Particulate air pollution, systemic oxidative stress, inflammation, and atherosclerosis

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Abstract Air pollution has been associated with significant adverse health effects leading to increased overall morbidity and mortality of worldwide significance. Epidemiological studies have shown that the largest portion of air pollution-related mortality is due to cardiovascular diseases, predominantly those of ischemic nature. Human studies suggest an association with atherosclerosis and increasing experimental animal data support that this association is likely to be causal. While both gasses and particles have been linked to detrimental health effects, more evidence implicates the particulate matter (PM) components as major responsible for a large portion of the proatherogenic effects. Multiple experimental approaches have revealed the ability of PM components to trigger and/or enhance free radical reactions in cells and tissues, both ex vivo as well as in vivo. It appears that exposure to PM leads to the development of systemic prooxidant and proinflammatory effects that may be of great importance in the development of atherosclerotic lesions. This article reviews the epidemiological studies, experimental animal, and cellular data that support the association of air pollutants, especially the particulate components, with systemic oxidative stress, inflammation, and atherosclerosis. It also reviews the use of transcriptomic studies to elucidate molecular pathways of importance in those systemic effects.

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Exposure to air pollution is associated with atherosclerosis

Extensive epidemiological evidence supports the association of air pollution with adverse health effects leading to increased morbidity and mortality of worldwide significance (Brook et al. 2004; Bhatnagar 2006; Brook et al. 2010) mostly due to cardiovascular diseases and predominantly those of ischemic character (Pope et al. 2004). Thus, exposure to air pollution is now recognized as a novel cardiovascular risk factor of great importance since it is modifiable and with the potential to affect large numbers of people around the globe. While air pollution is a complex mixture of compounds in gaseous (ozone, CO, and nitrogen oxides) and particle phases, the cardiovascular effects have been mostly ascribed to its particulate components (Bhatnagar 2006; Brook 2008; Araujo and Nel 2009). Ambient particles can be classified according to their aerodynamic diameter into size fractions such as particulate matter $(PM)_{10}$ ("thoracic" particles, <10 μm), $PM_{2.5-10}$ ("coarse" particles, 2.5–10 μm), $PM_{2.5}$ (fine particles, <2.5 μm) and ultrafine particles (UFP, <0.1 μm; U.S.EPA 2004) that are derived from various sources and by a variety of processes characteristic of each size fraction. For instance, UFP are mostly generated through tailpipe emission from mobile sources (motor vehicles, aircrafts, etc.), while major sources of $PM_{2.5}$ include power plants, oil refinery, wildfires, tailpipe, brake emissions from mobile sources and coarse particles are typically derived from soil, agricultural and road dust, construction debris, among others.

Various mechanisms have been proposed to explain how inhalation of ambient particulate could result in systemic cardiovascular effects such as: (1) activation of pulmonary receptors resulting in autonomic nervous system imbalance and the development of dysrhythmias; (2) induction of pulmonary and systemic inflammation; (3) access of particles or their chemical constituents to the systemic circulation (Fig. 1). The latter two mechanisms can lead to the induction of atherothrombotic effects responsible for acute coronary syndromes and ischemic heart disease. Indeed, several studies support the association between air pollution and atherosclerosis in humans (Table 1). Kunzli et al. reported in 2005 a cross-sectional study where the degree of carotid intima-medial thickness (CIMT) of 798 individuals correlated with an increase of 5.9% for every 10 μg/m^3 rise in PM$_{2.5}$ levels (Kunzli et al. 2005; Table 1). A recent study on a related population also showed that the annual rate of CIMT progression among individuals living within 100 m of a highway was accelerated and more than twice the population mean progression (Kunzli et al. 2010). Likewise, Hoffman et al. (2007) reported an association between long-term residential exposure to high traffic and coronary artery calcification (CAC) scores as a measure of coronary atherosclerosis. They found in a German cohort study including 4,494 participants, that as compared with subjects living >200 m away from a major road, subjects living within 101–200 m, 51–100 or less than 50 m showed 8%, 34%, and 63% increase in the probability of having a high CAC scores, respectively (Table 1). Data from the Multi-Ethnic Study of Atherosclerosis (Diez Roux et al. 2008; Allen et al. 2009) also support the association of PM with atherosclerosis. Diez Roux et al. (2008) reported that PM$_{10}$ exposures assessed over long-term (20-year means and 2001 mean) and 20-year PM$_{2.5}$ exposures did correlate with 1–3% increase in CIMT per 21 μg/m^3 increase in PM$_{10}$ or 12.5 μg/m^3 increase in PM$_{2.5}$, respectively. Likewise, Allen et al. (2009) reported that PM$_{2.5}$ exposures correlated with increased risk for aortic calcification in a related study (Table 1).

While epidemiological studies with PM$_{10}$ and PM$_{2.5}$ data support that a smaller particle size correlates with larger cardiovascular effects, there are only few reports supporting the association of UFP with increased total or cardio-respiratory mortality (Wichmann et al. 2000; Yue et al. 2007) and there are no reports that support an association between UFP and atherosclerosis yet, partly due to the difficulty to perform reliable measurements of UFP particle number and mass concentrations since they are very dependent on the proximity to the source of generation. Despite the lack of direct evidence, it has been suggested that associations between PM and cardiovascular (CV) morbidity and mortality could be even stronger with the smaller particles. In a study conducted in four large retirement communities in the Los Angeles basin, Delfino et al. (2009) followed 60 elderly subjects with history of CAD over 7-month periods with a very detailed pollutant exposure characterization and blood collection for the determination of systemic inflammatory, antioxidant and

