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PII: S0024-3205(16)30188-6
DOI: doi: 10.1016/j.lfs.2016.03.039
Reference: LFS 14822

To appear in: *Life Sciences*

Received date: 28 August 2015
Revised date: 9 March 2016
Accepted date: 21 March 2016

Please cite this article as: Kim Kyung Eun, Cho Daeho, Park Hyun Jeong, Air pollution and skin diseases: Adverse effects of airborne particulate matter on various skin diseases, *Life Sciences* (2016), doi: 10.1016/j.lfs.2016.03.039

Air pollution and Skin diseases:

Adverse effects of airborne particulate matter on various skin diseases

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Abstract

Environmental air pollution encompasses various particulate matters (PM). The increased ambient PM from industrialization and urbanization is highly associated with morbidity and mortality worldwide, presenting one of the most severe environmental pollution problems. This article focuses on the correlation between PM and skin diseases, along with related immunological mechanisms. Recent epidemiological studies on the cutaneous impacts of PM showed that PM affects the development and exacerbation of skin diseases. PM induces oxidative stress via production of reactive oxygen species and secretion of pro-inflammatory cytokines such as TNF-α, IL-1α, and IL-8. In addition, the increased production of ROS such as superoxide and hydroxyl radical by PM exposure increases MMPs including MMP-1, MMP-2, and MMP-9, resulting in the degradation of collagen. These processes lead to the increased inflammatory skin diseases and skin aging. In addition, environmental cigarette smoke, which is well known as an oxidizing agent, is closely related with androgenetic alopecia (AGA). Also, ultrafine particles (UFP) including black carbon and polycyclic aromatic hydrocarbons (PAHs) enhance the incidence of skin cancer. Overall, increased PM levels are highly associated with the development of various skin diseases via the regulation of oxidative stress and inflammatory cytokines. Therefore, anti-oxidant and anti-inflammatory drugs may be useful for treating PM-induced skin diseases.

Key words: Particulate matter; Inflammatory skin diseases; Aging; Alopecia; Skin cancer, Oxidative stress, Pro-inflammatory cytokine

1. Introduction

Particulate matter (PM), which is including the harmful suspended contaminants in the air, is generally encompassed in air pollution [65,27]. The airborne PM is a complex mixture including particulate contaminants (smog, tobacco smoke, soot, etc.), various types of dust, biological contaminants (pollen, house dust mite allergens, etc.), and gaseous contaminants (exhaust gas from traffic or hood, etc.). It comprises sulfates, nitrates, and carbon compounds in the atmosphere [65,27]. As a result of rapid industrialization and urbanization, environmental pollution is becoming a severe public problem worldwide. In particular, airborne PM in the ambient atmosphere is highly associated with the incidence of respiratory and cardiovascular diseases and with increased mortality [39,10,87]. The World Health Organization (WHO; Fact Sheet N 313, 2014) has established that premature death by air pollution occurs with cardiovascular diseases, respiratory diseases, and lung cancer at rates of 80%, 14%, and 6%, respectively. The ambient PM is the most intimate element of the human health impacts. Recent increased PM concentration in the air pollution is correlated with the increased mortality and morbidity. It affects human health even at low concentration. Due to the significant impacts of small PM, WHO has suggested guideline for limited concentration of PM. PM10 must not exceed 20 $\mu g/m^3$ (annual mean) and 50 $\mu g/m^3$ (24-hour mean). In the case of PM2.5, the mean of concentration must not exceed 10 $\mu g/m^3$ per year and 25 $\mu g/m^3$ for 24 hours.

Airborne PM is classified as particulate matter, fine particulate matter, and ultrafine particles depending on the aerodynamic diameter of particles. Particles that are less than 10 μm are called the particulate matter (PM10) and are inhalable. PM10 is composed of inhalable particles from dusts, industrial emissions, and traffic emissions [27]. Inhalation of PM10 is highly related to various respiratory diseases. Infiltration of PM10 into the lungs results in systemic immune responses, including enhanced lung inflammation due to increasing various pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1) from lung epithelial cells and macrophages. The lung inflammations cause various diseases of the lung and other inflammation-related conditions [29,27].

In the 1990s, a smaller PM particle size (less than 2.5 μm) was discovered and defined as fine PM (PM2.5). Fine PM is primarily comprised of organic carbon compounds, nitrates, and sulfates [17,95]. Ambient PM2.5 is increasingly present in the surrounding air and is significantly associated with human health and especially respiratory tract diseases because PM2.5 can reach bronchial tubes and deep lung. In addition, PM2.5 is associated with the exacerbation of cardiovascular diseases and systemic inflammation [24,16,80]. A cohort study in which participants were followed for decades has discovered that compared with larger particles, smaller particles like PM2.5 have much more adverse effects on human health [23].

Recently, ultrafine particles (UFPs) have been found in abundance in urban air and defined as a new particle type. UFPs are less than 100 nm in diameter and have greater potential for adverse effects to human health than PM2.5, because UFPs can penetrate into the blood stream and accumulate in the lung and other organs of the body [23,28]. As well as the size, the composition of UFPs is also important with regard to its impact on human health. Both indoor and outdoor UFPs are primarily from cigarette smoke, engines, cooking fumes, and industry. The most important sources of UFP are vehicular exhausts, especially diesel exhaust that includes black carbon, which contains large amounts of UFP [38] and is defined as a class one carcinogen by WHO. UFP, the smallest PM, result in chronic obstructive pulmonary disease (COPD) and asthma through their deposition in the lungs without the filtration through the nasal mucosa [3].

Although PM is divided into three different types based on the mean of aerodynamic diameter, PM10 generally includes all fractions of PM10, PM2.5, and UFPs [27]. Deposition by inhalation is primarily in the upper respiratory tract (head and comparatively large conducting airway), lower respiratory tract (larynx, small airway, and alveoli), and deep lung (alveoli) for PM10, PM2.5, and UFPs, respectively [27]. These three categorized particulate matters are globally implicated in severe environmental pollution due to significant increases in urbanization and industrialization processes. Given the growing concern about environmental pollution, we have chosen to discuss how PM air pollution affects various diseases, and especially skin diseases.

