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Oxidative stress pathways of air pollution mediated toxicity: Recent insights

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ABSTRACT

Ambient air pollution is a leading environmental cause of morbidity and mortality globally with most of the outcomes of cardiovascular origin. While numerous mechanisms are proposed to explain the link between air pollutants and cardiovascular events, the evidence supports a role for oxidative stress as a critical intermediary pathway in the transduction of systemic responses in the cardiovascular system. Indeed, alterations in vascular function are a critical step in the development of cardiometabolic disorders such as hypertension, diabetes, and atherosclerosis. This review will provide an overview of the impact of particulate and gaseous pollutants on oxidative stress from human and animal studies published in the last five years. We discuss current gaps in knowledge and evidence to date implicating the role of oxidative stress with an emphasis on inhalational exposures. We conclude with the identification of gaps, and an exhortation for further studies to elucidate the impact of oxidative stress in air pollution mediated effects.

1. Introduction

Air pollution is the leading environmental risk factor in the world today. Particulate matter < 2.5 μm ($PM_{2.5}$) is the most commonly implicated constituent that causes a disproportionate number of global deaths and contributes significantly to global disability. The global burden of disease study report indicated that ambient outdoor air pollution, particularly $PM_{2.5}$, was the fifth leading risk factor for global mortality in 2015, with cardiovascular deaths accounting for highest number of these deaths [1,2]. Recent work suggests that the impact of ambient air pollution may be even higher using integrated exposure response function curves [3]. Alterations in oxidative stress were the earliest pathophysiologic mechanism described in response to air pollution exposure in humans and animal models, and indeed alterations in pulmonary oxidative stress and vascular function are thought to be critical initiating events [4]. In this review, we will focus on the studies supporting the impact of air pollution and its particulate and gaseous constituents on oxidative stress. We will address to what extent alterations in oxidative stress are responsible for mediating systemic responses and diseases such as atherosclerosis and cardiac hypertrophy in response to air pollutants. We will discuss the impact of prevention measures to reduce oxidative stress in response to air pollution exposures and provide a perspective on remaining gaps in the field.

2. Air pollution sources, composition, regulatory thresholds and cardiovascular events

Ambient air pollution is heterogeneous complex mixture of both particulate matter (PM) and gaseous components, that vary considerably by season, source, and atmospheric conditions [5,6]. PM originates from a variety of sources including anthropogenic origins such as power, automobile exhaust, combustion, mining, industrial sources, fine dust from earth, road and tire abrasion, construction work and agricultural sources. Numerous factors determine the toxicity of particles including site of deposition (upper or lower airways, which is turn depending on particle size and reactivity), solubility, bio-persistence and leachable components [7–10]. Due to these heterogeneous compositional attributes, particle classification on physicochemical parameters is a challenge and therefore the most common method to classify PM particles is based on size; coarse PM < 10 μm (PM_{10}), fine PM < 2.5 μm ($PM_{2.5}$), and ultrafine PM < 0.01 μm ($PM_{0.1}$) (Fig. 1.). Ultrafine PM usually contains transition metal ions, organic compounds mostly polycyclic aromatic hydrocarbons (PAHs) and are well known to penetrate the systemic circulation [7,8,11]. The typical range of ambient concentrations for several air pollutants, according to the latest U.S. National Ambient Air Quality Standards (NAAQS) and the European Commission regulatory criteria, have been previously discussed [12–14]. Satellite based techniques use the optical properties of aerosol column (Aerosol optical depth, AOD) to produce indirect estimates of

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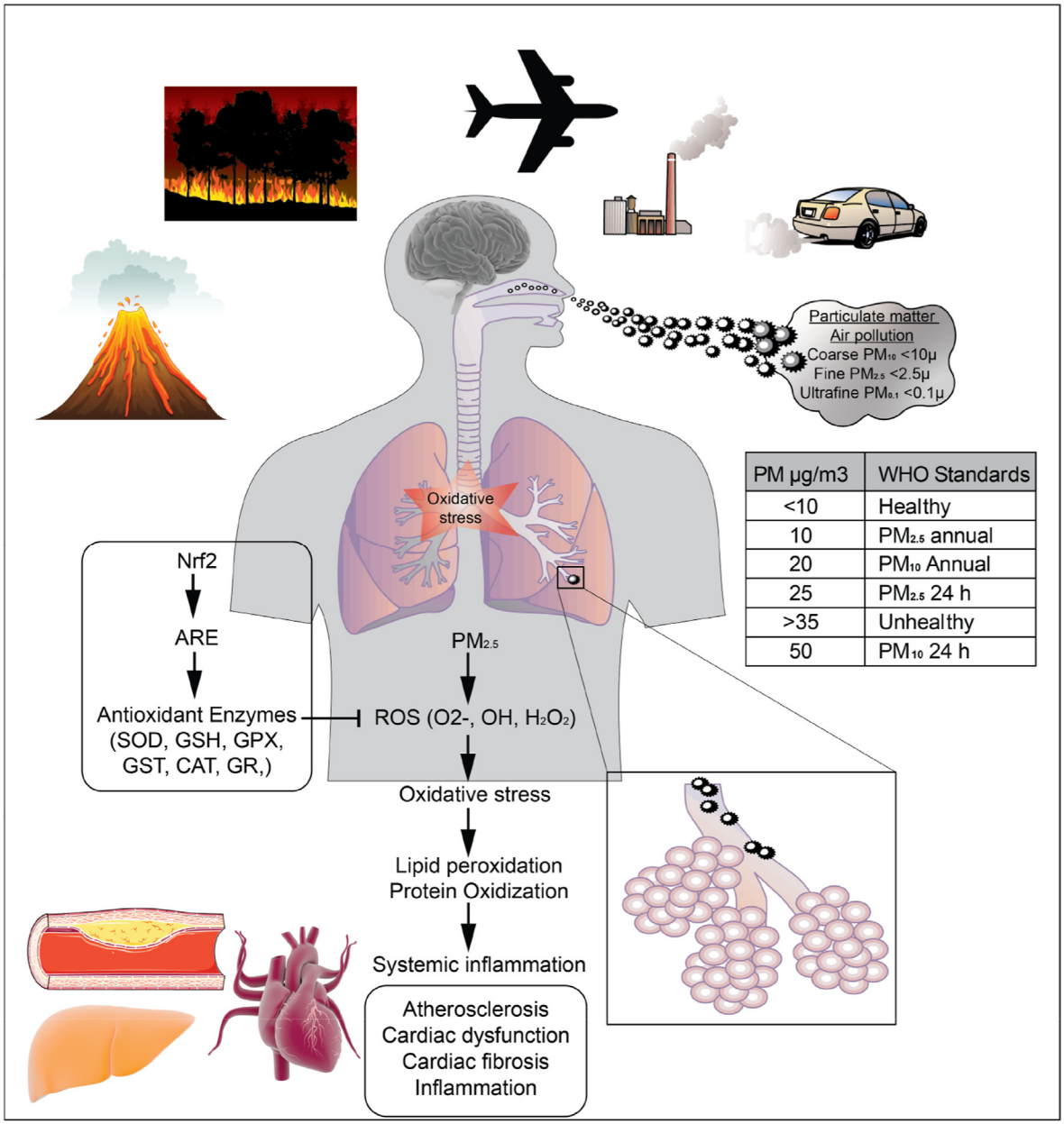

Fig. 1. Particulate Matter Air Pollution: source and health effects. Air pollution standards were obtained from WHO 2005 air quality guidelines (http://apps.who.int/iris/bitstream/10665/69477/1/WHO_SDE_PHE_OEH_06.02_eng.pdf). $PM_{2.5}$, particulate matter < 2.5 μm; PM_{10}, particulate matter < 10 μm.

ground-level pollutant concentrations and were the basis of global burden of disease estimates for air pollution. Satellite and ground-level measurements for particle levels highly correlate and are available for every location on earth at a ~1 × 1 km resolution [15]. Among the gaseous pollutants tropospheric, or ground level, ozone (O_3) has the most evidence linking it to health effects [2,5,16,17]. O_3 is a secondary pollutant resulting from chemical reactions between oxides of nitrogen (NOx) and volatile organic compounds (VOC) in the presence of sunlight. The current U.S. NAAQS, standard for O_3 is 70 ppb averaged over 8h. However, multiple epidemiological studies show an increased risk of asthma exacerbations and cardiopulmonary mortality at levels below 70 ppb [2,18]. It is important to mention here that although "criteria" pollutants are regulated individually through limits on emissions and/or ambient air quality standards set by the government, the overall effects of air pollution are driven by the mixture. These pollutants may, in turn, interact with other aspects of the physical environment, socioeconomic and biologic factors (exposome) to ultimately determine health effects (pollutome).

