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ORIGINAL ARTICLE

lncRNA NONHSAT021963, which upregulates VEGF in A549 cells, mediates PM2.5 exposure-induced angiogenesis in Shenyang, China

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Abstract

Background PM2.5 is airborne particulate matter that is involved in air pollution and has become an important problem endangering human health. LncRNAs play important roles in malignant tumors. However, few studies have reported the mechanisms by which PM2.5 affects lung cancer.

Objective To investigate the functional changes in PM2.5-exposed cells, we conducted tubule formation assays to determine angiogenesis and sequenced RNA to elucidate the key molecular effects of PM2.5 in Shenyang, China.

Results RNA sequencing showed that the overall exposure values were very similar to the QPCR values. We found that 1379 lncRNA signatures and 162 mRNAs were differentially expressed between PM2.5-exposed and neutral saline-exposed cells. We further validated these changes via quantitative PCR in A549 human non-small-cell lung cancer (NSCLC) cell lines. PM2.5-exposed A549 cells presented carcinogenic transformation via lncRNA NONHSAT021963, which upregulates VEGF levels. The tubule formation assays showed that PM2.5-exposed cells were more angiogenic.

Conclusion These results may help to clarify the proteins and signaling pathways affected by PM2.5 and lead to new diagnostic and therapeutic approaches in treating NSCLC.

Keyword PM2.5 · A549 · lncRNA · angiogenesis · VEGF

Abbreviations

PM2.5	Fine particulate matter
ROS	Reactive oxygen species
HIF-1	Hypoxia inducible factor-1
VEGF-β	Vascular endothelial growth factor-β
PTGS2	Prostaglandin endoperoxide synthase 2
HSPA1B	Heat shock 70 kDa protein 1B
bFGF	Basic fibroblast growth factor
MMPs	Matrix metalloproteinases
IL24	Interleukin24
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
KEGG	Kyoto Encyclopedia of Genes and Genomes
NSCLC	Non-small-cell lung cancer
ECM	Extracellular matrix

Introduction

Fog and haze occur frequently in China, and airborne particulate matter of < 2.5 μm (PM2.5) is ubiquitous. When PM2.5 is inhaled into the respiratory system, it has potential toxic effects (Lu et al., 2015; Ku et al., 2017). PM2.5 concentrations have been shown to be highly correlated with population density in some large- and medium-sized cities (Yao and Lu, 2014). Continuous increases in PM2.5 will increase hospitalization and mortality rates from lung cancer (Eckel et al., 2016; Yao et al., 2019). Air pollution at PM2.5 has become an important problem endangering human health and is consistently associated with lung cancer in epidemiological studies (Pope et al., 2009; Pothirat et al., 2019).

Cancer is the world's leading cause of death, and lung cancer has become a main cause of cancer-related deaths worldwide. Standard therapies for lung cancer include surgical resection, double chemotherapy and radiotherapy. However, these therapies rarely cure lung cancer,

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and the 5-year survival rate remains only 17% (Akamatsu et al., 2014). Research shows that a 10-μg/m^3 increase in the PM2.5 concentration increases the lung cancer mortality rate by ~ 8% (Pope et al., 2002). Research has confirmed that lung cancer mortality is strongly correlated with PM2.5 concentrations in China. Higher PM2.5 concentrations increase the risk of related diseases and mortality (Fu et al., 2015). Preventing and treating lung cancer is crucial, and researchers must urgently seek new cures. The pathogenesis of lung cancer has been deeply analyzed under conditions of PM2.5 exposure. Long noncoding RNAs (lncRNAs) are closely related to lung cancer occurrence and development and provide a new strategy for treating lung cancer (Herrera et al., 2017; Xiang et al., 2020).

Much of the human genome is transcribed into RNAs that lack known protein-coding functions, which far outnumber the coding transcription units. lncRNAs, which contain > 200 nucleotides, regulate specific gene expression at the genetic, transcriptional and posttranscriptional levels (Kopp and Mendell., 2018). Extensive studies of lncRNAs have demonstrated that lncRNAs play critical roles as both transcriptional activators and repressors, are involved in physiological and pathological processes, and play important roles in the occurrence and development of malignant tumors (Liang et al., 2020; Liu et al., 2020). However, few studies have been conducted on the mechanism by which PM2.5 affects lung cancer progression. In vitro experiments have confirmed that removing the factors that cause tumor cell death enables apoptotic cells to resume their vitality and continue growing (Tang et al., 2009). PM2.5 promotes apoptosis in portions of A549 cells, while metabolic products from dead cancer cells accelerate the growth rates of surrounding and surviving cancer cells (Yang et al., 2016; Deng et al., 2017).

