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Regulation of the immune response by the aryl hydrocarbon receptor

Cristina Gutiérrez-Vázquez[1] and **Francisco J. Quintana**[1,2]

[1]Ann Romney Center for Neurologic Diseases, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[2]The Broad Institute of MIT and Harvard, Cambridge, MA, USA

Abstract

The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor that is activated by small molecules provided by the diet, microorganisms, metabolism and pollutants. AhR is expressed by a number of immune cells, and thus, AhR signaling provides a molecular pathway that integrates the effects of the environment and metabolism on the immune response. Studies have shown that AhR signaling plays important roles in the immune system in health and disease. As its activity is regulated by small molecules, AhR also constitutes a potential target for therapeutic immunomodulation. In this review we discuss the role of AhR in the regulation of the immune response in the context of autoimmunity, infection and cancer, as well as the potential opportunities and challenges of developing AhR targeted therapeutics.

INTRODUCTION

The Aryl Hydrocarbon Receptor (AhR) is a member of the Pern-Arnt-Sim (PAS) superfamily of transcription factors that are involved in sensing environmental signals such as changes in the circadian rhythm (BMAL1 and BMAL2), oxygen tension or redox potential (HIF-1α, HIF-2α, HIF-3α) among others (Kewley et al., 2004). In response to activation by a ligand, AhR translocates from the cytoplasm to the nucleus where it controls the transcription of a wide variety of target genes. Although AhR was initially recognized as the mediator of the toxic effects of dioxins, multiple physiologic ligands are provided by the diet, the commensal flora and also the host metabolism. The identification of these natural ligands and the analysis of AhR-deficient mice has revealed important physiological roles for AhR.

Both genetic and environmental factors contribute to the regulation of the immune system in autoimmunity, infections and cancer. Although significant advances have been made in the identification of the genetic control of the immune response, limited information is still

Corresponding author: Francisco J. Quintana, Ann Romney Center for Neurologic Diseases, Harvard Medical School, 60 Fenwood Road, Boston, MA 02115, USA., fquintana@rics.bwh.harvard.edu, Tel.: +1 (617) 525-5317, Fax: +1 (617) 525-5325.

available regarding the contribution of environmental factors to immune regulation and the mechanisms involved. In this context, AhR provides a model signaling pathway to investigate the molecular mechanisms through which the environment modulates the immune response in health and disease. Moreover, as AhR activity is regulated by small molecules, a detailed understanding of the mechanisms through which AhR controls the immune response is likely to guide new approaches for therapeutic immunomodulation. In this review, we discuss current knowledge on the multiple roles of AhR signaling in T cells and dendritic cells (DCs), and its relevance for the regulation of the immune response in health and disease.

AhR-DEPENDENT SIGNALING PATHWAYS

When inactive, AhR is localized in the cytoplasm as part of a complex formed by a dimer of the 90-kDa heat shock protein (HSP90) (Denis et al., 1988; Perdew, 1988), the AhR-interacting protein (AIP, also known as XAP2 or Ara9) (Carver and Bradfield, 1997; Meyer and Perdew, 1999), the cochaperone p23 (Grenert et al., 1997; Nair et al., 1996) and the c-SRC protein kinase (Dong et al., 2011) (Figure 1). HSP90 stabilizes AhR in a conformation of high affinity for its ligands (Pongratz et al., 1992). In addition, AIP prevents AhR ubiquitination and degradation, maintaining AhR steady state cellular levels (Lees et al., 2003). Ligand binding releases AIP from the complex and triggers conformational changes in AhR that expose its nuclear localization signal, leading to AhR translocation to the nucleus (Ikuta et al., 1998). These conformational changes also expose a protein kinase C target site that when phosphorylated interferes with AhR nuclear translocation (Ikuta et al., 2004), constituting one of several mechanisms to control AhR. Of note, the regulation of AhR translocation to the nucleus is a potential target to for the specific modulation of the non-genomic AhR signaling discussed subsequently.

Data obtained in HeLa cells suggest that AhR translocates to the nucleus while still bound to HSP90 (Tsuji et al., 2014). However, it still remains to be seen whether this observation can be extrapolated to other cellular contexts and to all AhR agonists (Davarinos and Pollenz, 1999; Reyes et al., 1992). Once in the nucleus, the association of AhR with the AhR nuclear translocator (ARNT) results in the transcriptional control of multiple target genes (Furman et al., 2009). These genes include several xenobiotic metabolizing enzymes including the microsomal cytochrome P450-dependent monooxygenases including cytochrome P450 family-1 subfamily-A polypeptide-1 (CYP1A1), cytochrome P450 family-1 subfamily-A Polypeptide-2 (CYP1A2), cytochrome P450 family-1 subfamily-B polypeptide-1 (CYP1B1) and NAD(P)H-quinone oxidoreductase.

The genomic regulatory regions of AhR target genes contain the AhR binding DNA consensus motif (5’-TNGCGTG-3’), referred to as the dioxin- or xenobiotic-responsive element (DRE or XRE), (Durrin et al., 1987). The AhR/ARNT complex recognizes DREs, while it also interacts with other transcriptional regulators to control the expression of target genes. AhR has also been shown to influence chromatin remodeling by interacting with the SWI/SNF chromatin-remodeling complex (Wang and Hankinson, 2002), the steroid receptor coactivator-1 complex (SRC-1) (Beischlag et al., 2002) and by displacing histone deacetylase (HDAC) complexes (Schnekenburger et al., 2007). Additional epigenetic

mechanisms involved in the genomic control of biological processes by AhR include the regulation of retrotransposons, micro-RNAs and long non-coding RNAs, which can regulate the expression of multiple target genes (Chinen et al., 2015; Garcia et al., 2017; Goldstone et al., 2012; Gordon et al., 2015; Hanieh and Alzahrani, 2013; Hecht et al., 2014; Morales-Hernandez et al., 2016; Nakahama et al., 2013; Okudaira et al., 2010; Roman et al., 2008; Singh et al., 2016; Wragg et al., 2013; Zhang et al., 2012). In addition, AhR can also repress gene expression directly by interacting with target DNA sequences or indirectly by controlling the activity of additional molecules involved in the control of gene expression, such as transcription factors and regulatory RNAs.

AhR interacts with other transcription factors such as NF-κB, c-Maf, the retinoic acid receptor, the estrogen receptor, E2F and retinoblastoma protein (Rb) to modulate their activity and consequently, the expression of their target genes (Hankinson, 2005). Some of these interactions may participate on regulatory feedback loops highly relevant for immune regulation. For example, NF-κB induces AhR expression, but AhR can then regulate NF-κB signaling (Kimura et al., 2009; Rothhammer et al., 2016; Vogel et al., 2014; Vogel and Matsumura, 2009; Yeste et al., 2016).

The association of AhR to other transcription factors can direct its recruitment to target DNA sequences different from canonical DREs. For example, AhR dimerizes with RelA and RelB leading to its recruitment to NF-κB responding sites (Kim et al., 2000; Vogel et al., 2007b) and with KLF6, leading to its recruitment to non-consensus DNA elements (Wilson et al., 2013). Interestingly, different ligands have been suggested to induce the association of AhR with different proteins (Murray et al., 2010), potentially leading to AhR recruitment to different target DNA sequences and consequently triggering ligand-specific biologic responses.