3. Sources of ROS generation and methodological considerations

Given the fact that air pollution is inhaled, the initial locus of redox stress is typically the airways and lungs. Indeed, there is an extensive literature on generation of reactive oxygen and nitrogen species in airway epithelial cells and macrophages of the lung and have been reviewed extensively elsewhere [19–23]. The mechanism by which pulmonary oxidative stress triggers inflammation, along with the involvement of immune and non-immune cells is complex and varies depending on site, model, duration and composition [24]. In humans this is complex, with the ultimate response being affected by particle fate (e.g. lung clearance versus retention), intracellular distribution, sequestration, and ultimately on multiple host factors including susceptibility [24]. The evidence to date suggests that reactive oxygen species (ROS) generation in response to $PM_{2.5}$ could either involve

Table 1
In vivo animal studies inflammation and/or oxidative stress with whole body inhalational or intratracheal/intranasal $PM_{2.5}$, diesel exhaust and ozone exposures.

Study	Animals and model	Air pollutant	Major outcome	Ref.
CONCENTRATED AMBIENT $PM_{2.5}$ (CAP) USING A WHOLE-BODY EXPOSURE SYSTEM				
Chu C et al., 2019	Rats and wild type or Nrf2 k/o mice	Whole body exposure to $PM_{2.5}$ or FA for 9–12 weeks	Real-time sub-chronic $PM_{2.5}$ inhalation induced depressive-like responses. Toxic elements deposition in brain might contribute to the depressive-like response. NLRP3 signal pathway regulated by Nrf2 take part in depression caused by $PM_{2.5}$.	[115]
Rao X et al., 2019	Wild-type and Adra2b-transgenic mice	Whole body exposure to $PM_{2.5}$ or FA for 3 months	Adra2b overexpression induced 115(TLR2, TLR4, and IL-6) in the brains of mice exposed to $PM_{2.5}$. There were increased frequencies of activated effector T cells and increased expression of oxidative stress-related genes, such as SOD1, NQO1, Nrf2, and Gclm in Adra2bTg mice compared with wild-type mice.	[116]
Zhou J et al., 2019	Male BALB/c mice	Combined effects whole body exposure to $PM_{2.5}$ and cold stress – 4 weeks	$PM_{2.5}$ exposure and cold stress led to an increased inflammation and redox levels in mice, exacerbates asthma in mice by increasing the percentage of TH2 T cells. Increased TH2 T cells are correlated with hyperacetylation of H3K9 and H3K14 in IL-4 gene promoter in $CD4^+$ T cells and in IL-4 gene promoter in $CD4^+$ T cells. Furthermore, a significantly increased P300 and decreased HDAC1 were detected in $CD4^+$ T cells.	[117]
Wan Q et al., 2019	$ApoE^{-/-}$ mice	Whole body exposure to $PM_{2.5}$ or FA for 12 weeks (daily average $PM_{2.5}$ was 57.4 ± 25.6 μg/m3)	Chronic PM2.5 exposure results in promoting progression of atherosclerosis, and increased serum levels of IL-6, TNF-α, TC and LDL-C. Whereas, serum levels of IL-10, TGF-β, and $CD4^+CD25^+Foxp3^+$ TRegs population in splenocytes, Foxp3 protein and mRNA expressions in descending aorta and spleen were decreased in the $PM_{2.5}$ group compared to the FA group.	[118]
Ding S et al., 2019	C57BL/6J mice	Whole body exposure to $PM_{2.5}$ or FA for 5 months	Chronic $PM_{2.5}$ exposure caused elevated inflammatory cytokines and TGF-β1 in BALF and induced lung inflammation and fibrosis. PM exposure triggered autophagy-related-NLRP3 inflammasome in lung. Resveratrol (RES) treatment abolished PM-induced lung inflammation and fibrosis, and NLRP3 activation.	[119]
Ding S et al., 2019	C57BL/6J mice, fed with STD or HFD	Whole body exposure to $PM_{2.5}$ or FA for 5 months	Chronic airborne $PM_{2.5}$ exposure impaired oxidative homeostasis, caused inflammation, induced hepatic steatosis, increased the expression of hepatic Nrf2 and Nrf2-regulated antioxidant enzyme gene in mice. The combination of PM exposure and HFD treatment caused a synergistic effect on the changes of lipid accumulation oxidative stress, inflammation in the mouse liver.	[120]
Du X et al., 2019	$ApoE^{-/-}$ mice, (6 weeks old) fed with normal chow (NC) or high-fat chow (HFC) for 10 weeks, then exposed to $PM_{2.5}$	Whole body exposure to PM2.5 or FA for 16 weeks	The PM exposure resulted in cardiac dysfunction and injury in both NC and HFC groups. Increased $CD11c^+$ and decreased $CD206^+$ macrophages were seen in the bone marrow and of the PM exposed mice. Increased circulating TNF-α, decreased IL-10 and activation of NLRP3 inflammasome, which characterized by elevated protein expression of NLRP3, ASC, caspase-1, IL-1β and IL-18 was observed in the myocardium of PM exposed mice.	[55]
Xu MX et al., 2019	Male mice (C57BL/6)	Whole body exposure to moderate $PM_{2.5}$ (115 ± 1.5 μg/m3) or severe $PM_{2.5}$ (230 ± 2.5 μg/m3) FA for 24 weeks	Long-term $PM_{2.5}$ exposure increases lipid accumulation and hepatic-function loss, oxidative stress, increased insulin resistance, glucose tolerance, peripheral inflammation and dysarteriotony in $PM_{2.5}$ exposed mice. Suppression of inflammatory response and oxidative stress restrains abnormal lipids metabolism in vitro.	[121]
Wang H et al., 2018	Wild-type and $AMPK\alpha2^{-/-}$ mice	Whole body exposure to $PM_{2.5}$ (mean daily concentration ~64 μg/m3) or FA for 6 months	AMPK is protective in chronic $PM_{2.5}$ exposure-induced adverse health effects. Chronic exposure to $PM_{2.5}$ resulted in severe lung injury, left ventricular dysfunction, higher levels of fibrotic genes, collagen in heart and lungs, lower levels of peroxiredoxin 5 (Prdx5), increased oxidative stress and inflammation in $AMPK\alpha2^{-/-}$ mice.	[56]

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Table 1 (*continued*)

Study	Animals and model	Air pollutant	Major outcome	Ref.
Qiu Y et al., 2017	Male C57BL/6J mice	Whole body exposure to $PM_{2.5}$ for a duration of 10 weeks	$PM_{2.5}$ exposure to mice (fed normal chow diet) repressed hepatic transcriptional regulators involved in fatty acid oxidation and lipolysis, and thus promoted hepatic steatosis. However, $PM_{2.5}$ exposure relieved hepatic steatosis in high-fat diet-induced obese mice. Further investigation revealed that $PM_{2.5}$ exposure, induced hepatic autophagy in mouse livers via MyD88-mediated inflammatory pathway.	[122]
INTRATRACHEAL/INTRANASAL PM2.5 EXPOSURE				
Yang, J et al., 2019	Kunming mice and rats	Instillation of $PM_{2.5}$ (20 mg/kg body weight) or saline (0.9%), every other day for 3 months	$PM_{2.5}$ exposure can activate the inflammatory reaction and induce immune dysfunction. Exposure to $PM_{2.5}$ resulted in lung intracellular edema, increased number of microvilli and lamellar bodies, inflammatory cells (neutrophils, polylymphocytes and eosinophils), and increased levels of IL-4, TNF-α and TGF-β1 in the tissues.	[123]
Feng B et al., 2019	Male Wistar rat treadmill training followed by 3 $PM_{2.5}$ instillation	Intratracheal instillation of 10 mg/ml of $PM_{2.5}$ at 300 μl/kg body weight of rat, on every other day in week 7	$PM_{2.5}$ instillation decreased NO bioavailability. Exercise training promoted HDL function, prevented endothelium dysfunction induced by $PM_{2.5}$ instillation and significantly reduced the body weight of rats.	[124]
Peng J et al., 2019	Female Balb/c mice	Intratracheal instillation of $PM_{2.5}$ (1, 10, 50 or 100 μg in 50 μl sterile PBS) or PBS.	The surfactant protein A (SA-P) protein concentration and mRNA expression, showed a tendency to first rise then descend in response to the increase of $PM_{2.5}$ concentration. With the increase of the $PM_{2.5}$ concentration ROS production and inflammation infiltration are substantially accumulated. The damage under the high concentration of $PM_{2.5}$ exposure was well rescued by N-acetylcysteine as an oxidant inhibitor to antagonize ROS.	[125]
Duan S et al., 2019	BALB/c mice	Intratracheal instillation of $PM_{2.5}$ (4.0 mg/kg BW) for 5 days	$PM_{2.5}$ exposure, induced characteristic abnormal ECG changes, increased inflammatory cell infiltration and fibrosis in the heart tissue and increased the expression of α-SMA, NLRP3 activation-associated proteins of NLRP3, IL-1β, IL-18, Cleaved caspase-1 p10, and Cleaved IL-1β were upregulated in heart tissue of $PM_{2.5}$ exposed mice.	[126]
Xu M et al., 2019	C57/BL6 mice	Intranasal instillation of 50 μl of $PM_{2.5}$ (7.8 mg/kg) or PBS for 2 days	TRPV1 and TRPA1 channels play an important role in $PM_{2.5}$-induced lung inflammation and AHR. The inhibition of the TRPA1 channel or combined inhibition of TRPA1 and TRPV1 channels resulted in decreased inflammatory cytokine levels in BALF and decreased oxidant levels in the lung. The inhibitory effect on $PM_{2.5}$-induced lung injury was mediated through regulating the mitochondrial fission/fusion proteins and inhibiting the TLR4/NF-κB and NLRP3/caspase-1 pathway.	[127]
Su R et al., 2019	Sprague-Dawley (SD) rats	Intranasal instillation of $PM_{2.5}$ from summer and winter (0.2–2.7 mg/kg WB) or PBS, in 500 μl volume	$PM_{2.5}$ exposure triggered oxidative stress and ERS in spleen tissues of SD rats, and lead to apoptosis via upregulation of CHOP and caspase-12, and activated the autophagy of spleen in a concentration-dependent manner.	[128]
DIESEL EXHAUST (DE) EXPOSURE (ULTRAFINE PARTICLES)				
Kim HS et al., 2020	Female BALB/c mice exposed 1 h/day, 5 days/weeks, 4–8 weeks	DEP exposure using ultrasonic nebulizer, 1 ml/min and 1- to 5-μm particle size.	DEP exposure provokes an imbalance of the immune system via dysregulated inflammatory markers, predicted to disrupt protective responses against harmful exogenous substances in the body.	[42]
Wang X et al., 2019	4-weeks old C57BL/6J mice, exposed to DEP before conception, during pregnancy and fed normal chow or a high-fat diet.	Intratracheal instillation of diesel exhaust $PM_{2.5}$ (DEP) (200 μg in 50 μl) or sterile normal saline (50 μl)	Prenatal exposure to DEP programmed the hepatic steatosis in adult male offspring via SREBP-1c and PPAR-α pathway, and induced hepatic steatosis in offspring of mice fed normal chow food. Prenatal exposure to DEP alleviated the hepatic steatosis in offspring of mice fed high fat diet.	[129]
Shi R et al., 2019	BALB/c mice	Intratracheal instillation of 50 μl aqueous suspensions of 0.5 mg DEP	The study demonstrated that naringin had regulating effects on the DPM-induced abnormal secretion of the respiratory tract. DEP inhibited airway surface liquid secretion and increased the viscosity of the liquid. Naringin attenuate DPM-induced injury, reduce liquid viscosity by reducing MUC5AC and total protein secretion, increase DPM-induced CFTR, AQP1, and AQP5 mRNA and protein expression, positively regulate apical CFTR insertion and promote CFTR activation by increasing intracellular cAMP.	[130]

