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RESEARCH ARTICLE

Transcriptomic Analysis Reveals Conserved Inflammatory Gene Upregulation in Human Lung Cells Exposed to PM2.5 from China and South Korea

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ABSTRACT: Air pollution, particularly fine particulate matter with an aerodynamic diameter of 2.5 micrometers or smaller (PM2.5), poses a significant threat to human health. While many countries have undertaken measures to combat air pollution, its patterns remain fluctuating, warranting an assessment of the efficacy of past interventions and a projection of future outcomes to safeguard public health. This study aimed to investigate how exposure to PM2.5 from China and South Korea influences the transcriptomic profiles of lung cells, focusing on identifying conserved inflammatory responses. To achieve this, RNA-seq data from two studies—one involving human bronchial epithelial cells and the other using mouse lung tissue exposed to PM2.5—were analyzed. This research presents a list of ten genes identified as upregulated due to exposure to PM2.5 collected from China. To comprehensively explore the impact of particulate matter on gene expression, we conducted a parallel analysis utilizing PM2.5 samples collected from South Korea. Upon scrutinizing the Korean PM2.5 dataset, we tested the same set of upregulated genes after PM2.5 exposures. Our investigation showed that five specific genes exhibited upregulation: INHBA, CCL20, CXCL3, KIAA1644, and IL-8, with fold changes ranging from 5.11 to 6.88 compared to control samples. These identified genes are notably associated with inflammatory processes, suggesting a crucial role in regulating the cellular response following exposure to PM2.5. This association provides intriguing insights into a potential shared molecular mechanism underlying the impact of PM2.5 on biological systems. The upregulation of these five genes reveals a significant connection between PM2.5 exposure and the activation of inflammation-related pathways within lung cells. Interestingly, this research result also highlights a remarkable similarity in the effects induced by PM2.5 collected from South Korea and PM2.5 collected from China. The conserved upregulation of these specific genes across different geographical origins of PM2.5 underscores the robustness and universality of the cellular response to particulate matter exposure. Consequently, this research contributes to identifying potential therapeutic targets and strategies for mitigating the health risks associated with air pollution.

KEYWORDS: Biomedical and health sciences, Genetics and Molecular Biology of Disease, PM2.5, Transcriptomic analysis, Inflammation.

Introduction

These days, air pollution has become a significant concern due to producing harmful substances, particularly particulate matter (PM2.5), with an aerodynamic diameter equal to or less than 2.5 micrometers.[1] PM2.5 in the atmosphere has been linked to various detrimental health effects. Epidemiological studies have consistently demonstrated a strong correlation between exposure to PM2.5 and respiratory diseases.[2]

One of the concerning aspects of PM2.5 is its ability to penetrate deep into the respiratory system, reaching the lungs and even entering the bloodstream.[3] This characteristic raises the possibility of PM2.5 particles affecting various body organs.[4] Consequently, the adverse health impacts associated with PM2.5 extend beyond the respiratory system, making it a matter of utmost importance to understand and address this issue.[5]

Acknowledging air pollution as a significant determinant of public health, numerous countries have adopted measures to address this pressing issue.[6] However, in various regions, particularly those with robust economic development, air pollutants have exhibited fluctuating patterns of increase and decrease in recent decades.[7] Therefore, it is imperative to assess whether previous endeavors to mitigate air pollution have resulted in tangible enhancements to public health while also endeavoring to forecast the potential impact of future initiatives. By documenting these outcomes, we can gain valuable insights to guide future interventions and safeguard the population's well-being.

Prolonged exposure to PM2.5 has been linked to an elevated risk of developing lung cancer and cardiovascular disease.[8] Short-term exposure to PM2.5 has been associated with various cardiopulmonary ailments, including asthma, bronchitis, and arrhythmia.[9] Previous studies have suggested that oxidative stress and inflammatory responses induced by PM2.5 may contribute to the development of diverse lung diseases.[10] However, the precise mechanisms through which PM2.5 exerts its detrimental health effects remain unclear.[11]

While PM 2.5 may seem to cause short-term effects, it may lead to severe health issues, mainly cancer. To investigate the impact of PM2.5 on inducing cancer, RNA-seq and gene expression analyses were performed using two previous RNA-seq studies.

