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Causation by Diesel Exhaust Particles of Endothelial Dysfunctions in Cytotoxicity, Pro-inflammation, Permeability, and Apoptosis Induced by ROS Generation

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Abstract Epidemiological studies suggest that an increase of diesel exhaust particles (DEP) in ambient air corresponds to an increase in hospital-recorded myocardial infarctions within 48 h after exposure. Among the many theories to explain this data are endothelial dysfunction and translocation of DEP into vasculature. The mechanisms for such DEP-induced vascular permeability remain unknown. One of the major mechanisms underlying the effects of DEP is suggested to be oxidative stress. Experiments have shown that DEP induce the generation of reactive oxygen species (ROS), such as superoxide anion and H_2O_2 in the HUVEC tube cells. Transcription factor Nrf2 is translocated to the cell nucleus, where it activates transcription of the antioxidative enzyme HO-1 and sequentially induces the release of vascular permeability factor VEGF-A. Furthermore, a recent study shows that DEP-induced intracellular ROS may cause the release of pro-inflammatory TNF-α and IL-6, which may induce endothelial permeability as well by promoting VEGF-A secretion independently of HO-1 activation. These results demonstrated that the adherens junction molecule, VE-cadherin, becomes redistributed from the membrane at cell–cell borders to the cytoplasm in response to DEP, separating the plasma membranes of adjacent cells. DEP were occasionally found in endothelial cell cytoplasm and in tube lumen. In addition, the induced ROS is cytotoxic to the endothelial tube-like HUVEC. Acute DEP exposure stimulates ATP depletion, followed by depolarization of their actin cytoskeleton, which sequentially inhibits PI3K/Akt activity and induces endothelial apoptosis. Nevertheless, high-dose DEP augments tube cell apoptosis up to 70 % but disrupts the p53 negative regulator Mdm2. In summary, exposure to DEP affects parameters influencing vasculature permeability and viability, i.e., oxidative stress and its upregulated antioxidative and pro-inflammatory responses, which sequentially induce vascular permeability factor, VEGF-A release and disrupt cell–cell junction integrity. While exposure to a low dose of DEP actin triggers cytoskeleton depolarization, reduces PI3K/Akt activity, and induces a p53/Mdm2 feedback loop, a high dose causes apoptosis by depleting Mdm2. Addition of ROS scavenger *N*-acetyl cysteine suppresses DEP-induced oxidative stress efficiently and reduces subsequent damages by increasing endogenous glutathione.

Keywords Diesel exhaust particles · Reactive oxygen species · HUVEC · Pro-inflammation · Permeability · Apoptosis

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Introduction

A very high proportion of the particles in diesel exhaust is $PM_{2.5}$ (particulate matter $\leq$2.5 μm), which have been reported as a carcinogen and associated with adverse disorders [1–4]. The cardiopulmonary system is affected most by many substances in diesel exhaust particles (DEP), including carbon black, hydrocarbons, aldehydes,

quinones, benzo[*a*]pyrenes, polycyclic aromatic hydrocarbons (PAHs), and heavy metals, which levels parallel the incidence of allergies, asthma, rhinitis, cardiovascular disorders, as well as mutagenesis and carcinogenesis [5–11].

