Genetic and environmental factors contribute to the development of immune-mediated diseases. Although numerous genetic factors contributing to autoimmunity have been identified in recent years, our knowledge on environmental factors contributing to the pathogenesis of autoimmune diseases and the mechanisms involved is still limited. In this context, the diet, microbiome, geographical location, as well as environmental pollutants have been shown to modulate autoimmune disease development. These environmental factors interact with cellular components of the immune system in distinct and defined ways and can influence immune responses at the transcriptional and protein level. Moreover, endogenous metabolites generated from basic cellular processes such as glycolysis and oxidative phosphorylation also contribute to the shaping of the immune response. In this minireview, we highlight recent progress in our understanding of the modulation of the immune response by the aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor whose activity is regulated by small molecules provided by diet, commensal flora, environmental pollutants, and metabolism. We focus on the role of AhR in integrating signals from the diet and the intestinal flora to modulate ongoing inflammation in the central nervous system, and we also discuss the potential therapeutic value of AhR agonists for multiple sclerosis and other autoimmune diseases.

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS). In 85% of the affected individuals, MS initially presents with a relapsing-remitting course characterized by temporally defined relapses, which are followed by a varying degree of remission. Most patients eventually enter the secondary progressive phase of MS, which is characterized by the progressive and irreversible accumulation of neurological deficits (1). Several biological pathways are involved in the regulation of the immune response in MS both in the peripheral and central immune compartment and are thought to play dominant roles in the different stages of the disease. Although the role of several molecules such as cytokines and toll-like receptor agonists in MS pathology has been studied at length, particularly in relation to the relapsing-remitting phase of the disease, only recently has the role of metabolites generated in basic biological processes such as glycolysis and oxidative phosphorylation become appreciated with regard to their relevance for the development, propagation, and resolution of autoimmune inflammation. Prominent examples of endogenous metabolites with central roles in MS pathology include bioactive lipids, reactive oxygen species, and adenosine triphosphate (ATP) (2–13). The effects of these endogenous metabolites are modulated by a multitude of exogenous factors such as pollutants, dietary factors, and products from the commensal flora to trigger transcriptional programs that control the immune response during MS. Ultimately, the understanding of these molecular mechanisms is important for the identification of druggable targets for efficacious and safe therapeutic intervention in MS and other immune-mediated diseases.

Atomic hydrocarbon receptor (AhR) structure and function

AhR is a ligand-dependent transcription factor that can be activated by a broad range of molecules provided by the environment, diet, commensal microbiota, and metabolism (14, 15). Upon ligand binding, AhR translocates to the nucleus and regulates the expression of diverse and ligand-specific target genes involved in detoxification (Cyp1a1 (16)), NF-κB regulation (17), or immune regulation (15, 18–20), among others. In that way, AhR plays an important role in the regulation of autoimmune inflammatory diseases of the gut (e.g. Crohn’s disease and ulcerative colitis) (21, 22), connective tissue (rheumatoid arthritis) (23), the skin (psoriasis) (14, 24, 25), and the central nervous system (MS) (2, 6, 7, 9, 10, 26–30). AhR regulates the inflammatory response at multiple levels, acting on immune cells in the periphery (e.g. T-cells, dendritic cells, intraepithelial lymphocytes (IELs)) and locally at the site of ongoing inflam-
interaction. Thus, AhR integrates environmental and metabolic signals into systemic and local immune regulation.

AhR is responsive to a variety of ligands that fall into two major classes categorized by chemical structure. The first class is composed of tryptophan derivatives that can be derived from the diet or endogenously produced by the host organism (14, 15, 27, 31, 32). These tryptophan-derived ligands include indoles, 6-formylindololo(3,2-b)carbazole (FICZ), 2-(1H-indol-3-ylcarbonyl)-4-thiazolecarboxylic acid methyl ester, and kynurenine. A second class of AhR ligands contains aromatic hydrocarbons, which are largely derived from environmental toxins (33). Some aromatic hydrocarbon ligands that activate AhR include 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and polychlorinated dibenzofuran (34). Interestingly, in response to these distinct classes of ligands or even within subclasses of each group, AhR exhibits differential downstream cellular responses that may activate distinct downstream pathways, many of which will be discussed in this minireview.

