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Chemical sensing in development and function of intestinal lymphocytes

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The immune system of the intestinal tract has the challenging task of recognizing and eliminating intestinal pathogens while maintaining tolerance to dietary and commensal antigens; therefore, it must be able to sense environmental cues within the intestine and mount suitable responses dictated by their pathogenic or nonpathogenic nature. The aryl hydrocarbon receptor (AHR) was originally characterized as a chemical sensor of the environmental pollutant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) [12]. More recently, AHR has emerged as a major chemical sensor expressed in many intestinal immune cells that enables them to distinguish nutritional and microbial cues and is, therefore, important for development, maintenance and function of the intestinal immune system. In this review, we will highlight recent advances in our knowledge of the role of AHR signaling in intestinal innate lymphoid cells (ILC), T cells and B cells.

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Introduction

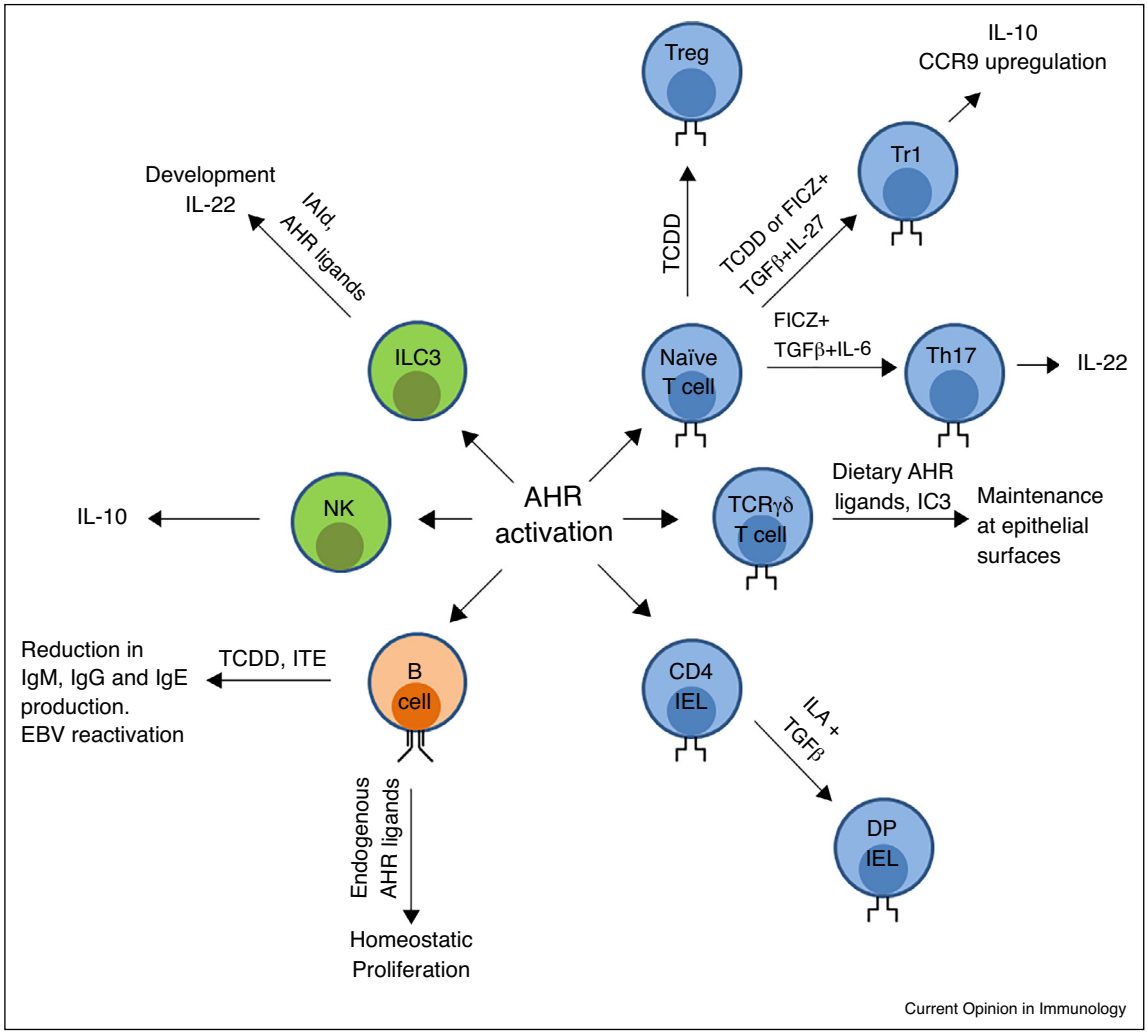
The aryl hydrocarbon receptor (AHR) belongs to the family of Per-Arnt-Sim (PAS) transcription factors, which are evolutionarily conserved and participate in the sensing of environmental stimuli. They encompass molecules that are involved in chemical sensing, such as AHR, in the regulation of circadian rhythm, such as BMAL1 and BMAL2, and in the detection of oxygen concentrations, such as HIF-1α, HIF-2α and HIF-3α [1–3]. AHR is widely expressed in different tissues [4] and its activity is tightly controlled. It is normally present in the cell cytoplasm in an inactive state bound to proteins, including the chaperone Hsp90 [5], AHR interacting protein (AIP) [6,7] and the cochaperone p23 [8], that enhance the ability of AHR to bind ligands and prevent its migration to the nucleus. Upon ligand binding, AHR is released from the chaperones, translocates to the nucleus and binds to the AHR-nuclear translocator (ARNT) [9]. This heterodimer binds to dioxin responsive elements (DRE) of various enhancers and promoters to induce transcription of target genes [10]. Typically, these include the microsomal cytochrome P450-dependent monooxygenases CYP1A1 and CYP1A2, which participate in the metabolism of AHR ligands [1]. The AHR signaling pathway has been recently reviewed in detail [11].