Vasculature Effects

Epidemiology indicates that long-term exposure to ambient $PM_{2.5}$ adversely affects the health of those exposed [12]. $PM_{2.5}$ from diesel vehicles is produced from several processes: (a) It is directly emitted from the tailpipes of on-road vehicles, (b) it is re-entrained from fugitive dust, and (c) it is reacted to form $PM_{2.5}$ with precursor emissions chemicals such as sulfur dioxide, nitrogen oxides, volatile organic compounds, and ammonia [13]. Items a and b are typically known as primary emissions of $PM_{2.5}$, for which exposure both indoors and outdoors has been shown to cause acute and chronic health effects [14]. Item c occurs due to chemical reaction in the atmosphere [13]. Some gas phase carbonyl compounds (aldehydes and ketones) are also known to have adverse effects on human health; for example, long-term exposure to high formaldehyde concentrations is known to increase the risk for asthma and cancer [15, 16]. Chronic bronchitis, chronic obstructive pulmonary disease (COPD), asthma, heart failure, and even lung cancer can result, due to the carcinogenic or mutagenic components in inhaled air [11]. Furthermore, for people living in areas where air pollution levels are high, long-term exposure correlates with higher levels of atherosclerosis [17]. Chronic exposure to polluted air indirectly places a tremendous burden on the health care system and is a significant cause of morbidity and mortality [18]. Short-term effects observed within 48 h after exposure include acute eye and nose irritation, neurophysiological symptoms, respiratory symptoms, headache, and fatigue. Ambient particulates have also been correlated with serious cardiovascular events, such as myocardial infarctions or strokes [3, 19]. Short-term elevations of DEP in the air at a concentration as low as 10 $\mu g/m^3$ increase mortality by 1 % [4]. Acute exposure to a concentration of 50 $\mu g/m^3$ of DEP causes an average of 1.2 deaths per day in a population of 1 million [4].

Heart and vascular consequences are frequently observed after exposure to pollution [18]. There is a higher incidence of ischemic heart disease in smokers who are chronically exposed to diesel emissions [20]. Men who had a previous myocardial infarction and who were exposed to diesel exhaust during moderate exercise showed an increase in ischemic and thrombotic effects [21]. Furthermore, upon exposure to high levels of traffic air for times as short as 1 h, there is an increased risk of coronary vasoconstriction and altered myocardial energetics [22]. Air pollutants reduce heart rate variability, cause ventricular arrhythmia, and increase left-ventricular end-diastolic pressure in animal models [23, 24]. At levels encountered in an urban environment, inhalation of diesel exhaust impaired two important and complementary aspects of vascular function in humans: the regulation of vascular tone, and endogenous fibrinolysis by increasing fibrinogen and plasminogen activator inhibitor-1 [21, 25]. Blood is not immune from the effects of air pollution. Two components in polluted air, CO and NO_2, reduced the prothrombin time (PT) for clotting blood for 1218 healthy people from Lombardy Region, Italy [26]. In addition, air pollutants may significantly increase fibrinogen, factor VIII, and platelet hyperactivity.

Oxidative Stress

Oxidative stress can be defined as the imbalance between cellular oxidant species production and antioxidant capability [27]. Reactive oxygen species (ROS) can be generated under normal cellular condition or can be elicited in response to exposure to environmental stress. Despite the major composition of ROS produced in cell exposed to DEP remaining unelucidated, these free radical species are very transient and cytotoxic [18, 28–30].

Exposure to DEP induces the generation of free radicals that lead to a state of cellular oxidative stress [31]. This has been shown to cause significant damage in both cell cultures and animal models [32–36]. In vitro studies demonstrate that DEP upregulate antioxidant enzymes in various types of cells, including bronchial and pulmonary epithelial cells [37, 38], macrophages, lymphocytes [39], and endothelial cells [40]. DEP induce the generation of H_2O_2 [41], a powerful oxidizer which can be converted into hydroxyl radicals (.OH). In organisms, hydrogen peroxide is naturally produced as a by-product of oxygen metabolism; therefore, enzymes such as catalase catalyze conversion of hydrogen peroxide to water and oxygen. In fact, catalase is the most abundant enzyme in the human body. DEP-induced ROS leads to NO production which associated with human pulmonary artery endothelial cell damage [40]. The major cause of cell damage may be excess NO production that contributes to reduction of NO bioavailability [42]. Endothelial nitric oxide synthase plays a key role in modulating NO production and cardiovascular homeostasis. Furthermore, the metabolites of arachidonic acid, so-called epoxyeicosatrienoic acids (EETs), enhance eNOS phosphorylation and upregulate eNOS protein expression [43]. eNOS not only mediates NO production but also is involved in the release of prostacyclin, which regulates vasodilatation [44]. On the other hand, DEP paralyze eNOS and cause dysfunction in coronary arterioles [21, 44]. Therefore, exposure to DEP

would result in higher risk of heart attack, coronary artery disease, or hypertension in those with existing cardiovascular disease.