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Table 1 (*continued*)

Study	Animals and model	Air pollutant	Major outcome	Ref.
Zheng X et al., 2019	C57BL/6 mice Single dose of DEP	Intratracheal instillation of 100 μg DEP/mouse and sacrificed after 30 min, 6 h, 12 h, 24 h, 48 h, and 72 h.	Single exposure to DEP induced transient oxidative stress in the lungs, with time-dependent effects on Nrf2 and antioxidant enzymes and phase II enzymes. 6 h post DEP exposure, ROS peaked, most of the enzymes were activated, and the histology showed the lungs were damaged. At 12 h, ROS returned to normal level and CAT activity decreased, while protein expression of Nrf2, HO-1, NQO1, GCLC, and GCLM increased, and the lungs were recovering from damage.	[41]
De Grove KC et al., 2018	C57BL/6J mice	Intranasal instillation of DEP alone, HDM alone or combined DEP + HDM	Combined exposure to DEP + HDM showed synergistic response and increased IL-33 and ST2 expression in lung, elevated inflammatory responses and bronchial hyperresponsiveness compared to saline, DEP alone or HDM alone exposure.	[131]
Liu J et al., 2018	Male 8-weeks old CD-1 mice	DEP exposure in chambers (350 μg/m [3] TPS) for 5 h/day and clean FA for 19 h/day throughout the 7-day exposure	DE exposure induced the proliferation of vascular smooth muscle cells (VSMCs) and apoptosis of endothelial cells in pulmonary artery and induces pulmonary arterial hypertension in mice. DE inhalation exposure induced an accumulation of $CD45^+$ lymphocytes and $CD68^+$ macrophages surrounding and infiltrating pulmonary arteriole. The levels of pro-inflammatory cytokines tumor necrosis factor (TNF-α), interleukin-6 (IL-6) and IL-13 produced by T helper 17 (Th17) and Th2 cells were markedly elevated in lung tissues of mice after DE inhalation exposure.	[132]
Cole TB et al., 2017	C57Bl/6 mice	Whole body exposure to DEP (250–300 μg/m3) or FA for 6 h.	Acute DEP exposure caused significant increases in lipid peroxidation and of pro-inflammatory cytokines (IL-1α, IL-1β, IL-3, IL-6, TNF-α) in various brain regions (particularly olfactory bulb and hippocampus). DE exposure also caused microglia activation, as measured by increased Iba1 (ionized calcium-binding adapter molecule 1) expression, and of TSPO (translocator protein) binding.	[133]
Li YJ et al., 2017	$Nrf2^{+/+}$ and $Nrf2^{-/-}$ C57BL/6J mice	Mice were exposed to DEP in inhalation chambers for 56 days, from 28 days before and 28 days after the bleomycin injection	Inhalation of DE induced significant inhibition of airway clearance function and the proinflammatory cytokine secretion in macrophages, an increase in neutrophils, and severe lung inflammatory injury, which were greater in $Nrf2^{-/-}$ mice than in $Nrf2^{+/+}$ mice.	[134]
OZONE GAS MIXTURES				
Fuentes N et al., 2019	C57BL/6J female and male mice	Exposed animals to 1 ppm of ozone or FA for 3 h	Ozone exposure resulted in increased airway hyperresponsiveness and expression of inflammatory genes. Response to ozone was higher in females and were affected by gonadectomy and 17β-estradiol treatment in a sex-specific manner. Gonadectomy reduced ozone-induced expression of lung IL-6 and MIP-3 in females, which was restored by treatment with 17β-estradiol.	[135]
Zhang JH et al., 2019	Balb/c mice, Ova induced asthma model	Ozone mixed with air for 3 h at a concentration of 3 ppm in a sealed Perspex container	Ozone exposure increased ROS release and asthma exacerbation and elevated neutrophil lung infiltration. Ozone increased pro-inflammatory cytokine production as well as the percentage of $IL\text{-}17^+$ γδT cells.	[136]
Xu M et al., 2019	C57/BL6 mice	Ozone exposure (2.5 ppm, 3 h).	Acute ozone exposure (single 24 h) induces mitochondrial dysfunction and NLRP3 inflammasome activation. Inflammasome activation has a critical role in the pathogenesis of ozone-induced airway inflammation and bronchial hyperresponsiveness. Ozone exposure resulted in increased total cells in BAL including neutrophils and eosinophils, and BAL inflammatory cytokines (IL-1α, IL-1β, KC, and IL-6).	[137]
Li F et al., 2018	C57/BL6 mice	Mice were exposed to ozone (2.5 ppm, 3 h) or FA twice a week for 6 weeks	Both mtROS and NLRP3 inflammasome play a role in ozone-induced lung inflammation while only NLRP3 is involved in ozone-induced emphysema. Ozone-exposed mice had increased BAL total cells, increased lung inflammation, and levels of IL-1β, KC and IL-6, enhanced oxidative stress with higher serum 8-OHdG concentrations, emphysema with greater mean linear intercept (Lm), airway remodeling with reduced lung functions.	[138]

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Table 1 (*continued*)

