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Predictive and Prognostic Biomarkers of Respiratory Diseases due to Particulate Matter Exposure

REVIEW

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Air pollution is getting severe and concerns about its toxicity effects on airway and lung disease are also increasing. Particulate matter (PM) is major component of air pollutant. It causes respiratory diseases, such as asthma, chronic obstructive pulmonary disease, lung cancer, and so on. PM particles enter the airway and lung by inhalation, causing damages to them. Especially, $PM_{2.5}$ can penetrate into the alveolus and pass to the systemic circulation. It can affect the cardiopulmonary system and cause cardiopulmonary disorders. In this review, we focused on PM-inducing toxicity mechanisms in the framework of oxidative stress, inflammation, and epigenetic changes. We also reviewed its correlation with respiratory diseases. In addition, we reviewed biomarkers related to PM-induced respiratory diseases. These biomarkers might be used for disease prediction and early diagnosis. With recent trend of using genomic analysis tools in the field of toxicogenomics, respiratory disease biomarkers associated with PM will be continuously investigated. Effective biomarkers derived from earlier studies and further studies might be utilized to reduce respiratory diseases.
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Key Words: Particulate matter, Biomarker, Oxidative stress, Inflammation, Epigenetic change

INTRODUCTION

In modern society, development of industry causes environmental pollutions, including air, water, and soil pollutions. Among them, the air pollution has been revealed to be one of the harmful factors affecting human health by various studies.[1-4] In accordance with World Health Organization (WHO) report, the exposure to air pollutant caused approximate 7 million of death in the world in 2012.[5] Air pollutants consist of carbon monoxide, volatile organic compounds, persistent free radicals, particulate matter (PM), and so on.[6] All these substances have some effects on human health. They especially induce lung and heart dysfunctions.

Among these major air pollutants, PM is the most harmful substance to human health by causing various diseases.[7,8] It is classified as a Group 1 carcinogen (induces carcinogenesis in human body) by International Agency for Research on Cancer. PM induces the premature death in people with heart or lung disease. It also induces nonfatal heart attacks, irregular heartbeat, aggravated asthma, decreased lung function, and increased respiratory symptoms, such as irritation of the airways, coughing, and difficulty breathing.

PM is a complex mixture of extremely small particles and liquid droplet in the atmosphere.[9] The complex mixture consists of organic carbon, ammonium, nitrates, sulphates, mineral dust, trace elements, and water. These substances exist as particles with diameters of less than 2.5 μm or less than 10 μm.[10,11] Particles with diameters of less than 2.5 μm are called $PM_{2.5}$ and those of less than 10 μm are called PM_{10}.[12] PM_{10} is composed of various dusts from sea salt, soil dust resuspension, construction/

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demolition, non-exhausted vehicle emissions, and industrial fugitives.[13] Sources of $PM_{2.5}$ are primarily emissions from natural event, such as forest fire, and industrial activities, such as mining and construction. Another sources of $PM_{2.5}$ are secondary particles converted from chemical or gas generated by industrial activities.[14] Heavy metals, such as Pb, Ni, Cd, Cr, V, Cu, and Mn, are well-known as hazardous substances. They are also sources of $PM_{2.5}$.[15]

Depending on its diameter, PM has detrimental effects on human. It has different transport efficiency and penetration ratio to the respiratory system.[16] PM_{10} leads to physical damage to the respiratory system, such as alveolus and larynx. It rarely induces chemical reaction to lung tissue.[16] It can reach alveolus or bronchioles but cannot penetrate alveolus. In contrast, $PM_{2.5}$ is able to penetrate into the alveolus and pass to the systemic circulation. It induces both physical and chemical damage to the respiratory system.[16] Therefore, $PM_{2.5}$ induces more serious damage to the lung than PM_{10}.