Here, we analyzed RNA sequencing data to identify differential lncRNA and mRNA expressions between PM2.5-exposed and neutral saline-exposed cells. We used the gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes pathway databases to confirm whether angiogenesis, the formation of new blood vessels from pre-existing blood vessels, becomes more important after PM2.5 exposure and identified the differential lncRNA and mRNA expressions in A549 cells via quantitative PCR. Further, to investigate the angiogenesis-associated functional changes in PM2.5-exposed cells, we conducted protein network analysis and determined that PM2.5-exposed A549 cells showed carcinogenic transformation by upregulating lncRNA NONHSAT021963. This work will increase the knowledge of cellular pathways and scientific interpretation PM2.5 exposure as well as provide social and economic benefits.

Materials and methods

Sampling of PM2.5

The concentration of PM2.5 solution was 5 mg/ml, and PM2.5 solution was stored at − 80 °C in our laboratory. PM2.5 samples were sonication before use and the analysis of PM2.5 composition was performed as described previously (Ma et al., 2015).

Cell culture and PM2.5 exposure

Human NSCLC cell lines A549 was cultured in F12 medium supplemented with 10% fetal bovine serum (Hyclone, USA), 100-U/ml penicillin G and 100-mg/ml streptomycin (Hyclone, USA) at 37 °C in a humidified incubator at 5% CO_2. For cell growth, the medium was renewed every 2 days and cells were subcultured after reaching an optical confluence of 85%. For RNA sequencing, before total RNA was extracted, the cells were seeded into 6-well plates, grown to 85% confluence and tackled with PM2.5 at the concentration of 50 mg/cm^2 for 24 h, and the same amount of angiogenesis was added in the control group.

Tubule formation assay

Both PM2.5-exposed and neutral saline-exposed A549 cells were seeded at 1×10^6 cells per well in 6-well plates and incubated for 20 h at 37 °C in F12 medium. The capillary-like structures were then examined with optical microscopy at 100 under an Olympus CKX31 microscope (Olympus Co., Tokyo, Japan). The experiments were done in triplicate and repeated 3 times.

RNA Extraction

Total RNA was extracted using TRIZOL Reagent (Life technologies, US) following the manufacturer's instructions. RNA integrity was checked by an Agilent Bioanalyzer 2100 (Agilent technologies, US). Qualified total RNA was further purified by RNeasy micro kit (QIAGEN, Germany) and RNase-Free DNase Set (QIAGEN, Germany).

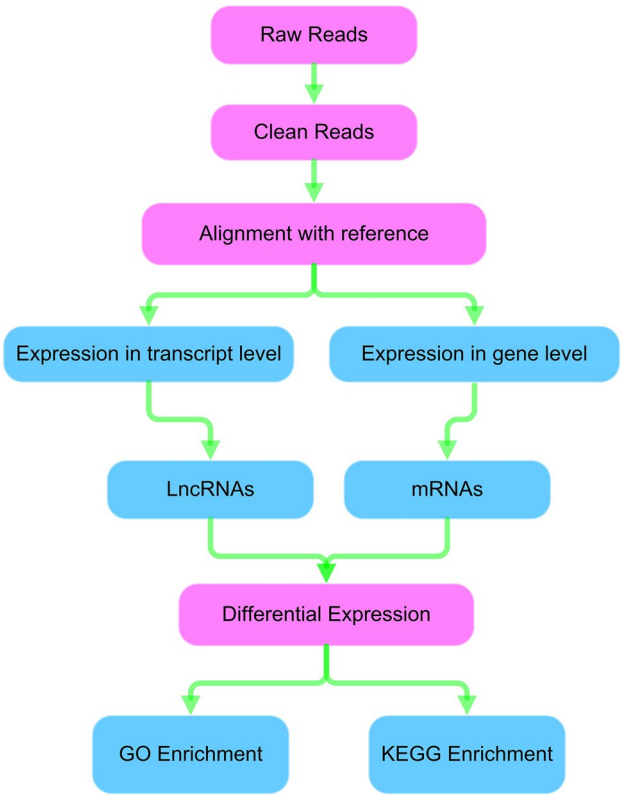

Fig. 1 Analytic Flowchart of RNA-seq. It mainly includes three aspects RNA Isolation and Deep Sequencing Data Analysis

Microarray and enrichment analysis

Transcriptome high-throughput sequencing was performed at the Shanghai Biochip Company, and the analytic Flowchart was shown as Fig. 1. Both differentially expressed lncRNAs (https://www.noncode.org/) and mRNA (https://www.genecards.org/) were identified through fold change 2 and false discovery rate 0.05. The data of LncRNA-mRNA co-expression are shown in Supplementary files 1 and 2. The gene ontology (GO) project aims to describe gene and gene product attributes (https://www.geneontology.org). Pathway analysis is a functional analysis according to KEGG (Kyoto Encyclopedia of Genes and Genomes) pathways (https://www.genome.jp/kegg/). The enrichment level was calculated by transforming the enrichment p values after false discovery rate (FDR) correction to negative log10 values, and the lower the p-value is the more significant the correlation (a p-value cut-off is 0.05).

