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REGULATION OF CENTRAL NERVOUS SYSTEM AUTOIMMUNITY BY THE ARYL HYDROCARBON RECEPTOR

Francisco J. Quintana

Center for Neurologic Diseases, Brigham and Women's Hospital, Harvard Medical School, 77 Avenue Louis Pasteur, Boston 02115, MA, USA

Abstract

The ligand-activated transcription factor aryl hydrocarbon receptor controls the activity of several components of the immune system, many of which play an important role in neuroinflammation. This review discusses the role of AhR in T cells and dendritic cells, its relevance for the control of autoimmunity in the central nervous system, and its potential as a therapeutic target for immune mediated disorders.

Keywords

AHR; EAE; FoxP3⁺ Tregs; Tr1 cells; Th17 cells

Introduction

Multiple sclerosis (MS) is the most common disabling neurological disease in young adults. MS is a chronic inflammatory disease that targets the central nervous system (CNS), leading to demyelination, axonal loss and, eventually, progressive disability [1]. Experimental autoimmune encephalomyelitis (EAE) is a T-cell mediated autoimmune disorder induced by immunization with CNS myelin proteins that models several aspects of MS [2]. The EAE model has led to significant advances in our understanding of mechanisms of disease pathogenesis and the development of disease modifying therapies for MS [3].

MS and EAE are driven by effector Th1 and Th17 cells reactive with CNS antigens [4,5]. *In vivo*, the activity of effector T cells is controlled by several types of regulatory T cells (Tregs), including FoxP3⁺ Tregs and FoxP3⁻ IL-10⁺ type 1 regulatory T cells (Tr1 cells) [6,7]. Thus, the equilibrium between effector and regulatory T cells is thought to control the course of EAE and MS. Moreover, since the generation of pathogenic and regulatory T cells *in vivo* is controlled by dendritic cells (DCs) [8,9], signaling pathways acting directly on T cells or indirectly on DCs are likely to affect the course of CNS inflammation.

Both MS and EAE are controlled by genetic and environmental factors. However, although much has been learnt about the genetics of CNS autoimmunity, little is known about the contribution of environmental factors. The ligand-activated transcription factor aryl hydrocarbon receptor (AhR) has been recently identified as an important pathway involved in the regulation of immune processes associated with MS and EAE. AhR is activated by a broad array of synthetic and natural ligands present in pollutants, the diet, the environment and even products of the commensal flora [10]. Thus, although AhR is obviously only one

of many signaling pathways involved, it provides a model pathway to investigate the mechanisms by which the environment shapes inflammation. In this review, we discuss the complex role of AhR in the regulation of immune processes associated to CNS autoimmunity.

The aryl hydrocarbon receptor

AhR is a ligand-activated transcription factor that can be activated by a broad array of synthetic and natural ligands [10]. When inactive, AhR is located in the cytoplasm as part of a protein complex that includes the 90kDa heat shock protein (HSP90), the c-SRC protein kinase and the AhR-interacting protein Ara9 [11]. The interaction of AhR with its ligands triggers its translocation to the nucleus, where AhR establishes protein-protein interactions with the AhR nuclear translocator (ARNT) and additional coactivators and transcription factors [11]. These AhR-containing protein complexes interact with specific sequences in target genes to control their transcriptional activity in what it is known as the “*genomic pathway of AhR signaling*”. Of note, although AhR complexes interact with the canonical AhR binding site 5'-TNGCGTG-3', the interaction of AhR with non-canonical sequences has also been reported [12-14]. In addition, it has been reported that several AhR protein interactions are only triggered by specific AhR ligands [15-17], suggesting that some transcriptional partners of AhR are recruited in a ligand-specific manner. Thus, it is possible that different ligands trigger the formation of AhR protein complexes that differ in their composition, leading to the recognition of non-canonical DNA sequences. Taken together, these data suggest that AhR might control the transcription of significantly more genes than previously appreciated, ongoing RNA-seq and ChIP-seq experiments should reveal the genome-wide effects of AhR on the transcriptional response of different cell types, and the physiological relevance of ligand-specific effects.

