAs) and a cluster of pseudogenes [2, 3]. Micro RNA (miRNA) are endogenous RNA transcripts that regulate gene expression by binding with the specific regions of mRNA [4] and promoting their degradation [5]. Dysregulated miRNA expression may cause many different cancers, including carcinomas of the breast, ovary and lung [5-7]. Long-non-coding RNAs

(lncRNA) are a cluster of RNA that can vary in length from 200 nucleotides to 1000 kilobases and have been confirmed that involve in a diverse range of biological processes from pluripotency to immune responses [8]. The best-studied example is XIST, an RNA gene that could recruit chromatin-modifying complexes to block the chromosome activate [8] and the non-coding transcriptome is often shows dysregulated in cancer [9]. As the best-known character of lncRNA as competing for endogenous RNAs (ceRNAs), the specific RNAs can impair microRNA (miRNA) activity through sequestration, thereby upregulating miRNA target gene expression [10-12]. Many studies proposed that naturally occurring coding-RNA and non-coding-RNA transcripts can act as endogenous miRNA sponges or a ceRNA [12-14]. With the ceRNAs communication and co-regulation, the gene which downregulated by miRNA may get an increasing expression. A lot of genes with known ceRNA interactors identified so far have been implicated in human disease [1]. For example, the KLK10 which is documented to be up-regulated in ovarian cancer caused by miRNA dysregulated [15]; The hsa-miR-1260b plays an important role in renal cancer cells by interacting with some molecule in the Wnt signaling pathway [16]. The discovery of ceRNA regulation in diverse species, such as viruses, plants, mice, and human suggest that it may represent a widespread layer of gene and biological process regulation [14, 17-20].

The Cancer Genome Atlas (TCGA) is a multi-institutional comprehensive collection of various molecularly characterized tumor types [21], various gene expression quantification and transcriptome profile is documented in the database. In recent decades, more and more researches are based on the data from TCGA [22-25]. For example, researchers could according to the mutation analysis, copy number analysis, mRNA or miRNA expression level

analysis, DNA methylation analysis and signal pathway analysis to evaluate the relationship between ceRNA and cancer, even to predict the survival rate from clinical data [22, 26]. Prediction and evaluation results of transcriptome may suggest rational advice that how to manipulate a gene that is involved in the cancer process [27]. Thus, analyzing the transcriptome from cancer patients to get some predictable results for clinical or risk evaluation, the TCGA database may a novel method.

Building fires typically involve furnishings and other items made of both natural and synthetic materials [28]. These materials may produce hundreds of combustion byproducts that usually toxic to human. The byproducts including polycyclic aromatic hydrocarbons (PAHs), acid gases, cyanide, aldehydes, hydrogen cyanide, polychlorinated biphenyls, sulfur dioxide (SO₂) and halogenated compounds [29-32]. Several of these compounds are known or suspected human carcinogens and pathogeny [33-35]. Some research suggests that firefighters have increased risk for numerous types of cancer. The International Agency for Research on Cancer (IARC) reported that occupational exposure as a firefighter to be possibly carcinogenic to humans [36]. Although firefighters usually wear a self-contained breathing apparatus (SCBA) to protect them from toxic smoke, recent studies reported that firefighters may not always wear the SCBA during exterior operations and some compounds could be absorbed through skin [28, 37-39]. In recent decades, the more and more flame-proof door is used in structures to block the fire through over each room of a building. However, the flame retardant that used in the door can produce a group of toxic compounds during a structure fire and it may have a bad influence on firefighter's health [40].

97 Researchers always concerned that how carcinogens from the environment influence an
98 mRNA or the structure of chromosome that may block transcription of some gene, in the past.
99 However, in recent years, more researchers noted that the carcinogen may dysregulate the
100 miRNA or lncRNA first, then they induced the mRNA dysregulated [41]. For example, DDT
101 and PAHs down-regulated the miRNA *hsa-miR-21*, *hsa-miR-221*, *hsa-miR-222* and
102 *hsa-miR-429* to induce the target of them that *CYP1A* and *CYP2B* up-regulated in the liver [1]
103 and they play an important role in various cancer [42]. Volatile organic compounds (VOCs)
104 could induce the miRNA that involved in the lung cancer process dysregulated [43, 44]. Some
105 studies suggested that the alteration of lncRNA expression is correlated with polycyclic
106 aromatic hydrocarbons (PAHs) exposure [45]. For the reason above, the carcinogen from
107 Vitro may involve in the cancer process via disturbing the expression level of lncRNA and
108 miRNA. Moreover, firefighters always exposed to PAHs and VOCs may have a high risk to
109 suffer lung cancer.

110 In our study, we tested the combustion byproducts from a fire-proof door, the results
111 showed that the main components of these byproducts were SO₂, polycyclic aromatic
112 hydrocarbons (PAHs), cyanide, aldehydes, polychlorinated biphenyls and halogenated
113 compounds. The analysis result from the TCGA-LUAD project was showed that in the
114 ceRNA network which was constructed by our method 17 mRNA up-regulated, 9 mRNA
115 down-regulated; 15 miRNA up-regulated, 3 miRNA down-regulated; 121 lncRNA
116 up-regulated, 20 lncRNA down-regulated. The survival curve result showed that the
117 expression level of 13 lncRNA, 3mRNA, and 4miRNA may have an impact on the survival
118 time of the cancer patients. These results provide a credible risk evaluation network for

119 firefighters whether suffering lung cancer, and it may supply a cluster of molecular
120 biomarkers to evaluate the health status of firefighters.

121 2Method and materials

122 2.1 Fire Smoke Analyzing

123 The smoke of the flame-proof door was collected by an independent intellectual property
124 system (authorizing, announcement number: CN110108546A), the sample door was flamed
125 in the combustion chamber, the smoke was collected from the window on the proof (Fig. 1A
126 and B). The collected smoke was analyzed by a multi-flue gas analyzer.

127 2.2 mRNA, miRNA and lncRNA expression data

128 Transcriptome profile and gene expression quantification data for 1145 lung cancer
129 specimens were downloaded from the TCGA data portal in February 2020. The microRNA
130 expression data for 1091 lung cancer specimens were also retrieved from the TCGA data
131 portal. The RNA-seq data were generated by Illumina HiSeqRNASeq and HiSeqmiRNAseq
132 platform. All the data were downloaded by a TCGA official tool with metafiles annotating
133 each dataset. All the significance level of expression data was set at $P < 0.01$ and the thresholds
134 were set as $|\log_2\text{FoldChange}| > 2$. The differentially expressed miRNAs, mRNAs, and
135 lncRNAs were annotated using ENSEMBL (<https://www.ensembl.org/>).

