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Air pollution and atherosclerosis — a brief review of mechanistic links between atherogenesis and biological actions of inorganic part of particulate matter

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Abstract: Atherosclerosis is considered as a chronic, low-grade inflammatory process involving the aorta and the medium-sized arteries. Exposure to air pollutants, especially particulate matter, is highly related to cardiovascular diseases including atherosclerosis. Many studies confirm that proatherogenic potential of particulate matter is determined by its ability to induce inflammation, oxidative stress and thrombosis formation. Recently, an important role in the pathogenesis of atherosclerosis has been attributed to autoimmune response. Moreover, harmful effects of PM particles strongly depend on their physicochemical properties. It is still not known what exact role air pollutants, and in particular their inorganic part, play in the development of atherosclerotic lesions. In this article, we will briefly discuss the different aspects of particulate matter activity and its implication with atherosclerosis progression.

Key words: air pollution, particulate matter, atherosclerosis.

Air pollution — core information

Chronic exposure to air pollutants is associated with numerous health problems [1]. Air pollution is a heterogeneous mixture consisting of various gaseous and solid substances. Among gaseous components we can distinguish: ozone (O_3), carbon monoxide (CO), carbon dioxide (CO_2), sulfur dioxide (SO_2) and nitrogen oxides (NO_x) [1]. Other components of air pollutants include: volatile organic compounds (benzopyrenes), coal dust, suspended dust and transition metals. A particularly unhealthy ingredient of air pollution is particulate matter emitted into the atmosphere as a result of anthropogenic processes, but also through natural phenomena. It widely recognized, that particulate matter has the greatest impact on human health of all air pollutants [2]. According to the World Health Organization (WHO) exposure to particulate matter can cause 3.7 million premature deaths worldwide per year [3].

Particulate matter (PM) may be defined as a mixture of particles and liquid droplets suspended in the air, containing a variety of organic and inorganic components. Examples of organic substances are polycyclic aromatic hydrocarbons (PAHs), furans and dioxins, while inorganic components include various ions and metals [3]. In this review we focused on the possible mechanisms linking biological actions of inorganic part of PM with atherogenesis.

The degree of hazard of PM depends on their physicochemical properties such as chemical composition, size and solubility [4]. On the basis of the aerodynamic diameter, particulate matter can be divided into 3 main categories: PM_{10} called coarse thoracic particles, $PM_{2.5}$ (fine particles) and $PM_{0.1}$ (ultrafine particles) [1]. PM_{10} consists of particles 10 μm and smaller, which. could accumulate mainly in the upper parts of respiratory tract. Particles of $PM_{2.5}$ (fine particles), which has a diameter less than 2.5 μm can accumulate in the deep parts of the lungs. They deposit on the surface of the bronchioles and alveoli resulting in local pulmonary inflammation. Importantly, fine particles may also enter into the blood and cause systemic response. The $PM_{2.5}$, may absorb on its surface bacteria, viruses and heavy metals such as lead, zinc, iron, cadmium, nickel, arsenic and chromium [5]. The American Heart Association point to $PM_{2.5}$ as an important risk factor for cardiovascular events [4]. Numerous studies confirm the link between exposure to particulate matter and the progression of cardiovascular disease, including atherosclerosis, but the exact mechanisms responsible for harmful effects of the particulate matter are still unknown [6, 7].

Atherosclerosis — core mechanisms

Cardiovascular disorders, including atherosclerosis still represent the most common cause of death in Poland and the developed countries [8]. Atherosclerosis is a chronic disease of multifactorial etiology, however the widely accepted basis of the disease is