In addition, “*non-genomic pathways of AhR signaling*” have also been described. For example, upon its release from the AhR/HSP90/c-SRC complex, c-SRC targets multiple cellular targets [18]. Moreover, Ohtake *et al* reported that AhR is a ligand-dependent E3 ubiquitin ligase, involved in the degradation of AhR interacting proteins through the proteasome [19]. However, the relevance of these pathways for the effects of AhR on the immune response is still unknown.

Physiological AhR ligands

AhR was initially characterized as the receptor for dioxins, but the immune and liver defects observed in AhR-deficient mice suggest that natural AhR ligands play a role in normal physiology [20,21].

The diet is an important source of AhR ligands, and flavonoids represent the largest group of naturally occurring dietary AhR ligands [22,23]. Usually, dietary AhR ligands have low affinity for AhR but are converted into high affinity ligands by poorly characterized enzymatic reactions. The d-Amino Acid Oxidase, for example, generates AhR ligands from the degradation of tryptophan (Trp) [24,25]. In addition, several indoles, mostly derivatives of Trp, are AhR agonists. Examples are two Trp-derived AhR ligands: 6-formylindolo[3,2-b]carbazole (FICZ) [26] and 2-(1 *H*-indole-3-carbonyl)-thiazole-4-carboxylic acid methyl ester [27] (ITE). Notably, endogenous ligands like ITE do not induce *in vivo* many of the toxic effects reported for dioxins [28,29].

L-Kynurenine is a Trp-derived AhR agonist of particular interest for the regulation of the immune response in the CNS. L-Kynurenine is generated as result of the enzymatic degradation of tryptophan [30], through a pathway that is controlled by the rate-limiting enzymes indoleamine 2,3-dioxygenase (IDO) or *tryptophan* 2,3-dioxygenase (TDO).

Notably natural and synthetic kynurenines have important immunoregulatory activities in neuroinflammation during EAE and experimental GBM. IDO expression by dendritic cells and the administration of synthetic kynurenins suppresses EAE [31,32]. Moreover, kynurenine produced by glioblastoma multiforme cells in a TDO-dependent manner mediates the suppression of the tumor specific immune response, through a mechanism that involves AhR signaling in T cells [33]. Finally, products produced by the commensal flora have also been reported to be AhR agonists with detectable effects on the immune response [34]. Taken together, these data suggest that endogenous and environmental AhR ligands play a significant role in the regulation of the immune response.

Role of AhR in T cells during EAE

EAE development is controlled by the balance between encephalitogenic and regulatory T cells. AhR is expressed by FoxP3⁺ Tregs, Tr1 and Th17 cells; thus, it is not surprising that AhR signaling in T cells has significant effects on the immune response and the development of EAE.

Effects of AhR signaling on Foxp3⁺ Tregs

CD4⁺ FoxP3⁺ Tregs differentiated in the thymus (nTregs) and the periphery (iTregs) play a central role in the control of immune reactivity to self and non-self antigens in humans and mice [7]. Accordingly, FoxP3⁺ Tregs are thought to play a significant role in EAE. Indeed, immunization protocols similar to those used to induce EAE have been shown to expand thymic FoxP3⁺ nTregs [35]. Moreover, DCs induce FoxP3⁺ iTreg differentiation during the course of EAE in a PD-1 dependent manner [9]. However, FoxP3⁺ Tregs fail to control effector T cells in the CNS of EAE mice [36], suggesting that FoxP3⁺ Tregs are mostly involved in the regulation of the encephalitogenic response in the periphery.

