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Review Article

Nanodomains in cardiopulmonary disorders and the impact of air pollution

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Air pollution is a major environmental threat and each year about 7 million people reported to die as a result of air pollution. Consequently, exposure to air pollution is linked to increased morbidity and mortality world-wide. Diesel automotive engines are a major source of urban air pollution in the western societies encompassing particulate matter and diesel exhaust particles (DEP). Air pollution is envisioned as primary cause for cardiovascular dysfunction, such as ischemic heart disease, cardiac dysrhythmias, heart failure, cerebrovascular disease and stroke. Air pollution also causes lung dysfunction, such as chronic obstructive pulmonary disease (COPD), asthma, idiopathic pulmonary fibrosis (IPF), and specifically exacerbations of these diseases. DEP induces inflammation and reactive oxygen species production ultimately leading to mitochondrial dysfunction. DEP impair structural cell function and initiate the epithelial-to-mesenchymal transition, a process leading to dysfunction in endothelial as well as epithelial barrier, hamper tissue repair and eventually leading to fibrosis. Targeting cyclic adenosine monophosphate (cAMP) has been implicated to alleviate cardiopulmonary dysfunction, even more intriguingly cAMP seems to emerge as a potent regulator of mitochondrial metabolism. We propose that targeting of the mitochondrial cAMP nanodomain bear the therapeutic potential to diminish air pollutant — particularly DEP — induced decline in cardiopulmonary function.

Introduction

Air pollution is related to several cardiopulmonary disorders, such as ischemic heart disease, cardiac dysrhythmias, heart failure, cerebrovascular disease, stroke, asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), lung cancer and also acute respiratory infections [1]. Air pollution is clearly linked to industry and transport typical characteristics of societal development. For this reason, most countries exceed recommended air pollution levels and thereby risk global health problems [1,2]. One of the main components of air pollution is particulate matter (PM), which is composed of carbonaceous and inorganic particles (metal, metal oxides) or produced from precursor gases such as sulfur oxides and nitrogen oxides. Diesel exhaust particles (DEP) result from automotive engines and are a major source of urban air pollution linked to cardiopulmonary dysfunction [3,4] (Figure 1).

The main trigger to air pollution — thus DEP — related cardiopulmonary dysfunction is most likely related to the induction of inflammation. For example, intranasal instillation of mice with DEP collected from a light medium duty Euro 1 diesel engine, with a size between 0.03 and 0.2 μm diameters containing polycyclic aromatic hydrocarbons (PAHs) elevated macrophages and neutrophils in bronchoalveolar lavage (BAL) measured 6 and 24 h after exposure to DEP [5]. In addition, rats exposed 5 h per day, 5 days per week for 12 weeks to a diesel exhaust engine of four cylinders containing concentrations of carbon monoxide, nitrogen dioxide and sulfur dioxide (15.32 ± 1.91, 3.28 ± 0.35, and 1.32 ± 0.15 ppm, respectively) demonstrated reduced levels of anti-inflammatory proteins, such as clara cell secretory protein and pulmonary surfactant protein D in both BAL and serum [6].

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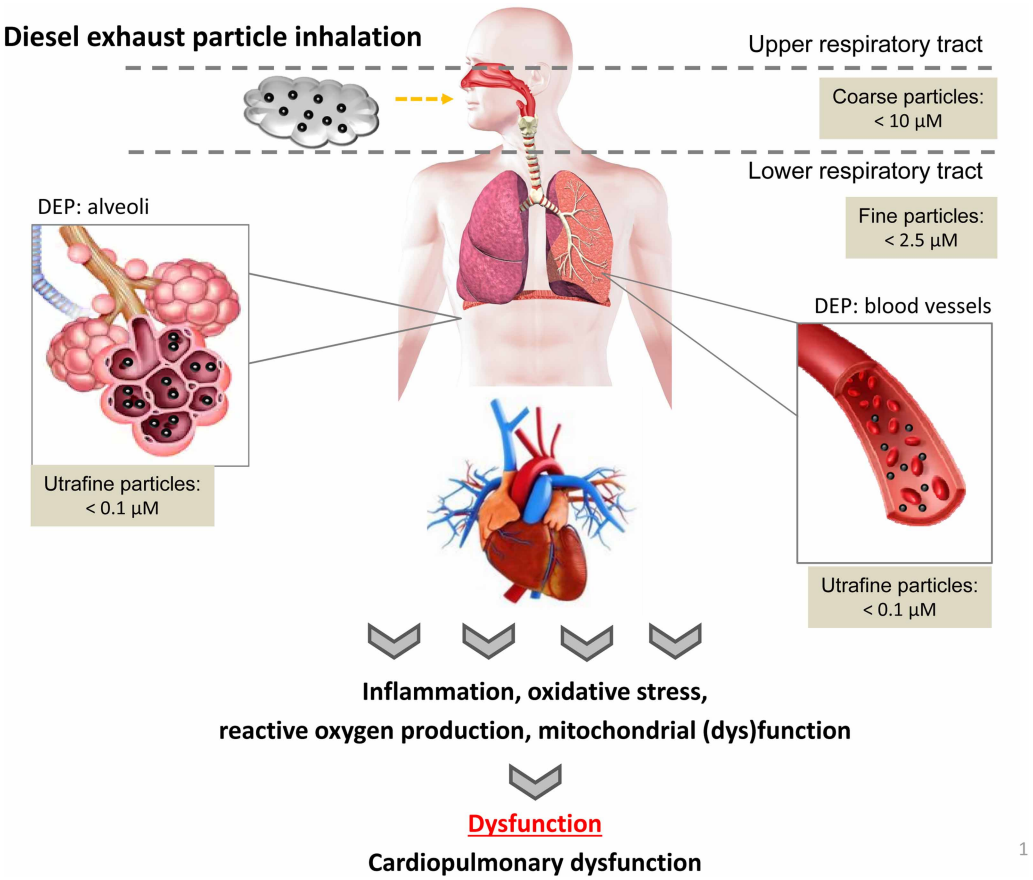