a chronic, low-grade inflammatory process in progress in the arterial wall [9]. The first step in the development of atherosclerosis is endothelial dysfunction. Among the factors that may damage the endothelium are reactive oxygen and/or nitrogen species (ROS/RNS), oxidized biomolecules (like LDL), proinflammatory stimuli (cytokines, chemokines) or physical factors (high blood pressure, shear stress). Damaged endothelial cells start to show "inflammatory phenotype" which is characterized by an increased expression of adhesion molecules VCAM-1 and ICAM-1 and increased permeability of endothelium [10]. This results with the deposition of LDL in the subendothelial space, trapping of LDL by proteoglycans matrix and their oxidation into ox-LD. Recruited via adhesion molecules monocytes-macrophages absorb oxidized LDL and transform into foam cells [9]. The differentiation of monocytes into macrophages and foam cells depends on the action of endothelium-derived M-CSF (Macrophage colony-stimulating factor) and GM-CSF (Granulocyte-macrophage colony-stimulating factor) with subsequent expression of the scavenger receptors (SAR) and CD36 molecule, crucial for the interaction with lipoproteins [11, 12]. It has been shown that T lymphocytes early enter the atherosclerotic plaques [9]. They provide important source of inflammatory and pro-angiogenic factors (IL-8, IL-1, TNF-α and VEGF). The vicious cycle of atherogenesis develops: the overproduction of ROS derived by activated phagocytes, lymphocytes, endothelial cells and smooth muscle cells leads to the increased release of plethora of pro-inflammatory mediators (e.g. cytokines, chemokines, endothelins, angiotensins, prostaglandins), which in turn aggravate oxidative stress [13]. It has been shown that immune reactions represent important causative factor for atherosclerosis. Importantly, macrophages, endothelial cells and smooth muscle cells all express MHC II antigens, and they are able to present antigens to T lymphocytes. Both, T-helper 1 (Th1 — cellular) and T-helper 2 (Th2 — humoral) types of cells operate in plaques [14]. Th_1 cells are considered as pro-atherogenic: they produce IFN-γ which is involved in the stimulation of the an expression of MHC class II molecules on antigen presenting cells (APC). It also stimulates the expression of VCAM-1 and ICAM-1, increases co-stimulatory signals (expression of CD40 and its ligand) and augment activity of metalloproteinases in phagocytes, endothelial and smooth muscle cells. The Th_2 cells, considered as anti-atherogenic produce the anti-inflammatory cytokines (IL-4, IL-5 and IL-10. IL-4 and IL-10) which inhibit the production of pro-inflammatory factors and metalloproteinases [14]. Regulatory T cells (T_{reg}) produce transforming growth factor beta (TGF-β) and IL-10 cytokines that also determines their anti-inflammatory and and antiatherogenic activities [15]. It seems, that the balance between Th1 and Th2 responses is tightly controlled by T_{reg} [16]. Importantly, the platelets also take part in the atherogenesis as are a source of growth factors such as PDGF (*platelet-derived growth factor*), responsible for the proliferation of smooth muscle cells and fibroblasts, and TGF-β which stimulates collagen

synthesis [17, 18]. In later stages of plaque development, chronic inflammation leads to an increased arterial calcification, which seems to be an active, organized and regulated process [19].

Mechanisms of atherogenic action of air pollutants

Oxidative stress and inflammation are considered the main culprits of endothelial dysfunction and development of atherosclerotic plaques. Thus, particulate matter can promote atherosclerosis, as a consequence of its inflammatory and oxidative properties [20]. Particulate matter can generally act in two ways and both of these ways may contribute to atherosclerosis.

The first, indirect manner consists on initiation an inflammatory response in the lungs by $PM_{2.5}$ and development of secondary systemic low-grade inflammation. Indeed, it has been shown that $PM_{2.5}$ may directly cause oxidative injury of the respiratory epithelium, thereby leading to massive release of pro-inflammatory cytokines, that enter the circulation and trigger systemic inflammatory response [21].

The second mechanism assumes that $PM_{2.5}$ passes from the respiratory tract into the circulation and cause *direct* damage and inflammatory stimulation of cells in vessel walls and blood (the mechanisms potentially involved in this way of action are described in details in next paragraphs).

Pro-oxidative activity of PM

Oxidative stress can be generally defined as an imbalance between the burden of reactive oxygen species (ROS) and the capacity of the cellular/tissue antioxidant systems. Importantly, ROS (esp. superoxide anion) may react with excess of nitric oxide (NO) to form a reactive nitrogen species (RNS) (esp. peroxynitrite) [4]. It is known, that severe oxidative stress may cause damage of macromolecules (proteins, lipids, nucleic acids) and cause cell apoptosis or necrosis. In vitro studies have demonstrated that $PM_{2.5}$ may dose-dependently induce the apoptosis of human umbilical vein endothelial cells (HUVECs) via the p53, Bax and caspase 9, 7 and 3 activation [22]. Such toxicity of PM is strongly associated with the capability of generating ROS/RNS and depends on chemical composition and the size of particles. Particulate matter contains transition metals, such as Fe, Pb, Cu, Cd and Mn, which participate in the formation of ROS and RNS. Transition metal ions can catalyze redox reactions and therefore generation of ROS on the surface of PM particles [23]. Ultrafine particles, due to their small size and relatively large surface, have a larger oxidative potential than fine and coarse particles. Increased levels of ROS have been observed in various types of cells upon exposure to particulate matter, also in macrophages, endothelial and bronchial epithelial cells [24, 25]. Oxidative stress

has been shown to activate specific transcription factors, including nuclear factor-kappa B (NF-κB) and activator protein-1 (AP-1), and pathways (e.g. Jun N-terminal kinase), which trigger the expression of genes for cytokines, chemokines, and other proinflammatory mediators [26]. Interestingly, the study on human aortic endothelial cells (HAEC), have shown that ambient ultrafine particles (UFP) also reduce physiological vascular nitric oxide (NO) production probably by stimulating S-glutathionylation of endothelial nitric oxide synthase (eNOS). Collectively, these observations indicate that exposure to ambient ultrafine pollutants can compromise the physiological, vascular action of NO by inhibition of its generation and/or by its scavenging by ROS with subsequent formation of toxic RNS [27]. It should be also noted that $PM_{2.5}$-derived ROS/RNS may act also within blood. It has been shown that they may promote oxidation of low density lipoproteins (LDL) to ox-LDL (see below) [28].

