Ah receptor: xenobiotic response meets inflammation

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AhR mediates a broad range of biological responses to environmental chemicals, including suppression of immune functions. In this issue of Blood, Lawrence and colleagues demonstrate that AhR is responsible for the anti-inflammatory activity of new antiallergic drug candidates, likely by blocking dendritic-cell function to generate proinflammatory T-helper cells.

Xenobiotic response is a set of genetic programs evolutionarily specialized to defend against xenobiotics—chemicals that humans encounter in the environment. Xenobiotic response is controlled by a group of ligand-activated transcription factors known as xenobiotic-activated receptors (XARs), such as the aryl hydrocarbon receptor (AhR). To mitigate chemical insults, XARs integrate a broad spectrum of biological functions ranging from chemical sensing, drug metabolism, and antioxidative function to immune response, inflammation, and tissue repair, all by regulating the expression of key mediators of a response. The interplay between XARs and immune/inflammatory functions is a particular one: very often, it provides critical protection against noxious chemicals and some microbes, and on occasion, it contributes to the pathogenesis of tissue damage and disease. In both scenarios, it serves as a potential therapeutic target.

AhR was initially identified as the receptor mediating the induction of CYP1A1, the P450 mono-oxygenase critical for metabolic activation of benzo(a)pyrene and 3-methylcholanthrene, carcinogens present in tobacco smoke and charcoal-broiled meat.1 AhR gained even wider notoriety after it was found to be required for most, if not all, adaptive and toxicological responses to a large group of widespread, man-made, environmental contaminants—the chlorinated aromatic hydrocarbons, 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD, dioxin) is the most potent agonist of AhR, causing a wide range of biological responses including thymic involution and suppression of immune and inflammatory responses, providing a direct link between AhR and immune/inflammatory functions. Although AhR ligands have been developed as antivirus drugs,2 the therapeutic potential of AhR in immune and inflammatory diseases has not been explored until now.

In this issue of Blood, Lawrence and colleagues describe a series of experiments demonstrating that AhR is required for both the in vivo and in vitro anti-inflammatory effects of a drug candidate, VAF347, which inhibits allergic lung inflammation. The initial clue of a connection between AhR and the immune-modulating drug came unexpectedly. In a search for molecular targets via RNA chip analysis, VAF347 was found to induce AhR target genes AhRR, CYP1B1, and TipARP, in addition to down-regulating IL-6 as expected; it also altered expression of several other genes in immature and anti-CD40–activated, monocyte-derived dendritic cells (DCs), which are critical in the development of T-helper (Th) cells and immune responses. Through a series of molecular and biochemical studies, the authors prove that VAF347 is indeed an agonist of AhR: it binds to AhR with a high affinity, activates AhR in vitro, and induces CYP1A1 in human peripheral monocytes, similarly to the prototypical agonist of AhR, TCDD. Conversely, TCDD was shown in the studies to inhibit IL-6 production by mature monocyte-derived DCs and to block DC-mediated autologous T-cell proliferation, in parallel with VAF347. On the other hand, VAG005, an inactive derivative of VF347, was only weakly bound to AhR and had no effect on the functions measured. These findings reveal a clear correlation between AhR binding and the immune-modulating activity of the agents in vitro; a causal relationship between the 2 was subsequently proven using genetic interventions. In cultured cells, a truncated AhR (AhR515, a dominant-negative form) was introduced into the human monocyte cell line MonoMac1 (MM1); overexpression of AhR515 was found to block VAF347 or

References


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TCDD-dependent inhibition of IL-6 expression in the cells. More importantly, AhR knockout mice with experimentally induced allergic lung inflammation were nonresponsive to VAG539, a derivative of VAF347 that efficiently converts to VAF347 in vivo for anti-inflammatory activity as observed in the wild-type mice. Together, these findings show that AhR is required for the immune-modulating function of the drugs by inhibiting DC function.

Initiation and maintenance of an immune response require the maturation of effector Th cells, which requires the physical interaction of naive T-cell precursors with antigen-carrying DCs. DCs provide MHC and CD86 molecules necessary for contact-mediated interactions; they also provide cytokines, such as IL-6, influencing the type and function of Th cells produced that, in turn, affect the development of inflammatory and immune diseases. Because VAF347 inhibits the expression of IL-6, CD86, and HLA-DR by DCs, the current study suggests a working model in which VAF347 activates AhR to inhibit the expression of IL-6 and other molecules in DCs necessary for Th maturation may provide a molecular approach to the latter question. Nonetheless, by demon-strating a causal relationship between AhR activation and the anti-inflammatory activity of VAF347, the authors of the current paper open a new avenue for anti-inflammatory drug development that focuses on AhR, which, in principle, is applicable to other XARs, such as PXR and Nrf2, that also cross-interact with immune and inflammatory pathways.

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Teasing out monocyte trafficking mechanisms
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Monocytes comprise approximately 5% of the blood leukocyte population and play critical roles in both innate and adaptive immunity. Circulating monocytes exhibit developmental plasticity and are able, upon entering tissues, to differentiate into dendritic cells (DCs) and macrophages. Under steady-state conditions, a subset of monocytes contribute to the homeostatic maintenance of resident DC and macrophage populations in the periphery. In the presence of an inflammatory stimulus or infection, the inflammatory subset of monocytes rapidly become recruited to affected tissues, where they differentiate and provide large numbers of local macrophages and DCs. These ultimately make their way to the secondary lymphoid organs by trafficking through the tissues and entering the afferent lymphatics. During inflammation, circulating monocytes can also traffic directly to the lymph nodes by crossing the high endothelial venules via a so-called remote-control mechanism involving lymph-transported chemokines.
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