AhR has been shown to play important roles both in nTregs and iTregs. AhR activation by different ligands boosts the differentiation of functional mouse and human FoxP3⁺ Tregs *in vitro* and *in vivo* [37-43]. Indeed, AhR activation by specific ligands has been shown to result in the suppression of EAE [40,41,43]. Several molecular mechanisms seem to account for these observations. AhR promotes FoxP3 expression directly [40], and also controls the epigenetic status of the *foxp3* locus, making it more accessible to additional transcription factors [44]. In addition to its direct effects on the *foxp3* locus, AhR activation was also found to increase the expression of SMAD1, which stabilizes FoxP3 expression [45].

As we already mentioned, AhR establishes protein-protein interactions with additional transcription factors to mediate its effects. Those interactions lead to the regulation of the transcriptional activity of AhR targets, but might also result in the regulation of the activity of AhR's interaction partner. For example, AhR has been shown to bind to STAT proteins to limit their activation, and this finding seems to be relevant to the effects of AhR on Foxp3⁺ Tregs. IFN signaling through STAT1 antagonizes the differentiation of FoxP3⁺ Tregs *in vitro* and *in vivo* [46,47]. We found that AhR in FoxP3⁺ Tregs limits STAT1 activation, boosting their differentiation in response to TGF 1 [48]. Moreover, in inflammatory environments a fraction of the FoxP3⁺ nTregs loses its suppressive activity and acquires an effector phenotype [49]. Thus, it is possible that by limiting STAT-dependent signaling, AhR regulates the plasticity of FoxP3⁺ Tregs *in vivo* in the context of inflammation.

FoxP3 promotes the differentiation of regulatory T cells by both inducing the expression of Treg-associated genes, and by suppressing the expression of genes linked to effector T-cell responses [50]. The inhibitory effects of FoxP3 on the expression of specific genes are mediated by its interaction with members of the Ikaros family of transcription factors, a family that includes Ikaros, Eos, Pegasus, Helios and Aiolos [51-53]. Eos, for example,

associates with FoxP3 to induce epigenetic modifications that effectively silence the expression of target genes [53]. Helios, an additional member of the Ikaros family of transcription factors, is also expressed by Foxp3⁺ Tregs, but its physiological function in FoxP3⁺ Tregs is still unknown [54,55]. We found that AhR controls the expression of Aiolos in both human and mouse FoxP3⁺ Tregs [45,56]. Indeed, we demonstrated that FoxP3⁺ interacts with the C-terminal zinc fingers in Aiolos to form a protein complex that silences IL-2 expression in FoxP3⁺ Tregs. Taken together, these data demonstrate that AhR participates both in the induction of Treg-specific genes such as *foxp3*, and in the inhibition of genes associated with effector T-cell function such as *il2*.

Several FoxP3⁺ Treg subpopulations have been identified based on the expression of transcriptional modules associated to the control of specific effector T cells [57,52,58]. We recently found that a subpopulation of FoxP3⁺ T cells characterized by the expression of TIGIT in its membrane expresses high levels of AhR (Quintana, personal communication). This FoxP3⁺ Treg population is specialized in the suppression of effector T-cell responses, suggesting that AhR expression might characterize functionally relevant subpopulations of FoxP3⁺ Tregs.

Effects of AhR signaling on Tr1 cells

FoxP3⁻ type 1 regulatory T cells (Tr1) were initially described following their generation by repeated cycles of *in vitro* stimulation in the presence of IL-10 [59]. Additional regimens, such as stimulation in the presence of antibodies to CD46, dexamethasone and vitamin D or rapamycin and IL-10 can also promote the differentiation of Tr1 cells [60,61]. Although Tr1 cells selectively outgrow in the presence of IL-10, IL-10 is not a Tr1 cell growth factor. Indeed, IL-27 has been shown to promote the differentiation of Tr1 cells [62-64].