Respiratory system has physical contact with air pollutant by respiration. After being exposed to air pollutant such as PM, inhalation toxicity to the respiratory system might be occured. Numerous research studies have suggested that PM is associated with respiratory toxicity in in vitro, in vivo, and epidemiological studies.[17-21] PM can induce oxidative stress and inflammation on respiratory organ tissue.[22-25] It triggers the development and exacerbation of diverse diseases of the respiratory system, such as asthma,[26,27] chronic obstructive pulmonary disease (COPD),[28-30] and so on. Besides, PM can generate reactive oxygen species (ROS) and some oxidative metabolite, causing oxidative stress.[31] It damages DNA and causes epigenetic changes.[32,33] According to this reason, PM can eventually induce cancer (Fig. 1).[34]

Once lung is damaged by chemical such as PM, regeneration of lung to normal state is almost impossible. Thus, prediction and early diagnosis of lung diseases are important and imperatively necessary. Biomarkers can be used for disease prediction.[35] Various epigenetic biomarkers of lung diseases induced by PM exposure have been discovered in recent researches.[36,37] Epigenetic changes do not alter the DNA sequences. However, they can modify methylation or acetylation of DNA and histone protein, and then induces changes in DNA structure and gene expression. In this review, we focused on PM-inducing toxicity mechanisms in the framework of oxidative stress, inflammation, and epigenetic changes. We also reviewed its correlation with respiratory diseases (Fig. 1). In addition, we reviewed biomarkers related to PM-induced respiratory diseases. These biomarkers might be used for disease prediction and early diagnosis.

TOXIC EFFECTS OF PARTICULATE MATTER ON RESPIRATORY SYSTEM

1. Oxidative stress

Oxidative stress can be defined as damage resulting from imbalance of oxidation and reduction status of the body.[38] As a result of oxidation, ROS can react with other molecules. Organism has antioxidant defense system for maintaining the stability of redox homeostasis.[38] However, antioxidant system cannot overcome the effect of excessively produced ROS.[38] Excessive ROS has various detrimental effects on the body, including cell function impairment and cell death.[38] In human,

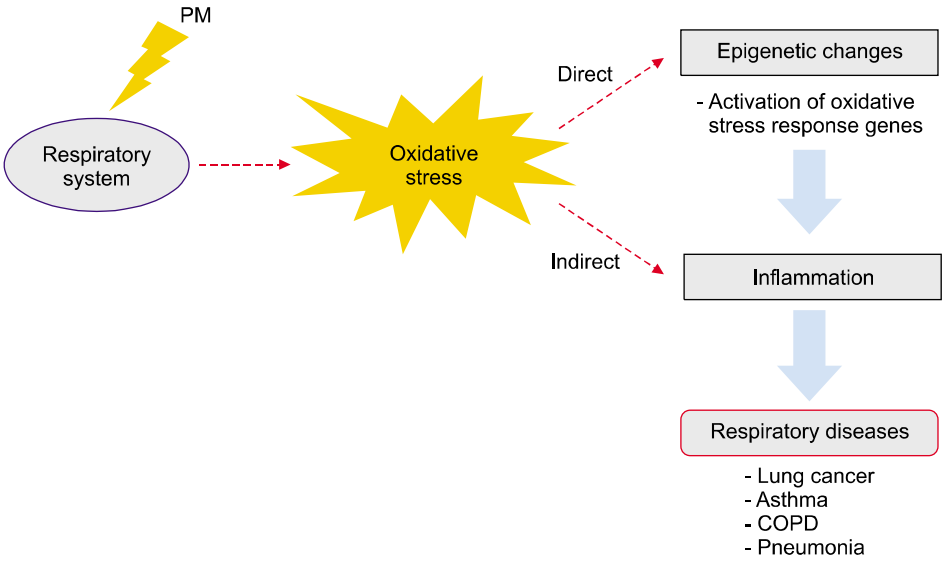

Figure 1. Schematic diagram of toxic effects of particulate matter (PM) on respiratory system. PM triggers oxidative stress in respiratory system, which induces epigenetic changes directly by activating oxidative stress response genes. Overproduced reactive oxygen species (ROS) and altered gene expressions can affect to inflammation indirectly as ROS stimulates signaling pathways. It contributes to development of respiratory diseases, such as asthma, chronic obstructive pulmonary disease (COPD), pneumonia, and lung cancer.

oxidative stress causes various diseases, such as cancers, neurological diseases, heart diseases, atherosclerosis, and pulmonary disease.[39,40]

It is well-known that PM induces oxidative stress in the lung. Because various chemicals and compounds, including PMs, can enter the airway directly, lung has a unique protecting system itself.[41] Higher glutathione (GSH) levels have been observed in alveolar epithelial surface (about 140 times higher than those of plasma).[42-44] GSH plays important role in protecting lungs against oxidative stress[45] by returning oxidized cell constituents to reduced form and by detoxifying lipid hyperoxides or other oxidants.[46] Thus, depletion of GSH is associated with disease development. Numerous studies have investigated the relationship between GSH level and disease development.[47-50] In addition, when there are high levels of oxidative stress in lung tissue, neutrophils will arrive and become activated, which can produce more ROS.[38] These over-produced ROS may cause oxidative stress, consequently leading to inflammatory response in the airway.