Quantitative real-time PCR

QPCR was performed in triplicate to detected the fold changes of candidate genes, using an ABI 7500 (Applied Biosystems, USA) and SYBR GREEN Master Mix (Applied Biosystems, USA) according to the manufacturer's instruction. Primer pairs used for real-time PCR are shown in Table 1. The results of the QPCR of mRNA levels were determined after normalization to the GAPDH expression. Relative expression levels were calculated using the $2^{-\Delta\Delta Ct}$ method.

Network construction on angiogenesis

We investigated the protein–protein interactions from the string database. The network of PM2.5-mediated non-small-cell lung cancer protein interactions was drawn, including activation, inhibition, binding, transcriptional regulation, positive, negative, and unspecified (Szklarczyk et al. 2011).

Table 1 List of primers for RT-PCR

Gene	Forward	Reverse
NONHSAT108842	GGACACTCCCCAACAAACTGC	TCTGCCTGAGAAACGGACC
NONHSAT021974	CTCAGGACGACGATTTGCG	ACTCCCTGTCTGCACACGATG
NONHSAT021963	CGAGCTCTGCGAATCACTTTATT	GCTCTGGAGATTCTGAACTGGA
NONHSAT068466	CTCCTGACCCTATTGCTCGG	AGGAGCCCTTGAGGAAACAC
VEGF-β	CAGACCTAAAAAAAAGGACAGTGCT	CCTGCTGAGTCTGAAAAGCCAT
PTGS2	CCGAGGTGTATGTATGAGTGTGG	AATCCCTTGAAGTGGGTAAGTATG
IL-1β	ATGATGGCTTATTACAGTGGCAA	GTAGTGGTGGTCGGAGATTCGT
HSPA1B	GAGCAGGTGTGTAACCCCATC	TCCTTGAGTCCCAACAGTCCA
HIF1α	AAACCACCTATGACCTGC	TGAGTTTCAACCCAGACA
bFGF	AAGAGCGACCCTCACATCAA	CGTTTCAGTGCCACATAACCAA
MMP9	CCAAAAC-TACTCGGAAGACTTGC	GGATACCCGTCTCCGTGCT
IL24	TCACTTACAGGACCAGAGGGACA	AGAAGGGTCTGCTGGCTAAAGTC
GAPDH	ACCCAGAAGACTGTGGATGG	ACCCAGAAGACTGTGGATGG

Statistical analysis

Experimental data were analyzed by the software GraphPad Prism 5 (GraphPad Software, USA). Data were reported as mean ± SD of three independent experiments. Statistical comparisons were done using an unpaired two-tailed Student's t test for two groups. Differences were considered significant if $p < 0.05$.

Results

Effect of PM 2.5 exposure on angiogenesis

We investigated whether the PM2.5 promotes in vitro angiogenesis using tubule formation assay. The results indicated that PM2.5-exposed condition significantly increased the A549 cells tubule formation ability. Representative images of the angiogenesis monitored on 20 h are shown in Fig. 2A and 2B. PM 2.5 exposure increased angiogenesis abilities of cells compared with the control cells.

