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Review

Allergic responses and aryl hydrocarbon receptor novel pathway of mast cell activation☆

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ABSTRACT

The activation of the transcription factor aryl hydrocarbon receptor (AhR) is modulated by a wide variety of xenobiotics and ligands deriving from products of metabolism. The study of the contribution of AhR to allergic diseases has gained much interest in recent years. Here we discuss the role that environmental factors and metabolic products, particularly acting on AhR-expressing mast cells (MCs), could have in the development of local allergic/atopic response. Thus, this review will cover: a brief overview of the AhR mechanism of action in the immune system; a description of different AhR ligands and their effects to IgE-mediated MC activation in the allergic response, with particular attention to the role of IL-17; a discussion about the potential involvement of AhR in immune tolerance; and a conclusion on human diseases in which direct AhR activation of MC might have a major impact.

1. Introduction: AhR mechanism of activation in the immune system

Geographical areas where autoimmune and allergic diseases are prevalent often coincide with the most industrialized regions of the globe. Toxicologists have associated the abundance of low molecular weight pollutants in these areas with a major incidence of risk developing these diseases (Vernon et al., 2012). In particular, the presence of airborne low molecular-weight aromatic molecules, deriving from several human activities such as industrial combustion processes, city smog, and cigarette smoke, can all contribute to the development of severe acute reactions, such as allergy and anaphylaxis, or chronic conditions, such as asthma, dermatitis, or autoimmunity (Peden and Bush, 2013). However, the consequences of low molecular-weight chemical exposure remain even more complicated, because these compounds are constantly present in everyday life – found in products ranging from cosmetics, to fertilizers and food – and have the property to form protein adducts, namely haptenize antigens (Esser et al., 2009).

The major challenge for immunologists is to explore the mechanisms that govern the genesis of these autoimmune and allergic pathologies, and to clarify how the innate immune response cooperates with the adaptive response to give rise to (and resolve) inflammation, cellular, and tissue damage. The aryl hydrocarbon receptor (AhR) was initially characterized as being important in immunity because of its unique properties related to the immunomodulation of dioxin, a well-known immunocytotoxic compound (Sun et al., 2004). In addition to this, other studies reported that dioxin is a potent immunosuppressive chemicals (Kerkvliet et al., 2009), suggesting that AhR-associated disease could be dependent on the lack of tolerance or of regulatory mechanisms.

AhR is commonly considered a cytosolic sensor of xenobiotics and products of cellular metabolites, which becomes activated after the interaction with its ligand(s), translocates to the nucleus, and activates a series of pro- and anti-inflammatory genes, historically grouped under the acronym DRE (dioxin responsive elements) (Ma, 2001). In the last 15 years we have witnessed an increasing excitement around the study of AhR, the results of which have revealed even broader implications for AhR-mediated functions in modulating an immune response, such as its ability to respond to a large number of chemicals and environmental factors beyond dioxin itself (Table 1).

Abbreviations: AhR, aryl hydrocarbon receptor; BAL, bronchoalveolar lavage fluid; COPD, chronic obstructory pulmonary disease; DRE, dioxin responsive element; FcεRI, high affinity receptor for IgE; FICZ, 6-formylindolo[3,2-b]carbazole; MC, mast cell.

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Table 1
Most studied ligands of AhR.[a]

Endogenous	*Tryptophan photoproducts*: 6-formylindolo[3,2-b]carbazole (FICZ), kynurenine, indigo dye, indirubin *Product of heme metabolism*: bilirubin *Eicosanoid with anti-inflammatory properties*: lipoxin A4, prostaglandin G *In lung tissues*: 2-(10H-indole-30-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE)
Environmental	*From combustion of organic material*: 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), benzo(a)pyrene, 3-methylcholanthrene, benzanthracenes, benzoflavones
Dietary	*In many Brassicaceae* (*e.g.* cabbage): indol-3-carbinol *In apples and onions*: quercetin *In red wine*: resveratrol *Spice of Indian cuisine*: curcumin
Synthetic	3-[2-(2-Phenylethyl) benzoimidazole-4-yl]-3-hydroxypropanoic acid (M50354), [4-(3-chloro-phenyl)-pyrimidin-2-yl]-(4-trifluoromethyl-phenyl)-amine (VAF347)

[a] For an omnicomprehensive list, see Refs.: Esser et al. (2009), Denison and Nagy (2003), and Kerkvliet (2009).

AhR is widely expressed in the cells of both the innate and adaptive immune system, suggesting a different role of AhR in different pathological settings. In this review, we focus on the role of AhR in allergic settings, with a particular overview of AhR and IL-17. Furthermore, based on the recent discovery of AhR in mast cells (MCs) (Maaetoft-Udsen et al., 2012; Sibilano et al., 2012a; Zhou et al., 2013), we discuss on one hand, the role of MC costimulation through the simultaneous engagement of the antigen (Ag)-bound high affinity receptor for IgE and AhR, and on the other, the implication of AhR-driven responses in MCs for allergy and chronic diseases. In conclusion, we also briefly summarize and discuss how AhR activation can be considered a promising target to induce immunotolerance for allergic-related responses, by inducing regulatory T cell (Treg) expansion and/or MC anergy.