136 2.3 ceRNAs network construction

137 According to the theory of ceRNAs, lncRNAs can act as endogenous RNA and thereby
138 regulating target gene transcripts by competing with shared miRNAs [46]. For network
139 construction, all the gene was matched with miRDB (<http://mirdb.org>), miRTarBase
140 (<http://mirtarbase.mbc.nctu.edu.tw/php/index.php>) and Target Scan

(http://www.targetscan.org/vert_72/), the different gene which could find it upstream or downstream was involved in the ceRNA network [47,48]. Besides, by combining the discriminatory expression profiles data, the interaction between lncRNAs and mRNAs was identified. The ceRNA network of mRNA-lncRNA-miRNA was visualized with Cytoscape v3.7.1.

2.4 Statistical Analyses

The heatmap, volcano plots, Venn diagram, and survival curve were computed and plotted for each mRNA, miRNA, and lncRNA using R. Sequencing data were log-transformed for plotting. The direct read counts and counts normalized according to thousands of mRNAs, miRNAs, and lncRNAs were examined as part of our research.

2.5 Survival Analyses

The survival curve was analyzed from a clinical file that annotated all the status of patients. Patients survival was calculated as time in months elapsed from data diagnosis until data of last contact.

2.6 Prognosis risk scoring in differentially expressed RNAs

Univariate Cox regression analysis was conducted where $P < 0.001$ was considered statistically significant. The significant mRNAs in univariate Cox regression were subsequently analyzed in a multivariate Cox regression proportional hazards model. Furthermore, based on the median risk score, lung cancer patients were divided into “high-risk” and “low-risk” groups. The risk scoring system was constructed by previous research [49] and the formula as follows for predicting overall survival (OS): $\text{risk score} = \beta_1 \times \text{expr}_1 + \beta_2 \times \text{expr}_2 + \dots + \beta_n \times \text{expr}_n$.

Kaplan-Meier survival analysis and ROC (receiver operating characteristic) analysis were then performed to assess the risk scoring system with high and low scores. The survival and ROC analyses were accomplished by using the R package that “survival” and “survival ROC”.

3 Result

3.1 Fire smoke analyses

The smoke of the sample door was collected for components analysis. The main combustion was SO₂, PAHs, cyanide, aldehydes, polychlorinated biphenyls, and halogenated compounds and the concentration of each part was shown in Fig. 2.

3.2 Gene expression pattern analyses and ceRNA network construction

Clinical information about lung cancer patients from the TCGA database was available in 1037 of 1145 cases. The total number of differently expressed mRNA was 2695 and 670 of them were down-regulated, 2295 of them were up-regulated. The differently expressed mRNAs are visualized in the heatmap and a volcano plot (Fig. 3A and Fig. 4A). The total number of differently expressed miRNA was 134, and 16 of them were down-regulated, 118 was up-regulated. The differently expressed miRNAs are visualized in the heatmap and a volcano plot (Fig. 3B and Fig. 4B). The total number of differently expressed lncRNA was 1915, and 247 of them were down-regulated, 1668 was up-regulated. The differently expressed lncRNAs are visualized in the heatmap and a volcano plot (Fig. 3C and Fig. 4C). All the RNAs that differently expressed were listed in Table1-3.

According to our differential expression analysis, the ceRNA network was constructed. After ceRNA network construction, 26 different expressed mRNA was the target of different

expressed lncRNA and miRNA (Fig. 5A). All the relationship of miRNA-mRNA and lncRNA-miRNA was listed in Table 4-5.

The ceRNA network was showed that the key target of lncRNA was *hsa-hsa-miR-210*, *hsa-miR-96*, *hsa-miR-137*, *hsa-miR-183*, *hsa-miR-503*, *hsa-miR-372*, *hsa-miR-205*, *hsa-miR-144*, *hsa-miR-143*, *hsa-miR-182*, *hsa-miR-373*, *hsa-miR-215*, *hsa-miR-192*, *hsa-miR-31*, *hsa-miR-122*, *hsa-miR-206*, *hsa-miR-301b* and *hsa-miR-383* (Fig. 5A and B).

To understand the key molecule in the ceRNA network clearly, we were constructed a miRNA-mRNA, lncRNA-miRNA, and miRNA-lncRNA-mRNA network (Fig. 5A-C). The result of the miRNA-mRNA network showed that *hsa-miR-373*, *hsa-miR-372* and *hsa-miR-144* may play an important role in the ceRNA-network (Fig. 5B). The target gene of the miRNA is involved in energy metabolism and cancer development processes, such as *TMEM100*, *ATAD2*, *PFKP* and *KPNA2*. The *KPNA2* may play an adaptor molecule between *hsa-miR-373* and *hsa-miR-144*, the expression level of it may co-regulated by *hsa-miR-373* and *hsa-miR-144* (Fig. 5B). In the lncRNA-miRNA network, numerous lncRNA was involved in the network that plays an important role in tumor development and migration, about 120 lncRNAs was up-regulated and 20 lncRNAs was down-regulated (Fig. 5C).

3.3 Survival Analyses

To perform the survival curve, we were analyzed the lncRNA, miRNA and mRNA that expression level with a significantly different ($P < 0.01$). The results showed that the expression level of 13 lncRNAs, 3 mRNAs and 4 miRNAs may have an impact on the patient survival time (Fig. 6). Interestingly, most of these genes whatever miRNA, mRNA and

lncRNA, have no significant difference in the first 3 years, and after 5 years the different expression level showed a more significant impact on survival time.

According to the results of the ceRNA network and survival curve of lung cancer patients indicated that mRNA *CCNB1* (cyclin B1) was up-regulated by miRNA *hsa-miR-183* and the *hsa-miR-183* was up-regulated by *LINC00392*, *AL161908.1*, *AL139385.1*, *AL513123.1*, *LSAMP-AS1* and *TTY16* (Fig. 5A). The mRNA of *COL1A1* (Collagen 1A1) was up-regulated by *hsa-miR-143*, and miRNA *hsa-miR-143* was down-regulated by lncRNA *LPP-AS1*, *AL391152.1* and *LINC00519* (Fig. 5A). The mRNA of *PFKP* (phosphofructokinase) was up-regulated by miRNA *hsa-miR-372* and *hsa-miR-372*, and they were co-regulated by lncRNA *LINC00337*, *LNX1-AS1* and *MUC2* (Fig. 5A and C). The miRNA all above was also co-regulated by numerous lncRNA that not mentioned in the article and showed in the ceRNA network (Fig. 5A). However, some lncRNAs such as *AC080129.1*, *AL163952.1* and *MIR31-HG*, showed a relationship with survival time, but the downstream molecule of them have no significant relationship with survival time.

