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FORUM INVITED REVIEW

Particulate matter induces tissue OxInflammation: from mechanism to damage.

Giuseppe Valacchi[1,2,3], Natalia Magnani[4,5], Brittany Woodby[1], Sandra María Ferreira[4,5], Pablo Evelson[4,5]

[1]Plants for Human Health Institute, Dept. of Animal Science, NC Research Campus, NC State University, Kannapolis, 28081 NC, USA.

[2]Department of Biomedical and Specialist Surgical Sciences, University of Ferrara, 44121 Ferrara, Italy.

[3]Department of Food and Nutrition, Kyung Hee University, 02447 Seoul, South Korea.

[4]Universidad de Buenos Aires. Facultad de Farmacia y Bioquímica. Departamento de Química Analítica y Fisicoquímica. Cátedra de Química General e Inorgánica.

[5]Universidad de Buenos Aires. CONICET. Instituto de Bioquímica y Medicina Molecular (IBIMOL), Facultad de Farmacia y Bioquímica.

Correspondence: Pablo Evelson. Facultad de Farmacia y Bioquímica. Universidad de Buenos Aires. Junín 956 (C1113AAD) Buenos Aires. Argentina. Phone: +54 (11) 5287-4251. e-mail: pevelson@ffyb.uba.ar

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ABSTRACT

Significance: Oxidative stress and oxidative damage are central hypothetical mechanisms for the adverse effects of airborne particulate matter (PM). Activation of inflammatory cells capable of generating reactive oxygen and nitrogen species is another proposed damage pathway. Understanding the interplay between these responses can help us understand the adverse health effects attributed to breathing polluted air.

Critical issues: Reactive oxygen species (ROS) are generated during phagocytosis of the particles, leading to enhancement of oxidative stress and triggering the inflammatory response. The activation of inflammatory signaling pathways results in the release of cytokines, and other mediators that can further induce ROS production by activating endogenous enzymes, leading to a positive feedback loop, which can aggravate the effects triggered by PM exposure.

Recent advances: The consequences of PM exposure on different organs results in oxidative damage, decreased function, and inflammation, which can lead to the development/exacerbation of proinflammatory disorders. Mitochondrial damage is also an important event in PM-induced cytotoxicity.

Future directions: Further research is required to elucidate the exact mechanisms by which PM exposure results in adverse health effects, in terms of the relationship between the redox responses triggered by the presence of the particles and the inflammation observed in the different organs, so the development/exacerbation of PM-associated health problems can be prevented.

1. Introduction

The exposome consists of all the environmental exposures (i.e. non-genetic), such as lifestyle factors and pollutants, that a person is exposed to (beginning from conception) and evolves throughout the life of a person (29,179). The study of the exposome, which includes air pollutants and traffic noise, is necessary to understand the role of environmental risk factors in various diseases to improve prevention strategies (184). In fact, there is strong evidence indicating that ambient air pollution particles currently present a serious risk to human health. Numerous epidemiological studies have shown associations between particulate matter (PM) and adverse health effects. These studies have shown a significant association between exposure to PM and increased mortality and morbidity. Other important effects include aggravation of respiratory problems, like lung disease, decreased lung function, asthma attacks, besides cardiovascular diseases, such as heart attacks and cardiac arrhythmia. Moreover, recent studies have shown the association between genetic variations and disease state after adverse environmental exposure events (27). Indeed, the pattern of epigenetic markers such as specific histone methylation and acetylation and DNA methylation patterns, and small interfering RNAs and long non-coding RNAs, that ultimately regulate chromatin structure or gene activity, is influenced by a variety of environmental stressors, including PM (25, 140,148).

In its last report, the World Health Organization (WHO) estimated that 91% of the world's population breathe polluted air. Therefore, almost 9 million premature deaths occur every year due to air pollution exposure (1,22,82), as stated in the 2018 Lancet Commission on pollution and health, which has focused on the global effects of pollution and solutions for policy makers (77). Individuals particularly sensitive to particle exposure include older adults, people with previous heart and lung diseases, and children (50). In the present review, we will discuss the impact of PM exposure on human health, considering that numerous clinical studies have shown greater deleterious outcomes after PM exposure (9,56,141). However, in this review, we have primarily focused on the molecular and biological changes that result in response to exposure of non-diseased tissue models to PM, since even the general population of healthy adults can be negatively affected by pollution exposure. Furthermore, we have focused our review on discussing the effects of PM exposure on organs that directly interact with PM present in air pollution: lung, eye,

skin and gut. The aim of this review is to discuss the state of the art, compare effects on different organs, and offer a comprehensive perspective to promote the exchange of ideas from scientists in different fields of pollution research. However, in this review, we have not discussed the effects of PM exposure on the heart, since negative consequences of PM exposure on this organ are mostly due to systemic effects that develop after lung inflammation (20), it is worth to note that in this same Forum Issue this topic is comprehensively reviewed (21,36,135,137,160). In putting together this review, we searched PubMed, Google Scholar and other relevant scientific databases for pertinent articles published from 2000 to 2020 using keywords (i.e. particulate matter and gut, etc.) in English.

2. Particulate matter present in air pollution.

Air pollution is a complex mixture of gaseous and particulate components, and exposure can cause deleterious effects on humans, animals, materials, or the environment, due to their quantities or permanence in the atmosphere (41).

Air pollutants can be classified considering their source, including natural pollutants (forest fires, windblown soil, volcanic emissions, and sea spray) or anthropogenic (industry, vehicle exhaust, road dust, smokestacks) (9,112). Also, air pollutants can be categorized as primary pollutants, which are released directly into the air, or secondary pollutants that are formed within the atmosphere after a reaction between other components (113). Regarding their composition, air pollution is comprised of gaseous components including nitrogen dioxide (NO_2), nitric oxide ($^{\cdot}NO$), sulfur dioxide (SO_2), ozone (O_3), carbon monoxide (CO), and particulate matter (PM), which are heterogeneous solid and liquid particles suspended in air (56,103).

PM contain carbonaceous particles with diverse compounds adsorbed to their surface. Some of the more frequent components of the PM mixture are nitrates (NO_3^-), sulfates (SO_4^{2-}), polycyclic aromatic hydrocarbons (PAH), endotoxin, and metals such as iron (Fe), copper (Cu), nickel (Ni), zinc (Zn), and vanadium (V) (64,87). Given the heterogenous composition of the mixture, PM are subclassified into 3 groups, according to particle size: (1) Coarse particles (PM_{10}) have an aerodynamic diameter greater than 2.5 µm, (2) Fine particles ($PM_{2.5}$) exhibit a range between 0.1 to 2.5 µm in diameter, and (3) ultrafine (PM_{10}) are smaller than 0.1 µm in diameter. The size of PM determines not only their

lifetime in the atmosphere but also their distribution within the target organs' structure (10,70,119).

Although the relative composition of PM is different in each microenvironment, due to variation in size, chemical components, and sources of origin, it has consistently been correlated with significant increased morbidity and mortality (21,34,162). Several characteristics have been associated with an increased susceptibility to PM-related health risks, namely age (i.e., children and older adults), preexisting diseases, obesity, genetic polymorphisms, and low-socioeconomic status (145). Therefore, PM exposure has been pointed out as a major environmental concern from the public health perspective, not only to susceptible people, but to all members of the population as well (42,89,134). In that sense, a deeper understanding of the PM-toxic mechanisms that impact human health are required, in order to prevent the deleterious effects of exposure to this global environmental hazard.

3. Oxidative stress and inflammation as main mechanisms in PM-associated health effects.

Oxidative stress and oxidative damage are central hypothetical mechanisms for the adverse effects of PM. The mechanisms by which PM causes oxidative stress have not been defined yet, but the phenomenon may be attributed to different causes, that include: (a) generation of oxidants at the particle surface, (b) release of metals or organic components from the particle, and (c) triggering of an inflammatory response (4). Activation of inflammatory cells capable of generating reactive oxygen and nitrogen species is another proposed mechanism: chronic inflammatory lung diseases are characterized by activation of epithelial cells and resident macrophages and the recruitment and activation of neutrophils, eosinophils, monocytes, and lymphocytes. It is understood that the oxidative stress caused by the activation of the inflammatory system plays an important role in the deleterious effects of PM in multicellular organisms. Reactive oxygen species (ROS) are generated during phagocytosis of the particles, leading to enhancement of oxidative stress and triggering inflammatory responses (159).

In this sense, ROS and Reactive Nitrogen Species (RNS) produced by the occurrence of oxidative stress can be considered molecules with an ambivalent behavior, whenever their role in inflammatory pathways is considered (133). Moreover, it can be considered that

ROS/RNS are important inflammatory effectors involved in the effects caused by the presence PM by resolving PM-associated damage and inducing tissue repair. However, ROS/RNS can also be inflammatory initiators by oxidizing biomolecules such as lipids, proteins, and DNA, leading to tissue damage and promoting switching from acute to chronic inflammation. The association between inflammation and oxidative stress and the redox signaling involved in inflammatory-associated diseases has been termed "OxInflammation". OxInflammation embodies the outcome of the crosstalk between oxidative stress (defined as increased ROS and RNS steady state concentrations) and inflammation (170). ROS/RNS and their related chemical species can be considered as efficient secondary messengers able to promote inflammatory responses by activating several transcription factors, (i.e. NF-κB, AP-1, c-Jun) and intracellular protein kinases (i.e. ERK, MAPK, INK and p38) (154). The activation of inflammatory signaling pathways results in the release of cytokines, chemokines, and other mediators that, in turn, can further induce the production of ROS and RNS by activating endogenous enzymes, leading to a positive feedback loop that can aggravate or promote the development of health effects triggered by exposure to PM.

4. Lung

4.1. Alveolar epithelium structure and function.

The exchange of CO_2 and O_2 required for cellular respiration is the most important function of mammalian lungs (59). The respiratory system can be classified into two main regions: the conducting region (upper airways) and the respiratory section (lower airways). The upper airways consist of the nose, nasal passages, pharynx, and larynx. The respiratory region consists of the trachea, the bronchi and bronchioles, and the alveoli of the lungs where O_2 uptake occurs.

The constant process of gas exchange between inhaled air and the bloodstream takes place in a very complex network of open-ended spherical sacs called alveoli and blood capillaries. The structure of the alveoli is fundamental in providing an extensive surface, where O_2 can be extracted from the inhaled air, and CO_2 can be removed during exhalation (54). Moreover, to achieve an efficient diffusion of gases, the alveolar walls and the capillary endothelium are only one epithelial cell layer thick, which allows the gases to rapidly cross through the cell layers (126). As the alveolar epithelium represents the 99%

of the surface area of the lung, its normal functioning is essential for optimal gas diffusion (54). The alveolar epithelium consists of equal numbers of squamous alveolar type I (ATI) and cuboidal type II (ATII) cells (63). However, ATI cells are elongated, covering 95% of the surface area, with long thin cytoplasmic extensions that are associated with capillaries for blood-air interface while ATII cells, placed in the alveolar corners, cover the remaining 5% of the surface area (99). ATII cells produce, secrete, and recycle surfactant, a fluid which maintains surface tension, facilitates gas exchange, and protects against pathogens (99). It has also been demonstrated that ATII cells serve as progenitors of the alveolar epithelium; they are multipotent cells with high plasticity, are capable of self-renewal, and can also differentiate into AT1 cells (19,45,59).

Since the lung is constantly interfacing with the environment, it is permantently exposed to noxious substances present in the lumen. Therefore, the alveolar epithelium also functions as a mechanical, restrictive barrier, in order to maintain selective permeability (54). Alveolar epithelial cells interact with each other through tight and adherens junctions, which provide a physical barrier between the alveolar airspace and the interstitium. Tight junctions are composed of integral membrane proteins, including occludins, claudins, scaffolding proteins, and immunoglobulins (38). These junctions surround the cells, forming apical rings and preventing large molecules from crossing the epithelial layer (17). Adherens junctions consist of E-cadherin and diverse catenins, which are connected to the actin cytoskeleton through anchoring proteins (139). In addition to tight junctions, cell-to-cell interactions are also involved in providing a physical barrier by dividing the epithelial plasma membrane into the apical and basolateral domains, creating an asymmetric distribution of ion transporters and other membrane proteins in these two domains, resulting in an osmotic gradient necessary for the excess lung fluid removal required for lung homeostasis (38).

In order to guarantee correct gas exchange, besides a tight barrier, the alveolar epithelium also requires a selectively permeable barrier, which is critical for the removal of its active, protein-rich fluid to prevent edema (16,17,139). Thus, during acute lung injury and acute respiratory distress syndrome, there is an impairment of the alveolo-capillary barrier, leading to flooding of the air spaces and impaired gas exchange (130,180). The initial injury to the lung that disrupts barrier function can be due to a variety of insults (110,143,169),

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although exposure to air pollution has been mentioned as a factor that can trigger direct lung injury.

4.2. PM effects in the lung.

It is accepted that exposure to air pollution PM triggers inflammation, endothelial activation, and oxidative stress in the lung (35,69,90,115,149). This response may be caused by the deposition of PM into the alveolar space in the lung, inducing the release of cytokines from alveolar macrophages. It has been shown that environmental particles, when internalized by phagocytosis after inhalation, trigger an increase in the numbers of alveolar macrophages (11). Therefore, a critical component of the inflammatory response to particles in the lung is the release of cytokines from activated macrophages and lung epithelial cells, resulting in neutrophil recruitment. Cultured human alveolar macrophages produce tumor necrosis factor-α (TNF-α) and proinflammatory cytokines, such as granulocyte-macrophage colony-stimulating factor, interleukin (IL)-6, and IL-1β after phagocytosing PM (120). The release of proinflammatory mediators from PM-exposed macrophages appears to be important in stimulating cytokine release from lung epithelial cells, thus amplifying the inflammatory response (64).