Tr1 cells play an important role in immune homeostasis and the control of graft versus host disease, and have been linked to long-term tolerance following transplantation [65,60]. In the context of CNS inflammation, Tr1 cells outnumber Th1 and Th17 cells during the recovery phase of EAE [36]. Conversely, IL-10-deficient mice do not recover from EAE and Tr1-deficits have been reported in MS [66,67]. These observations support a physiological role for Tr1 cells in the control of CNS inflammation, particularly in the control of the effector T-cell response in the CNS, a response that is not effectively controlled by FoxP3⁺ Tregs [36].

Several transcription factors have been reported to control IL-10 expression in different scenarios, including Sp1, Sp3, C/EBP β , IRF1, STAT3 and c-Maf [68]. Among those c-Maf, in particular, has been proposed to be a universal transcription factor that regulates the production of IL-10 by T cells [68]. Recent data suggest that AhR cooperates with c-Maf to regulate Tr1 cell differentiation and IL-10 production by T cells.

Kerkvliet and coworkers reported that AhR activation by 2,3,7,8-tetrachlorodibenzo(p)dioxin induces Tr1 like cells that express granzyme B and suppress cytotoxic T-cell responses [69]. Similarly, we found that AhR activation induces the differentiation of suppressive human Tr1 cells, which can trigger apoptosis of effector T cells *in vitro* in a granzyme B dependent manner [45]. We also found that AhR controls the differentiation of murine Tr1 cells triggered by IL-27 *in vitro*, and their expansion *in vivo* in response to treatment with anti-CD3 [70,71]. Moreover, we found that AhR signaling mediates the inhibition of encephalitogenic T-cells by IL-27 [70].

Several mechanisms mediate the effects of AhR on the differentiation of Tr1 cells. c-Maf transactivates the *il10* promoter in T cells [72]. We found that AhR forms a complex with c-Maf to cooperatively transactivate the human and mouse *il10* promoter [70,45]. Although

our experiments were initially performed on T cells, AhR and c-Maf deficiency also impairs IL-10 production by macrophages, suggesting that the c-Maf/AhR complex might contribute to the role of c-Maf as a universal regulator of *il10* expression.

We recently showed that AhR in co-operation with STAT3 transactivates the *ikzf3* promoter and induces the expression of the transcription factor Aiolos, which is expressed by Tr1 cells differentiated with IL-27 [56]. Ikaros, a transcription factor closely related to Aiolos, has also been shown to transactivate the *il10* promoter in T cells [73]. Thus, it is possible that AhR controls the transcriptional activity of the *il10* promoter directly through its association with c-Maf, and also indirectly through the induction of Aiolos.

Finally, IL-21 is an autocrine growth factor that controls the expansion and stabilization of IL-27 induced Tr1 cells [74]. Impaired IL-21 signaling reduces c-Maf and IL-10 expression in Tr1 cells [74]. Conversely, c-Maf transactivates the *il21* promoter in Tr1 cells [74]. We found that the AhR complexed to c-Maf transactivates the *il21* promoter, inducing IL-21 production by Tr1 cells, and that IL-21 signaling is required for AhR expression by Tr1 cells [70]. These findings suggest an AhR-dependent positive feedback loop that stabilizes the phenotype of Tr1 cells. Moreover, taken together these data show that AhR affects multiple aspects of Tr1 cell development.

Effects of AhR signaling on Th17 cells

Th17 cells, characterized by the production of IL-17, IL-17F, IL-21 and IL-22, play a central role in MS and EAE [4]. T-cell activation in the presence of IL-6 or IL-21 and TGF β 1 promotes Th17 cell differentiation by STAT3-dependent mechanisms, and IL-21 and IL-23 expand and stabilize Th17 cells [4]. The differentiation of Th17 cells is driven by the transcription factors ROR γ t [75] and ROR γ [76], indeed mice deficient in ROR γ t and ROR γ , or mice treated with ROR γ t inhibitors [77,78] show an impaired generation of Th17 cells. However, additional transcription factors are involved in the control of specific transcriptional modules during the differentiation of Th17 cells. For example, we [79] and others [80,81] have shown that AhR controls the expression of IL-22 and IL-21 and the encephalitogenic potential of Th17 cells.