In addition to the genomic mechanisms through which AhR regulates gene expression, AhR can also control biological processes through non-genomic signaling events. For example, the release of c-SRC from the AhR cytoplasmic complex results in the phosphorylation of multiple c-SRC target proteins (Dong et al., 2011; Matsumura, 2009). AhR can also act as an E3 ubiquitin ligase that targets substrates for ubiquitination and degradation by the proteasome, for example triggering the degradation of the estrogen receptor (Ohtake et al., 2007). Although the relevance of these non-genomic pathways has not been yet evaluated in depth in the immune system, their importance for immune regulation is starting to emerge, as shown in a recent report by Bessede *et al* that describes the role of AhR-controlled activation of c-SRC in limiting macrophage responses to inflammatory stimuli (Bessede et al., 2014; Quintana, 2014).

Finally, it has been proposed that AhR can act independently of ligand activation under certain circumstances (Han et al., 2008; Ikuta et al., 2000; Murray et al., 2005), but the physiological relevance of these observations remains to be evaluated.

Inhibitory mechanisms target AhR signaling at multiple levels. As mentioned, AhR is a ligand-activated transcription factor. Thus, ligand availability effectively controls AhR-dependent signaling as recently shown by studies in which the overexpression of CYP1A1

led to the depletion of physiologic AhR agonists, resulting in a phenotype that resembles that of AhR-deficient mice with regards to intestinal immunity (Schiering et al., 2017). In addition, the AhR repressor (AhRR) binds to ARNT, inhibiting the transcriptional activity of the AhR/ARNT complex (Mimura et al., 1999). Finally, AhR is degraded via the 26S proteasome (Davarinos and Pollenz, 1999; Ma and Baldwin, 2000). Interestingly, *Cyp1a1* and *Ahrr* are transcriptional targets of AhR, and 26S proteasome-driven degradation is triggered by AhR activation, highlighting the importance of negative feedback loops that limit AhR activation to avoid potential deleterious effects of unrestricted chronic AhR signaling.

AhR LIGANDS

AhR was first identified as the receptor for 2,3,7,8-tetracholrodibenzo-p-dioxin (TCDD) (Poland and Knutson, 1982). Additional xenobiotic AhR ligands have been identified, differing in their structures and affinities for the receptor as extensively reviewed elsewhere (Nguyen and Bradfield, 2008). However, in spite of the initial association of AhR with these xenobiotic compounds, natural AhR ligands have also been identified. The physiological relevance of natural AhR ligands is highlighted by the upregulation of AhR-target genes during development (Campbell et al., 2005; Choudhary et al., 2003), and reports of defects in the development and physiology of AhR deficient mice (Fernandez-Salguero et al., 1995; Lahvis et al., 2005; Schmidt et al., 1996).

Diverse sources of physiological AhR ligands have been identified so far, including ligands provided by the diet, free radical formation and enzymatic activities in the host and the commensal flora (Quintana, 2013, 2014; Quintana and Sherr, 2013). In Table 1 we highlight major sources of physiological AhR ligands relevant to the immune system

An abundant source of AhR agonists is the diet. The *Brassica* genus (broccoli, cauliflower, Brussel sprouts and cabbages) contains significant amounts of indole-based glucobrassicin. Myrosinases, enzymes present in plants, the gut flora, and also induced by chewing, metabolize glucobrassicin into the AhR agonist precursors indole-3-carbinol (I3C) and indole-3-acetonitrile (I3ACN) (Loub et al., 1975). I3C and I3ACN are further transformed by nonenzymatic acid condensation into AhR agonists including 3,3’diindolylmethane (DIM), 2-(indol-3-ylmethyl)-3,3’-diindolylmetane, and indolo[3,4-b]carbazole (ICZ) (Bjeldanes et al., 1991; Chen et al., 1996; Degner et al., 2009; Ociepa-Zawal et al., 2007) (Figure 2A). Among them, ICZ shows the highest AhR agonistic activity. Dietary I3C and its condensation products are potentially important in the context of autoimmunity and inflammation since they have been shown to have therapeutic activity in experimental murine models of multiple sclerosis and colitis through the AhR-dependent induction of $FoxP3^+$ regulatory T cells (Tregs) (Huang et al., 2013; Rouse et al., 2013). Moreover, I3C and its condensation products are also critical for the development of gut-associated intraepithelial lymphocytes and the maintenance of gut epithelial barrier integrity (Kiss et al., 2011; Li et al., 2011).

Additional AhR ligands are originated in plants. Indirubin and indigo are plant-derived phytochemicals with mild AhR agonistic activity; they have also been proposed to be

produced by human cytochrome P450 (Gillam et al., 2000). However, despite being detectable in human urine (Adachi et al., 2001), their concentrations are too low to be considered important under physiological conditions unless specific mechanisms increase their production and/or accumulation in microenvironments that may benefit from AhR activation, for example to maintain the integrity of intestinal tissues.

The metabolism of tryptophan (Trp) is also a physiological source of AhR agonists. The primary route of Trp metabolism is the kynurenine (Kyn) pathway, which transforms Trp into nicotinamide adenine dinucleotide and different intermediate byproducts, some of which activate AhR (Figure 2B). Indoleamine-2,3-dioxygenase (IDO) and Tryptophan-2,3-dioxygenase (TDO) are the two main enzymes that catalyze the conversion of Trp into Kyn in the context of inflammation and cancer with important immune effects. Kyn, for example, is produced by glioma cells (Opitz et al., 2011) and has been described to boost the differentiation of Tregs (Mezrich et al., 2010). Thus, AhR activation by Kyn produced in the tumor microenvironment has been linked to glioma-associated immunosuppression (Gabriely et al., 2017; Takenaka et al., 2016). Kyn can also be metabolized into additional potent AhR ligands like kynurenic acid, xanthirenic acid or cinnabarinic acid.

Tryptamine and serotonin metabolism can also provide AhR agonists derived from Trp through a pathway independent of IDO/TDO. Indeed, tryptamine itself and its downstream metabolite indole acetic acid may act as direct AhR agonists (Heath-Pagliuso et al., 1998; Vikstrom Bergander et al., 2012). Interestingly, trypatmine is also a CYP1A1 substrate (Chiaro et al., 2007). In addition, 5-Hydroxy-Trp, a proximal serotonine metabolite, has been identified as a mild AhR ligand (Bittinger et al., 2003) (Figure 2B).

Trp is also thought to provide AhR agonists through additional mechanisms. The AhR agonist 2-(1'H-indole-3'-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE), purified from porcine lung, has been hypothesized to be formed through a condensation reaction between Trp and cysteine (Song et al., 2002). The pathways involved in ITE synthesis and metabolism, however, are still unknown and its synthesis under physiological conditions is still debatable.

Finally, exposure of Trp to ultraviolet light triggers its photo-oxidation to 6-formylindolo[3,2-b]carbazole (FICZ) a potent AhR ligand (Rannug et al., 1987; Wincent et al., 2009) with broad implications in UV light response, genomic stability, circadian rhythms and the immune response (Quintana et al., 2008; Veldhoen et al., 2008; Wincent et al., 2012). Additional Trp photometabolites exist, such as 1-(1H-indol-3-yl)-9H-pyrido[3,4-b]indole which exhibits a potency similar to that of FICZ (Diani-Moore et al., 2011). These photometabolites may have both local effects in the skin, and also systemic effects because FICZ has been detected in human urine (Wincent et al., 2012). In fact, the generation of FICZ through light-independent pathways has been recently reported (Smirnova et al., 2016).

