



Contents lists available at ScienceDirect

Molecular Immunology

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## Review

# Allergic responses and aryl hydrocarbon receptor novel pathway of mast cell activation<sup>☆</sup>

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## ARTICLE INFO

### Article history:

Received 9 December 2013

Received in revised form 20 February 2014

Accepted 25 February 2014

Available online xxx

### Keywords:

Mast cells

Aryl hydrocarbon receptor

Allergy

FICZ

IL-17

## 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.

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## 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 fer-

tilizers 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 obstructive pulmonary disease; DRE, dioxin responsive element; FcεRI, high affinity receptor for IgE; FICZ, 6-formylindolo[3,2-b]carbazole; MC, mast cell.

<sup>☆</sup> This article belongs to Special Issue on Mast Cells and Basophils in Innate and Acquired Immunity.

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<http://dx.doi.org/10.1016/j.molimm.2014.02.015>

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**Table 1**  
Most studied ligands of AhR.<sup>a</sup>

|               |                                                                                                                                                                                                                                                                                                                                                         |
|---------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Endogenous    | <i>Tryptophan photoproducts:</i><br>6-formylindolo[3,2-b]carbazole (FICZ), kynurenine, indigo dye, indirubin<br><i>Product of heme metabolism:</i> bilirubin<br><i>Eicosanoid with anti-inflammatory properties:</i> lipoxin A4, prostaglandin G<br><i>In lung tissues:</i><br>2-(10H-indole-30-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE) |
| Environmental | <i>From combustion of organic material:</i><br>2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), benzo(a)pyrene, 3-methylcholanthrene, benzantracenes, benzoflavones                                                                                                                                                                                          |
| Dietary       | <i>In many Brassicaceae (e.g. cabbage):</i> indol-3-carbinol<br><i>In apples and onions:</i> quercetin<br><i>In red wine:</i> resveratrol<br><i>Spice of Indian cuisine:</i> 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)                                                                                                                                                                                               |

<sup>a</sup> 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-Stemann, 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- $\kappa$ B (NF- $\kappa$ B) 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<sup>+</sup> T cells (Th17) express relatively high levels of AhR compared to other CD4<sup>+</sup> 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

experimental immune encephalomyelitis (EAE, a murine model of multiple sclerosis), but these findings have also been extended to other models of diseases, including arthritis, rhinitis and gut immunity (Esser et al., 2009). On the other hand, AhR activation can also induce Treg expansion in EAE (Duarte et al., 2013). Indeed, dioxin administration confers protection from EAE, not as a *de novo* Treg generation, but as a consequence of the inhibition of Th17 cell differentiation. These data are conflicting with other findings showing that *in vitro* Th17 differentiation in the presence of AhR agonists, including dioxin, promoted IL-17 and IL-22 expression, but did not induce Treg differentiation (Duarte et al., 2013). Such effect can be ascribed to the presence the *in vivo* microenvironment which could influence Th17 differentiation, differently from *in vitro* settings. More recently, the attention has been focused on the process that leads to AhR activation and AhR-dependent IL-17 production in cells of the innate immune system, such as TCR $\gamma\delta$  T cells (Martin et al., 2009). The underlying concept is that simultaneous exposure to pathogens and AhR ligands at the level of mucosal barriers of the skin or the gastrointestinal tract can influence the first phases of the immune response, inducing a marked IL-17 response from the reservoir of tissue-resident TCR $\gamma\delta$  T cells (Stange and Veldhoen, 2013). Interestingly, in the past two years, several groups have investigated the distribution, activation, and effect of IL-17-dependent-IL-13 induction (partly responsible of airway remodeling) on allergic inflammation in the airways, offering a novel perspective on the understanding of how innate cells contribute to the allergic inflammation process (Kinyanjui et al., 2013; Urboniene et al., 2013). In this general view, it is worth mentioning that a link between the initiation of the allergic process and the cross-talk between the innate and the acquired response is still missing or largely unclear.

In the last 2 years we and other groups (Maaetoft-Udsen et al., 2012; Sibilano et al., 2012a; Zhou et al., 2013) have reported the presence and the functional activation of AhR in MCs. As we will summarize and discuss in the following section, these studies set the stage for further investigation of previously unappreciated roles of MCs as sensors of the microenvironment.

#### 4. AhR and MCs

Upon activation, MCs can produce a broad spectrum of inflammatory cytokines, chemokines, lipid compounds and vasoactive amines, which autoconfer the peculiar capacity to respond to a wide range of external stimuli and drive the immune response (Galli et al., 2008; Gri et al., 2012). The idea that MCs can also translate the immunological effect of AhR activation is extremely new and has been investigated in only 3 papers in the last 2 years.

