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Review

Environmental carcinogens and mutational pathways in atherosclerosis

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ABSTRACT

Atherosclerosis is associated with DNA damage in both circulating and vessel-wall cells and DNA adducts derived from exposure to environmental mutagens are abundant in atherosclerotic vessels. Environmental chemical carcinogens identified as risk factor for atherosclerosis include polycyclic aromatic hydrocarbons (benzo(a)pyrene, dimethylbenz(a)anthracene, beta-naphthoflavone, pyrene, 3-methylcolanthrene), arsenic, cadmium, 1,3-butadiene, cigarette smoke. Accordingly, polymorphisms of genes encoding for phase I/II metabolic reaction and DNA repair are risk factor for cardiovascular diseases, although their role is negligible as compared to other risk factors. The pathogenic relevance of mutation-related molecular damage in atherosclerosis has been demonstrated in experimental animal models involving the exposure to chemical mutagens. The relevance of mutation-related events in worsening atherosclerosis prognosis has been demonstrated in human clinical studies mainly as referred to mitochondrial DNA damage. Atherosclerosis is characterized by the occurrence of high level of oxidative damage in blood vessel resulting from both endogenous and exogenous sources. Mitochondrial damage is a main endogenous source of oxidative stress whose accumulation causes activation of intrinsic apoptosis through BIRC2 inhibition and cell loss contributing to plaque development and instability. Environmental physical mutagens, including ionizing radiation, are a risk factor for atherosclerosis even at the low exposure dose occurring in case of occupational exposure or the high exposure doses occurring during radiotherapy. Conversely, the role of exciting UV radiation in atherosclerosis is still uncertain.

This review summarizes the experimental and clinical evidence supporting the pathogenic role of mutation-related pathway in atherosclerosis examining the underlying molecular mechanisms.

Abbreviations: LDL, low-density lipoprotein; WHO, World Health Organization; 8-oxo-G, 8-oxoguanine; ROS, reactive oxygen species; PHAs, polycyclic aromatic hydrocarbons; AHR, aryl hydrocarbon receptor; SCD, stearoyl-CoA desaturase; LXR, liver X receptors; PUFAs, polyunsaturated fatty acids (PUFAs); 4-HNE, 4-hydroxy-2-nonenal 4-HNE; VSMCs, vascular smooth muscle cells; TGF-β, transforming growth factor-β; CSE, cigarette smoke extract; EH, epoxide hydrolase; PON 1, paraoxonase 1; HDL, high-density lipoprotein; SNPs, single nucleotide polymorphisms; BD, 1,3-butadiene; mitoOS, mitochondrial oxidative stress; GWAS, genome-wide association study; B[a]P, benzo[a]pyrene; DMBA, 7,12-dimethylbenz(a,h)anthracene; TPA, 12-O-tetradecanoylphorbol-13-acetate; SMC, smooth muscle cell; AHH, arylhydrocarbon hydroxylase; MMP, metalloproteinases; MCP1, monocyte-chemoattractant protein-1; ICAM-1, intercellular adhesion molecule-1; EPC, endothelial progenitor cells; NPC1, Niemann–Pick type C1 protein; LSS, Life Span Study; UV, exciting radiation; CDV, cardiovascular disease; SSBs, DNA single strand breaks; DSBs, DNA double strand breaks.

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Introduction

Atherosclerosis is the primary cause of death in the developed world, with a dramatically increasing global incidence. In the 20-year period from 1990 to 2010, deaths from cardiovascular disease have risen by more than 30% worldwide (Moran et al., 2012).

Gabriele Falloppio first described atherosclerosis in Italy in 1575. In 1775, Edward Jenner, primarily known for discovering the cowpox vaccination, was the first scientist to establish the association between coronary atherosclerosis and heart angina. This discovery occurred during the post-mortem examination of his mentor, John Hunter, who died suddenly following an alteration in an academic committee after a 10-year history of anginal episodes. Albrecht von Haller described aortic plaques using the word 'atheroma', which is derived from the Greek word aθhra, meaning gruel, to indicate the yellow mush that effuses between the muscular fiber and the intima. In 1815, Michel Eugène Chevreul extracted "cholesterol" from gallstones and named this substance from the Greek words χολη (bile) and stereoζ (solid). In 1843, John Vogel demonstrated that cholesterol is present in atherosclerotic plaques. In the following years, the first pathogenic theories for atherosclerosis were proposed by Carl Von Rokitansky, who developed the 'thrombotic theory', and by Rudolf Virchow, who developed the 'inflammatory theory'. The first experimental studies to validate these theories were conducted in 1909 by Nikolay Nikolaevich Anitschkow, who achieved experimental atherosclerosis induction in rabbits via the administration of a cholesterol-rich diet.

In the 1950s, the 'response to injury' theory was proposed, which stated that atherosclerosis is a reaction of the artery to an insulting stimulus. In 1970, Earl Philip Benditt demonstrated that atherosclerotic plaques have a monoclonal origin, thus triggering the development of the 'somatic mutation theory'.

In the following years, substantial experimental evidence indicated that mutation and genotoxic damage plays a major role in atherosclerosis and that environmental agents that induce DNA damage are atherogenic. As shown by De Flora et al. (1996), DNA damage is pathogenic for cancer when it occurs in proliferating epithelial tissue and for degenerative diseases, such as atherosclerosis, when it occurs in non-dividing perennial tissues (De Flora et al., 1996).

