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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

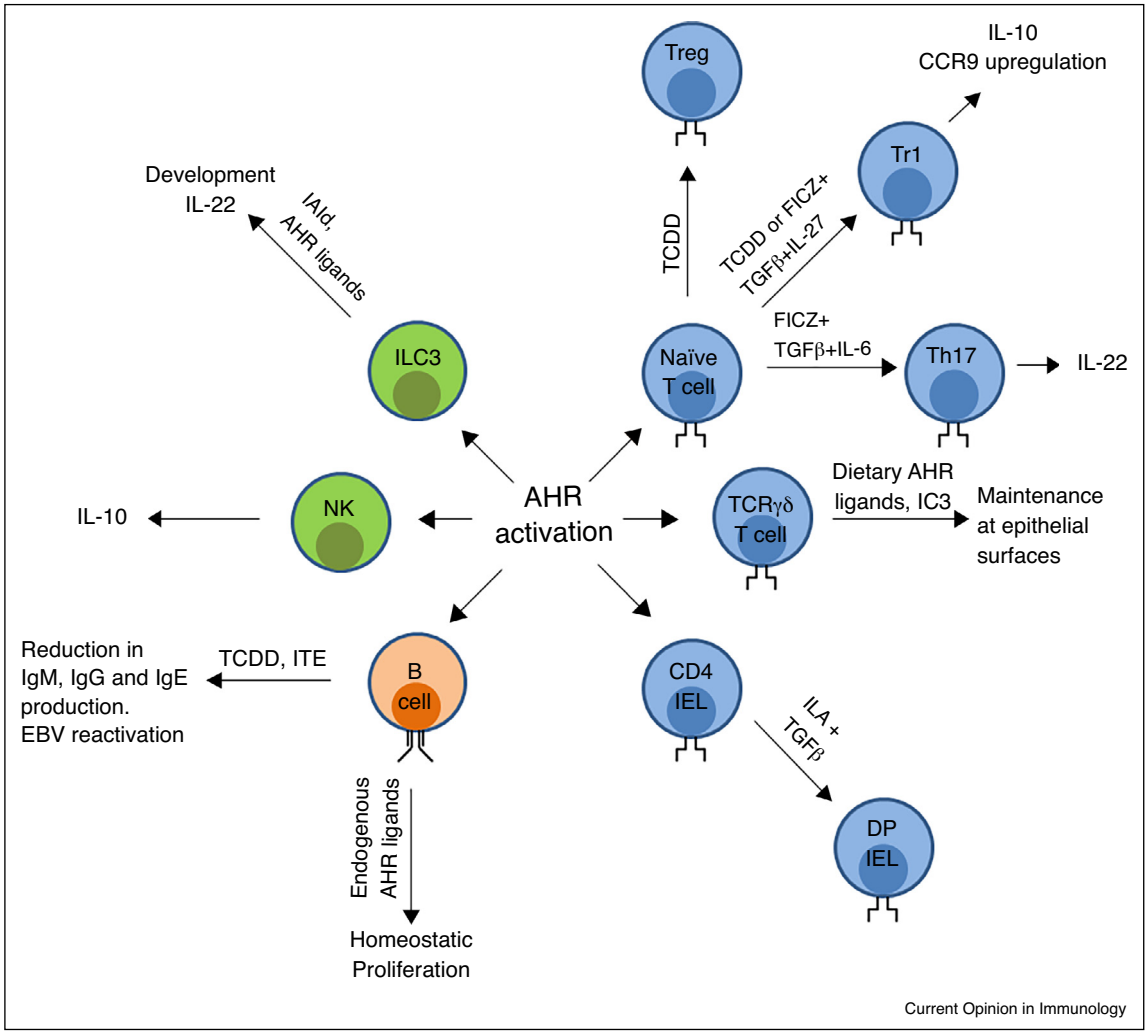
The aryl hydrocarbon receptor (AHR) belongs to the family of Per-Arnt-Sim (PAS) transcription factors, which are evolutionarily conserved and participate in the sensing of environmental stimuli. They encompass molecules that are involved in chemical sensing, such as AHR, in the regulation of circadian 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.