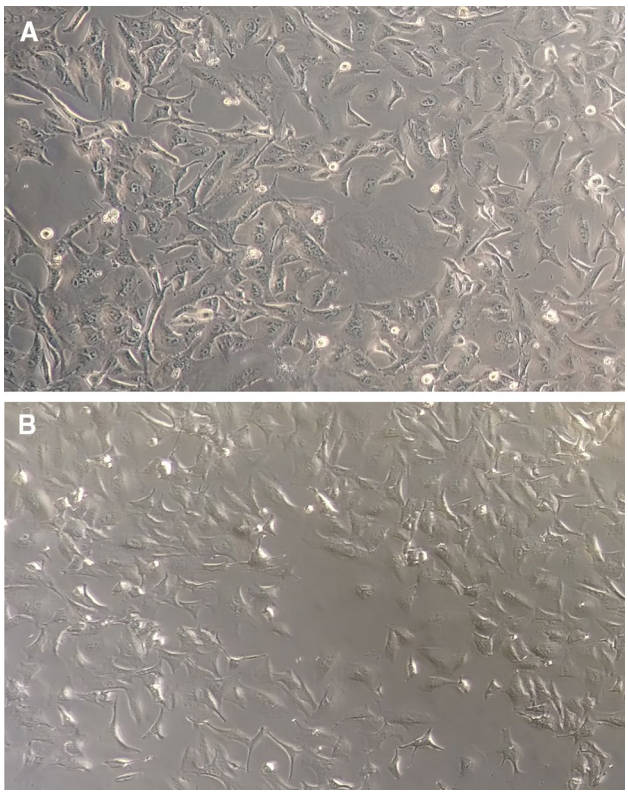

Fig. 2 In vitro Angiogenesis. A. PM2.5-exposed cells. The ability of cell proliferation is stronger and the morphology changes. B. Natural saline-exposed cells. Cells show typical polyhedral morphology

Differential expression profiling by RNA-seq

In PM2.5-exposed cells, we performed the microarray analysis and identified 645 up-regulated and 734 down-regulated lncRNAs (Fig. 3), and found 64 protein-coding differentially up-regulated and 98 protein-coding mRNAs differentially down-regulated. These results indicated that PM2.5 exposure produced a striking profile of lncRNAs and mRNAs compared with the control sample.

GO and Pathway analysis

Functions of the differentially expressed genes are shown in Fig. 4. We found that the most common functions targeted by these lncRNAs were response to protein binding, positive regulation vascular endothelial growth factor production, cellular protein metabolic process, cell division, negative regulation of transforming growth factor beta receptor signaling pathway, enzyme binding, protein import into peroxisome matrix, extracellular negative regulation of signal transduction, oxygen homeostasis, and endoplasmic reticulum unfolded protein response.

Pathway analysis indicated that 10 types of pathways were affected by these deregulated lncRNAs, including legionellosis, systemic lupus erythematosus, glycerophospholipid metabolism, protein processing in endoplasmic reticulum, thiamine metabolism, cytokine–cytokine receptor interaction, purine metabolism, T cell receptor signaling pathway, beta-alanine metabolism, and mineral absorption (Fig. 5).

Validation of differential expression of lncRNA and mRNA with PCR

To validate lncRNA and mRNA expression levels, 12 genes with significantly different expressions were randomly selected from the microarray data to be verified by QPCR, using cDNA from two experimental samples, that is to say, PM2.5-exposed cells and their control groups in A549 cell line. These genes included 4 lncRNAs and 8 mRNAs, including NONHSAT108842, NONHSAT021974, NONHSAT021963, NONHSAT068466, VEGF-β, PTGS2, IL1β, HSPA1B, HIF1α, bFGF, MMP9, IL24. We found expression for these genes in the exposure group to significantly differ from their expression in the control group, similar to the change trends shown in microarray data (Fig. 6).

STRING database network

Using the String database, analysis of the selected genes revealed a significant association in angiogenesis. The results of RNA-seq of PM2.5-exposed cells indicated

