Review

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Genomic Approach to the Assessment of Adverse Effects of Particulate Matters on Skin Cancer and Other Disorders and Underlying Molecular Mechanisms

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Air pollutants are in the spotlight because the human body can easily be exposed to them. Among air pollutants, the particulate matter (PM) represents one of the most serious toxicants that can enter the human body through various exposure routes. PMs have various adverse effects and classified as severe carcinogen by International Agency for Research on Cancer. Their physical and chemical characteristics are distinguished by their size. In this review, we summarized the published information on the physicochemical characteristics and adverse effects of PMs on the skin, including carcinogenicity. Through comparisons of biological networks constructed from relationships discussed in the previous scientific publications, we show it is possible to predict skin cancers and other disorders from particle-size-specific signaling alterations of PM-responsive genes. Our review not only helps to grasp the biological association between ambient PMs and skin diseases including cancer, but also provides new approaches to interpret chemical-gene-disease associations regarding the adverse effects of these heterogeneous particles.

Key Words Air pollutants, Particulate matter, Skin diseases, Carcinogens, Toxicogenetics

INTRODUCTION

Studies of air pollution have been spotlighted for decades. Since air quality is highly critical to human life and health, research into air quality has been ongoing to promote living in fresh air conditions [1]. Many researchers have studied diseases that are induced by air pollutants, with focus on identification of related biological reactions in which they are involved. The rate of diseases caused by air pollution has increased every year, and these diseases can occur without distinction between indoor and outdoor pollution [2,3]. Among the airborne pollutants, particulate matter (PM) has been extensively investigated as the major toxic particles. PM is categorized in reference to its diameter (μm): PM_{10} and $PM_{2.5}$. Size differences of PM are derived from their sources of origin and are related to their components [4]. Because of these heterogeneous characteristics and their micro-scale size, PMs can expose living things through various routes, provoking diverse detrimental effects [5-7].

Investigations on different biological effects caused by different sizes of PMs have mainly focused on the cardiovascular and respiratory diseases [8,9]. The micro-scale size of PM allows for penetration through the skin or vascular system, subsequently leading to adverse effects in the internal organs [10]. Furthermore, recent studies demonstrated the physical damage to the skin caused by particle penetration [11]. Accordingly, the adverse effects on skin resulting from PM exposure has become an important issue, but the underlying mechanistic signaling alterations of PM-induced skin disorders are not fully understood.

The carcinogenic effects of PMs represent a serious toxicological issue. Based on significant cancer incidence and mortality data from epidemiological studies [12,13], pathogenic mechanisms underlying the cancerous effects of PM on the respiratory system are actively being studied using in vivo and in vitro experiments [14,15]. Based on sufficient evidence

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for the cancerous effects of PM, the International Agency for Research on Cancer of the World Health Organization classified PM as a Group 1 carcinogen [16]. However, there is still a lack of knowledge on its carcinogenic effects on skin; an indirect etiological association between skin cancer incidence and carcinogenic PM components, such as black carbon and polycyclic aromatic hydrocarbons (PAHs), has been suggested [17,18], although insufficient experimental details have been reported.

In this review, we summarized the physical and chemical properties of PM_{10} and $PM_{2.5}$, and the biological adverse effects on skin. By screening the scientific literature using a text-mining algorithm, we explored the biological relationships between skin disorders and various sized PM in terms of gene-gene and gene-disease networks. This review presents not only the existing knowledge of PM-induced skin disorders, but also supplements the detailed comparative biological association between PM and skin disorders even including cancer with information about the differences between PM_{10} and $PM_{2.5}$.

DIFFERENCES IN THE PHYSICAL AND CHEMICAL CHARACTERISTICS OF PM

On April 14, 2020, the United States Environmental Protection Agency proposed revised National Ambient Air Quality Standards for PMs with different standards for different particle types [19]. They are continuously reviewing and updating the standards about things considered harmful to the public health and the environment. PM shows a wide spectrum of differences depending on their characteristics, especially their size and ambient areas. PM is a mixture of heterogeneous molecules. It forms a mixture of solid particles and liquid droplets consisting of various organic or inorganic particles with various micrometer sizes [20]. This complexity should be considered importantly in identifying its real toxicity and preparing regulatory standards for PM, because there is a lack of sufficient knowledge on the vast differences resulting from variances of particle characteristics as well as chemical or physical interactions among the co-existing multiple molecules.