2. AhR signaling: an overview

Although the structure of AhR:ligand complexes has not been yet crystallized and characterized, in the last decade many efforts have been made to clarify the function and the mechanisms of AhR activation in the cell. AhR is a cytosolic receptor of xenobiotic and natural chemicals and a member of the highly conserved family of bHLH-PAS transcription factors (Sogawa and Fujii-Kuriyama, 1997; Denison et al., 2002). In the cytosol, AhR is chaperoned by Hsp90, ARA9 and p23, which together act to regulate its translocation to the nucleus. The process of nuclear translocation begins when hydrophobic AhR ligands that pass through the cell membrane by diffusion bind AhR, which in turn causes a conformational change in the protein. Then AhR:ligand rapidly enter the nucleus, and subsequently bind to the co-activator ARNT leading to the transcription of DRE (Hahn et al., 2009; Abel and Haarmann-Stemmann, 2010). Some well characterized DREs include genes coding for proteins involved in the process of detoxification such as cytochrome P450 enzymes (CYP1A1, CYP1A2, CYP1B1), glutathione S-transferases, uridine diphospho-glucuronosyltransferases, NAD(P)H-dependent quinone oxydoreductase-1, aldehyde dehydrogenase 3A1 (Shen and Whitlock, 1992; Nebert et al., 2000; Stejskalova et al., 2011). Interestingly, Hsp90 and more recently p21, have been associated with enhanced allergic inflammation (Joseph and Kaplan, 2005) or activation of MC degranulation (Allen et al., 2009).

Protein:protein interactions are necessary for AhR activity in the nucleus and interaction with signal transducer and activators of transcription (STATs), the retinoic acid receptor (RAR), the estrogen receptor (ER) and nuclear factor-κB (NF-κB) have been reported (Hämäläinen et al., 2007; Klinge et al., 2000; Andreola et al., 1997).

3. AhR, IL-17 and allergy, revving things up

Presently, the impact of AhR activation on the allergic process is a completely open question. It is well established that the onset of allergic disorders, which affect approximately 30% of the population in developed countries, has a genetically determined component as well as an environmental component, caused by exposure to pollutants (Busse and Lemanske, 2001; Oboki et al., 2008). These disorders are associated first with potent acute and then chronic inflammation, characterized by increased numbers of eosinophils, B cell-driven production of IgE, and activation of MCs. In allergic asthma – a chronic airway disease that affects million people worldwide and is characterized by strong inflammation, airway hyperresponsiveness, and pulmonary fibrosis – higher numbers of IL-17 producing T cells have been reported to be present in the lungs, sputum, bronchoalveolar lavage (BAL) fluids or sera from asthmatics (Molet et al., 2001), and the levels of IL-17 correlated with the degree of severity of airway hypersensitivity in asthmatic patients (Barczyk et al., 2003). IL-17 is currently considered one of the hallmarks of airway inflammation since it can potentiate the activation of local structural cells of the airway, such as bronchial fibroblasts (IL-6, IL-8, IL-11 and CXCL1), epithelial cells (beta-defensin-2, ICAM-1, IL-8, CXCL1, CCL20, G-CSF, MUC5B and MUC5AC), and smooth muscle cells (IL-6 and IL-8) (Oboki et al., 2008; Cua and Tato, 2010).

Chronic obstructive pulmonary disease (COPD) is another inflammatory disease of the airways, and interestingly, it shares many features with allergic asthma based on overlapping clinical characteristics, epidemiologic studies, and the association of genes common to both diseases (Barnes, 2008; Kaneko et al., 2013). COPD is marked by progressive and non-reversible tissue damage due to emphysematic changes in the lung, and it is both serious and prevalent, being the fourth cause of death in Western countries. IL-17 is clearly detectable in the BAL fluid of COPD patients and its function has been mainly attributed to the upregulation of local matrix metalloproteinase (MMP) expression and the recruitment of innate immune cells (Brusselle et al., 2011).

Interestingly, inhalation of airborne pollutants or cigarette smoke has been identified as one factor causing susceptibility to both asthma and COPD. Airborne pollutants (*i.e.* from combustion deriving from industrial processes and organic materials; exhaust gas smoke) and cigarette smoke are complex mixes containing low molecular-weight organic compounds, able to contribute to the induction of and, even more importantly, to the modulation of an immune response. AhR mediates the effect of these toxins through the production of a series of pro-inflammatory mediators, including IL-17 (Stockinger et al., 2011).

The main question for immunologists is to understand how AhR can drive the ongoing allergic/inflammatory process and the extent by which this process is coordinated by cells of the innate and acquired immune system.

To offer a historical perspective, the first understandings of the role of AhR in the immune system came from studies from Veldhoen et al. (2008), which showed that IL-17 expressing $CD4^+$ T cells (Th17) express relatively high levels of AhR compared to other $CD4^+$ T cells including Tregs. On one hand, AhR caused expansion of Th17 subset *in vivo*, interfering with Treg development (activated by FICZ (Quintana et al., 2008)), and it is responsible for production of the Th17-associated cytokine IL-22 (Qiu et al., 2012). This process has been associated with an exacerbation of the specific pathology in murine models of autoimmune disease, such as

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