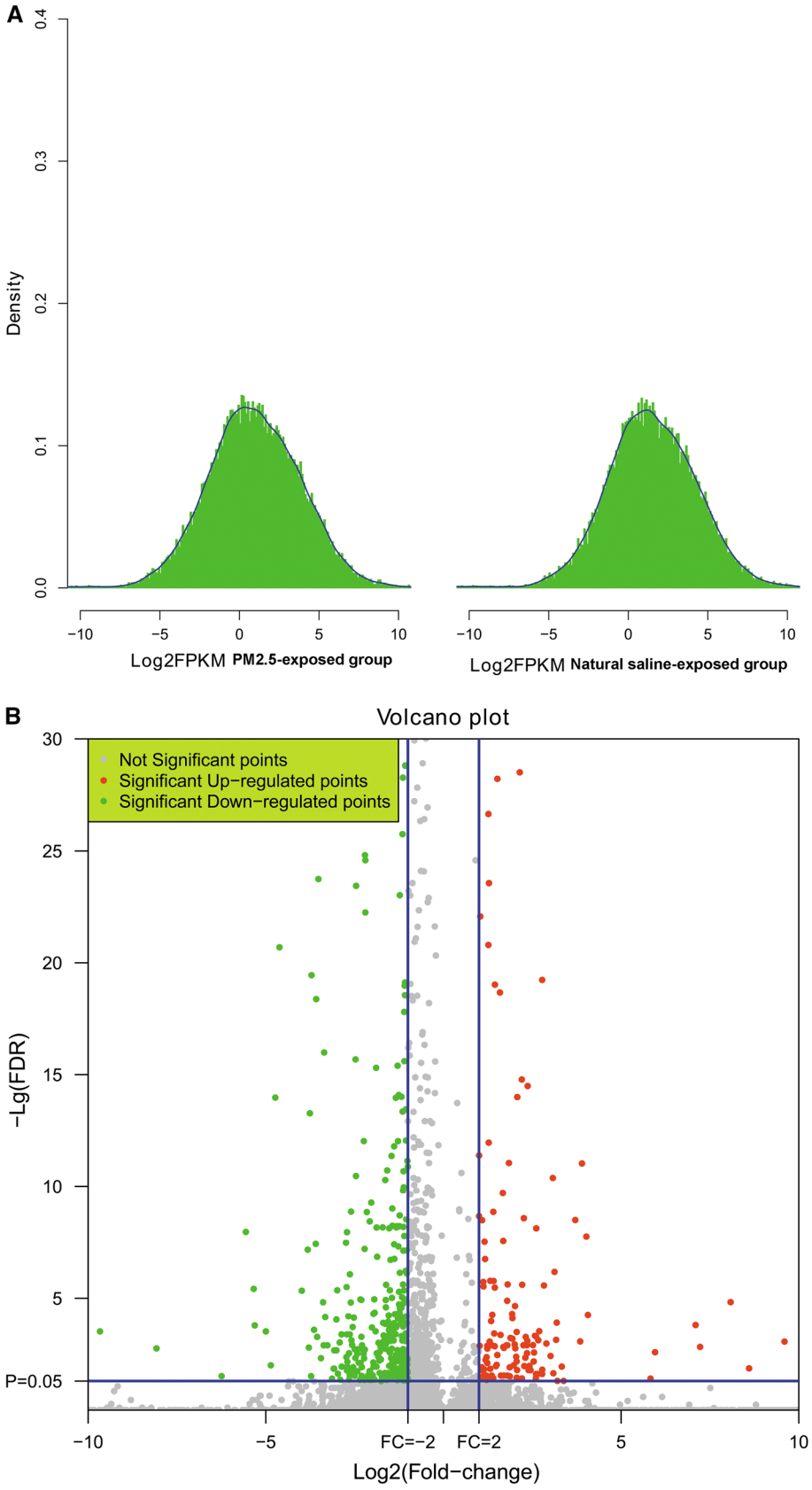

Fig. 3 lncRNAs expression profiling to characterize PM2.5 exposure. A lncRNAs expression distribution plot. B Volcano plot. Vertical blue lines: twofold changes; horizontal blue line: p = 0.05

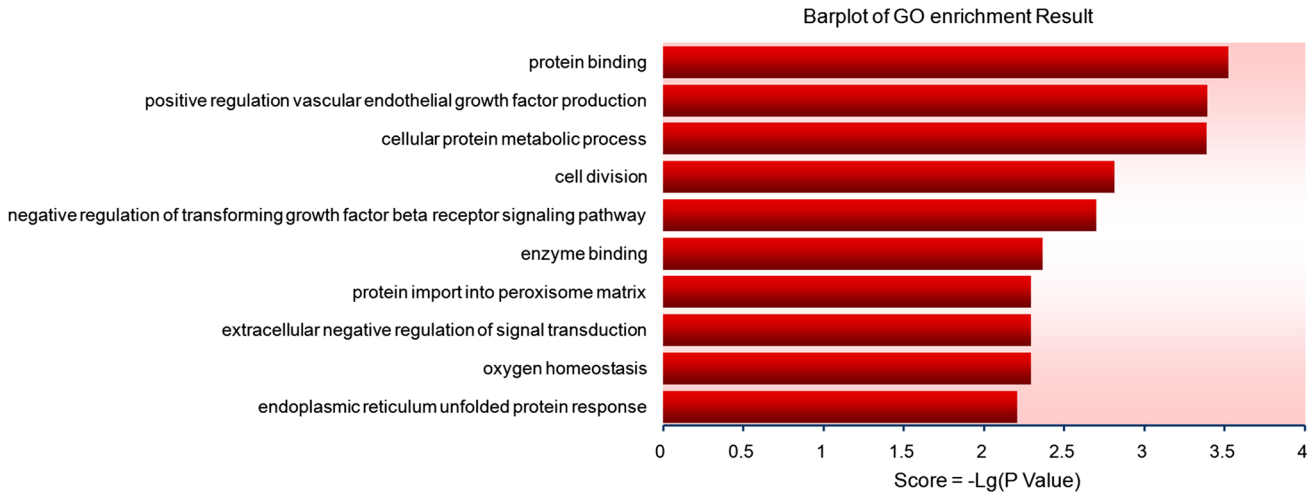

Fig. 4 Annotated functional analysis of significantly differential genes. The ontology covers biological processes, cellular components, and molecular functions ($p < 0.05$)