Figure 1. Particulate matter — known as coarse particles — has the size less than 10 μm and has the ability to deposit in the upper respiratory tract.

Fine particles are less than 2.5 μm and are able to penetrate into the lower respiratory tract. Ultrafine particles are less than 0.1 μm and are able to penetrate into alveoli region and may even reach the vascular system [35,36]. Diesel exhaust particles (DEP) induces inflammation, oxidative stress, production of reactive oxygen species (ROS) and mitochondria dysfunction potentially leading to cardiopulmonary dysfunction. See text for further details.

Moreover, chronic exposure of rats to diesel exhaust engine elevated pro-inflammatory markers, including interleukin (IL)-8, IL-6, and tumor necrosis factor (TNF)-α in BAL, serum and lung homogenates [6]. Moreover, exposure of both rats and mice to diesel engine exhausts and to DEP, respectively, increased the total number of inflammatory cells, neutrophils, eosinophils and lymphocytes in BAL [6,7] (Table 1).

Next to the induction of inflammation, air pollution — thus DEP — provokes oxidative stress. It is generally envisioned that oxidative stress is caused by a severe imbalance between oxidants and antioxidants due to a cellular excess of oxidants and a depletion of antioxidants, subsequently leading to overproduction of reactive oxygen species (ROS), a process linked to mitochondrial dysfunction [8]. As a consequence of such mechanisms, DEP seems to impair structural cell function and initiate epithelial-to-mesenchymal transition (EMT), a process leading to dysfunction in endothelial as well as epithelial barrier, hamper tissue repair and eventually leading to fibrosis [9,10]. Important to note that the DEP driven processes are hallmarks of cardiopulmonary disorders diverse as cardiac dysrhythmias, heart failure, asthma, COPD acute and respiratory infections [9,10]. Pharmacological targeting of cyclic adenosine monophosphate (cAMP) seems to profoundly alleviate cardiopulmonary dysfunction [11–15]. Importantly, cAMP has recently emerged as a potent regulator of mitochondrial metabolism. The mitochondrial matrix holds a unique cellular cAMP nanodomain independent of the cytosol [16,17], and its targeting has been even implicated in the preservation of cardiomyocyte function [18]. Mitochondrial cAMP nanodomains seem to embrace a unique subset of members of the adenylyl cyclase (AC)

Table 1. Effects of air pollution on proteins, transcription factors and cells

Air pollution type	Type of study	Proteins, transcription factors, cells	Tissue/ localization	Effect	Reference
DEP collected from a light medium duty Euro 1 diesel engine, with a size between 0.03 and 0.2 μm diameters containing polycyclic aromatic hydrocarbons (PAHs)	Mice intranasal instillation	Macrophages and neutrophils	BAL	Elevation	[5]
Diesel exhaust engine of 4 cylinders containing concentrations of carbon monoxide, nitrogen dioxide and sulfur dioxide (15.32 ± 1.91, 3.28 ± 0.35, and 1.32 ± 0.15 ppm, respectively)	Rats exposure by inhalation	Clara cell secretory protein (CC16) and pulmonary surfactant protein D	Serum and BAL	Reduction	[6]
		IL-8, IL-6, and TNF-α	Serum and BAL	Elevation	
		Total cells number, neutrophil, eosinophil, and lymphocyte	BAL	Elevation	
Diesel exhaust particles	Mice intratracheal instillation	IL-8, IL-6, and TNF-α protein expression	BAL and lung homogenates	Elevation	[7]
		Total cells number and neutrophil	BAL	Elevation	
Diesel exhaust	18 blinded atopic volunteers	IL-5, IL-8, MCP-1	BAL	Elevation	[45]
Diesel exhaust particles generated and collected from a three-cylinder, 3.8 l tractor engine	Primary bronchial epithelial cells	CXCL8, TNF-α, NF-κB, HMOX1 and glutathione peroxidase gene expression	—	Elevation	[82]
	Primary bronchial epithelial cells and THP-1 derived macrophage co-cultured	CXCL8, TNF-α, NF-κB and HMOX1 gene expression	—	Reduction	
DEP (Standard Reference Material 1650b)	BEAS-2B	CYP1A1, CYP1B1, of E-cadherin, vimentin and N-cadherin gene expression	—	No difference	[83]
Primary ultrafine particles (UFP) from diesel	BEAS-2B	CYP1A1, CYP1B, IL24, IL1A, IL1B, NFE2L2, HMOX1, TXNRD1, and NQO1	—	Elevation	[85]
Ultrafine particulate matter	BEAS-2B	E-cadherin gene expression	—	Reduction	[84]
		A–smooth muscle actin gene expression		Elevation	