3.4 Prognostic risk score based on differentially expressed mRNAs

A total of 3365 differently expressed mRNAs, we found 50 mRNAs to be significantly associated with survival using univariate Cox regression, the significant genes demonstrated in the univariate Cox regression model was listed in Table 6. According to the multivariate Cox regression analysis, 18 mRNA expression profiles were identified as coupled to overall survival and included in the overall survival prediction model (Fig. 7A). The mRNA expression profiles for prediction of overall survival in lung cancer by multivariate Cox regression were listed in Table 7 (Events: 395, N=999, p= 2.2e-16). On the basis of the

overall survival prediction model, a prognostic risk model was constructed where the high-risk group was significantly associated with lower overall survival ($P < 0.01$) (Fig. 7B). The discriminative evaluation of the risk scoring system was performed with ROC-curve analysis were found an AUC (Area Under Curve) = 0.722 (Fig 7B and C). These results showed that the patients could live longer in the condition to do cancer testing and treatment earlier.

Thus, there is more benefit to detect lung cancer biomarkers for firefighters.

4 Discussion

In our study, the major chemical that produced by a flame-proof door when it is on fire was PAHs, VOCs, SO₂ and cyanide, they were well-known carcinogens for a long time. All the combustion byproducts in our study were researched in many other kinds of research [50-52]. Research showed that in hundreds of lung cancer cases there was a clear trend of increasing risk of lung cancer with increasing cumulative exposure to PAHs [53]. VOCs could produce oxidative stress with DNA damage and increasing the endogenous catechol levels by catechol-O-methyl transferase (COMT) inhibition [54]. For firefighters, they have more chance to breathe or face the air with high concentration VOCs, and researches showed that VOCs could absorb via skin directly [55-57]. Cyanide and SO₂ were typically toxic for human health, they not only induce oxidative damage in many organisms simultaneously but the toxic effects permanently [58, 59]. The SO₂ and its derivatives SO₃²⁻ could promote cancer development and metastasis through integrin $\alpha\beta 3$ activation or other molecules [60, 61].

About 13 lncRNAs, 3 mRNAs and 4 miRNAs were involved in the ceRNA network of lung cancer process and have a significant impact on survival time. These RNA molecules were played an important role in lung cancer development such as initiation, invasion and migration [62, 63]. The different expression levels of *COL1A1*, *CCNB1* and *PFKP* have an influence on survival time in our research. Researches showed that the expression level of *COL1A1* and *CCNB1* can dysregulate by PAHs and VOCs [64-67]. However, there has no evidence to prove that the VOCs or PAHs could impact the expression level of *PFKP* directly. More researches on *PFKP* was about how it works in the metabolism process of tumor cell [1, 2].

The down/overexpression of protein-coding genes such as *COL1A1*, *PTK6*, elongation factor 1 gamma in tumor tissues may provide preoperative useful information for predicting the development and aggressiveness of tumors. Besides, some studies showed that *hsa-miRNA-211*, *hsa-miRNA-143*, *hsa-miRNA-183*, and lncRNA *CASC9*, *HOTAIR*, *POU3F3* contributed to the development of cancer via a variety of mechanisms [70]. The relationship between *COL1A1* and *hsa-miR-143*, *hsa-miR-183* was proofed in our ceRNA network (Fig. 5A). The *hsa-miR-143* work as a tumor inhibitor to block the vascular development from the tumor [71]. The smoke of cigarettes was confirmed that containing PAHs and VOCs, the concentration of them from a cigarette lower than a construction fire could damage the human health and increase the risk for suffering a lung cancer [72, 73]. Papers on the *hsa-miR-143* suggested that cigarette exposure could down-regulate the expression level of *hsa-miR-143* and causes a variety of cancers including lung cancer [74]. The lncRNA *UCA1* negatively regulated *has-miR-143* expression in a dose-dependent manner in various cancer cells [75,

76]. In our research, the lncRNA *UCA1* not only as a regulator for *hsa-miR-143* but other miRNAs (Fig. 5A). However, how it works in lung cancer cell need further research. Thus, *hsa-miR-143* may up-regulate the expression level of *COL1A1* to induce lung cancer by down-regulating the expression level of itself in our study. The expression level of *hsa-miR-143* was down-regulated by *UCA1* and co-regulated by other lncRNAs.

CCNB1 as one of the essential cyclins play an important role in the cell cycle and ensuring completion of M phase [77]. Research on *CCNB1* was showed that it associated with lung cancer and could promote *NSCLC* (non-small cell lung cancer) cell proliferation and cell cycle progression [78]. Silencing lncRNA *CRNDE* inhibited cell proliferation, migration and invasion, restricted solid tumor growth and promoted cell apoptosis [79]. Moreover, *hsa-miR-183* silencing could inverse the antitumor function of *CRNDE* inhibition and partially eliminated the attenuated expression of *CCNB1* induced by silencing *CRNDE*, indicating that *CRNDE* could positively regulate *CCNB1* expression by sponging *hsa-miR-183*[79]. The function of *hsa-miR-183* to regulate *CCNB1* was showed in our study, however, the *hsa-miR-144* also showed *CCNB1* regulating function. Researchers showed that *hsa-miR-144* directly targeted *CCNB1* and inhibited *CCNB1* expression [80]. For all the reasons above, our study suggested that *CCBN1* was co-regulated by *hsa-miR-144* and *hsa-miR-183*. *LSAMP-AS1* binds to *hsa-miR-183* to suppress the cancer progression by up-regulating the tumor suppressor DCN (decorin) [81]. However, *hsa-miR-183* was up-regulated and *LSAMP-AS1* was up-regulated too, thus, the lncRNA *LSAMP-AS1* may not the key role to *hsa-miR-183* regulation. The smoke that contains PAHs and VOCs could alter the normal expression pattern of *hsa-miR-183* and involve in early-stage non-small cell lung

cancer [82, 83]. The lncRNA *TTY16* was down-regulated and associated with *hsa-miR-183-CCBN1* signaling in our ceRNA network. Recent research also showed that *TTY16* associated with *hsa-miR-183*[84]. However, there is no enough evidence to prove that *TTY16* up-regulates *CCBN1* by up-regulates *hsa-miR-183*. According to our study, we predicted that *TTY16* may play an important role in *hsa-miR-144/hsa-miR-183-CCBN1* signaling in lung cancer.

PFKP plays an important metabolic role in the process of tumor development, migration and invasion. Low expressed *PFKP* could promote autophagy of tumor cells and overexpressed it could enhance the invasion and metastasis ability of tumor cells [68, 69, 85]. The microRNA *hsa-miR-372/373* was suggested that working as a competing endogenous to *PFKP* in prostate cancer [86]. Moreover, researchers reported that not all the ceRNA have a negative relation between each other and the cross-link of them may more difficult than what we have known already [10] and that may the reason for the expression level of *PFKP*, *hsa-miR-372* and *hsa-miR-373* was all up-regulated in our study. A lot of studies were reported that *hsa-miR-372/373* was regulated by *LINC00337* but the mechanism of that was not clear [87-89]. The lncRNA *LNX1-AS1* was a new role that found have a relation with *hsa-miR-372/373*, it may a novel molecule for ceRNA researching in lung cancer. We can confirm that *PFKP* and miRNA which it associates was played an important role in lung cancer from our study.