In vivo studies (50) have demonstrated that PM exposure can induce an influx of inflammatory cells, such as polymorphonuclear cells and macrophages, into the airways. Cultured macrophages exhibit increased secretion of cytokines such as IL-1β and TNF-α when exposed to other types of particles, such as the fungus Micropolyspora faeni, mineral dusts, crystalline silica, titanium dioxide, and asbestos. It has been observed that the respiratory tract generates an inflammatory response after inhalation or intratracheal instillation of different pollutants, such as residual oil fly ashes (ROFA), cooper particles (CMP), and coal fly ashes (CFA), resulting in increased numbers of neutrophils, protein concentration, and ROS in the lungs (50,174). Several mechanisms have been suggested to explain the observed raise in ROS, such as increased enzymatic activities and changes in mitochondrial respiration. NADPH oxidase (NOX) is of interest as an important non-mitochondrial source of reactive O_2 species and can be activated by airway inflammation (172). Alternatively, another enzyme, myeloperoxidase, which is also released by neutrophils, can be activated by inflammation, uses H_2O_2 as a substrate, and produces HClO, another powerful oxidant.

The inflammatory genes induced after exposure to PM (TNF-α and IL-8, for example) are regulated by redox sensitive transcription factors such as NF-κB, AP-1 and C/EBP (CCAAT enhancer binding protein) family. NF-κB is one of the key transcription factors that is involved in the inflammatory responses to PM in the lungs. The result of NF-κB activation is the generation of proinflammatory cytokines such as TNF-α, IL-6, IL-8 by airway and alveolar epithelial cells (154). Quay et al. reported that ROFA activated NF-κB by increasing ROS, which were likely produced in response to the presence of vanadium in the particles; this effect could be inhibited by the addition of the antioxidants deferoxamine and N-acetyl cysteine (136).

Recently, it has also been pointed out the ability of pollution exposure to disrupt the circadian clock. As previously mentioned, pollutant exposure alters redox homeostasis, and cellular redox status controls circadian timing, which has been extensively reviewed (55,84,161). Furthermore, circadian timing also controls expression of antioxidant defense factors, resulting in pollutant susceptibility at different times of day (55). In rat lungs, inhalation of PM resulted in lung inflammation, oxidative stress, and decreased levels of clock genes Per1, Per2, Per3, Rev-erba and Dbp and increased levels of Bmal1 transcripts (157). In addition, tobacco smoke, which is also a source of PM, altered expression of Bmal1 and Dbp expression of genes in rat lungs (48). Hwang et al have also shown that tobacco smoke altered clock gene expression, induced acetylation and degradation of brain and muscle arnt-like protein-1 (BMAL1), which is a positive regulator of circadian timing, due to decreasing sirtuin1 (SIRT1) levels, and increased lung inflammation, leading to lung emphysema (60). Oxidative stress in the lungs can reduce SIRT1 levels, which alters levers of Per2, resulting in clock dysfunction (161). Although beyond the scope of this review, the heart is another target of pollution-induced clock disruption, and effects on the heart have been nicely reviewed previously (54,84,161).

Taking all this data into consideration, the probable sequence of events for PM-induced lung inflammation involves the following: (a) injury to epithelial cells by ROS, possibly enhanced in the presence of metals via Haber-Weiss and Fenton chemistry, accompanied by activation of nuclear regulatory factors, leading to the production of proinflammatory cytokines, including IL-8 and IL-6, and increased expression of nitric oxide synthase (NOS) with increased levels of NO in exhaled air; (b) activation of vascular endothelium and

circulating leukocytes; emigration of inflammatory cells from blood to tissue sites, which involves up-regulation of adhesion molecules and other markers on vascular endothelium and on circulating leukocytes; and (c) the process of leukocyte-endothelial binding, which includes increased expression of adhesion molecules followed by their shedding, leukocyte activation, stable adhesion, and transmigration through the epithelium.

As mentioned in section 3, the mechanisms by which PM causes oxidative stress are still unknown, but the phenomenon may be attributed to different causes, which include: (a) generation of oxidants at the particle surface, (b) release of metals from the particle, and (c) triggering of an inflammatory response (163).

The direct generation of ROS at the surface of the particles is supported by the concept that the particle surface offers a unique physicochemical interface to catalyze reactions resulting in oxidant production. The interaction of PM with membrane components was recognized by the presence of free radicals and oxidants on the particle surface (164).

Several studies were performed that established associations between the toxic effects of air pollution and specific PM components. In fact, transition metals within the fine PM fraction are of great toxicological interest (37,83,172). Research has often been focused on Fe, V, Ni, Cr, Cu, and Zn, given that they are able to increase the production of free radicals in biological tissues through their ability to participate in Fenton-like chemical reactions and generate hydroxyl radicals (26). In line with these findings, previous results from our group using a PM surrogate with high transition metal content (ROFA), showed an imbalance in pulmonary oxidative metabolism in vivo after the instillation of the ROFA suspension (95,96). Indeed, the production of oxidative damage, as measured by TBARS levels, showed significant correlations with the overall metal content and with the content of individual metals, such as Fe and Va. This effect was inhibited by the presence of antioxidants, such as dimethylthiourea and deferoxamine (160). This data, in combination with the work of others, have led to the suggestion that the dose of bioavailable transition metal, rather than particulate mass, may be the principal determinant of the acute inflammatory response (94,152).

Activation of inflammatory cells capable of generating reactive oxygen and nitrogen species is another proposed mechanism: ROS are generated during phagocytosis of the

particles, leading to enhancement of oxidative stress, and triggering the inflammatory response (162).

It has been shown that mitochondrial damage is an important event in PM-induced cytotoxicity (58), but there is little information available about the specific effects of exposure to PM. The first response to PM observed in isolated mitochondria is a decrease in the mitochondrial membrane potential and augmented production of O_2^{-}, which is followed by cytochrome c release and inner mitochondrial membrane damage (170). Several studies have demonstrated that environmental PM exposure triggers a decrease in mitochondrial membrane potential. Membrane depolarization was observed during active mitochondrial respiration in ROFA-exposed mice, which could be responsible for the decreased ATP production rate observed in the ROFA group (31,168). It is also important to point out that ultrafine particles, the smallest and probably the most toxic component of PM, were found deposited inside the damaged mitochondria (86). In mitochondria, an increase in the levels of inflammatory mediators can induce complex I to generate substantially more reactive oxygen species, compared to physiological conditions. Moreover, elevated levels of cytokines have been associated with increased reactive oxygen species generation, and it has been suggested that release of oxidant species into the cytoplasm is regulated by Ca^{2+} homeostasis. The release of cytochrome c into the cytosol as a pro-apoptotic signal has been suggested as a transduction signaling pathway as well; it initiates the recruitment and activation of the caspases relevant in triggering cell death via apoptosis (40). An imbalance in oxidant production can trigger intracellular signaling cascades, causing oxidative damage to cellular and mitochondrial macromolecules, which have also been associated with the development of inflammatory disorders (5). In addition, mitochondrial reactive species, especially H_2O_2, are also engaged in intracellular signaling. In this scenario, a feed-forward regulation of the more relevant ROS sources, such as mitochondria and NADPH oxidases, has been reported. From this point of view, mitochondria are not only a target for ROS produced by NADPH oxidase but also a significant source of ROS, which under certain conditions may stimulate NADPH oxidases (33). This crosstalk between mitochondria and NADPH oxidases, therefore, might result in a vicious feed-forward cycle of ROS production, which might be relevant under conditions of oxidative stress. It also represents an opportunity of pharmacological

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intervention, since it has been demonstrated that mitochondria-targeted antioxidants such as mitoQ can inhibit ROS production by mitochondria, thereby reducing NADPH oxidase activity (174). However, it is still controversial if PM can damage mitochondria in a direct way or whether they enter the organelle because of oxidative damage. PM-induced mitochondrial disruption has important biological effects, which include the initiation of apoptosis and decreased ATP production (62,86). A key mitochondrial target for oxidizing chemicals is the permeability transition pore (PTP) (14). PTP is permeable to molecules of < 1.5 kDa and opens in the mitochondrial inner membrane when matrix Ca^{2+} levels are increased, especially when this is accompanied by oxidative stress (161). The opening of PTP results in mitochondrial swelling, outer membrane rupture, and the release of proapoptotic factors, such as cytochrome c. In addition, mitochondria become depolarized, causing inhibition of oxidative phosphorylation and stimulation of ATP hydrolysis (40). The mechanisms of oxidative damage described in this section are summarized in Figure 1.

5. Effects of particulate matter on the ocular surface.

5.1 Ocular surface anatomy.

In addition to the lungs, the eyes are also constantly exposed to the environment and highly vascularized, so they are particularly vulnerable to the effects of air pollution. The anatomical ocular surface is composed of mucosa that line the globe and palpebral surface, the corneoscleral limbus, the corneal epithelium, and the tear film. The ocular surface is now considered an important target of air pollution because it is almost constantly exposed to air pollutants, separated from the environment only by the tear film. The epithelia of the cornea and the conjunctiva represent the first physical barrier of the eye, protecting the underlying tissues. The conjunctiva is an ectodermally-derived mucosa epithelium that varies from 2-6 cell layers to 6-9. Globet cells constitute 5-10 % of the conjunctival epithelium and produce mucin. The capacity of conjunctiva epithelia to respond quickly to infections and trauma is important to protect the eye from the environment; however, this ability also makes the epithelia particularly sensitive to mechanical, toxic, and immunological injuries (167). The ocular surface plays a fundamental role in the defence against the oxidant species generated by environmental causes, which makes it more vulnerable to oxidative damage (154).

5.2. Underlying mechanisms of the effects of particulate matter (PM) on the ocular surface.

People who live at urban centers are exposed to high levels of air pollutants; therefore, they often present with irritation, burning, foreign body sensation, redness, itching in the eyes, and instability of the tear film in the clinic. Several studies have demonstrated that air pollutants aggravate the symptoms and signs present in patients with dry eye or other chronic diseases of the conjunctiva (15,44,61,106,114,166). Furthermore, the incidence of dry eye disease is particularly increased in megacities, where environmental factors could be major players, thus a new subtype of dry eye disease termed “Environmental Dry Eye Disease” has been proposed (6,47,85).

In recent years, only a few in vitro studies have aimed to elucidate the mechanisms underlying the effects of particulate matter (PM) on corneal and conjunctival epithelial cells; these studies suggest that oxidative stress and pro-inflammatory responses play a key role in the development of the observed toxicity (78,79,80,164,165). Previous studies involving different experimental models using instillation of different kinds of PM reported that exposure to PM also lead to an increase in the number of cell layers of the corneal and conjunctival epithelia (47,188). If the morphological changes as well as disorganized growth are prolonged over time, these consequences of exposure could result in irreversible damage, affecting the refractive power of the cornea and the vision process (30,153).

It has been described that corneal epithelial cells release IL-10, stabilizing the NF-κB inhibitor in the cytoplasm, thus suppressing the transcription of pro-inflammatory cytokines (187). The involvement of IL-10 could be important at early stages after the exposure to urban air to regulate the inflammatory response triggered by air pollutants. Moreover, Matsuda and co-workers found decreases in Th2-associated cytokines in the tears of individuals chronically exposed to high PM levels in the metropolitan area of San Pablo, Brazil (101), suggesting an adaptive strategy of the ocular surface. Additionally, inflammatory mediators could transiently increase the number of epithelial cells, leading to cellular hyperplasia. The release of pro-inflammatory cytokines such as IL-6, IL-8, TNF-α, IL-1β, and MCP-1 has been described in vitro as a response of corneal epithelial cells to different types of PM (124,186,189). Furthermore, *in vitro* exposure of human corneal and

conjunctival epithelial cells to urban air PM elicits an inflammatory response, decreases cellular viability and proliferation, and alters mucin production (46,164).

Conjunctival epithelial cells are capable of entrapping Diesel Exhaust Particles (DEP); in fact, the interaction between plasma membrane protrusions and DEP seems to be important for particle uptake. The accumulation of DEP inside the cell and the interaction of DEP chemicals, including polycyclic aromatic compounds, with intracellular targets could be one of the main causes of the cytotoxic effects observed (79). The antioxidant response, as well as the increased mucin expression, in inflammatory conditions in human conjunctival epithelial cells could be interpreted as an adaptive response to oxidative stress triggered by DEP. The involvement of oxidative stress in the mechanism of DEP-induced damage of the ocular surface, in particular, in human conjunctival epithelial cells is described in Figure 2. The response of human conjunctival epithelial cells to DEP differs over time. For instance, there is a persistent increase of ROS, reaching a maximum level after 1 hour of incubation with DEP. After 1 hour of DEP exposure, mitochondria appear to be altered, since increased levels of superoxide anion are observed. It has been demonstrated that the organic chemical compounds adsorbed to DEP are capable of damaging mitochondria and increasing ROS production (85,124). DEP induces an early redox imbalance, followed by an IL-6-mediated inflammatory response. At first, the oxidative environment, principally generated by mitochondrial superoxide anion, results in an adaptive cellular response, consisting of both enzymatic and non-enzymatic antioxidants. However, the mitochondrial membrane potential reaches a minimum level after 24 h. After 3 h, NADPH oxidase-4 (NOX4) is presented as the main source of reactive oxygen species (ROS), when the cell also starts to initiate a proinflammatory response mediated by IL-6. At this time point, Nrf2 translocates to the nucleus to enhance the cellular antioxidant capacity. Although Nrf2 signaling is still occurring after 24 h, the epithelial cell capacity to maintain redox balance is exceeded, as the antioxidant enzymes and the depleted glutathione (GSH) pool are not capable of detoxifying the overwhelming levels of ROS. The decrease in non-enzymatic antioxidants and the compensatory increase of superoxide dismutase (SOD), glutathione peroxidase (GPX) and glutathione transferase (GST) activities are consequences of the increased ROS production due to DEP exposure and its accumulation inside the cells. The decay in glutathione reductase (GR) activity leads

to compromised recycling, which entails changes in the cellular redox state maintenance. Furthermore, as previously mentioned, NOX4 activity is induced after 3 h of incubation with DEP. This event appears later than the mitochondrial response, when the cell also undergoes a proinflammatory response mediated by IL-6. There is a link between both IL-6 and NADPH oxidase induction, in which IL-6 promotes NADPH oxidase expression and vice versa (12,32,125,191). Maximal ROS production coincides with the lipid damage detected after 1 hour of incubation with DEP, suggesting that lipids could be the earliest molecular targets of oxidative damage. In contrast, protein carbonylation seems to be a late event, since protein damage was detected after 3 hours of incubation with DEP and persisted over 24 hours. The accumulation of protein carbonyls over time is consistent with the fact that carbonylated proteins cannot be repaired by cellular enzymes (43).