DEP have a carbonaceous core onto which the toxic components of exhaust are absorbed. These chemicals contain two main families of organic compounds: polycyclic aromatic hydrocarbons (PAHs) and quinines, which can be oxygenated to quinone derivatives that produce ROS in the cells via redox cycling. PAHs desorbed from DEP bind the cytosolic aryl hydrocarbon receptor and induce phase I metabolization enzymes cytochrome P450 1A1 (CYP1A1) and cytochrome P450 1A2 (CYP1A2) in the lung and heart [45–47]. This mechanism produces electrophilic and reactive metabolites such as 1-nitropyrene (1-NP), 1,3-dinitropyrene (1,3-DNP), and 1,8-dinitropyrene (1,8-DNP). Such oxidative stress can induce DNA damage [48]. Furthermore, in the lung, DEP-induced chemical derivatization of quinones causes free radicals and diminishes the antioxidant capacity of redox cycling via the enzymes CYP reductase and NADPH oxidase. Quinones are suspected to be responsible for the production of superoxide anion (O_2^-) and hydroxyl radicals [10, 49]. This can occur as follows: Redox cycling quinones undergo a one-electron reduction to form semiquinones [50], and then semi-quinones are recycled to the original quinones with the formation of O_2^-. The detoxification of quinones occurs by a two-electron reduction initiated by the phase II reaction with NADPH-quinone oxidoreductase-1 (NQO-1). Quinones are electrophiles that are able to participate in ROS damage by inducing covalent modification of proteins and DNA strands. Thus, the modification of DEP organics results in DNA adducts and DNA strand breakages, and can result in cell death [36, 51, 52].

DEP exposure has been shown to generate an ROS response that can overwhelm antioxidative proteins [40]. To maintain redox cycling equilibrium for cell survival, the cells release antioxidants such as glutathione S-transferase (GST), superoxide dismutase (SOD), NADPH-quinone oxidoreductase-1 (NQO-1), and heme oxygenase-1 (HO-1). These help neutralize the potent injuries ROS can cause. For example, in response to a 24-h free radical stimulation, endothelial cells upregulate heme oxygenase-1 (HO-1) [53]. This is accomplished by cytoplasmic nuclear factor erythroid 2-related factor 2 (Nrf2) translocating from the cytoplasm to the nucleus, where it binds to the antioxidant response element (ARE) that resides in the promoter regions of antioxidant genes. This upregulates HO-1 mRNA levels via Nrf2/ARE enhancement of transcription [54–56].

DEP also induce lipid peroxidation, as well as massive protein oxidation and mitochondria superoxide production [57, 58]. ROS are involved in a variety of cellular processes, ranging from cell proliferation and carcinogenesis to cell death [27]. Previous studies showed that excessive production of ROS causes irreversible damage to lipids, DNA, and proteins, thus provoking cell death through several modes, including autophagy and apoptosis [59]. Furthermore, recent results have suggested that DEP function by changing the levels of its effector, H_2O_2, which triggers Nrf2 translocation from the cytoplasm to the nucleus [56, 60]. Downstream heme oxygenase (HO)-1 is then upregulated to facilitate antioxidative stress response in the endothelium [61–64]. HO-1 also functions to induce vascular permeability and contributes to the secretion of vascular endothelial growth factor A (VEGF-A) [65]. VEGF-A, also called vascular permeability factor (VPF), has been shown to induce vascular permeability [66, 67]. Upon exposure of in vitro capillary tube cells to DEP, the VE-cadherin/VEGF receptor 2 (VEGF-R2) complex on the cell membrane dissociates [56]. Partial internalization of VE-cadherin and discontinuity of the cell–cell border are also induced following these junctional alternation [56, 68]. Moreover, these events cause endothelial junctions to become disrupted and may explain how VEGF-A initiates vascular permeability following inhalation of DEP.

Pro-inflammatory

Many reports have suggested that DEP initiate an inflammatory response that ultimately causes injury. In vitro studies have demonstrated that $PM_{2.5}$ upregulates the secretion of pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) in macrophages, as well as epithelial and endothelial cells [69–72]. Additionally, cultured bronchial epithelial cells exposed to DEP also released interleukin-8 (IL-8) and granulocyte macrophage colony stimulating factor (GM-CSF) in a time- and dose-dependent manner. Both of these are known to be involved in allergic diseases [38, 45].