We have identified a large number of differentially expressed mRNAs, lncRNAs, and miRNAs in lung cancer which were strongly associated with PAHs and VOCs. Many of these RNAs have not been reported in the current literature as related to lung cancer and represent

novel and promising future targets. However, larger cohorts of patients and future mechanistic studies are necessary to validate our results and investigate their functional roles in lung cancer for firefighters.

Thus, the mRNA expression level of *COL1A1*, *CCBN1* and *PFKP*; the miRNA expression level of *hsa-miR-143*, *hsa-miR-183*, *hsa-miR-144*, *hsa-miR-372* and *hsa-miR-373*; the lncRNA expression level of *UCA1*, *TTY16*, *LSAMP-AS1*, *LINC00337* and *LNK1-AS1* may recommend as a bio-mark to evaluate the risk of a firefighter suffering lung cancer and other cancers. The ceRNA network showed in our study should be a reference for lung cancer evaluation.

5 Declarations

5.1 Ethics approval and consent to participate

All the experiments were supervised and approved by the ethics committee of Tianjin Fire Research Institute.

5.2 Consent for publication

All the authors in this research have read the final version of the manuscript.

5.3 Availability of data and materials

All of the transcriptome data were obtained from TCGA database and the code for R and Perl could obtain from the corresponding author by email Binbaicom@163.com.

5.4 Competing interests

All authors have no potential conflicts of interest.

5.5 Funding

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5.6 Author's contribution

Bin Bai: Conceptualization, Methodology, Writing - review & editing. **Qinghao Meng:** Software, Data curation, Writing – original draft.

340 5.7 Acknowledgements

341 Not applicable.

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Figure legends

Fig. 1. The test equipment system of smoke. (A) The sketch map of the equipment system. The combustion chamber was marked by “1”. The smoke collecting window was marker by “2”. (B) The practicality picture of the system. The smoke collecting window was marker by “a”. The smoke collecting window was marker by “b”.

Fig. 2. The toxic smoke concentration of the door-flame experiment. The number on the column marked the arithmetic mean concentration of the smoke and bar indicated the mean $\pm$ SD.

Fig. 3. The heatmap of the differently expressed RNAs. (A) The heatmap of differently expressed mRNA. The green box showed mRNA was down-regulated and red box showed mRNA up-regulated. (B) The heatmap of differently expressed miRNA. The green box showed miRNA was down-regulated and red box showed

miRNA up-regulated. (C) The heatmap of differently expressed lncRNA. The green box showed lncRNA was down-regulated and red box showed lncRNA up-regulated.

Fig. 4. Differentially expressed RNAs in lung cancer are visualized by volcano plots. The red dots show upregulated genes while the green dots show downregulated genes. (A) Differentially expressed mRNAs in lung cancer. (B) Differentially expressed miRNAs in lung cancer. (C) Differentially expressed lncRNAs in lung cancer.

Fig. 5. The ceRNA network of lung cancer. mRNA was in rounded rectangle, miRNA was in round, lncRNA was in diamond. The blue show downregulated gene while red show upregulated gene. (A) ceRNA network that involve mRNA, miRNA and lncRNA. (B) The RNAs network between miRNA and mRNA. (C) The RNAs network between miRNA and lncRNA.

Fig. 6. The Kaplan-Meier plots of differentially expressed RNAs in the ceRNA network which are also related to high-grade, stages, and overall survival ($P<0.01$). (A) The survival curve of mRNAs. (B) The survival curve of miRNAs. (C) The survival curve of lncRNAs.

Fig. 1.

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Fig. 5.

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Fig. 7.

717 **Table 1.** Differentially expressed mRNAs in ceRNA network. **Table 2.** Differentially expressed miRNAs in ceRNA network.

DEmRNAs	Regulation	logFC	FDR	DEmiRNAs	Regulation	logFC	FDR
HOXC13	upregulation	7.900168814	9.49E-69	hsa-mir-372	upregulation	7.42568468	4.90E-15
PAX3	upregulation	5.030883608	7.85E-26	hsa-mir-122	upregulation	5.49171687	7.80E-11
HOXA10	upregulation	4.879826226	5.41E-63	hsa-mir-373	upregulation	5.40601511	1.35E-10
PBK	upregulation	3.892566513	1.91E-108	hsa-mir-205	upregulation	5.25048736	1.55E-35
SLC7A11	upregulation	3.758359723	9.29E-50	hsa-mir-31	upregulation	5.00984484	1.10E-42
CCNB1	upregulation	3.394316559	4.19E-136	hsa-mir-210	upregulation	4.60093232	1.86E-112
ELAVL2	upregulation	3.36504559	8.76E-24	hsa-mir-301b	upregulation	3.54614623	6.93E-54
NPTX1	upregulation	2.884592852	8.78E-19	hsa-mir-137	upregulation	3.42899329	1.48E-17
KCNQ5	upregulation	2.823401018	2.16E-42	hsa-mir-96	upregulation	2.83954332	4.79E-85
TBX18	upregulation	2.78409373	1.11E-20	hsa-mir-215	upregulation	2.74212669	2.91E-15
KPNA2	upregulation	2.348067799	5.66E-97	hsa-mir-183	upregulation	2.65645895	7.40E-80
GRHL1	upregulation	2.28610654	8.94E-55	hsa-mir-192	upregulation	2.50206211	5.75E-19
COL1A1	upregulation	2.182573341	3.09E-33	hsa-mir-383	upregulation	2.47380472	7.48E-06
ATAD2	upregulation	2.126839658	5.58E-96	hsa-mir-503	upregulation	2.43042528	1.39E-46
HOXA9	upregulation	2.104643042	1.62E-18	hsa-mir-182	upregulation	2.14139645	3.47E-58
TSKU	upregulation	2.086024777	4.92E-55	hsa-mir-206	downregulation	-2.1170367	8.89E-12
PFKP	upregulation	2.014985289	1.24E-66	hsa-mir-143	downregulation	-2.2620671	2.13E-111
TGFBR2	downregulation	-2.079739895	3.15E-144	hsa-mir-144	downregulation	-3.3426405	2.81E-184
LIMCH1	downregulation	-2.152042067	5.92E-81				
PROK2	downregulation	-2.285552885	1.26E-52				
LEFTY2	downregulation	-2.382885057	3.17E-53				
LRRK2	downregulation	-2.539663204	2.13E-71				
SLC1A1	downregulation	-2.587327755	2.95E-116				
SELE	downregulation	-2.896579638	1.06E-85				
SERTM1	downregulation	-4.526338137	4.91E-126				
TMEM100	downregulation	-4.594473407	1.59E-260				

719 **Table 3.** Differentially expressed lncRNAs in ceRNA network.