Generation and degradation of intestinal AHR ligands

Although the most extensively studied ligands for AHR are pollutants and xenobiotics, such as benzo(a)pyrene, 3-methylcolantrene and TCDD [11,12], the broad expression of AHR in intestinal immune cells has suggested the presence of intestinal physiological ligands that activate AHR. Several AHR ligands with diverse origins and affinities have been reported (Figure 1) [13,14]. Exogenous ligands comprise molecules derived from the diet, particularly cruciferous vegetables like broccoli, cauliflowers or cabbages. These vegetables convert tryptophan into glucobrassicin, which is metabolized into indole-3-carbinol (IC3). IC3 dimerizes in the acidic environment of the stomach, generating diindolylmethane (DIM) and indolylcarbazole (ICZ), which activate AHR [15]. Other dietary ligands of AHR are natural flavonoids present in fruits and vegetables, such as galangin, genystein, chrysin, apigenin and quercetin [16].

Members of the intestinal microbiota are also able to catabolize tryptophan into AHR ligands, which prolong the healthspan of the host [17]. Species of lactobacilli, including *Lactobacillus bulgaricus* [18] and *Lactobacillus reuteri* produce AHR ligands, such as indole-3-aldehyde (IAId) and indole-3-lactic acid (ILA), that modulate responses of intestinal innate and adaptive lymphocytes, and ameliorate inflammation [19,20••,21]. Pathogenic bacteria, such as *Mycobacterium tuberculosis* (*Mtb*) and *Pseudomonas aeruginosa* (*P. aeruginosa*), produce pigmented virulence factors that act as AHR ligands. Phenazines from *P. aeruginosa* and naphthoquinone phthiocol (Pht) from *Mtb* bind AHR, eliciting an innate immune defense pathway that contains the infection in hematopoietic and epithelial cells [22]. *Malassezia furfur*, a yeast that can be found in the skin, secretes AHR ligands, such as malassezin and ICZ [23,24]. Thus, because it can sense such a wide range of nutritional and microbial molecules from

Figure 1



Impact of AHR activation on different lymphocyte populations. The effect of diverse AHR ligands on lymphocyte populations are depicted. TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, FICZ = 6-formylindolo(3,2-b)carbazole, IC3 = indole-3-carbinol (IC3), ITE = 2-(1′H-indole-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester, ILA = indole-3-lactic acid, IAld = indole-3-aldehyde.

different origins, AHR plays a prominent role in deciphering environmental cues within the intestine.

AHR ligands also include tryptophan derivatives such as kynurenine, which is generated by an endogenous pathway of tryptophan metabolism that utilizes the enzymes indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) [25]. Although kynurenine is a low affinity AHR agonist, two novel condensation products derived from kynurenine, called trace extended aromatic condensation products (TEACOPs), were recently shown to be active at low picomolar levels; this suggests that kynurenine may act as an AHR pro-ligand that requires yet undefined chemical conversions to become an effective AHR agonist [26•]. Exposure of tryptophan to UV light also generates a potent metabolite that activates AHR, known as 6-formylindolo(3,2-b)carbazole (FICZ) [27]. Whether the endogenous and exogenous pathways that degrade dietary tryptophan to generate AHR ligands affect each other and/or AHR activation remains unclear.

The bioavailability of AHR ligands also depends on AHR activation and subsequent transcriptional activation of monooxygenases, such as CYP1A1, because monooxygenases participate in the metabolism of AHR ligands. Accordingly, constitutive expression of CYP1A1 in mice in which the *Cyp1a1* gene is placed under control of the *Rosa26* promoter results in much lower concentrations of AHR ligands in the intestine [28••]. Thus, AHR activation by AHR ligands triggers a negative feed-back loop that limits the availability of AHR ligands and hence regulates AHR activation.