The microbial metabolism of dietary Trp also produces additional AhR ligands such as indole-3-acetic acid (IAA) (Jin et al., 2014b; Miller, 1997), tryptamine (TA) and 3-methyl indole (skatole) (Hubbard et al., 2015; Weems and Yost, 2010). Bacterial tryptophanase

converts dietary Trp to indole, and is indeed essential for the subsequent production of indoxyl-3-sulfate (I3S) by the liver (Schroeder et al., 2010; Wikoff et al., 2009). Other derivatives of Trp catabolism produced by commensal *Lacobacillus* species (e.g. indole-3-adehyde (Iald)) maintain intestinal homeostasis preventing not only colonization by pathogenic microorganisms like *Candida albicans* (Zelante et al., 2013) but also the worsening of inflammatory disorders affecting the intestinal tract such as inflammatory bowel disease (IBD) and cancer. Indeed, it has been recently reported that deficits in commensal bacteria that produce Trp-derived AhR agonists may contribute to the pathogenesis of human IBD (Lamas et al., 2016). Accordingly, microbiota-based interventions may provide an efficacious therapeutic approach to deliver AhR ligands and re-establish intestinal homeostasis. Finally, it is worth to mention that novel AhR ligands have been recently identified in bacteria. For example, pigmented virulence factors from pulmonary pathogens activate AhR as we will discuss later (Moura-Alves et al., 2014).

Some Heme-derived metabolites present AhR agonistic activities. Bilirubin induces the expression of the AhR-target gene *CYP1A1* in hepatoma cells (Sinal and Bend, 1997); biliverdin also activates AhR (Phelan et al., 1998). AhR activation by bilirubin was recently reported to suppress experimental colitis, suggesting that bilirubin contributes to AhR-dependent anti-inflammatory effects *in vivo* (Longhi et al., 2017). Interestingly, the deficiency in UDP-glucuronosyltransferase, which degrades bilirubin, results in increased *CYP1A1* expression likely as a result of bilirubin-triggered AhR activation (Kapitulnik and Gonzalez, 1993). Indeed, CYP1A1, CYP1A2 and UDP-glucuronosyltransferase participate in bilirubin catabolism as part of a negative feedback loop that can potentially limit AhR activation by removing physiologically relevant agonists.

Finally, some arachidonic acid derivatives have been shown to activate AhR. Prostaglandins and leukotrienes activate AhR, being prostaglandin G2 the most potent agonist (Seidel et al., 2001). Interestingly, AhR activation induces the expression of cyclooxygenase 2 (Degner et al., 2009; Vogel et al., 2007a), which is responsible of the synthesis of prostaglandin. Moreover the product of the AhR-induced gene *CYP1A1* catalyzes the generation of eicosanoids from arachidonic acid (Capdevila et al., 2002). However, it should be noted that the molecular structure of these compounds differs significantly from the structure of other AhR ligands and their agonistic activity is generally weak. Thus, it is still unclear whether arachidonic acid derivatives play a physiological role as AhR agonists unless their local levels are highly increased by specific mechanisms, for example in the microenvironment of inflamed tissues.

AhR IN T CELLS

AhR has significant effects in the control of adaptive immunity, modulating T-cell differentiation and function directly and indirectly through its effects on antigen presenting cells. AhR activation by its potent xenobiotic ligand TCDD was found to inhibit immune responses (Kerkvliet et al., 1990), an effect that was later linked to the induction of $CD4^+$ T cells with a regulatory phenotype (Funatake et al., 2005; Kerkvliet et al., 2002; Marshall et al., 2008). Additionally, a role for AhR in Th17 biology and the control of IL-22 production by T cells was also established (Quintana et al., 2008; Rutz et al., 2011; Veldhoen et al.,

2009; Veldhoen et al., 2008; Yeste et al., 2014). In the following sections we discuss illustrative examples of the multiple roles of AhR on effector and regulatory T cells.

AhR in Treg cells

FoxP3$^+$ Treg cells (Fontenot et al., 2003; Hori et al., 2003) and IL-10 producing type 1 regulatory T cells (Tr1 cells) (Groux et al., 1997) are the best-characterized regulatory T-cell populations. Both Foxp3$^+$ Tregs and Tr1 cells have been linked to AhR.

AhR activation by TCDD, ITE, Kyn or Laquinimod metabolites increases FoxP3$^+$ Tregs trough different mechanisms, including direct transactivation and the induction of epigenetic modifications that control *Foxp3* transcription, and also through the modulation of DCs (Goettel et al., 2016; Kaye et al., 2016; Kerkvliet et al., 2009; Mezrich et al., 2010; Quintana et al., 2008; Singh et al., 2016; Singh et al., 2011). AhR activation with TCDD in the presence of TGF-β1 also induces the expression of SMAD1 in human Tregs, stabilizing FoxP3 expression (Gandhi et al., 2010). The analysis of murine AhR deficient T cells demonstrated that AhR also prevents STAT1 activation, which can inhibit FoxP3$^+$ Treg differentiation (Kimura et al., 2008; Quintana et al., 2010). Additionally, AhR drives the expression of the epigenetic modifier Aiolos, which suppresses the expression of genes associated to effector T-cell function like IL-2 (Gandhi et al., 2010; Goettel et al., 2016; Quintana et al., 2012). The effects of AhR on FoxP3$^+$ Tregs, however, may be influenced by the experimental model used, probably reflecting tissue specific effects and/or the differential contribution of AhR agonists provided by the commensal flora (Dant et al., 2017). In addition, it has been also suggested that xenobiotic AhR agonists may selectively induce effector T-cell death, contributing to the relative increase in FoxP3$^+$ Tregs observed after AhR activation (Stockinger et al., 2009). Collectively, these findings suggest a role for AhR agonists in the control of functional FoxP3$^+$ Tregs, as indicated by the protective effects of AhR activation in experimental models of autoimmune disease like EAE (Quintana et al., 2008; Quintana et al., 2010), colitis (Goettel et al., 2016), uveitis (Nugent et al., 2013) and diabetes (Kerkvliet et al., 2009). It is not clear yet whether specific subpopulations of FoxP3$^+$ Tregs express higher levels of AhR, as recently described for TIGIT$^+$ FoxP3$^+$ Tregs (Joller et al., 2014), making them more susceptible to modulation by AhR agonists.

Tr1 cells are induced Foxp3$^-$ IL-10$^+$ CD4$^+$ Tregs implicated in the control of tissue inflammation through their capacity to secrete IL-10 among other mechanisms (Groux et al., 1997). IL-27 promotes Tr1 cell differentiation (Awasthi et al., 2007; Fitzgerald et al., 2007; Stumhofer et al., 2006), while IL-21 acts in an autocrine manner to stabilize these cells (Pot et al., 2009; Spolski et al., 2009). IL-27 induces AhR expression in Tr1 cells through a mechanism driven by STAT3; AhR expression is then maintained by the transactivation of the *Ahr* promoter by AhR (Apetoh et al., 2010; Gandhi et al., 2010; Mascanfroni et al., 2015; Wu et al., 2011). The importance of AhR for Tr1 cells in vivo is highlighted by the deficient differentiation of Tr1 cells triggered by chronic administration of anti-CD3 to AhR mutant mice (Apetoh et al., 2010; Wu et al., 2011). Interestingly, additional factors controlled by the environment, such as melatonin, boost AhR expression in Tr1 cells (Farez et al., 2015).