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Methods

Data Collection:

Two RNA-seq studies were selected for analysis: one involving human bronchial epithelial cells exposed to PM2.5 and the other involving mouse lung tissue exposed to PM2.5. Raw RNA-seq data from both studies were obtained. Standard quality control measures were applied to the raw RNA-seq data to ensure data integrity and reliability.

Differential Gene Expression Analysis:

Differential gene expression analysis techniques were used to identify genes significantly altered in response to PM2.5 exposure in each dataset. A list of differentially expressed genes was generated for each dataset.

Network Analysis:

Network analysis methods were employed to construct gene networks based on the identified differentially expressed genes. GeneMania was used for network analysis. The top 10 upregulated genes in human bronchial epithelial cells exposed to PM2.5 were identified. Gene-specific functional analysis was conducted for each of these genes.

Word Cloud Analysis:

A word cloud analysis was performed to visually represent key terms describing the findings associated with PM2.5 exposure. The top 10 upregulated genes and their associated functions were highlighted in the word cloud. Terms related to immune response, cell functions, leukocytes, lymphocytes, and cytokines were identified, indicating their potential involvement in the effects of PM2.5 exposure.

Sample Preparation and Treatment:

Human lung cell line MRC5 was selected for the study. A range of PM2.5 concentrations (0.1%, 2%, 5%, 8%, 10%) and a control group with no PM2.5 treatment were prepared. Cell morphology and viability were assessed in each group.

Cell Morphology and Viability Assessment:

Human lung cell morphology and viability were analyzed under different PM2.5 concentration conditions. The control group served as the baseline for normal cell morphology and viability. Alterations in cell morphology and changes in viability were observed and recorded.

RT-PCR Gene Expression Analysis:

Reverse Transcription Polymerase Chain Reaction (RT-PCR) was employed to analyze gene expression in human lung cells treated with 0.1% PM2.5. A specific set of genes was tested, and their expression levels were measured.

Results and Discussion

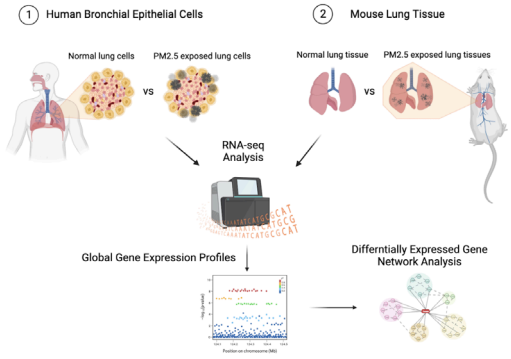

Figure 1: Schematic illustration of differentially expressed gene network analysis using two previous RNA-seq data: 1) A study with the human bronchial epithelial cells exposed to PM2.5, 2) A study with the mouse lung tissue exposed to PM 2.5. This figure demonstrates the differential gene expression patterns identified between human bronchial epithelial cells and mouse lung tissue upon PM2.5 exposure. The shared and unique gene networks suggest species-specific responses with notable overlap in inflammation-related pathways.

This study comprehensively analyzed differentially expressed gene networks using two previously conducted RNA-seq studies. The first study involved human bronchial epithelial cells exposed to PM2.5, while the second used mouse lung tissue exposed to PM2.5 (Figure 1).[12,13] We aimed to examine the shared and unique gene expression patterns in response to PM2.5 exposure between these two species.

To perform the analysis, we first obtained the raw RNA-seq data from both studies and processed it using standard quality control measures. We then applied differential gene expression analysis techniques to identify genes significantly altered in response to PM2.5 exposure in each dataset. Next, we employed network analysis methods to construct gene networks based on the identified differentially expressed genes.

Table 1: Top 10 up-regulated genes in PM2.5 treated 16HBE cells. The table highlights key genes significantly upregulated in response to PM2.5 exposure, including CYP1A1, INHBA, and TNF, indicating activation of detoxification pathways and inflammatory responses.