PM_{10} has an aerodynamic diameter of less than 10 μm. Their main components are soil dust, ash, several metal oxides, and biological components (pollen, plant parts, and microorganisms) derived from natural sources. They can float for minutes to hours and can move through the air from 1 to 10 km, and mostly cause allergic or immune responses when inhaled. Silicon, aluminum, potassium, sodium, and calcium are road dust derived from pavement abrasion, and the human body can be exposed to them when they form metal oxides in the PM_{10} [21,22]. Oxide metal ions on the particle surface can lead to forced ion transitions of cell membranes and imbalances of reactive oxygen species (ROS) in the cells [23].

PMs that have a less than 2.5 μm of aerodynamic diameter are categorized as $PM_{2.5}$. The main components of $PM_{2.5}$ are sulfate, nitrate, ammonium, polyaromatic hydrocarbons (PAHs), organic compounds, and several heavy metals, which tend to be generated by industrial activities such as manufacturing processes in factories and solid fuel combustion. It can remain airborne for days to weeks and can widely spread from 100 to 1,000 km, and this means they can easily float in the air for a long period until finally reach human bodies. Micro-sized heavy metals such as copper, antimony, lead, and cadmium are major toxic components of $PM_{2.5}$ [21,22]. They accumulate in human organs and can trigger chronic illnesses; they can easily be inhaled into the respiratory system and come into contact with the skin [24]. Furthermore, the organic components, including PAHs and their oxygenated derivatives, cause mitochondrial malfunction with excessive ROS generation in the cells [25]. Indeed, most of the organic or inorganic components of $PM_{2.5}$ are derived from chemical reactions and their derivatives [26]. Along with a strong penetrating level of $PM_{2.5}$ due to their smaller particle size, researchers have suggested that $PM_{2.5}$ has higher toxicity than PM_{10} in human organs [27,28].

Diverse epidemiology studies have suggested that PM components and their size distribution are flexible and variable based on regional and seasonal factors [21,29,30]. Zhang et al. [31] collected PM_{10} and $PM_{2.5}$ in the Beijing area and conducted a pulmonary toxicity study using Wister rats. They confirmed the differences in components distribution between PM_{10} and $PM_{2.5}$ through element analysis, and the Wister rats treated with PMs demonstrated increased levels of inflammation biomarkers including interleukin (IL)-1, IL-6, and TNF-α, and also increased DNA damage in lung cells. Experimental studies using human bronchial epithelial cells reported seasonal differences in PM components, and different particle sizes were significantly related to different changes in the expression of lung cancer marker proteins [32-34]: KRAS oncoprotein, PTEN, and tumor suppressor p53 (TP53) showed dose- and time-dependent activation under chronic $PM_{2.5}$ exposure [35].

The above knowledge revealed the importance of considering each characteristic of PM_{10} and $PM_{2.5}$ in studying their adverse effects. Evidence of the different biological activity of PM_{10} and $PM_{2.5}$ has already been discussed [36]; accordingly, comparisons between particle types of PM are actively being made by in vitro and in vivo studies. In most cases of respiratory system-based experimental studies, $PM_{2.5}$ is responsible for PM-induced oxidative stress, DNA damage, and excessive activation of inflammatory mediators [37-39]. The carcinogenic risk of PM is also variable depending on the particle size. Compared with PM_{10}, $PM_{2.5}$ is generally considered to confer a higher risk of respiratory cancer because of the smaller particle size, which can, therefore, more easily penetrate tissue [12,35,40]. However, compared with the knowledge on respiratory toxicity, a complete understanding of the adverse dermatological effects of PM is still lacking,

even though skin is also frequently in contact with ambient pollutants, possibly even more so than the respiratory tract.