Studies involving animal models are required in order to evaluate the mechanism of damage triggered by air pollutants on the ocular surface. Whole-body exposures are biologically relevant and contribute to the better understanding of the idiopathic eye discomfort symptoms experienced by urban population. A recent study involving mice exposed to urban or filtered air in exposure chambers for 1 to 12 weeks demonstrated that air pollution produces alterations on the ocular surface supported by cellular hyperplasia, redox imbalance, as well as the increase of inflammatory mediators|. The corneas exhibited a continuous increase in NOX4 levels throughout the exposure time, suggesting an increased production of ROS. After four weeks, the enzymatic antioxidants were decreased, meanwhile an increase of the glutathione was shown, as a later compensatory antioxidant response. However, redox imbalance took place, evidenced by the increased oxidized proteins, which persisted up to 12 weeks. The inflammatory response was modulated by the increase in IL-10 levels after 1 week, which early regulates the release of TNF-α and IL-6 (78).

6. PM effects on the skin.

6.1. Skin anatomy

The skin primarily consists of two layers: the dermis and the epidermis. The dermis consists of fibroblasts that synthesize collagen and elastin, endothelial cells, and nerve cells. Skin resident immune cells in the dermis include dendritic cells, macrophages, mast cells, and different types of T cells (100). Structures such as nerve endings, hair follicles,

blood and lymphatic vessels, and sebaceous glands are embedded in the dermis. The epidermis is the outer layer of the skin and consists of keratinocytes organized into multiple layers and contains the main skin resident-immune cells, Langerhans cells, which are a specialized subset of dendritic cells (100). The lowest layer of the epithelium or basal layer contains transiently amplifying keratinocytes that can undergo differentiation, forming higher layers of the epithelium. During the process of differentiation, keratinocytes begin to express keratins and other differentiation-dependent factors and withdraw from the cell cycle to eventually form the uppermost layer of the epithelium or stratum corneum (SC). The SC is composed of anucleated, keratinized corneocytes held together in a brick-and-mortar fashion by a lipid-laden extracellular matrix. The barrier function of the skin resides in this compartment, and one of its essential functions is to prevent excess transepidermal water loss (TEWL). Since the skin is the main interface between the body and the environment, it is one of the primary organs exposed to chemical and physical environmental pollutants, including PM.

6.2. Effects of particulate matter exposure on the skin.

Exposure to PM has been associated with a variety of inflammatory skin diseases, including atopic dermatitis, acne, and psoriasis (71,98). Since the SC is the uppermost layer of the epithelium, it is the first target of PM exposure. PM exposure has been shown to alter the ratio of skin surface lipids, decreasing cholesterol content and squalene levels, which are also components of sebum (81,132,138). Our lab has also shown that treating 3D in vitro skin models with $PM_{2.5}$ increases levels of the lipid peroxidation product 4-HNE (97). Pan et al. 2015 demonstrated that PM containing PAHs, regardless of size, increased TEWL and decreased filaggrin and E-cadherin levels (proteins involved in the barrier function and tight junctions in the skin) in vivo in pig skin (123). Furthermore, cigarette smoke, which is characterized by particulate and PAH composition, has also been shown to induce lipid peroxidation in human skin and decreased TEWL (107,128).

However, whether or not particles directly penetrate the skin is a controversial topic. Due to its brick-and-mortar construction, the SC can prevent penetration of particles. For instance, Jin et al. 2018 demonstrated that PM2.5 could not penetrate intact murine skin due to the SC (65). However, hair follicles extend from the dermis to the open surface of the skin, providing a route of penetration for particles, depending on particle size.

Lademann et al. 2004 demonstrated that particles >1 micron are unable to penetrate the skin, forming a film, although particles <1.5 microns can penetrate > 2 mm into the skin through hair follicles (76). Jin et al. 2018 also demonstrated that PM could enter intact and barrier-disrupted murine skin in vivo through hair follicles (65); however, particles could not directly enter the epidermis of intact skin. Since PM can enter hair follicles, there a variety of possibilities of how the particulates can contribute to skin-associated inflammation in this compartment. It is possible that PM could be expelled when follicle-associated sebocytes release sebum, reaching the skin surface and inducing a cascade of lipid peroxidation and ROS generation, thanks to the redox active components present on their surfaces. Alternatively, it is also possible that PM can reach the skin dermis through transport in follicle-associated blood vessels, stimulating dermal immune cell recruitment. Moreover, particles could also fail to be cleared from the follicle, resulting in follicle-associated inflammation. In addition, PAHs, which are components of PM, are lipophilic and can easily penetrate skin (75). This is described in Figure 3. What is clear, however, is that a clinical feature of PM exposure of the skin is the development of hyperpigmentation (176), due to the ability of PM to stimulate melanocyte melanin synthesis through inducing AhR activation (111).

As in the gut, the primary mechanism involved in the PM-induced inflammation in the skin is the alteration of redox homeostasis (65,131). PAHs, components of PM, can disrupt the structure of the mitochondria (23,86), resulting in superoxide production and increased hydroxyl radical formation (71). In addition, some particles can have surface reactivity, generating extracellular ROS production (122). Increased ROS can activate various MAPK signaling pathways in the skin, such as ERK1/2, JNK, and p38 MAPK, resulting in the activation of redox-sensitive transcription factors NF-κB and AP1. These transcription factors can then promote the transcription of a variety of proinflammatory cytokines, including TNF-α, IL-1α, IL-6, and IL-8. IL-1α and IL-1β, produced in response to activation of p38 MAPK by PM exposure in keratinocytes, can induce an inflammaging state in co-cultured dermal fibroblasts (72). Inflammaging is defined as chronic, low-grade inflammation that is associated with aging (192). Ryu et al. 2019 observed that PM2.5 exposure of keratinocytes stimulated TLR5 activation and NAPDH oxidase 4-dependent ROS production, resulting in epigenetic modifications to the IL-6 promoter and NF-κB-

dependent transcription of IL-6 (144). IL-6 can regulate the production of IL-17 and IL-10 and Th17 cells and stimulate STAT3 activation (180). Our lab has demonstrated that PM2.5 stimulates NF-κB activation and IL-1α release due to increased oxidative stress and prevents Nrf2 transactivation to inhibit the production of phase II antioxidant enzymes (142). Choi et al. 2011 demonstrated that PM increased transcript levels of IL-6, IL-8, and GM-CSF in primary human keratinocytes (28). Since PM exposure induces IL-8 production, exposure in the skin is also associated with neutrophil infiltration in vivo as IL-8 is a potent neutrophil chemoattractant (65). Neutrophil infiltration is a major cause of tissue inflammation (18). Furthermore, PM stimulates activation of AhR, which regulates the activity of the cytochrome P450 enzyme family and T cell differentiation (116). The cytochrome P450 enzyme CYP1A1b can convert PAHs, components of PM, into redox active quinones (128). Our lab has shown in keratinocytes that redox active quinones can stimulate ROS production, NF-κB translocation and NF-κB–dependent transcription, and alter mitochondrial structure, resulting in apoptosis (23). Transition metals contained in PM, such as iron or copper, can also generate ROS through undergoing Fenton or Haber-Weiss reactions (23). All these mechanisms are depicted in Figure 4. This was also confirmed by our group in a 3D skin model where $PM_{2.5}$ exposure increased levels of oxidative markers (F2-α isoprostanes and 4-HNE). The consequences of exposure resulted in activation of NF-κB, increased levels of proinflammatory marker COX-2, release of IL-1α, and DNA damage (97). In addition, we have reported that an intact circadian clock protects against ozone-induced skin damage by promoting activation of the major antioxidant transcription factor Nrf2 (13), suggesting that disruption of circadian rhythms may result in excessive pollution-induced skin damage (84). Ozone is formed when PM interacts with sunlight. Therefore, the consequences of PM exposure on the skin results in oxidative damage to the skin, decreased barrier function, and inflammation, which can lead to the development/exacerbation of proinflammatory skin disorders.

Since exposure to air pollution is associated with a variety of inflammatory skin diseases, including psoriasis (71,98), as well as dysfunction of other organs, such as the heart (20,21,36,135,137,160), it is possible that the skin could be a gateway for the noxious effects of pollution exposure on other organs. In support of this idea, multiple studies have demonstrated that the skin is an entry route for ambient pollutants (105,182,186). In

fact, Weschler et al. observed that the ability of the skin to absorb pollutants from the outdoor environment is likely as efficient as the respiratory tract (182). Thus, skin exposure to ambient air pollution may result in systemic effects like cardiovascular dysfunction. For instance, psoriasis, an inflammatory skin disease that is associated with pollutant exposure and driven by IL-17, is associated with increased risk of cardiovascular mortality (102). This is likely due to the fact that overexpression of IL-17 in the skin, which results in psoriasis-like skin inflammation, stimulates ROS production, endothelial dysfunction, arterial hypertension, and increased mortality in mice (68,150).

7. A novel target of PM: The gastrointestinal tract.

7.1 Anatomy of the gut.

The gastrointestinal tract (GI tract) is an organ that is responsible for digesting food and extracting energy and nutrients then expelling the remaining waste as fecal matter. The upper part of the GI tract consists of the mouth, esophagus, and stomach. The lower part of the GI tract consists of the majority of the small intestine and all the large intestine. The small intestine is composed of the duodenum, jejunum and ileum, while the large intestine is composed of the cecum, colon, and rectum. The structure of this organ is similar across all areas and consists of a layer of polarized simple columnar epithelial cells supported by connective tissue (lamina propria) and an underlying layer of smooth muscle. There are four types of columnar epithelial cells in the gut including enterocytes, goblet cells, Paneth cells, and enteroendocrine cells (produce hormones). Goblet cells synthesize mucins and other components of mucus, which defends against invading pathogens. Paneth cells are also involved in gut defense and secrete antimicrobial peptides. The role of enterocytes in the gut is to transport molecules into the intestinal lumen. To prevent contents of the intestinal lumen from leaking out into the bloodstream, these intestinal epithelial cells are held together by tight junctions near the apical surface to form a relatively impermeable membrane.

The GI tract contains more than 1013 microbes which play an important role in functions, such as ion absorption, vitamin production, immunity, and in histological development (57). Importantly, due to low pH, lower numbers of bacteria are found in the upper part of the GI tract; however, the highest biodiversity of the gut microbiome is found in the colon, due to low redox potential and cell turnover (57). Organisms in the kingdom Bacteria

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constitute most of the microbiome, and members of the Firmicutes and Bacteroidetes phyla are the most common bacteria found in the gut, although members of Actinobacteria, Fusobacteria, and Verrucomicrobia are also commonly found (39). In the gut, the primary products responsible for the multifaceted effects of the microbiome on the host are short chain fatty acids (SCFAs), such as butyrate, acetate, and propionate, which can enter circulation and regulate the function of multiple organs, including the skin. SCFAs are made by the microbiome as products of the fermentation of non-digestible fibers (184).

7.2. Effects of particulate matter exposure on the gut.

Recently, exposure to PM has been associated with a variety of GI tract issues, including Crohn's disease (67,92,93), inflammatory bowel disease (IBD) (7), appendicitis (66), and colorectal cancer (49,53). The gut can become exposed to particles directly from ingestion or indirectly as a result of inhalation. In fact, in a typical western diet, 1012-1014 particles are ingested daily by an individual (92,93). Moreover, multiple studies in both humans and rodents have shown that inhaled particles can be cleared from the lungs and reach the gut through mucocillary clearance (74,104,176). Specifically, inhaled UFP particles are taken up by alveolar macrophages in the lungs and then transported to the luminal side of the respiratory epithelium and carried to the oropharynx via mucocillary transport, where they can then be swallowed and enter the GI tract, ultimately being excreted in fecal matter (151,152). However, this process is specific to smaller particles as larger particles are primarily sequestered in the lungs (74,104,118,151), although larger particles can still be directly ingested. Moreover, it is currently unclear how long the particles can stay in the gut after reaching it either directly or indirectly. Data from Semmler-Behnke et al. 2007 demonstrated that particles can be found in fecal matter up to six months after inhalation (151). Furthermore, it is unclear exactly what kinds of particles are ingested.