2. Inflammation

Inflammatory response is a process that react on tissues receiving harmful stimuli. It protects human body involving immune cells. It is activated when immune cells express pattern recognition receptor which binds to pathogen-associated molecular patterns, such as lipopolysaccharide.[51] Besides, other stimuli, such as cytokines, can bind to plasma membrane or stress signal and activate inflammatory response. A number of kinases are associated with inflammatory response.[52] Many studies have shown that inflammatory response is related to PM exposure.[53] It has been reported that bacteria-derived endotoxin bound to the surface of PM particle is one of the causative agent in PM-mediated lung injury.[54-56] As the major factor of PM induces lung toxicity, transition metal content of PM_{10} cause oxidative stress.[57,58] Fe and Cu are common chemicals inducing hydroxyl radical via Fenton reaction. When they are included in PM particles,[59,60] they can induce oxidative stress and cause inflammatory diseases.[61,62]

In a recent animal study, PM exposure has been demonstrated to cause early immune suppression in severe allergic response of adult mouse.[63] PM affects specific antigen tolerance when the level of immunoglobulin E is elevated. It also increases the risks of asthma. PM_{10} change can induce cell proliferation, leading to cancer development. In addition, chemokines and selectins induced by inflammatory response can be used by cancer cells and increase malignant effects. Although inflammatory response prevents cancer development in some case, inflammatory response by PM exposure can lead to lung cancer. Exposure to low concentration of PM induces inflammatory response and damage to lung tissues of healthy mouse.[64] In addition, when human lung epithelial cells are exposed to PM_{10}, pyruvate kinase related to carcinogenesis is up-regulated while annextin 1, an anti-inflammation response protein, is down-regulated.[53] $PM_{2.5}$ also induces inflammatory response as a result of oxidative stress caused by ROS. Oxidative stress changes the expression of proteins, such as NF-κB and interleukin (IL)-8 which are associated with inflammatory response.[65]

3. Epigenetic change

Epigenetic change means molecular change that regulates gene expression without changing DNA primary sequence.[66] Epigenetic change is related to diverse biological mechanisms through alterations in gene expression or mRNA degradation. Epigenetic change occurs frequently by environmental factors, such as aging and diet.[67,68] Recent studies have revealed that oxidative stress and redox status induced by PM regulates epigenetic changes, such as histone modification, methylation, acetylation, and chromatin remodeling.[69-71]

One of studies has shown that DNA methylation pattern in human is altered by exposure to traffic particles, such as PM and black carbon.[72] Exposure to $PM_{2.5}$ particles is associated with demethylation of long interspersed nucleotide element (LINE)-1.[72] In addition, in in vitro and in vivo studies, black carbon, diesel exhausted particles (DEPs), and metal components of air pollutant particles, such as arsenic and cadmium, also induce DNA methylation.[73,74] Several studies have suggested that histone modification is also induced by PM. For example, PM_{10} and DEP exposure have increased histone H4 acetylation at the IL-8 and COX-2 promoter in human lung and bronchial cells, respectively.[75,76] Moreover, short-term exposure to PM can induces epigenetic changes, specifically in the promoter region of mitogen-activated protein kinase pathway genes such as LINE-1.[71,72] These epigenetic changes might be associated with inflammation or increased oxidative stress.[71] Thus, oxidative stress, inflammation, and epigenetic changes are intimately connected. They play important roles in the development and acceleration of respiratory diseases.

RESPIRATORY DISEASE INDUCED BY PARTICULATE MATTER EXPOSURE

Various lung diseases, such as COPD, asthma, and lung cancer,

Table 1. Potential biomarkers of respiratory diseases induced by particulate matter