family — the soluble AC (sAC) [16,19] — and the phosphodiesterase (PDE) family — the dual-specific PDE2, the latter has been linked to both cardiac and lung injury models [20,21]. Next to sAC and PDE2, the exchange protein directly activated by cAMP (Epac)1 [19,22], and the A-kinase anchoring family member AKAP1 also maintain mitochondrial function [23] (Figure 2). Several lines of evidence indicate that mitochondrial cAMP nanodomains exhibit a high level of subcellular organization — which might be repressed under cardiopulmonary disease pressure as shown for the signaling properties of several cAMP-producing G protein-coupled receptors such as those for β_2-agonists and prostaglandin E_2 (PGE_2) [15,24–27].

In the current review, we propose that targeting of the mitochondrial cAMP nanodomain bear the therapeutic potential to diminish air pollutant — particularly DEP — induced decline in cardiopulmonary function.

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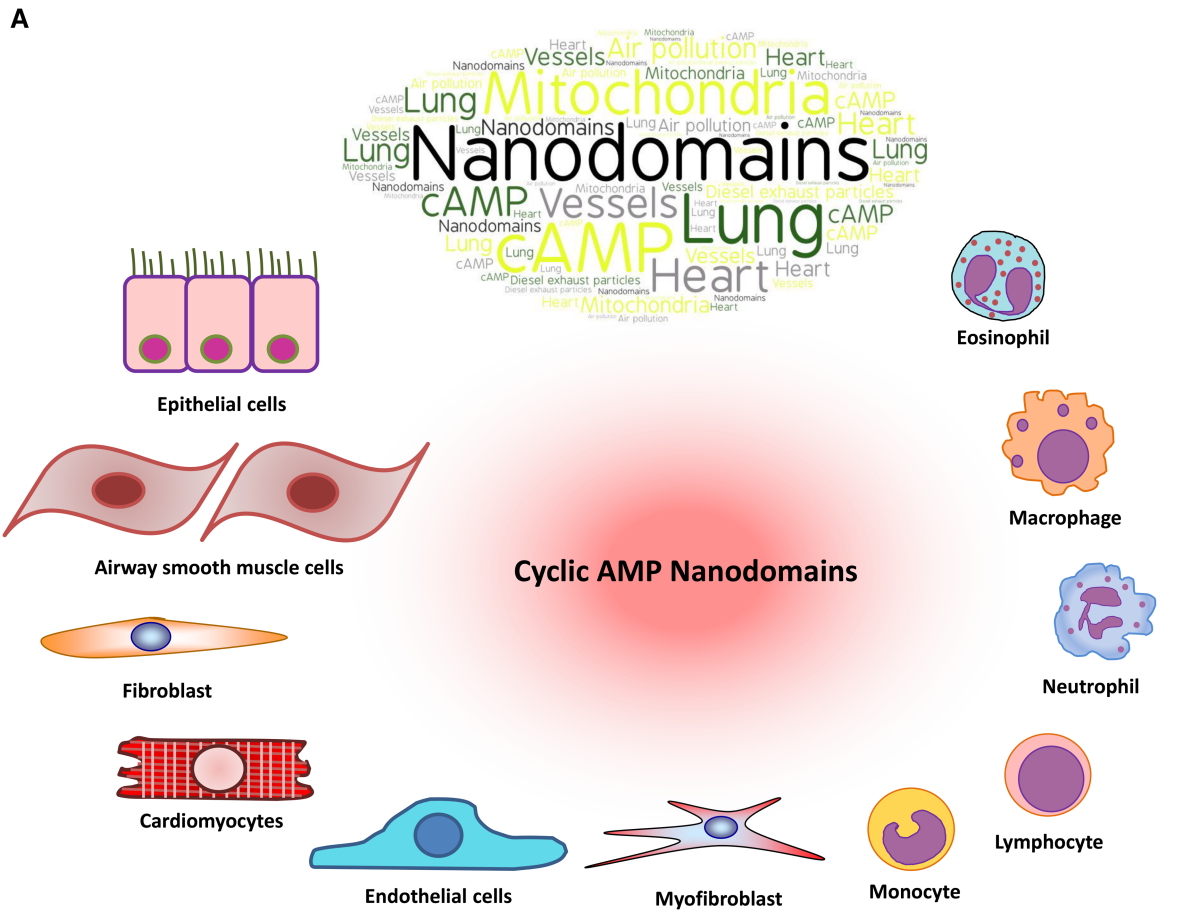

Part 1 of 2

Figure 2. Cyclic AMP Nanodomains.