2. Review

Skin is the largest organ in body, and acts as the first and most important defense barrier against environmental contaminants. Skin is always exposed to the contaminants, and various industrial chemicals can be absorbed into the skin. These absorbed compounds can cause local toxicity in the skin and systemic toxicity in other organs, although it may enter by percutaneous penetration. The severity of these toxicities depends on the age and medical history of skin diseases. Percutaneous penetration is significantly related with the integrity of the barrier, anatomic site, age, and properties of the contaminants. Therefore, children and patients with impaired skin barriers are easily affected by dermal exposure due to the increased absorption [88]. Skin consists of three main layers: epidermis, dermis, and hypodermis. The stratum corneum of the epidermis is the outermost skin layer, acting as the main functional barrier. A "brick and mortar" model describes pathways for skin penetration across the stratum corneum. According to the arrangement of the corneocytes, which are nonviable keratinocytes, there are four pathways for skin penetration, including mechanical delivery, an intracellular route, a transcellular route, and a transfollicular route [56,9]. Skin has numerous pores, which are decidedly larger than PM, there is no direct evidence that PM can penetrate into skin regardless of smaller size. However, it is undoubtedly reported that the particles can penetrate skin though hair follicles depending on their size, indicating the penetration of PM through transfollicular route [47]. Hair follicles interrupt the functions of stratum corneum barrier through the formation of intrusions in the stratum corneum, thus providing a route for penetration. In addition, chemical compounds are accumulated in the orifice of hair follicles. Because the hair follicles on the scalp and face, which are easily exposed to the environment, constitute approximately 10% of the total skin surface, the follicles allow greater absorption by the transfollicular route [9]. Also, there are many reports that PM contribute to various skin diseases, such as inflammatory skin diseases, skin aging, androgenetic alopecia (AGA), and skin cancer. In this article, we review what is known about the association between ambient PM and skin diseases.

2.1 Particulate matter air pollution and Inflammatory skin diseases: Atopic dermatitis, Acne, and Psoriasis

Recent epidemiological investigations into the effect of environmental contamination, especially ambient air pollution, on several skin diseases indicate that some PM affects the progression of inflammatory skin diseases, such as atopic dermatitis (AD), acne, and psoriasis [77,94,83,34]. AD is a chronic and recurrent inflammatory skin disease with symptoms of itching and eczema that usually begins during infancy or childhood. The incidence of AD worldwide is on the rise [90,5]. Although the mechanism of AD is still not clear, environmental pollution have been implicated one of the complicating factors of AD with genetic predisposition and immunologic mechanisms [44,74,22,79]. PM adversely affects patients with allergic diseases, including asthma and AD [59,27]. Moreover, the increased concentration of PM in ambient air is strongly related to progression of AD in children. Long-term exposure to PM2.5 and nitrogen dioxide from vehicle exhaust is significantly associated with eczema and allergic sensitization [59]. Also, high levels of PM10, PM2.5, and UFP intensify AD symptoms, such as itching, among children with pre-existing AD [77]. These studies provide evidence that PM-exposed children have a high risk for developing AD and/or for exacerbation of pre-existing disease. Furthermore, short-term exposure of the UFP nitrogen dioxide mainly impairs the epidermal barrier function (e.g., transepidermal water loss), resulting in the exacerbation of AD symptoms [18]. Recent epidemiologic studies suggest that indoor and outdoor air pollution exacerbate AD symptoms [42,43]. In nine randomly selected kindergarteners, reduced PM10 concentration following improvement of air quality considerably influenced symptoms of AD [42]. PM10 concentration in the indoor air was reduced from 182.7 ± 23.68 $\mu g/m^3$ to 73.4 ± 22.05 $\mu g/m^3$ after improvement of indoor air quality. The reduced PM10 concentration considerably influenced the eczema area and severity index (EASI) score, as well as the mean body surface area affected by AD. The EASI score was significantly decreased from 2.37 to 1.19. Additionally, the mean body surface area was decreased from 7.06% to 4.22% after the improvement program. In addition to indoor air pollution, outdoor air pollution is highly associated with AD [43]. An epidemiologic study, in which researchers measured outdoor PM concentrations (e.g., PM10, PM2.5, toluene, and TVOC), showed

that patients exhibiting AD symptoms had been exposed to significantly higher outdoor PM concentrations than patients not showing AD symptoms. Also, the symptoms of AD were shown to increase by 0.44% and 0.67% following 1 ug/m^3 increases of PM10 and PM2.5, respectively [43]. These data show the direct positive correlation between PM concentration in the air and AD, and suggest the importance of reducing PM concentration in the ambient air to improve the symptoms of AD.

Acne is another chronic inflammatory disease that affects the sebaceous gland and is characterized by skin changes, such as comedones, papules, pustules, and nodules. The exact cause of acne is not known, but, hormone imbalance, genetic predisposition, and environmental factors alone or in combination have been associated with the pathogenesis of acne [6]. Cigarette smoke increases production of interleukin (IL)-1α, which is a representative pro-inflammatory cytokine, and oxidation in the comedones in acne patients [94]. The expression of IL-1α and lipid peroxide is higher in comedone extracts from smokers than from non-smokers, indicating that cigarette smoke is related to the pathogenesis of acne. Also, benzo(a)pyrene (BaP), which exists as a type of polycyclic aromatic hydrocarbon (PAHs) in cigarette smoke, enhances IL-8 secretion from human epidermal keratinocytes [83]. IL-8 is expressed in association with inflammatory acne vulgaris more than with normal skin [1]. BaP-induced IL-8 production depends on ROS production and aryl hydrocarbon receptor (AhR) activation, which is a known receptor for PAHs, in normal human keratinocyte cells. Upon cellular entry of BaP, BaP binds to AhR in the cytoplasm of keratinocytes. The BaP-AhR complex is translocated into the nucleus, and then the AhR nuclear translocator (ARNT) binds to the BaP-AhR complex, resulting in the induction of the cytochrome P450 enzyme family, including subfamily A polypeptide 1 (CYP1A1) transcription. It has been reported that quinones, which are converted from PAHs through the functions of CYP1A1, induce ROS formation [50]. The increased ROS results in the enhancement of pro-inflammatory cytokines, such as TNF-α and IL-8 from keratinocytes (Figure 1A). These experimental studies suggested that cigarette smoke worsens symptoms of acne via increasing ROS and IL-8 production [83].