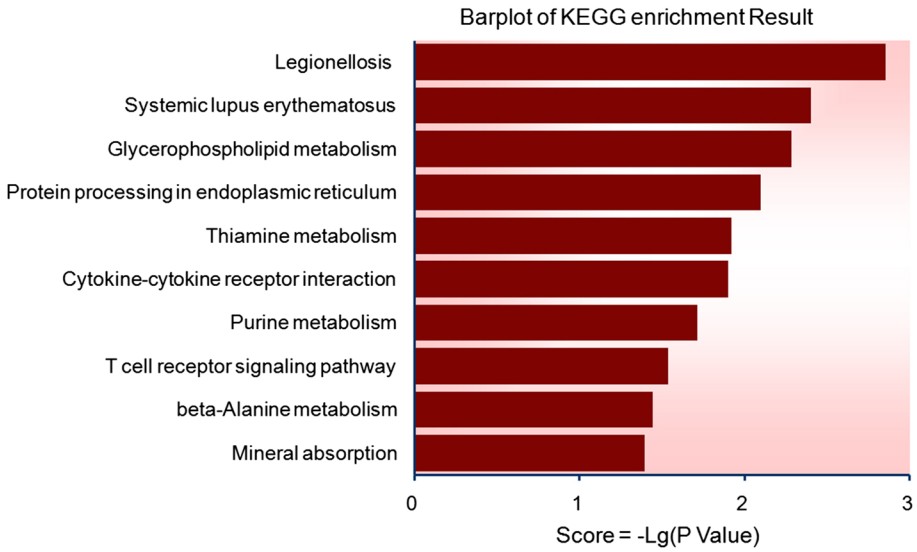

Fig. 5 Pathway analysis maps for differentially expressed genes ($p < 0.05$)

enhancement of a network of seven interacting proteins (Fig. 7) that are strongly associated with connectivity and integration: VEGF, MMP9 and HIF1α. In the constructed network, VEGF played crucial roles, possibly because of the cell lines represent the ability of angiogenesis, suggesting that the expression of these genes may be maintained in NSCLC after PM2.5 exposure.

Discussion

PM2.5 inflicts damage at the cellular level. Numerous investigations of the effects of PM2.5 on human health have mainly addressed its cytotoxic effects (Xu et al., 2016; Kim et al., 2017). PM2.5 has increased reactive oxygen species (ROS) production in both in vitro and in vivo experiments (Yuan et al., 2015; Hamad et al., 2016). ROS are normal antioxidative metabolites produced by cells. When the oxidant and antioxidant systems are unbalanced, too many oxidation products can damage cells, destroy cell structure, activate inflammation-related transcription factors to promote the release of inflammatory mediators, and lead to poor health and serious illnesses.

Epidemiological surveys have shown the negative effects of air pollution on the human body, especially in the respiratory system (Goodman et al., 2003; Grommes and Soehnlein 2011). Cancer incidence and mortality are increasing, and lung cancer, especially non-small-cell lung cancer (NSCLC), is the leading cause of cancer-related deaths worldwide. However, the mechanisms underlying the effects of PM2.5 on NSCLC remain unclear. Abnormal lncRNA expression often leads to tumor occurrence,