The primary cause of PM-induced GI tract inflammatory-related diseases is believed to be altered redox homeostasis in the gut due to PM exposure, resulting in a leaky gut and secretion of proinflammatory factors and bacterial metabolites (Figure 5). This hypothesis primarily extends from the results of studies investigating PM exposure on other epithelial cells (i.e. airway epithelial cells), which have been extrapolated to intestinal epithelial cells. Since inflammatory (like toll-like receptor) pathways in epithelial tissues are conserved,

pathways that have been demonstrated to be activated in response to PM in other epithelial tissues (i.e. airway and skin) are likely to be activated in the gut, such as the inflammasome and aryl hydrocarbon receptor (AhR), particularly since the respiratory epithelium and the intestinal epithelium share the same embryonic origin. However, there are a few studies directly investigating the effects of PM exposure on gut inflammation and permeability. For instance, Mutlu et al. 2011 demonstrated that exposure of intestinal epithelial cells to PM increased ROS generation, resulting in increased activity of the redox-sensitive transcription factor NF-κB (109), and NF-κB regulates transcription of myosin light chain kinase (MLCK) (3), which can reorganize perijuctional actin, occludin, and ZO1 at tight junctions, resulting in alteration of gut permeability (28). Thus, Mutlu et al. 2011 also observed that exposure of intestinal epithelial cells to PM increased permeability and disrupted tight junctions in vitro and in vivo (109). In another study investigating the effects of PM exposure on both wild-type (WT) and IL-10 knockout (KO) mice (as a model of IBD), Kish et al. 2013 demonstrated that PM10 exposure (7 -14 and 35 days) via gastric lavage increased expression of proinflammatory cytokines in the gut including IFNγ, molecules involved in lymphocyte adhesion/migration, and co-stimulatory molecules (73). After 7 days of exposure, these authors observed increased secretion of CXCL1, IL-1B, and IL-10 in the small intestine and increased gut permeability over two weeks (73). Salim et al. demonstrated that PM_{10} exposure increased serum LPS levels through inducing bacterial translocation, increased levels of proinflammatory cytokines TNF-α and IL-1β in the small intestine and colon, and decreased levels of IL-17A in the gut (produced by proinflammatory Th17 cells) in neonatal IL-10 KO mice (147). They also observed that PM10 exposure increased epithelial permeability through TNF-α and inhibited the antibacterial activity of macrophages in vitro.

In an inhalation study, Vignal et al. observed that PM_{10} increased serum MDA levels and myeloperoxidase activity in the colon, which are both markers of oxidative stress (177). These authors also observed increased levels of inflammatory cytokines (TNF-α, CXCL10, and IFNγ) in the colons of exposed mice. Li et al. observed that inhalation of UFPs increased levels of arachidonic acid and prostaglandin D_2 in the intestine of exposed Ldlr KO mice (a model of atherosclerosis) (87). Furthermore, they observed that inhalation of UFPs decreased villus length (alters nutrient absorption) and increased intestinal

macrophage and neutrophil infiltration. In a different study, Li et al. demonstrated that oral gavage of UFPs in Ldlr KO mice fed a high fat diet increased macrophage and neutrophil infiltration in the small intestine (88). They also observed that gavaged UFP increased plasma levels of proinflammatory TNF-α and MCP-1, which is a monocyte chemoattractant. TNF-α has been demonstrated to alter intestinal permeability through upregulation of myosin light chain kinase (MLCK) and NFκB activity (3). These authors did not observe an increase in gut permeability in response to long-term exposure of UFPs, although they were able to notice this effect in the short-term exposure of CaCo2 cells to UFPs. Therefore, the potential consequences of PM exposure on the gut are increased oxidative stress and inflammation, resulting in a leaky gut, leading to increased circulating levels of bacterial metabolites, proinflammatory cytokines, and endotoxin, which are known to regulate cutaneous immune responses (117). Thus, the consequences of PM exposure can result in systemic inflammation, resulting in dysfunction of a variety of organs, including the heart, which is reviewed nicely by the following articles (20,36,135,137,160). Furthermore, exposure of the gut may potentially affect the skin as well through the gut-skin axis.

8. Pollution and the gut-skin-brain axis

In the gut-skin-brain axis, the primary player is the gut microbiome, despite the involvement of multiple organs. For instance, in this axis, stress induces the production of neurotransmitters, hormones, and other secreted factors that can directly regulate pathways in the skin and/or induce intestinal permeability and/or dysbiosis, resulting in the production of secreted factors that can then regulate the skin (2,8,117,127,147,156). Furthermore, the gut microbiome can also produce its own neurotransmitters that can move from the intestinal epithelium into the bloodstream, and, upon reaching the skin, can regulate cutaneous barrier function, hair growth, and melatonin synthesis (184). In addition to neurotransmitters, SCFAs, such as butyrate, can bind to G-protein coupled receptors (GPCRs) expressed on endothelial cells, immune cells, and keratinocytes, regulating cutaneous inflammation (185). Furthermore, SCFAs can systemically promote the differentiation of peripheral induced Tregs, development of hematopoietic/dendritic cell progenitor cells, and regulate iNKT cell numbers through binding GPCRs and regulating histone deacetylase activity (52,91). Thus, SCFAs contribute to the development of

systemic immunity. In this way, SCFAs are also mediators of the gut-lung axis in addition to the gut-skin axis, which is reviewed by Lloyd et al. 2017 (91). Moreover, SCFAs produced by gut bacteria may be able to regulate members of the skin and lung microbiomes, since SCFAs can be found in the blood in concentrations from 1-150 μM (120).

There are no current studies investigating the effects of pollution on the gut-skin axis. However, multiple studies have shown that PM exposure alters the composition of the gut microbiome. For instance, in IL-10 KO mice, PM exposure altered the abundance of Bacteroidetes, Firmicutes, and Verrucomicrobia in feces and decreased levels of the SCFA butyrate in the cecum (73). In neonatal IL-10 KO mice, ingestion of PM10 resulted in decreased levels of Bifidobacteria and Actinobacteria (147). In a separate study, Li et al. demonstrated that ingestion of UFPs decreased abundance of Firmicutes, Cyanobacteria, and Actinobacteria in the cecum, while increasing abundance of Verrumicrobia in Ldlr-KO mice fed a high-fat diet (model of atherosclerosis) (88). They believe that reduction in the levels of Actinobacteria, Cyanobacteria, and Firmicutes was responsible for increased inflammation in the gut. Mutlu et al. demonstrated that inhaled $PM_{2.5}$ decreased abundance of Firmicutes and Lactobacillus (used in probiotics), increased levels of Bacteroidetes, and increased levels of TNF-α in the colon (108). However, none of these studies investigated the effects of exposure of the gut to PM on the skin, likely due to the fact that they all used mice that have fur, preventing examination of the effects of exposure on the skin without depilation.

9. Concluding remarks.

The mechanisms by which PM exposure results in adverse health effects are still poorly understood. However, as described in this manuscript, PM exposure negatively affects the eyes, lungs, gut, and skin, and impact on these organs can result in systemic complications. For instance, the eyes are highly vascularized, providing a gateway for PM-induced secreted mediators. Particles can also be directly inhaled and ingested (via contaminated food) and alter levels of circulating mediators. Therefore, exposure to pollutants should initially be thought to be localized at the tissue level.

Moreover, a better understanding of the mechanisms underlying PM-induced health problems would allow a more targeted approach to prevent the toxic effects of PM exposure and could possibly provide different ways to decrease individual sensitivity to

PM. Studies in isolated cells and in animal models suggest that there are a variety of possible mechanisms, including direct effects of particle components and indirect effects due to proinflammatory mediators. The current hypothesis is that the inflammation induced by the presence of ambient particles induces a systemic inflammatory response, with endothelial activation and oxidative and nitrosative stress. These changes contribute to the increase in morbidity and mortality associated with polluted areas.

In conclusion, we must reduce emissions of PM in the air, preventing exposure of organs that directly interact with PM, such as the lungs, eye, gut, and skin, thereby reducing the development/exacerbation of PM-associated lung dysfunction, environmental dry eye disease, inflammatory skin disorders, GI tract issues, and systemic complications resulting from exposure of these organs (like cardiovascular defects). Another way to reduce adverse pollution-related health effects is to limit individual exposure to pollution and utilize air quality apps, such as AirVisual, AirMatters, AIR, Blueair Friend, and Air Quality Index to help predict the least polluted day or time of day for people to engage in outdoor activities. Similar to tobacco use, preventing exposure to this pollutant is the most effective strategy to reduce PM-related health effects in the global population.

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List of Abbreviations

AhR: aryl hydrocarbon receptor

AP-1: Activator protein 1

ATI: alveolar type I cells

ATII: alveolar type II cells

ATP: Adenosine triphosphate

BMAL1: Brain and muscle arnt-like protein-1

CXCL1: chemokine (C-X-C motif) ligand 1

COX: Cyclooxygenase

DEP: Diesel Exhaust Particles

ERK: extracellular signal–regulated kinase

GI tract: gastrointestinal tract

GM-CSF: Granulocyte-colony stimulating factor

GPCR: G-protein coupled receptor

4-HNE: 4-hydroxynonenal

IBD: inflammatory bowel disease

IFNγ: Interferon γ

IL: interleukin

KO: Knockout

MAPK: Mitogen-activated protein kinase

MCP-1: monocyte chemoattractant protein 1

MLCK: myosin light chain kinase

NADPH: Nicotinamide adenine dinucleotide phosphate

NF-κB: Nuclear Factor-κB

Nrf2: Nuclear factor erythroid 2-related factor 2

PAH: Polycyclic Aromatic Hydrocarbons

PM: Particulate Matter

PTP: permeability transition pore

ROFA: residual oil fly ashes

ROS: Reactive Oxygen Species

RNS: Reactive Nitrogen Species

SC: stratum corneum

SCFA: short chain fatty acids

SIRT1: sirtuin 1

TBARS: thiobarbituric acid reactive substances

TEWL: transepidermal water loss

TNF-α: Tumor necrosis factor

UFP: ultrafine particle

WHO: World Health Organization

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References

1. (WHO) *Burden of disease from the joint effects of household and ambient Air pollution for 2016*. Geneva, Switzerland; 2018. pp. 5.

2. Aberg KM, Radek KA, Choi EH, Kim DK, Demerjian M, Hupe M, Kerbleski J, Gallo RL, Ganz T, Mauro T, Feingold KR, Elias PM. Psychological stress downregulates epidermal antimicrobial peptide expression and increases severity of cutaneous infections in mice. *J Clin Invest* 117: 3339-49, 2007.

3. Al-Sadi R, Guo S, Ye D, Rawat M, Ma TY. TNF-alpha Modulation of Intestinal Tight Junction Permeability Is Mediated by NIK/IKK-alpha Axis Activation of the Canonical NF-kappaB Pathway. *Am J Pathol* 186: 1151-65, 2016.

4. Alsberg T, Stenberg U, Westerholm R, Strandell M, Rannug U, Sundvall A, Romert L, Bernson V, Pettersson B, et al. Chemical and biological characterization of organic material from gasoline exhaust particles. *Environ Sci Technol* 19: 43-50, 1985.

5. Alvarez S, Evelson PA. Nitric oxide and oxygen metabolism in inflammatory conditions: sepsis and exposition to polluted ambients. *Front Biosci* 12: 964-74, 2007.

6. Alves M, Novaes P, Morraye MdA, Reinach PS, Rocha EM. Is dry eye an environmental disease? *Arq Bras Oftalmol* 77: 193-200, 2014.

7. Ananthakrishnan AN, McGinley EL, Binion DG, Saeian K. Ambient air pollution correlates with hospitalizations for inflammatory bowel disease: an ecologic analysis. *Inflamm Bowel Dis* 17: 1138-45, 2011.

8. Arck P, Handjiski B, Hagen E, Pincus M, Bruenahl C, Bienenstock J, Paus R. Is there a 'gut-brain-skin axis'? *Exp Dermatol* 19: 401-5, 2010.

9. Bai L, Wang J, Ma X, Lu H. Air Pollution Forecasts: An Overview. *Int J Environ Res Public Health* 15: 780, 2018.

10. Baird C, Cann, M. Environmental Chemistry New York: W. H. Freeman; 2005.

11. Becker S, Soukup JM, Gallagher JE. Differential particulate air pollution induced oxidant stress in human granulocytes, monocytes and alveolar macrophages. *Toxicol in vitro* 16: 209-18, 2002.

12. Behrens MM, Ali SS, Dugan LL. Interleukin-6 mediates the increase in NADPH-oxidase in the ketamine model of schizophrenia. *J Neurosci* 28: 13957-66, 2008.

13. Benedusi M, Frigato E, Beltramello M, Bertolucci C, Valacchi G. Circadian clock as possible protective mechanism to pollution induced keratinocytes damage. *Mech Ageing Dev* 172: 13-20, 2018.

14. Bernardi P. Mitochondrial transport of cations: channels, exchangers, and permeability transition. *Physiol Rev* 79: 1127-55, 1999.

15. Berra M, Galperin G, Dawidowski L, Tau J, Marquez I, Berra A. Impact of wildfire smoke in Buenos Aires, Argentina, on ocular surface. *Arq Bras Oftalmol* 78: 110-4, 2015.

16. Bhattacharya J, Matthay MA. Regulation and repair of the alveolar-capillary barrier in acute lung injury. *Annu Rev Physiol* 75: 593-615, 2013.

17. Bhowmick R, Gappa-Fahlenkamp H. Cells and Culture Systems Used to Model the Small Airway Epithelium. Lung 194: 419-28, 2016.

18. Bian Z, Guo Y, Ha B, Zen K, Liu Y. Regulation of the inflammatory response: enhancing neutrophil infiltration under chronic inflammatory conditions. *J Immunol* 188: 844-53, 2012.

19. Borok Z. Alveolar epithelium: beyond the barrier. *Am J Respir Cell Mol Biol* 50: 853-6, 2014.

20. Brook RD, Franklin B, Cascio W, Hong Y, Howard G, Lipsett M, Luepker R, Mittleman M, Samet J, Smith SC, Jr., Tager I, Expert Panel on Population and Prevention Science of the American Heart Association. Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. *Circulation* 109: 2655-71, 2004.