It is important to realize that ROS and pro-inflammatory responses go hand in hand. For example, in the bloodstream, TNF-α has pro-oxidative properties and stimulates generation of ROS in the cardiac muscle of patients with heart failure [73]. In such patients, TNF-α enhances platelet superoxide anion (O_2^-) production [74]. Also, in airway epithelial cells, the components of DEP adsorbed on particles elicit inflammation through CYP reductase and NADPH oxidase [75]. These activate cytokine secretion as well as an oxidative stress response.

Inhalation of DEP for 24 h upregulates TNF-α and leads to accumulation of large amounts of TNF-α in human plasma [76]. This changes the expression of adhesion molecules on endothelial cells, facilitating the transmigration of neutrophils and thereby leading to changes in

vascular permeability [77]. Furthermore, there is a positive correlation between vascular permeability and adherens junction integrity [78]. Nwariaku et al. [79] found that TNF-α-induced tyrosine phosphorylation of VE-cadherin, which permits regulation of microvascular permeability, increases the formation of intercellular gap formation. IL-6 has also been shown to be directly involved in increasing monolayer endothelial permeability [80]. Maruo et al. [81] suggested that IL-6 induces increased endothelial permeability by rearranging VE-cadherin and altering the shape of endothelial cells. This implies that the endothelial cell–cell barrier may also be altered.

Vascular Permeability

Exposure to DEP is associated with adverse pulmonary and cardiovascular health effect due to its composition and particle size. DEP contribute to fine PM ($PM_{2.5}$) and ultrafine PM (diameters of 0.1 μm, i.e., 100 nm, or smaller, or $PM_{0.1}$) [82], both of which are capable of entering the alveolar region. Reports have suggested that inhaled ultrafine titanium dioxide particles were found on the luminal side of airways and alveoli, in lung tissues and cells, and within capillaries. The ultrafine particles translocated into the bloodstream after inhalation by a volunteer [83, 84]. Particle uptake in vitro into cells did not occur by any of the expected endocytic processes, but rather by diffusion or adhesive interactions. Study demonstrated that the role of particles translocated into circulation might be mediated by endothelial cell–cell adherens junctions [82]. VE-cadherin is an endothelial-specific cadherin of adherens junctions that regulates not only vascular permeability, but also leukocyte transmigration [85]. Disruption of VE-cadherin endothelial barrier integrity has also been shown to alter vascular permeability [86, 87]. The pulmonary endothelium acts as a semipermeable barrier, and the integrity of the barrier is necessary for efficient pulmonary function [88]. Furthermore, DEP induce oxidative stress in differential endothelial cells [56]. Cells respond by transporting Nrf2 to the nucleus to facilitate transcription of genes to defend against ROS. HO-1 is a defense enzyme induced by Nrf2, which consequently secretes vascular permeability factor VEGF-A to contribute to vasculature being permeable. Recently, our unpublished results also reported that DEP-induced intracellular ROS is able to release the pro-inflammatory cytokines TNF-α and IL-6, which might also contribute to VEGF-A secretion and disrupt cell–cell borders to increase vasculature permeability. Interestingly, addition of ROS scavenger *N*-acetyl cysteine (NAC) suppresses DEP-induced ROS efficiently and reduces subsequent damages by increasing endogenous glutathione [89].

Apoptosis

Epidemiological studies have suggested that exposure to high concentration DEP might cause acute cardiovascular symptomatic flares within even 48 h of exposure [58, 90]. The DEP-induced symptoms include myocardial infarction and atherosclerosis. Studies indicated that induction of apoptosis in endothelial cells, smooth muscle cells, and immune cells has been involved in the formation of atheromatous plaques [91]. Apoptosis is a type of cell death characterized by cell shrinkage, membrane blebbing, and chromatin condensation [92]. Apoptosis in cells has also been implicated when mitochondrial functions are attenuated or intracellular ATP is depleted [93]. It would link to derangement of actin cytoskeleton [94, 95] and dephosphorylation of cell survival Akt signaling [96], which potentially contribute to induction of myocardial ischemia and infarction [97, 98].