AhR influences the transcriptional program of human (Gandhi et al., 2010) and mouse (Apetoh et al., 2010; Mascanfroni et al., 2015; Wu et al., 2011) Tr1 cells at multiple levels (Apetoh et al., 2010; Gandhi et al., 2010; Mascanfroni et al., 2015; Wu et al., 2011) (Figure 3). AhR synergizes with cMaf to drive the expression of IL-10 and IL-21 in Tr1 cells (Apetoh et al., 2010; Gandhi et al., 2010; Wu et al., 2011). In addition, AhR and STAT3 in Tr1 cells cooperate to drive the expression of CD39, an ectonucleotidase that depletes proinflammatory extracellular ATP (eATP), while cooperating with CD73 to generate immunosuppressive adenosine (Gandhi et al., 2010; Goettel et al., 2016; Mascanfroni et al., 2015; Takenaka et al., 2016). Indeed, CD39 contributes to the suppressive activity of Tr1 cells *in vivo* and *in vitro* (Gandhi et al., 2010; Goettel et al., 2016; Mascanfroni et al., 2015).

AhR-induced CD39 also affects Tr1 cell differentiation. Following activation, T cells release eATP (Takenaka et al., 2016). eATP interferes with Tr1 cell differentiation by signaling via the hypoxia inducible factor-1α (HIF1-α). HIF1-α outcompetes AhR for its interaction with ARNT and promotes AhR degradation via the immunoproteosome, suppressing AhR-dependent Tr1 cell differentiation (Mascanfroni et al., 2015). AhR-driven expression of CD39 depletes eATP and allows Tr1 cell differentiation to proceed. Thus, AhR actively drives the expression of genes central in the transcriptional program of Tr1 cells, while it limits the suppressive activity of eATP-driven HIF1-α activation on Tr1-cell differentiation.

High local levels of eATP and hypoxia, which activate HIF1-α, characterize the microenvironment of inflamed tissues (Takenaka et al., 2016). Thus, these findings suggest that although IL-27 is produced at sites of inflammation (Fitzgerald et al., 2007), these sites do not support local Tr1 cell differentiation. Instead, the production of IL-27 at local sites may limit inflammation by Tr1 independent mechanisms such as direct inhibitory effects on pathogenic Th17 cells (Batten et al., 2006; Rostami and Ciric, 2013; Stumhofer et al., 2006) and also indirect effects, for example by acting on recruited dendritic cells (Mascanfroni et al., 2013).

Finally, some of the transcriptional modules controlled by AhR in Tr1 cells may be coopted by other cell types. For example, the interaction between AhR and HIF1α controls glucose metabolism in Tr1 cells (Mascanfroni et al., 2015). These effects of HIF1α and AHR on cellular metabolism may contribute to the role of these transcription factors in the differentiation of other T cell types such as Th17 cells (Dang et al., 2011; Shi et al., 2011). Moreover, AhR was implicated in the trans-differentiation of Th17 cells into IL-10 expressing Tr1-like cells (Gagliani et al., 2015), and may also control transcriptional modules coopted by tumor-infiltrating lymphocytes (Regateiro et al., 2011; Whiteside, 2014) and FoxP3$^+$ Tregs that express IL-10 and CD39 (Deaglio et al., 2007; Maynard et al., 2007). Collectively, these findings identify AhR as a potential therapeutic target to for immune modulation.

AhR in Th17 cells

Th17 cells characterized by the production of IL-17A and the expression of the transcription factor ROR-γt participate in the immune response to extracellular bacteria and fungi, and also contribute to the pathology of several autoimmune disorders (Ivanov et al., 2006; Korn et al., 2009). Th17 cell differentiation is initiated by TGFβ in combination with IL-6 or

IL-21 (Korn et al., 2007a; Nurieva et al., 2007; Veldhoen et al., 2006). AhR is highly expressed in Th17 cells and its activation by FICZ enhances Th17 cell differentiation and promotes IL-22 production (Quintana et al., 2008; Veldhoen et al., 2009; Veldhoen et al., 2008). Conversely, AhR deficiency impairs IL-22 production by Th17 cells, probably reflecting the role of AhR in facilitating the recruitment of the transcription factor RORγt to the IL-22 promoter (Qiu et al., 2012; Veldhoen et al., 2008; Yeste et al., 2014) (Figure 3).

IL-2 has been shown to inhibit Th17 differentiation (Chen et al., 2011; Laurence et al., 2007; Yang et al., 2011). AhR contributes to Th17 development by inducing the expression of Aiolos, which silences *il2* expression (Quintana et al., 2012). AhR also inhibits the activation of STAT5 and STAT1, which interfere with Th17 cell differentiation (Kimura et al., 2008; Veldhoen et al., 2009). Collectively, these data identify a role for AhR during the early stages of the differentiation of Th17 cells, at a stage when they produce significant amounts of IL-10 and their pathogenic potential has not fully developed (McGeachy et al., 2007) (Lee et al., 2012). Indeed, additional factors such as IL-23 are needed for the differentiation of Th17 cells into fully pathogenic effector cells (Korn et al., 2009; Lee et al., 2012). Thus, considering reports on the AhR-dependent differentiation of Th17 cells into IL-10 producing Tr1-like cells (Gagliani et al., 2015), AhR may be associated with plastic Th17 cell populations that require additional signals to complete their differentiation into fully pathogenic Th17 cells or regulatory Tr1 cells (Figure 3).

AhR in OTHER T CELLS

Th22 cells have been identified as a population of $CD4^+$ T cells characterized by the production of IL-22 in the absence of IL-17, differentiated in response to IL-6, IL-21 or IL-23. AhR regulates IL-22 production in these cells, as well as the expression of additional factors important for their function in mucosal immunity (Basu et al., 2012; Duhen et al., 2009; Ramirez et al., 2010; Trifari et al., 2009; Yeste et al., 2014).

AhR signaling also seems to have significant effects on $CD8^+$ T cells. Systemic AhR activation by TCDD results in the indirect suppression of the primary $CD8^+$ T cell response to influenza virus through a mechanism mediated by the modulation of DC function (Lawrence et al., 2006). Additionally, $CD8^+$ T cells from mice exposed to the AhR agonist TCDD during development are less responsive to influenza virus infection later in life (Winans et al., 2015). These findings reflect epigenetic changes that cause long-term defects in $CD8^+$ T-cell function detectable upon viral challenge (Winans et al., 2015).

AhR expression is much higher in tissue-resident $CD8^+$ memory cells (TRMs) compared to other $CD8^+$ T cells subsets. In fact, AhR controls the persistence TRMs in the skin, contributing to their protective role against microbial challenge (Zaid et al., 2014). Moreover, AhR activation by TCDD or Trp metabolite indole-3-lactic acid (ILA) derived from *Lactobacillus reuteri* has been recently associated to the induction of $CD4^+CD8\alpha\alpha^+$ double positive intraepithelial lymphocytes (DP IELs) which display regulatory functions associated to the induction of tolerance to dietary antigens (Cervantes-Barragan et al., 2017). Collectively these findings suggest that, similarly to previous observations on $CD4^+$ T cells,

AhR signaling may have major roles in the modulation of specific $CD8^+$ T-cell subsets like TRMs and DP IELs.

