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Fine particulate matter air pollution and atherosclerosis: Mechanistic insights☆

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ABSTRACT

Background: Atherosclerosis is a progressive disease characterized by the accumulation of lipids and fibrous plaque in the arteries. Its etiology is very complicated and its risk factors primarily include genetic defects, smoking, hyperlipidemia, hypertension, lack of exercise, and infection. Recent studies suggest that fine particulate matter ($PM_{2.5}$) air pollution may also contribute to the development of atherosclerosis.
Scope of review: The present review integrates current experimental evidence with mechanistic pathways whereby $PM_{2.5}$ exposure can promote the development of atherosclerosis.
Major conclusions: $PM_{2.5}$-mediated enhancement of atherosclerosis is likely due to its pro-oxidant and pro-inflammatory effects, involving multiple organs, different cell types, and various molecular mediators.
General significance: Studies about the effects of $PM_{2.5}$inhalation on atherosclerosis may yield a better understanding of the link between air pollution and major cardiovascular diseases, and provide useful information for policy makers to determine acceptable levels of $PM_{2.5}$ air quality. This article is part of a Special Issue entitled Air Pollution, edited by Wenjun Ding, Andy Ghio and Weidong Wu.

1. Introduction

Atherosclerosis, the primary cause of heart disease and stroke, is a progressive syndrome characterized by the accumulation of lipids and fibrous plaque in the arteries. The etiology of atherosclerosis is very complicated; Age is a major risk factor for atherosclerosis; accumulated oxidative products during aging are believed to contribute to vascular injury through inflammation and endothelial dysfunction [1,2]. The risk factors include genetic defects, smoking, hyperlipidemia, hypertension, lack of exercise and infectious agents. Genome-wide association studies in humans have revealed dozens of discrete genetic loci that are associated with myocardial infarction, coronary artery disease and other circulating biomarkers related to atherosclerosis [3]. The availability of novel animal models accelerates the process of identifying the causal gene at each loci and elucidates molecular and physiological mechanisms. Mice deficient in apolipoprotein E ($apoE^{-/-}$) or low-density lipoprotein ($LDL^{-/-}$) receptor develop advanced atherosclerotic lesions and are the models most used in genetic and physiological studies [4–6]. Diet appears to be an important etiological factor for atherosclerosis [7]. High-fat or high-cholesterol diet is mostly required for the development of atherosclerotic lesion in these experimental animals [8,9]. Other well-defined environmental factors associated with atherosclerosis include tobacco smoking [10–12], lack of exercise [13,4], and infectious agents [15–17].

Recent epidemiological and experimental studies demonstrate that fine particulate matter ($PM_{2.5}$) air pollution is another risk factor that contributes to the development of atherosclerosis [18–21]. PM is a mixture of microscopic solid and liquid droplets suspended in the air, consisting of numerous components, e.g. acids, organic chemicals, metals, solids or dust particles, and allergens. According to its aerodynamic diameter, PM is generally classified into thoracic (<10 μm; PM_{10}), fine (<2.5 μm; $PM_{2.5}$), and ultrafine (<0.1 μm; $PM_{0.1}$) particles. Although PM_{10} and $PM_{0.1}$ may have the capacity to induce atherosclerosis, few studies have focused on these size fractions. Most data to date have provided the consistent association of increased atherosclerotic risk with exposure to $PM_{2.5}$. After briefly discussing the key events of atherosclerotic development, the present review integrates the current experimental evidences with mechanistic pathways whereby $PM_{2.5}$ exposure promotes the development of atherosclerosis.

☆ This article is part of a Special Issue entitled Air Pollution, edited by Wenjun Ding, Andy Ghio and Weidong Wu.