Gene	Gene length	log2(FC)	Description
CYP1A1	2608	9.54	Cytochrome P450, Family 1, Subfamily A, Polypeptide 1
INHBA	2175	6.88	inhibin beta A chain precursor
TNF	1669	6.57	tumor necrosis factor
SERPINB2	2180	6.46	plasminogen activator inhibitor 2 precursor
IL6	1201	6.28	interleukin-6 precursor
IL8	1718	5.75	interleukin 8
CXCL3	1166	5.39	C-X-C motif chemokine 3
CCL20	851	5.31	C-C motif chemokine 20 isoform 1
TNFAIP3	4446	5.29	tumor necrosis factor alpha-induced protein 3
KIAA1644	6741	5.11	Uncharacterized Protein

After analyzing the gene expression data from human bronchial epithelial cells exposed to PM2.5, we identified overexpressed genes that exhibited significant upregulation compared to control samples. These genes included CYP1A1, INHBA, TNF, SERPINB2, I $L6, IL8, CXCL3, CCL20, TNFAIP3, and KIAA1644 (Table 1).

Among these gene $s, CYP1A1, a member of the cytochrome P450 enzyme family, showed a robust increase in expression. This finding is consistent with previous studies linking CYP1A1 induction to exposure to environmental pollutants, including particulate matter. The upregulation of CYP1A1 suggests activating detoxification pathways as a response to PM2.5 exposure.

INHBA, another overexpressed gene, encodes a protein belonging to the transforming growth factor beta (TGF-β) superfamily. The upregulation of INHBA indicates the involvement of TGF-β signaling in the cellular response to PM2.5 exposure. TGF-β signaling pathways regulate various cellular processes, including inflammation and tissue repair.

We also observed the upregulation of pro-inflammatory cytokines, such as TNF, IL6, IL8, and chemokines, such as

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CXCL3 and CCL20. These findings suggest an inflammatory response from PM2.5 exposure in human bronchial epithelial cells. The upregulation of these cytokines and chemokines indicates the activation of immune cells and the recruitment of inflammatory cells to the exposure site.

Furthermore, the overexpression of SERPINB2, TNFAIP3, and KIAA1644 suggests the involvement of additional regulatory mechanisms in response to PM2.5 exposure. SERPINB2 regulates protease activity and has been implicated in various physiological processes, including inflammation and tissue remodeling. TNFAIP3 is a negative regulator of NF-κB signaling and has a crucial role in modulating inflammatory responses. The upregulation of KIAA1644, a gene with poorly characterized function, indicates a potential novel pathway or mechanism involved in the cellular response to PM2.5 exposure.

In summary, our analysis of the overexpressed genes in human bronchial epithelial cells exposed to PM2.5 revealed the activation of various pathways and processes related to detoxification, inflammation, and immune response. These findings provide insights into the molecular mechanisms underlying the adverse effects of PM2.5 on respiratory health and highlight potential targets for future studies to mitigate the harmful impacts of air pollution on human health.

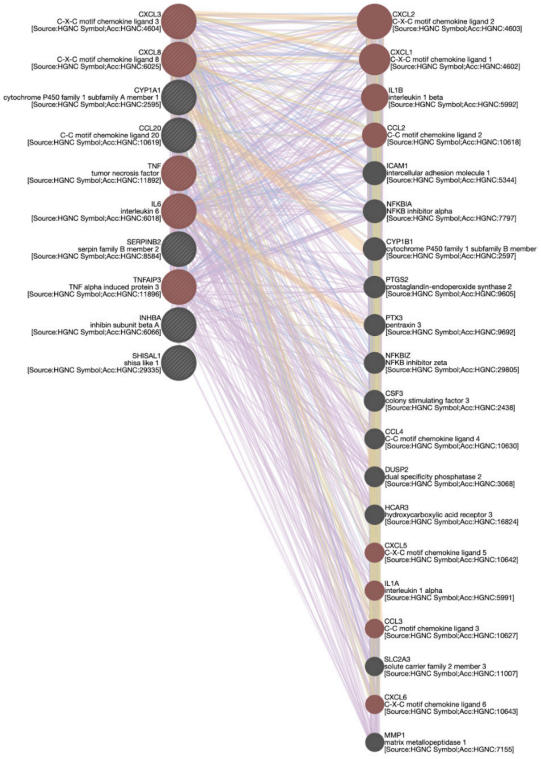

Figure 2: Gene network analysis results using the top 10 up-regulated genes. Network analysis shows that PM2.5 exposure leads to upregulation of genes associated with the cellular response to molecules of bacterial origin, particularly involving chemokines and cytokines crucial in inflammation and immune responses.