We [40] and others [82,81] reported that AhR activation promotes the differentiation of IL-17⁺ T cells, and increases production of IL-21 and IL-22. Conversely, AhR deficiency abrogates IL-22 production by Th17 cells [83,81]. However, differently from the role of AhR in Tr1 cells in which it directly controls the expression of the cytokine that defines the lineage (IL-10), AhR does not directly control the expression of *il17a* or *il17f* in Th17 cells [84,85].

The dysregulated activity of TH17 cells results in tissue inflammation; thus, several mechanisms are in place to control their generation. IL-2, for example, interferes with the early stages of Th17 cell differentiation [86-88]. Thus, it has been postulated that the differentiation of Th17 cells *in vivo* requires the uptake of IL-2 by FoxP3⁺ Tregs. However, new data suggest that AhR expressed in Th17 cells plays an active role in limiting the inhibitory effects of IL-2 on Th17 cell differentiation. Veldhoen and coworkers reported that AhR limits the activation of STAT5 in Th17 cells [83], interfering with the inhibitory signals provided by IL-2 on Th17 cell differentiation. In addition, we have recently found that AhR is part of a transcriptional module that limits the autocrine effects of IL-2 during Th17 cell differentiation. Specifically, we found that AhR in cooperation with STAT3 induces the expression of Aiolos in Th17 cells, which then modifies the epigenetic status of the *il2* promoter effectively silencing IL-2 expression [56]. This cell-autonomous inhibition of IL-2 production alleviates the inhibitory effects of IL-2 on the early stages of Th17 cell differentiation.

Several stages can be identified during the differentiation of Th17 cells. An initial stage can be defined after T-cell activation in the presence of TGF 1 and IL-6, followed by a second stage that involves the expansion and stabilization of fully pathogenic Th17 cells by IL-21 and IL-23. The expression of AhR is highest during the early stages of Th17 cell differentiation induced by TGF 1 and IL-6 [89]. These Th17 cells express AhR, IL-10, and additional molecules associated with IL-10 production, such as c-Maf and Aiolos [89]. Indeed, these Th17 cells are not fully pathogenic [89] and do indeed limit the development of EAE in co-transfer experiments [90]. In these cells, IL-10 production is AhR-dependent (Quintana, personal communication). IL-21 and IL-23 signaling later on activate transcriptional modules that expand and stabilize Th17 cells, and lead them to acquire a pathogenic phenotype [91,89,92,85]. In these pathogenic Th17 cells, AhR controls IL-21 and IL-22 expression [82,40,83,81]. Taken together, these data suggest that AhR plays different roles at each stage of Th17 cell differentiation: it promotes IL-10 production and limits the inhibitory effects of IL-2 during the early events of Th17 cell differentiation, and controls IL-21 and IL-22 production in fully pathogenic Th17 cells.

Role of AhR in DCs during EAE

DCs control effector and regulatory T cells *in vivo* [93]. Indeed, abnormalities in the expression of Th1 and Th17 polarizing cytokines are found in DCs from MS patients [94]. However, the role of DCs in CNS autoimmunity is not restricted to the polarization of T cells in peripheral immune organs. DCs promote T-cell entry into the CNS [95], the polarization of encephalitogenic T cells within the CNS [8,96], and the spreading of the autoimmune response to new CNS epitopes [97]. Therefore, pathways regulating DC activity are likely to play a significant role in MS and might also offer new targets for therapeutic intervention. Recent data suggest that AhR controls DC activation *in vitro* and *in vivo*, affecting the course of CNS inflammation.