Air pollution and adverse health problems

Air pollution has been identified as a major source for adverse health problems [28]. Development and progression of cardiopulmonary disorders inversely correlate with the air quality index. In several countries worldwide, the quality of air has reduced over time due to the constant development of industry and transport. Trucks and buses of the transport sector primarily use diesel combustion engines and are thereby substantially responsible for the air quality reduction [4,29,30]. Combustion of diesel fuel releases a plethora of compounds toxic for health, including black smoke known to easily dissipate in the air. Particularly, black smoke contains small particles known as DEP eventually loaded with elemental carbon, metal and adsorbed organic compounds including PAHs each of which highly toxic compounds for health [2,3,31,32]. PAH activates its receptor — the aryl hydrocarbon receptor (AHR) — known to act as a transcription factor and to regulate responses to endogenous and exogenous ligands of the xenobiotic drug metabolism. Cytochrome P450 CYP1A1 known to metabolically activate and detoxify PAHs — is also induced by PAH, and thereby leads to fine-tuning of its pharmacological profile [33] (Table 1).

PM is divided by size and size has been linked to its ability to invade the respiratory tract such as airways and deeper parts as alveoli of lungs, being able even to reach the systemic circulation. The coarse size is named PM_{10}, with a diameter of particles less than 10 μm, fine particles $PM_{2.5}$ has the diameter less than 2.5 μm and ultrafine particles $PM_{0.1}$ with a diameter less than 0.1 μm. Coarse particles are able to penetrate upper airway; fine and ultrafine particles can penetrate small airway reaching alveoli regions and may enter into the vascular system [34–36]. The main source of fine and ultrafine particles ($PM_{2.5}$ — $PM_{0.1}$) is from diesel exhaust emissions known as DEP (Figure 1).

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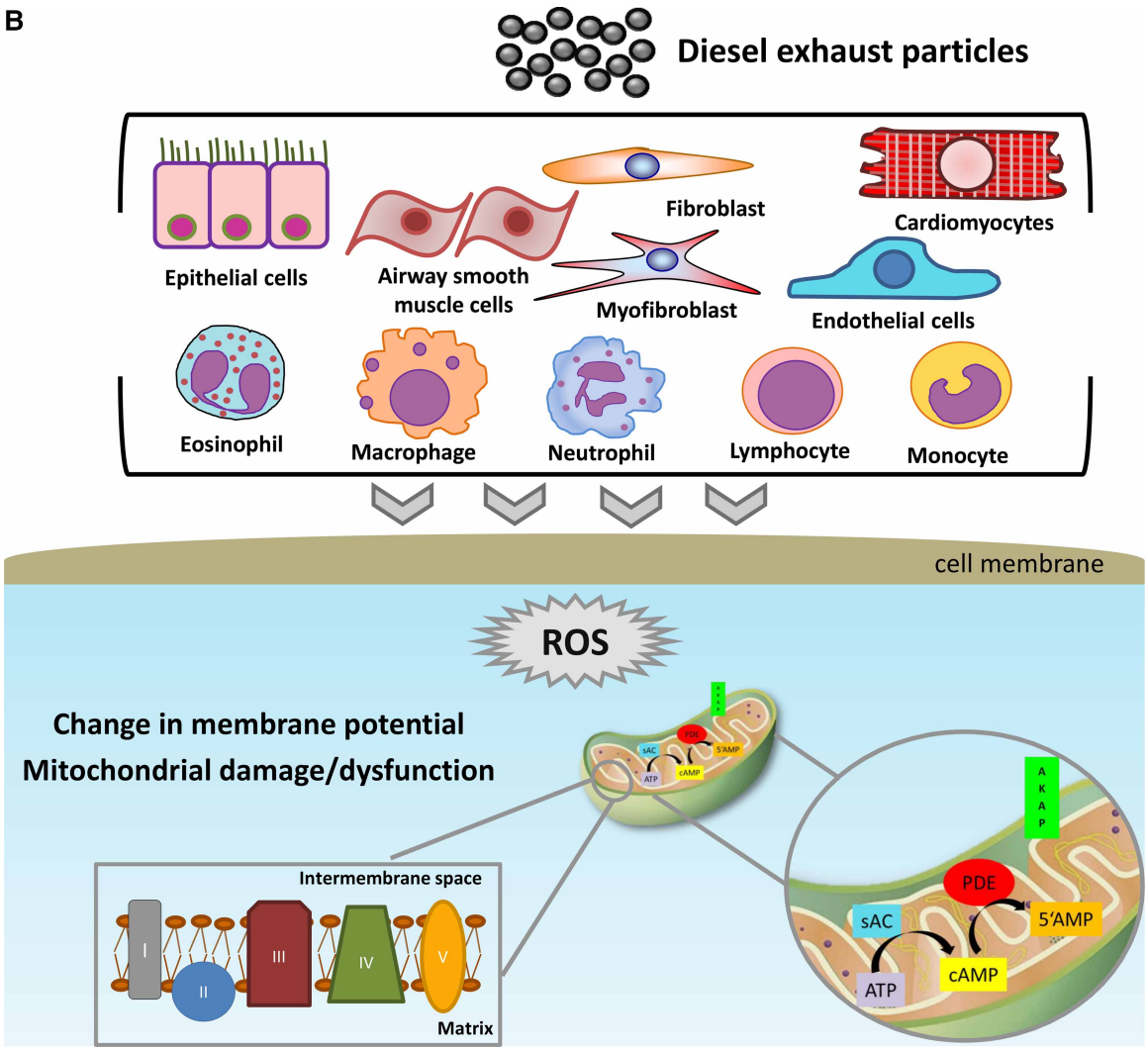