Impact of AHR on innate lymphoid cells

Innate lymphoid cells (ILCs) are non-T, non-B lymphocytes that are present throughout the body and enriched in frequency at mucosal surfaces. They are activated primarily through cytokine receptors and respond by producing signature cytokines that mirror adaptive T cell responses. Natural killer cells (NK) represent the innate counterpart of cytotoxic T cells, while ILC1s, ILC2s and ILC3s share key features with Th1, Th2 and Th17/Th22 cells respectively [29,30]. ILC3s secrete IL-22 and promote postnatal development of cryptopatches and isolated lymphoid follicles through expression of lymphotoxin [31]. AHR is a central node in ILC3 development (Figure 1): while Runx3 and its downstream target RorγT promote ILC3 development through AHR induction [32], Ikaros inhibits ILC3 development through inhibition of AHR expression [33]. AHR acts by inducing expression of Notch [31], and by stabilizing c-Kit expression [34]. AHR-deficient mice harbor very few ILC3s and consequently have poorly developed cryptopatches and isolated lymphoid follicles [34] as well as insufficient production of IL-22 in the intestine; these defects result in susceptibility to *Citrobacter rodentium* [35]. Moreover, minimal intestinal IL-22 permits overgrowth of segmented filamentous bacteria (SFB). This dysbiosis causes a compensatory increase in Th17 that induces colitis [36]; inadequate intestinal IL-22 also exacerbates weight loss after *Toxoplasma gondii* infection due to an enhanced T cell response to *T. gondii* and microbiota antigens [37]. AHR ligands that are produced by members of the microbiota under conditions of unrestricted tryptophan supply (like indole-3-aldehyde generated by *Lactobacilli*) foster IL-22 production by ILC3s and resistance to *Candida albicans* colonization [19]. Conversely, constitutive expression of Cyp1a1, which severely limits the amount of AHR ligands present in the intestine, results in fewer effective ILC3s and consequent susceptibility to enteric infections [28••]. In humans, IL-22 producing ILC3s differentiate into IFNγ-producing ILCs if AHR signaling is blocked, suggesting that ongoing AHR signaling is required to maintain the prototypic ILC3 phenotype [38]. In addition to ILC3s, AHR ligands promote NK cell cytotoxic activity and IFNγ production, which support NK cell-mediated antitumor activity *in vivo* [39]. Moreover, AHR is required for IL-10 production by NK cells after *T. gondii infection* [40]. Thus, AHR signaling impacts several arms and cell types within the intestinal innate lymphoid system.

Requirement of AHR for differentiation of intestinal T cells

The role of AHR in T cells was initially demonstrated by the induction of T cells with regulatory potential in graft-versus-host-disease after administration of TCDD to mice [41]. AHR signaling contributes to the differentiation and function of several T cell populations (Figure 1). AHR is required for IL-22 production by TH17 cells *in vivo* and *in vitro* [42–45], particularly in the presence of TGFβ [46]. Moreover, distinct AHR ligands — TCDD and FICZ — promote the differentiation of Tregs and Th17 cells respectively [42,43]. The induction of either Tregs or Th17 cells by high affinity ligands depends on the dose and duration of AHR activation [47••]. AHR signaling also promotes the development of Tr1 cells in mice and humans. Specifically, stimulation of T cells with TGFβ and IL-27 induces AHR, which binds to the transcription factor c-Maf. AHR and c-Maf transactivate the IL-10 and IL-21 promoters, resulting in the differentiation of Tr1 cells [48•]. Moreover, AHR contributes to metabolic programming of Tr1 cells: while HIF1-α promotes the early glycolytic metabolism of Tr1 cells, AHR promotes HIF1-α degradation and takes control of late Tr1 cell glycolysis [49]. Finally, AHR enhances Tr1 expression of genes involved in intestinal homing, such as CCR9 [50]. In the small intestine, AHR signaling is required for development and maintenance of diverse T cell populations located underneath the epithelial cell layer of the small intestine, collectively defined as intraepithelial lymphocytes (IEL) (Figure 1). TCRγδ IELs (TCR Vγ5 cells) and TCRαβ CD8αα+ IELs require dietary AHR ligands. While these IELs can develop, home to their target organs, and proliferate in the absence of AHR, they require AHR to persist at epithelial sites in both the intestine and skin [51]. More recently, AHR signaling was found to be critical for the development of another IEL population located in the small intestine. The differentiation of TCRαβ CD4+CD8αα+ IELs (DP IELs) from TCRαβ CD4+ IELs requires cell-intrinsic AHR activation by indole-3-lactic acid produced by *L. reuteri* [20••] together with TGFβ [52,53]. Collectively, these findings illustrate how AHR signaling bridges environmental cues with intestinal T cell responses.