Mechanisms of DC modulation by AhR

AhR regulates the activity of DCs in several experimental models, but the molecular mechanisms involved are mostly unknown. AhR is known to interact with and regulate the activity and degradation of NF- B and AP-1 [98,99], transcription factors that have been recently shown to control of the transcriptional response of DCs to stimulation [100,101]. Thus, it is possible that by mean of its ability to establish protein-protein interactions that result in the functional regulation of its interaction partners, AhR controls the activity of DCs. Nevertheless, regardless of the transcriptional mechanisms involved, AhR has been clearly shown to affect the ability of antigen presenting cell (APC) function of DCs.

AhR activation decreases the expression of MHC class-II and costimulatory molecules, and also the production of Th1 and Th17 polarizing cytokines by DCs [37,102-104,41,105,106,42]. Indeed, AhR activation boosts the ability of DCs to promote the differentiation and expand FoxP3⁺ Tregs [102-104,41]. These effects involve at least two types of tolerogenic metabolites: 1) *Kynurenins*. AhR activation up-regulates the expression of IDO in DCs [103,104], which catalyzes the production of kynurenine. As we already mentioned, kynurenine is an AhR ligand, and promotes FoxP3⁺ Treg differentiation through a mechanism that, strikingly, is also dependent on AhR signaling in T cells. 2) *Retinoic acid (RA)*. AhR activation in DCs results in the up-regulation of the enzymatic machinery that controls the production of RA [48], a metabolite that promotes the differentiation of FoxP3⁺ Tregs [107]. Indeed, the differentiation of FoxP3⁺ Tregs by DCs pre-treated with the AhR ligand ITE can be significantly inhibited with inhibitors of RA signaling [48].

Although these immunomodulatory effects of AhR signaling have been described in DCs, they are likely to extend to additional APCs, such as macrophages. Indeed, AhR deficient macrophages develop a dysregulated response to stimulation *in vitro* and *in vivo* [108,109]. Considering the important role played by microglia and inflammatory monocytes in EAE, AhR signaling in these cells is likely to have significant effects on CNS inflammation.

Therapeutic targeting AhR in APCs with nanoparticles

The broad expression pattern of AhR constitutes a challenge for the therapeutic exploitation of its immunomodulatory effects. Nanotechnology, however, offers new approaches for the delivery of one or several compounds to specific cell-types *in vivo* [110]. Based on the tolerogenic effects of AhR activation in DCs, we engineered nanoparticles (NPs) to co-deliver the AhR ligand ITE together with myelin-specific antigens to APCs *in vivo* [43].

We found that NPs protect ITE from degradation by liver enzymes, increasing its half life *in vitro* and *in vivo* [43]. Moreover, ITE-loaded NPs activated AhR signaling in DCs, inducing a tolerogenic phenotype characterized by the reduced ability to generate Th1 and Th17 cells, and an increased ability to promote FoxP3⁺ Treg differentiation *in vitro* and *in vivo*. Accordingly, NPs loaded with ITE and myelin antigens suppressed the development of EAE both in preventive and therapeutic paradigms, and these effects were linked to the generation of myelin-specific Tregs. Taken together, these data suggest that NP-based administration offers a new avenue for the selective activation of AhR in APCs and its therapeutic exploitation in immune-mediated disorders.

Conclusions

AhR signaling regulates several disease-relevant immune processes in EAE, and likely in MS; these processes are summarized in Figure 1. AhR signaling controls the immune response by acting at several levels: it affects the differentiation of specific T-cell lineages, and also controls the expression of effector cytokines, autocrine growth/stabilizing factors, and transcriptional modules that limit inhibitory signals. The ubiquitous expression of AhR poses a challenge for its use as a therapeutic target. However nanoparticle-based approaches to co-deliver AhR ligands and antigens to APCs *in vivo* might offer a new therapeutic avenue for the induction of antigen specific tolerance in immune-mediated disorders. In addition, AhR provides a molecular pathway to investigate the complex effects of the environment on the immune response.

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Figure 1.
Effects of AhR in the regulation of the encephalitogenic T cell response.