Gene name	Description	Related process	Related disease	Reference
CYP1A1	Cytochrome P450 family 1 subfamily A member 1	Oxidative stress Inflammation	Lung cancer Asthma	97
OGG1	8-oxoguanine DNA glycosylase	Oxidative stress Inflammation	Lung cancer Asthma COPD	88
IFNG	Interferon gamma	Oxidative stress Inflammation	Lung cancer Asthma COPD	97
TLR4	Toll-like receptor 4	Oxidative stress Inflammation	Lung cancer Asthma COPD	92
IL-13	Interleukin 13	Oxidative stress Inflammation	Lung cancer Asthma COPD	98
IL-10	Interleukin 10	Oxidative stress Inflammation	Lung cancer Asthma COPD	98
IL-4	Interleukin 4	Oxidative stress Inflammation	Lung cancer Asthma COPD	98
IL-13	Interleukin 13	Oxidative stress Inflammation	Lung cancer Asthma COPD	98
IL-6	Interleukin 6	Oxidative stress Inflammation	Lung cancer Asthma COPD	99
TNF	Tumor necrosis factor	Oxidative stress Inflammation	Lung cancer Asthma COPD	99
PDGFA	Platelet-derived growth factor subunit A	Oxidative stress Inflammation	Lung cancer Asthma	99
TGFB1	Transforming growth factor beta induced	Oxidative stress Inflammation	Lung cancer Asthma COPD	99
CSF2	Colony stimulating factor 2	Oxidative stress Inflammation	Lung cancer Asthma COPD	99
CXCL8	C-X-C motif chemokine ligand 8	Oxidative stress Inflammation	Lung cancer Asthma COPD	99
BMP4	Bone morphogenetic protein 4	Oxidative stress Inflammation	Lung cancer	100
SMAD6	SMAD family member 6	Inflammation		100
ID1	Inhibitor of DNA binding 1, HLH protein	Oxidative stress Inflammation	Lung cancer	100
ID2	Inhibitor of DNA binding 2, HLH protein		Lung cancer	100
GCLM	Glutamate-cysteine ligase modifier subunit	Oxidative stress Inflammation		100
HMOX1	Heme oxygenase 1	Oxidative stress Inflammation	Lung cancer Asthma COPD	100
SLC7A11	Solute carrier family 7 member 11	Oxidative stress Inflammation	Asthma	100
SQSTM1	Sequestosome 1	Oxidative stress Inflammation		100
SRXN1	Sulfiredoxin 1	Oxidative stress	COPD	100

Table 1. Continued

Gene name	Description	Related process	Related disease	Reference
STC2	Stanniocalcin 2	Oxidative stress	Lung cancer	100
DNM1L	Dynamin 1 like	Oxidative stress		101
FIS1	Fission, mitochondrial 1	Oxidative stress	COPD	101
MFN2	Mitofusin 2	Oxidative stress	Lung cancer	101
OPA1	Mitochondrial dynamin like GTPase	Oxidative stress		101

COPD, chronic obstructive pulmonary disease.

are related to PM exposure.[77-79] COPD is a progressive disease causing abnormal inflammatory response by harmful particles or gas. It can lead symptoms, such as constantly cough, shortness of breath, wheezing, and chest tightness.[80] When stable COPD patients are exposed to $PM_{2.5}$, the number of patients who progress to acute exacerbation of COPD (AECOPD) is increased.[7] It is caused by effects of $PM_{2.5}$ exposure, such as increased phagocytosis, oxidant stress, and pro-inflammatory cytokines. One of epidemiologic investigations performed at Cleaveland, OH has revealed that risk of AECOPD was increased according to the concentration of $PM_{2.5}$,[81] supporting the relationship between COPD and $PM_{2.5}$ exposure.

Asthma is a chronic illness that makes the airway sensitive and narrow. Symptoms of this disease are coughing, shortness of breath, chest tightness, and wheezing.[82] One study has suggested that increased exposure to PM_{10} and biological endotoxins are important factors in asthma pathogenesis.[83] PM_{10} induces pro-inflammatory response in lung tissue through toll-like receptor (TLR) pathway and affects NF-κB activation. It is probably one of the pathogenic factors of asthma. $PM_{2.5}$ is also associated with the pathogenesis of asthma.[84] Through meta-analysis using various database (PubMed, Ebsco, Ovid, and four Chinese), one study has shown that acute elevation of PM concentration in the air may increase hospital admission of Chinese children for asthma.[84] When the concentration of $PM_{2.5}$ is increased to 10 $\mu g/m^3$, the increment of hospital admission for asthma is nearly twice than that when the concentration of PM_{10} is increased to 10 $\mu g/m^3$.[84]