Fig. 1 Potential mechanisms how exposure to PM leads to CV disease. Three main pathways could mediate PM-related cardiovascular effects: (1) induction of autonomic nervous system imbalance, (2) development of pulmonary oxidative stress and inflammation with systemic "spill-over" of inflammatory mediators (e.g., cytokines, activated cells), (3) translocation of particles and/or chemical constituents to the systemic circulation. CHF congestive heart failure, CV cardiovascular, CVA cerebrovascular accident, EC endothelial cells, IHD ischemic heart disease, PVD peripheral vascular disease. Pulmonary inflammation may range from activation of inflammatory molecular pathways without histological evidence of it to overt infiltration by inflammatory cells. Taken from Araujo and Brook (2011)
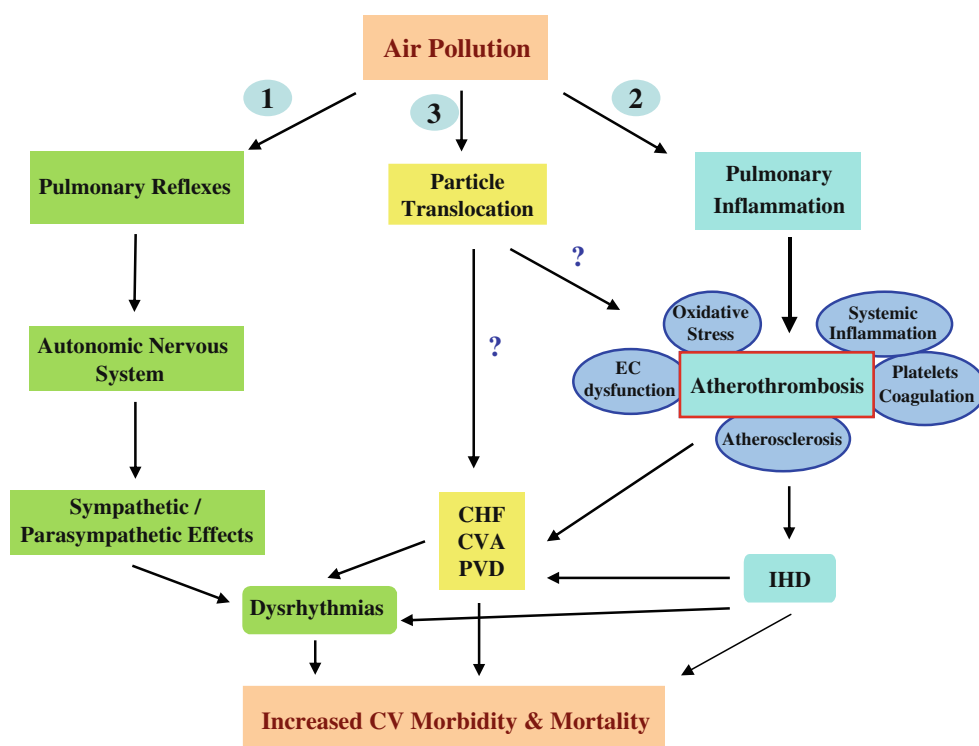
Table 1 Human studies linking exposure to air pollution with atherosclerosis

Study	Air pollutant	Evaluation of atherosclerosis	Major findings	Reference
Kunzli et al. 2005	$PM_{2.5}$-Ozone	CIMT	5.9% increased in CIMT per every 10 $\mu g PM_{2.5}/m^3$	(Kunzli et al. 2005)
Hoffmann et al. 2007	$PM_{2.5}$-Distance to major road	CACS	Increased CAC scores with shorter distances to a major road	(Hoffmann et al. 2007)
Diez Roux et al. 2008	PM_{10}-$PM_{2.5}$	CIMT CACS BAI	1–3% increase in CIMT per every increase in 21 and 12.5 $\mu g/m^3$ of PM_{10} and $PM_{2.5}$ respectively	(Diez Roux et al. 2008)
Allen et al. 2009	$PM_{2.5}$-distance to major road	Aortic calcification	6% increase in the risk of aortic calcification with a 10 $\mu g/m^3$ increase in $PM_{2.5}$	(Allen et al. 2009)
Hoffman et al. 2009	$PM_{2.5}$-distance to major road	BAI	Decreased BAI in subjects living within 50 meters from a major road, especially women	(Hoffman et al. 2009)
Kunzli et al. 2010	$PM_{2.5}$-distance to highway or major road	CIMT	Greater annual progression of CIMT among individuals living <100 m from a highway	(Kunzli et al. 2010)

Studies are listed in chronological order based on the year of publication. *CIMT* carotid intima-media thickness, *CACS* coronary artery calcium score, *BAI* brachial artery index. Modified from Araujo (2011)

coagulation markers. They found positive associations of particle number (dominated by UFPs) and outdoor quasi-ultrafine $PM_{0.25}$ (<0.25 μm) with biomarkers of systemic inflammation such as interleukin (IL)-6, soluble tumor necrosis factor receptor II (sTNF-RII), and C-reactive protein (CRP; Delfino et al. 2008, 2009). This study is in agreement with a previous report where exposure to UFP correlated with increased plasma levels of soluble CD40 ligand (sCD40L), a marker for platelet activation that can cause increased coagulation and inflammation (Ruckerl et al. 2007) as well as other repeated-measure studies showing associations between ambient air pollution and biomarkers of systemic inflammation in healthy young adults (Chuang et al. 2007) and susceptible subjects with CAD (Dubowsky et al. 2006; Ying et al. 2009b).

Role of particle size and chemical composition

The cardiovascular toxicity of particles may depend on several physicochemical parameters that can determine their ability to travel through the tracheobronchial tree upon inhalation, interact with cellular components in the lungs and either penetrate into the systemic circulation or trigger responses in the lungs that can be transduced systemically. Particle cardiopulmonary toxicity appears to correlate with their prooxidant and proinflammatory potentials. In this article, we mostly refer to evidence accrued using ambient particulate matter and/or diesel exhaust particles (DEP) as a model pollutant. Multiple studies have demonstrated that DEP can promote the generation of reactive oxygen species (ROS) in macrophages, bronchial epithelial cells and lung microsomes incubated with the particles or their organic extracts (Hiura et al. 1999; Li et al. 2002). DEP can also induce oxidative stress and cellular effects in target vascular cells such as endothelial cells (Bai

et al. 2001; Hirano et al. 2003; Gong et al. 2007; Li et al. 2009) as indicated in more details below.

It appears that DEP redox properties reside in their polar and aromatic fractions as they most actively induce the expression of heme oxygenase-1 (HO-1), glutathione S-transferase and other phase II enzymes in response to increased oxidative stress (Li et al. 2004). This antioxidant response is modulated by the p45-NFE2 related transcription factor 2 (Nrf2) (Li et al. 2004), which is able to escape proteosomal degradation in the cytoplasm and translocate to the nucleus under the influence of electrophiles (Li et al. 2004). Ambient PM can also induce tissue oxidative stress and trigger Nrf2-regulated antioxidant gene expression in response to its content of prooxidative and electrophilic chemicals that differ markedly among the various particle sizes. Different particle sizes are apparently married to different chemical compositions resulting in different prooxidant and proatherosclerotic effects as it is described below. Thus, UFP collected from various locations and seasons differ significantly in their ability to trigger Nrf2-regulated responses, in strong relationship with their chemical composition (e.g., content of polycyclic aromatic hydrocarbons; PAHs) and prooxidant potential (Li et al. 2003).