lncRNA	Regulation	logFC	FDR	lncRNA	Regulation	logFC	FDR	lncRNA	Regulation	logFC	FDR
LINC00392	upregulation	8.72365096	5.61E-24	LINC00302	upregulation	3.58925951	2.20E-12	AC092811.1	upregulation	2.378492104	6.00E-14
DSCAM-AS1	upregulation	7.559173342	2.67E-15	LINC00483	upregulation	3.579760338	1.17E-16	LINC00379	upregulation	2.368040346	7.23E-05
POU6F2-AS2	upregulation	6.899411957	1.13E-49	SOX21-AS1	upregulation	3.546142143	1.34E-35	AP000525.1	upregulation	2.349829402	1.22E-29
LINC00393	upregulation	6.831108084	1.18E-29	LINC00488	upregulation	3.496926005	3.15E-10	AC007731.1	upregulation	2.336351149	7.73E-08
LINC00491	upregulation	6.711133389	4.79E-50	AP002478.1	upregulation	3.496585224	3.13E-25	LINC00184	upregulation	2.330161426	1.73E-24
HOTAIR	upregulation	6.667013314	5.14E-40	PART1	upregulation	3.448251622	7.54E-21	FNDC1-IT1	upregulation	2.325388201	2.07E-21
AL513123.1	upregulation	6.522870587	6.26E-49	H19	upregulation	3.380493581	1.12E-19	ANO1-AS2	upregulation	2.322949207	4.33E-11
AC061975.6	upregulation	6.499111498	2.92E-33	LINC00404	upregulation	3.357818927	9.44E-09	ADIPOQ-AS1	upregulation	2.271735723	3.45E-05
DLX6-AS1	upregulation	6.138232274	4.59E-51	AL139002.1	upregulation	3.311246271	7.75E-08	LINC00303	upregulation	2.266302816	4.34E-08
AL160271.1	upregulation	5.974577748	3.61E-13	GDNF-AS1	upregulation	3.302623066	5.15E-25	AC078778.1	upregulation	2.235358325	1.60E-61
MUC2	upregulation	5.841647051	8.69E-26	LINC00200	upregulation	3.257754381	3.09E-07	DSCR10	upregulation	2.224335212	6.77E-07
ERVMER61-1	upregulation	5.810350515	4.53E-19	KIRREL3-AS1	upregulation	3.203454755	8.09E-12	AL161645.1	upregulation	2.188757957	1.52E-16
MIR137HG	upregulation	5.707767706	2.26E-29	CHODL-AS1	upregulation	3.166863642	2.82E-17	LPP-AS1	upregulation	2.162658251	1.11E-05
CLDN10-AS1	upregulation	5.678116773	3.66E-26	NRG1-IT1	upregulation	3.124374039	3.33E-11	ADARB2-AS1	upregulation	2.16082016	6.30E-09
LINC00355	upregulation	5.671714261	5.58E-29	AC006372.1	upregulation	3.089681379	1.31E-11	C17orf77	upregulation	2.157207561	1.83E-06
NOVA1-AS1	upregulation	5.610343379	9.13E-29	WASIR2	upregulation	3.055691654	4.03E-44	CHL1-AS1	upregulation	2.150783173	5.00E-16
NAALADL2-AS2	upregulation	5.578902155	3.25E-39	AC100791.1	upregulation	3.011767881	2.33E-19	AC022762.1	upregulation	2.13925834	1.76E-12
LINC00221	upregulation	5.510712499	3.72E-15	GRM7-AS3	upregulation	2.98128837	2.51E-15	SMCR2	upregulation	2.121908877	6.21E-27
UCA1	upregulation	5.304773278	4.89E-38	AL391152.1	upregulation	2.915318047	3.15E-30	AC011453.1	upregulation	2.12129079	5.86E-09
LINC00519	upregulation	5.295823455	1.34E-50	FER1L6-AS1	upregulation	2.913523387	5.27E-08	LINC00485	upregulation	2.067134768	7.48E-09
MIR205HG	upregulation	5.269535341	6.69E-39	C2orf48	upregulation	2.907859487	2.34E-54	MIAT	upregulation	2.063677441	4.45E-24
LINC00536	upregulation	5.13834641	3.49E-28	STEAP2-AS1	upregulation	2.907616811	9.33E-36	HNF1A-AS1	upregulation	2.02342963	3.39E-09
LINC00501	upregulation	4.959928728	1.51E-28	GRM5-AS1	upregulation	2.881478365	2.34E-19	TTY16	downregulation	-2.1487186	4.51E-17
RMRP	upregulation	4.920366731	1.69E-11	LINC00524	upregulation	2.881052804	1.64E-14	LINC00472	downregulation	-2.159857625	1.15E-81
LINC00518	upregulation	4.827316836	4.21E-26	LINC00052	upregulation	2.851137022	3.14E-10	AC135178.1	downregulation	-2.301664894	6.10E-65
HOTTIP	upregulation	4.819521783	1.40E-27	LINC00525	upregulation	2.780593868	8.24E-32	MED4-AS1	downregulation	-2.311450511	4.96E-134
LINC00461	upregulation	4.717928933	2.41E-39	MLIP-IT1	upregulation	2.779815814	1.29E-18	AC025431.1	downregulation	-2.367756111	3.72E-35
AC011374.1	upregulation	4.638297493	7.45E-30	AC025211.1	upregulation	2.768529094	1.66E-20	ADAMTS9-AS2	downregulation	-2.379059044	5.49E-89
TDRG1	upregulation	4.62373323	3.34E-17	AC005035.1	upregulation	2.74862971	7.34E-17	HHATL-AS1	downregulation	-2.411711238	5.41E-33
TTY20	upregulation	4.527855848	6.70E-10	AC087269.1	upregulation	2.743424581	2.11E-15	C5orf64	downregulation	-2.458553843	1.24E-94
KCNH1-IT1	upregulation	4.524685923	1.37E-21	C10orf91	upregulation	2.735134183	3.46E-36	LINC00211	downregulation	-2.467647583	3.42E-64
SOX2-OT	upregulation	4.45146114	2.20E-34	LINC00337	upregulation	2.734808352	2.40E-41	AC004832.1	downregulation	-2.471226235	1.83E-42
LINC00466	upregulation	4.332511438	4.44E-33	TBL1XR1-AS1	upregulation	2.684479477	6.01E-22	RMST	downregulation	-2.515181357	2.77E-34
LSAMP-AS1	upregulation	4.331711057	6.56E-29	LINC00473	upregulation	2.676480204	9.71E-08	SFTA1P	downregulation	-2.611316389	2.74E-55
C10orf126	upregulation	4.307018389	4.44E-12	AC084262.1	upregulation	2.672753996	1.32E-15	AP003064.2	downregulation	-2.636828373	8.19E-58
LINC00462	upregulation	4.175615441	3.90E-19	AC012640.1	upregulation	2.625021162	1.07E-41	NAV2-AS2	downregulation	-2.670668007	2.93E-68
AL021395.1	upregulation	4.152580608	5.32E-14	AP000553.1	upregulation	2.620583522	5.01E-43	SRGAP3-AS2	downregulation	-2.700440489	8.89E-33
AC006305.1	upregulation	4.148651654	6.60E-29	LINC00319	upregulation	2.613645232	3.77E-17	AP000438.1	downregulation	-3.09695993	1.50E-138
ERVH48-1	upregulation	4.122573456	1.86E-22	AC022148.1	upregulation	2.611552174	1.23E-16	AL109754.1	downregulation	-3.194424806	2.91E-77
POU6F2-AS1	upregulation	4.115521037	3.70E-24	LNK1-AS1	upregulation	2.610820679	1.32E-12	ADAMTS9-AS1	downregulation	-3.244655828	3.90E-168
AL356133.2	upregulation	4.080182829	1.72E-13	C20orf197	upregulation	2.598043322	3.28E-24	AC105206.1	downregulation	-3.352351093	1.19E-64
MIR31HG	upregulation	3.961901772	5.59E-27	AL136131.2	upregulation	2.579991252	1.73E-12	LINC00163	downregulation	-3.558682363	1.66E-130
IL20RB-AS1	upregulation	3.88783337	1.87E-24	AL139385.1	upregulation	2.579188647	4.12E-38				
AC080129.1	upregulation	3.848577909	1.98E-18	C12orf77	upregulation	2.570470676	1.12E-10				
LINC00460	upregulation	3.841618924	1.31E-26	PVT1	upregulation	2.554565875	1.14E-92				
LINC00051	upregulation	3.840558609	5.84E-16	IGF2-AS	upregulation	2.541379042	5.03E-12				
LINC00470	upregulation	3.813773	2.95E-22	AL161908.1	upregulation	2.46859159	3.18E-11				
AL163952.1	upregulation	3.696332935	2.34E-26	C11orf44	upregulation	2.457968156	1.40E-12				
LINC00308	upregulation	3.694563001	9.57E-16	AC112721.1	upregulation	2.426570505	5.69E-22				
				KIF25-AS1	upregulation	2.386889821	5.77E-11				