Study	Animals and model	Air pollutant	Major outcome	Ref.
Zhong et. al., 2016	Diabetes prone KK mice exposed to ozone or filtered air.	Ozone (0.5 ppm) exposure for 13 consecutive weekdays (Monday to Friday, 4 h/day).	Repeated Ozone inhalation induces oxidative stress, adipose inflammation and insulin resistance. Ozone increased monocytes/ macrophages in both blood and visceral adipose tissue. Systemic $CD4^+$ T cell activation enhanced by the exposure of O3. Multiple inflammatory genes including CXCL-11, IFN-gamma, TNF alpha, IL-12, and iNOS up-regulated in visceral adipose tissue.	[139]
Ying et. al 2016	Male KKAy mice were exposed to ozone or filtered air for 13 days	Ozone (0.5 ppm) exposure or FA for 13 consecutive weekdays	Pro-inflammatory CD11b(+)Gr-1lo7/4hi macrophages increased in adipose but unchanged in blood. Fasting insulin and HOMA-IR in ozone-exposed animals reduced without change in glucose. Paradoxic increased insulin signaling in skeletal muscle/liver. Ozone associated with weight loss and reduced plasma leptin that may have confounded results.	[140]
Pafett et al., 2015	Male Sprague-Dawley rats	Ozone (1 ppm) for 4 h	Ozone exposure augmented BAL cells and neutrophil count and numbers of circulating neutrophils and macrophages. Coronary artery constriction in response to serotonin was pronounced in ozone exposed rats with endothelial dysfunction (ACh) that was corrected in the presence of superoxide dismutase and prevented by SOD/catalase as well as NADPH oxidase inhibitor apocynin.	[141]
COMPARATIVE STUDIES				
Tong H et al., 2019	Female C57Bl/6 mice exposed to diesel exhaust (DE)	Mice were exposed to either freshly emitted DE, photochemically altered diesel exhaust (aged DE), or FA for 4 h using an environmental irradiation chamber	Fresh DE (contained 460 μg/m [3] of PM, 0.29 ppm of NO2 and no O_3), significantly decreased LVDP, dP/dtmax, and dP/dtmin compared to FA, while aged DE (consisted of 330 μg/m [3] of PM, 0.23 ppm O_3 and no NO2) significantly reduced LVDP and dP/dtmax. Acute inhalation to either fresh or aged DE lowered LVDP and dP/dt, with a greater fall noted with fresh DE, suggesting that the composition of DE may play a key role in DE-induced adverse cardiovascular effects in female C57Bl/ 6 mice.	[142]
Hasari MS et al., 2018	Female WT mice exposed to smog generated in the Mobile Reaction Chamber (MRC)	Mice were exposed to simulated high PM/low ozone (SA-PM) or low PM/high ozone (SA-O_3) smog atmosphere for 4 h.	This study demonstrates that a single exposure to smog causes cardiac effects in mice. The responses of SA-PM and SA-O_3 are similar, but the latter is more potent in causing electrical disturbances and breathing changes potentially due to the effects of irritant gases, which should therefore be accounted for more rigorously in health assessments.	[143]
Wong EM et al., 2018	Normotensive and spontaneously hypertensive (SH) Wistar-Kyoto rats exposed to PM and Ozone	Exposed to one of the following atmospheres: FA, UFPM (~250 μg/ m3), O3 (1.0 ppm), or UFPM + O_3 (~ 250 μg/m3 + 1.0 ppm) combined for 6 h, followed by an 8 h FA recovery period.	SH rats were particularly susceptible to O_3 exposure, exhibiting increased injury scores in terminal bronchioles and epithelial degeneration in large airways. UFPM-exposure groups had minimal histologic changes. The chemical composition of UFPM was altered by the addition of O_3, indicating that ozonolysis promoted compound degradation. O_3 increased the biologic potency of UFPM, resulting in greater lung injury following exposure	[144]
Aragon MJ et al., 2016	C57BL/6 mice exposed to varied complex mixtures	Mice exposed to a single (6-h) road dust, MVE (a combination of gasoline and diesel engine emissions) PM, MVE gases, road dust plus ozone, road dust plus MVE, and hardwood smoke for 24 h	Road dust and wood smoke exposures were most potent at inducing inflammatory gene expression, while MVE atmospheres and wood smoke were most potent at impairing vasorelaxation to acetylcholine. Responses are consistent with recent reports on MVE toxicity, but reveal novel serum bioactivity related to wood smoke and road dust. These studies suggest that the compositional changes in serum and resultant bioactivity following inhalation exposure to pollutants may be highly dependent on the composition of mixtures.	[45]

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Table 1 (*continued*)

Study	Animals and model	Air pollutant	Major outcome	Ref.
Wang G et al., 2015	Wistar rats exposed to PM2.5, Ozone or both together	Rats were inhaled 0.8 ppm ozone or air for 4 h and then placed in air for 3 h following intratracheal instillation with 0–3.2 mg/rat $PM_{2.5}$ in sterile saline (0.25 ml/rat), repeated twice per week for 3 weeks	The study demonstrated that inflammation and oxidative stress were involved in toxicology mechanisms of $PM_{2.5}$ in rat lung and ozone potentiated these effects induced by PM2.5. $PM_{2.5}$ exposed group showed increased total cells in BALF than control and a dose-dependent increase in TNF-α, interleukin-6, lactate dehydrogenase, and total protein of BALF. Exposure to ozone alone resulted in increased TNF-α. On the other hand, ozone enhanced $PM_{2.5}$-induced inflammatory changes and pathological characters in rat lungs. SOD and GSH-Px activities in lung were reduced in $PM_{2.5}$-exposed rats with and without prior ozone exposure compared to control.	[145]

disruption of cellular redox signaling and/or upregulation of endogenous ROS production resulting in exaggerated responses. Endogenous ROS, as described in some excellent reviews [25], may be generated from diverse sources including mitochondrial respiratory chain, NADPH oxidases (NOXs), nitric oxide synthases (NOS), cyclooxygenases, lipoxygenases, xanthine oxidase, and cytochrome P450s [19, 26, 27]. Chemical transformation of thiols and fatty acids ($^{\bullet}NO_2$ and $^{\bullet}NO$); lipid peroxidation, ketone and endoperoxide fatty acid products, reactive aldehyde formation; oxidation of thiols to disulfides or sulfoxides and DNA base oxidation can also occur. The lung endogenous defenses include the airway epithelial cells, protective surfactant material comprising of a complex mixture of proteins and phospholipids and anti-oxidants that are constantly replenished and alveolar macrophages. An imbalance in the levels of antioxidants, either from depletion or from exhaustion, such as glutathione, ascorbate, and tocopherol with subsequent depletion of reduced cofactors such as NADPH may result in potentiation of oxidative stress. The alveolar macrophages continually phagocytize particulate matter and over long periods at high levels of exposure may be unable to proliferate and replenish, evidence for which is emerging (discussed later in this review).

Investigators have used primarily three different approaches to understand the health effect of PM exposure, **a)**. in vitro/ex vivo using simple cell culture exposed to PM particles, **b)**. intra-tracheal or intranasal mode of exposure which are not physiologic but provide insights on pulmonary and systemic effects **c)**. inhalational exposure to concentrated ambient particles. Data obtained from in vitro/ex vivo studies using cell lines or primary cells although useful in defining the specific cellular pathways modulated by PM exposure, provide limited insights into transduction of PM induced systemic responses. Many of these cells may never encounter particulates especially at the concentrations commonly used [9,28,29]. Intra-tracheally/intranasally administered PM often results in uneven intrapulmonary distribution of the particles and may not mimic inhalational exposure. PM exposure using particle concentrator systems is a preferred approach as it allows physiologic route of exposure over prolonged time to mimic real-world conditions. Both a limitation and strength is that only certain particle size ranges are typically concentrated, contrary to ambient air which contains a mixture of particle sizes and gases. Inhalational exposure typically is performed in rodent models and although likely to provide valuable information about mechanisms, can sometimes make extrapolation to human pathology difficult, since rodent models differ in their breathing patterns, nasal anatomy and filtering mechanisms. Human exposure studies are typically performed only for over a few hours and do not provide a perspective on chronic exposure. Panel studies in humans and analysis of surrogate end-points also provide windows into potential pathways, but are associative.

4. Pathophysiologic insights into mechanisms of air pollution oxidant stress

4.1. Oxidative stress as an underlying basis of vascular toxicity

The vascular endothelium is a critical barrier that modulates a myriad of exposures and prevents inflammation, thrombosis and vascular injury through a variety of pathways. A principal pathway involves the generation of nitric oxide ($NO^{\cdot}$) [30]. Alteration in vascular function to a large extent has its genesis in the dysregulated generation of excess ROS and the reaction of superoxide with $NO^{\cdot}$ to form the highly reactive intermediate peroxynitrite (ONOO). The rate of this reaction is 10-fold compared to dismutation of superoxide by superoxide dismutase (rate constant 5–10 $\times$ 10^9/M/s) [31]. $ONOO^{-}$ may act as a vasoconstrictor and also more like a cytotoxic molecule that cause oxidative damage. It can also cause uncoupling of endothelial nitric oxide synthase and tyrosine nitration of prostacyclin synthase, decreasing endothelial function. The S-nitrosylation of target proteins following $NO^{\cdot}$ release, results in a stable post-translationally modified

product that directly regulates function of proteins [32]. Defective nitrosylation has been linked to endothelial barrier dysfunction, abnormal release of $NO^{\cdot}$ and may represent an important link between risk factors and cardiovascular disease [32].

4.2. Systemic vascular oxidative stress with air pollution exposure

Table 1 summarizes some of the key in vivo studies from 2017 onwards (a prior review has discussed prior papers in great detail [33]), describing the health effects of $PM_{2.5}$ utilizing whole body exposure system and intratracheal/intranasal instillation of concentrated ambient $PM_{2.5}$ particles. Key findings from these studies establish that air pollution exposure manifests in rapid systemic effects often within hours. Recent findings from human studies suggest that inhaled nanoparticles and their constituents could rapidly cross the alveolar membrane in lung and appear systemically [34]. In rodents, both sub-acute and chronic exposure to air pollution alone and/or in conjunction with other agents has contributed to increased superoxide ($O_2^{\bullet -}$) production, potentiation of vasoconstrictor responses and inflammation. $O_2^{\bullet -}$ production in response to chronic $PM_{2.5}$ exposure was neutralized by NAD(P)H oxidase inhibitor apocynin and NOS inhibitor N-omega-nitro-L-arginine methyl ester (L-NAME), suggesting that coupling of $O_2^{\bullet -}$- with nitric oxide to reduce the latter's bio-availability to NADPH oxidases, may be an important mechanism responsible for inducing adverse vascular effects [35,36]. Concentrated $PM_{2.5}$ exposure resulted in increased microvascular adhesion of inflammatory monocytes in the adipose microcirculation together with perivascular deposition of mononuclear cells, with deficiency of Nox2 and Tlr4 improving vascular responsiveness [37,38]. There is limited evidence comparing the effect of ultrafine PM vs $PM_{2.5}$ in inducing systemic oxidant stress. However, one study demonstrated that exposure of $ApoE^{-/-}$ mice to ultrafine particles leads to greater atherosclerosis compared to $PM_{2.5}$ [39]. Exposure to ultrafine particles have higher systemic penetration, and may also result in inhibition of anti-inflammatory potential of high-density lipoprotein (HDL) and greater systemic oxidative stress as evidenced by up-regulation of Nrf2-regulated antioxidant genes, lipid peroxidation products in the plasma and liver, and increased hepatic malondialdehyde [39,40]. Recent data with whole body exposures add to the overall literatures suggesting systemic effects including alterations in oxidant stress, metabolism, inflammation and central nervous system effects (Table 1). These results seem to generally confirm the relationship between oxidant stress inflammation and systemic organ dysfunction.