Atherosclerosis can be regarded as an inflammatory disorder which arises from accumulation of chemokines, cytokines, growth factors, and lipoproteins; it gave birth to vascular pathology [99]. On the other hand, the apoptosis of endothelium is also triggered in atherosclerosis. Denudation of the endothelial monolayer in aortic segment is associated with endothelium apoptosis, which initiates the migration of smooth muscle cells to the denuded segment. The smooth muscle cells proliferate and increase the intimal mass of the denuded segment, but the subsequent reendothelialization of the denuded segment replaces the smooth muscle cells and intimal mass which initiate the death of smooth muscle cells into the intima, further damaging the vasculature and propagating plaque development [100]. Atherosclerosis may also depend on increased coagulation of apoptotic endothelial cells. Apoptotic cells are procoagulant of the circulation system, and the activated platelets are aggregated in areas rich in apoptotic cells. Our recent studies showed that DEP induce mitochondrial superoxide anion generation, which leads to ATP depletion followed by depolarization of actin cytoskeleton and prohibits PI3K/Akt activity and contributes to endothelial apoptosis [58]. The performance is accompanied by induction of the p53/Mdm2 feedback regulation at 10 μg/mL DEP and produces 20 % cell apoptosis. Nevertheless, a high dose of DEP (100 μg/mL) augments tube cell apoptosis up to 70 %, but dysfunction of p53 negative regulator, Mdm2.

Autophagy

There is growing interest in the role of autophagic flux in maintaining normal vessel wall biology and a growing suspicion that autophagic dysregulation may be a normal mechanism through which vascular abnormalities and

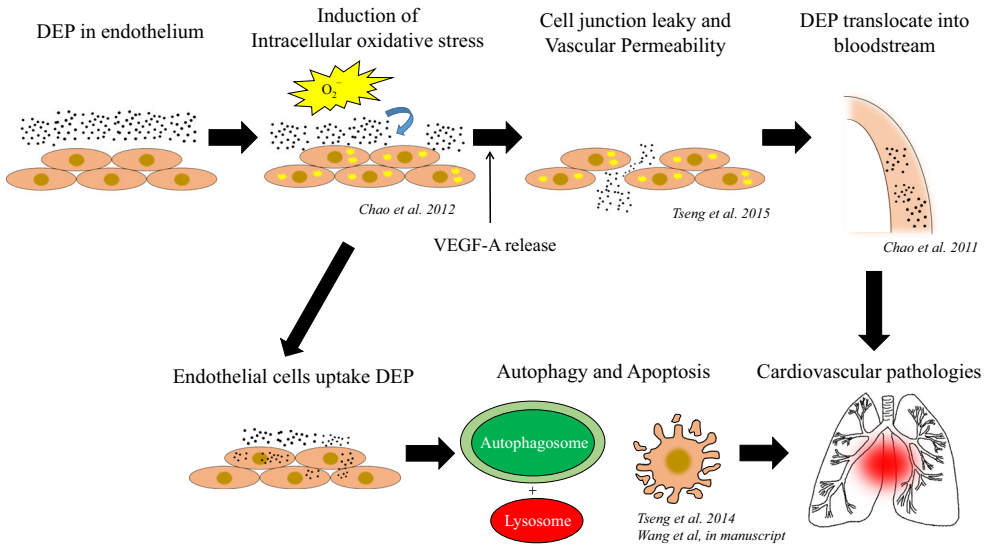

Fig. 1 Mechanism of DEP contributes to cardiovascular pathologies. Exposure of endothelial cells to DEP results in two potential pathways to cardiovascular disorders. First, the DEP-induced intracellular ROS production causes cell–cell junction leakage with VEGF-A release and vascular permeability. Then, DEP translocate into bloodstream and result in vasculature illness. Second, the DEP-induced ROS trigger endothelial phagocytosis of the particles. The ingested DEP will be embedded by lysosome and sequentially fused with autophagosome, which results in autophagy. However, the DEP is not able to be digested, and these autolysosome-embedded DEP accumulate in the cytosol, leading to higher oxidative stress and the eventual causation of apoptosis