Part 2 of 2

Figure 2. Cyclic AMP Nanodomains.

(**A**) Cyclic AMP nanodomains in inflammatory and structural cells diverse such as eosinophils, macrophages, neutrophils, lymphocytes, monocytes, epithelial cells, airway smooth muscle cells, fibroblasts, cardiomyocytes, endothelial cells and myofibroblasts. (**B**) Cellular effects caused by diesel exhaust particles (DEP) in inflammatory cells and structural cells. DEP induces the production of reactive oxygen species (ROS). Subsequently, ROS production induces changes in mitochondrial membrane potential leading to mitochondria dysfunction and mitochondria damage. Mitochondrial cAMP is generated from ATP by soluble adenylyl cyclase (sAC) present in the mitochondria matrix. Levels of cAMP are regulated by phosphodiesterase (PDE) degrading cAMP to 5′AMP. A-kinase anchoring protein (AKAP) 1 recruits macromolecules to mitochondria. Shown are the mitochondrial respiratory chain complexes I–V localized in the inner membrane of mitochondria. See text for further details.

In general, PM caused by air pollution has been associated with the risk of lung cancer and to coronary events in eleven cohorts from Finland, Sweden, Denmark, Germany and Italy [37,38]. Additionally, the recent EAGLE and DUELS studies demonstrated an association of long-term exposure to coarse particles — PM_{10} — and the risk of lung cancer and cardiovascular mortality [39–41]. Moreover, subjects acutely exposed to high levels of PM_{10}, demonstrated an elevation of IL-1β and IL-6 in serum [42]. In a case control study in a cohort with miners exposed to diesel exhaust, an elevated risk of lung cancer has been reported [43]. Moreover, short-term exposure to diesel exhaust in asthmatic subjects increased airway hyperresponsiveness [44], indicating that air pollution mainly by diesel exhaust is able to worsen asthma symptoms in asthmatic patients. Exposure of 18

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blinded atopic volunteers to diesel exhaust extended the allergen-induced increase in airway eosinophils and IL-5, diesel exhaust alone also increased markers of non-allergic inflammation and monocyte chemotactic protein (MCP)-1 and suppressed the activity of macrophages and myeloid dendritic cells [45]. These results implicate that allergic people may be more vulnerable and suffer from worsening of allergic responses due to diesel exhaust exposure. In line with our conclusion, it has been recently published that the incidence of pediatric asthma is associated with exposure to traffic-related air pollution. It has been reported that black carbon particles as part of PM reached the fetal side of the human placenta. Meta-analysis even revealed a correlation between prenatal exposure to PM and preterm birth and small for gestational age [46–48] (Table 1).

Air pollution and mitochondrial function

Excessive production of ROS is known to induce oxidative stress, the latter known to be linked to cardiopulmonary disorders. However, it is important to realize that under physiological circumstances, production of ROS is not solely linked to deleterious consequences but is a *sine qua non* to drive several beneficial cellular signaling pathways and subsequently train the fitness of organisms [49,50]. Firstly, ROS act as an essential second messenger able to modulate pro-inflammatory cytokines, cell proliferation and signaling pathways including but not limited to phosphoinositide 3-kinase/AKT, AMP-activated protein kinase, hypoxia-inducible transcription factors, calcium and NF-κB (Figures 1 and 2, Table 1) [51–53]. Initial studies in isolated mitochondria unraveled their ability to produce superoxide and hydrogen peroxide production [54–56]. Excessive production of ROS most likely results in mitochondrial damage, subsequently modifying normal mitochondria functions. Mitochondria functions play an important in the entire cell metabolism due to their central role in cellular respiration and mitochondrial malfunctions trigger cardiopulmonary disorders encompassing stem cell hyperplasia and ischemia-reperfusion injury [57–59].