Of even larger importance to the data generated by in vitro approaches, it is the fact that several studies have demonstrated the ability of PM to promote systemic prooxidant and proinflammatory effects in vivo as well as enhanced atherosclerotic lesion development. This body of evidence not only confirms the relevance of the in vitro data but also brings support to the notion that the particle prooxidative and proinflammatory potentials may be important determinants of particle vascular toxicity. Table 2 summarizes several of those studies that support the causal association between particulate air pollution and athero-sclerosis using various animal models. Exposures to air pollutants have been performed via intratracheal instillations

Table 2 Animal studies evaluating the effect of particulate air pollution on atherosclerosis

Study	PM fraction (mode of administration)	Animal model	Diet	Assessment of atherosclerosis (method)	Effect of PM on atherosclerosis	Ref
Suwa et al. 2002	PM_{10} (IT)	Watanabe rabbits	Chow	Percent lesional volume in coronary arteries and aorta (histology)	Increase	(Suwa et al. 2002)
Chen and Nadziejko 2005	$PM_{2.5}$ (inhaled CAPs)	apoE$^{-/-}$, LDL$^{-/-}$ mice and apoE$^{-/-}$ mice	Chow	Percent lesional area in whole aorta (histology)	No change (apoE$^{-/-}$, LDL$^{-/-}$ mice) increase (apoE$^{-/-}$ mice)	(Chen and Nadziejko 2005)
Sun et al. 2005	$PM_{2.5}$ (inhaled CAPs)	apoE$^{-/-}$ mice	Chow or CED	Percent lesional area in cross-sections of aorta (histology)	N.S. increase (chow-fed mice). Increase (CED-fed mice)	(Sun et al. 2005)
Niwa et al. 2007	Carbon black (IT)	LDL-R$^{-/-}$ mice	CED	Percent lesional area in whole aorta (histology)	Increase	(Niwa et al. 2007)
Sun et al. 2008	$PM_{2.5}$ (Inhaled CAPs)	apoE$^{-/-}$ mice	Chow or CED	Percent lesional area in aorta (ultrasound)	N.S. increase (chow-fed mice). Increase (CED-fed mice)	(Sun et al. 2008)
Yatera et al. 2008	PM_{10} (IT)	Watanabe rabbits	Chow	Percent lesional volume and% lesional area in the aorta (histology)	Increase	(Yatera et al. 2008)
Araujo et al. 2008	$PM_{2.5}$ and UFP (Inhaled CAPs)	apoE$^{-/-}$ mice	Chow	Mean lesional area in aortic root (histology)	N.S. increase ($PM_{2.5}$-exposed mice) Increase (UFP-exposed mice)	(Araujo et al. 2008)
Castro-Soares et al. 2009	PM (inhaled polluted air)	LDLR$^{-/-}$ mice	CED	Percent lesional area in aortic root. Aortic wall thickness (histology)	No change in lesional area. Increase in wall thickness	(Soares et al. 2009)
Ying et al. 2009a	$PM_{2.5}$ (inhaled CAPs)	apoE$^{-/-}$ mice	CED	Percent lesional area in cross-sections of aorta (histology)	Increase	(Ying et al. 2009a)
Campen et al. 2010	PM+gasses (Inhaled DE)	apoE$^{-/-}$ mice	CED	Percent lesional area in the aortic root plaque composition	N.S. increase. Increase in macrophage content	(Campen et al. 2010)
Chen et al. 2010	$PM_{2.5}$ (inhaled CAPs)	apoE$^{-/-}$ mice	Chow	Percent lesional area in brachiocephalic and left common arteries (ultrasound)	Increase	(Chen et al. 2010)
Quan et al. 2010	PM±/− gasses (Inhaled CAPs vs. Inhaled whole DE or DE gasses)	apoE$^{-/-}$ mice	Chow	Percent lesional area in brachiocephalic artery (ultrasound)	Increase (CAPs≥whole DE≥DE gasses=filtered air)	(Quan et al. 2010)

Studies are shown in chronological order based on the year of publication. *IT* inttratraqueal, *CAPs* concentrated ambient particles, *DE* diesel emissions, *CED* cholesterol-enriched diet, *NS* not significant. Modified from Araujo (2011)

(IT) of PM as well as inhalation of polluted air, concentrated ambient particles (CAPs), or diesel exhaust emissions. These various exposure modalities differ in their degree of difficulty and their ability to model "real life" scenarios. Thus, while IT inhalations can be manipulated experimentally at ease, they may be more limited to reflect physiologically relevant exposures. On the other hand, inhalation of CAPs can model physiological conditions better but are more difficult to be conducted. Importantly, the convergence of similar findings derived from different exposure modalities helps in data interpretation and brings robustness to the conclusions derived.

Indeed, IT PM_{10} and IT carbon black have been reported to stimulate atherosclerotic lesion formation in Watanabe hyperlipidemic rabbits (Suwa et al. 2002; Yatera et al. 2008) and low-density lipoprotein-receptor (LDL-R)$^{-/-}$ mice (Niwa et al. 2007), respectively. In those studies, atherosclerosis was assessed both in the coronary arteries (Suwa et al. 2002) and in the aorta (Suwa et al. 2002; Niwa et al. 2007; Yatera et al. 2008). On the other hand, the effect of $PM_{2.5}$ has been mostly evaluated by long-term inhalation exposures to concentrated $PM_{2.5}$. Five studies have been reported where concentrated $PM_{2.5}$ led to enhanced atherosclerosis in apoE null mice exposed to CAPs at Sterling Forest, New York (Chen et al. 2010; Chen and Nadziejko 2005; Sun et al. 2005; Sun et al. 2008) or in Manhattan, New York (Ying et al. 2009b). Chen and Nadziejko (2005) reported that 39–41 week-old apoE$^{-/-}$ mice fed a chow diet and exposed to 10X ambient concentrations of $PM_{2.5}$ for 6 h per day, 5 days per week for 5 months led to a 57% increase in the percentage of atherosclerotic plaque area in the aortic root (Table 2). Sun et al. (2005) showed that younger 6-week-old apoE$^{-/-}$ mice fed a chow diet and exposed to similar conditions for 6 months displayed a 45% increase in the percentage of aortic atherosclerotic plaque area, which was not statistically significant however. The feeding of a high-fat diet resulted in a greater promotion of atherosclerosis that was statistically significant, as $PM_{2.5}$-exposed mice displayed a 58% increase in aortic root plaque area (Sun et al. 2005), together with impaired vasomotor response (Table 2). In another study, Sun et al. (2008) reported that apoE$^{-/-}$ mice fed a high fat diet and exposed to concentrated $PM_{2.5}$ also resulted in enhancement of aortic atherosclerosis as assessed by the percentage of the plaque area in the aortic arch by ultrasound bio-microscopy. $PM_{2.5}$ exposures led to atherosclerotic plaques that were also richer in tissue factor (Sun et al. 2008), which could play a causative role or simply be an indicator of greater atherosclerotic plaque burden. When compared to inhaled side-stream tobacco smoke, concentrated $PM_{2.5}$ appears to exert greater promotion of plaque formation as assessed by ultrasound bio-microscopy (Chen et al. 2010). Importantly, concentrated

$PM_{2.5}$ from a different location, such as an exposure laboratory in Manhattan, also resulted in similar proatherogenic effects (Ying et al. 2009b).