Lung cancer (also known as lung carcinoma) is one of the fatal cancers in worldwide. Lung cancer has two main types: small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC).[1] WHO announced that cancer caused 8.2 million deaths in 2012 and lung cancer caused 1.59 million deaths.[5] Among cancer deaths, lung cancer death had the highest number in 2012.[5] A number of studies have determined the factors that lead to lung cancer. Through various studies, the causes of lung cancer include tobacco, radon gas, asbestos, genetic source, PM, and so on. Although major cause of lung cancer is known as smoking, recent studies have revealed that exposure to PM also leads to lung cancer.[2,9] Lung cancer does not show initial symptom. Symptom of lung cancer is very similar to that of common cold. Thus, only a few patients are diagnosed of lung cancer at early stage. Most lung cancer patients are diagnosed after lung cancer has processed. As a result, untreated SCLC patients have a survival time of 6 to 17 weeks and treated SCLC patients have a survival periods of 40 to 70 weeks.[85] Their 5-year survival rate is lower than 10%. The 5-years survival rate of all lung cancer patients (including male and female SCLC and NSCLS patients) during 2006 to 2010 year in South Korea was 19.7%.[86] Therefore, it is important to prevent lung cancer to reduce mortality. Many clinical studies have reported the association between PM exposure and lung cancer occurrence. The concentrations of diverse compositions of PM have been measured by research staff at many cites. The long-term lung cancer occurrence rate and death rate are also recorded. Although detailed mechanisms of PM carcinogenic effect remain unclear, the relationship between PM and lung cancer is being studied by many institutions.

BIOMARKERS OF LUNG DISEASES CAUSED BY PARTICULATE MATTER

Genetic and epigenetic patterns associated with air pollutant, such as PM, might be useful biomarkers.[87] Some studies have shown that epigenetic change caused by PM exposure can lead to increased susceptibility to lung diseases, including cancer. Epigenetic changes alter the expression of diverse genes and the regulation of mRNAs. Through screening of epigenetic patterns, it is possible to predict disease development of respiratory system. For this reason, biomarkers can be used to detect long-term effects of PM exposure. They are very useful for the prediction or early detection of respiratory diseases. Up to date, numerous studies have suggested that biomarkers are associated with PM exposure (Table 1, Fig. 2).[88-93]