Pro-inflammatory effects of PM

Inhalation of air pollutants can induce both local (pulmonary) and systemic inflammatory response. Several reports point to alveolar macrophages as to the key cells involved in local response to PM [29]. It has been shown, that they can recognize $PM_{2.5}$ via TLR2 or TLR4 Toll-like receptors (TLRs) and via NF-κB pathway activation release various pro-inflammatory mediators, such as IL-1, IL-6, TNF-a, GM-CSF and MCP-1 [24]. Pro-inflammatory cytokines and chemotactic proteins cause important local and systemic actions [4]. IL-6 may stimulate the bone marrow to produce white blood cells, platelets and acute phase proteins, what results in an increased white blood cell and platelet count in the blood. There are clear signs of systemic inflammatory response in people exposed to air pollution, e.g. there is positive correlation between exposure to particulate matter and the plasma concentration of C-reactive protein (CRP) [26]. In vitro studies clearly showed that $PM_{2.5}$ and PM_{10} increase expression of the cell adhesion molecules: intercellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1) in human umbilical vein cells (HUVECs), as well as induce many other genes involved in inflammation [30]. Thus, systemic inflammatory response caused by particulate air pollution seems to play an important role in the development of cardiovascular diseases [29].

The impact of PM on plasma lipoproteins

Ambient particles were shown to alter lipid metabolism and properties of lipoproteins. They aggravate LDL oxidation as well as impair the function of scavenger receptors and LDL receptors and foster accumulation of lipids in atherosclerotic

plaques [31]. Indeed, the studies on apolipoprotein E (apoE)-knockout mice model of atherosclerosis have shown increased content of cholesterol and macrophages in plaques after long-term exposure to low concentration of $PM_{2.5}$ [32]. Particulate matter can also affect high density lipoprotein (HDL) by suppression of its anti-inflammatory and antioxidative capacity. It has been shown that the prolonged exposure of LDL-R null mice to ultrafine particles results in decrease of plasma HDL levels and their paraoxonase activity (PON), with simultaneous increase of triglycerides concentration [28]. The impairment of antioxidant and anti-inflammatory functions of HDL have been linked to an increase of oxidative stress and enhanced atherosclerosis progression [33].

The pro-thrombotic effect of PM

The exposure on particulate matter has been shown to increase thrombotic events [34]. PM may increase the concentrations of P-selectin and plasminogen activator inhibitor (PAI-1) in plasma while the levels of tissue factor pathway inhibitor (TFPI) are reduced. Particles of PM can also increase activation of platelets and attenuate fibrinolysis, which may contribute to formation of arterial thrombus [35, 36]. It has been also demonstrated that long-term exposure to high concentrations of particulate matter results in changes in fibrin clot structure in patients with deep vein thrombosis. These patients have a denser fibrin clot structures compared to patients exposed to low concentrations of PM [37]. Exposure to particulate matter may also lead to a hypercoagulability because of the increased levels of platelets and coagulation factors in the blood, such as fibrinogen, von Willebrand factor and factor VIII [34].

PM and atherosclerosis — a possible autoimmune connection

Several reports suggested, that immune reaction against autoantigen(s) might play significant role in the pathogenesis of atherosclerosis. Some studies pointed to the potential targets of immune response in atherosclerosis: the heat shock proteins (HSP), oxidized low density lipoproteins (ox-LDL), the β2 glycoprotein or the structural components of some microorganisms [38]. HSPs are expressed by the endothelial cells in response to shear stress and ox-LDLs and recognized by the T cells. It has been shown, that such scenario may play a role in autoimmune reaction against the HSP60, which contribute to atherosclerosis [39, 40]. Intriguingly, in vitro studies showed that the exposure of endothelial cells to extract from cigarette smoke results in increased expression of HSP60 mRNA. HSP60 is localized in the mitochondria and it is responsible for their protection, however in response to cigarette smoke it is released from the mitochondria, transported to the endothelial cells surface and eventually shed to the circulation. Interestingly, elevated levels of

HSP60 in the serum have been reported in young healthy people exposed to passive smoking [39]. Few other mechanisms have been proposed to link atherogenesis, autoimmunity and air pollution. Pentraxin 3 (PTX3) plays an important role in the inflammatory and autoimmune diseases [41]. Recently, it was shown that inorganic part of PM in vitro induces release of long pentraxin 3 (PTX3) from THP-1 human leukemia monocytes and A549 human adenocarcinoma alveolar pneumocytes [42]. There are also some clues pointing to the disturbances in function of suppressor regulatory T cells (T_{reg}) upon exposure to common air pollutants [43]. Clearly, the involvement of autoimmune mechanisms in the pro-atherogenic action of particulate matter requires further extensive studies.

Summary

Many epidemiological studies and experimental data have shown that exposure to particulate matter is strongly associated with cardiovascular diseases. The pro-atherogenic activity of particulate matter strongly depends on its physicochemical properties and could be attributed to its pro-oxidative, pro-inflammatory and pro-thrombotic potential. Several lines of evidence point to the important role of autoimmunity in pro-atherogenic action of particulate matters, however exact mechanistic links between atherogenesis and biological actions of inorganic part of particulate matter are still unclear and require further extensive studies.

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Conflict of interest

None declared.

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