When inactive, AhR is located in the cytosol complexed to the 90-kDa heat-shock protein (HSP90), c-SRC, and AhR-interacting protein (35). Upon binding of an agonist, AhR undergoes conformational changes that lead to its heterodimerization with the AhR nuclear translocator (ARNT) and subsequent translocation to the nucleus. In the nucleus, this AhR-ARNT complex binds to xenobiotic response elements in regulatory regions of responsive genes to induce specific transcriptional programs (5, 14, 29, 30). Through this mechanism, AhR affects the differentiation of several cell types in the immune system relevant for inflammation in the gut and the central nervous system (2, 7, 26, 36). Of note, AhR can also control cellular responses through non-genomic mechanisms that involve the activation of specific kinases in the cytoplasm, also in a ligand-dependent manner (18, 20, 23, 37).

**AhR-dependent immune cell regulation**

AhR has been shown to affect the transcriptional programs of regulatory- and interleukin-17 (IL-17)-producing T helper cells (Tregs and Th17 cells, respectively) (7, 28, 38), among others. In FoxP3+ Tregs, AhR regulates the transcription and epigenetic status of the Treg master transcription factor FoxP3 (7, 29, 30, 39, 40). In addition, AhR has been shown to participate in the differentiation of FoxP3–IL-10–producing type 1 regulatory T-cells (Tr1 cells) induced by IL-27 (41–43). IL-27 induces the expression of AhR and the transcription factor c-Maf through a STAT3-dependent mechanism (6, 30), suggesting a cross-talk between AhR, IL-27, and c-Maf. Indeed, we detected the presence of AhR-responsive elements in the promoter of IL10 in spatial proximity to c-Maf-binding sites (Maf-responsive elements (MAREs)) (30, 42), and we observed that both AhR and c-Maf are required for the induction of IL-10 expression (8, 44). AhR and c-Maf also cooperatively induce the expression of IL-21, which acts as an autocrine growth factor to stabilize and expand Tr1 cells (30).

AhR has additional roles in the transcriptional control of Tr1 cells, as it mediates the control of their transcriptional program by metabolic and environmental cues. The membrane-bound ectonucleotidase CD39 catalyzes the conversion of extracellular adenosine triphosphate (ATP) to adenosine diphosphate (ADP), which is further processed by CD73 to generate the anti-inflammatory metabolite adenosine (45). We found that STAT3–AhR signaling promotes CD39 expression in Tr1 cells (28). Indeed, CD39 boosts Tr1 cell differentiation by depleting extracellular ATP, which promotes AhR degradation and consequently arrests Tr1 cell differentiation, through a mechanism mediated by hypoxia-inducible factor 1-α (HIF1-α). Thus, AhR participates in regulatory feedback loops that promote and stabilize Tr1 cell differentiation (Fig. 1).

AhR also controls transcriptional programs associated with the epigenetic regulation of cellular responses. Aiolos is a transcription factor of the Ikaros family involved in the development of lymphoid cell lineages (5, 29, 46) through different mechanisms, for example the regulation of the epigenetic status of target genes (47–49). In human Treg cells, for instance, FoxP3 and Aiolos form a heterodimERIC complex that binds the Il2 promoter and suppresses IL-2 expression (29). AhR pro-

![Figure 1. AhR transcriptional mechanisms that regulate the function of T-cell subsets.](image-url)
motes the expression of both FoxP3 and Aiolos (5, 29). For example, AhR activation in a colitis model using the AhR agonist TCDD led to demethylation of CpG islands in the Foxp3 promoter and subsequent methylation of the Il17 promoter in T-cells from the lymph node, increasing the FoxP3+/Treg/Th17 cell balance (40). Moreover, AhR also promotes the expression of the epigenetic modifier Aiolos, which suppresses IL-2 expression in the early stages of Th17 cell differentiation (50, 51), to influence the development of pathogenic and regulatory T-cells in mice and humanized mouse models of inflammatory bowel disease (IBD) (5, 52). Thus, through its effects on the control of epigenetic regulators, AhR plays an important role on the regulation of transcriptional programs that control the immune response.