Diesel exhaust (DE) exposures have been shown to induce oxidant stress and systemic inflammation. These have been previously reviewed and therefore only recent studies highlighted (Table 1). For example, Zheng et al., 2019, found that intratracheally instilled, single exposure of diesel exhaust particles induced transient oxidative stress in the lungs of mice. ROS peaked at 6 h, with time dependent regulation of Nrf2 and antioxidant enzymes and phase II enzymes in the DEP exposed mice [41]. In a very recent report, Kim et. al. 2020, reported that DE exposure results in gene expression (nasal cavity) that in turn provokes an imbalance of the immune system via dysregulated inflammatory markers (S100A9, S100A8, CAMP, and IL20)[42] **(**Table 1**).**

Ozone is another important constituent of ambient air pollution. Most ozone exposure studies published to date are acute exposures and demonstrate rapid (hours) endothelial dysfunction and abnormal vasoconstriction. Mechanistically, a rapid depletion of NO with concomitant decrease in aortic eNOS levels that can be, reversed with $O_2^{\bullet -}$ scavengers (Table 1) are some key events contributing to the above stated pathology. Some studies suggest the presence of serum factors to be responsible for inducing endothelial dysfunction and neuronal inflammation. Others have suggested an endothelial locus of generation of putative factors that circulate to perpetrate systemic vascular and neuronal injury, these findings need to be confirmed [43]. In a primate study, acute exposure to ozone (0.5 ppm) resulted in increased aortic mitochondrial damage [44]. Evidence from one short-term 2-day study supported findings that no additive effects were noted in ozone and diesel exhaust. The downside of all these studies is that the concentrations of O_3 used in rodent studies (0.5–1 ppm) are far from the concentration of doses used in human studies or for that matter the regulatory standards (current U.S. National Ambient Air Quality Standard is 0.075 ppm averaged for an 8 h period while the European Commission has set a standard at 0.057 ppm). (Table 1).

There have been direct comparative studies examining the differential impact of gases on vascular function but have tested limited endpoints. In one study brief 6 h exposures to the plasma of various emissions demonstrated that plasma from road dust and wood smoke exposure were most potent in inducing in-vitro inflammatory gene expression and impairment of vasorelaxation to acetylcholine [45] (Table 1).

4.3. Cardiac oxidant stress in response to air pollution exposure

Very early observations by Gurgeiera and Gonalez-Fletcha have shown that short term inhalation (5-h) of concentrated ambient $PM_{2.5}$ but not inert carbon results in oxidative stress, determined by in situ chemiluminescence in the and heart, but not liver. Increase in chemiluminescence in the heart showed strong association with Fe, aluminum, silicon, and titanium levels in the particles [46]. Five-hour exposure to CAPs induced oxidant stress that was associated with slight but significant increases in heart water content and to tissue-specific increases in the activities of the antioxidant enzymes catalase and superoxide dismutase. This observation suggested that episodes of increased particulate air pollution not only have potential for oxidant injurious effects but may also trigger adaptive responses such as cardiac hypertrophy. This has indeed been seen in chronic exposure studies where a strong association of $PM_{2.5}$ to cardiac hypertrophy has been noted [47,48]. Further cessation of exposures has the potential of reversing these changes. Chronic exposure to PM for 15 weeks resulted in increased -blood pressure, -heart weight, -cardiac expression of hypertrophic markers (ACTA1 and MYH7) and decreased cardiac stroke volume in spontaneously hypertensive rats and withdrawal from PM exposure restored these parameters to normal [47]. Qin et. al., intratracheally exposed mice to $PM_{2.5}$ and observed reversible cardiac dysfunction and fibrosis in mice of different age groups [49]. In this study, PM-exposed 4-weeks and 10-months old mice developed cardiac fibrosis while 10-months old mice demonstrated cardiac diastolic dysfunction, elevated heart rate/blood pressure, and cardiac systolic dysfunction. $PM_{2.5}$ exposure also resulted in increased expression of cardiac fibrosis markers (Col1a1, Col3a1), NOX-4, and TGFβ1, and generated more ROS in the myocardium of both the 4-week-old and 10-month-old mice. The withdrawal of $PM_{2.5}$ exposure restored the cardiac function, blood pressure, heart rate, collagens expression, and malonaldehyde (MDA) levels in hearts of mice of both age groups [49]. Evidence from recent studies strongly support the argument that exposure that $PM_{2.5}$ led to systolic disfunction, cardiac hypertrophy and fibrosis in mice [48,50–52]. Fibrosis is the aftermath of chronic inflammation and it has been shown that macrophages play a key role in development of fibrosis [53,54]. In a recent mechanistic study, Su et. al., exposed C57BL/6 mice to $PM_{2.5}$ or filtered air for 8 or 16 weeks and pointed out that cardiac hypertrophy developed in $PM_{2.5}$ exposed mice is regulated by PI3K/Akt/FoxO1 pathway and the role of cardiac macrophages in fibrosis development [48]. FoxO (a transcription factor regulated by Akt) regulates several cellular functions, including survival, metabolism, proliferation, and differentiation that play key roles in regulating cardiac hypertrophy [48]. Du et. al., 2019, found that $PM_{2.5}$-induced cardiac injury is mediated by macrophages polarization and NLRP3 inflammasome activation using $ApoE^{-/-}$ mice exposed to $PM_{2.5}$ for 16-weeks [55]. In this study authors found increased $CD11C^{+}$ and decreased $CD206^{+}$ macrophages in bone marrow, elevated levels of circulating inflammatory cytokine TNF-α and decrease of anti-

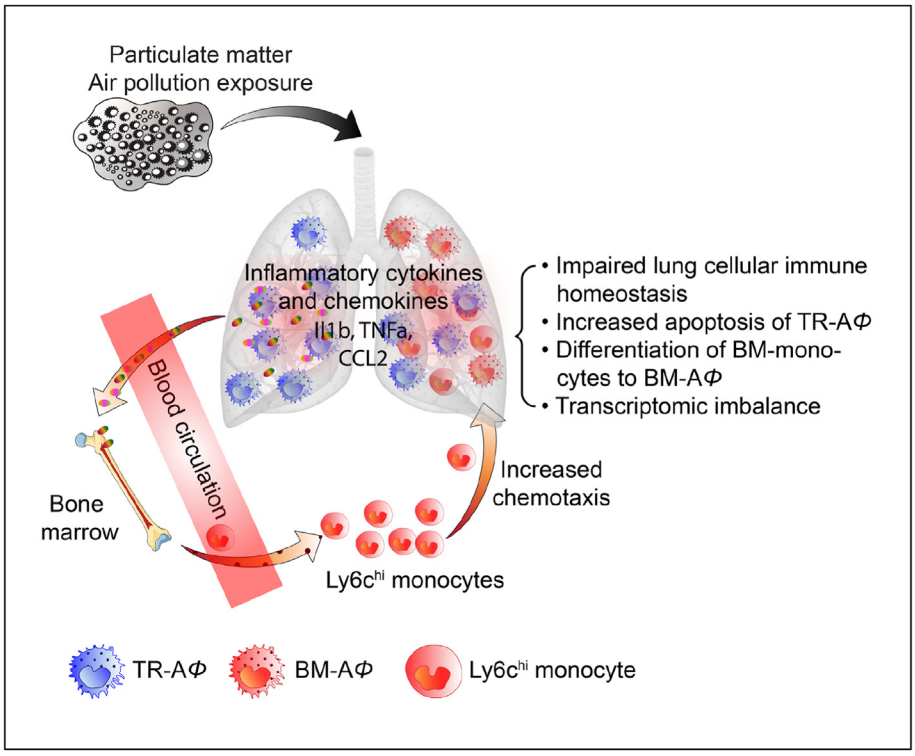

Fig. 2. Schematic illustration of key changes in the lung inflammation in chronic $PM_{2.5}$ exposure. Chronic exposure to $PM_{2.5}$ results in release of inflammatory cytokines and chemokines in the blood circulation that leads to infiltration of $Ly6c^{hi}$ monocytes in the lungs from bone marrow. Continual exposure to $PM_{2.5}$ cause persistent inflammatory environment in the lungs that resulted in increased apoptosis of tissue resident alveolar macrophage and differentiated of recruited BM-monocytes into BM-alveolar macrophages.

inflammatory cytokine IL-10 in $PM_{2.5}$ compared to FA exposed mice. Activation of NLRP3 inflammasome was also observed in the myocardium of $PM_{2.5}$ exposed mice as evidenced by elevated protein expression of NLRP3, ASC, caspase-1, IL-1β and IL-18 in the myocardium [55]. AMPKα$2^{-/-}$ mice chronically exposed for 6 months, showed higher expression of pro-fibrotic genes, increased collagen deposition, lower levels of peroxiredoxin 5 (Prdx5), and increased oxidative stress and inflammation in the hearts and lungs $PM_{2.5}$ exposed mice [56]. All these results suggest that oxidative stress, inflammation and tissue damage are direct sequelae of exposures and could represent targets for intervention.