Gene network analysis was employed to predict the function of genes of interest, revealing valuable insights. To this end, the top 10 upregulated genes were analyzed using GeneMania. The analysis indicated that the most prominent predicted function associated with these genes was "cellular response to molecule of bacterial origin" (highlighted in red, as depicted in Figure 2). Notably, this gene set includes CXCL3, CXCL8, TNF, IL6, and TNFAIP3, among the top 10 upregulated genes. Furthermore, closely related genes such as CXCL2, CXCL1, IL1B, and CCL2 were also found to be involved in the cellular response to molecules of bacterial origin. The data strongly suggest that cells treated with PM2.5 exhibited an upregulation of genes associated with bacterial response, indicating a significant correlation.

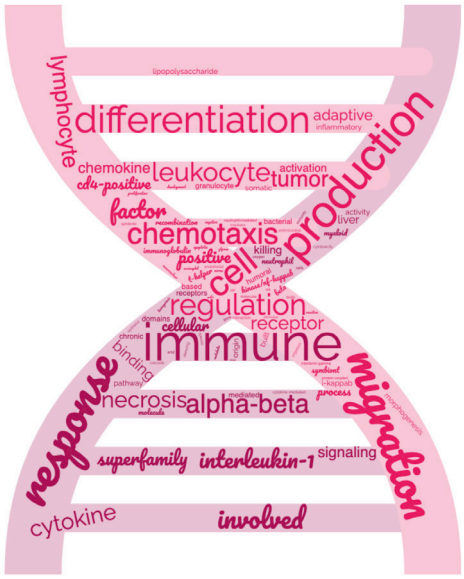

Figure 3: Word cloud analysis result using predicted top 10 up-regulated gene function. The word cloud analysis visually emphasizes the key functional roles of upregulated genes, focusing on immune response, inflammation, and cytokine signaling, underscoring the biological impact of PM2.5 exposure.

Additionally, a word cloud analysis was conducted to visually depict the key terms describing the findings associated with PM2.5. The size and prominence of words in the cloud correspond to their relevance and significance. The larger font size represents the top 10 upregulated genes and their associated functions, which were found to be upregulated in response to PM2.5 exposure (Figure 3). Notably, this analysis facilitated the identification of cell functions such as immune response production, migration, and differentiation, all of which were strongly linked to PM2.5 exposure. Furthermore, terms like leukocyte, lymphocyte, and cytokine emerged, highlighting their potential involvement in the ultimate effects of P2.5 exposure.

Table 3: Top ten upregulated genes in PM2.5 inhaled mouse lung for three months with low concentration. This table presents genes significantly upregulated in mouse lung tissue after prolonged exposure to low concentrations of PM2.5, suggesting the involvement of pathways linked to immune response, energy metabolism, and cellular stress.

Gene	Gene length	log2(FC)	Description
Prok2	2608	7.77	Prokineticin 2
Rps27rt	2175	7.35	Ribosomal Protein S27 RNA Pseudogene
Ccl19	1669	6.41	C-C Motif Chemokine Ligand 19
LOC108168952	2180	5.89	Locus 108168952
Gm13278	1201	5.60	Gene Model 13278
Gm40369	1718	5.34	Gene Model 40369
Gm21320	1166	5.13	Gene Model 21320
Ucp1	851	4.58	Uncoupling Protein 1
Ugt2b34	4446	4.56	UDP Glucuronosyltransferase Family 2 Member B34
Gm5639	6741	4.55	Gene Model 5639

Analysis of PM2.5-inhaled mouse lung tissue revealed several upregulated genes, including Prok2, Rps27rt, Ccl19, LOC108168952, Gm13278, Gm40369, Gm21320, Ucp1, Ugt2b34, and Gm5639. Prok2, known as Prokineticin 2, plays a role in various physiological processes. Rps27rt, a pseudogene of Ribosomal Protein S27, may have regulatory functions (Table 3). Ccl19, or C-C Motif Chemokine Ligand 19, is involved in immune responses and inflammation. LOC108168952, Gm13278, Gm40369, and Gm21320 are gene loci that might not yet have been assigned official names. Ucp1, or Uncoupling Protein 1, is associated with energy expenditure and thermogenesis. Ugt2b34, or UDP Glucuronosyltransferase Family 2 Member B34, metabolizes various substances. Gm5639 represents another gene locus that might not have an assigned official name. The upregulation of these genes in PM2.5-inhaled mouse lung tissue suggests their potential involvement in the biological response to PM2.5 exposure. Further investigations are warranted to elucidate their specific roles and mechanisms in the context of PM2.5-induced lung effects.