21. Brook RD, Rajagopalan S, Pope CA, 3rd, Brook JR, Bhatnagar A, Diez-Roux AV, Holguin F, Hong Y, Luepker RV, Mittleman MA, Peters A, Siscovick D, Smith SC, Jr., Whitsel L, Kaufman JD, American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, and Council on Nutrition, Physical Activity and Metabolism. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. *Circulation* 121: 2331-78, 2010.

22. Burnett R, Chen H, Szyszkowicz M, Fann N, Hubbell B, Pope CA, 3rd, Apte JS, Brauer M, Cohen A, Weichenthal S, Coggins J, Di Q, Brunekreef B, Frostad J, Lim SS, Kan H, Walker KD, Thurston GD, Hayes RB, Lim CC, Turner MC, Jerrett M, Krewski D, Gapstur SM, Diver WR, Ostro B, Goldberg D, Crouse DL, Martin RV, Peters P, Pinault L, Tjepkema M, van Donkelaar A, Villeneuve PJ, Miller AB, Yin P, Zhou M, Wang L, Janssen NAH, Marra M, Atkinson RW, Tsang H, Quoc Thach T, Cannon JB, Allen RT, Hart JE, Laden F, Cesaroni G, Forastiere F, Weinmayr G, Jaensch A, Nagel G, Concin H, Spadaro JV. Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. *Proc Natl Acad Sci USA* 115: 9592-9597, 2018.

23. Cervellati F, Benedusi M, Manarini F, Woodby B, Russo M, Valacchi G, Pietrogrande MC. Proinflammatory properties and oxidative effects of atmospheric particle components in human keratinocytes. *Chemosphere* 240: 124746, 2020.

24. Chen LC, Lippmann M. Effects of metals within ambient air particulate matter (PM) on human health. *Inhal Toxicol* 21: 1-31, 2009.

25. Cheng, M, Wang B, Yang M, Ma J, Ye Z, Xie L, Zhou M, Chen W. microRNAs expression in relation to particulate matter exposure: A systematic review. *Environ Poll* 260: 113961, 2020.

26. Choi H, Shin DW, Kim W, Doh SJ, Lee SH, Noh M. Asian dust storm particles induce a broad toxicological transcriptional program in human epidermal keratinocytes. *Toxicol Lett* 200: 92-9, 2011.

27. Citron J, Willcocks E, Crowley G, Kwon S, Nolan A. Genomics of Particulate Matter Exposure Associated Cardiopulmonary Disease: A Narrative Review. *Int. J. Environ. Res. Public Health* 16: 4335, 2019.

28. Cunningham KE, Turner JR. Myosin light chain kinase: pulling the strings of epithelial tight junction function. *Ann N Y Acad Sci* 1258: 34-42, 2012.

29. Daiber A, Lelieveld J, Steven S, Oelze M, Kroller-Schon S, Sorensen M, Munzel T. The "exposome" concept - how environmental risk factors influence cardiovascular health. Acta Biochim Pol 66: 269-283, 2019.

30. Del Monte DW, Kim T. Anatomy and physiology of the cornea. J Cataract Refract Surg 37: 588-98, 2011.

31. Di Pietro A, Visalli G, Baluce B, Micale RT, La Maestra S, Spataro P, De Flora S. Multigenerational mitochondrial alterations in pneumocytes exposed to oil fly ash metals. Int J Hyg Environ Health 214: 138-44, 2011.

32. Didion SP. Cellular and Oxidative Mechanisms Associated with Interleukin-6 Signaling in the Vasculature. Int J Mol Sci 18, 2017.

33. Dikalov S. Cross talk between mitochondria and NADPH oxidases. *Free Radic Biol Med* 51: 1289-301, 2011.

34. Dominici F, Peng RD, Bell ML, Pham L, McDermott A, Zeger SL, Samet JM. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *JAMA* 295: 1127-34, 2006.

35. Dreher KL, Jaskot RH, Lehmann JR, Richards JH, McGee JK, Ghio AJ, Costa DL. Soluble transition metals mediate residual oil fly ash induced acute lung injury. *J Toxicol Environ Health* 50: 285-305, 1997.

36. Du Y, Xu X, Chu M, Guo Y, Wang J. Air particulate matter and cardiovascular disease: the epidemiological, biomedical and clinical evidence. *J Thorac Dis* 8: E8-E19, 2016.

37. Dunea D, Iordache S, Liu HY, Bohler T, Pohoata A, Radulescu C. Quantifying the impact of PM2.5 and associated heavy metals on respiratory health of children near metallurgical facilities. *Environ Sci Pollut Res Int* 23: 15395-406, 2016.

38. Ebnet K, Aurrand-Lions M, Kuhn A, Kiefer F, Butz S, Zander K, Meyer zu Brickwedde MK, Suzuki A, Imhof BA, Vestweber D. The junctional adhesion molecule (JAM) family members JAM-2 and JAM-3 associate with the cell polarity protein PAR-3: a possible role for JAMs in endothelial cell polarity. J Cell Sci 116: 3879-91, 2003.

39. Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, Gill SR, Nelson KE, Relman DA. Diversity of the human intestinal microbial flora. *Science* 308: 1635-8, 2005.

40. Elmore S. Apoptosis: a review of programmed cell death. *Toxicol Pathol* 35: 495-516, 2007.

41. Elsom DM. *Atmospheric Pollution: A Global Problem*: Blackwell Publishers; 1992.

42. Fajersztajn L, Veras M, Barrozo LV, Saldiva P. Air pollution: a potentially modifiable risk factor for lung cancer. *Nat Rev Cancer* 13: 674-8, 2013.

43. Fedorova M, Bollineni RC, Hoffmann R. Protein carbonylation as a major hallmark of oxidative damage: update of analytical strategies. *Mass Spectrom Rev* 33: 79-97, 2014.

44. Fu Q, Mo Z, Lyu D, Zhang L, Qin Z, Tang Q, Yin H, Xu P, Wu L, Lou X, Chen Z, Yao K. Air pollution and outpatient visits for conjunctivitis: A case-crossover study in Hangzhou, China. *Environ Pollut* 231: 1344-1350, 2017.

45. Fujino N, Kubo H, Suzuki T, Ota C, Hegab AE, He M, Suzuki S, Suzuki T, Yamada M, Kondo T, Kato H, Yamaya M. Isolation of alveolar epithelial type II progenitor cells from adult human lungs. *Lab Invest* 91: 363-78, 2011.

46. Fujishima H, Satake Y, Okada N, Kawashima S, Matsumoto K, Saito H. Effects of diesel exhaust particles on primary cultured healthy human conjunctival epithelium. *Ann Allergy Asthma Immunol* 110: 39-43, 2013.

47. Gao ZX, Song XL, Li SS, Lai XR, Yang YL, Yang G, Li ZJ, Cui YH, Pan HW. Assessment of DNA Damage and Cell Senescence in Corneal Epithelial Cells Exposed to Airborne Particulate Matter (PM2.5) Collected in Guangzhou, China. *Invest Ophthalmol Vis Sci* 57: 3093-102, 2016.

48. Gebel S, Gerstmayer B, Kuhl P, Borlak J, Meurrens K, Muller T. The kinetics of transcriptomic changes induced by cigarette smoke in rat lungs reveals a specific program of defense, inflammation, and circadian clock gene expression. *Toxicol Sci* 93: 422-31, 2006.

49. Gerhardsson de Verdier M, Plato N, Steineck G, Peters JM. Occupational exposures and cancer of the colon and rectum. *Am J Ind Med* 22: 291-303, 1992.

50. Ghio AJ, Huang YC. Exposure to concentrated ambient particles (CAPs): a review. *Inhal Toxicol* 16: 53-9, 2004.

51. Ghio AJ, Silbajoris R, Carson JL, Samet JM. Biologic effects of oil fly ash. *Environ Health Perspect* 110 Suppl 1: 89-94, 2002.

52. Grainger J, Daw R, Wemyss K. Systemic instruction of cell-mediated immunity by the intestinal microbiome. *F1000Res* 7, 2018.

53. Guberan E, Usel M, Raymond L, Bolay J, Fioretta G, Puissant J. Increased risk for lung cancer and for cancer of the gastrointestinal tract among Geneva professional drivers. *Br J Ind Med* 49: 337-44, 1992.

54. Guillot L, Nathan N, Tabary O, Thouvenin G, Le Rouzic P, Corvol H, Amselem S, Clement A. Alveolar epithelial cells: master regulators of lung homeostasis. *Int J Biochem Cell Biol* 45: 2568-73, 2013.

55. Haberzettl P. Circadian toxicity of environmental pollution. Inhalation of polluted air to give a precedent. *Curr Op Physiol* 5: 16-24, 2018.

56. Hamanaka RB, Mutlu GM. Particulate Matter Air Pollution: Effects on the Cardiovascular System. *Front Endocrinol* 9: 680, 2018.

57. Hillman ET, Lu H, Yao T, Nakatsu CH. Microbial Ecology along the Gastrointestinal Tract. *Microbes Environ* 32: 300-313, 2017.

58. Hiura TS, Kaszubowski MP, Li N, Nel AE. Chemicals in diesel exhaust particles generate reactive oxygen radicals and induce apoptosis in macrophages. *J Immunol* 163: 5582-91, 1999.

59. Hsia CC, Hyde DM, Weibel ER. Lung Structure and the Intrinsic Challenges of Gas Exchange. *Compr Physiol* 6: 827-95, 2016.

60. Hwang J-W, Sundar IK, Yao H, Sellix MT, Rahman I. Circadian clock function is disrupted by environmental tobacco/cigarette smoke, leading to lung inflammation and injury via a SIRT1-BMAL1 pathway. *FASEB J* 28: 176-194, 2014.

61. Hwang SH, Choi YH, Paik HJ, Wee WR, Kim MK, Kim DH. Potential Importance of Ozone in the Association Between Outdoor Air Pollution and Dry Eye Disease in South Korea. *JAMA Ophthalmol* 134: 503-510, 2016.

62. Jajte JM. Chemical-induced changes in intracellular redox state and in apoptosis. Int *J Occup Med Environ Health* 10: 203-12, 1997.

63. Jansing NL, McClendon J, Henson PM, Tuder RM, Hyde DM, Zemans RL. Unbiased Quantitation of Alveolar Type II to Alveolar Type I Cell Transdifferentiation during Repair after Lung Injury in Mice. *Am J Respir Cell Mol Biol* 57: 519-526, 2017.

64. Jimenez LA, Drost EM, Gilmour PS, Rahman I, Antonicelli F, Ritchie H, MacNee W, Donaldson K. PM(10)-exposed macrophages stimulate a proinflammatory response in lung epithelial cells via TNF-alpha. *Am J Physiol Lung Cell Mol Physiol* 282: L237-48, 2002.

65. Jin SP, Li Z, Choi EK, Lee S, Kim YK, Seo EY, Chung JH, Cho S. Urban particulate matter in air pollution penetrates into the barrier-disrupted skin and produces ROS-dependent cutaneous inflammatory response in vivo. *J Dermatol Sci* 91: 175-83, 2018.

66. Kaplan GG, Dixon E, Panaccione R, Fong A, Chen L, Szyszkowicz M, Wheeler A, MacLean A, Buie WD, Leung T, Heitman SJ, Villeneuve PJ. Effect of ambient air pollution on the incidence of appendicitis. *CMAJ* 181: 591-7, 2009.

67. Kaplan GG, Hubbard J, Korzenik J, Sands BE, Panaccione R, Ghosh S, Wheeler AJ, Villeneuve PJ. The inflammatory bowel diseases and ambient air pollution: a novel association. *Am J Gastroenterol* 105: 2412-9, 2010.

68. Karbach S, Croxford AL, Oelze M, Schuler R, Minwegen D, Wegner J, Koukes L, Yogev N, Nikolaev A, Reissig S, Ullmann A, Knorr M, Waldner M, Neurath MF, Li H, Wu Z, Brochhausen C, Scheller J, Rose-John S, Piotrowski C, Bechmann I, Radsak M, Wild P, Daiber A, von Stebut E, Wenzel P, Waisman A, Munzel T. Interleukin 17 drives vascular inflammation, endothelial dysfunction, and arterial hypertension in psoriasis-like skin disease. *Arterioscler Thromb Vasc Biol* 34: 2658-68, 2014.

69. Kelly FJ, Fussell JC. Air pollution and public health: emerging hazards and improved understanding of risk. *Environ Geochem Health* 37: 631-49, 2015.

70. Kelly FJ, Fussell, J. C. Size, source and chemical composition as determinants of toxicity attributable to ambient particulate matter. *Atmosph Environ* 60: 504-526, 2012.

71. Kim KE, Cho D, Park HJ. Air pollution and skin diseases: Adverse effects of airborne particulate matter on various skin diseases. *Life Sci* 152: 126-34, 2016.

72. Kim M, Kim JH, Jeong GJ, Park KY, Lee MK, Seo SJ. Particulate matter induces pro-inflammatory cytokines via phosphorylation of p38 MAPK possibly leading to dermal inflammaging. *Exp Dermatol* 28: 809-815, 2019.

73. Kish L, Hotte N, Kaplan GG, Vincent R, Tso R, Ganzle M, Rioux KP, Thiesen A, Barkema HW, Wine E, Madsen KL. Environmental particulate matter induces murine intestinal inflammatory responses and alters the gut microbiome. *PLoS One* 8: e62220, 2013.

74. Kreyling WG, Blanchard JD, Godleski JJ, Haeussermann S, Heyder J, Hutzler P, Schulz H, Sweeney TD, Takenaka S, Ziesenis A. Anatomic localization of 24- and 96-h particle retention in canine airways. *J Appl Physiol* 87: 269-84, 1999.