An additional inflammatory skin disease is psoriasis, which is a recurring systemic chronic disease with histological features of epidermis hyperplasia and dermal inflammation. Immunologically, Th17 cells are dominant in psoriatic skin lesions, and IL-17 aggravates psoriasis pathogenesis [2,57]. *In vitro* and *in vivo* PM exposure due to diesel exhaust and cigarette smoke increases Th17 differentiation by activation of the AhR transcription factor via the presence of the AhR ligand PAHs [84]. Therefore, AhR activation is one of the mechanisms of inflammation by PM exposure. Also, the percentage of Th17 in peripheral blood mononuclear cells (PBMC) of patients with psoriasis is significantly higher among smokers than non-smokers, indicating that smoking is involved in Th17 cell generation [81]. In addition to Th17 polarization, PM enhances the production of pro-inflammatory cytokines, such as TNF-α and IL-8, from human keratinocytes *in vitro*, suggesting in the exacerbation of psoriasis [34,83]. Cigarette smoke extract (CSE) promotes the expression and secretion of TNF-α through the activation of early growth response-1 transcription factor, which is increased in psoriatic skin lesions [34]. As shown in Figure 1B, CSE activates mitogen-activated protein kinase (MAPK), including ERK1/2, JNK, and p38 MAPK. The activated ERK1/2 and JNK, but not p38 MAPK, induce early growth response-1 (Egr-1) transcription. In addition to the increased expression of Egr-1 by CSE, CSE stimulates translocation of Egr-1 into the nucleus, resulting in the accumulation of Egr-1 in the cell nuclei of keratinocytes. The translocated Egr-1 is involved in the process of TNF-α synthesis in human keratinocytes, indicating a correlation between cigarette smoke and psoriasis [34]. Additionally, as with acne, BaP influences the pathogenesis of psoriasis by upregulation of IL-8 production and activation of the AhR transcription factor [83].

In conclusion, ambient air pollutants such as PM are involved in the pathogenesis of inflammatory skin diseases (e.g., AD, acne, and psoriasis) via the enhancement of oxidative stress and pro-inflammatory cytokines. These findings indicate the increased PM concentration may play an important role in the increased incidence of inflammatory diseases.

2.2 Cutaneous impacts of particulate matter air pollution: Skin aging

Two main processes cause skin aging: extrinsic aging due to environmental factors and intrinsic aging due to time [20]. Many reports suggest that environmental factors affect extrinsic skin aging, which is characterized by coarse wrinkles and unevenly distributed pigmentation, but not intrinsic aging [55,92]. Intrinsic aging is related to the accumulation of cellular damage from the active oxygen radicals in the body. On the other hand, extrinsic aging is caused by harmful free radicals created by various environmental factors, including sun exposure and smoking [20,63,85]. These radicals induce damage to the skin by causing an inflammatory reaction. Sun exposure (ultraviolet) is known as a major cause of aging. However, it was reported that environmental contaminants, in particular PM, also significantly increased the symptoms of aging [86,60]. A cohort study shows the cutaneous impact of PM on skin aging using a scoring measurement (SCINEXA: score of intrinsic and extrinsic skin aging [86]. Ambient PM10 concentration was determined to be markedly higher in the urban areas than in the rural areas due to traffic emissions. The relatively high concentrations of PM in the urban areas increased facial pigment spots by more than 20%, indicating that the increased level of traffic-related PM in the air exacerbates skin aging [86]. Also, ultraviolet (UV) radiation and PAHs-loaded air pollutants stimulate melanin synthesis in melanocyte, resulting in the formation of environment-induced lentigines [60].

One of the mechanisms associated with the adverse effects of PM is the increased generation of oxidative stress. The increased ROS decreases skin functions that prevent pathogen entry and repair DNA damage, resulting in the acceleration of the skin aging process [89,49,66]. ROS production inhibits collagen synthesis as a result of activation of matrix metalloproteinases (MMPs). ROS increases MMP-12 to degrade collagen 5 and fibronectin [97]. MMP-2, which is induced by ROS and UVA, is increased in fibroblasts, indicating degradation of the connective tissue matrix in the skin [41].

Pro-inflammatory reactions by PM exposure are associated with skin aging as well. PM enhances pro-inflammatory cytokines, such as TNF-α, IL-1α, and IL-8, from human keratinocytes

[34,94,83]. TNF-α impairs the DNA repair system by allowing accumulation of DNA mutations [21] and promotes skin aging by inhibiting collagen synthesis through upregulation of MMP-9 [12,96]. TNF-α, IL-1α, and IL-6, which are induced by solar radiation *in vitro*, promote skin aging by inducing lipolysis and reducing lipogenesis, as loss of fat in the subcutaneous layer leads to facial wrinkling [53].

