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Review

# Current basis for discovery and development of aryl hydrocarbon receptor antagonists for experimental and therapeutic use in atherosclerosis

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ABSTRACT

The important role played by aryl hydrocarbon receptor activation in the pathophysiology of atherosclerosis induced by cigarette smoke exposure has spurred the clinical interest in the development of aryl hydrocarbon receptor antagonists with atheroprotective efficacy. A few aryl hydrocarbon receptor antagonists were developed but the lack of structural information regarding the receptor ligand binding domain resulted in several limitations in the pharmacological properties of these compounds including partial agonism, allosterism, non-selectivity, cytotoxicity and susceptibility to bioactivation. These limitations make the progress of preclinical and clinical assays with the available aryl hydrocarbon receptor antagonists difficult. There is a great interest in developing pure, competitive, selective, nontoxic and resistant to bioactivation aryl hydrocarbon receptor antagonists. Current technology permits the development of pharmacologically ideal antagonists based on the chemical features of the aryl hydrocarbon receptor ligand binding domain. According to these characteristics, chlorinated derivatives of *trans*-stilbene *meta*-substituted with electrophilic aromatic directing groups would be effective prototypes for pure, competitive, selective, nontoxic and resistant to bioactivation antagonists for such receptor.

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## 1. Introduction

The last four decades have been characterized by a substantial advance in the identification of toxicological and biological effects mediated by aryl hydrocarbon receptor (AhR), which was first reported as a cytosolic receptor for polycyclic aromatic hydrocarbons (Poland et al., 1976) involved in the regulation of target genes encoding for phase I and phase II enzymes from drug metabolism (Denison et al., 2011). Aryl hydrocarbon receptor is a ligand-dependent transcription factor that belongs to the superfamily of *basic helix loop helix/Per–Arnt–Sim* (bHLH/PAS) proteins, which are characterized by the presence of *basic helix loop helix* (bHLH) and *Per–Arnt–Sim* (PAS) domains (Abel and Haarmann-Stemmann, 2010). The *basic helix loop helix* domain from aryl hydrocarbon receptor is a N-terminal region involved in DNA binding while the *Per–Arnt–Sim* domain is a middle conserved motif that contains the degenerated subdomains *Per–Arnt–Sim* A (PAS-A) and

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*Per–Arnt–Sim* B (PAS-B) required for protein dimerization and ligand binding, respectively (Coumailleau et al., 1995). The *Per–Arnt–Sim* domain from aryl hydrocarbon receptor also contains a nuclear localization signal (NLS) that drives receptor translocation into the nucleus upon ligand binding (Ikuta et al., 1998). Finally, the C-terminal end of aryl hydrocarbon receptor encodes a glutamine-rich transactivation domain (TAD) that dimerizes with transcriptional co-activators during gene transduction (Rowlands et al., 1996).

Early studies on aryl hydrocarbon receptor were focused in characterizing adaptive responses to xenobiotics but recent evidences have pointed key regulatory roles played by the receptor in normal physiology and several diseases. Aryl hydrocarbon receptor mediates redox-proinflammatory events that lead to the development of atherosclerotic lesions upon cigarette smoke exposure (Hanieh, 2014). These evidences have spurred the clinical interest in using aryl hydrocarbon receptor antagonists as atheroprotective agents for active or passive smokers. However, the currently available antagonists present a few pharmacological limitations that preclude their clinical use. Here we provide an overview of the current basis for developing pharmacologically ideal aryl hydrocarbon receptor antagonists based on comparative homology with the receptor ligand binding domain.

## 2. Chemical and biological properties from aryl hydrocarbon receptor

Human aryl hydrocarbon receptor is a 96 kDa protein formed by 848 amino acids while the murine receptor has 805 amino acids and a molecular mass of 90 kDa (Burbach et al., 1992; Dolwick et al., 1993). As a constitutively expressed receptor in vertebrate cells, aryl hydrocarbon receptor mediates multiple functions in several biological processes including environmental toxicity, immune and inflammatory responses (Hanieh, 2014), vascular remodeling and atherogenesis (Wu et al., 2011).

The unbound aryl hydrocarbon receptor exists as a cytosolic complex containing two layers of heat shock protein 90 (Hsp90), one *p*23, one aryl hydrocarbon receptor-interacting protein (AIP) and one c-Src. The cytosolic aryl hydrocarbon receptor complex avoids uncontrolled receptor translocation into the nucleus, keeps the receptor in a high-affinity configuration for ligand binding (Abel and Haarmann-Stemmann, 2010) and protects the receptor against proteolytic degradation (Kazlauskas et al., 2000). Upon ligand binding, the aryl hydrocarbon receptor releases c-Src that triggers a non-genomic pathway in the cytosol (Dong et al., 2011). Ligand binding also exposes the nuclear localization signal from *Per–Arnt–Sim* domain. This exposed signal induces receptor translocation into the nucleus, where the layers of heat shock protein 90 are displaced from the receptor upon aryl hydrocarbon receptor nuclear translocator (ARNT) binding (Soshilov and Denison, 2008). The heterodimer formed by aryl hydrocarbon receptor and its nuclear partner (AhR/ARNT) binds to xenobiotic responsive elements (XRE) and regulates the expression of several genes. The classic target of the nuclear signaling underlying aryl hydrocarbon receptor activation is the transcription of monooxygenase 1A1 from cytochrome P450 (CYP1A1) (Abel and Haarmann-Stemmann, 2010; Hanieh, 2014). The cellular signaling underlying aryl hydrocarbon receptor activation is illustrated in Fig. 1A.