The different degrees how aortic atherosclerosis was enhanced by $PM_{2.5}$ in the various CAPs studies can be due to several factors such as differences in the length of exposures, the type of experimental diet or the PM composition. In addition, while 4–6 month exposures to concentrated $PM_{2.5}$ in New York (Chen et al. 2010; Chen and Nadziejko 2005; Sun et al. 2005; Sun et al. 2008; Ying et al. 2009a) have shown positive results, 5-week exposures to concentrated $PM_{2.5}$ in Los Angeles only resulted in a non-statistically significant trend for increased atherosclerotic lesions (Araujo et al. 2008), which raises important questions about toxicological aspects such as effective dose, threshold or latency of effects. In addition, there have been discrepancies in whether the feeding of cholesterol-enriched diets and/or extreme hyperlipidemia exert or not an additive effect to the PM exposures. Thus, two studies have reported a significant enhancement of atherosclerosis when apoE$^{-/-}$ mice were fed a cholesterol-enriched diet (CED) but only suggestive trends when mice were fed a chow diet (Sun et al. 2005, 2008). On the other hand, one study showed that the $PM_{2.5}$ proatherogenic effects were not seen under the condition of extreme hyperlipidemia exhibited by apoE$^{-/-}$, LDL-R$^{-/-}$ mice (Chen and Nadziejko 2005).

Another important aspect relates to the different degree how PM promotes atherogenesis in different locations where particulates may originate from different sources, under different climatological conditions and resulting in different physicochemical characteristics. Thus, the study from Ying et al. (2009a) showed that 4-month inhalation exposures to concentrated $PM_{2.5}$ in the Upper East side of Manhattan (6 h/day, 5 days/week) of CED-fed 6-week-old apoE$^{-/-}$ mice resulted in ~89% increase in aortic atherosclerotic plaques over controls. This is in contrast to the other CAPs $PM_{2.5}$ studies where CED-fed mice were exposed for 5–6 months in Sterling Forest, New York resulting in an increase from 58% to 68% increase in atherosclerotic lesions over controls (Sun et al. 2005; 2008). Larger effects with the Manhattan $PM_{2.5}$ could have been due to greater $PM_{2.5}$ levels and/or greater relative content in organic carbon and elemental carbon as mentioned by their authors (Ying et al. 2009a).

In relation to the role of particle size, only one study has approached the question whether particle size has any role in PM-mediated proatherogenic effects. Thus, Araujo et al. tested the hypothesis that the smaller size and greater redox potential of UFP would result in greater proatherogenic effects than $PM_{2.5}$ in an animal study at the University of California in Los Angeles. ApoE$^{-/-}$ mice were fed a chow diet and subjected to concentrated $PM_{2.5}$, UFP or filtered air for 5 h/day, 3 days per week for 5 weeks. UFP-exposed

mice developed 25% and 55% greater aortic atherosclerotic plaques, assessed by the mean atherosclerotic lesional area in the aortic root, as compared to $PM_{2.5}$ or FA-exposed mice, respectively (Araujo et al. 2008), despite an exposure mass that was ~4 times less. Given that the concentrator technology employed (Versatile Aerosol Concentration Enrichment System) in this study generated overlapping CAPs aerosols, it is difficult to estimate the true relative proatherogenic strength of UFP vs. $PM_{2.5}$. While it is possible that the UFP fraction could concentrate the PM proatherogenic effects, a clear demonstration of this will require the straight comparison of UFP to the accumulation mode particles in the 0.1–2.5 μm range (Araujo and Nel 2009). Interestingly, in this study, UFP exhibited a greater relative content of PAHs, a whole group of redox-active compounds that can facilitate free radical reactions (Li et al. 2003; Ntziachristos et al. 2007; Ayres et al. 2008). Additional studies are required to compare $PM_{2.5}$ and UFP exposures in other locations in the world where the effects of different particle size and composition on atherosclerosis, can be assessed.

It has been debated whether PM at ambient levels could cause similar effects to those induced by CAPs over perhaps longer periods of time. Castro-Soares et al. addressed this issue by exposing LDL-R$^{-/-}$ mice to 1X ambient air (non-filtered) vs. filtered air at a location 20 m away from the roadside in downtown Sao Paulo, Brazil. Although mice exposed to non-filtered air developed atherosclerotic plaques that were comparable in lipid content to those developed by controls', their aortic walls were thicker, suggesting a greater contribution of other components (either cellular or non-cellular; Soares et al. 2009). Another important point is whether the gasses could contribute to the vascular proatherogenic effects of particulates, perhaps by cooperative interactions with them. There is indeed experimental data that show that gaseous pollutants could also play a role in promoting atherosclerosis. Lewis et al. showed that exposures of CED-fed C57BL6 mice to carbon disulfide (CS_2), a known volatile organic compound, at 500 and 800 ppm CS_2 6 h/day, 5 days/week for up to 20 weeks, markedly enhanced aortic atherosclerosis (1999). In addition, Chuang et al. (2009) reported that apoE$^{-/-}$ mice exposed to 0.5 ppm O_3 for 8 h/day, 5 days/week for 8 weeks exhibited more than double the degree of aortic atherosclerosis exhibited by filtered air-exposed controls (Table 2). Furthermore, Campen et al. examined the effect of whole vs. particle-filtered diesel exhausts emissions on atherosclerotic lesion formation of CED-fed 10-week-old male apoE$^{-/-}$ mice over 50 days. Although they did not find significant differences in the extent of aortic plaque formation between the various groups, mice exposed to whole diesel exhausts developed atherosclerotic lesions with greater macrophage content

(Campen et al. 2010; Table 2). Interestingly, exposure to whole diesel exhausts led to upregulation of MMP-9 in the aorta, consistent with similar effects reported for gasoline exhausts (Lund et al. 2007). While particle-filtering tended to diminish the effects of the diesel emissions on plaque macrophage content, it did not alter the degree of aortic MMP-9 upregulation (Campen et al. 2010), suggesting that both gaseous and particulate components could be affecting different pathways. It is possible then that gaseous and particulate pollutants could exert different but cooperative effects, which will need to be explored in more details in the future, in spite of a recently published study that did not find any contribution of diesel exhaust gasses to the effects exerted by CAPs inhalations (Quan et al. 2010).

Altogether, the reported literature suggests that particle size and chemical composition are important determinants in the ability of particulates to enhance atherosclerotic lesion formation. In addition, while the epidemiological data mostly points towards the contribution of the particulate matter, the experimental animal data suggests that gaseous components may also play a role.

How does particulate matter promote atherosclerosis?