Figure 2 summarizes the molecular mechanisms for PM-induced ROS generation and pro-inflammatory cytokines such as IL-1α, IL-6, IL-8, and TNF-α, resulting in increased skin aging. PM, including cigarette smoke, generates cellular oxidative stress. ROS activates the MAPK signaling pathway including ERK1/2, JNK, and p38 MAPK, and then the activated MAPK induces various transcription factors, such as NF-kB and AP-1. As a result of translocation of the activated transcription factors, inflammatory cytokines and MMPs are synthesized. TNF-α, IL-1α, IL-6, and IL-8 are closely related with inflammatory skin diseases and skin aging. Pro-inflammatory cytokine production and various MMPs are produced and activated by ROS generation. MMP-1, which is well-known as a collagenase, MMP-3, which is known as a stromelysin, MMP-2 and MMP-9, which are known as gelatinases, all induce collagen degradation. Collagens are initially degraded by collagenases, and then they are further degraded by gelatinases and stromelysins, resulting in skin aging. In addition, ROS impairs the skin repair DNA system, accumulating DNA damage and further resulting in the acceleration of the skin aging process.

Taken together, there are many certain evidences that the increase of PM in the ambient air is likely to cause damage to the skin although there is no direct evidence that PM can penetrate into skin regardless of smaller size. PM exposure induces many adverse effects in the skin, including the formation of pigmented spots, generation of ROS, and the production of pro-inflammatory cytokines, leading to extrinsic skin aging.

2.3 Environmental cigarette smoke and Alopecia

Androgenetic alopecia (AGA), which is also known as androgenic alopecia or baldness, is the most common male-pattern hair loss disease in men, affecting up to 70% of men by the age of 70 years. AGA also affects approximately 30 ~ 40% of women over 70 years of age [7]. Hair loss in men begins in the area of frontal hair and temples, and the recession of the hairline progresses towards the vertex, resulting in balding [7,61]. The most important causes of AGA are genetic factors and the male hormone androgen [40]. Among various androgens in human body, testosterone is converted to dihydrotestosterone (DHT) by 5α-reductase. DHT acts as a major contributor within the dermal papilla to decreased hair growth, resulting in the induction of hair loss and miniaturization. [40,46,98].

Recent studies show evidence that air pollutants, especially environmental cigarette smoke, are closely related with AGA [25,78,82]. It is well known that genetic factors are highly associated with AGA, but the study of balding patterns between active smoker and nonsmoker twins shows that environmental factors also play a key role in the development of baldness. Although the twins were genetically identical, those with a longer smoking history showed increased hair loss in the frontal hair area [25]. Within twin pairs, smokers had significantly more hair loss in the vertex lesion compared with nonsmokers, suggesting the adverse effects of environmental factors on baldness [25]. Also, analysis of odds ratios for smoking status, smoking number per day, and smoking intensity indicated a significant positive correlation between cigarette smoke and AGA [78]. Volunteers who had smoked before or were current smokers had a 1.77 odds ratio compared with nonsmokers with an odds ratio = 1. The odds ratio is 2.34 in smokers who have more than 20 cigarettes/day and 1.78 in smokers who have higher smoking intensity. These smokers exhibit moderate or severe AGA.

Indeed, smoke-exposed mice exhibit hair loss and premature grey hair, which are symptoms of alopecia. In cigarette smoke-exposed mice, melanin synthesis (pigmentation) in hair bulbs is significantly decreased, and cell apoptosis in hair follicles and hair bulbs is massively increased, whereas the development of alopecia is reversed by treatment with the antioxidant n-acetyl cysteine (NAC) in drinking water [15]. The data indicate that cigarette smoke plays a key role in the development of alopecia through oxidative stress, suggesting that the regulation of oxidative stress

may be an effective therapeutic target for improvement of AGA.

In summary, exposure to smoke influences alopecia (especially AGA), independent of genetic factors. The development of alopecia is much higher in cigarettes-smoking twins than non-smoking twins. Additionally, smoking history and intensity are positively correlated with severe AGA. In fact, exposure to smoke enhances alopecia directly in a mouse model, and the smoke-induced alopecia is markedly reduced by the oral administration of the anti-oxidant NAC. These reports indicate that cigarette smoke is significantly associated with the development and progression of AGA via oxidative stress, suggesting that the regulation of oxidative stress is an effective therapeutic target for the improvement of AGA.

2.4 Adverse effect of particulate matter air pollution on Skin cancer

In recent decades, epidemiological studies have demonstrated the relationship between PM air pollution and cancer incidence [19,67,70]. Exposure to PM10 induces cellular changes in lung epithelial cells by formation of F-actin and activation of signaling molecules such as cytoplasmic p21 and ERK1/2, suggesting a carcinogenic potential of PM10 [71]. The direct impact of air pollution particulates on the increasing mortality rate was investigated in a cohort study by the American Cancer Society [19]. The results show that the increased concentration of PM2.5 is highly associated with increased mortality rate. Extended exposure to PM increased mortality due to cardiopulmonary disease and lung cancer.

Additionally, recent study shows evidence that PM is a high risk factor with regard to the incidence of skin cancer, especially malignant melanoma [68]. PM from vehicles (including nitrogen dioxide, sulfur dioxide, organic compounds, and fine particles) has been recognized as a very serious problem. In particular, black carbon from diesel exhausts, a type of UFP, is classified as a class one carcinogen. It was reported that the incidence of melanoma was increased in a group of workers exposed to black carbon [68]. A survey of dockyard workers shows that exposure to black carbon is

positively associated with the incidence of melanoma. The standardized incidence ratio (SIR) of melanoma was 355 among the workers hired before 1958, and 185 among the workers hired after 1958. Because unloading black carbon was significantly decreased after 1958, the difference of SIR between the two groups indicates the influence of black carbon on the incidence of melanoma. Interestingly, there are no significant correlations between exposure to black carbon and skin cancers other than melanoma [68].