THE ADVERSE EFFECTS OF PM ON SKIN

In recent years, detrimental health effects caused by PM exposure have become a serious worldwide issue. Through numerous approaches, researchers and government officers demonstrated adverse effects caused by PMs and utilized this information for establishing regulatory standards, and proposed the toxicity reports of their health risk [41]. The strong association between PM exposure and adverse health effects was established by showing the accumulated damage of various cells and tissues in human organs, especially the respiratory and cardiovascular systems [42-44]. However, skin toxicity and carcinogenicity due to ambient PM have been less understood than the respiratory system response.

Skin comprises the largest surface area of the human body and it functions as a barrier for protection from the external environment. Frequent contact with extrinsic harmful substances stimulates the defense systems of the skin, including dynamic responses of the immune system. These effects occurring in the epidermis, dermis, and deeper subcutaneous layer have been studied as the first-line physical response caused by contact with toxicants via skin absorption [45]. Biological effects of particles in multilayer structures are dependent on their ability to penetrate through tissue layers, and this knowledge is important to interpret how the differences in particle characteristics of PM contribute to their different harmful effects and their ability to disrupt cell signal functions [46].

Although the particle type distribution and the concentration of PM vary depending on the weather and location, phenomenological associations between the increase in levels of airborne PMs and the diagnosis frequency of skin diseases have been commonly reported in epidemiological studies. Exposure to PM, which results in increased oxidative stress and pro-inflammatory cytokines, is known to cause common inflammatory skin disorders, such as atopic dermatitis, acne, and psoriasis [47-49]. Despite geological and seasonal differences among the countries involved in the research, statistical associations between PM exposure and skin disorders are commonly reported for PM_{10} and $PM_{2.5}$ [50] and are difficult to discuss separately. Epidemiologic study has provided a comprehensive scope of the associations between PM and skin diseases based on statistical interpretations, but it is hard to demonstrate a link between pollution-mediated skin damage and specific characteristics of the ambient PM fraction.

PM-mediated adverse effects on skin have also been assessed in in vivo and in vitro studies. Electron microscopy analysis showed that PMs were able to penetrate the skin tissue [10], and the apoptotic process appeared in the reconstructed human epidermis model in response to treatment with PM [51]. Also, PMs treated to porcine skin had a detrimental effect on the skin barriers, allowing greater amounts of test substances to permeate the skin sample [52]. The micro-size PMs penetrate the skin, breaking down the skin barrier and causing a cutaneous inflammatory response, which results in various skin disorders [11]. Several studies using human keratinocytes (HaCaT) found excessive inflammation, oxidative stress, and apoptosis in cells exposed to PM_{10} and $PM_{2.5}$, which may drive keratinocyte dysfunction [53,54]. In a human epidermis mimicry model study, $PM_{2.5}$ penetration caused skin damage with ROS production and NF-κB-mediated inflammatory responses [51]. Based on the above findings, ROS-mediated inflammatory responses are thought to be major reasons for PM-induced skin damage, but the evidence is still insufficient to demonstrate the underlying mechanisms and, moreover, the differences between the effects of $PM_{2.5}$ and PM_{10} are unclear.

The risk of skin cancer from PM exposure is also not fully understood. Approximate correlations between increased ambient concentrations of PM and diagnoses of skin cancer have been observed in epidemiological studies, but opinions are inconsistent on whether PM_{10} or $PM_{2.5}$ is more carcinogenic. Although there are no clear significant associations between PM_{10} and skin cancer incidences in epidemiological studies, several indirect inferences have been suggested from in vitro studies evaluating PM_{10}-induced cytotoxicity in human dermal fibroblasts, including accumulated autophagy and proinflammatory effects [55]. According to several cohort studies, there is a positive correlation between urban $PM_{2.5}$ exposure and the incidence of skin cancers, including melanoma [11,56,57]. A study using HaCaT cells also reported a risk of cancer from $PM_{2.5}$ exposure with increasing apoptosis and interleukin-mediated inflammatory responses [58]. Despite the efforts described above, research on PM-induced skin carcinogenicity has produced fragmentary descriptions of the mechanisms involved compared with studies on the respiratory system. Almost all risk factors are based on the cancerous effects of the hazardous components of $PM_{2.5}$, including black carbon and PAHs [59,60], or on the stimulation of cytotoxic signals that leads to carcinogenesis. Severe levels of ROS production and pro-inflammatory cytokine secretion are actively discussed as major promoters of skin cancer [61,62], and have been demonstrated to occur upon PM exposure in other experimental studies. However, the studies neither cover the oncological aspects nor distinguish between the numerous species of skin cancer, which makes it difficult to clarify any differences between PM_{10} and $PM_{2.5}$.