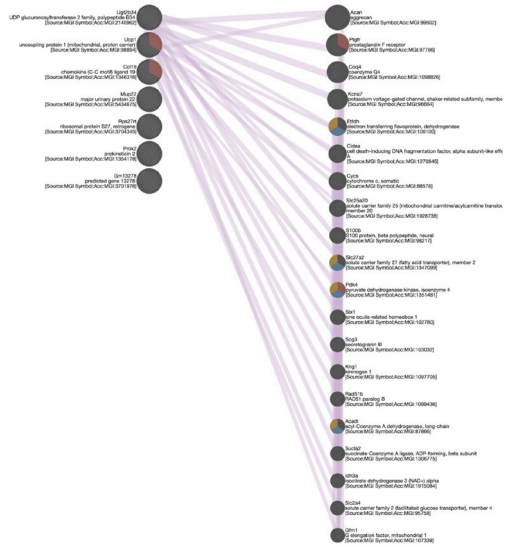

Figure 4: Gene network analysis results using upregulated genes in PM2.5-inhaled mouse lung tissue after three months of low-concentration exposure. Network analysis of upregulated genes reveals associations with fatty acid metabolism and oxidative stress responses, indicating that prolonged PM2.5 exposure affects metabolic and inflammatory processes in the lungs.

The functional prediction analysis using GeneMania revealed that upregulated genes in PM2.5-inhaled mouse lung tissue, after three months of low-concentration exposure, were prominently associated with functions related to fatty acid response, lipid oxidation, and fatty acid oxidation. Notably, the genes Ucp1 and Ccl19 are significantly associated with the reaction to fatty acids (Figure 4). These findings are consistent with previous studies that have reported the induction of the fatty acid pathway by PM2.5. The figure also suggests that Ptgfr was affected by PM2.5. This gene is linked with inflammation and urine contraction of the cell, which we can observe a correlation back to Figure 2 and Table 1. These results suggest that PM2.5 exposure elicits a specific response to fatty acid metabolism in the mouse lung. Further investigations are warranted to understand better the mechanistic links between PM2.5 exposure and fatty acid-related processes in the lung.

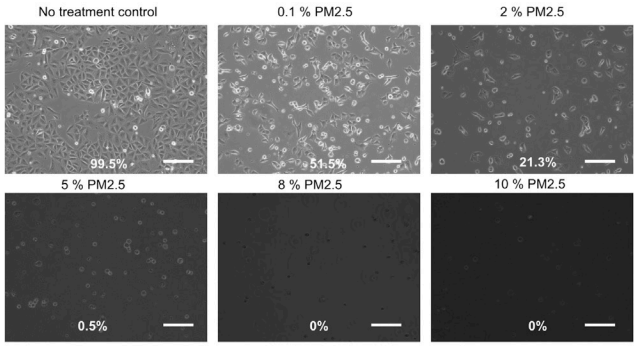

Figure 5: Effect of PM2.5 treatment on human lung cell morphology and viability MRC5. No treatment control, 0.1%, 2%, 5%, 8%, and 10% PM2.5 treated samples were analyzed. The cell viability is indicated at the bottom of the image. This figure illustrates the dose-dependent toxic effect of PM2.5 on lung cell viability and morphology, with higher PM2.5 concentrations significantly reducing cell survival and altering cell structure.

Next, our investigation revealed a clear concentration-dependent relationship between PM2.5 exposure and human lung cell viability. Without PM2.5 treatment (control), the cells exhibited normal morphology and maintained high viability. As the concentration of PM2.5 increased, alterations in cell morphology became evident. Furthermore, a notable reduction in cell viability was observed in samples treated with higher concentrations of PM2.5 (Figure 5).

The quantitative analysis of cell viability corroborated these observations. The control group exhibited a cell viability of 99.5%, indicating the live cells. In contrast, the cell viability progressively decreased with increasing PM2.5 concentrations: 0.1% (51.5%), 2% (21.3%), 5% (0.5%), 8% (0%), and 10% (0%). These results demonstrated a significant and concentration-dependent decline in cell viability upon exposure to PM2.5. For the downstream experiment, we selected 0.1% PM2.5 condition to find the upregulated genes in the human lung cells.