Exposure of the hairless skin of mice to cigarette smoke and ultraviolet light simultaneously has shown a synergistic effect in increasing squamous cell carcinomas (SCC) [64]. Also, cigarette smoke and light exposure induce various gene alteration related to oxidative stress and stress response in skin and lung of mice, indicating systemic adverse effects [31]. Cigarette smoke can promote not only the incidence, but also exacerbation of skin cancer, by increasing proliferation in epidermal thickness [14]. At the molecular level, cigarette extract induces oxidative stress through the induction of ROS production, leading to oxidative DNA damage in fibroblasts [13]. The exposed fibroblasts secrete soluble factors, including IL-1α, IL-6, IL-8, basic fibroblast growth factor (bFGF), MCP-1, and IGFBP4. These factors stimulate keratinocyte proliferation, suggesting that cigarette extract affects skin carcinogenesis via its regulation of cell proliferation (Figure 2). Acute oxidative stress impairs the DNA repair system [72]. ROS-treated fibroblasts have a longer interval time to repair DNA damage than normal fibroblasts. Also, the accumulation of DNA damage is significantly higher in the smoking group than in the non-smoking group. This study indicates that smoking-induced ROS production modulates the DNA repair capacity in the skin, resulting in increased skin diseases like skin cancer and aging [72].

In urban air pollution, PAHs, which are potentially carcinogenic [76], co-exist with PM in environmental complex mixtures. Ambient PAHs mixtures are mainly derived from coal tar, diesel exhausts, and cigarette smoke [48,11]. Epidemiologic study shows that exposure to PAHs is associated with a development of various types of cancers, including skin cancer [8]. In addition to inhalation, PAHs can be absorbed through the skin, indicating the relationship between PAHs and skin

diseases [54,69]. Topical application of PAHs mixtures enhances the incidence of skin cancers like papilloma, carcinoma, and squamous cell carcinoma [75]. Depending on the types of PAHs mixtures, different patterns of skin cancer are generated. Overall, PAHs can promote cancer incidence and malignancy and shows a high potential as a carcinogenic PM [75]. The absorbed PAHs contribute to carcinogenesis by interacting with a specific receptor, AhR, which is known as a transcription factor [58]. Interaction between PAHs and AhR induces PAHs-mediated carcinogenicity in many kinds of cells by generating numerous carcinogenic metabolites. Indeed, PAHs did not show a carcinogenic effect on the skin of AhR-deficient mice, indicating the involvement of AhR in the regulation of PAHs-induced squamous cell carcinomas. In Figure 3, the incidence of squamous cell carcinoma by airborne particulate extracts is shown in AhR positive mice via CYP1A1 expression. Also, it was reported that by binding with other airborne particles, PAHs can exist as a complex including particle-phase PAHs or gas-phase PAHs [91]. Gas-phase PAHs are more abundant in the atmosphere but less carcinogenic than particle-phase PAHs, which is concentrated in airborne particles (e.g., PM2.5 and UFPs).

Overall, PM including black carbon, cigarette smoke, PAHs, and particle-bound PAHs affects cellular changes, such as ROS production, pro-inflammatory cytokine secretion, and transcription factor activation, resulting in the incidence of skin cancers. Also, cohort studies revealed that UFP including black carbon was significantly associated with the incidence of melanoma [68], and PM10 air pollution had positive correlation with the incidence of skin cancer as well as other types of cancer, such as lung cancer [93], indicating the adverse effects of ambient PM on skin cancer incidence.

2.5 Impacts of oxidative stress on the Skin

Oxidative stress is caused by excessive production or insufficient elimination of ROS [73]. Accumulation of oxidative stress by the excessive ROS in the body causes DNA damages and cellular signaling disruptions, resulting in the dysregulation of immune systems and induction of various

diseases including inflammatory skin diseases, aging, and cancers [26]. Many studies have reported that PM induces oxidative stress through ROS formation [4,45,52,50,51]. Diesel exhaust particles (DEP) components cause the production of superoxide ($O_2^{\bullet-}$) and hydroxyl radical ($^{\bullet}OH$) from mouse lung microsomes [45]. PAHs increase heme oxygenase (HO)-1 expression, which is a marker for oxidative stress. Also, PAHs are able to induce mitochondrial damage via the disruption of major structure of mitochondria [51]. Damaged mitochondria produces a lot of superoxide, resulting in the increased hydroxyl radical [4]. Additionally, several particles have surface reactivity, inducing ROS generation directly. It suggests that extracellular ROS via surface reactive particles is also involved in the source of ROS in the PM-exposed cells as well as intracellular ROS as shown in Figure 2 [62]. It is reported that PM2.5, PM10, and UFPs trigger oxidative stress in murine macrophage cells. PM induces nitric oxide (NO) production and pro-inflammatory cytokines such as TNF-α and IL-6. The increased oxidative stress and inflammatory responses lead to the cytotoxic activities of PM, indicating the harmful effects and oxidative potentials of urban air particulate mixtures [32]. As shown in Figure 1 and 2, a number of experimental studies provide evidence for the impact of PM on skin diseases and related mechanisms. Both short- and long-term exposure to PM enhance oxidative stress by increasing the production of ROS, causing the inflammatory responses by the production of pro-inflammatory cytokines such as TNF-α, IL-8, and IL-1α [34,83,94]. The increased pro-inflammatory cytokines via ROS generation exacerbate the development of inflammatory skin diseases, including AD, acne, and psoriasis. Other inflammation-related disease, skin aging is also positively correlated with ambient PM [12,96,41,97]. PM-induced cellular oxidative stress via ROS production leads to impaired DNA repair processes, promotion of collagen degradation via up-regulation of MMPs, and inhibition of collagen synthesis, resulting in extrinsic skin aging with characteristics of coarse wrinkles and unevenly distributed pigmentations. Additionally, WHO classifies types of UFP, such as black carbon and PAHs, as class one carcinogens. Indeed, it was reported that PM acts as a carcinogen and is able to induce skin cancer by up-regulating oxidative stress, pro-inflammatory cytokines, and cell proliferation directly [13,72,75]. Oxidative stress impairs the DNA repair system, resulting in the accumulation of DNA damage [72]. The accumulation of

DNA damage is significantly higher in the smoking group than in the non-smoking group, indicating that cigarette smoke-induced ROS production modulates the DNA repair capacity in the skin, resulting in increased skin diseases like skin cancer and aging [72]. It has been also reported that oxidative stress promotes the initiation and progression of melanoma, a malignant skin cancer. Especially, mutations in melanoma-associated genes such as loss of p16 are involved in oxidative stress-induced melanoma. Loss of p16 significantly increases ROS production from melanocytes, indicating that oxidative stress acts as an inducer of melanomagenesis [33]. In addition, AGA is also directly affected by cigarette smoke, which is well known as an oxidizing agent [25,78,82]. Incidence of hair loss in the frontal and vertex area is higher in active smokers than in non-smokers, and there are positive correlation between smoking intensity and severe AGA. It has been reported that cigarette smoke-induced alopecia is markedly reduced by the oral administration of the anti-oxidant NAC *in vivo* mouse model, indicating that cigarette smoke is significantly associated with the development and progression of AGA via oxidative stress [15].