PM-enhanced atherosclerosis is most likely the result of systemic prooxidant and proinflammatory effects. These systemic effects could derive from increased ROS production and development of inflammation in the lungs that somehow may get transduced to the systemic tissues (e.g., release of inflammatory mediators into the blood; pathway 2 of Fig. 1) or they could be the result of translocation of particles or their chemical constituents into the systemic circulation with direct action at the target vascular sites (pathway 3 of Fig. 1). There are multiple reports that support the ability of PM to induce local prooxidant and proinflammatory effects in the lungs. The latter may include activation of inflammatory molecular pathways without histological evidence of overt pulmonary inflammation, local activation of cells leading to pan-systemic activation of the adaptive immune system or infiltration of the lungs by inflammatory cells with the development of histologically defined pulmonary inflammatory foci (Fig. 1). This article focuses however on the experimental evidence that supports the occurrence of those effects in systemic tissues, especially at the target vessels (summarized in Table 3) as follows:

Systemic oxidative stress Human studies have associated exposure to PM with increased systemic oxidative stress, which include the detection of biomarkers of oxidative alteration of proteins, lipids and/or DNA in the circulating blood or in products excreted in the urine, as recently

Table 3 Mechanisms mediating PM-induced proatherogenic effects. In vitro and experimental animal evidence

Mechanisms	Indicators	References
Evidence in cellular and/or animal studies		
Oxidative stress in systemic tissues	Increased liver peroxidation and upregulation of antioxidant genes in liver	(Gong et al. 2007; Araujo et al. 2008)
Alteration of circulating lipoproteins	Oxidative modification of LDL	(Soares et al. 2009)
	Generation of dysfunctional HDL	(Araujo et al. 2008)
Vascular prooxidant effects	Increased ROS production in ECs and macrophages	(Goldsmith et al. 1998; Hiura et al. 1999; Soukup et al. 2000; Bai et al. 2001; Lee and Kang 2002; Hirano et al. 2003; Li et al. 2004; Li et al. 2006; Chio et al. 2007; Li et al. 2010; Montiel-Davalos et al. 2010)
	Upregulation of antioxidant genes in ECs and macrophages	(Hirano et al. 2003; Li et al. 2004; Gong et al. 2007; Li et al. 2010)
	Activation of NADPH oxidase in ECs and macrophages	(Beck-Speier et al. 2005; Li et al. 2006; Mo et al. 2009)
	Induction of electron leaks in mitochondrial electron transport complexes in ECs	(Li et al. 2006)
	Increased ROS in vessels with atherosclerotic plaques	(Sun et al. 2005; Ying et al. 2009a)
Vascular proinflammatory effects	Greater proinflammatory cytokine production in ECs and macrophages	(Alfaro-Moreno et al. 2002; Fujii et al. 2002; Jimenez et al. 2002; Amakawa et al. 2003; Osornio-Vargas et al. 2003; Pozzi et al. 2003; Brown et al. 2004; Becker et al. 2005a; Ishii et al. 2005; Imrich et al. 2007; Li et al. 2010)
	Increased expression of cell adhesion molecules in ECs	(Li et al. 2010)
	Greater monocyte adhesion to ECs	(Li et al. 2010)
	Monocyte migration and recruitment in atherosclerotic vessels	(Yatera et al. 2008)
	Activation of NF-kB in ECs and macrophages	(Mondal et al. 2000; Montiel-Davalos et al. 2010)
	Activation of MAPK in ECs and macropages	(Hiura et al. 1999; Sumanasekera et al. 2007; Mo et al. 2009)
	Activation of ERK1/2 pathways in ECs and macrophages	(Beck-Speier et al. 2005; Mo et al. 2009)
	Increased proinflammatory cytokines in circulating blood	(Mutlu et al. 2007; Tamagawa et al. 2008)
Vascular toxic effects	Decrease in viability of ECs and macrophages	(Hiura et al. 1999; Bai et al. 2001; Lee and Kang 2002)
	Increased in ECs and macrophages	(Hiura et al. 1999; Lee and Kang 2002; Montiel-Davalos et al. 2010)
	Increase in EC permeability and/or upregulation of genes involved in EC permeability	(Nadadur et al. 2009; Wang et al. 2010)
	Antiproliferative effects in ECs	(Yamawaki and Iwai 2006)
Evidence in humans	**Subclinical measures**	
Systemic inflammation	Elevated circulating pro-inflammatory biomarkers/mediators (figrinogen, CRP, TNF-α, IL 1-ß, IL-6, IL-7, GM-CSF, ICAM-1)	(Ibald-Mulli et al. 2001; van Eeden et al. 2001; Pope et al. 2004; Riediker et al. 2004; Analitis et al. 2006; Peters et al. 2006; Zeka et al. 2006; Chuang et al. 2007; O'Neill et al. 2007; Ruckerl et al. 2007)
Systemic oxidative stress	Increased biomarkers of lipid, protein or DNA oxidation	(Sorensen et al. 2003; Vinzents et al. 2005; Brauner et al. 2007)
	Elevated plasma homocysteine	(Baccarelli et al. 2007; Park et al. 2008)
	Inhibition of oxidative response by w-3 PUFA	(Romieu et al. 2008)
Systemic hypertension	Elevated systemic diastolic and/or systolic blood pressure	(Ibald-Mulli et al. 2001; Lippmann et al. 2003; Choi et al. 2007; Chuang et al. 2007; Diez Roux et al. 2008; Dvonch et al. 2009; Zanobetti and Schwartz 2009)
	Elevated endothelin-1 levels	(Peters et al. 2006)

CRP C-reactive protein, *ECs* endothelial cells, *ET-1* endothelin 1, *GM-CSF* granulocyte macrophage colony-stimulating factor, *ICAM-1* intercellular adhesion molecular 1; *IL* interleulin, *PUFA* polyunsaturated fatty acids, *ROS* reactive oxygen species, *TNF-α* tumor necrosis factor α

reviewed (Moller and Loft 2010). Reports include controlled exposure studies, panel and cross-sectional studies, generally small in size. Measures of oxidation in circulating blood are highly relevant since they may imply the involvement of oxidatively modified plasma lipoproteins such as LDL and/or high-density lipoprotein (HDL), key players in the promotion or protection from atherosclerosis, respectively (Araujo and Nel 2009). Liu et al. (2009) reported the association of increases in exposure to black carbon and $PM_{2.5}$ with elevation in plasma levels of thiobarbituric acid reactive substances (TBARS) of 28 nonsmoking seniors, in agreement with earlier reports of increased serum TBARS in association with $PM_{2.5}$ (Sorensen et al. 2003) or after moving or living in a polluted urban location such as Mexico city (Medina-Navarro et al. 1997; Sanchez-Rodriguez et al. 2005).