One study recently demonstrated that AhR can regulate microRNA (miR) signatures, which is an additional mechanism by which AhR can control the epigenetic status of Foxp3 (53). For instance, application of dietary indoles, which are known to activate AhR, induced the differentiation of naïve CD4+ T-cells toward a Treg fate instead of a Th17 fate, but this effect was lost in AhR-deficient mice. Moreover, indole activation of AhR recruited distinct miRs to the promoter of IL17 but prevented miR recruitment to the Foxp3 promoter. However, treatment with FICZ, a known inducer of Th17 cell differentiation through AhR activation (7), caused the silencing of FoxP3 by miRs and the expression of IL17. These interesting results point to yet another mode of AhR-dependent regulation of gene expression, by non-coding miRs, and also highlight the importance of cellular context where ligand-specific effects of AhR signaling regulate critical cellular events. Collectively, these observations suggest that AhR participates in the transcriptional control of T-cell gene expression and cell fate in response to the local milieu, for example within inflamed tissues and exogenous signals, such as pollutants and metabolites.

The gut, for instance, is rich in both AhR ligands and extracellular ATP produced by commensal bacteria (54, 55). AhR activation induces the expression of the receptor tyrosine kinase Kit, which contains AhR-responsive elements in its promoter and plays a central role in innate lymphoid cell (ILC) development (22). Thus, AhR activation by ligands provided by the diet and the commensal flora promotes the development of ILCs that contribute to intestinal homeostasis. Similarly, AhR agonists provided by the diet and the gut flora control the development of IELs that contribute to intestinal homeostasis (21). The specific effects of AhR in each immune cell type, however, are determined by its interaction with additional cell type and tissue-specific transcription factors (e.g. c-Maf, Aiolos, STAT3, and HIF1-α) (5, 6, 30). Considering that deficits in AhR signaling have been linked to experimental and human IBD (56), these findings highlight the important function of AhR as a modulator of the activity of immune cells in response to cues provided by the local microenvironment in health and disease (14, 22, 28). Moreover, they identify AhR as a modulator of commensal/host interactions.

Beyond modulating the function of T-cell subsets in the periphery and lymphocytes in the gut, AhR has been shown to modulate the function of the immune system more generally, for example by modulating the function of B cells, dendritic...
cells, and monocytes (14, 57–63). One mechanism of increasing interest is the interaction between IL-4 and AhR signaling pathways. For instance, upon engagement of B cell receptors and treatment with IL-4, AhR is up-regulated and promotes efficient cell cycle transitions in proliferative B cells at least in part by regulating cyclin expression (57). Conversely, loss of AhR leads to impaired proliferative capacity in B cells, an important phenotype given the role AhR plays in cancer (58).

In dendritic cells, activation of AhR by endogenous tryptophan-derived agonists led to the suppression of EAE (27) as a result of the induction of a tolerogenic phenotype in dendritic cells that promoted Treg differentiation. In monocytes, however, activation of AhR using the halogenated aromatic hydrocarbon agonist VAF347 caused arrest of monocyte differentiation (64). Together, these results observed in distinct types of immune cells suggest that AhR functions both in a ligand-dependent and a cell type-specific manner to regulate normal and pathogenic cellular events. For summary, see Table 1.