721 **Table 4.** Differentially expressed miRNAs targeting mRNAs in the ceRNA network.

miRNA	mRNA
hsa - mir - 372	TGFBR2, ELAVL2, PFKP, TMEM100, KPNA2, ATAD2, SLC7A11
hsa - mir - 373	KPNA2, LEFTY2, ELAVL2, ATAD2, TGFBR2, PBK, PFKP, SLC7A11, TMEM100
hsa - mir - 144	HOXA10, TBX18, KCNQ5, KPNA2
hsa - mir - 210	SERTM1
hsa - mir - 31	HOXC13, SELE
hsa - mir - 96	TSKU, SLC1A1, PROK2
hsa - mir - 182	NPTX1, HOXA9
hsa - mir - 137	LIMCH1
hsa - mir - 183	CCNB1
hsa - mir - 192	GRHL1
hsa - mir - 205	LRRK2
hsa - mir - 143	COL1A1
hsa - mir - 206	PAX3

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723 **Table. 4.**

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Table 5. Differentially expressed lncRNAs targeting miRNAs in the ceRNA network.

lncRNA	miRNA	lncRNA	miRNA	lncRNA	miRNA	lncRNA	miRNA	lncRNA	miRNA	lncRNA	miRNA	lncRNA	miRNA	lncRNA	miRNA
LOC4345	hsa-mi-503, hsa-mi-122	AC003763	hsa-mi-495, hsa-mi-137, hsa-mi-146, hsa-mi-483	AC006052	hsa-mi-495, hsa-mi-430	C12orf77	hsa-mi-372, hsa-mi-423, hsa-mi-38, hsa-mi-417, hsa-mi-131, hsa-mi-402, hsa-mi-215, hsa-mi-205, hsa-mi-2	RP001	hsa-mi-403	AC011742	hsa-mi-473, hsa-mi-475	AC011652	hsa-mi-415, hsa-mi-435		
H19	hsa-mi-1033, hsa-mi-205	P0514-AS1	hsa-mi-137, hsa-mi-432, hsa-mi-415, hsa-mi-425, hsa-mi-4	AL311311	hsa-mi-19	AB010463	hsa-mi-372, hsa-mi-373, hsa-mi-143, hsa-mi-148, hsa-mi-123, hsa-mi-461, hsa-mi-383	CH024-05	hsa-mi-137, hsa-mi-430, hsa-mi-415	AC001382	hsa-mi-122, hsa-mi-483	AL302352	hsa-mi-205		
LOC30470	hsa-mi-503, hsa-mi-143, hsa-mi-144, hsa-mi-122, hsa-mi-383	C11orf77	hsa-mi-372, hsa-mi-473, hsa-mi-415, hsa-mi-476, hsa-mi-3	AL303851	hsa-mi-495, hsa-mi-432, hsa-mi-373	NM_015214-02	hsa-mi-135, hsa-mi-205	LOC4451	hsa-mi-495, hsa-mi-472, hsa-mi-373, hsa-mi-143, hsa-mi-415, hsa-mi-402, hsa-mi-22	AL303332	hsa-mi-172, hsa-mi-473, hsa-mi-383	AP009761	hsa-mi-405, hsa-mi-225, hsa-mi-122		
LOC30325	hsa-mi-1033, hsa-mi-95, hsa-mi-102, hsa-mi-31, hsa-mi-483	LOC0519	hsa-mi-145, hsa-mi-376	LOC1	hsa-mi-495, hsa-mi-415, hsa-mi-432, hsa-mi-403	SC01-051	hsa-mi-103, hsa-mi-303	TTT05	hsa-mi-405	AP003842	hsa-mi-102, hsa-mi-475, hsa-mi-383	LOC0491	hsa-mi-403, hsa-mi-372, hsa-mi-473, hsa-mi-143, hsa-mi-137, hsa-mi-145, hsa-mi-415, hsa-mi-383, hsa-mi-122, hsa-mi-141		
PART1	hsa-mi-1033, hsa-mi-143, hsa-mi-475, hsa-mi-145, hsa-mi-137, hsa-mi-31	LOC0300	hsa-mi-495, hsa-mi-405	AL310861	hsa-mi-103	LOC0306	hsa-mi-103, hsa-mi-122	LOC0017	hsa-mi-103, hsa-mi-415, hsa-mi-383	AL309761	hsa-mi-122, hsa-mi-403	LOC0481	hsa-mi-403, hsa-mi-143		
C2orf68	hsa-mi-372, hsa-mi-373, hsa-mi-415, hsa-mi-183, hsa-mi-122	LOC0021	hsa-mi-1033, hsa-mi-473, hsa-mi-475, hsa-mi-495, hsa-mi-432, hsa-mi-43	AL311311	hsa-mi-19	LOC0302	hsa-mi-183	LOC031	hsa-mi-403	AL309712	hsa-mi-172, hsa-mi-182, hsa-mi-403	PART	hsa-mi-403, hsa-mi-372, hsa-mi-115, hsa-mi-143, hsa-mi-103, hsa-mi-205, hsa-mi-122, hsa-mi-483		
LOC0483	hsa-mi-372, hsa-mi-373, hsa-mi-495, hsa-mi-144, hsa-mi-143, hsa-mi-145, hsa-mi-215, hsa-mi-122, hsa-mi-31	LOC0310	hsa-mi-145, hsa-mi-405, hsa-mi-422	LOC01-051	hsa-mi-137, hsa-mi-415	H0749	hsa-mi-103, hsa-mi-415	AC002974	hsa-mi-203, hsa-mi-495, hsa-mi-405	LOC0481	hsa-mi-103	LOC0306	hsa-mi-495, hsa-mi-415, hsa-mi-402, hsa-mi-205		
M03195	hsa-mi-206	AC110761	hsa-mi-372, hsa-mi-473, hsa-mi-122	LOC0473	hsa-mi-120	LOC04-052	hsa-mi-135, hsa-mi-125, hsa-mi-108	LOC0360	hsa-mi-403, hsa-mi-143, hsa-mi-405	AP003582	hsa-mi-103, hsa-mi-183	LOC0491	hsa-mi-122		