Experimental animal work brings support to the causality notion. Indeed, we have reported that exposure to CAPs in the $PM_{2.5}$ and UFP size ranges led to increased hepatic lipid peroxidation, accompanied by a higher upregulation of Nrf2-regulated antioxidant genes and unfolded protein response (UPR) genes of UFP-exposed mouse livers (Gong et al. 2007; Araujo et al. 2008). Castro-Soares et al. (2009) have shown that chronic exposure to urban air pollution led to enhanced susceptibility of LDL to oxidation in hyperlipemic LDL-R$^{-/-}$ mice fed a high fat diet as determined by a kinetics of LDL oxidation by CuSO4. Interestingly, animals exposed to polluted air also developed increased plasma levels of anti-oxidized LDL antibodies (Soares et al. 2009). Although LDL oxidation has not been demonstrated in any of the CAPs studies using apoE$^{-/-}$ mice, we have reported that 5-week exposures of apoE$^{-/-}$ mice to concentrated PM led to the development of dysfunctional HDL (Araujo et al. 2008) as it is discussed below. It is not known how PM inhalations can modify HDL function but it could likely be the result of oxidative modifications on either its protein and/or lipid components that may result in abrogation of its antioxidant enzymatic activities as well as anti-inflammatory and reverse cholesterol-transport properties. Thus, PM prooxidant effects could be enhancing the proatherogenic properties of LDLs and diminishing the antiatherogenic properties of protective HDLs.

Vascular prooxidative effects PM has been shown to exert prooxidative effects in vitro in cell types that are key players in the development of atherosclerotic lesions such as endothelial cells (Bai et al. 2001; Hirano et al. 2003; Li et al. 2006, 2010; Montiel-Davalos et al. 2010), macrophages (Goldsmith et al. 1998; Hiura et al. 1999; Soukup et al. 2000; Lee and Kang 2002; Li et al. 2004; Chio et al. 2007; Ohyama et al. 2007) and possibly smooth muscle cells (Sun et al. 2008). Indeed, DEP or ambient PM have been reported to increase ROS production in human aortic

endothelial cells (Li et al. 2010; Montiel-Davalos et al. 2010), likely by activation of the endothelial NADPH oxidase (Mo et al. 2009) and/or electron leaks in the mitochondrial electron transport complexes (Li et al. 2006). It seems that DEP in the ultrafine size range stimulates superoxide production in human aortic endothelial cells, partly mediated by JNK activation (Li et al. 2009). PM can also lead to increased nitric oxide production in pulmonary artery endothelial cells (Bai et al. 2001). Increased ROS can lead to the upregulation of antioxidant genes such as HO-1 in human aortic endothelial cells (Li et al. 2010), human microvascular endothelial cells (Gong et al. 2007) and rat heart microvessel endothelial cells (Hirano et al. 2003). PM can exert similar in vitro prooxidant effects in macrophages, which has been demonstrated in cultures of immortalized immune cells such as THP-1 (Hiura et al. 1999; Chio et al. 2007) and RAW264.7 cells (Hiura et al. 1999; Li et al. 2004) or in primary cell cultures of blood monocytes (Ohyama et al. 2007), thyglycolate-stimulated peritoneal macrophages (Lee and Kang 2002; Li et al. 2004) or alveolar macrophages (Goldsmith et al. 1998; Soukup et al. 2000; Beck-Speier et al. 2005). The use of the latter macrophages could give clues about the effects on systemic macrophages despite their different localization.

Exposure to PM also results in prooxidant vascular effects in vivo. Nurkiewicz et al. (2004, 2006) showed in rats that intratracheal instillation of residual oil fly ash (ROFA) led to greater vascular ROS generation, as assessed by the tetranitrobluetetrazolium reduction method (Nurkiewicz et al. 2006), resulting in a dose-dependent impairment of systemic endothelium-dependent arterial dilation as well as proinflammatory effects. Likewise, inhalation exposures to concentrated $PM_{2.5}$ has led to enhanced ROS generation in the aortic plaques, increased formation of 3-nitrotyrosine residues (Sun et al. 2005; Ying et al. 2009b) and upregulation of the NADPH oxidase subunits p47phox and Rac1 (Ying et al. 2009b).

Systemic inflammation PM exposure has been associated with increased proinflammatory mediators in the systemic circulation, both in animals (Mutlu et al. 2007; Tamagawa et al. 2008) and humans (van Eeden et al. 2001). IT administration of ROFA to rats led to increased leukocyte rolling and adhesion as well as deposition of myeloperoxidase in the spinotrapezius muscle microcirculation (Nurkiewicz et al. 2004, 2006) together with the prooxidant effects mentioned above. In New Zealand White Rabbits and mice, IT PM_{10} administration resulted in significantly increased serum IL-6 levels (Mutlu et al. 2007; Tamagawa et al. 2008) as well as TNF-α (Mutlu et al. 2007). Interestingly, lack of IL-6 ameliorated the PM_{10}-mediated systemic proinflammatory response as well as a PM_{10} procoagulant state in mice (Mutlu et al. 2007),

suggesting an important role for IL-6 in the mediation of PM systemic inflammatory effects. Likewise, CAPs PM$_{2.5}$ inhalation exposures led to elevation in circulating IL-6 and TNF-alpha (Sun et al. 2009) together with increases in circulating adipokines, such as resistin and a change in the balance of macrophages in adipose tissue towards the proinflammatory M1 phenotype, suggestive of a systemic proinflammatory state (Sun et al. 2009). Furthermore, it has been shown that PM induces increased monocyte migration to atherosclerotic vessels in Watanabe rabbits (Yatera et al. 2008). In humans, PM exposures has been reported to associate with increased blood levels of granulo-cyte macrophage colony-stimulating factor (GM-CSF), IL-6, IL-1, sTNF-RII, CRP, and sCD40L (van Eeden et al. 2001; Dubowsky et al. 2006; Chuang et al. 2007; Ruckerl et al. 2007; Delfino et al. 2008).

We have shown that CAPs exposures led to the development of dysfunctional HDL in apoE$^{-/-}$ mice as mentioned above. Interestingly, the degree of HDL dys-function was particle size-dependent since UFP exposures led to a greater degree of dysfunction than did PM$_{2.5}$ (Araujo et al. 2008). Using a monocyte chemotactic assay in a co-culture of endothelial cells and smooth muscle cells that evaluated the HDL anti-inflammatory capacity by determining the degree of inhibition of LDL-induced chemotaxis, UFP exposures not only failed to inhibit LDL-mediated inflammatory effects as PM$_{2.5}$ exposures did, but it promoted more monocyte migration. This greater degree of HDL dysfunction correlated with the greater degree of atherosclerosis and a systemic Nrf2-regulated antioxidant response, supporting the notion that dysfunc-tional HDL could either play a role in disease pathogenesis or serve as a marker for the PM-mediated systemic prooxidant and/or proinflammatory effects. Indeed, proin-flammatory HDL has been reported to predict susceptibility to atherosclerosis in humans (Ansell et al. 2003) and in rabbits (Van Lenten et al. 2007) and although there is no firm evidence yet that greater levels of proinflammatory HDL do promote atherogenesis, better characterization of this phenotype would be helpful since it could contribute to a better understanding of the pathogenesis and/or lead to the identification of a useful biomarker for the exposures or PM systemic effects.