4.4. Mechanisms by which pulmonary oxidative stress is systemically transduced

The underlying mechanisms by which pulmonary oxidative stress leads to systemic inflammation in response to air pollution is still not fully understood, but almost certainly involves the lung. There are several studies demonstrating an effect of $PM_{2.5}$ in inducing a systemic inflammatory response through the release of inflammatory cytokines and chemokines into the circulation from lung immune cells [37,57]. Early studies from Terashima et. al. demonstrated that human alveolar macrophages incubated with latex particles of different sizes (0.1, 1, and 10 μm) or inert carbon particles produced inflammatory cytokines and chemokines (M-CSF and MIP) in response to phagocytosis and the response was similar (regardless of size) to when they were exposed to particle suspensions of residual oil fly ash (ROFA), ambient urban particles (EHC 93), suggesting that the act of phagocytosis, irrespective of other considerations was responsible for inflammatory cytokine production [58]. Furthermore, the types of cytokines were comparable to that seen with exposure to high levels of PM10 particles based on plasma samples collected in subjects in Singapore during and following a South Asian haze (mean PM_{10} levels of (125.4 ± 44.9 versus 40 ± 14.3 mg/m3, haze versus post haze) [58]. In a subsequent publication, the role of alveolar macrophage in this response was further investigated by incubating isolated human alveolar macrophages in tissue culture medium either with or without the presence of colloidal carbon and measuring the effect of the supernatants on the release of polymorphonuclear cells from the bone marrow [59]. The supernatant of alveolar macrophages incubated with colloidal carbon shortened the transit time of release of cells through the bone marrow, when compared with the supernatant from the unstimulated alveolar macrophages or with cell culture medium alone. These experiments provided the first evidence that air pollution through pulmonary alveolar macrophage dependent chemokine release stimulated the release of inflammatory cells into the systemic circulation. Subsequently we and others demonstrated that pattern recognition receptors such as TLR4 were involved in the release of $Ly6C^{hi}$ monocytes from the bone marrow likely via CCR2/CCR5 dependent mechanisms [37]. In a recent report we investigated the differential contribution of tissue resident alveolar macrophages and bone marrow-derived infiltrating monocytes to persistent lung inflammation in mice exposed to $PM_{2.5}$ for 4 or 32 weeks (Gangwar RS. et al., 2020, Scientific Reports, *under review*). We used special chimeric (CD45.2/CD45.1) mice in which chest was shielded before irradiation (to protect the resident lung macrophage and monocyte population) followed by bone marrow transplantation from CD45.1 mouse. We found that short term $PM_{2.5}$ exposure (4-weeks) induces an influx of bone marrow-derived monocytes to lungs, with no contribution to the tissue resident alveolar macrophage population, while chronic (32-weeks) $PM_{2.5}$ exposure resulted in recruitment of bone marrow-derived alveolar macrophages in inflamed lung, coupled with increased apoptosis and decreased proliferation of the tissue resident alveolar macrophage. Transcriptomic analysis of isolated tissue resident and bone marrow alveolar macrophages from 4 and 32-weeks exposed mice, revealed a time-dependent pattern of differentially expressed genes with $PM_{2.5}$ exposure with a pro-inflammatory bias (Gangwar RS. et al., 2020, Scientific Reports, *In press*), (Fig. 2). We examined the effects of chronically inhaled $PM_{2.5}$ on pulmonary and systemic inflammation and role of CCR2 and CXCR3 in two separate experiments [60,61]. These findings, suggest a robust innate and adaptive immune activation in response to the air pollution that is dependent on chemokine mechanisms.

Phospholipids and surfactant proteins present in the bronchioloalveolar fluid are an important line of defense that are continually

replenished to provide a potent barrier against air pollution. Chronic ongoing exposure to air pollution may obviate the necessity of surfactant defenses in order to prevent increase in oxidatively modified derivatives such as 1-palmitoyl-2-arachidonyl-sn-glycero-3-phosphorylcholine (PAPC) and 7-ketocholesterol from contributing to endothelial barrier dysfunction, inflammatory cell recruitment, allowing facile transgression of air pollutants, chemokines and other secondary mediator signals to the bone marrow and systemic circulation [37].These mediators may also enhance oxidative stress in the vasculature resulting in TLR4 activation in monocytes and macrophages [62,63]. Consequently, depletion of TLR4, NOX2 or p47phox have all been shown to attenuate ROS generation, reduce inflammatory monocyte infiltration into vasculature and improve vascular function in response to inhalational exposure to concentrated $PM_{2.5}$ [37,64]. $PM_{2.5}$ exposure-induced formation of 7-ketocholesterol, its bio-distribution in LDL and subsequent uptake by scavenger receptor CD36, and entrapment within plaque macrophages may represent a paradigm for air pollution mediated endothelial dysfunction and potentiation for atherosclerosis [65,66]. Two studies provide evidence that pulmonary surfactant antioxidant barrier may be critical in modulation of systemic responses [67,68]. First, $PM_{2.5}$ induced reduction in Akt/eNOS signaling in the aorta in 9 days exposure was effectively reversed by the antioxidant TEMPOL or via overexpression of lung-specific extracellular SOD (ecSOD) [67]. ecSOD in this animal model is driven by a Surfactant C promoter targeting it to cells that produce Surfactant C. Second study, similar to 9-day exposure to CAP reduced endothelial progenitor cell numbers (EPCs) and downregulated VEGF (vascular endothelial growth factor)-stimulated aortic Akt phosphorylation suggesting that impairment of endothelial regeneration owing to depletion of endothelial progenitor cells may represent an important mechanism of sustained endothelial dysfunction. Additionally, the study reported blunted plasma NO levels in wild-type mice but not in mice overexpressing extracellular superoxide dismutase (ecSOD-Tg) in the lungs. Finally, EPCs from CAP-exposed wild-type mice failed to augment hindlimb perfusion when injected into unexposed mice subjected to hindlimb ischemia. In contrast, EPCs derived from CAP-exposed ecSOD-Tg mice restored hind limb ischemia [68].

$PM_{2.5}$ exposure confers activation of sympathetic nervous system and hypothalamic inflammation that is consistent with abnormal blood pressure responses [69]. PM particles can permeate the central nervous system and induce inflammation in areas that responsible for blood pressure regulation and metabolic control [13,25,70,71]. Receptors such as TRPA1 (transient receptor potential cation channel, subfamily A, member 1) in airway sensory neurons can also sense the environmental toxicants and aerogenic oxidants, resulting in neurogenic inflammation [72]. It has been shown that inhibition of central IKKβ prevented peripheral inflammation and abnormalities in insulin resistance and improved whole body metabolism [63,69].

4.5. PM exposure: oxidative stress, anti-oxidant mechanisms and redox balance

While there is a plethora of information on oxidant stress in response to air pollution exposure, in-depth information on regulation and expression of anti-oxidant defenses in $PM_{2.5}$ in vivo exposure model is relatively sparse. In the event of oxidative stress, the major antioxidant defense mechanisms including superoxide dismutase (SOD), glutathione peroxidase, catalase, glutamate-cysteine ligase catalytic subunit (GCLC), thioredoxin reductases, hemeoxygenase-1 (HO-1), NADPH quinone oxidoreductase 1 (NQO-1) and methionine sulphoxide reductases] and non-enzymatic entities (such as glutathione, vitamins A, C, and E, and flavonoids) are induced to restore cellular redox homeostasis [73–76]. The enzymatic defense mechanisms are regulated at the transcriptional level by Nrf2 (nuclear factor-erythroid 2-related factor 2) transcription factor and its associated gens [77]. Nrf2, a basic leucine zipper protein coded by NFE2L2 gene in humans, is the master transcription factor, that regulates the transcriptional induction of antioxidant response elements, (ARE). AREs protect against oxidative stress induced by injury and inflammation. The major detoxication enzymes such as SOD, glutathione S-transferase A2 (GSTA2), and NQO1, contain ARE in their promoter region and during oxidative stress, Keap1, dissociates from Nrf2, releasing it to bind to the ARE of the target anti-oxidant genes [25,78,79]. The magnitude of antioxidative response depends upon several factors namely duration of exposure, PM concentration and toxicity, and susceptibility of the subjects to air pollutants. For instance, during low level of oxidative stress antioxidants may increase in the early phase to limit the oxidative damage while chronic exposure, or highly toxic air pollutants may cause exhaustion of endogenous antioxidant responses. Rats exposed to $PM_{2.5}$ for two weeks showed vascular oxidative stress and up-regulated expression of Cu/Zn-SOD and Mn-SOD in the pulmonary artery and also a reduction in eNOS and vasorelaxation [80]. Xu et al. demonstrated increased mRNA expression of Nrf2 and downstream genes Nqo1 and Gclm in mice chronically exposed to $PM_{2.5}$ for 10 months [81]. The contribution of locus and tissue specific Nrf2 in attenuating $PM_{2.5}$ effects are important questions and would need to be examined. Ex vivo Gene expression analysis of $PM_{2.5}$ exposed airway epithelial cells (obtained from normal individuals) showed Nrf2-mediated oxidative stress response as one of the top pathways [82].