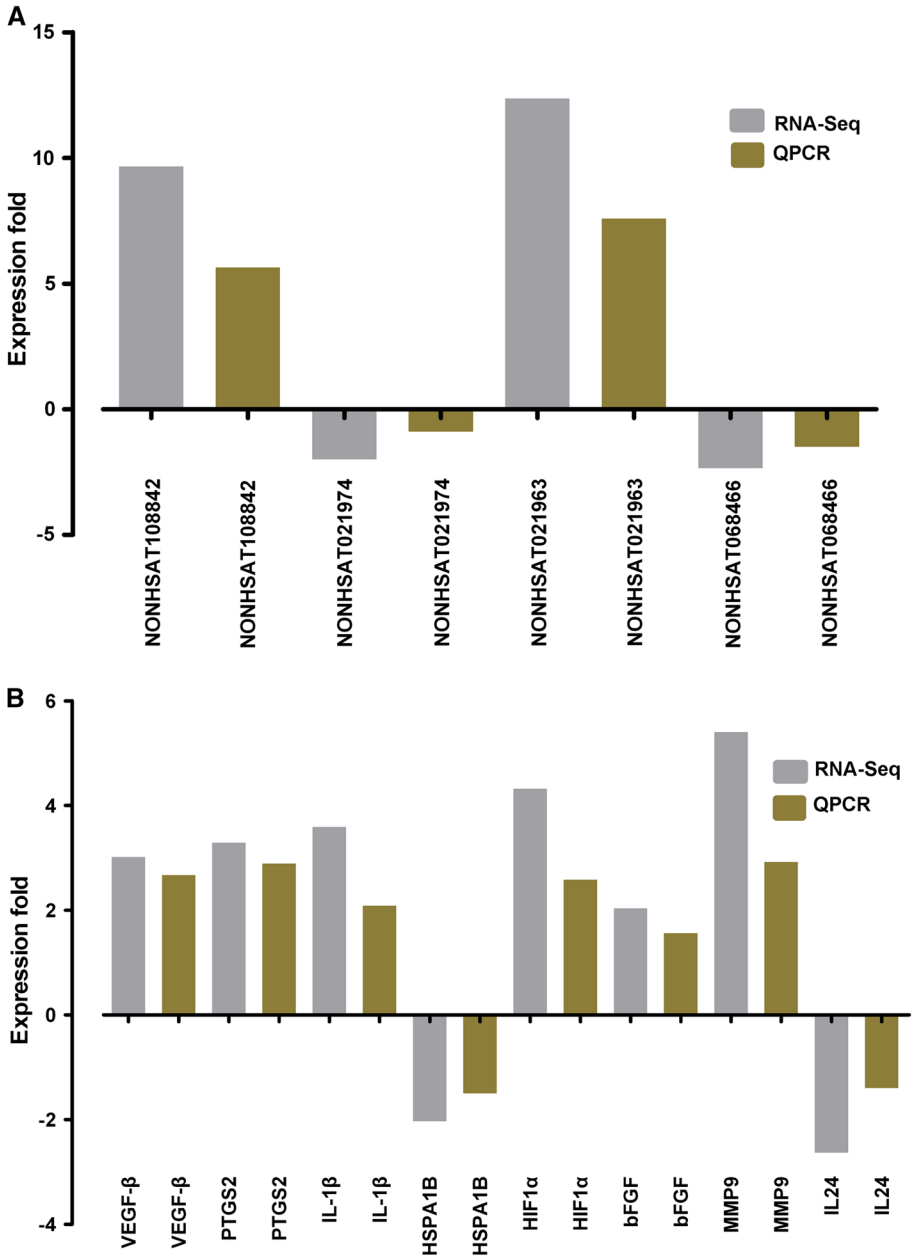

Fig. 6 Correlation of transcriptional changes assayed by RNA-seq with those assayed by qRT-PCR. The GAPDH was used as an internal control to target genes

development and metastasis; thus, changes in lncRNA and mRNA expressions in lung cancer upon PM2.5 exposure must be evaluated. LncRNAs have many functions such as regulating protein and gene interactions, acting as decoys to bind proteins or microRNAs (miRNAs), and acting as enhancers to modulate transcription of their targets after being transcribed from enhancer regions or their neighboring loci (Kopp and Mendell., 2018). Recent studies reported that lncRNAs may function as competing endogenous RNAs and crosstalk with mRNAs by competitively binding their common miRNAs. lncRNAs can promote or inhibit tumor growth to regulate or maintain gene expression (Liang et al., 2020).

Here, we investigated lncRNA expression profiles from NSCLC cells after PM2.5 exposure and compared them with unexposed cells to identify specific lncRNAs and trace dynamic relationships between lncRNAs and their regulated genes. Comparing lncRNA and mRNA expression profiles revealed 1379 lncRNA signatures (645 up-regulated and 734 down-regulated), 64 differentially up-regulated protein-coding mRNAs, and 98 differentially down-regulated protein-coding mRNAs in PM2.5-exposed cells. We further quantified the expression levels of several genes via qRT-PCR, which showed that the overall exposure vs. normal values were very similar to those measured via RNA sequencing. The results showed that PM2.5-exposed A549 cells showed

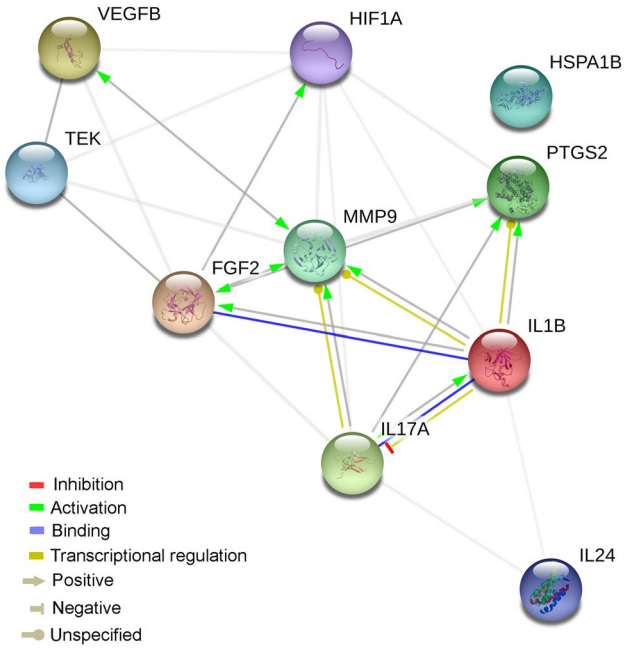

Fig. 7 Interactive composite network view of PM2.5 exposure-related protein. Connected lines show tightly connected functional modules. Lower left corner: function information. The degree level of each gene is represented by the size of the node

carcinogenic transformation by lncRNA NONHSAT021963, which up-regulated vascular endothelial growth factor (VEGF) levels.