C13orf64	hsa-mi-103, hsa-mi-182, hsa-mi-215	M042	hsa-mi-103, hsa-mi-473, hsa-mi-415, hsa-mi-402, hsa-mi-412, hsa-mi-43	M0432	hsa-mi-103, hsa-mi-415	M054-01	hsa-mi-143, hsa-mi-144	LOC0802	hsa-mi-473, hsa-mi-475	LOC0473	hsa-mi-103, hsa-mi-145, hsa-mi-143, hsa-mi-415, hsa-mi-403, hsa-mi-1	LOC0481	hsa-mi-403, hsa-mi-372, hsa-mi-473, hsa-mi-145, hsa-mi-122		
LOC03002	hsa-mi-415	M049	hsa-mi-405, hsa-mi-412	LOC05-051	hsa-mi-145, hsa-mi-475	LOC0303	hsa-mi-103, hsa-mi-103, hsa-mi-103, hsa-mi-1	LOC04-052	hsa-mi-137, hsa-mi-483	LOC04-051	hsa-mi-473, hsa-mi-475, hsa-mi-405, hsa-mi-415, hsa-mi-41	LOC0481	hsa-mi-145, hsa-mi-146, hsa-mi-405, hsa-mi-183		
AC007091	hsa-mi-31	AC003762	hsa-mi-472, hsa-mi-473	LOC0304	hsa-mi-148, hsa-mi-415, hsa-mi-412, hsa-mi-403	LOC0304	hsa-mi-103	LOC04-051	hsa-mi-473, hsa-mi-475	LOC04-052	hsa-mi-472, hsa-mi-473, hsa-mi-405	LOC0481	hsa-mi-403, hsa-mi-205		
C2orf597	hsa-mi-372, hsa-mi-373, hsa-mi-415, hsa-mi-143, hsa-mi-144, hsa-mi-122, hsa-mi-383	LOC0501	hsa-mi-1033, hsa-mi-415, hsa-mi-430, hsa-mi-405	LOC0303	hsa-mi-103, hsa-mi-473	LOC04-051	hsa-mi-135, hsa-mi-473	LOC04-051	hsa-mi-145, hsa-mi-103, hsa-mi-403, hsa-mi-412, hsa-mi-1	AC007782	hsa-mi-103	LOC0482	hsa-mi-475, hsa-mi-143, hsa-mi-122, hsa-mi-1		
LOC03003	hsa-mi-145, hsa-mi-205, hsa-mi-122	LOC0501	hsa-mi-1033, hsa-mi-415, hsa-mi-430, hsa-mi-405	LOC0303	hsa-mi-103, hsa-mi-473	LOC04-051	hsa-mi-135, hsa-mi-473	LOC04-051	hsa-mi-145, hsa-mi-103, hsa-mi-403, hsa-mi-412, hsa-mi-1	AC003642	hsa-mi-137, hsa-mi-405, hsa-mi-172, hsa-mi-415, hsa-mi-383	LOC0482	hsa-mi-475, hsa-mi-143, hsa-mi-122, hsa-mi-1		
AP001071	hsa-mi-503, hsa-mi-372, hsa-mi-144, hsa-mi-143, hsa-mi-205, hsa-mi-122	AC008111	hsa-mi-495, hsa-mi-182	LOC0304	hsa-mi-103, hsa-mi-473, hsa-mi-415, hsa-mi-403	LOC04-051	hsa-mi-103, hsa-mi-182, hsa-mi-403	PART1-01	hsa-mi-144	LOC04-051	hsa-mi-103, hsa-mi-145, hsa-mi-143, hsa-mi-103, hsa-mi-415, hsa-mi-403, hsa-mi-122, hsa-mi-403	LOC0481	hsa-mi-172, hsa-mi-173, hsa-mi-405, hsa-mi-143, hsa-mi-145, hsa-mi-103, hsa-mi-122, hsa-mi-403		
AC103041	hsa-mi-1033, hsa-mi-372, hsa-mi-473, hsa-mi-182, hsa-mi-122, hsa-mi-141, hsa-mi-383	T0861	hsa-mi-405, hsa-mi-182, hsa-mi-415, hsa-mi-412	LOC0307	hsa-mi-473, hsa-mi-473, hsa-mi-415, hsa-mi-403	AL310761	hsa-mi-103, hsa-mi-182, hsa-mi-103, hsa-mi-122	LOC04-051	hsa-mi-137, hsa-mi-143, hsa-mi-122	AC007712	hsa-mi-103, hsa-mi-415, hsa-mi-383	LOC0482	hsa-mi-475, hsa-mi-143, hsa-mi-122, hsa-mi-1		
C2orf64	hsa-mi-143, hsa-mi-182, hsa-mi-415, hsa-mi-122, hsa-mi-21, hsa-mi-383	C13orf20	hsa-mi-103, hsa-mi-115, hsa-mi-405, hsa-mi-41	LOC0473	hsa-mi-103, hsa-mi-415	M03195	hsa-mi-103, hsa-mi-182, hsa-mi-103, hsa-mi-122, hsa-mi-183	M04-01	hsa-mi-205	AC002112	hsa-mi-103, hsa-mi-145	LOC0481	hsa-mi-143		
C13orf61	hsa-mi-137, hsa-mi-373, hsa-mi-143, hsa-mi-122	AC003954	hsa-mi-403, hsa-mi-137, hsa-mi-415, hsa-mi-405	M047	hsa-mi-145, hsa-mi-205, hsa-mi-103, hsa-mi-415, hsa-mi-403	M03195	hsa-mi-145, hsa-mi-103, hsa-mi-115, hsa-mi-41	AC110761	hsa-mi-403	AC003612	hsa-mi-127	LOC0481	hsa-mi-172, hsa-mi-173, hsa-mi-405, hsa-mi-143, hsa-mi-145, hsa-mi-103, hsa-mi-122, hsa-mi-403		
AC001481	hsa-mi-372, hsa-mi-373, hsa-mi-415, hsa-mi-182, hsa-mi-143, hsa-mi-205	AP001071	hsa-mi-403, hsa-mi-143	LOC04-051	hsa-mi-103, hsa-mi-415	T0861-051	hsa-mi-103, hsa-mi-182, hsa-mi-103	LOC04-051	hsa-mi-143, hsa-mi-182, hsa-mi-182, hsa-mi-182	LOC04-051	hsa-mi-103, hsa-mi-143, hsa-mi-182, hsa-mi-182, hsa-mi-182	LOC0482	hsa-mi-172, hsa-mi-173, hsa-mi-405, hsa-mi-143, hsa-mi-145, hsa-mi-103, hsa-mi-122, hsa-mi-403		