5. E. Evidence of particulate matter air pollution association with oxidative stress/vascular dysfunction in humans

5.1. Evidence from panel studies and large epidemiologic databases

Several human studies demonstrate that acute exposure to air pollution can induce systemic oxidative stress that depend on numerous factors including chemical composition of the air pollutants, associated co-pollutants and host susceptibility [25]. A variety of exposures including wood smoke (4-h exposure to concentrated wood smoke associated with increased urinary excretion of 8-iso-prostaglandin2α); $PM_{2.5}$ exposure (increased malondialdehyde (MDA) in women but not men in Copenhagen) [83,84]. A recent study evaluated lipid peroxidation markers amongst healthy volunteers traveling from Los Angeles to Beijing. Accompanying a significant rise in PM and ambient air pollution was the concentrations of 6 lipid peroxidation biomarkers: 5-, 12-, and 15-hydroxyeicosatetraenoic acid as well as 9- and 13-hydroxyoctadecadienoicacid levels. However, 8-isoprostane was not significantly elevated [85]. Concentrations of oxidized LDL (oxLDL) have also been shown to increase following exposure to ambient air pollution. A study in Belgium correlated proximity to a major road and increases in airway macrophage carbon load with oxLDL. Each increase of 0.25 μm^2 (interquartile range) of carbon load was associated with an increase of 7.3 U/L (95% CI: 1.3–13.3 U/L) plasma oxLDL and each doubling in distance from patient residence to major roads was associated with a 2.9 U/L (95% CI: −5.2 to −0.72) decrease in plasma oxLDL [86]. Concentrations of oxLDL were found to be independently associated with iron and nickel content of $PM_{2.5}$ in one study of students relocating to an urban location [87]. Changes in vascular function in panel studies have demonstrated significant associations between multiple acute time windows across a range of concentrations including most recently with very high exposure levels in China (Table 2). Evidence from both the MESA-Air and the Framingham cohort have demonstrated that long-term exposures to ambient levels of $PM_{2.5}$ are linked to compromised brachial endothelial function [88,89]. Collectively this supports the concept that air pollution exposure in humans through changes in oxidative stress causes vascular endothelial dysfunction. Recently, HDL oxidation index, oxidized LDL (low-density lipoprotein), and malondialdehyde were associated with $PM_{2.5}$ exposure in 74 adults apart of the Beijing AIRCHD study (Air Pollution and Cardiovascular Dysfunction in Healthy Adults) [90]. There have been inadequate studies on the impact of effect modifiers that may

Table 2
Human studies on association of endothelial dysfunction/oxidative stress with air pollution.

Study	Population /cohort	Air pollutant	Major outcome	Ref
			PANEL STUDIES	
Lin et al., 2019 Los Angeles, USA	26 nonsmoking, healthy adults	10 weeks in Beijing in the summers of 2014 and 2015. association of $PM_{2.5}$ with panel of circulating biomarkers indicative of lipid peroxidation and inflammation	Traveling from a less-polluted to a more-polluted city induces systemic pro-oxidative and proinflammatory effects. Changes in the levels of 5-, 12-, and 15-hydroxyeicosatetraenoic acid and 9- and 13-hydroxyoctadecadienoic acid as well as paraoxonase and arylesterase activities in the blood, in association with exposures to PAH metabolites, might have important implications in preventive medicine as indicators of increased cardiovascular risk caused by air pollution exposure.	[85]
Li et al., 2019, Beijing, China	73 healthy adults were followed-up with 4 repeated study visits in 2014–2016.	ambient air pollution (black carbon, nitrogen dioxide, and carbon monoxide) concentrations, HDL function metrics, and parameters of inflammation and oxidative stress were measured in study participants	A significant decrease in HDL cholesterol efflux capacity of 2.3%–5%, associated with $PM_{2.5}$ levels was observed. Higher ambient air pollutant levels were associated with significant reductions in circulating HDL cholesterol and apoA-I, elevations in HDL oxidation index, oxidized LDL, malondialdehyde, and high-sensitivity C-reactive proteins. Higher ambient air pollution concentrations were associated with impairments in HDL functionality, potentially because of systemic inflammation and oxidative stress	[90]
Zhang et al., 2016 California, USA	93 elderly non-smoking adults. Reactive hyperemia index (RHI), was measured weekly for 12 weeks	Road way distance Ambient $PM_{2.5}$ and black carbon	RHI was inversely associated with ambient $PM_{2.5}$, black carbon, NOx, and carbon monoxide. An interquartile range change increase (1.06 μg/m(3)) in 5-day average black carbon was associated with decreased RHI, -0.093 (95% CI: -0.151 to -0.035)	[146]
Pope CA 3rd et al., 2016 Utah, USA	24 persons recruited for each of 3 consecutive winter/spring study periods in Utah	Circulating markers of endothelial apoptosis and inflammation in relation to ambient $PM_{2.5}$ during winter inversion periods in Utah	Elevated levels of endothelial microparticles (annexin $V^+/CD41^-/CD31^+$). Decreased VEGF, PDGF, RANTES, GROα and VEGF and an increase in TNFα, IP-10, MCP-1, MIP-1α/β, IL-6, and IL-1β), and markers of endothelial adhesion sICAM-1 and sVCAM-1.	[147]
Mirowsky et al., 2017 Durham, NC, USA	15 individuals with established from a prospective cohort with CAD presenting to the cardiac catheterization lab at Duke University (CATHGEN cohort)	Daily measurements of O_3 and $PM_{2.5}$ from central monitoring stations. Circulating markers of endothelial function (PAI-1, tPA), brachial endothelial function, diameter and inflammation (IL-6) with various lag structures	Per 0.014 ppm (interquartile) increase in ambient ozone and various lag structures (0–5), tissue plasminogen factor and PAI-1 increased (6.6%, 41% respectively); neutrophil, monocytes and IL-6 also positively correlated. The large-artery elasticity index (−19.5%, 95% CI = −34.0, −1.7), and the baseline diameter of the brachial artery (−2.5%, 95% CI = −5.0, 0.1) were negatively correlated with ozone levels.	[148]
Ambroz et al., 2016, Czech Republic	342 nonsmoking mothers, 344 newborns,	$PM_{2.5}$ exposure, Blood/urine was collected in the summer and winter season to account for differences in air pollution	$PM_{2.5}$ concentrations significant predictor for 8-oxodG and 15-F2t-IsoP levels. In the polluted region, $PM_{2.5}$ was a significant predictor of oxidative DNA damage. Winter season and exposure to air pollution predicted lipid oxidation in newborns.	[149]
Li et al., 2016, Boston, Massachusetts, USA	2035 participants, were not current smokers and had at least one valid measurement of plasma myeloperoxidase or urinary creatinine-indexed 8-epi-PGF2α.	$PM_{2.5}$, black carbon (BC), SO_4^{2-}, NO_x and O_3 exposure	Positive associations of short-term $PM_{2.5}$ and BC exposure with myeloperoxidase; 2- to 7-day moving averages of $PM_{2.5}$ and sulfate were positively associated with 8-epi-$PGF_{2\alpha}$ was observed. Stronger positive associations of black carbon and sulfate with myeloperoxidase were observed among participants with diabetes than in those without.	[150]
Byun et al., 2016, Quincy, Massachusetts, USA	48 healthy men	$PM_{2.5}$ exposure	Interaction of $PM_{2.5}$ exposure and D-loop mtDNA promoter was significantly associated with adverse effect of heart rate variability. Blood mtDNA methylation levels were negatively associated with $PM_{2.5}$ exposure and modified the adverse relationships between PM2.5 exposure and heart rate variability outcomes.	[151]
DeJarnett et al., 2015 Kentucky, USA	A cross-sectional study measuring circulating angiogenic cells in 316 participants with moderate-to-high cardiovascular risk and roadway distance	Road way distance Ambient $PM_{2.5}$ and black carbon	CD31(+)/AC133(+), AC133(+), CD34(+)/AC133(+) cell numbers after adjustment of co-variates, negatively associated with roadway distance suggesting a relationship between vascular repair and traffic exposure	[152]
Wu et al., 2015 Beijing, China	40 male university students	Ambient $PM_{2.5}$	$PM_{2.5}$ iron and nickel were positively associated with Ox-LDL. There were a 1.9% increase and a 1.8% increase in OxLDL, for each interquartile range increase in iron (1-day, 0.51 μg/m^3) and nickel (2-day, 2.5 ng/m^3) in $PM_{2.5}$, respectively.	[87]
CONTROLLED EXPOSURE STUDIES				
				[153]