To overcome the above limitations in the interpretation of differences between the adverse effects of PM_{10} and $PM_{2.5}$ on skin, we utilized a new approach using transcriptomic profiles related to PM. By screening relationships among the PM-responsive gene lists based on the literature information, we reviewed the predicted biological alterations of skin by PM. As the physical and chemical properties of PMs vary with size,

comparing PM_{10} and $PM_{2.5}$ may provide helpful information on how each size of PM contributes to adverse skin effects, including cancer.

COMPARISON OF PM_{10} & $PM_{2.5}$ IN TERMS OF BIOLOGICAL PATHWAY ALTERATIONS

Although diverse studies have focused on the adverse effects of PM in skin at a visible level, relevant interactions among biomolecules and the subsequent alterations of biological pathways are not clearly understood. In the present study, we suggest differences of PM_{10} and $PM_{2.5}$ in their contribution to pathogenesis of skin cancers and other disorders, in terms of the biological networks among genomic data, according to information in the scientific literature. Our approach allows for interpreting the alteration of various cellular processes of diseases in response to certain experimental changes.

We collected a set of genes associated with PM_{10} and $PM_{2.5}$ from studies that identified the alterations of gene expression after exposure to a particular PM. The overlapping genes of PM_{10} and $PM_{2.5}$ were excluded from the network configuration to compare the differences. The gene subsets of each PM size-relevant gene set were separately used to create molecular signaling networks. Literature-based software Pathway Studio web 12.3.0.16 (Elsevier) was utilized to present the biological networks among the identified genes. Pathway studio is a text-mining based pathway analysis software that contains a curated database with their own text-mining module. Pathway Studio navigates biological information such as information about of genetic interactions, cellular processes, and diseases referring to relevant sentences from the literature databases.

We used PM_{10} associated 200 genes and $PM_{2.5}$ associated 696 genes to explore the networks related to the skin system from PM exposure along with cellular process and disease information. We found biological information on association between genes, cellular processes, and diseases by the curated network analysis results based on the number of references ≥ 10. According to the constructed network of PM_{10} associated genes in terms of the skin system, 41 genes known as skin disease-related, including TP53 and VEGFA, were used to construct a network among the gene-gene interactions, diseases, and cellular processes (Fig. 1A) [63-65]. In the $PM_{2.5}$ related molecular signaling network, the biological network of skin system-related 53 genes, including EGF receptor (EGFR) and jun proto-oncogene (JUN), known as skin disease- and cancer-related genes, was constructed (Fig. 1B) [66-68]. These genes are the main components that make up the network, highlighting skin diseases that can occur due to changes in expression during skin exposure to PMs. It was associated with cellular processes such as 'epithelization' and 're-epithelialization' in skin, which means that expression changes of related genes may weaken the protection and recovery function of the skin in both networks [69,70]. In addition, the biological network among PM-related genes showed associations with alteration of the skin barrier and morphological structures [52,71,72]. These networks also provide predicted diseases from the PM-related genes. Among diseases predicted by the molecular signaling networks, 'dermatitis', 'psoriasis', and several skin cancers have been shown to be important diseases in both the PM_{10} and $PM_{2.5}$ associated genetic networks (Fig. 1) [73,74].