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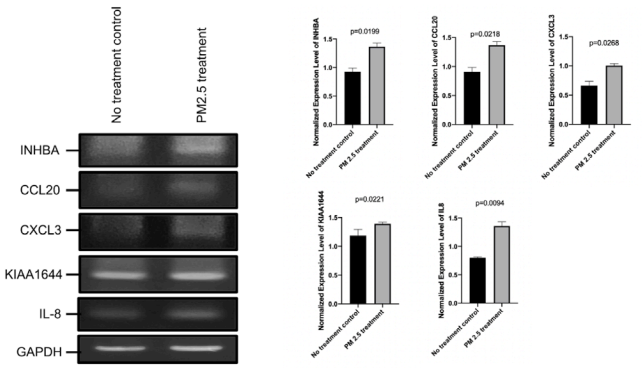

Figure 6: RT-PCR gene expression analysis reveals upregulation of five genes in lung cells treated with PM2.5 collected from South Korea: INHBA, CCL20, CXCL3, KIAA1644, IL-8. RT-PCR analysis confirms the upregulation of genes involved in inflammatory and immune responses in lung cells treated with PM2.5 from South Korea, highlighting the potential for shared molecular pathways triggered by particulate matter exposure from different regions.

Table 1 presents a list of ten genes identified as upregulated due to exposure to PM2.5 collected from China. To comprehensively explore the impact of particulate matter on gene expression, we conducted a parallel analysis utilizing PM2.5 samples collected from South Korea. Upon scrutinizing the Korean PM2.5 dataset, we tested the same gene set as in Table 1. Our investigation showed that five specific genes exhibited upregulation: INHBA, CCL20, CXCL3, KIAA1644, and IL-8 (Figure 6).

The identified genes—INHBA, CCL20, CXCL3, KIAA1644, and IL-8—are strongly associated with inflammatory processes, underscoring their pivotal role in regulating cellular responses to PM2.5 exposure. Their upregulation suggests a shared molecular mechanism linking PM2.5 exposure to the activation of inflammation-related pathways in lung cells. These genes likely contribute to PM2.5-induced inflammation through a network of cytokine signaling, chemokine-mediated immune cell recruitment, and cellular stress responses. Specifically, they are hypothesized to activate critical regulators of inflammation, including the nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, which drive the expression of inflammatory mediators and amplify the immune response. Collectively, these findings highlight the potential for these genes to mediate the adverse health effects of PM2.5 exposure, providing insights into therapeutic targets for mitigating air pollution-induced inflammation.

Our study adds a critical layer of understanding to the complex interplay between environmental pollutants and cellular responses by uncovering the conserved upregulation of inflammatory genes triggered by PM2.5 exposure. The identification of INHBA, CCL20, CXCL3, KIAA1644, and IL-8 as key players in PM2.5-induced inflammation provides a molecular foundation for exploring how fine particulate matter disrupts lung homeostasis. These genes are central to the activation of cytokine and chemokine pathways, suggesting they orchestrate immune cell recruitment, tissue remodeling, and inflammatory cascades. Their robust and consistent upregulation not only highlights their pivotal role in driving the inflammatory response but also positions them as promising therapeutic targets for mitigating the adverse health effects associated with air pollution.

Interestingly, this research also highlights a remarkable similarity in the effects induced by PM2.5 collected from South Korea and China. The conserved upregulation of these specific genes across different geographical origins of PM2.5 underscores the robustness and universality of the cellular response to particulate matter exposure. This observation further strengthens the notion of a shared mechanism of action, transcending geographical boundaries and reinforcing the significance of these genes in the context of PM2.5-induced inflammation.

