Another Important Biological Function for the Aryl Hydrocarbon Receptor

David H. Sherr

For many years, the aryl hydrocarbon receptor (AhR) had been studied primarily for its contribution to environmental chemical-induced organ toxicity or carcinogenicity.1–3 The prevailing paradigm fashioned from these studies held that activation of the cytosolic AhR by any one of a variety of environmental pollutants (eg, planar polychlorinated biphenyls, polycyclic aromatic hydrocarbons, and dioxins) results in nuclear AhR translocation and transcriptional upregulation of prototypic target genes encoding cytochrome P450 enzymes (eg, CYP1A1 and CYP1B1).4–6 These enzymes are capable of metabolizing at least some of the environmental AhR ligands into toxic or mutagenic intermediates, thereby affecting biological outcomes. Although these studies were extremely important for defining the AhR as an environmental ligand-induced transcription factor and in mapping out portions of the AhR signaling pathway, they did not directly provide evidence of the “normal” physiological function of this evolutionarily conserved7 protein. However, in the last few years, it has become evident that the AhR is involved in several critical cellular functions, including but not limited to regulation of normal and neoplastic cell growth,8–12 invasion,13–18 and apoptosis.19–23 Most recently, an important role for the AhR in the development or function of T-cell subsets that mediate or regulate autoimmunity and tumor immunity, ie, helper T cells (Th17) and regulatory T cells, has been demonstrated.24–28 Now, Wu et al demonstrate yet another important immune system–related function of the AhR, regulation of macrophage-dependent inflammation contributing to atherosclerosis.

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Previous studies performed by Vogel et al provided important information on the effects of AhR activation in monocytes/macrophages.29,30 Specifically, they demonstrated that, in a macrophage cell line, activated AhR physically interacts with the RelB subunit of nuclear factor-κB, a well-known contributor to inflammatory processes, and induces production of inflammatory cytokines and extracellular matrix-degrading matrix metalloproteinases. Their demonstration that 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (dioxin) induces phenotypic changes characteristic of foam cells provided evidence that the AhR, activated either by some endogenous ligand or by environmental ligands such as TCDD or polycyclic aromatic hydrocarbons in cigarette smoke, plays a role in the formation of atherosclerotic plaques. Here, Wu et al31 extend these studies to demonstrate, very clearly, that AhR activation does indeed contribute to the formation of atherosclerotic plaques in apolipoprotein E−/− mice whether or not mice are fed an atherogenic high-fat diet. Moreover, they demonstrate that the likely signaling pathway leading from AhR activation to atherosclerotic plaque formation involves induction of matrix metalloproteinase-12, the proinflammatory cytokines/chemokines interleukin-8 (IL-8) and keratin chemoattractant, activation of CXC chemokine receptor (a receptor for several inflammatory molecules, including IL-8 and keratin chemoattractant), and ultimately production of the CXCR2 target gene VEGF (Figure). These studies were performed in the context of exposure to TCDD or the complex chemical mixture found in cigarette smoke extract. As such, they provide, for the first time, a molecular and cellular pathway that may account for the association between exposure to TCDD or cigarette smoke and increased risk of atherosclerosis. Just as importantly, these studies, together with those demonstrating AhR-regulated, Th17-mediated inflammation, extend the prevailing paradigm fashioned from these studies held that activation of the cytosolic AhR by any one of a variety of environmental pollutants (eg, planar polychlorinated biphenyls, polycyclic aromatic hydrocarbons, and dioxins) results in nuclear AhR translocation and transcriptional upregulation of prototypic target genes encoding cytochrome P450 enzymes (eg, CYP1A1 and CYP1B1).4–6 These enzymes are capable of metabolizing at least some of the environmental AhR ligands into toxic or mutagenic intermediates, thereby affecting biological outcomes. Although these studies were extremely important for defining the AhR as an environmental ligand-induced transcription factor and in mapping out portions of the AhR signaling pathway, they did not directly provide evidence of the “normal” physiological function of this evolutionarily conserved protein. However, in the last few years, it has become evident that the AhR is involved in several critical cellular functions, including but not limited to regulation of normal and neoplastic cell growth, invasion, and apoptosis. Most recently, an important role for the AhR in the development or function of T-cell subsets that mediate or regulate autoimmunity and tumor immunity, ie, helper T cells (Th17) and regulatory T cells, has been demonstrated. Now, Wu et al demonstrate yet another important immune system–related function of the AhR, regulation of macrophage-dependent inflammation contributing to atherosclerosis.

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Figure. A model of AhR control of vascular inflammation. AhR activation in vascular macrophages by environmental ligands (TCDD, polycyclic aromatic hydrocarbon in cigarette smoke) leads to upregulation of matrix metalloproteinase-12 (MMP-12), monocyte chemoattractant protein-1 (MCP-1), IL-8, and keratin chemoattractant (KC). Matrix metalloproteinase-12 contributes to extracellular matrix (ECM) degradation; MCP-1 and IL-8 recruit and activate inflammatory cells to vascular endothelium; and IL-8 and KC activate the CXCR2 chemokine receptor on macrophages or infiltrating neutrophils, resulting in transcriptional upregulation of vascular endothelial growth factor (VEGF) and increased vascular endothelial cell growth. Collectively, the coordinated upregulation of these mediators of inflammation contributes to formation of the atherosclerotic plaque.
mediated inflammatory responses, strongly support the hypothesis that the AhR plays a central role in both T-cell and macrophage-mediated inflammation in several tissues. Furthermore, they suggest the intriguing possibility that the AhR may serve as a therapeutic target for downregulation of vascular inflammatory responses. As such, this work from the Vogel laboratory helps transport the AhR from the circumscripted realm of a "sensor of toxin exposure" to the more generalized and perhaps more clinically relevant world of "mediator of pathological inflammation."

References


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