75. Krutmann J, Liu W, Li L, Pan X, Crawford M, Sore G, Seite S. Pollution and skin: from epidemiological and mechanistic studies to clinical implications. *J Dermatol Sci* 76: 163-8, 2014.

76. Lademann J, Schaefer H, Otberg N, Teichmann A, Blume-Peytavi U, Sterry W. [Penetration of microparticles into human skin]. *Hautarzt* 55: 1117-9, 2004.

77. Landrigan PJ, Fuller R, Acosta NJR, Adeyi O, Arnold R, Basu NN, Balde AB, Bertollini R, Bose-O'Reilly S, Boufford JI, Breysse PN, Chiles T, Mahidol C, Coll-Seck AM, Cropper ML, Fobil J, Fuster V, Greenstone M, Haines A, Hanrahan D, Hunter D, Khare M, Krupnick A, Lanphear B, Lohani B, Martin K, Mathiasen KV, McTeer MA, Murray CJL, Ndahimananjara JD, Perera F, Potocnik J, Preker AS, Ramesh J, Rockstrom J, Salinas C, Samson LD, Sandilya K, Sly PD, Smith KR, Steiner A, Stewart RB, Suk WA, van Schayck OCP, Yadama GN, Yumkella K, Zhong M. The Lancet Commission on pollution and health. *Lancet* 391: 462-512, 2018.

78. Lasagni Vitar RM, Hvozda Arana AG, Janezic NS, Marchini T, Tau J, Martinefski M, Tesone AI, Racca L, Reides CG, Tripodi V, Evelson P, Berra A, Llesuy SF, Ferreira SM. Urban air pollution induces redox imbalance and epithelium hyperplasia in mice cornea. *Toxicol Appl Pharmacol*. 2019 1; 384: 114770.

79. Lasagni Vitar RM, Tau J, Janezic NS, Tesone AI, Hvozda Arana AG, Reides CG, Berra A, Ferreira SM, Llesuy SF. Diesel exhaust particles (DEP) induce an early redox imbalance followed by an IL-6 mediated inflammatory response on human conjunctival epithelial cells. *Exp Eye Res* 171: 37-47, 2018.

80. Lasagni Vitar RM, Tau J, Reides CG, Berra A, Ferreira SM, Llesuy SF. Evaluation of Oxidative Stress Markers in Human Conjunctival Epithelial Cells Exposed to Diesel Exhaust Particles (DEP). *Invest Ophthalmol Vis Sci* 56: 7058-66, 2015.

81. Lefebvre MA, Pham DM, Boussouira B, Bernard D, Camus C, Nguyen QL. Evaluation of the impact of urban pollution on the quality of skin: a multicentre study in Mexico. *Int J Cosmet Sci* 37: 329-38, 2015.

82. Lelieveld J, Klingmuller K, Pozzer A, Poschl U, Fnais M, Daiber A, Munzel T. Cardiovascular disease burden from ambient air pollution in Europe reassessed using novel hazard ratio functions. *Eur Heart J* 40: 1590-1596, 2019.

83. Leonard SS, Harris GK, Shi X. Metal-induced oxidative stress and signal transduction. *Free Radic Biol Med* 37: 1921-42, 2004.

84. Li H, Kilgallen AB, Munzel T, Wolf E, Lecour S, Schulz R, Daiber A, Van Laake LW. Influence of mental stress and environmental toxins on circadian clocks: Implications for redox regulation of the heart and cardioprotection. *Br J Pharmacol*, 2019.

85. Li J, Tan G, Ding X, Wang Y, Wu A, Yang Q, Ye L, Shao Y. A mouse dry eye model induced by topical administration of the air pollutant particulate matter 10. *Biomed Pharmacother* 96: 524-534, 2017.

86. Li N, Sioutas C, Cho A, Schmitz D, Misra C, Sempf J, Wang M, Oberley T, Froines J, Nel A. Ultrafine particulate pollutants induce oxidative stress and mitochondrial damage. *Environ Health Perspect* 111: 455-60, 2003.

87. Li R, Navab K, Hough G, Daher N, Zhang M, Mittelstein D, Lee K, Pakbin P, Saffari A, Bhetraratana M, Sulaiman D, Beebe T, Wu L, Jen N, Wine E, Tseng CH, Araujo JA, Fogelman A, Sioutas C, Navab M, Hsiai TK. Effect of exposure to atmospheric ultrafine particles on production of free fatty acids and lipid metabolites in the mouse small intestine. *Environ Health Perspect* 123: 34-41, 2015.

88. Li R, Yang J, Saffari A, Jacobs J, Baek KI, Hough G, Larauche MH, Ma J, Jen N, Moussaoui N, Zhou B, Kang H, Reddy S, Henning SM, Campen MJ, Pisegna J, Li Z, Fogelman AM, Sioutas C, Navab M, Hsiai TK. Ambient Ultrafine Particle Ingestion Alters Gut Microbiota in Association with Increased Atherogenic Lipid Metabolites. *Sci Rep* 7: 42906, 2017.

89. Li X, Jin L, Kan H. Air pollution: a global problem needs local fixes. *Nature* 570: 437-439, 2019.

90. Lippmann M, Chen LC. Health effects of concentrated ambient air particulate matter (CAPs) and its components. *Crit Rev Toxicol* 39: 865-913, 2009.

91. Lloyd CM, Marsland BJ. Lung Homeostasis: Influence of Age, Microbes, and the Immune System. *Immunity* 46: 549-561, 2017.

92. Lomer MC, Hutchinson C, Volkert S, Greenfield SM, Catterall A, Thompson RP, Powell JJ. Dietary sources of inorganic microparticles and their intake in healthy subjects and patients with Crohn's disease. *Br J Nutr* 92: 947-55, 2004.

93. Lomer MC, Thompson RP, Powell JJ. Fine and ultrafine particles of the diet: influence on the mucosal immune response and association with Crohn's disease. *Proc Nutr Soc* 61: 123-30, 2002.

94. Magnani ND, Marchini T, Garces M, Mebert A, Caceres L, Diaz L, Desimone M, Evelson PA. Role of transition metals present in air particulate matter on lung oxygen metabolism. *Int J Biochem Cell Biol* 81: 419-426, 2016.

95. Magnani ND, Marchini T, Tasat DR, Alvarez S, Evelson PA. Lung oxidative metabolism after exposure to ambient particles. *Biochem Biophys Res Commun* 412: 667-72, 2011.

96. Magnani ND, Marchini T, Vanasco V, Tasat DR, Alvarez S, Evelson P. Reactive oxygen species produced by NADPH oxidase and mitochondrial dysfunction in lung after an acute exposure to residual oil fly ashes. *Toxicol Appl Pharmacol* 270: 31-8, 2013.

97. Magnani ND, Muresan XM, Belmonte G, Cervellati F, Sticozzi C, Pecorelli A, Miracco C, Marchini T, Evelson P, Valacchi G. Skin Damage Mechanisms Related to Airborne Particulate Matter Exposure. *Toxicol Sci* 149: 227-36, 2016.

98. Marrot L. Pollution and Sun Exposure: A Deleterious Synergy. Mechanisms and Opportunities for Skin Protection. *Curr Med Chem* 25: 5469-5486, 2018.

99. Mason RJ. Biology of alveolar type II cells. *Respirology* 11 Suppl: S12-5, 2006.

100. Matejuk A. Skin Immunity. *Arch Immunol Ther Exp (Warsz)* 66: 45-54, 2018.

101. Matsuda M, Bonatti R, Marquezini MV, Garcia ML, Santos UP, Braga AL, Alves MR, Saldiva PH, Monteiro ML. Lacrimal Cytokines Assessment in Subjects Exposed to Different Levels of Ambient Air Pollution in a Large Metropolitan Area. *PLoS One* 10: e0143131, 2015.

102. Mehta NN, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. *Eur Heart J* 31: 1000-6, 2010.

103. Mills NL, Donaldson K, Hadoke PW, Boon NA, MacNee W, Cassee FR, Sandstrom T, Blomberg A, Newby DE. Adverse cardiovascular effects of air pollution. *Nat Clin Pract Cardiovasc Med* 6: 36-44, 2009.

104. Moller W, Haussinger K, Winkler-Heil R, Stahlhofen W, Meyer T, Hofmann W, Heyder J. Mucociliary and long-term particle clearance in the airways of healthy nonsmoker subjects. *J Appl Physiol* (1985) 97: 2200-6, 2004.

105. Morrison GC, Weschler CJ, Beko G, Koch HM, Salthammer T, Schripp T, Toftum J, Clausen G. Role of clothing in both accelerating and impeding dermal absorption of airborne SVOCs. *J Expo Sci Environ Epidemiol* 26: 113-8, 2016.

106. Moss SE, Klein R, Klein BE. Prevalence of and risk factors for dry eye syndrome. *Arch Ophthalmol* 118: 1264-8, 2000.

107. Muizzuddin N MK, Vallon P, Maes D. Effect of cigarette smoke on skin. *J Soc Cosmet Chem* 48: 235-242, 1997.

108. Mutlu EA, Comba IY, Cho T, Engen PA, Yazici C, Soberanes S, Hamanaka RB, Nigdelioglu R, Meliton AY, Ghio AJ, Budinger GRS, Mutlu GM. Inhalational exposure to particulate matter air pollution alters the composition of the gut microbiome. *Environ Pollut* 240: 817-830, 2018.

109. Mutlu EA, Engen PA, Soberanes S, Urich D, Forsyth CB, Nigdelioglu R, Chiarella SE, Radigan KA, Gonzalez A, Jakate S, Keshavarzian A, Budinger GR, Mutlu GM. Particulate matter air pollution causes oxidant-mediated increase in gut permeability in mice. *Part Fibre Toxicol* 8: 19, 2011.

110. Mutlu GM, Sznajder JI. Mechanisms of pulmonary edema clearance. *Am J Physiol Lung Cell Mol Physiol* 289: L685-95, 2005.

111. Nakamura M, Morita A, Seite S, Haarmann-Stemmann T, Grether-Beck S, Krutmann J. Environment-induced lentigines: formation of solar lentigines beyond ultraviolet radiation. *Exp Dermatol* 24: 407-11, 2015.

112. Nel A, Xia T, Madler L, Li N. Toxic potential of materials at the nanolevel. *Science* 311: 622-7, 2006.

113. Newby DE, Mannucci PM, Tell GS, Baccarelli AA, Brook RD, Donaldson K, Forastiere F, Franchini M, Franco OH, Graham I, Hoek G, Hoffmann B, Hoylaerts MF, Kunzli N, Mills N, Pekkanen J, Peters A, Piepoli MF, Rajagopalan S, Storey RF, Esc Working Group on Thrombosis EAfCP, Rehabilitation, Association ESCHF. Expert position paper on air pollution and cardiovascular disease. *Eur Heart J* 36: 83-93b, 2015.

114. Nucci P, Sacchi M, Pichi F, Allegri P, Serafino M, Dello Strologo M, De Cilla S, Villani E. Pediatric Conjunctivitis and Air Pollution Exposure: A Prospective Observational Study. *Semin Ophthalmol* 32: 407-411, 2017.

115. Nurkiewicz TR, Porter DW, Barger M, Millecchia L, Rao KM, Marvar PJ, Hubbs AF, Castranova V, Boegehold MA. Systemic microvascular dysfunction and inflammation after pulmonary particulate matter exposure. Environ Health Perspect 114: 412-9, 2006.

116. O'Driscoll CA, Mezrich JD. The Aryl Hydrocarbon Receptor as an Immune-Modulator of Atmospheric Particulate Matter-Mediated Autoimmunity. *Front Immunol* 9: 2833, 2018.

117. O'Neill CA, Monteleone G, McLaughlin JT, Paus R. The gut-skin axis in health and disease: A paradigm with therapeutic implications. *Bioessays* 38: 1167-1176, 2016.

118. Oberdorster G. Lung dosimetry: pulmonary clearance of inhaled particles. *Aerosol Sci Tech* 18: 279-289, 1993.

119. Oberdorster G, Oberdorster E, Oberdorster J. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. *Environ Health Perspect* 113: 823-39, 2005.

120. Ohira H, Tsutsui W, Fujioka Y. Are Short Chain Fatty Acids in Gut Microbiota Defensive Players for Inflammation and Atherosclerosis? *J Atheroscler Thromb* 24: 660-672, 2017.

121. Oury TD, Chang LY, Marklund SL, Day BJ, Crapo JD. Immunocytochemical localization of extracellular superoxide dismutase in human lung. *Lab Invest* 70: 889-98, 1994.

122. Ovrevik J, Refsnes M, Lag M, Holme JA, Schwarze PE. Activation of Proinflammatory Responses in Cells of the Airway Mucosa by Particulate Matter: Oxidant- and Non-Oxidant-Mediated Triggering Mechanisms. *Biomolecules* 5: 1399-440, 2015.

123. Pan TL, Wang PW, Aljuffali IA, Huang CT, Lee CW, Fang JY. The impact of urban particulate pollution on skin barrier function and the subsequent drug absorption. *J Dermatol Sci* 78: 51-60, 2015.

142. Park EJ, Chae JB, Lyu J, Yoon C, Kim S, Yeom C, Kim Y, Chang J. Ambient fine particulate matters induce cell death and inflammatory response by influencing mitochondria function in human corneal epithelial cells. *Environ Res* 159: 595-605, 2017.

125. Park HS, Chun JN, Jung HY, Choi C, Bae YS. Role of NADPH oxidase 4 in lipopolysaccharide-induced proinflammatory responses by human aortic endothelial cells. *Cardiovasc Res* 72: 447-55, 2006.