To interpret the potential comprehensive key networks and to clarify differences between PM_{10} and $PM_{2.5}$, we selected the major elements considered as the centrality of the network components from the analyzed pathways of PM_{10} and $PM_{2.5}$. By sorting the major regulators in Figure 1 using the classified network components, we constructed their hub pathways (Fig. 2). According to the PM-related hub pathways reconstructed using key regulators, the PM_{10} specific molecular signaling network was identified from the information of interactions among key genes, such as TP53, VEGFA, fibronectin 1, colony stimulating factor 2, and peroxisome proliferator activated receptor gamma, cellular process and disease. We found a correlation between the TP53 gene and skin pigmentation in the network of PM_{10}. Box and Terzian [75] mentioned the role of TP53 in skin pigmentation. In the $PM_{2.5}$ specific molecular signaling network, the information of biological interactions among EGFR, JUN, fibroblast growth factor 2, CC motif chemokine ligand 2, and the intercellular adhesion molecule 1 (ICAM1) gene were identified. We could find an association between the 5 key regulators and the various skin diseases and skin cancer in numerous studies [66,76,77]. We also found a correlation between ICAM1 and skin barrier function and dermatitis. Matsunaga et al. [78] mentioned that the expression of ICAM1 was associated with epidermal barrier function, and that the expression of ICAM1 was not checked in atopic dermatitis. Figure 3 shows final summary of main genes, cellular processes, and diseases into the hub pathway from Figure 2. It provided a scheme to find out how the adverse effects on the skin differ by the size of the naturally occurring PM_{10} and the artificially occurring $PM_{2.5}$ in the air.

Diverse studies on the respiratory system show that $PM_{2.5}$ has stronger carcinogenic effects than PM_{10}. However, our skin-focused screening suggests that PM_{10}, as well as $PM_{2.5}$, significantly correlates with several skin cancers. As we reviewed in a previous section, the cancerous effects and detailed mechanisms of PM toxicity on skin are poorly understood compared with the effects on the respiratory system. Further validation is required to clarify whether the biological associations predicted in this review are specific to the skin or are due to bias by the data screening algorithm. In fact, our network-based literature review is based on relationships mentioned in the existing scientific literature. Therefore, experimental mechanism studies will be required to verify our findings, which indicate differences between the PM_{10}- and $PM_{2.5}$-induced alterations of intracellular signaling pathways