(*continued on next page*)

Table 2 (*continued*)

Study	Population /cohort	Air pollutant	Major outcome	Ref
Liu et. al. 2015, Toronto, Canada	single-blind randomized crossover trial, 50 healthy young non-smoking volunteers	Ambient coarse (2.5–10 μm; mean, 213 μg/m^3), fine (0.15–2.5 μm; mean, 238 μg/m^3) and ultrafine particles (< 0.3 μm; mean, 136 μg/m^3) for 130 min	One-hour post-exposure, for every 100-μg/m^3 increase, coarse particles increased circulating VEGF, fine particles elevated urinary malondialdehyde and ultrafine particles augmented urinary 8-hydroxydeoxyguanosine. Ambient particles with various sizes/constituents may influence systemic biomarkers differently. Endotoxin in ambient particles may contribute to vascular mediator changes and oxidative stress.	
Byrd, J.B. et. al. 2016, Michigan, USA	29 healthy young adults underwent a randomized double-blind crossover study involving 2-h exposures to concentrated ambient coarse PM	Course ambient coarse PM exposure versus filtered air over 2 h (164.2 ± 80.4 μg/m^3)	Both systolic (1.9 mm Hg) and diastolic (1.9 mm Hg) blood pressure levels were higher throughout coarse PM compared with filtered air exposure. Heart rate variability, endothelial function, and arterial compliance not significantly affected.	[154]

determine individual patient susceptibility. Polymorphisms in oxidative stress-related genes (such as GSTM1, GSTP1, GSTT1, HFE C282Y, CAT and Hem-oxygenase) have been found to be associated with the vulnerability to $PM_{2.5}$ [25]. Heart rate variability (HRV) on exposure to $PM_{2.5}$ has been associated with glutathione-S-transferase M1 (GSTM1) allele as has the GT long tandem repeat polymorphism but not the short in the heme-oxygenase-1 (HO1) promoter [91,92]. Similarly, HFE C282Y and CAT (rs2300181) modified the effects of $PM_{2.5}$ on plasma homocysteine, a marker of inflammation well associated to cardiovascular disease [93]. However, multiple studies have failed to show antioxidant gene variant impact on the effect of $PM_{2.5}$ on blood pressure [94,95].

5.2. Controlled exposure studies

Several studies exhibit rapid vascular dysfunction that manifests as conduit or microvascular endothelial dysfunction or transient reversible constriction of a peripheral conduit vessel owing to acute exposures to $PM_{2.5}$ and dilute diesel exhaust. (Table 2). While many of these studies did not include oxidant stress markers the genesis of rapid endothelial function, changes may involve rapid degradation of $NO^{\cdot}$ but often compensated by increased production of NO. In a classic experiment performed with diesel exhaust (DE)exposures in humans as part of a randomized double-blind crossover study, nonsmokers were exposed to DE or filtered air, and microvascular function tested using plethysmography in the forearm during intrabrachial infusions of acetylcholine and sodium nitroprusside, in the presence of a NO synthase inhibitor N^G-monomethyl-L-arginine (L-NMMA) co-infused with the NO donor SNP to maintain basal blood flow (NO clamp). Following DE inhalation, plasma nitrite concentrations increased (68 ± 48 versus 41 ± 32 nmol/L; $P = 0.006$) despite similar L-NMMA–induced reductions in basal blood flow compared to air [96]. In the presence of the NO clamp, acetylcholine and sodium nitroprusside, caused local dose-dependent vasodilatation of the forearm, that was not affected by diesel exhaust inhalation ($P > 0.05$ for both). However, following exposure to diesel exhaust, systemically administered L-NMMA caused a greater increase in blood pressure ($P = 0.048$) and central arterial stiffness, suggesting that, reduced NO bioavailability secondary to air pollution exposure, cannot be adequately compensated for by increased basal NO generation [96]. $PM_{2.5}$ has not always been shown to induce endothelial dysfunction, underscoring the importance of composition, individual susceptibility and methods of determining endothelial function among many factors that determine vascular responses [97]. Consistent with this, some studies conclude that $PM_{2.5}$ exposure diminished conduit artery endothelial-dependent vasodilatation in a delayed fashion post 24 h [98]. $PM_{2.5}$ mass and TNF-α levels have both been associated with the level of endothelial dysfunction, suggesting that systemic inflammation induced by PM particles and the degree of pollution are likely responsible. While ozone exposures have been shown to impair conduit vessel endothelial function in panel studies, the results from one randomized study seems to indicate lack of acute effects on brachial endothelial function. In summary, the available evidence supports an effect of particulate air pollutants on endothelial function in both conduit and resistance vessels including the coronary circulation. Moreover, chronic exposure may be responsible for endothelial dysfunction from changes in arterial stiffness and afterload that may translate into persistent hypertension. Both low and high levels of traffic related air pollutants are well associated with incident hypertension [99,100]. Similarly, persistent variations in endothelial function and blood pressure may confer susceptibility to atherosclerosis. In the largest study linking chronic exposures to coronary artery calcium (MESA-Air cohort, n = 6795 across 6 U S. regions), each 5 μg/m^3 increase in long-term $PM_{2.5}$ exposure was associated with a greater progression of CAC (4.1 Agatston units/year). $PM_{2.5}$ was not associated with IMT progression in this study [101].

5.3. Insights from prevention studies

The effect of several dietary supplements have been studied in relation to the effects of air pollution on cardiovascular system [102]. Because oxidative stress is a major initiating pathway with a relationship between levels of pollutants and anti-oxidant systems, many studies have focused on antioxidant supplementation [103]. Vitamin C supplementation prevents acute lung effects induced by NO2 and ozone exposure and has been shown to modify the relationship between PM_{10} and COPD/asthma hospitalizations [104–106]. In a study of coal power-plant workers in Brazil, 6 months of vitamins C and E normalized oxidative stress markers (e.g., SOD, catalase, glutathione peroxidase, glutathione reductase, and glutathione S-transferase) [107]. In a randomized trial in Detroit, one-time vitamin C supplementation did not affect acute BP effect of concentrated PM on blood pressure [108]. At least one study has shown that antioxidant supplementation (vitamin C and NAC) increased vasoconstriction in response to diesel-exhaust inhalation [109]. At the population level, a recent study of more than half a million individuals in the United States followed for 17 years showed that Mediterranean diet was associated with attenuation of the association between $PM_{2.5}$ and cardiovascular events [110]. In a recently published randomized, double-blinded, placebo-controlled trial of 65 healthy young adults in China, fish-oil supplementation (2.5 g/day) prevented $PM_{2.5}$ increase in blood markers of inflammation, coagulation, endothelial function, oxidative stress, and neuroendocrine stress response [111]. Thus, while there is protective effects of vitamins and nutrient supplementation against air pollution effects, these effects are often with short term administration on surrogate end-points. Further research is needed to identify whether additional dietary supplements or specific diet can attenuate or prevent the effects of air pollution.

6. Current challenges in elucidation of the role of oxidant stress in air pollution toxicity

The underlying mechanisms by which PM-induced oxidant stress responses mediate inflammation and exert biological effects are very complex. There are three broad strenuous questions listed below related to delineating the exact role of ROS in the air pollution mediated pathologies and these need to be kept in consideration while defining the mechanism involved in air pollution mediated adverse health complications.

6.1. Sources of oxidant stress

Oxidant stress can directly originate from the PM including redox cycling of PM components as well as through various intracellular sources. There are several animal studies that provide evidence for the contribution of endogenous cellular sources that manipulation of ROS pathways through knock out or other models modulate effects of air pollution exposure that have been reviewed previously [25].

Cellular Contributions From Immune Cells and Non-Immune Cells: The exact contribution of reactive oxygen species from immune cells versus non-immune cells such as endothelial and epithelial cells is important to understand the locus of effects and in identifying the potential therapeutic targets [23].

6.2. Transduction of PM-induced pulmonary oxidative stress in mediating systemic responses

Elements present the PM could directly induce oxidative damage in the pulmonary system. The initial inflammation and ROS generated in the lung is beneficial to remove the deleterious stimuli and initiate tissue repair. However, the protracted inflammation in the lung and dysregulated ROS and antioxidant response may lead to systemic effects. The role of pulmonary oxidative stress and various damage associated molecular patterns (DAMPs) including, oxidatively modified lipoproteins, oxDNA, ssRNA, dsRNA, HMGB1 and mitochondrial protein and their impact by binding to various receptors (Toll-like receptors [TLRs] and RAGE) in triggering systemic cytokine and chemokines are also important areas of research [23,112–114].

6.3. Conclusions and future studies

In conclusion, oxidative stress is a critical intermediator in the transduction of systemic toxicity associated with air pollution exposure. The role of endogenous antioxidant defenses particularly, with chronic exposure will need further exploration. The importance of personal protective measures in reducing air pollution exposure and their effects on key oxidative stress pathways and anti-oxidant defense mechanisms are important areas in future research.

Declaration of competing interest

The authors have no competing interests to declare.

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