Vascular proinflammatory effects In vitro work with endo-thelial cells in culture has shown that DEP and ambient PM can lead to the activation of NF-kB (Li et al. 2010; Montiel-Davalos et al. 2010), p38 MAPK (Sumanasekera et al. 2007; Mo et al. 2009), and ERK1/2 pathways (Mo et al. 2009) with subsequent upregulation of proinflammatory TNF-α (Li et al. 2010; Montiel-Davalos et al. 2010). Likewise, treatment of endothelial cells with PM results in increased expression of cell adhesion molecules such as

VCAM (Li et al. 2010), E-selectin, P-selectin (Montiel-Davalos et al. 2007) and increased cytokine production such as IL-8 and monocyte chemotactic protein 1 (Li et al. 2010).

Similar proinflammatory effects occur in PM-treated macrophages of various sources (Table 3). Both DEP and ambient PM treatments of either human/rat/mouse alveolar macrophages, human blood monocytes, THP-1 monocytes, RAW 264.7 macrophages, and/or J774A macrophages have been reported to result in increased production of TNF-α, IL-6 (Alfaro-Moreno et al. 2002; Fujii et al. 2002; Amakawa et al. 2003; Osornio-Vargas et al. 2003; Pozzi et al. 2003; Becker et al. 2005a), IL-8 (Monn and Becker 1999; Becker et al. 2005b), IL1-α (Brown et al. 2004), IL1-β (Jimenez et al. 2002), GM-CSF (Fujii et al. 2002; Ishii et al. 2005), and macrophage-inflammatory protein-2 (Imrich et al. 2007). Furthermore, it has been reported that PM induces greater monocyte adhesion to human aortic endothelial cells (Li et al. 2010). Interestingly, the ability of DEP in the ultrafine range generated from a same engine, under an idling vs. driving mode led to particles with different chemical composition that diverged on their prooxidant vs proinflam-matory potentials (Li et al. 2010) which indicate that PM could activate various pathways, not all ROS related.

Vascular cytotoxic effects PM has been shown to exert toxic effects in endothelial cells (Li et al. 2010; Montiel-Davalos et al. 2010) and macrophages (Hiura et al. 1999; Lee and Kang 2002; Table 3). PM can lead to increased permeability of endothelial cells (Wang et al. 2010), which could facilitate systemic translocation of particles or their chemical constituents onto the systemic circulation, release of inflammatory mediators from the lungs or monocyte migration to vascular sites. PM toxic effects also lead to stimulation of apoptosis (Hiura et al. 1999; Lee and Kang 2002; Montiel-Davalos et al. 2010), inhibition of cellular proliferation (Yamawaki and Iwai 2006) and decreased cell viability in cultures (Hiura et al. 1999; Bai et al. 2001; Lee and Kang 2002). Overall, vascular cytotoxicity may have various effects on atherogenesis that can depend on the stage of plaque development. For instance, while apoptosis has been thought to limit early atherogenesis, it may actually do the opposite in more advanced lesions (Tabas 2007).

Vascular dysfunction Several studies have reported the ability of both particulate and gaseous pollutants to cause vascular dysfunction, both on its constricting ability as well as its vasodilatory capacity, by mechanisms that could be either endothelial-dependent (O'Neill et al. 2005; Briet et al. 2007; Ruckerl et al. 2007; Rundell et al. 2007; Liu et al. 2009) or independent (O'Neill et al. 2005). Accumulating evidence suggests that endothelial dysfunction could be an early marker for atherosclerosis (Davignon and Ganz 2004) but less likely that it could independently increase the

propensity for atherosclerosis per se. Therefore, the alteration in vascular reactivity function could be a consequence of the same PM-induced systemic prooxidant and proinflammatory effects described above, in addition to neurohormonal mechanisms (pathway 1 of Fig. 1).

Hypertension Several studies report the association of air pollutants with hypertension (Ibald-Mulli et al. 2001; Lippmann et al. 2003; Choi et al. 2007; Chuang et al. 2007; Diez Roux et al. 2008; Dvonch et al. 2009; Zanobetti and Schwartz 2009; Table 3), a well-known risk factor for atherosclerosis. Pro-hypertensive and vasoconstrictive effects appear to occur both in the pulmonary and systemic circulation and seem to include a variety of mechanisms that range from increased ROS generation and endothelial cell dysfunction to neurohormonal activation. The latter may occur due to increased activity of the sympathetic nervous system as well as enhanced endothelin 1 and angiotensin II receptor pathways, all leading to decreased endothelial-dependent vasodilatation and enhanced vasoconstrictor activity in several studies. Thus, while some of the systemic prooxidant and proinflammatory effects mentioned above could be partially responsible, it is also likely that neurohormonal mechanisms could contribute in some degree to those effects (pathway 1 of Fig. 1; Brook 2008). Indeed, it is possible that PM-induced hypertension could play a role in the promotion of atherosclerosis; however, no hypertensive effects have been reported in any of the atherosclerosis studies conducted with experimental animals so far.

Altogether, cumulative evidence suggests that PM-induced systemic prooxidant and proinflammatory effects appear to be at the center of its ability to enhance atherosclerosis as shown by several studies using in vitro and in vivo approaches. While the data from some studies may carry higher significance than from others, it is the convergence of similar findings from different experimental designs and approaches what brings more robustness to this notion. These prooxidant and proinflammatory effects could be mediated by various pathways with various degrees of involvement of the lungs (Fig. 1). It appears that UFP may exhibit greater ability to enhance atherosclerosis than larger particulate. Various reasons that could explained their greater proatherogenic potential include larger particle number, greater lung retention, larger content of redox active compounds, and greater bioavailability as we have recently reviewed in details (Araujo and Nel 2009).

Effects of particulate matter on vascular gene expression

Several transcriptomic studies have been performed either in tissues harvested from animals exposed to PM or in cells treated in culture with PM or their chemical constituents.

The large majority of studies have focused on the PM effects in the lungs which may help to determine the degree of pulmonary involvement in the development of systemic vascular effects. Fewer studies have been performed in vascular cells, either on endothelial cells (Yamawaki and Iwai 2006; Gong et al. 2007; Nadadur et al. 2009), macrophages (Verheyen et al. 2004; Huang et al. 2009) or atherosclerotic plaques from exposed mice (Floyd et al. 2009; Table 4), which have provided clues on some of the molecular pathways that may be responsible for the phenotypes observed. This article focuses on the latter.