It has been reported that 8-oxo-2'-deoxyguanosine (8-OHdG) is

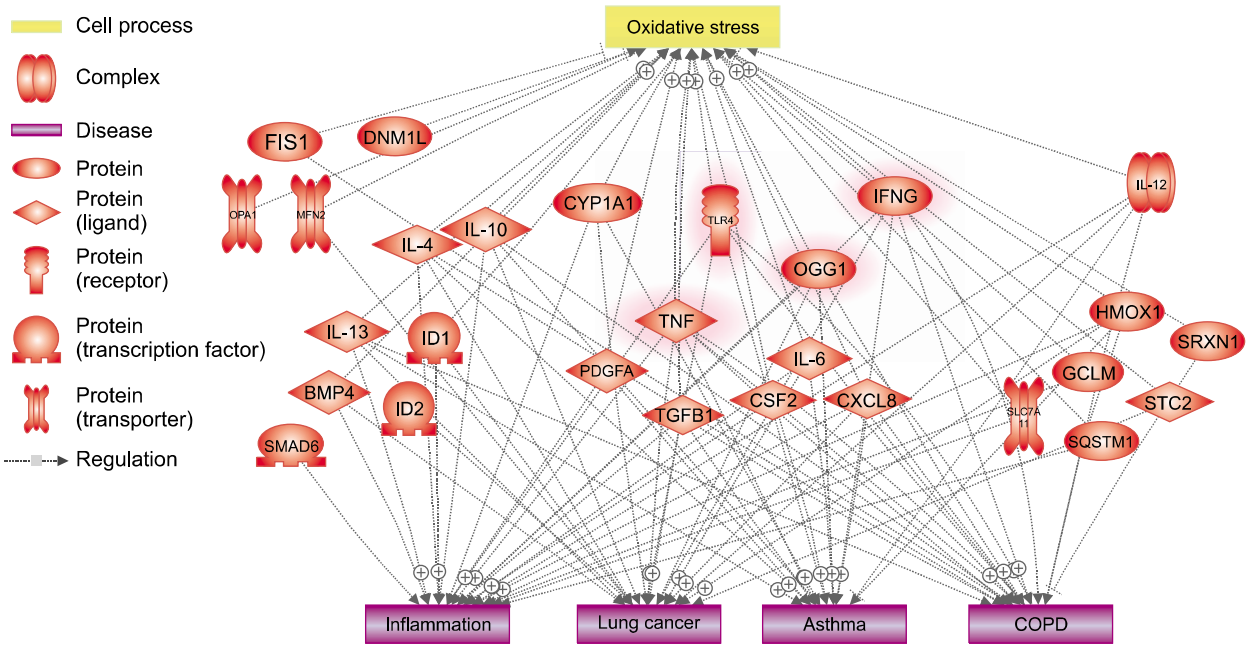

Figure 2. Related cell process and diseases with potential disease biomarkers induced by particulate matter visualized by Pathway Studio. Most of all proteins known as potential biomarker have relationship with oxidative stress and inflammation. Respiratory diseases also relates to diverse biomarkers. Highlighted proteins represents entire connection with cell process (oxidative stress) and diseases (inflammation, lung cancer, asthma, and COPD). FIS1, mitochondrial fission 1; DNM1L, dynamin 1 like; OPA1, mitochondrial dynamin like GTPase; MFN2, mitofusin 2; IL, interleukin; ID1, inhibitor of DNA binding 1, HLH protein; ID2, inhibitor of DNA binding 2, HLH protein; CYP1A1, cytochrome P450 family 1 subfamily A member 1; TLR4, toll-like receptor 4; IFNG, IFN gamma; OGG1, 8-oxoguanine DNA glycosylase; PDGFA, platelet-derived growth factor subunit A; TGFB1, transforming growth factor beta induced; CSF2, colony stimulating factor 2; CXCL8, C-X-C motif chemokine ligand 8; HMOX1, heme oxygenase 1; SRXN1, sulfiredoxin 1; GCLM, glutamate-cysteine ligase modifier subunit; SLC7A11, solute carrier family 7 member 11; STC2, stanniocalcin 2; SQSTM1, sequestosome 1; COPD, chronic obstructive pulmonary disease.

a biomarker of DNA damage.[88,94] 8-OHdG is one of several oxidative damage markers. It is induced by metal contents of PM, such as Fe, Cu, Ni, and Cd, in lung cells. Transition metals generates excessive ROS, which significantly increases oxidative stress.[95,96] Formatted 8-OHdG causes DNA damage and mediate the cytotoxicity and carcinogenicity.[88] LINE-1, one of oxidative damage-related markers, has been suggested as a gene expression and DNA methylation markers.[71,72,97] Other markers, such as *Arthrobacter luteus* restriction endonuclease (Alu) and TLR-4, also alters their gene expression levels in response to ambient particles.[97] In addition, 8-oxoguanine DNA glycosylase (OGG1) is regarded as a DNA methylation biomarker based on previous studies.[88] Takano et al.[98] have demonstrated that cytochrome P450 1A1 is induced by DEP exposure in the lung. Biomarkers are induced by acute inhalation exposure to DEP and may result in ROS generation, subsequently causing lung injury.[98] In field of toxicogenomics, global gene expression profiles have been well studied in diverse researches.[99,100] These studies provide important information on biomarkers which can be used to predict the development of lung diseases. Biomarkers might play important role in preventing disease occurrence.

CONCLUSION

PM air pollutant is well known to have harmful components in many studies. It has been demonstrated that respiratory diseases and cardiovascular diseases are associated with exposure to PM. PMs can trigger pulmonary pathogenic effect and cause pulmonary disease subsequently. Lung is a core organ of the respiratory system. Once lung is damaged, it is very hard to recover to normal pulmonary function.[101] COPD, asthma, and lung cancer, referred in this review as major pulmonary diseases, are all caused by PM exposure. Although diverse mechanisms are involved in PM-induced respiratory disease, there are three major mechanisms: induction of oxidative stress, inflammation, and epigenetic changes. Oxidative stress is a well-known cause of various diseases, especially cancer. PM induces oxidative stress in the lung by producing ROS which damages DNA and leads to apoptosis and other symptoms. In addition, oxidative stress may induces inflammatory injuries and epigenetic changes. There-

fore, these three mechanisms are connected to each other. Biomarkers of PM-induced diseases are based on these mechanisms. Recently, toxicogenomic studies are being performed very actively due to recent development of genomic analysis tools. With this highly advanced genomic tools such as NGS, the new studies for finding biomarkers of PM-induced diseases can be conducted. Through such studies, if the most effective biomarkers can be identified, they will be useful for the prediction of PM-induced diseases and early detection. Eventually, studies on biomarkers will contribute to the prevention of lung diseases.

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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