One may envision that mitochondria functions and air pollution are closely related as exposure to different types of air pollution surely bear the potential to drive to an alteration in the function of different mitochondria complexes and thereby to contribute to mitochondrial dysfunction (Figure 2, Table 1). Indeed, exposure of alveolar macrophages from wild-type and inducible nitric oxide (NO) synthase knockout mice to DEP from National Institute of Standards and Technology (Standard Reference Material 2975), resulted in a time-dependent elevation of the intracellular superoxide anion production and a reduction of the mitochondria membrane potential [60]. These data demonstrate that DEP indeed bear the potential to induce ROS production and mitochondrial damage. Chronic exposure of rats to diesel exhaust from a supercharged common rail direct injection diesel engine, for 3 h per day, 5 days per week, during 3 weeks reduced left ventricle homogenate mitochondrial respiratory chain complex I activity compared with control rats, leaving mitochondrial respiratory chain complex activity III and IV unchanged [61]. These results indicate that diesel exhaust selectively changes the mitochondrial respiratory chain complex activities, and as largest enzyme complex of the respiratory chain complex I profoundly contribute to the first step of the mitochondrial electron transport (Figure 2).

Elevation of ROS upon exposure to a different type of air pollution also contributed to mitochondrial dysfunction in RAW 264.7 macrophages. Exposure of RAW 264.7 macrophages to DEP extract from a light-duty diesel source resulted in an increase in superoxide and hydrogen peroxide markers and induction of macrophage apoptosis [62]. In addition, the authors reported on a decrease of mitochondrial membrane potential ($\Delta\Psi m$) pointing to a structural damage of the macrophage mitochondrial inner membrane. Moreover, the authors showed that exposure of RAW 264.7 macrophages to the antioxidant N-acetylcysteine diminished the reduction in $\Delta\Psi m$ and superoxide production, thereby providing experimental evidence linking oxidative stress to a reduced $\Delta\Psi m$ [62]. Taken together, these studies demonstrate that diverse components of air pollution — particularly DEP — bear the ability to induce ROS production as a powerful biological effect that is directly related to mitochondria dysfunction as exemplified by the impairment of $\Delta\Psi m$ (Figures 1 and 2).

Air pollution and the cardiopulmonary function

Several cohort studies reported on associations between air pollution and a higher percentage of cardiovascular mortality [63–65]. Due to size, PM such as DEP is able to enter the endothelial cells of blood vessels [34]. It is generally believed that it is this ability of air pollutants to enter the blood vessels — therefore the blood circulation and subsequently the systemic circulation — to cause cardiovascular dysfunction (Figures 1 and 2). Exposure of 21 healthy adult subjects to diesel exhaust from a generator induced acute vasoconstriction, a process sensitive to the antioxidant N-acetylcysteine [66]. Interestingly, exposure of nineteen healthy volunteers

to diesel engine exhaust inhalation in the absence or presence of a particle trap demonstrated that the particle trap reduced the DEP number, a process associated with increased vasodilatation and reduced thrombus formation [67]. This study demonstrates the direct impact of DEP on blood vessel function, and further highlight the potential of air pollution to impair cardiovascular functions.

Of interest, also a study with a total of 34 non-smoking healthy adults from the New York City metropolitan area and New Jersey traveling to East and South cities expected to exhibit high levels of $PM_{2.5}$, showed significant changes in respiratory symptoms measured as forced expiratory volume in the first second (FEV_1) as well as changes in heart rate and heart rate variability [68]. Furthermore, in a cohort of 772 patients with myocardial infarction in the greater Boston area cardiac symptoms were correlated with exposure to $PM_{2.5}$, carbon black, and gaseous air pollutants [69]. It has also been reported an association between increased levels of PM_{10} with the risk of coronary events, such as myocardial infarction, and elevation in hospitalizations for respiratory diseases including COPD [70,71]. These studies demonstrate the ability of coarse particles and fine PM from air pollution in the induction of cardiopulmonary impairments potentiality inducing the elevation of health adverse problems.

Air pollution and the lung

Air pollution not only induces inflammation and/or oxidative stress in the lungs but — importantly — it seemed to have a more profound impact on the normal physiological function of the lung, to be precise it seemed to impair normal breathing [72,73]. Lungs are in direct contact with air eventually loaded with toxic pollutant gases and PM [74]. Due to size, PM such as DEP is able to enter deeply into the lungs thereby reaching alveoli spaces [30] (Figures 1 and 2). It is generally believed that in particular long-term exposure to air pollution of the lung epithelium severely limit lung function [10]. Moreover, the adverse health effect of air pollution is not restricted to long-term exposure, but also to acute exposure. Air pollution exposure has been associated with acute exacerbations of chronic bronchitis and asthma as well severe acute exacerbations of COPD [75–77].