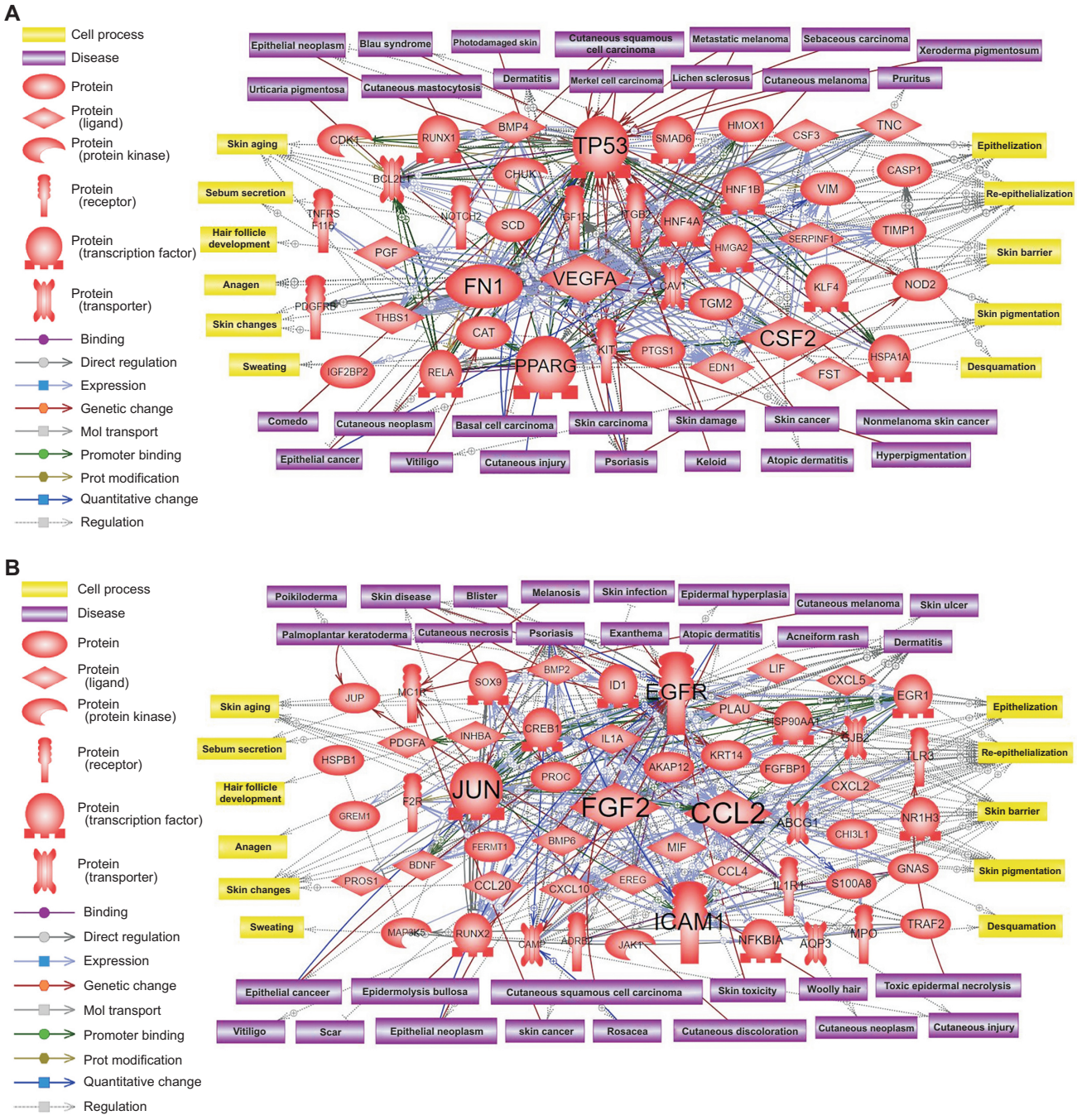

Figure 1. Potential biological signaling networks related to PM_{10} & $PM_{2.5}$ exposure inducing skin-related cellular processes and diseases. Molecular signaling network results using collected PM associated genes. Pathway Studio software was utilized to analyze the biological signaling networks. (A) Analysis of the PM_{10} related genes, and (B) analysis of the $PM_{2.5}$ related genes for understanding how the biological reaction from exposure to PM_{10} & $PM_{2.5}$ affects related cellular processes and diseases. Large-sized entities indicate key genes in the networks regarding their connectivity with the surrounding entities. Schematic legends are located on the left side of each pathway. CDK, cyclin-dependent kinase; TNFRS, TNF receptors; PDGFR, platelet-derived growth factor receptors; PGF, placental growth factor; IGF, insulin like growth factor 1; THBS1, thrombospondin 1; PPARG, peroxisome proliferator activated receptor gamma; FN1, fibronectin 1; CSF2, colony stimulating factor 2; JUN, jun proto-oncogene; FGF2, fibroblast growth factor 2; CCL2, CC motif chemokine ligand 2; ICAM1, intercellular adhesion molecule 1.

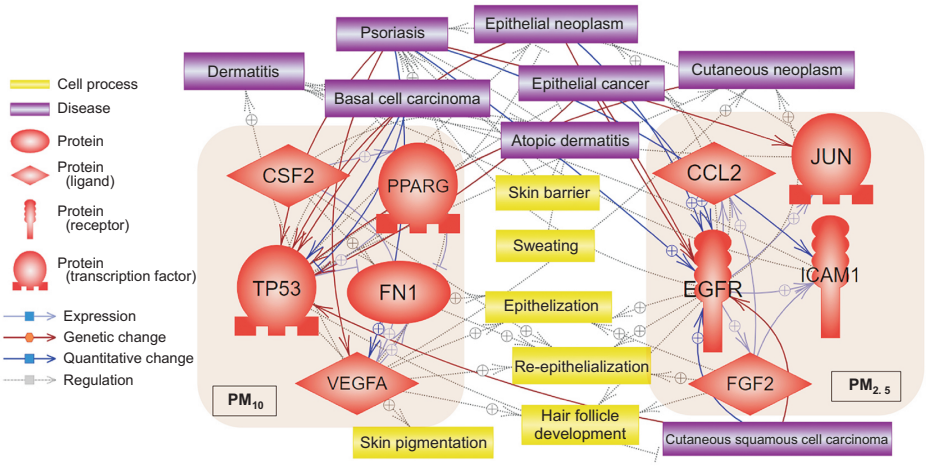

Figure 2. Hub potential biological signaling network with key regulators and related signaling pathways. Key regulators with expression changes due to PM_{10} & $PM_{2.5}$ exposure and associated molecular signaling networks have biological effects related to each size, while the same effects differ in related genes. CSF2, colony stimulating factor 2; TP53, tumor protein p53; PPARG, peroxisome proliferator activated receptor gamma; FN1, fibronectin 1; CCL2, CC motif chemokine ligand 2; EGFR, EGF receptor; FGF2, fibroblast growth factor 2; JUN, jun proto-oncogene; ICAM1, intercellular adhesion molecule 1; VEGFA, vascular endothelial growth factor A.