126. Patel VI, Metcalf JP. Airway Macrophage and Dendritic Cell Subsets in the Resting Human Lung. *Crit Rev Immunol* 38: 303-331, 2018.

127. Paus R, Theoharides TC, Arck PC. Neuroimmunoendocrine circuitry of the 'brain-skin connection'. *Trends Immunol* 27: 32-9, 2006.

128. Pelle E, Miranda EP, Fthenakis C, Mammone T, Marenus K, Maes D. Cigarette smoke-induced lipid peroxidation in human skin and its inhibition by topically applied antioxidants. *Skin Pharmacol Appl Skin Physiol* 15: 63-8, 2002.

129. Penning TM, Burczynski ME, Hung CF, McCoull KD, Palackal NT, Tsuruda LS. Dihydrodiol dehydrogenases and polycyclic aromatic hydrocarbon activation: generation of reactive and redox active o-quinones. *Chem Res Toxicol* 12: 1-18, 1999.

130. Peteranderl C, Sznajder JI, Herold S, Lecuona E. Inflammatory Responses Regulating Alveolar Ion Transport during Pulmonary Infections. *Front Immunol* 8: 446, 2017.

131. Piao MJ, Ahn MJ, Kang KA, Ryu YS, Hyun YJ, Shilnikova K, Zhen AX, Jeong JW, Choi YH, Kang HK, Koh YS, Hyun JW. Particulate matter 2.5 damages skin cells by inducing oxidative stress, subcellular organelle dysfunction, and apoptosis. *Arch Toxicol* 92: 2077-2091, 2018.

132. Picardo M, Ottaviani M, Camera E, Mastrofrancesco A. Sebaceous gland lipids. *Dermatoendocrinol* 1: 68-71, 2009.

133. Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, Squadrito F, Altavilla D, Bitto A. Oxidative Stress: Harms and Benefits for Human Health. *Oxid Med Cell Longev* 2017: 8416763, 2017.

134. Pope CA, 3rd. Epidemiology of fine particulate air pollution and human health: biologic mechanisms and who's at risk? *Environ Health Perspect* 108 Suppl 4: 713-23, 2000.

135. Pope CA, 3rd, Cohen AJ, Burnett RT. Cardiovascular Disease and Fine Particulate Matter: Lessons and Limitations of an Integrated Exposure-Response Approach. *Circ Res* 122: 1645-1647, 2018.

136. Quay JL, Reed W, Samet J, Devlin RB. Air pollution particles induce IL-6 gene expression in human airway epithelial cells via NF-kappaB activation. *Am J Respir Cell Mol Biol* 19: 98-106, 1998.

137. Rajagopalan S, Al-Kindi SG, Brook RD. Air Pollution and Cardiovascular Disease: JACC State-of-the-Art Review. *J Am Coll Cardiol* 72: 2054-2070, 2018.

138. Rembiesa J RT, Engblom J, and Holefors A. The impact of pollutionon skin and proper efficacy testing for anti-pollution claims. *Cosmetics* 5, 2018.

139. Rezaee F, Georas SN. Breaking barriers. New insights into airway epithelial barrier function in health and disease. Am J Respir Cell Mol Biol 50: 857-69, 2014.

140. Rider CF, Carlsten C. Air pollution and DNA methylation: effects of exposure in humans. *Clin Epigenetics* 11: 131, 2019.

141. Robertson S, Miller MR. Ambient air pollution and thrombosis. *Part Fibre Toxicol* 15: 1, 2018.

142. Romani A, Cervellati C, Muresan XM, Belmonte G, Pecorelli A, Cervellati F, Benedusi M, Evelson P, Valacchi G. Keratinocytes oxidative damage mechanisms related to airbone particle matter exposure. *Mech Ageing Dev* 172: 86-95, 2018.

143. Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, Stern EJ, Hudson LD. Incidence and outcomes of acute lung injury. *N Engl J Med* 353: 1685-93, 2005.

144. Ryu YS, Kang KA, Piao MJ, Ahn MJ, Yi JM, Hyun YM, Kim SH, Ko MK, Park CO, Hyun JW. Particulate matter induces inflammatory cytokine production via activation of NFkappaB by TLR5-NOX4-ROS signaling in human skin keratinocyte and mouse skin. *Redox Biol* 21: 101080, 2019.

145. Sacks JD, Stanek LW, Luben TJ, Johns DO, Buckley BJ, Brown JS, Ross M. Particulate matter-induced health effects: who is susceptible? *Environ Health Perspect* 119: 446-54, 2011.

146. Salem I, Ramser A, Isham N, Ghannoum MA. The Gut Microbiome as a Major Regulator of the Gut-Skin Axis. *Front Microbiol* 9: 1459, 2018.

147. Salim SY, Jovel J, Wine E, Kaplan GG, Vincent R, Thiesen A, Barkema HW, Madsen KL. Exposure to ingested airborne pollutant particulate matter increases mucosal exposure to bacteria and induces early onset of inflammation in neonatal IL-10-deficient mice. *Inflamm Bowel Dis* 20: 1129-38, 2014.

148. Saenen ND, Martens DS, Neven KY, Alfano R, Bové H, Janssen BG, Roles HA, Plusquin M, Vrijens K, Nawrot TS. Air pollution-induced placental alterations: an interplay of oxidative stress, epigenetics, and the aging phenotype? *Clin Epigenetics* 11: 124, 2019.

149. Schaumann F, Borm PJ, Herbrich A, Knoch J, Pitz M, Schins RP, Luettig B, Hohlfeld JM, Heinrich J, Krug N. Metal-rich ambient particles (particulate matter 2.5) cause airway inflammation in healthy subjects. *Am J Respir Crit Care Med* 170: 898-903, 2004.

150. Schuler R, Brand A, Klebow S, Wild J, Veras FP, Ullmann E, Roohani S, Kolbinger F, Kossmann S, Wohn C, Daiber A, Munzel T, Wenzel P, Waisman A, Clausen BE, Karbach S. Antagonization of IL-17A Attenuates Skin Inflammation and Vascular Dysfunction in Mouse Models of Psoriasis. *J Invest Dermatol* 139: 638-647, 2019.

151. Semmler-Behnke M, Takenaka S, Fertsch S, Wenk A, Seitz J, Mayer P, Oberdorster G, Kreyling WG. Efficient elimination of inhaled nanoparticles from the alveolar region: evidence for interstitial uptake and subsequent reentrainment onto airways epithelium. *Environ Health Perspect* 115: 728-33, 2007.

152. Semmler M, Seitz J, Erbe F, Mayer P, Heyder J, Oberdorster G, Kreyling WG. Long-term clearance kinetics of inhaled ultrafine insoluble iridium particles from the rat lung, including transient translocation into secondary organs. *Inhal Toxicol* 16: 453-9, 2004.

153. Shoham A, Hadziahmetovic M, Dunaief JL, Mydlarski MB, Schipper HM. Oxidative stress in diseases of the human cornea. *Free Radic Biol Med* 45: 1047-55, 2008.

154. Shukla A, Timblin C, BeruBe K, Gordon T, McKinney W, Driscoll K, Vacek P, Mossman BT. Inhaled particulate matter causes expression of nuclear factor (NF)-kappaB-related genes and oxidant-dependent NF-kappaB activation in vitro. *Am J Respir Cell Mol Biol* 23: 182-7, 2000.

155. Sies H. Oxidative stress: a concept in redox biology and medicine. Redox Biol 4: 180-3, 2015.

156. Slominski A. A nervous breakdown in the skin: stress and the epidermal barrier. *J Clin Invest* 117: 3166-9, 2007.

157. Song P, Li Z, Li X, Yang L, Zhang L, Li N, Guo C, Lu S, Wei Y. Transcriptome Profiling of the Lungs Reveals Molecular Clock Genes Expression Changes after Chronic Exposure to Ambient Air Particles. *Int J Environ Res Public Health* 14: 90, 2017.

158. Sorensen M, Schins RP, Hertel O, Loft S. Transition metals in personal samples of PM2.5 and oxidative stress in human volunteers. *Cancer Epidemiol Biomarkers Prev* 14: 1340-3, 2005.

159. Soukup JM, Becker S. Human alveolar macrophage responses to air pollution particulates are associated with insoluble components of coarse material, including particulate endotoxin. *Toxicol Appl Pharmacol* 171: 20-6, 2001.

160. Sun Q, Hong X, Wold LE. Cardiovascular effects of ambient particulate air pollution exposure. *Circulation* 121: 2755-65, 2010.

161. Sundar IK, Sellix MT, Rahman I. Redox regulation of circadian molecular clock in chronic airway diseases. *Free Radic Biol Med* 119: 121-28, 2018.

162. Susin SA, Zamzami N, Kroemer G. Mitochondria as regulators of apoptosis: doubt no more. *Biochim Biophys Acta* 1366: 151-65, 1998.

163. Tao F, Gonzalez-Flecha B, Kobzik L. Reactive oxygen species in pulmonary inflammation by ambient particulates. *Free Radic Biol Med* 35: 327-40, 2003.

164. Tau J, Novaes P, Matsuda M, Tasat DR, Saldiva PH, Berra A. Diesel exhaust particles selectively induce both proinflammatory cytokines and mucin production in cornea and conjunctiva human cell lines. *Invest Ophthalmol Vis Sci* 54: 4759-65, 2013.

165. Tesone AI, Lasagni Vitar RM, Tau J, Maglione GA, Llesuy S, Tasat DR, Berra A. Volcanic ash from Puyehue-Cordon Caulle Volcanic Complex and Calbuco promote a differential response of pro-inflammatory and oxidative stress mediators on human conjunctival epithelial cells. *Environ Res* 167: 87-97, 2018.

166. Torricelli AA, Matsuda M, Novaes P, Braga AL, Saldiva PH, Alves MR, Monteiro ML. Effects of ambient levels of traffic-derived air pollution on the ocular surface: analysis of symptoms, conjunctival goblet cell count and mucin 5AC gene expression. *Environ Res* 131: 59-63, 2014.

167. Tsubota KT, S. C.; Nordlund, M.L. *Anatomy and Phsyiology of the Ocular Surface*. New York, NY: Springer; 2002.

168. Upadhyay D, Panduri V, Ghio A, Kamp DW. Particulate matter induces alveolar epithelial cell DNA damage and apoptosis: role of free radicals and the mitochondria. *Am J Respir Cell Mol Biol* 29: 180-7, 2003.

169. Vadasz I, Sznajder JI. Gas Exchange Disturbances Regulate Alveolar Fluid Clearance during Acute Lung Injury. *Front Immunol* 8: 757, 2017.

170. Valacchi G, Cervellati C, Evelson P, Rahman I. Redox regulation of inflammatory processes. Int J Biochem Cell Biol 81: 234-235, 2016.

171. Valacchi G, Virgili F, Cervellati C, Pecorelli A. OxInflammation: From Subclinical Condition to Pathological *Biomarker* 9: 849-858, 2018.

172. Van Den Heuvel R, Den Hond E, Govarts E, Colles A, Koppen G, Staelens J, Mampaey M, Janssen N, Schoeters G. Identification of PM10 characteristics involved in cellular responses in human bronchial epithelial cells (Beas-2B). *Environ Res* 149: 48-56, 2016.

173. van der Vliet A. Nox enzymes in allergic airway inflammation. Biochim Biophys Acta 1810: 1035-44, 2011.

174. van Eeden SF, Tan WC, Suwa T, Mukae H, Terashima T, Fujii T, Qui D, Vincent R, Hogg JC. Cytokines involved in the systemic inflammatory response induced by exposure to particulate matter air pollutants (PM(10)). *Am J Respir Crit Care Med* 164: 826-30, 2001.

175. Veith C, Boots AW, Idris M, van Schooten FJ, van der Vliet A. Redox Imbalance in Idiopathic Pulmonary Fibrosis: A Role for Oxidant Cross-Talk Between NADPH Oxidase Enzymes and Mitochondria. *Antioxid Redox Signal* 31: 1092-1115, 2019.

176. Vidgren M. WJC, Arppe J., Black M., Rodarte J.A., Cole W., and Knight V. A study of 99mtechnetium-labeled beclomethasone dipropionate dilauroylphosphatidylcholine liposome aerosol in normal volunteers. *Int J Pharm* 115: 209-216, 1995.

177. Vierkotter A, Schikowski T, Ranft U, Sugiri D, Matsui M, Kramer U, Krutmann J. Airborne particle exposure and extrinsic skin aging. *J Invest Dermatol* 130: 2719-26, 2010.

178. Vignal C, Pichavant M, Alleman LY, Djouina M, Dingreville F, Perdrix E, Waxin C, Ouali Alami A, Gower-Rousseau C, Desreumaux P, Body-Malapel M. Effects of urban coarse particles inhalation on oxidative and inflammatory parameters in the mouse lung and colon. *Part Fibre Toxicol* 14: 46, 2017.

179. Vrijheid M. The exposome: a new paradigm to study the impact of environment on health. *Thorax* 69: 876-8, 2014.

180. Wang Y, van Boxel-Dezaire AH, Cheon H, Yang J, Stark GR. STAT3 activation in response to IL-6 is prolonged by the binding of IL-6 receptor to EGF receptor. *Proc Natl Acad Sci USA* 110: 16975-80, 2013.

181. Ware LB, Matthay MA. Alveolar fluid clearance is impaired in the majority of patients with acute lung injury and the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 163: 1376-83, 2001.

182. Weschler CJ, Beko G, Koch HM, Salthammer T, Schripp T, Toftum J, Clausen G. Transdermal Uptake of Diethyl Phthalate and Di(n-butyl) Phthalate Directly from Air: Experimental Verification. *Environ Health Perspect* 123: 928-34, 2015.