AhR signaling also controls γδ T cells, tissue-resident lymphocytes that have important functions in regulating not only the first line immune response at epithelial sites but also tissue homeostasis (Hayday, 2009). Although AhR is expressed by all γδ T-cell subsets, AhR deficiency dramatically reduces the number of intraepithelial lymphocytes which in the skin mainly comprise Vγ3 and in the intestine Vγ5 γδ T cells as well as CD8αα αβ T cells (Kadow et al., 2011; Li et al., 2011). AhR is also essential for the production of IL-22 by IL-17 producing γδ T cells (Cibrian et al., 2016; Martin et al., 2009). These findings point to significant effects of AhR on tissue-resident T cells, supporting further investigations on the role of AhR on non-$CD4^+$ T cells.

In summary, AhR regulates the T-cell response at multiple levels, affecting the expression of effector molecules, enzymes, transcription factors and epigenetic modifiers that control T-cell stability and metabolism. Lineage-specific responses to AhR activation are likely to result ligand-specific effect in combination with cytokine-driven effects on the genomic context that modulate the expression of AhR interaction partners as well as the accessibility of AhR direct and indirect transcriptional targets (Yosef and Regev, 2016). The comprehensive investigation of those interactions should guide the development of AhR-targeted immunomodulatory agents.

AhR IN DENDRITIC CELLS

Dendritic cells (DCs) have a central role in the control of T-cell responses and the regulation of immune tolerance (Guermonprez et al., 2002). AhR controls both the differentiation and function of DCs, with a profound impact on T-cell immunity (Quintana et al., 2015).

The AhR antagonist StemRegenin 1 promotes the expansion of human $CD34^+$ hematopoietic stem cell progenitors (Boitano et al., 2010) and their differentiation into plasmacytoid and myeloid DCs (Thordardottir et al., 2014). Conversely, while AhR deficient murine DCs do not display impaired development *in vivo* or when differentiated *in vitro* from bone marrow (Chng et al., 2016; Nguyen et al., 2010), AhR activation by the AhR agonists VAF347, β-naphtoflavone (β-NF) or TCDD inhibits the differentiation of human monocytes into Langerhans DCs *in vitro*, arresting them at an early precursor cell stage (Platzer et al., 2009). VAF347 and its derivative VAG539 have been described to promote tolerance *in vitro* in human monocyte-derived DCs (Ettmayer et al., 2006; Lawrence et al., 2008) and *in vivo* in experimental models of asthma and pancreatic islets allotrasplantation by affecting the function of DCs and lymphocytes (Ettmayer et al., 2006; Hauben et al., 2008). Interestingly, the in vivo effects of VAF347 in DCs were found to be mediated by AhR when analyzed using mice expressing a dominant negative AhR and AhR knock-out mice (Lawrence et al., 2008).

AhR can also affect antigen presentation by DCs. The exposure of bone marrow derived dendritic cells (BMDCs) to TCDD decreases CD11c expression but increases MHC-II and CD86 as well as IL6 and TNFα production by BMDCs. (Bankoti et al., 2010b). Similar

results were obtained in splenic DCs treated with TCDD (Bankoti et al., 2010a). Different results, however, were obtained when the AhR agonist ITE was used. AhR stimulation with ITE decreases the expression of MHC-II and co-stimulatory molecules by splenic DCs, as well as the production of Th1 and Th17 polarizing cytokines (Quintana et al., 2010). Indeed, AhR activation by ITE during EAE decreased CD86 and CD103 expression in DCs, reducing their ability to trigger proliferation and proinflammatory cytokine production in T cells, while increasing their production of TGF-β1 and IL-10. Moreover, ITE treatment increased the ability of DCs to expand $Foxp3^+$ Tregs and IL-10^+ Tr1 cells and suppress EAE (Quintana et al., 2010). $Foxp3^+$ Tregs are thought to display limited ability to suppress local CNS inflammation (Korn et al., 2007b). Thus, the suppression of EAE by ITE administration likely involves multiple AhR-dependent mechanisms such as the suppression of effector T cells and CNS-resident cells by $FoxP3^+$ Tregs and Tr1 cells in addition to the modulation of DC function. Taken together, however, the reports on the effects of AhR agonists on DCs point to ligand-specific effects of AhR activation in DCs.

Additional evidence for a physiologic regulatory function of AhR in DCs *in vivo* was recently provided by experiments performed in an ovalbumin-induced asthma model in which AhR deficient mice presented higher inflammatory response as well as Th2 differentiation and higher MHC-II and CD86 expression in DCs (Thatcher et al., 2016). Moreover it has been described during influenza virus infection that AhR signaling modulates the activity of $CD103^+$ DCs and $CD11b^+$ DCs, limiting the activation of protective $CD8^+$ T cells (Jin et al., 2014a). Collectively, this evidence identifies AhR as a potential therapeutic target in DCs to modulate the T-cell response.

Several mechanisms contribute to the modulation of DC function by AhR. AhR induces the expression of the enzymes indoleamine 2,3-dioxigenase (IDO) 1 and 2 (Nguyen et al., 2010; Vogel et al., 2008). IDO1 and IDO2 catalyze Kyn production, which boosts $FoxP3^+$ Treg differentiation (Fallarino et al., 2006). In fact AhR-deficient DCs fail to promote Treg differentiation and boost Th17 cell generation *in vitro* (Mezrich et al., 2010; Nguyen et al., 2010). In agreement with an immunosuppressive role for AhR in DCs, it has been recently described that in tumor infiltrating tolerogenic DCs the expression of IDO is sustained by an autocrine loop that involves AhR and Kyn (Li et al., 2016). In addition, AhR activation in DCs has been shown to upregulate the expression of the enzymatic machinery involved in the production of retinoic acid (RA) (Quintana et al., 2010), which boosts $FoxP3^+$ Treg differentiation and suppresses effector T cells (Coombes et al., 2007; Mucida et al., 2007; Nolting et al., 2009; Pino-Lagos et al., 2011; Sun et al., 2007).

Although AhR activation in DCs seems to play mostly an anti-inflammatory role, no data are yet available on the expression of AhR by different DC subsets. This is an important point considering reports of DC populations specialized in the differentiation of effector and regulatory T cells (Heink et al., 2017; Quintana, 2016; Takenaka and Quintana, 2017). Similar to what is observed in T cells, it is likely that a combination of ligand-specific effects together with tissue-specific signals results in specific AhR-driven responses better suited to control inflammation in the local microenvironment. For example, intestinal DCs are exposed to relatively high levels of LPS and other bacterial products. Indeed, AhR expression is upregulated in DCs following LPS stimulation through a mechanism mediated

by NF-κB (RelA/p50) (Vogel et al., 2014). Interestingly, AhR limits the immune response to LPS challenge through a mechanism mediated by TDO and Kyn (Bessede et al., 2014). Thus, these findings suggest a role for AhR in the tissue-specific adaptation of DCs and other immune cells.

AhR IN THE RESPONSE TO MICROORGANISMS

AhR is increasingly recognized as a regulator of the immune response to microbial pathogens and the commensal flora. AhR plays a significant role in host defense against extracellular (*Streptococcus pneumonia*, (Vorderstrasse and Lawrence, 2006)) and intracellular (*Listeria monocytogenes*, (Shi et al., 2007)) bacterial infections, as evidenced by the increased susceptibility to these microorganisms that results from AhR deficiency. In addition, Moura-Alves *et al* recently identified AhR as a sensor of infection by *Pseudomonas aeruginosa* and *Mycobacterium tuberculosis* (Moura-Alves et al., 2014). Indeed, AhR signaling in hematopoietic and non-hematopoietic compartments contributed to the anti-bacterial response, with a critical role for macrophages and neutrophils during *P. aeruginosa* infection (Moura-Alves et al., 2014). Based on these observations, AhR is likely to play a dual role during bacterial infections, driving certain anti-bacterial activities while simultaneously enforcing “disease tolerance” to minimize immunopathology to the host (Bessede et al., 2014).