In 2012, Maaetoft-Udsen et al., reported the presence of AhR in the rat RBL2H3 MC line (Maaetoft-Udsen et al., 2012). Upon stimulation with the AhR agonists, kynurenin and kynurenic acid (both endogenous ligands, derived from the metabolism of tryptophan and known for their immuno-modulatory properties), RBL2H3 cells showed calcium-dependent enhanced production of IL-6, which is a well known downstream target of AhR activation in many cell types (DiNatale et al., 2010). Two other studies published in 2012 and 2013, report the presence of and discuss the function of AhR activation in mouse (Zhou et al., 2013) or both mouse and human MCs (Sibilano et al., 2012a). The particular aspect of MC biology investigated in these papers was the effect of AhR activation on cytokine production, maturation and homeostasis, in the presence of the endogenous ligand 6-formylindolo[3,2-b]carbazole (FICZ) – a product of the metabolism of tryptophan. In both cases AhR activation was studied alone or together with canonical IgE/antigen (Ag) activation. Similar to Th17 cells, MCs express AhR at high levels, but the protein is suddenly degraded upon ligation with its

agonists (Abel and Haarmann-Stemmann, 2010). After ligation of the AhR ligand FICZ, MCs potentiate the classical IgE/Ag-dependent response by enhancing the production of histamine, LTC<sub>4</sub>, and the pro-inflammatory cytokines IL-6 and IL-13, through the activation of PKC $\delta$  and ERK. Another important MC feature, remarked in both papers, is the MC production of reactive oxygen species (ROS) in response to AhR activation, underlining a potential impact of AhR ligands – through MCs – on blood vessels and on the nervous system (Swindle and Metcalfe, 2007). Moreover, Zhou et al. reported a role for AhR in the maturation and homeostasis of MCs, showing that AhR-null MCs are characterized by impaired production of IL-13 and mitochondrial damage.

Notably, different MC responses can be achieved depending on the duration of FICZ stimulation. A single dose (that is, singular AhR activation) boosted proinflammatory features of MC activation (histamine and IL-6 production), whereas prolonged exposure shifted MCs toward IL-17 production and impaired degranulation (Sibilano et al., 2012a).

MCs can also produce IL-17 and are the major IL-17 *in situ* reservoirs in some diseases. In Sibilano et al., the authors reported MC IL-17 production resulting from prolonged exposure to FICZ in both mouse and human *in vitro* cultured MCs and the presence of IL-17<sup>+</sup> MCs in the lung parenchyma of COPD patients (likely deriving from the prolonged exposure to cigarette smoke). Different from cells of the Th17 lineage, MCs do not use the transcription factor RORC to produce IL-17 in response to FICZ, a property which opens the perspective that MCs are able to use their own unique pathway to induce IL-17 transcription upon AhR activation (Sibilano et al., 2012a).

It is important to note that both studies employed the AhR agonist FICZ, which is at present considered the strongest agonist for AhR. However, the two studies differed on the concentration used – high for Sibilano et al., lower for Zhou et al., indicating that differences in MC activation are likely to occur, even during the activation with the same agonist.

Lastly, the impact of non-endogenous ligands (*i.e.* dioxin) or of the combination of endogenous and non-endogenous ligands has not been tested on MCs yet, suggesting an opportunity to explore another aspect of AhR-mediated MC activation according to the molecular etiology (*e.g.* inhalation of pollutants might worsen the outcome of the disease combined with the prevalence of some dietary components) of the allergic disease.

Fig. 1 summarizes recent findings in MC signaling and activation and underlines the difference between acute and “chronic” or prolonged exposure to FICZ.

#### 5. AhR and tolerance

In the previous section we described the major pro-inflammatory effects of AhR ligands in many pathological settings, mainly achieved by the presence of IL-17 from T cells, and through the boosted production of MC proinflammatory mediators, including IL-6, IL-13 and IL-17 itself. In this view, the role of AhR activation may be to eliciting a pro-inflammatory response of the effector cells involved in the allergic response. There is nonetheless, a consistent body of literature showing that AhR activation can sustain local tolerance acting in the opposite way from the development of the inflammatory response. It would be worth speculating that the balance between the pro- and the anti-inflammatory responses might reflect the recruitment and the number within the inflamed tissue, not only of MCs but also of different cell types, which can respond to AhR-ligands and directly influence MC activation and response, such as dendritic cells, macrophages and Tregs. In this regards, the outcome of ligand:AhR interaction has been best characterized in Tregs. Several papers have shown that direct expansion