It is interesting how all these studies have shown the involvement of inflammatory pathway genes in vascular cells such as chemokin (C-X-C motif) ligand 2 (CXCL2), CXCL3, IL-8 which confirms both in vitro and experimental animal studies described in previous sections. Various antioxidant genes have also been found upregulated in endothelial cells (Yamawaki and Iwai 2006), macrophages (Huang et al. 2009; Table 4) and atherosclerotic plaques (Floyd et al. 2009) such as HO-1, superoxide dismutase 2, NAD(P)H:quinone oxidoreductase 1, and various metallothioneins, likely in response to the PM-mediated enhancement of ROS in the vasculature. ROS and inflammatory stressors result in the activation of UPR genes (e.g., activating factor 3, activating factor 4, and X box-binding protein 1; XBP1) as we have shown in endothelial cells treated with DEP (Gong et al. 2007), also found to be upregulated after treatment with carbon black (Yamawaki and Iwai 2006). Importantly, the identification of this pathway by an in vitro transcriptomic approach (Gong et al. 2007) led to the identification of the involvement of that same pathway in vivo (Araujo et al. 2008), which underscores the importance of these approaches in identifying molecular footprints of relevance.

While the individual contribution of air pollutants to atherogenesis might be small, we have thought that their effects could be exacerbated in synergy with other known proatherogenic factors. We tested this hypothesis by evaluating the antioxidant response of microvascular endothelial cells to DEP in the absence and presence of oxidized PAPC (1-palmitoyl-2-arachidonyl-sn-glycero-3-phosphorylcholine), one of the key prooxidative components generated in LDL particles. As both DEP and ox-PAPC led to prooxidative effects that were expected (Bai et al. 2001; Hirano et al. 2003), the combination of both treatments synergized in increasing antioxidant gene expression, including HO-1 (Gong et al. 2007). In addition, network analysis of the genomic profiles of cells subjected to the various treatments revealed groups of genes enriched in synergistic interactions between DEP and ox-PAPC leading to activation of several pathways (e.g., inflammation, apoptosis, unfolded protein response) of relevance in atherogenesis. Some representative examples included proinflammatory genes such as IL-8 and

Table 4 Transcriptomic studies evaluating the effect of PM on vascular cells

Study	PM source	Cells or tissue/platform	Design	Findings	Refs
Verheyen et al. 2004	DEP	THP-1 differentiated macrophages/incyte cDNA clone set	PMA-differentiated cells were treated with DEP for 6 and 24 h vs. controls	50 and 39 clones were up or downregulated at 6 h; 54 and 60 clones were up or downregulated at 24 h (>1.3-fold). Genes were enriched in immune response, cell adhesion, apoptosis, metabolism, signal transduction and transport pathways	(Verheyen et al. 2004)
Yamawaki and Iwai 2006	Carbon black (CB)	HUVECs/Affimetrix	Cells treated with CB for 24 h vs. controls	Top 89 upregulated probesets included IL-8, CXCL2, CXCL3, VCAM1, HO-1, MMP10, BMP2.	(Yamawaki and Iwai 2006)
Gong et al. 2007	DEP	HMECs/Illumina	Cells treated with DEP, oxPAPC and DEP+oxPAPC for 4 h vs. controls	1,555 regulated genes>1.5-folds. 664 genes of those exhibited synergistic effects between DEP and oxPAPC. Genes were enriched in antioxidant, inflammatory, unfolded protein response and apoptosis pathways	(Gong et al. 2007)
Nadadur et al. 2009	ROFA and Vanadium	HUVECs/Clontech cDNA array	Cells treated with ROFA or Vanadium for 30 min vs. controls	810 genes regulated by ROFA >2-folds (339 upregulated and 471 downregulated). Genes were enriched in cytokines/groth factors, cell adhesion molecules, transporters, signal transduction families. Nine transcription factors were activated by ROFA (>2-fold by TranSignal Protein/DNA arrays) which included AP-1, Nrf2, and USF-1	(Nadadur et al. 2009)
Huang et al. 2009	PM$_{2.5}$	Alveolar macrophages/Agilent	Cells treated with PM$_{2.5}$ for 4 h vs. control	38 and 43 differentially up or downregulated genes, respectively. Upregulated genes were enriched in metal binding, antioxidant functions including Metallothioneins, NQO1, MMP9, ATOX1	(Huang et al. 2009)
Floyd et al. 2009	PM$_{2.5}$	Aortic atherosclerotic plaques/ Affymetrix	Plaques harvested by LCM from apoE$^{-/-}$ exposed to PM$_{2.5}$ vs. filtered air for 5 months	611 differentially expressed genes (216 upregulated, 395 downregulated) enriched in inflammation, immunological disease, lipid metabolism, cell death ontological categories among others	(Floyd et al. 2009)

DEP diesel exhaust particles, *HMECs* human microvascular endothelial cells, *HUVECs* human umbilical vein endothelial cells, *LCM* laser capture microdissection, *ox-PAPC* oxidized PAPC, *oxidized PAPC* (1-palmitoyl-2-arachidonyl-sn-glycero-3-phosphorylcholine), *PMA* phorbol myristate acetate, *ROFA* residual oil fly ash, *AP-1* activating protein 1, *ATOX1* Atx1 antioxidant protein 1 homolog, *BMP2* Bone morphogenetic protein 2, *CXCL2* chemokin (C-X-C motif) ligand 2, *CXCL3* chemokin (C-X-C motif) ligand 3, *HO-1* heme oxygenase 1, *IL-8* interleukin 8, *MMP10* matrix metalloproteinase 10, *NQO1* NAD(P)H dehydrogenase, quinone 1, *Nrf2* NFE-E2 related factor 2, *USF1* upstream stimulating factor 1, *VCAM1* vascular cell adhesion molecule 1

CXCL1 production, immune response genes such as IL-11 and UPR genes such as ATF 4, heat shock 70 kDa protein 8 and XBP1. Here again, the use of a transcriptomic approach helped us to identify cooperative interactions between PM and oxidized lipids that could also be of importance in the development of atherosclerotic lesions in vivo.

Conclusions and perspectives

Exposure to air pollution leads to increased cardiovascular morbidity and mortality, predominantly of ischemic nature. Epidemiological studies show there is a positive association between exposure to PM and measures of atherosclerosis, that is likely to be causal as supported by animal studies. PM-mediated enhancement of atherosclerosis is likely to be the result of its systemic prooxidant and proinflammatory effects.

It will be important to dissect the mechanisms for the development of vascular systemic effects and to determine whether the lungs play an active role. Effects on circulating lipoproteins need to be characterized in details and confirmed in humans, since they may yield a better understanding of the PM-mediated pathogenesis and could lead to the identification of a biomarker of exposures and/or development of PM systemic effects. Likewise, there is need of epidemiological and exposure studies to evaluate UFP toxicity in humans. Transcriptomic and proteomic studies in cells and/or tissues harvested from animals or subjects exposed to air pollutants are highly promising tools to give clues on the molecular pathways involved. Genomic studies are also required to unravel gene–environment interactions of importance and to identify profiles that could result in increased genetic susceptibility to air pollution-mediated CV effects.

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