AhR-deficient mice show reduced numbers of skin and gut intraepithelial lymphocytes (Li et al., 2011) and intestinal innate lymphoid cells (ILC), resulting in increased susceptibility to *Citrobacter rodentium* infection (Kiss et al., 2011; Qiu et al., 2012). These cell types, as well as the formation of proper intestinal lymphoid follicles, are controlled by dietary AhR ligands (Kiss et al., 2011; Li et al., 2011). Additionally, AhR activation by microbial metabolites also controls the generation of DP IELs, another important population in the control of intestinal immunity (Cervantes-Barragan et al., 2017). AhR deficiency also affects the commensal flora, probably due to the reduced production of IL-22 (Qiu et al., 2013; Zenewicz et al., 2013). Indeed, the transcription factor ID2 regulates IL-22 expression in ILCs through AhR and IL-23 dependent mechanisms, controlling gut colonization by *C. rodentium* (Guo et al., 2015). Moreover, IL-22 production by Th22 cells is also controlled by AhR and provides protection from enteropathogenic bacteria (Basu et al., 2012; Yeste et al., 2014). All these data point to an important role of AhR in the control of interactions with microorganisms at environmental interfaces via the regulation of the production of IL-22 and other molecules. Interestingly, the depletion of physiologic AhR ligands by overexpression of *Cyp1a1* also increases susceptibility to infection by enteric bacteria (Schiering et al., 2017), highlighting the importance of AhR ligand availability and metabolism on the control of AhR-dependent immune effects.

Although it will not be thoroughly reviewed here, it is important to mention that AhR has also been studied in the context of viral and parasitic infections (Barroso et al., 2016; Sanchez et al., 2010). As we discussed, AhR activation by TCDD worsens influenza virus infection by suppressing $CD8^+$ T cells indirectly, potentially through the modulation of antigen presenting cell function (Jin et al., 2010; Jin et al., 2014a; Lawrence et al., 2006; Warren et al., 2000). More recently, it was reported that constitutive AhR activation reduces

the type I IFN (IFN-I) antiviral response (Yamada et al., 2016). AhR expression is induced in some cell types by IFN-I (Rothhammer et al., 2016), suggesting that AhR participates in a negative feedback loop that limits potential IFN-I triggered immunopathology.

AhR IN TUMOR IMMUNOLOGY

Mice with constitutively active AhR develop gastric tumors (Andersson et al., 2002). Similar findings were made in other types of cancer, highlighting tumor-intrinsic roles for AhR in multiple processes including tumor formation, proliferation and tissue invasion (Gramatzki et al., 2009; Jin et al., 2015; Lin et al., 2003; Opitz et al., 2011; Peng et al., 2009; Stanford et al., 2016; Wang et al., 2013; Yang et al., 2008). Conversely, the AhRR has been described as a tumor suppressor (Zudaire et al., 2008).

Interestingly, a positive feedback loop controlled by AhR drives IL-6 expression and promotes IDO expression and Kyn production in tumor cells (Litzenburger et al., 2014). Similarly, stem cell-like cancer cells become resistant to IFNγ-induced apoptosis through an IDO-Kyn-AhR autocrine pathway (Liu et al., 2017). Considering the effects of AhR and Kyn on the T-cell response, these findings suggest that the production of Trp-derived AhR agonists is an important mechanism of tumor immunosuppression.

Indeed, the effects of AhR on tumor development may also involve the modulation of tumor-specific immunity through the AhR-dependent depletion of Trp and the generation of Trp-derived AhR agonists. In DCs, AhR induction by TCDD promotes the expression of IDO, which degrades Trp and while it produces Kyn (Bankoti et al., 2010a; Quintana and Sherr, 2013; Vogel et al., 2008). Low Trp levels induce T-cell cycle arrest and death (Uyttenhove et al., 2003). Moreover, Trp depletion and Kyn down-regulate the TCRζ chain in $CD8^+$ T cells (Fallarino et al., 2006; Mezrich et al., 2010; Nguyen et al., 2010). Thus, based on the role of Kyn in the modulation of T cells and APCs, these findings identify AhR activation by Kyn as an important regulator of both tumor-intrinsic functions and tumor-specific immunity.

These data also highlight the potential of the IDO/TDO-Kyn-AhR axis as a target for cancer immunotherapy. Indeed, IDO and TDO inhibitors are currently under evaluation in clinical trials (Balachandran et al., 2011; Litzenburger et al., 2014; Muller et al., 2005; Pilotte et al., 2012). AhR inhibition, however, may offer a better approach for tumor immunotherapy, likely to avoid the undesired side effects linked to IDO and TDO inhibition (Metz et al., 2012). Because of the tumor-intrinsic roles of AhR (Gabriely et al., 2017), AhR inhibitors may offer the added benefit of acting not only on tumor-specific immunity but also, directly on cancer cells.

CONCLUDING REMARKS

AhR signaling has important effects on the immune response. The development of AhR targeted therapeutics, however, should consider ligand- and cell-specific effects of AhR signaling and how these effects are modulated by the tissue microenvironment. A deep understanding of the mechanisms involved in these ligand- and cell-specific effects, their modulation by the tissue context, the role of different AhR structural conformations and

interactions with protein partners, as well as the control of AhR target accessibility by epigenetic modifications should guide the design of therapeutic approaches targeting AhR.

AhR agonists and antagonists may provide new therapeutic approaches for autoimmunity and cancer immunotherapy. However, the expression of AhR in multiple tissues and cell types represents a challenge that should be addressed for the therapeutic target of this pathway. Nanoparticles, for example, may be used to deliver AhR modulators to specific cell-targets *in vivo* to minimize potential toxicity while maximizing therapeutic effects in specific tissues and/or cell types (Yeste et al., 2012; Yeste et al., 2016). In the context of autoimmune diseases may also control pathogenic activities associated to tissue-resident cells. AhR activation, for example, limits astrocyte-driven neurodegeneration in the CNS (Rothhammer et al., 2016) and favors the re-establishment of intestinal epithelial barrier integrity (Kiss et al., 2011; Li et al., 2011). In the context of cancer therapy, AhR antagonists may have intrinsic effects on tumor cells, affecting their metabolism and invasiveness among other beneficial effects (Gabriely et al., 2017; Opitz et al., 2011). In conclusion, AhR is not only an important regulator of the immune response in health and disease, AhR also provides an attractive target for therapeutic immunomodulation.

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In brief

AhR signaling integrates the effects of the environment and metabolism on the immune response. Gutiérrez-Vázquez and Quintana review the role of AhR in the regulation of the immune response in the context of autoimmunity, infection and cancer, and discuss the potential opportunities and challenges of developing AhR targeted therapeutics.