Cytochrome P450 monooxygenase 1A1 is one of the most important enzymes in inactivating xenobiotic substances that activate aryl hydrocarbon receptor signaling (Abel and Haarmann-Stemmann, 2010). The metabolism of such xenobiotic substances avoids their accumulation in body fat and the subsequent harmful effects resultant from aryl hydrocarbon receptor-mediated redox-proinflammatory signaling in several cell types including vascular and immunocompetent cells, hepatocytes, cardiomyocytes and fibroblasts. The main harmful effects promoted by accumulated aryl hydrocarbon receptor ligands include atherosclerosis, immunotoxicity, hepatotoxicity, cardiotoxicity, dermal toxicity, teratogenesis and carcinogenesis (Denison et al., 2011).

Natural ligands that activate aryl hydrocarbon receptor

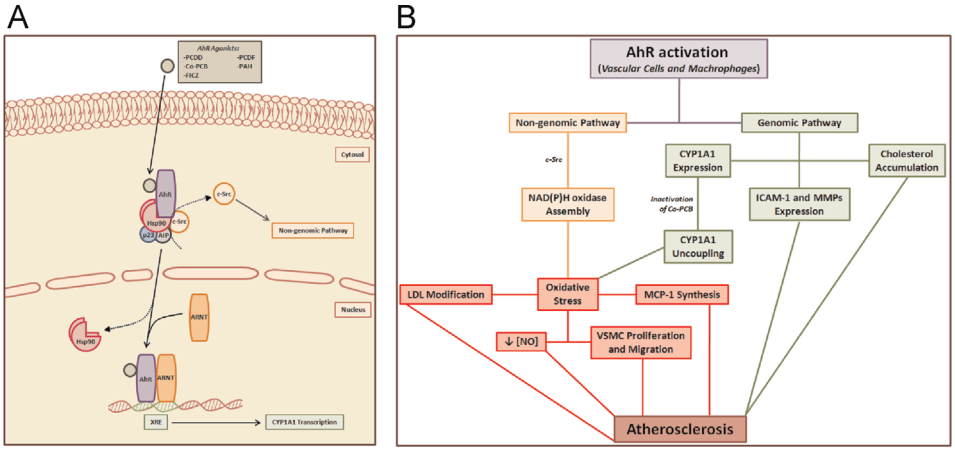


**Fig. 1.** Physiological and proatherogenic roles played by aryl hydrocarbon receptor (AhR) activation. (A) cellular signaling underlying the activation of aryl hydrocarbon receptor by agonists (PCDD, polychlorinated dibenzo-*p*-dioxins; PCDF, polychlorinated dibenzofurans; Co-PCB, coplanar polychlorinated biphenyls; PAH, polyaromatic hydrocarbons; FICZ, 6-formylindolo[3,2-*b*]carbazole). The unbound aryl hydrocarbon receptor is a cytosolic complex containing two layers of heat shock protein 90 (Hsp 90), one *p* 23, one aryl hydrocarbon receptor- interacting protein (AIP) and one c-Src. Upon ligand binding, aryl hydrocarbon receptor releases c-Src, which triggers a non-genomic pathway in the cytosol. Ligand binding also leads to receptor translocation into the nucleus, where the layers of heat shock protein are displaced from the receptor upon aryl hydrocarbon receptor nuclear translocator (ARNT) binding. The heterodimer formed by aryl hydrocarbon receptor and its nuclear partner (AhR/ARNT) binds to xenobiotic responsive elements (XRE) and regulates the transcription of monooxygenase 1A1 from cytochrome P450 (CYP1A1). (B) proatherogenic effects resultant from redox-proinflammatory pathways triggered by aryl hydrocarbon receptor activation. c-Src release to the cytosol upon ligand binding leads to NAD(P)H oxidase-derived reactive oxygen species accumulation in the vascular wall by inducing NAD(P)H oxidase assembly. Expression of cytochrome P450 monooxygenase 1A1 triggers endothelial oxidative stress due to the uncoupling of the monooxygenase during the inactivation of coplanar polychlorinated biphenyls. Vascular oxidative stress evoked by genomic and non-genomic pathways underlying aryl hydrocarbon receptor activation contributes to atherogenesis by impairing the endothelial bioavailability of nitric oxide (NO), modifying low-density lipoprotein (LDL) molecules in the subendothelial space, activating monocytes chemoattractant protein-1(MCP-1) synthesis in endothelial cells and inducing vascular smooth muscle cells (VSMC) proliferation and migration. Receptor activation also induces the expression of the adhesion molecule ICAM-1 in endothelial cells, the accumulation of cholesterol in macrophages and the expression of metalloproteinases (MMPs) involved in vascular smooth muscle cells migration. These mechanisms are directly involved in the pathophysiology of atherosclerosis.

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