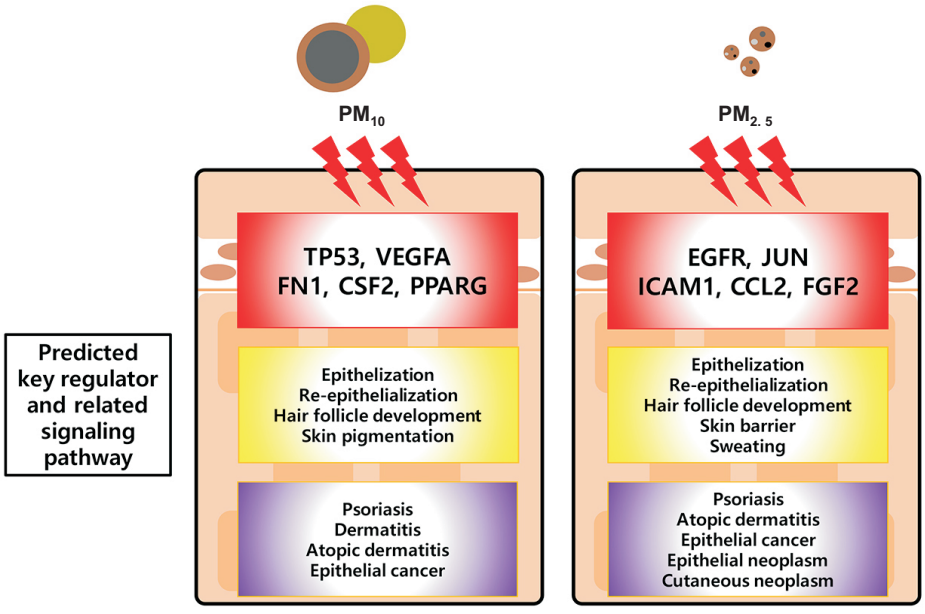

Figure 3. Summary of effects of PM_{10} and $PM_{2.5}$ exposure on skin. The scheme illustrates the associated biological signaling pathways followed by expression changes of the key regulators expected during skin exposure to PM_{10} & $PM_{2.5}$. This model provides the potential biological mechanisms differentiated by exposure and size of PMs. TP53, tumor protein p53; FN1, fibronectin 1; CSF2, colony stimulating factor 2; PPARG, peroxisome proliferator activated receptor gamma; EGFR, EGF receptor; JUN, jun proto-oncogene; ICAM1, intercellular adhesion molecule 1; CCL2, CC motif chemokine ligand 2; FGF2, fibroblast growth factor 2; VEGFA, vascular endothelial growth factor A.

that lead to adverse effects on the skin.

CONCLUSION

PMs are composed of micro-sized heterogeneous particles that have various organic and inorganic components. Harmful effects derived from human PM exposure is a worldwide issue, but the mechanisms underlying its skin toxicity remain unclear, especially in relation to the PM size. Here, we introduced the characteristics of PM, discussed their adverse effects on skin, and attempted to compare the underlying signaling alterations by PM_{10} and $PM_{2.5}$ associated with skin cancer and other disorders. Although the related gene lists are different, the predicted cellular processes and diseases from gene-gene interaction were similar in each PM size. A significant relationship with skin cancer was predicted for both the PM_{10}- and $PM_{2.5}$-related pathways. Further validation studies will be required to demonstrate the exact pathway, but our review with simple genomic approaches can help clarify the skin-related biological alterations caused by PM exposure, as well as provide evidence for a genomic-based outline to screen for the biological relationships between chemicals and diseases.

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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