A recent study in China has shown that long-term exposure of 137 diesel engine testing workers to diesel engine exhaust of heavy-duty diesel engines significantly decreased the FEV_1, the ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC), maximal mid expiratory flow curve (MMF), forced expiratory flow at 50% of FVC ($FEF_{50\%}$), and forced expiratory flow at 75% of FVC ($FEF_{75\%}$) compared with non-exposed workers [73]. Exposure of eighteen healthy volunteers to diluted diesel exhaust in a chamber for 3 h in a double-blind set up demonstrated a moderate but persistent reduction in peak expiratory flow compared with the control group exposed to filtered air [72]. These data indicate that low levels of diluted diesel exhaust as a part of air pollutant induce deleterious — though temporary — effects on lung function.

Next to adults, newborns and children are affected by air pollution thereby representing vulnerable subgroups in the population. Post-natal exposure to air pollution seems to reduce lung growth during school age [78–80]. In 2009 in Switzerland, a prospective birth cohort of 241 healthy term-born neonates and maternal exposure to PM_{10} revealed a strong association between the exposure to PM_{10} during pregnancy and reduction of lung function of newborns seen by higher respiratory need [81]. Meanwhile, several studies implicate that long-term maternal or postnatal exposure to different types of air pollution, such as traffic-related air pollution, impact the development of lungs subsequently leading to an impairment of lung function in childhood [78–81].

Next to animal experiments and studies in population cohorts, researchers use as a valuable tool structural and/or immune cells of the lungs such as but not limited to epithelial cells, smooth muscle cells and macrophages to understand adverse effects of air pollution on the cellular level, particularly to gather insights into mechanistic pathways linked to inflammation, oxidative stress and modifications in cellular phenotypes [82–84].

In a very recent study, exposure of primary bronchial epithelial cells to a 0.57 μm median diameter aerosolized DEP for 24 h increased gene expression of inflammatory markers such as the C-X-C motif chemokine ligand 8 (CXCL8) and TNF-α, next to the gene expression of oxidative stress markers such as NF-κB, heme oxygenase (decycling) 1 (HMOX1) and glutathione peroxidase. In contrast, in DEP generated and collected from a three-cylinder, 3.8 l tractor engine, exposed to co-cultures of primary bronchial epithelial cells with THP-1 derived macrophages the expression of both CXCL8 and TNF-α was reduced, similar as the gene expression of NF-κB and HMOX1 [82] (Table 1). These studies implicate that cell–cell interactions determine the net-outcome of the deleterious effects of air pollutants on airway physiology.

Lung cells are the most vulnerable type of cells affected by air pollutants including DEP probably due to the direct contact of the respiratory tract with air [74]. The inevitable contact with air during years most likely

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drive not only inflammation but also trigger cell differentiation and/or cell phenotype alterations, a process referred to as EMT [84]. The superfamily of CYP1 genes are closely intermingled with the metabolism of xenobiotics, a process mainly regulated by the AHR known to be in turn activated by PAH known to be released by combustion system. Chronic exposure of human bronchial epithelial cells (BEAS-2B) to low concentration of DEP (Standard Reference Material 1650b) with known concentrations of PAH and nitro-PAH, and with a mean particle diameter of 0.18 μm, for 6 months did not change basal mRNA expression of both CYP1A1 and CYP1B1 mRNA [83]. Moreover, under the outlined experimental design long-term DEP-exposed BEAS-2B did not undergo EMT studied by gene expression of E-cadherin, vimentin and N-cadherin [83]. However, in another recent study BEAS-2B were exposed to primary ultrafine particles (UFP) from diesel and transcriptional changes were followed with an RNA-seq time-course. Genes related to the xenobiotic metabolism such as CYP1A1, CYP1B and to inflammation such as IL24, IL1A and IL1B were profoundly changed in BEAS-2B cells exposed to UFP diesel. In addition, the transcription factor NFE2L2 was up-regulated together with genes related to the antioxidant response such as HMOX1, TXNRD1 and NQO1 [85] (Table 1). A recent study using human bronchial smooth muscle cell and human bronchial fibroblasts exposed to $PM_{2.5}$ showed an increase in human bronchial smooth muscle migration but not of human bronchial fibroblasts [86]. The data demonstrate that human bronchial smooth muscle migration may contribute to airway structure modification during $PM_{2.5}$ exposure. Taken together the current studies indicate that cellular responses of lung cells profoundly differ depending on the type of air pollutants used and interval of exposure implicating that cellular imprinting by air pollutants change in time and space.