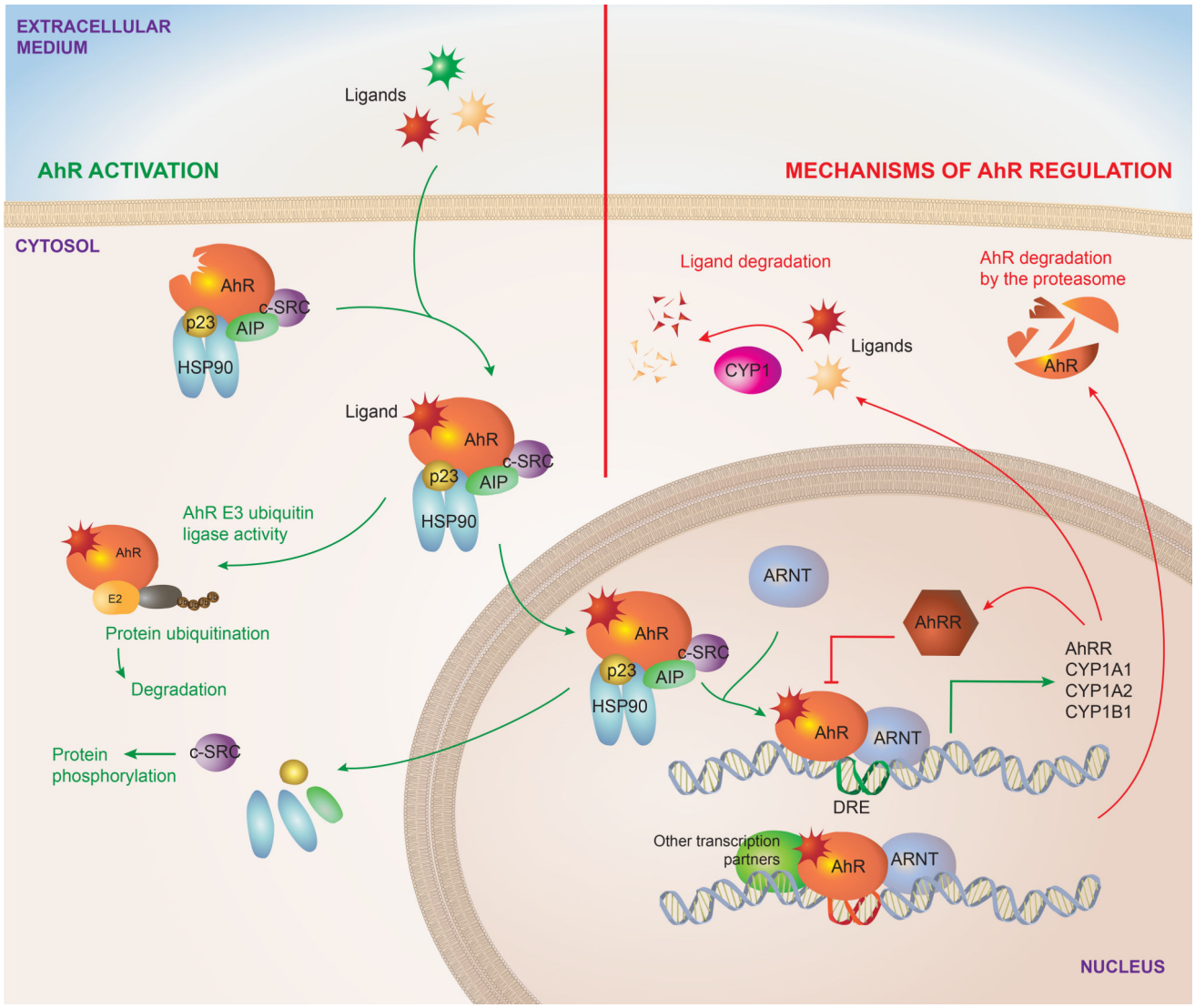

FIGURE 1. AhR signaling pathway

Inactive AhR is localized in the cytosol complexed to HSP90, AIP, p23 and c-SRC. Upon interaction with an agonist, conformational changes result in the translocation of the complex to the nucleus and the interaction of AhR with ARNT after the dissociation of the cytoplasmic complex. The AhR-ARNT heterodimer controls the transcription of DRE containing genes. AhR signaling also includes non-genomic pathways, for example AhR functions as an E3 ubiquitin ligase, while the release of the c-SRC kinase results in the phosphorylation of multiple targets. AhR activation is limited by regulatory mechanisms, some of which are actually triggered by AhR activation. AhR drives the expression of CYP enzymes, which degrade AhR ligands. AhR also induces the expression of its repressor AhRR, which inhibits the formation of AhR/ARNT complex required for AhR signaling.