VEGF is important in tumor vessel maturation and remodeling, and protein overexpression is associated with tumor progression and prognosis in NSCLC (Hainaud et al., 2006; Kaya et al., 2004). In the present study, significantly higher levels of lncRNA NONHSAT021963 and VEGF were detected after PM2.5 exposure; thus, PM2.5 exposure may stimulate and exacerbate NSCLC.

The tumor microenvironment consists of vascular components, stromal fibroblasts, inflammatory cells and the extracellular matrix (ECM) (Oskarsson et al., 2014). The development of most carcinomas requires establishing intricate communication networks within and between the surrounding microenvironment. Our microarray studies and statistical analyses showed that the differentially expressed genes enabled the affected cellular areas to efficiently cope with the stresses of PM2.5 exposure, but with high angiogenic ability. To study the other effects, we evaluated the differentially expressed GO terms and pathways involved in PM2.5 exposure. For example, VEGF contributes to hypoxia response, wound healing, survival, regulation of cell division, and angiogenic ability.

In this study, we found a complex and interacting protein regulatory network, which included hypoxia inducible factor-1 (HIF-1), VEGF and basic fibroblast growth factor (bFGF). VEGF plays a key role in the cross-linked signaling network. Within the hypoxic environment of the inner tumor mass, the dimeric protein complex of HIF-1 is stabilized and activates the expression of multiple genes that contribute to angiogenesis (Soni and Padwad, 2017). HIF-1-induced proteins include VEGF and bFGF, which promote vascular permeability and NSCLC cell growth, respectively (Giatromanolaki et al., 2011). Other HIF-1-induced gene products include matrix metalloproteinases (MMPs) that break down the ECM to facilitate cancer cell migration (Singh et al., 2011).

Angiogenesis plays an important role in tumor progression and metastasis. MMP-9 promotes tumor invasion and metastasis by degrading ECM molecular materials, regulating cellular adhesion, and degrading the vascular basement membrane and perivascular matrix with other enzymes, which are important conditions for vascular tree growth (Keeratichamroen et al., 2018). Endothelial cells can migrate into the surrounding tissues only via degradation and gradually form vascular trees, promoting tumor cell metastasis and metastatic invasion. bFGF, a potent stimulator of angiogenesis, affects endothelial cells via paracrine mechanisms after its release from tumor and stromal cells. bFGF also stimulates VEGF secretion and works synergistically with VEGF to induce angiogenesis. These findings suggest the need for research on the important regulatory pathways involved in PM2.5 exposure.

Previous studies showed that PM2.5-exposed cells contained high levels of MMP1 and IL1β in the supernatant (Yang et al., 2016). These high levels benefit regulating the microenvironment and stimulating tumor cell growth and invasion (Hanahan and Weinberg, 2011). Within the protein network, VEGF signals promote cell survival, significantly increase tumor growth, and speed up changes in the tumor volume. As in our previous studies, PM2.5 exposure from air pollution was positively associated with total protein levels in the respiratory tract (White et al., 2014). Formation of a high-protein environment stimulates local inflammation, and increased bronchoalveolar lavage (BAL) fluid protein concentrations reduce lung function. This environment can profoundly influence tumor development. Our data showed that PM2.5 exposure induced chronic inflammation, allowing cancer cells to proliferate and metastasize faster.

In summary, significantly high levels of lncRNA NONHSAT021963 and VEGF were closely correlated with lung cancer progression. In addition, PM2.5 exposure may exacerbate NSCLC progression. These results may help to identify the proteins and signaling pathways affected by PM2.5, leading to new diagnostic and therapeutic targets. In future research, we will use a larger number of clinical samples to determine the role of lncRNA in lung cancer after PM2.5 exposure, explore the mechanisms involved, and

provide more accurate and reliable data for developing novel therapies for NSCLC.

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Author contributions BY and CX contributed conception and design of the study; BY carried out all experimental assays. HT and BY performed the statistical analysis; BY wrote the first draft of the manuscript; BY and HT wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

Compliance with ethical standards

Conflict of interest The authors declare that no potential competing interests exist.

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