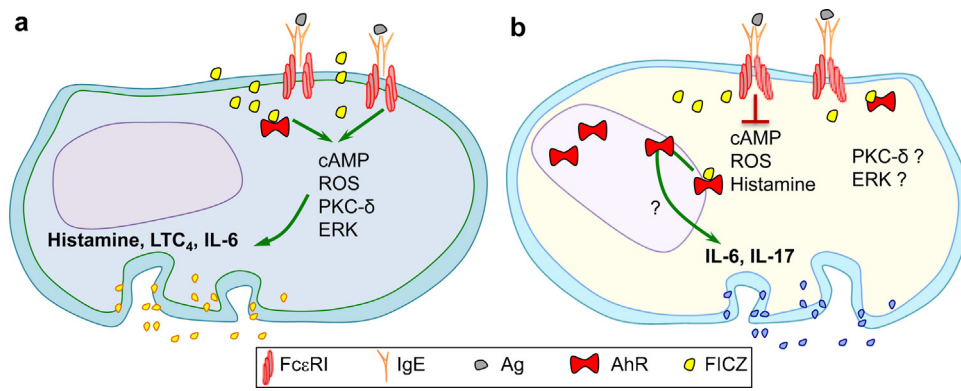


Fig. 1. Short-term (a) and long-term (b) MC responses by AhR stimulation with FICZ.

of Foxp3<sup>+</sup> Tregs occurs after AhR translocation to the nucleus, though indirect induction by AhR-triggered dendritic cells has been described too (Kerkvliet et al., 2009; Hauben et al., 2008; Singh et al., 2011; Weiner et al., 2011). A study reporting AhR-mediated activation in Tregs in the context of allergic responses showed that AhR ligation improved disease outcomes in an animal model of peanut allergy, by inducing a shift from a canonical Th2 response to instead a Treg expansion (Schulz et al., 2011). AhR-derived Treg expansion could be one of the mechanisms responsible for tolerance, perhaps through direct action on MC activation. As we have previously discussed, Tregs can inhibit MC effector functions, namely degranulation and the release of preformed mediators. OX40L-engagement on MCs by its counterpart OX40 on Tregs is at present the only known contact mechanism by which Tregs directly inhibits MC degranulation (Gri et al., 2008; Sibilano et al., 2012b). However, our most recent observations add another element to this complex puzzle. Prolonged or long term stimulation of AhR confers anergy to MCs, reducing degranulation *in vitro* and the gravity of anaphylaxis *in vivo*, thus contributing to the overall amelioration of allergic acute reactions. However, more studies are required to clarify the single or the combined contribution of different AhR ligands to the expansion of Tregs and to determine if from a therapeutic perspective, AhR-induced MC anergy can be considered an alternative treatment to Treg expansion for allergic reactions.

## 6. Concluding remarks

It is emerging now that a single compound is able to shift MCs toward IL-6, IL-17, and IL-13 production by specifically activating AhR. The consequences of this event could be evaluated in diseases where MCs represent a potent source of proinflammatory cytokines and exposure to AhR ligands is likely to occur. For instance, MCs, alone or together with other non-T cells, are the predominant IL-17<sup>+</sup> cells in psoriatic lesions in human skin (Lin et al., 2011) and atherosclerotic plaques (de Boer et al., 2010), as well as in rheumatoid arthritis, osteoarthritis, and spondyloarthritis synovium (Hueber et al., 2010; Suurmond et al., 2011; Noordenbos et al., 2012). Consequently, the role of MCs in orchestrating inflammatory responses through AhR activation may potentially be extended to all pathologies where tissue/organ homeostasis is broken by an inflammatory, MC-rich infiltrate, likely accessible by AhR ligands derived from tryptophan metabolism, such as inflammatory bowel disease (Monteleone et al., 2011), eosinophilia-myalgia syndrome (Smith and Garrett, 2005) and endometriosis (Sugamata et al., 2005; Rier et al., 1993).

## Acknowledgements

R.S. is supported by the Lucile Packard Foundation for Children's Health and the Stanford NIH/NCRR CTSA award number UL1 RR025744. C.P. is supported by the Italian Ministry of Health, AIRC (Associazione Italiana Ricerca sul Cancro), Ministero dell'Istruzione, Università e Ricerca (PRIN 2009) and LR.26 FVG. G.G. is supported by Fondazione Cariplo, Milan and FIRB accordi di programma 2011 pr. RBAP11ETKA.007 "Nanotechnological approaches for tumor therapeutic".

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