729 **Table 6.** Significant genes demonstrated in univariate Cox regression model (P<0.001)

gene	HR	z	pvalue
QDEC	1.130155519	5.068559547	4.01E-07
OR2W3	1.159398455	4.734716363	2.19E-06
TRIM58	1.114151415	4.463796912	8.05E-06
LIPK	1.097950277	4.302133412	1.69E-05
BEST3	1.101691764	4.244695096	2.19E-05
C1QTNF6	1.21473153	4.199190658	2.68E-05
IGFBP1	1.094122986	4.182470294	2.88E-05
DKK1	1.08072014	4.136233568	3.53E-05
ARL14	1.079831726	4.064975749	4.80E-05
FAM83A	1.089982158	4.040543173	5.33E-05
NTSR1	1.088928234	3.963993815	7.37E-05
C20orf141	1.144831011	3.963106674	7.40E-05
ANLN	1.169526571	3.927598316	8.58E-05
LINGO2	1.085344834	3.834882417	0.000125624
KCNJ18	1.100206952	3.806435294	0.000140984
COL22A1	1.088747223	3.798463907	0.000145596
APCDD1L	1.087012549	3.770075508	0.000163198
PLEK2	1.143716829	3.696100107	0.000218937
GPRIN1	1.181742559	3.691616261	0.000222833
PLK1	1.17087653	3.626260431	0.000287555
NEIL3	1.130993732	3.617155528	0.000297858
HMMR	1.178465138	3.579578006	0.00034415
RHOV	1.100478191	3.576446425	0.000348297
KIF14	1.14936952	3.572023027	0.000354234
PTX3	1.106026777	3.5706393	0.000356111
WFIKN2	0.889481471	-3.567005287	0.000361084
PRR11	1.171569877	3.564783346	0.000364157
KCNV1	1.074663227	3.561295522	0.000369029
RGS20	1.091826086	3.550639745	0.000384296
TFAP2A	1.102128673	3.509734411	0.000448554
ERO1A	1.200652464	3.509685404	0.000448637
IGSF10	0.905837474	-3.492369091	0.000478756
LY6K	1.0644751	3.481825426	0.000498008
PFKP	1.193699308	3.466273311	0.000527727
ANOS1	0.891564746	-3.452198359	0.000556039
CGB8	1.10652386	3.441381498	0.000578752
CDC25C	1.169975497	3.439991943	0.000581732
MYEOV	1.066277073	3.430010983	0.000603557
F2	1.078652907	3.428497983	0.000606931
FSCN1	1.111404413	3.423223202	0.000618832
KLK8	1.048228806	3.406675511	0.000657593
KRT81	1.067195661	3.383367627	0.000716027
CREG2	1.076864904	3.377360757	0.00073185
KLK6	1.050684412	3.360353597	0.000778428
GJB3	1.068373162	3.347764011	0.000814664
TNS4	1.06538775	3.341780834	0.000832428
UMODL1	0.93069226	-3.341348721	0.000833724
POPDC3	1.061240666	3.337769753	0.000844537
IL11	1.100268069	3.32036034	0.000899013
ARHGAP11A	1.163292756	3.299473315	0.000968664

731 **Table 7.** 18 mRNAs expression profiles for prediction of overall survival in lung cancer by multivariate Cox regression.

Gene	HR	P-value
ANOS1	0.91977	0.029259
TFAP2A	1.1122	0.004444
FAM83A	1.08183	0.001032
IGSF10	0.93809	0.056385
WFIKKN2	0.93087	0.033323
PTX3	1.09537	0.0053
GJB3	0.9496	0.085902
COL22A1	1.05869	0.020412
LY6K	1.03246	0.117689
KLK6	0.95278	0.066225
FSCN1	1.07893	0.097713
KLK8	1.0358	0.151775
TRIM58	1.10451	6.36E-05
KCNV1	1.04437	0.048754
C20orf141	0.93072	0.100641
IGFBP1	1.06865	0.010148
LINGO2	1.04839	0.051753
CIDEA	1.10421	0.000968

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Figures

Figure 1

The test equipment system of smoke. (A) The sketch map of the equipment system. The combustion chamber was marked by "1". The smoke collecting window was marker by "2". (B) The practicality picture of the system. The smoke collecting window was marker by "a". The smoke collecting window was marker by "b".

Figure 2

The toxic smoke concentration of the door-flame experiment. The number on the column marked the arithmetic mean concentration of the smoke and bar indicated the mean $\pm$ SD.

Figure 3

The heatmap of the differently expressed RNAs. (A) The heatmap of differently expressed mRNA. The green box showed mRNA was down-regulated and red box showed mRNA up-regulated. (B) The heatmap of differently expressed miRNA. The green box showed miRNA was down-regulated and red box showed miRNA up-regulated. (C) The heatmap of differently expressed lncRNA. The green box showed lncRNA was down-regulated and red box showed lncRNA up-regulated.

Figure 4

Differentially expressed RNAs in lung cancer are visualized by volcano plots. The red dots show upregulated genes while the green dots show downregulated genes. (A) Differentially expressed mRNAs in lung cancer. (B) Differentially expressed miRNAs in lung cancer. (C) Differentially expressed lncRNAs in lung cancer.

Figure 5

The ceRNA network of lung cancer. mRNA was in rounded rectangle, miRNA was in round, lncRNA was in diamond. The blue show downregulated gene while red show upregulated gene. (A) ceRNA network that involve mRNA, miRNA and lncRNA. (B) The RNAs network between miRNA and mRNA. (C) The RNAs network between miRNA and lncRNA.

Figure 6

The Kaplan-Meier plots of differentially expressed RNAs in the ceRNA network which are also related to high-grade, stages, and overall survival ($P < 0.01$). (A) The survival curve of mRNAs. (B) The survival curve of miRNAs. (C) The survival curve of lncRNAs.

Figure 7

Thus, there is more benefit to detect lung cancer biomarkers for firefighters.