Air pollution and cardiopulmonary cAMP nanodomains

There is an unmet need to unravel the molecular mechanisms initiated due to the exposure of lung cells to air pollution. Without any doubt oxidative stress — characterized by an imbalance between oxidants and antioxidants and ultimately linked to mitochondrial dysfunction [8] — plays an important role in cardiopulmonary impairments related to air pollution exposure. Pharmacological targeting of cAMP seems to profoundly alleviate cardiopulmonary dysfunction [11–15]. Of note, cAMP has recently emerged as a potent regulator of mitochondrial metabolism [18], and even more intriguingly a unique mitochondrial cAMP nanodomain seem to exist composed of sAC, PDE2, Epac1 and AKAP1 [16,19–23]. Several lines of evidence indicate that cAMP-producing G protein-coupled receptors for β_2-agonists and PGE_2 are repressed under settings of diseased lungs [15,24–27]. In addition to cAMP-producing receptors, expression and function of PDEs (primarily PDE4, PDE3, PDE2) are altered in cardiopulmonary pathologies [87,88]. Epac1 and Epac2 act as lung cAMP 'receptors'. Our research group has been the first to demonstrate that oxidative stress severely alters expression and function of both (anti-fibrotic) Epac1 and (pro-inflammatory) Epac2, and that PGE_2 receptors signal through Epac1, in a process involving beta-catenin the latter closely related to lung repair [13,89–91] (Figures 1 and 2). As air pollution provokes oxidative stress, it is rather likely to assume that different types of air pollutants severely alter cAMP signaling properties, whether mitochondrial cAMP nanodomains are altered and if so to which extent and by which air pollutant remains to be studied in more detail. However, exposure of primary murine tracheal epithelial cells and human airway smooth muscle to PAH — known to be released by diesel combustion — reduced cAMP production by β_2-adrenoreceptors, a process expected to profoundly limit the responsiveness to the standard pharmacotherapy [92]. Further studies are needed in order to understand the molecular mechanisms underlying the mechanisms of DEP as the main source for air pollution and their potential cross-talk to cAMP.

Lung remodeling plays an important role in lungs diseased due to exposure to air pollution. Exposure of mice to diesel particles collected after 1 day of the routine operation of a bus from São Paulo city induced alterations in lung morphology such as alveolar enlargement [93]. EMT — one driver of lung remodeling [94] is characterized by a loss of cell to cell junctions subsequently leading to a loss in cell interactions with basal membrane [13,95,96]. Used as *in vitro* model, exposure of BEAS-2B cells to an ultrafine PM induced phenotypic changes for EMT exemplified by a reduction in the epithelial marker E-cadherin and an increase in the mesenchymal marker α–smooth muscle actin, seen by immunohistochemistry and mRNA expression [84]. In contrast, chronic exposure of BEAS-2B cells to DEP (Standard Reference Material 1650b) did not induce EMT [83] (Table 1). Such seemingly differences are most likely due to different types of air pollutions and further point to the importance of studies in subcellular domains in space and time. Of particular interest are studies linking mitochondrial dysfunction to a potential therapeutic targeting of cAMP, the latter known to diminish cardiopulmonary dysfunction [11–15].

Conclusions

Exposure to air pollution is related to several cardiopulmonary disorders. Adverse cardiopulmonary effects are most likely linked to the small size of particles present in air pollution and their ability to reach deep lung parts and to even enter blood vessel endothelial cells [34]. Though adverse health effects of air pollution, including diesel exhaust, particulate of air pollution and traffic-related air pollution, are generally prevalent in the population, some groups are more vulnerable and therefore need special attention such as asthmatic subjects, heart failure patients, newborns and children [44,69,78–81]. Several studies — particular in recent times — evaluate the impact of air pollution on cardiopulmonary dysfunction. As mitochondria fulfill a central role in balancing cellular energy metabolism, we propose the mitochondrial dysfunction induced by exposure to DEP is key to cardiopulmonary impairments. Targeting of the mitochondrial cAMP nanodomain bear the therapeutic potential to diminish air pollutant — particularly DEP — induced decline in cardiopulmonary function.

Perspectives

- Air pollution exposure increases the risk of several disorders mainly in the cardiopulmonary system, which is related to the elevation of morbidity and mortality. PM and DEP originated from diesel automotive engines are envisioned as the primary cause for cardiopulmonary dysfunction.
- DEP induces inflammation and ROS production ultimately leading to mitochondrial dysfunction. DEP impair structural cell function and initiate the EMT, a process leading to dysfunction in endothelial as well as epithelial barrier, hamper tissue repair and eventually leading to fibrosis. Mitochondrial dysfunction seems to be linked to alterations in cyclic AMP signaling properties and seem to foster cardiopulmonary decline.
- Furthermore, studies are urgently required to decipher the molecular mechanisms underlying the devastating effects of the major air pollutant knowns as DEP on the mitochondrial cAMP nanodomain. Targeting of the mitochondrial cAMP nanodomain as therapeutic intervention potentially diminish air pollutant induced decline in cardiopulmonary function.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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Author Contributions

I.C.-C and M.S. wrote the manuscript. S.S.V. performed the proof-reading.

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Abbreviations

AHR, aryl hydrocarbon receptor; cAMP, cyclic adenosine monophosphate; COPD, chronic obstructive pulmonary disease; DEP, diesel exhaust particles; EMT, epithelial-to-mesenchymal transition; FEV_1, forced expiratory volume in the first second; PGE_2, prostaglandin E_2; ROS, reactive oxygen species.

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