Astrocytes in MS

Astrocytes are the most abundant cell type in the mammalian brain, outnumbering neurons ~4:1 (65, 66). In addition to their important roles in neural development, plasticity, metabolism, and neural circuit repair (65, 67–69), astrocytes have been recognized to control inflammatory processes in the central nervous system during MS since the work of Charcot in the 19th century (70, 71), but only recently are the molecular mechanisms being defined (2, 10, 95). Astrocyte activity is regulated by several stimuli relevant for MS (3), including a variety of cytokines and chemokines (65), metabolites such as ATP (72), and apoptotic cell debris (e.g. lipids) (73), among others. Several of these pathways converge on common downstream transcriptional programs that activate pro-inflammatory molecules such as AP-1, NF-κB, and STATs (74). The activation of these pathways contributes to the pathology of MS and other neurological diseases through astrocyte intrinsic and extrinsic mechanisms. For instance, astrocytes interact with inflamed microglia during MS pathogenesis (75) to control their activation status and disease-promoting function (76, 95). Astrocytes also recruit inflammatory monocytes into the CNS through the production of chemokines (77). Astrocytes also interact with neurons (3, 78) through mechanisms that can modulate neuronal death. Indeed, astrocytes secrete neurotoxic molecules such as pro-inflammatory cytokines (e.g. TNF-α), reactive oxygen species, IL-6 and IL-1β, and nitric oxide (3). It was recently reported that microglia induce formation of neurotoxic astrocytes through a combination of IL-1α, TNFα, and complement component 1q, which could be a pathway relevant in MS pathogenesis (97). Astrocytes, however, are also capable of producing a variety of both pro- and anti-inflammatory signals such as CCL2 (77, 79–81), IGF-1 (82), ciliary neurotrophic factor (83), and leukemia inhibitory factor (LIF) (84, 85). These features identify astrocytes as important regulators of inflammation and neurodegeneration.

Role of AhR in astrocyte-mediated inflammatory processes

We recently described a new role for AhR in controlling astrocyte-driven pathology in MS (2). We found that type-I interferons (IFN-Is) induce AhR expression in astrocytes, triggering AhR-dependent anti-inflammatory transcriptional responses. Conditional ablation of AhR in astrocytes led to exacerbated disease and failure to recover during EAE. Mechanistically, AhR deletion as well as lack of AhR-activating ligands resulted in the increased production of pro-inflammatory mediators, including Ccl2, Csf2, and Nos2, reflecting the exacerbated activation of NF-κB. As mentioned previously, AhR activity is regulated by small molecules such as dietary tryptophan generated by commensal bacteria (14, 15). Indeed, we found that AhR agonists provided by the diet and the commensal flora reached the CNS and activated this anti-inflammatory response in astrocytes, limiting CNS inflammation during EAE (Fig. 2).
In complementary studies using samples taken from MS patients, we detected the up-regulation of AhR in astrocytes, which coincided with activation of the IFN-1 pathway in astrocytes (2). Strikingly, we detected decreased AhR activity in MS lesions as compared with controls, reflecting the presence of reduced levels of AhR agonists in serum samples from MS patients. These findings have several implications for our understanding of disease pathogenesis in MS and potentially other inflammatory diseases. First, it identifies AhR activation as a potential therapeutic approach. Indeed, laquinimod, a drug being developed to treat MS (86–88), crosses the blood-brain barrier and ameliorates EAE (and potentially MS) in an AhR-dependent manner (89, 90). In a phase III clinical trial, laquinimod reduced brain atrophy in MS, a process thought to reflect neurodegeneration driven at least partially by astrocytes (91). Second, it suggests that deficits in AhR ligand availability may contribute to MS pathogenesis. The origin of these ligands is unknown. However, it possibly reflects alterations in the uptake and metabolism of physiological AhR agonists in MS. Dietary or probiotic interventions to boost the levels of these AhR agonists may be of therapeutic value for MS patients. Third, these data point to a new gut-brain signaling axis in controlling the development of inflammatory and degenerative pathology in humans. These findings also add to recent advancements made in studies of neuropsychiatric disease where the gut microbiota modulate transcriptional programs that control social behavior (92), modulate synaptic dysfunction (93), and can modulate phenotypes associated with autism (94). It should also be kept in mind that, besides acting as a CNS sensor for immunomodulatory metabolites produced in the gut, based on its effects on gut immunity AhR may also shape the gut flora, impacting the gut-brain axis at multiple levels.

Concluding remarks

AhR integrates environmental and metabolic signals to modulate both peripheral immunity and local CNS inflammation. Thus, investigating the role of AhR signaling in health and disease provides an opportunity to understand the mechanisms by which the environment controls the development of autoimmune immunity in MS and other diseases. More importantly, AhR offers unique therapeutic opportunities based on the design of AhR targeting synthetic small molecules or the use of dietary or probiotic approaches to modulate the levels of natural AhR ligands.

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