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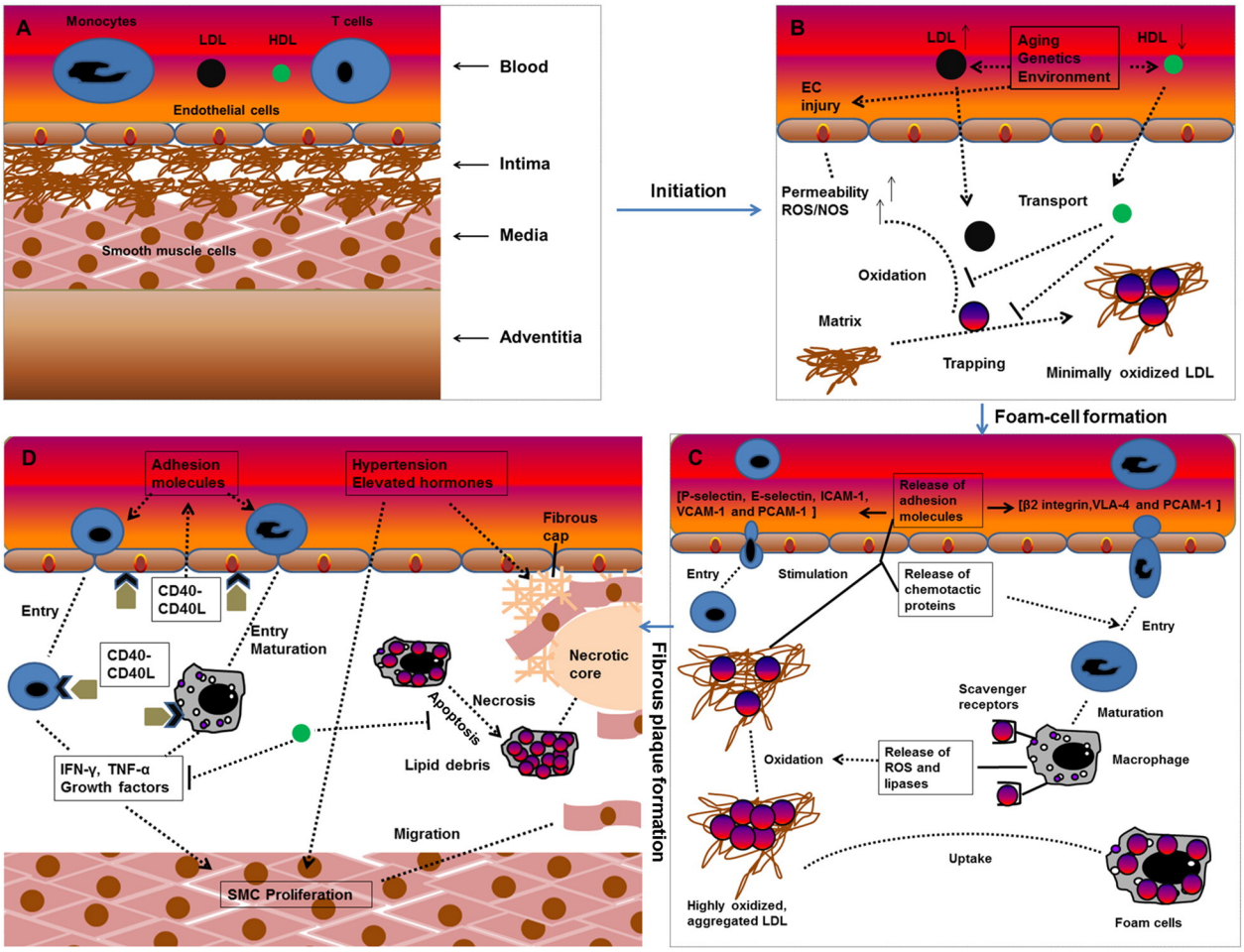

Fig. 1. Development of atherosclerosis. (A) Normal structure of artery. (B–D) Initiation, foam cell formation, and fibrous plaque formation. LDL: low-density lipoprotein; HDL: high-density lipoprotein; EC: endothelial cell; ROS: reactive oxygen species; NOS: nitrite oxygen species; ICAM: intercellular adhesion molecule; VCAM: vascular cell adhesion molecule; PCAM: platelet cell adhesion molecule; VLA: very late antigen; CD: cluster of differentiation; IFN: interferon; TNF: tumor necrosis factor; SMC: smooth muscle cell.

2. Main text

2.1. Development of atherosclerotic plaque

A normal artery consists of three distinct layers (Fig. 1A). The intima, the innermost layer, is bounded by a monolayer of endothelial cells (ECs) and is supported by an internal elastic lamina. The ECs are in direct contact with the blood flow and serve as a selectively permeable barrier between blood and tissues. Massive extracellular connective tissue matrix, primarily proteoglycans and collagen, exists in the intima. The media, the middle layer, consists of smooth muscle cells (SMCs). The adventitia, the outer layer, consists of connective tissues with interspersed fibroblasts. Atherosclerotic lesion occurs in the intima and involves multiple cell types, e.g. monocytes, T cells, ECs and SMCs [22].

The key events of atherosclerotic plaque development consist of lesion initiation, foam cell formation and fibrous plaque formation, which have been well demonstrated by animal studies [23]. Lesion initiation is characterized by the disruption of vascular endothelial integrity and the accumulation of LDL in the extracellular matrix (Fig. 1B). The risk factors may cause EC injury and change the lipid profile in circulation. For example, overexpression of human apoB in transgenic rabbits results in increased levels of LDL and decreased levels of high-density lipoprotein (HDL) [24]. After passing through EC junction, LDL tends to bind to the subendothelial extracellular matrix, a process known as LDL retention. The interactions between apoB, the ligand of LDL receptor, and matrix proteoglycans play an important role in LDL retention in the artery wall [25]. LDL in the intima undergoes the first oxidation to form minimally oxidized LDL. Injured ECs and 12/15-lipoxygenase may provide a source of reactive oxygen species (ROS) and seed the extracellular LDL through inserting molecular oxygen, respectively [26].

As shown in Fig. 1C, LDL must be further modified before it can be phagocytized by macrophages to form foam cells. Minimally oxidized LDL has pro-inflammatory properties and stimulates ECs, resulting in the release of adhesion molecules and chemotactic proteins [33]. These molecules facilitate leukocytes, e.g. monocytes and T cells, to roll on along the endothelial surface and direct them to the lesion sites [34]. LDL can be highly oxidized via ROS produced by ECs and macrophages and several enzymes such as myeloperoxidase, sphigomyelinase and a secretory phospholipase [23,35,36]. Macrophages recognize the modified LDL via two major scavenger receptors, SR-A [37] and CD 36 [38], and rapidly take up these particles, leading to foam cell formation.

The oxidized LDL can cause macrophage apoptosis and therefore contribute to foam cell death at the edge of fibrous plaque [39], which is characterized by a growing necrotic core, accumulation of SMCs and SMC-derived extracellular matrix (Fig. 1D). In addition, overloaded foam cells may impair engulfment mechanisms, causing defective efferocytosis and conversion of apoptotic into necrotic cells [40]. Under inflammatory conditions, the receptor CD40, expressed by both immune and non-immune cells, binds its ligand CD40L, which is transiently expressed on T cells and other cells [41]. The interaction between CD40 ligand and CD40 expressed on T cells and macrophages contribute

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