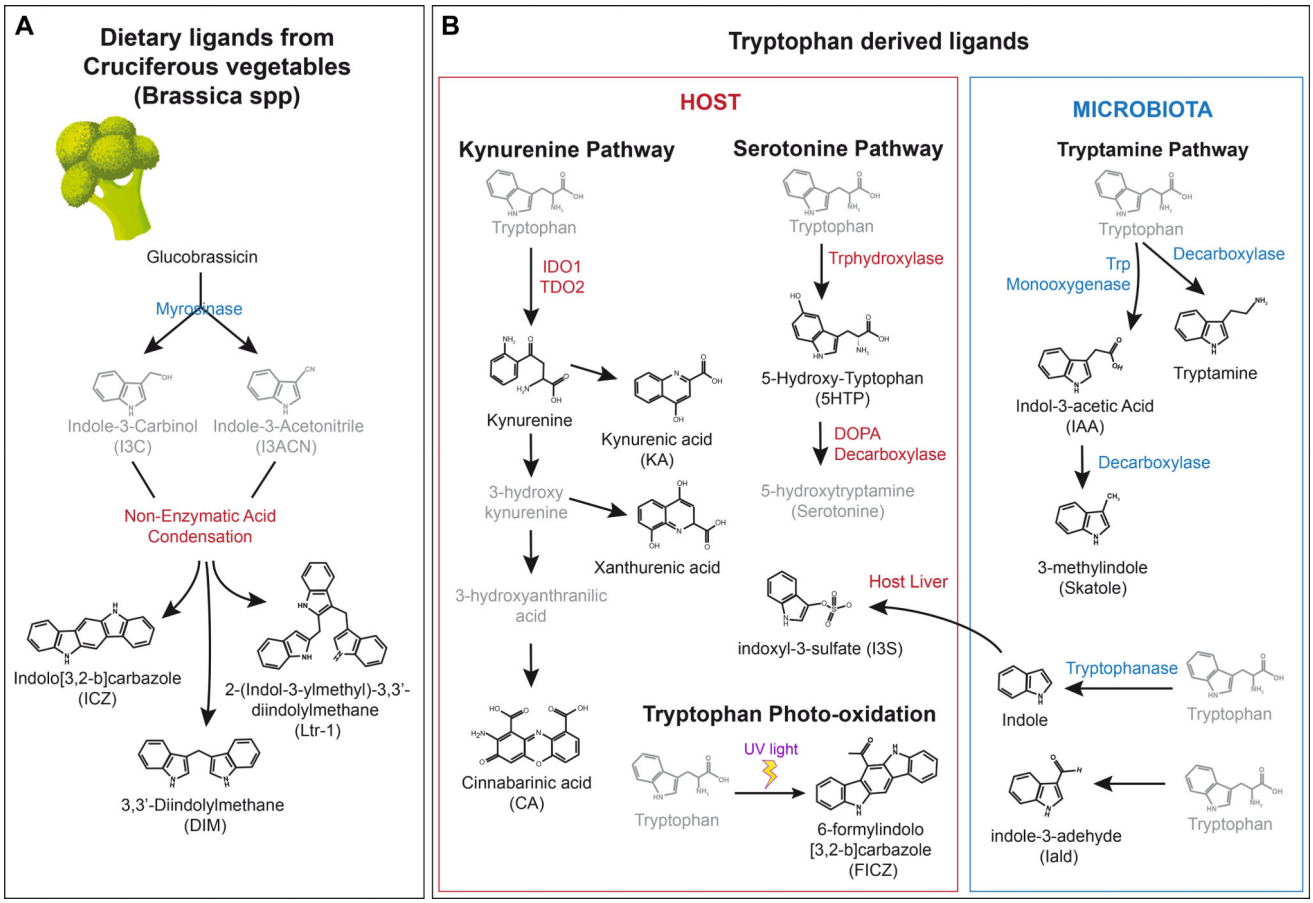

FIGURE 2. AhR physiological ligands

A. Indole-derived AhR agonists provided by the diet. **B**. Tryptophan-derived AhR agonists. Both the host and the microbiota are implicated in the generation of these agonists.

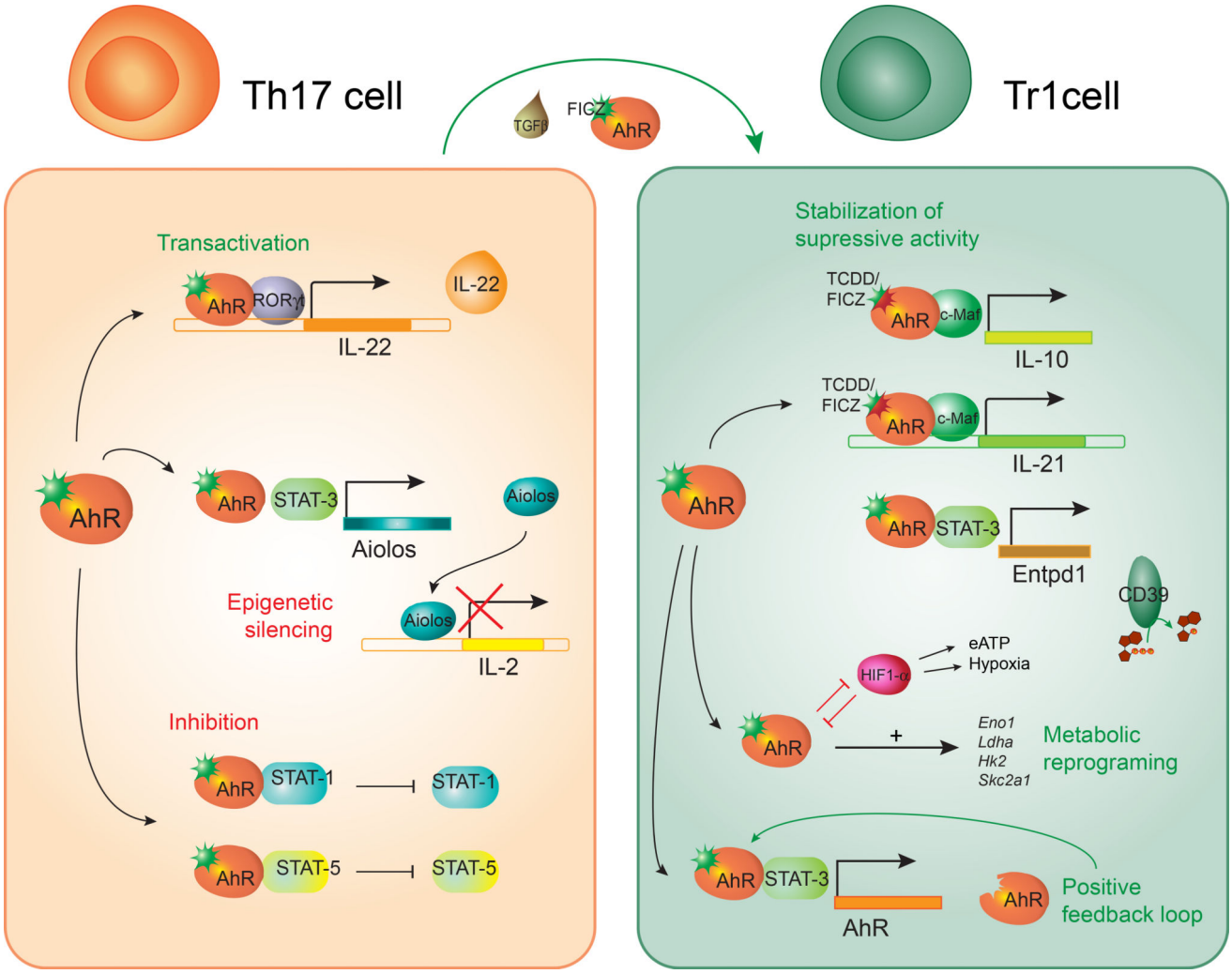

FIGURE 3. Effects of AhR signaling in Th17 and Tr1 cells

In Tr1 cells, AhR cooperates with c-Maf to induce the expression of IL-10 and IL-21 and with STAT 3 to drive CD39 expression; AhR also drives its own expression. AhR mediates the metabolic reprogramming of Tr1 cells by controlling the expression of enzymes ivolved in glucose metabolism. In Th17 cells, AhR induces IL-22 expression in cooperation with RORγt. AhR also inhibits STAT1 and STAT5 activation, as well as IL-2 expression by inducing the epigenetic modifier Aiolos in cooperation with STAT3. AhR has been implicated in the plasticity of Th17 by driving their trans-differentiation into Tr1 cells.

TABLE 1

AhR Endogenous Ligands

Group	Compound	Origin
Indole Metabolites	Indole	Dietary metabolite and microbiota metabolism
	Indolo[3,2-b]carbazole (ICZ)	Dietary metabolite
	2-(Indol-3-ylmethyl)-3,3'-diindolylmethane (Ltr-1)	Dietary metabolite
	3,3'-Diindolylmethane (DIM)	Dietary metabolite
	2-(1'H-indole-3'-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE)	Endogenous/Chemical process
Phytochemicals	Indigorubin	Plants
	Indigo	Plants
Tryptophan Metabolites	Kynurenine (Kyn)	Host Metabolism
	Kynyrenic acid (KA)	Host Metabolism
	Zanthurenic acid	Host Metabolism
	Cinnabarinic acid (CA	Host Metabolism
	6-Formylindolo[3,2-b]carbazole (FICZ)	Photo-oxidation
	5-hydroxy-tryptophan (5HTP)	Host Metabolism
	Tryptamine (TA)	Microbiota metabolism
	Indol-3-acetic Acid (IAA)	Microbiota metabolism
	3-methylindole (Skatole)	Microbiota metabolism
	Indole-3-aldehyde (IAld)	Microbiota metabolism
	Indoxyl-3-sulfate (I3S)	Microbiota and Host Metabolite
Heme-derived	Bilirubin	Host Metabolism
	Biliverdin	Host Metabolism
Arachidonic Acid Metabolites	Lipoxin 4A	Host Metabolism
	Prostaglandin PGG2	Host Metabolism
	Hydroxyeicosatrienoic acid ([12(R)-HETE])	Host Metabolism