183. Wild CP. Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer *Epidemiol Biomarkers Prev* 14: 1847-50, 2005.

184. Wong JM, de Souza R, Kendall CW, Emam A, Jenkins DJ. Colonic health: fermentation and short chain fatty acids. *J Clin Gastroenterol* 40: 235-43, 2006.

185. Woodby B, Penta K, Pecorelli A, Lila MA, Valacchi G. Skin Health from the Inside Out. Annu Rev Food Sci Technol, 2020.

186. Wu CC, Bao LJ, Tao S, Zeng EY. Dermal Uptake from Airborne Organics as an Important Route of Human Exposure to E-Waste Combustion Fumes. *Environ Sci Technol* 50: 6599-605, 2016.

187. Xiang P, He RW, Han YH, Sun HJ, Cui XY, Ma LQ. Mechanisms of housedust-induced toxicity in primary human corneal epithelial cells: Oxidative stress, proinflammatory response and mitochondrial dysfunction. *Environ Int* 89-90: 30-7, 2016.

188. Yan XT, Zhuang M, Oakes JE, Lausch RN. Autocrine action of IL-10 suppresses proinflammatory mediators and inflammation in the HSV-1-infected cornea. *J Leukoc Biol* 69: 149-57, 2001.

189. Yang Q, Tang L, Shen M, Wang Y, Wei Y, Jeyalatha V, Chen P, Dong F, Wang G, Wu S, Liu Z, Li C. Effects of diesel exhaust particles on the condition of mouse ocular surface. *Ecotoxicol Environ Saf* 163: 585-593, 2018.

190. Yoon S, Han S, Jeon KJ, Kwon S. Effects of collected road dusts on cell viability, inflammatory response, and oxidative stress in cultured human corneal epithelial cells. *Toxicol Lett* 284: 152-160, 2018.

191. Yu JH, Lim JW, Kim H, Kim KH. NADPH oxidase mediates interleukin-6 expression in cerulein-stimulated pancreatic acinar cells. *Int J Biochem Cell Biol* 37: 1458-69, 2005.

192. Zhuang Y, Lyga J. Inflammaging in skin and other tissues - the roles of complement system and macrophage. *Inflamm Allergy Drug Targets* 13: 153-61, 2014.

Figure Legends

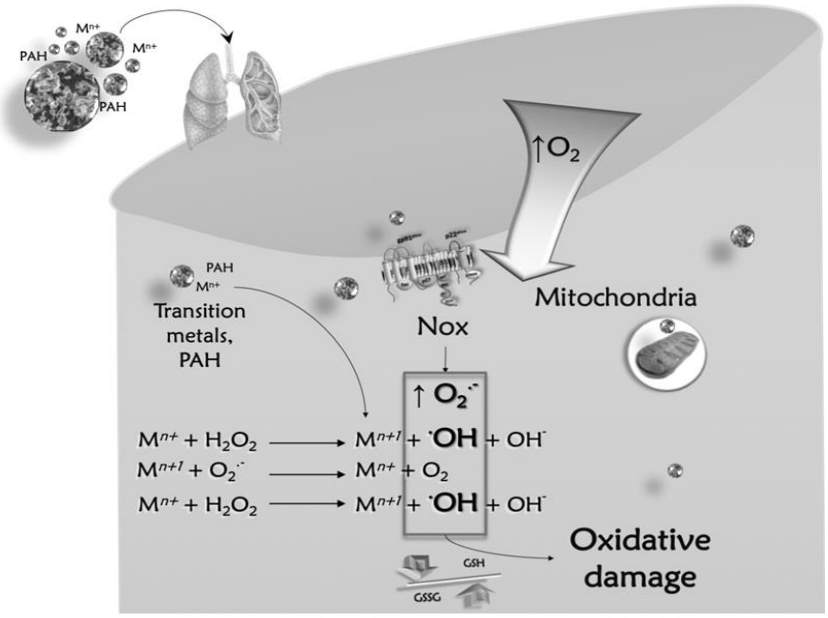

Figure 1. Proposed mechanism for PM effects in the lung. Particulate matter (PM) enters in the lung, where it interacts directly with alveolar macrophages and epithelial cells. PM components, mainly transition metals (via Fenton reaction) and polycyclic aromatic hydrocarbons (PAHs), have the ability of generate reactive oxygen species and directly participate in the observed oxidative damage. The activation of NADPH oxidase and the mitochondrial disfunction also contribute to the generation of superoxide anion ($O_2^{\cdot -}$).

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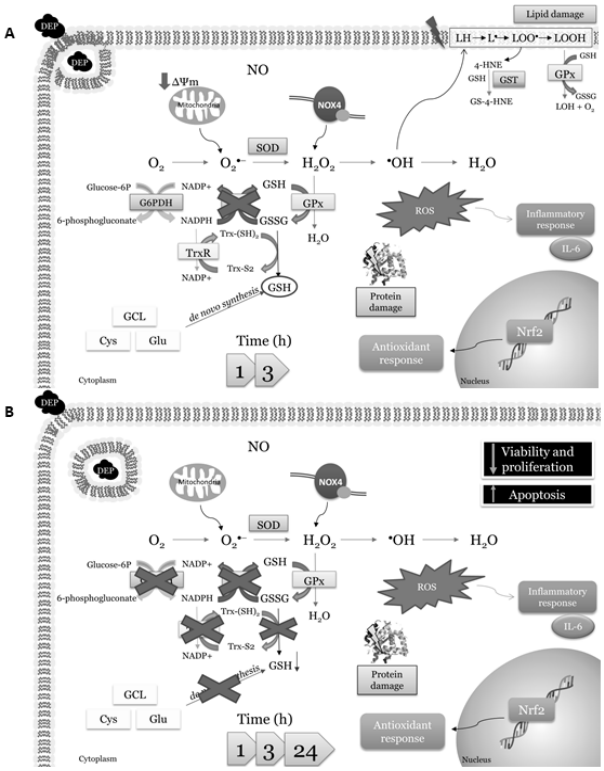

Figure 2. **Time course effects of Diesel Exhaust Particles (DEP) on human conjunctival epithelial cells.** At first, the oxidative environment generated principally by mitochondrial superoxide anion produce a cellular adaptive response consisted of an increase of both enzymatic and non-enzymatic antioxidants. After 3 h, NADPH oxidase-4 is presented as the main source of ROS, when the cell also starts to experiment a proinflammatory response mediated by IL-6. At this time point, the nucleus translocation of Nrf2 is stimulated, attempting to enhance the cellular antioxidant capacity. Despite the fact that under short periods of exposure to DEP lipids and then proteins are targets of oxidative damage, the viability of the cells is not affected at early stages, since cell hyperplasia was detected as compensatory mechanism (**A**). Although after 24 h Nrf2 pathway is still enhanced, the epithelial cell capacity to maintain redox balance is exceeded, as the antioxidant enzymes activation and the depleted GSH pool are not capable of counteracting the increased ROS production. Under these conditions, significant increase of oxidative damage, a decrease in cell proliferation viability, and apoptosis take place (**B**).

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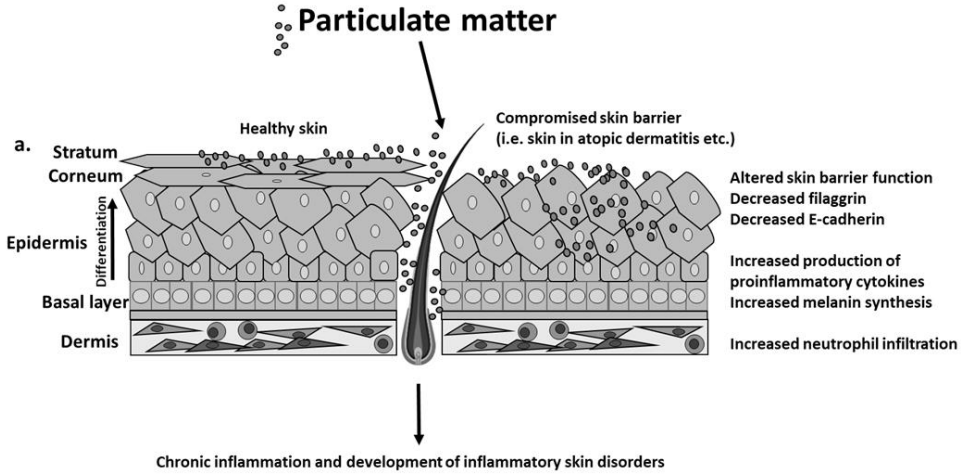

Figure 3. The effects of particulate matter exposure on the skin. Particulate matter (PM) penetrates the epidermis through hair follicles, since skin barrier function prevents direct penetration. Alternatively, components of PM, polycyclic aromatic hydrocarbons (PAHs), can penetrate skin directly due to lipophilic nature. Exposure of the skin to PM alters skin barrier function due to decreasing filaggrin and E-cadherin levels in the skin. PM exposures also induces alterations in redox homeostasis, resulting in the production of melanin and proinflammatory cytokines. These cytokines can stimulate neutrophil infiltration into the skin, leading to chronic inflammation and the development of inflammatory skin conditions.

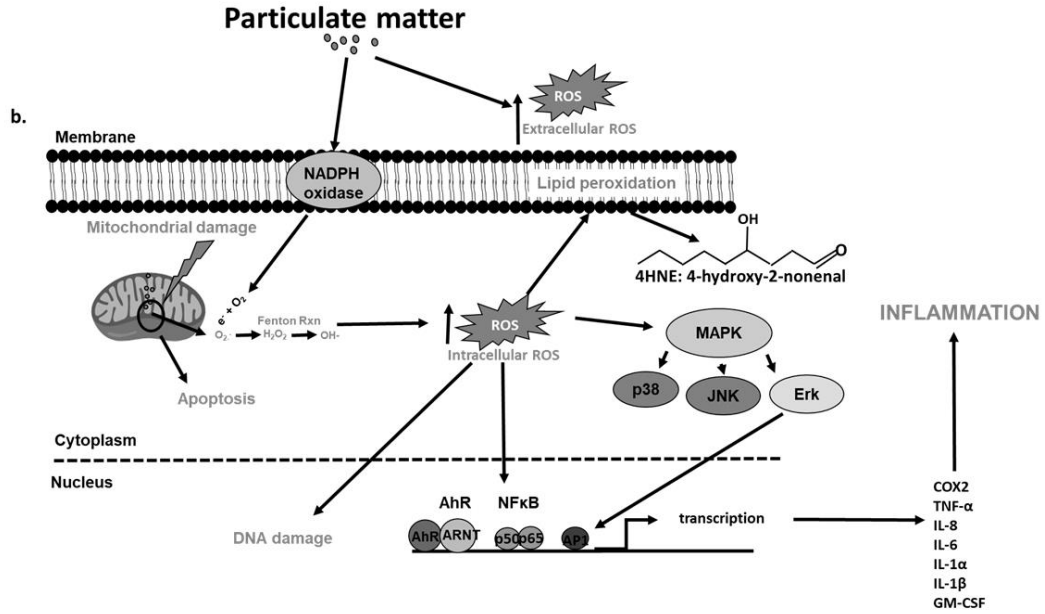

Figure 4. Proposed mechanism for PM effects in keratinocytes. In exposed keratinocytes, PM induces extracellular ROS production due to surface reactivity as well as intracellular ROS production due to increasing activity of NAPDH oxidase and damaging mitochondria. Increased ROS can stimulate lipid peroxidation, resulting in the formation of 4-hydroxyl-nonenal (4HNE). Furthermore, ROS can induce apoptosis through mitochondrial damage and DNA damage. ROS can also MAPK pathways and activation of redox sensitive transcription factors, such as NFκB and AP1. Activation of these transcription factors results in the production of proinflammatory cytokines, such as interleukin (IL) 8, IL-1α, IL-1β, IL-6, TNF-α, COX2, and GM-CSF. These proinflammatory cytokines can then stimulate the recruitment of immune cells, such as neutrophils and macrophages, to the skin, resulting in further inflammation.

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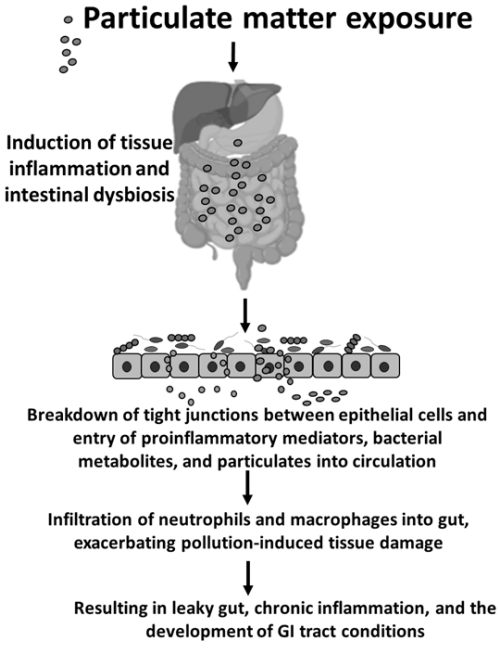

Figure 5. Effects of particulate exposure on the gut. The gut can become exposed to particulate matter (PM) directly via ingestion or indirectly via inhalation and subsequent mucocilliary clearance. In the gut, exposure to PM results in tissue inflammation and intestinal dysbiosis, causing the breakdown of tight junctions between intestinal epithelial cells and leakage of proinflammatory mediators, bacterial metabolites, and particulates into circulation. The release of these proinflammatory mediators can induce the infiltration of neutrophils and macrophages into the gut, exacerbating pollution-induced tissue damage. Ultimately, PM exposure of the gut results in a leaky gut, chronic inflammation, and the development of GI tract conditions.