3. Conclusion

PM, including PM10, PM2.5 and UFPs, has been adversely related to human health [39,10]. Many epidemiological studies have shown that the increased ambient PM concentration is highly associated with premature deaths in individuals with cardiovascular and respiratory diseases [39,10]. Based on the severity of PM-associated human health problems, WHO limits the mean concentration of PM in the air. Here, we focused on the human health impacts of PM, especially cutaneous impacts, such as inflammatory skin diseases, skin aging, AGA, and skin cancers. Skin is important as the outermost barrier and first defense immune system for the protection of the human body. Although there is no direct evidence that particles can penetrate into skin, it is reported that the particles can penetrate skin though hair follicles depending on their size [47]. This review shows that PM disrupts skin barrier functions through oxidative stress and pro-inflammatory cytokines. Oxidative stress via excessive ROS production by PM exposure increases pro-inflammatory cytokines, such as TNF-α and

IL-8, and MMPs, such as MMP-1, -2, and -9, as shown in Figure 3. The increased cytokines and MMPs are involved in the development and exacerbation of skin diseases including inflammatory skin diseases, skin aging, and skin cancers. Recent studies suggest that anti-inflammatory and/or anti-oxidative drugs inhibit PM-induced adverse effects (Figure 4) [15,35,30]. Smoke-exposed mice in *in vivo* mouse models exhibit the hair loss and premature grey hair, leading to the development of alopecia. However, smoke-induced alopecia areata is inhibited by treatment with antioxidant NAC in drinking water, indicating that the anti-oxidant agent protects the human body from damage induced by exposure to PM [15]. Caffeic acid phenethyl ester, which is an anti-inflammatory and anti-oxidative agent, significantly decreases PM-induced TNF-α production and ROS production, resulting in decreased inflammation in ear epithelial cells [35]. Dehydroepiandrosterone (DHEA) also has anti-inflammatory and anti-oxidative activities. DHEA inhibits inflammatory responses in endothelial cells induced by PM and nanoparticles by reducing adhesion, proliferation, ROS production, and nitrite production [30]. We previously demonstrated that erythroid differentiation regulator 1 (Erdr1) is negatively regulated by pro-inflammatory cytokine IL-18, suggesting that Erdr1 may exert anti-inflammatory effects in contrast to the pro-inflammatory effect of IL-18 [37,36]. Erdr1 plays an important role in cancer progression due to its suppression of tumor cell migration and metastasis in melanoma and gastric cancer. Due to the anti-inflammatory and anti-cancer activities of Erdr1, we suggest that Erdr1 may be involved in the defense mechanisms against PM-induced inflammation.

Overall, PM promotes the development and exacerbation of various skin diseases. A few epidemiological studies suggest that increased PM concentration is not correlated with skin diseases; however, many reports suggest that there is a strong indication for the positive correlation between PM concentration and the incidence of various skin diseases. Therefore, more epidemiological and additional experimental studies are required to investigate the related mechanisms of PM-induced skin diseases.

Acknowledgements: This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2012R1A2A2A02046972).

Conflict of Interest Disclosure: The authors declare that they have no conflict of interest.

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Figure Legends

Figure 1. PM induces ROS generation and pro-inflammatory cytokines.

(A) Benzo(a)pyrene (BaP) induces pro-inflammatory cytokines, such as TNF-α and IL-8, via ROS generation. BaP binds to AhR, leading to formation BaP-AhR complex. The complex is translocated into the nucleus, and then binds with ARNT, resulting in the activation of CYP1A1 transcription. ROS generated by CYP1A1 stimulates the production of TNF-α and IL-8.

(B) Cigarette smoke extract (CSE) triggers TNF-α production in the keratinocytes through regulation of Egr-1 transcription and nuclear translocation of Egr-1. CSE activates MAPK pathway including ERK1/2, JNK, and p38. The activated ERK1/2 and JNK activates Egr-1 transcription process. In addition, CSE triggers nuclear translocation of Egr-1, leading to the activation of TNF-α transcription. The increased TNF-α by CSE is involved in the various skin diseases, such as inflammatory skin diseases and skin aging.

Figure 2. Molecular mechanisms for PM-induced ROS generation and pro-inflammatory cytokines.

PM including cigarette smoke generates ROS, such as superoxide ($O_2^{\bullet -}$) and hydroxyl radical ($^{\bullet}OH$), with subsequent cellular oxidative stress. PM induces not only the intracellular ROS formation through the mitochondrial damage and redox cycling, but also the direct formation of ROS through particle surface reactivity. The increased ROS by PM exposure activates MAPK signaling pathway including ERK1/2, JNK, and p38 in the PM-exposed cells. It also induces various transcription factors, such as NF-kB and AP-1. As results of translocation of the activated transcription factors, pro-inflammatory cytokines and MMPs are synthesized. Especially, TNF-α, IL-1α, IL-6, and IL-8 are closely related with inflammatory skin diseases, skin aging, and skin cancers. In addition to pro-inflammatory cytokine production, various MMPs are produced and activated by ROS generation. Collagens are degraded by MMPs including MMP-1, MMP-2, MMP-3, and MMP-9, resulting in the skin aging. In addition, ROS impairs skin function to repair DNA system, accumulating DNA damage

resulting in the acceleration of the skin aging.