The World Health Organization (WHO) estimates that approximately 24% of environmental diseases is caused by environmental exposures that can be averted and that more than 2.6 million individuals worldwide die from chronic vascular diseases annually (WHO, 2006). Recent research has indicated that the increased prevalence of chronic vascular diseases is due to exposure to several different chemicals (Lind and Lind, 2012). The chemicals known to cause cardiovascular disease include persistent organic pollutants, such as polybrominated biphenyl ethers, dioxins, furans, esters of perfluorooctanoic acid, phthalates, bisphenol A and hydrocarbons (Lind et al., 2012), including polycyclic and monocyclic aromatic hydrocarbons and aliphatic hydrocarbons (Sjöberg Lind et al., 2013). These chemicals differ widely in their properties, reactivities and rates of metabolism and elimination from the body. However, an attribute shared by these chemicals is the ability to induce DNA alterations.

Increasing evidence indicates that human atherosclerosis is associated with DNA damage in both circulating and vessel-wall cells. Many of the most important risk factors associated with atherogenesis, such as smoking and diabetes mellitus, may induce DNA damage. For example, smoking causes bulky DNA adduct and oxidative DNA damage, inhibits DNA repair, and induces the production of advanced glycation and products, which cause DNA mutations (Izzotti et al., 1995). In addition, advanced glycation and products, which are highly abundant in diabetes, are involved in low-density lipoprotein (LDL) oxidation (Bucala et al., 1993) and elevated 8-oxoguanine (8-oxo-G) levels. Although direct damage from specific risk factors or environmental agents may contribute to DNA damage in atherosclerosis, the most likely triggers of damage are reactive oxygen species (ROS). Atherosclerosis is a process that starts early in an individual's life; however, atherosclerosis in adults is enhanced by various factors: (e.g., age, sex, hyperlipidemia, hypertension, *diabetes mellitus*, obesity, lack of physical activity, heredity) (Riccioni and Sblendorio, 2012). Several studies have demonstrated that common carotid intima-media thickness increases following radiotherapy to the head and neck (Gianicolo et al., 2010). In addition, the general population is exposed to polycyclic aromatic hydrocarbons (PAHs) from the environment through small respirable particles, water and food, as well as from the occupational environment (Jakovljević and Zužul, 2011). PAH exposure also has an important role in atherosclerotic etiopathology, particularly through the PAH-induced activities of biotransformation enzymes. PAHs from particulate matter (also containing bacterial contaminants, transition elements, salts, and carbonaceous material) may increase monocyte cell adhesion to human aortic endothelia and cytokine attenuation (Den Hartigh et al., 2010).

The purpose of this review is to present the current knowledge regarding the important roles of chemical and physical environmental carcinogens in atherosclerosis occurrence and development.

The pathogenic relevance of environmental mutagenesis in atherosclerosis

Mutagenic PAHs are ubiquitous environmental contaminants that mainly originate as a result of pyrolytic processes, from multiple sources, including cigarette smoke, vehicle exhaust emissions, and industrial processes (Hattemer-Frey and Travis, 1991), and induce various toxicological effects, such as carcinogenesis, atherogenesis, and teratogenesis (Miller and Ramos, 2001). PAHs exhibit toxicological effects through activation of the aryl hydrocarbon receptor (AHR) (Shimizu et al., 2000), which is a ligand-activated transcription factor regulating the expression of various genes involved in metabolism and carcinogenesis, including CYP1A1, CYP1A2, and CYP1B1 (Hankinson, 1995).

Other mutagenic compounds involved in atherosclerosis are lipid peroxide derivatives. Miyazaki et al. reported that FAS and stearoyl-CoA desaturase SCD are responsible for cholesterol esterification to produce oleoyl-CoA and palmitoyl-CoA, which is the detoxification pathway for free cholesterol. The transcriptional activities of genes regulated by LXRα, such as ABCA1, SREBP-1c, FAS, and SCD, are down-regulated by 3-methylcholanthrene, depending on the AHR. Accordingly, environmental exposure to PAHs is able to hamper cholesterol detoxification pathways. FAS and SCD produce oleoyl-CoA and palmitoyl-CoA, which are used for cholesterol esterification to detoxify the free cholesterol (Miyazaki et al., 2000). Furthermore, LXRα, which is a member of the nuclear hormone receptor superfamily, is activated by oxysterols (Lehmann et al., 1997). LXRα is abundantly expressed in the liver, adipose, kidney, intestine, lung, adrenals, and macrophages. LXRα acts as a cholesterol sensor to activate the genes that govern the transport, catabolism, and elimination of cholesterol (Repa and Mangelsdorf, 2000).

Thus, atherosclerosis is most likely induced by PAHs through the following mechanisms: PAH exposure causes an increased free cholesterol level in plasma because of LXR-target gene suppression by PAHs, which occurs via AHR. Cholesterol detoxification is inhibited by PAHs via the down-regulation of the FAS and SCD genes by PAHs via AHR. These molecular mechanisms most likely account for PAH-induced atherosclerosis.