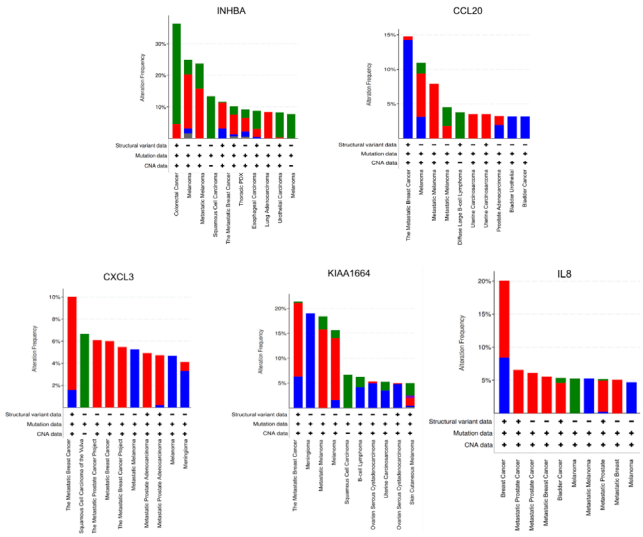

Figure 7: The upregulated five genes were associated with various alterations in human cancers. This figure demonstrates the frequent genetic alterations of five key upregulated genes across multiple cancers, suggesting that PM2.5 exposure may contribute to oncogenic pathways, particularly in lung and other cancer types.

Next, we analyzed the genetic changes in five genes—INHBA, CCLC20, CXCL3, KIAA1664, and IL8—related to human cancer. Our findings showed that these genes are frequently altered across various cancer types, such as lung cancer, breast cancer, colorectal cancer, prostate cancer, and melanoma (Figure 7). These results indicate that PM2.5 could potentially cause changes in these genes, leading to the development of other forms of human cancer.

Conclusion

Air pollution worldwide, PM2.5, threatens modern human health by causing various diseases and inflammatory responses. Current studies and efforts to minimize such deadly pollutants have been ineffective due to a lack of understanding of the apparent effect of PM2.5 on human health. To gain deeper insights into PM2.5, transcriptomic analyses were conducted using RNA-seq data from two studies involving human bronchial epithelial cells and mouse lung tissue exposed to PM2.5. Furthermore, this research focused on twenty upregulated and downregulated genes affected by PM2.5 collected in China. To comprehensively explore the impact of particulate matter

on gene expression, we conducted a parallel analysis utilizing PM2.5 samples collected from South Korea. The results suggested that PM2.5 upregulated five overlapping genes: NHBA, CCL20, CXCL3, KIAA1644, and IL-8. These genes showed close associations with inflammatory processes and cellular responses in lung cells, suggesting that PM2.5 directly affects molecular mechanisms in human biology.

To address the limitations mentioned in the conclusion of this study, we propose conducting experiments using multiple human lung cell types, including alveolar epithelial cells (A549) and bronchial epithelial cells (BEAS-2B), to validate the conserved upregulation of the five genes (INHBA, CCL20, CXCL3, KIAA1644, and IL-8) in response to PM2.5 exposure. Additionally, *in vivo* studies involving animal models, such as mice or rats, should be implemented to observe the systemic effects of PM2.5 exposure under controlled conditions. To better understand the chemical composition of PM2.5 from different geographical locations, comprehensive chemical profiling should be conducted using mass spectrometry and gas chromatography. This will enable the identification of specific toxicants or mutagens and their contribution to observed gene expression changes. Lastly, longitudinal studies assessing the chronic impact of low-dose PM2.5 exposure on inflammatory pathways and potential oncogenic mechanisms in vivo would provide insights into long-term health risks, bridging the gap between in vitro findings and real-world health outcomes.

Moreover, biological responses and effects induced by PM2.5 from China and South Korea showed remarkable similarities. The conserved upregulation of these specific genes across different geographical origins of PM2.5 underscores the robustness and universality of the cellular response to particulate matter exposure. Consequently, this research contributes to identifying potential therapeutic targets and strategies for mitigating the health risks associated with air pollution. However, this research was limited to only one type of human lung cell, thus requiring future research with various types of lung cells in the human body. Also, this research was not conducted from a living organism but in a lab culture cell model, which may differ in reality. Lastly, the particulate matters from China and Korea were not analyzed thoroughly. They might contain perfectly different toxins or mutagens, which should be considered in future research to effectively analyze the effects of PM2.5 on different geographical locations.

Acknowledgments

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Hyunsoo Kim is a rising high school junior attending Saint Paul Preparatory Seoul, Korea. He plans to major in biotechnology in the future. His inherent curiosity towards molecular and genetic biology has led him to experiment and research various biological processes.

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