associated pathologies develop [101]. Autophagy is considered a protective process which proceeds cell survival by recycling organelles and long-lived proteins during nutrient deprivation, hypoxia, and infection [102]. Nevertheless, autophagy may be a type of cell death under certain circumstances [103]. Lysosomal coordination regulates the late state of autophagic flux [104]. Some nanoscale materials were identified with contribution of lysosomal dysfunction, including multi-wall carbon nanotube (MWCNT) [105], glass wool [106], titanium dioxide (TiO_2) [107], polystyrene [108], and zinc oxide [109]. Nanoparticles are usually sequestered within the lysosomal compartment; therefore, the nanoparticles inhibit lysosomal enzyme activity and cause biopersistence; the above legions contribute to autophagy dysfunction and cell death. Accordingly, DEP are nanoscale-like particles; our unpublished research indicates that DEP are uptaken and accumulated in the endothelial cells within 2 h exposure and induce autophagy, while p62 was simultaneously accumulated in the cytoplasm for 8 h, suggesting that autophagosome is not able to digest DEP and lead to autophagy-independent endothelium apoptosis. On the other hand, the upregulated expression of antioxidative enzymes was observed at various time points as well, suggesting that these undigested DEP cause oxidative stress in the endothelial cytoplasm and sequentially lead to endothelial apoptosis.

Conclusion

The mechanisms for DEP-induced endothelial dysfunction that possibly result in atherosclerosis remain unknown. One of the major mechanisms underlying the effects of DEP is suggested to be oxidative stress. As shown in Fig. 1, investigations have suggested that DEP induces the generation of oxidative stress in the HUVEC tube cells. Transcription factor Nrf2 is translocated to the cell nucleus and activates transcription of the antioxidative enzyme HO-1 and sequentially induces the release of vascular permeability factor VEGF-A. Additionally, DEP-induced intracellular ROS may cause the release of pro-inflammatory TNF-α and IL-6, which may induce endothelial permeability as well by promoting VEGF-A secretion independently of HO-1 activation. These effects cause the adherens junction molecule, VE-cadherin, to become redistributed from the membrane at cell–cell borders to the cytoplasm in response to DEP, separating the plasma membranes of adjacent cells. DEP translocate occasionally in the endothelial cell cytoplasm and in the tube lumen. Furthermore, acute DEP exposure stimulates ATP depletion, followed by depolarization of their actin cytoskeleton, which sequentially inhibits PI3K/Akt activity and induces endothelial apoptosis. Nevertheless, while exposure to a low dose of DEP actin triggers cytoskeleton depolarization, reduces PI3K/Akt activity, and induces a p53/Mdm2

feedback loop, a high dose causes apoptosis by depleting Mdm2. *N*-acetyl cysteine suppresses DEP-induced oxidative stress efficiently and reduces subsequent damages by increasing endogenous glutathione. Although autophagy is considered a protective process which proceeds cell survival by recycling organelles and long-lived proteins during nutrient deprivation, hypoxia, and infection, DEP are sequestered within the lysosomal compartment and inhibit lysosomal enzyme activity and contribute to autophagy dysfunction and apoptosis. It might be the mechanism that these undigested DEP cause oxidative stress in the endothelial cytoplasm and sequentially lead to endothelial apoptosis.

$PM_{2.5}$-DEP threaten our daily life. It is important to elucidate how DEP affect our bodies. The continued expansion of the field of respiratory and cardiovascular toxicology requires a thorough understanding of the mechanism of DEP for appropriate safety assessment and identification of exposure biomarkers. With increasing research of respiratory toxicology, the comprehensive mechanism of several respiratory toxicants has begun to emerge. Researchers should be conscious that air pollution like DEP can have deleterious effect on inflammatory, apoptosis, and autophagy pathways, giving rise to respiratory toxicity and lung pathology. Overall, expanding knowledge of the implications and biological significance of DEP-induced reactive oxidative stress, inflammatory response, apoptosis, and autophagy pathways has tremendous potential to aid in our understanding of respiratory toxicology and design of suitable pharmaceutical therapy and chemoprevention.

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