Figure 3. Airborne particulate extracts are involved in the carcinogenicity, resulting in the induction of squamous cell carcinomas.

Airborne particulate extracts do not show a carcinogenic effect on the skin of AhR-deficient mice, however, the incidence of squamous cell carcinoma by airborne particulate extracts is detected in AhR positive mice via CYP1A1 expression, indicating the involvement of AhR in the regulation of PM-induced squamous cell carcinomas.

Figure 4. Therapeutic effects of anti-oxidant and anti-inflammatory drug on particulate matter-induced inflammatory skin diseases.

PM induces oxidative stress and inflammatory reactions, leading to the development and exacerbation of various skin diseases. However, recent studies suggest that anti-inflammatory and anti-oxidative drugs inhibit PM-induced adverse effects and are thus useful as therapeutic agents.

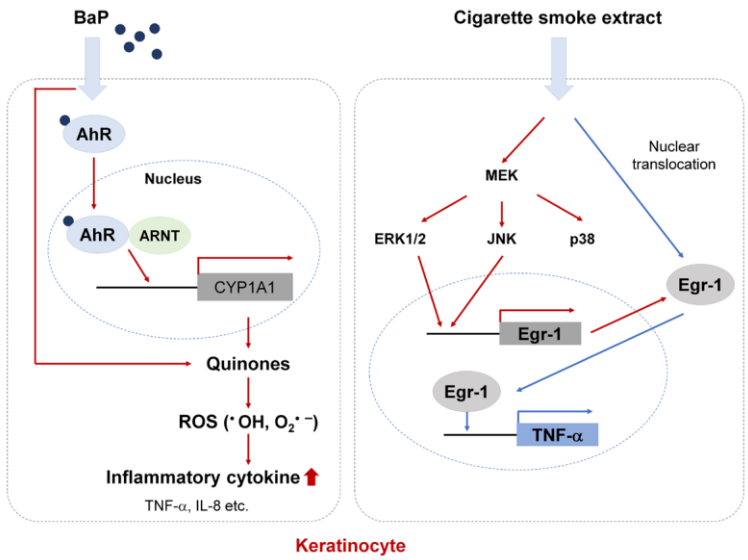


Figure 1

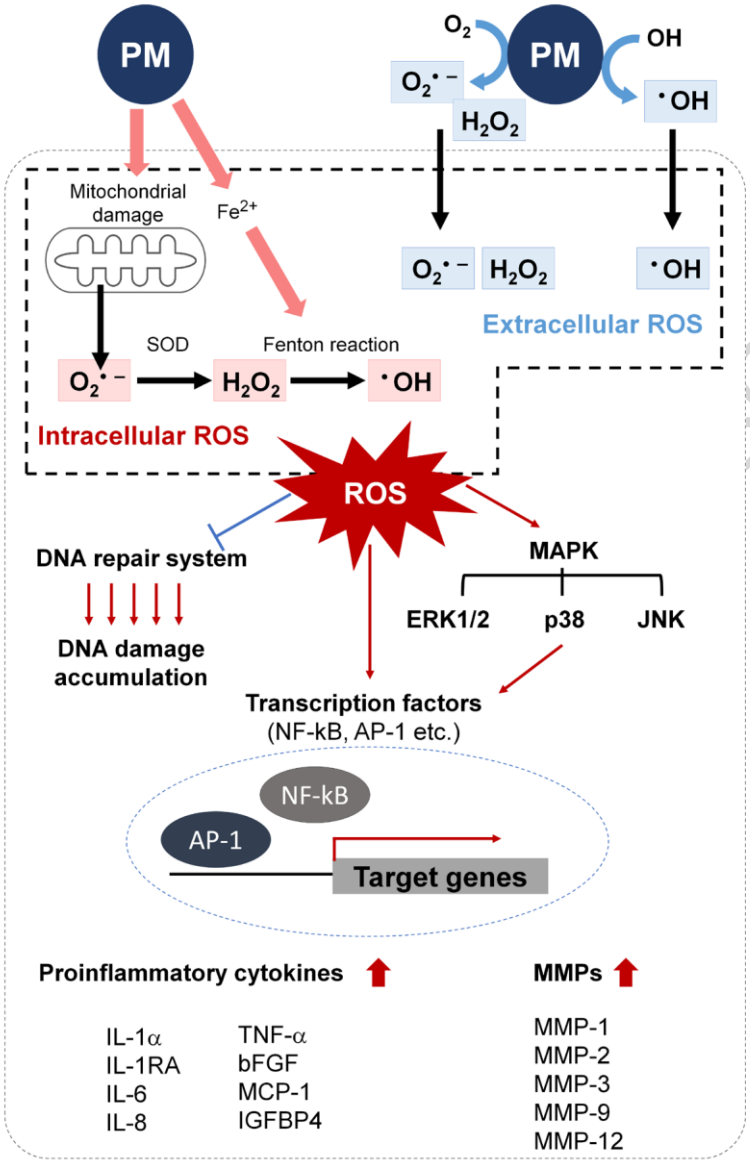


Figure 3

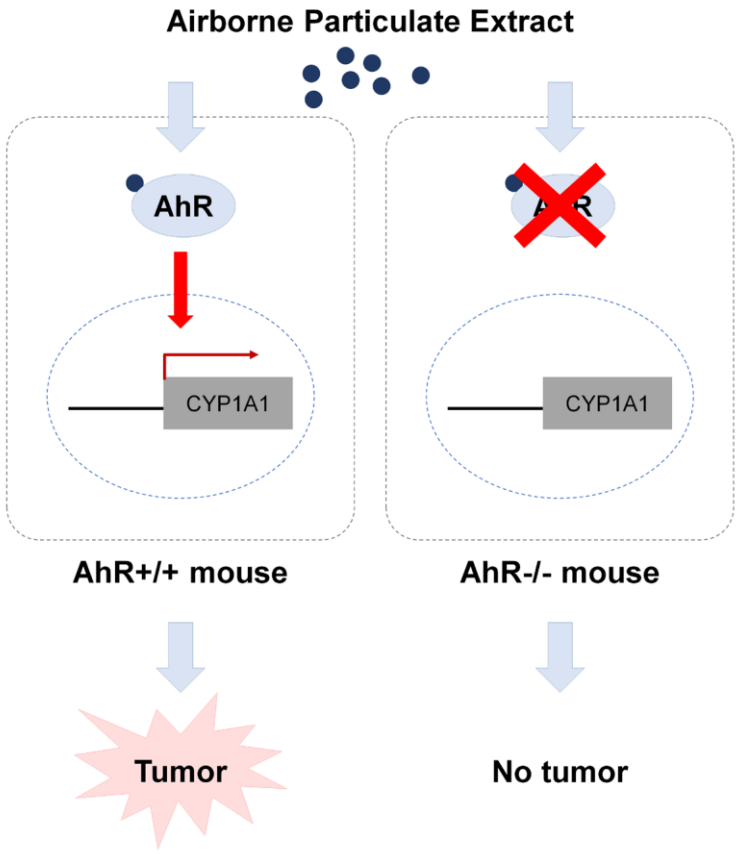


Figure 4

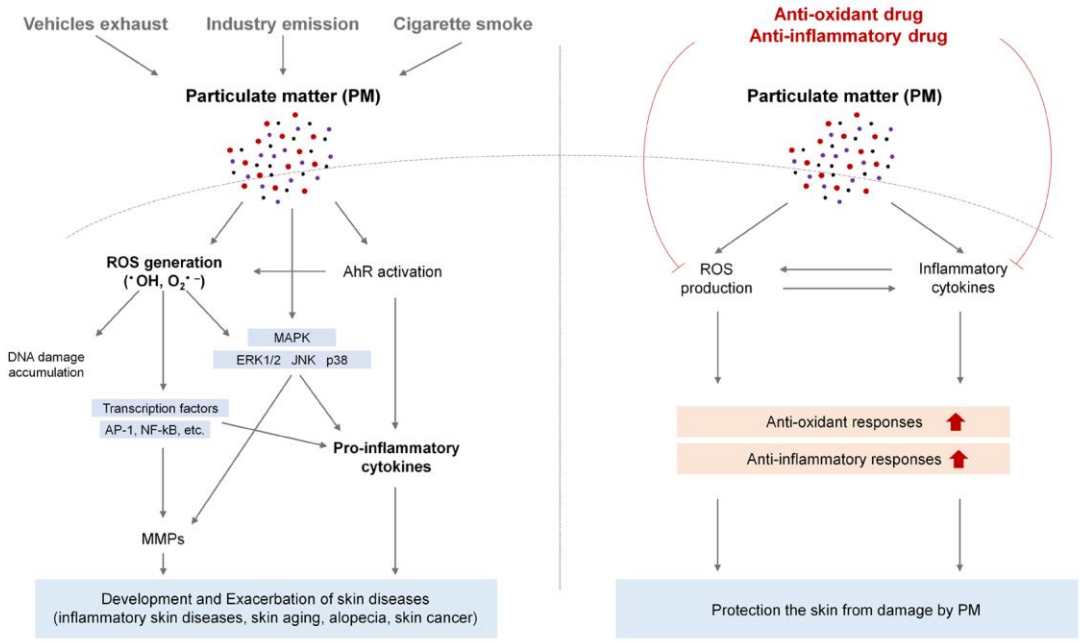
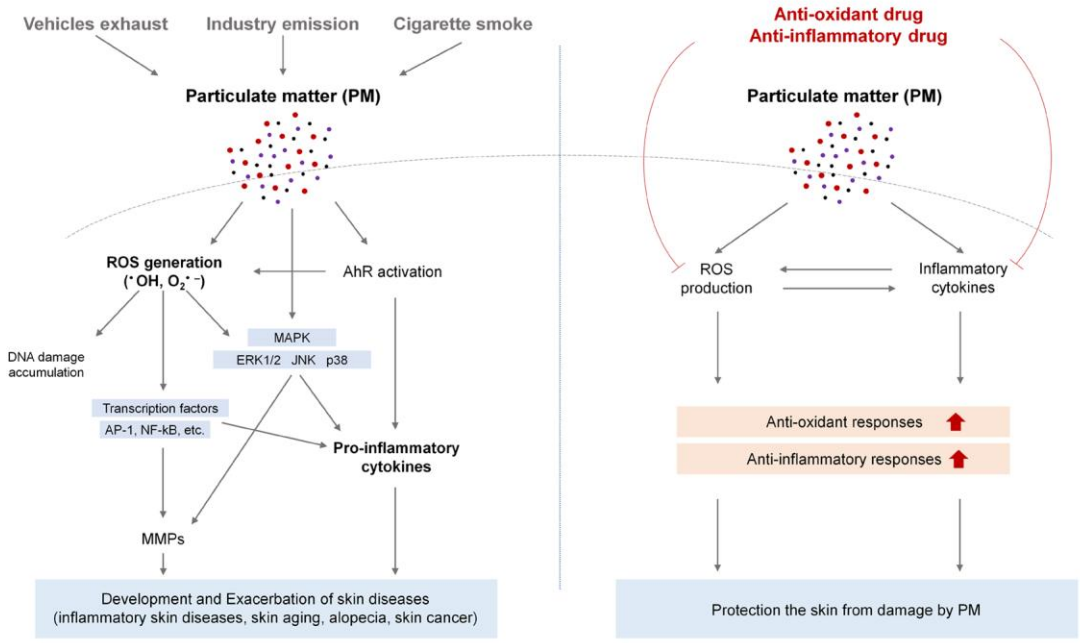


Figure 5



Graphical abstract