Impact of AHR on B cells

The suppression of humoral immune responses by TCDD exposure has been known since the 1970s [54]. B cells express low levels of AHR, which increase after BCR activation and IL-4 treatment through a STA6-dependent pathway [55]. Notably, marginal zone B cells, B1 B cells and plasma cells have higher levels of AHR than do other subsets [56••]. TCDD binding to AHR induces BACH2 expression, which inhibits PRDM1 expression and B cell differentiation [57]. The AHR ligand 2-(1′H-indole-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE), which derives from tryptophan metabolism, suppresses the expression of IgM, IgG1, and IgE in purified B cells activated with anti-CD40 antibody and IL-4 [58]. Interestingly, *in vivo*, adoptively transferred AHR-deficient B cells proliferate poorly compared to AHR sufficient cells, due to their inability to express cyclin O [56••] (Figure 1). Thus, endogenous ligands may have a different impact on B cells than do exogenous ligands like TCDD. In humans, TCDD stimulation of B cells activates SHP-1, augments BCL-6 protein levels and curtails CD80 and CD69 expression, which collectively

indicate impaired cellular activation [59]. TCDD also enhances transcription of BZLF1, an immediate-early gene of the Epstein–Barr virus (EBV) that mediates the switch from the latent to the lytic form of infection in B cell lines and in a salivary gland epithelial cell line [57]. AHR activation in human B cells can also reduce IgM production; a combination of 3 variants (P517S + R554K + V570I) of AHR is necessary to impair TCDD-mediated suppression of IgM secretion [60]. While the studies outlined above have shown that AHR can temper B cell responses, extensive work still needs to be done to understand how AHR ligands affect humoral responses at mucosal sites.

Concluding remarks

Research from the past few years has emphasized the crucial role of AHR signaling in several intestinal populations. While we now know that diverse T cell populations, as well as ILC3s rely on AHR ligand binding to develop, produce cytokines and/or remain at mucosal sites, more research is needed to determine how the vast array of AHR ligands have such disparate impacts on immune cell populations. Several factors likely affect the outcome of the interaction of an AHR ligand with the immune system: firstly, the origin of the ligand — is it an endogenous ligand, produced by the microbiota, a pathogen or a product of the diet? secondly, the concentration of the AHR ligand as well as its localization in the organism — is it present at similar concentrations throughout the intestine or is produced in particular areas? thirdly, how susceptible is the AHR ligand to degradation by enzymes like CYP1A1 — can it be metabolized into compounds with higher or lower affinity?

While the AHR pathway may be an attractive candidate to modify the intestinal immune response in order to control the overt inflammation characteristic of inflammatory bowel disease, more studies are needed to understand the nature of each AHR ligand so that we can identify specific ligands that render the desired effect.

Conflicts of interest

None.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Gu YZ, Hogenesch JB, Bradfield CA: **The PAS superfamily: sensors of environmental and developmental signals**. *Annu Rev Pharmacol Toxicol* 2000, **40**:519-561.

2. McIntosh BE, Hogenesch JB, Bradfield CA: **Mammalian Per-Arnt-Sim proteins in environmental adaptation**. *Annu Rev Physiol* 2010, **72**:625-645.

3. Kewley RJ, Whitelaw ML, Chapman-Smith A: **The mammalian basic helix-loop-helix/PAS family of transcriptional regulators**. *Int J Biochem Cell Biol* 2004, **36**:189-204.

4. Frericks M, Meissner M, Esser C: **Microarray analysis of the AHR system: tissue-specific flexibility in signal and target genes**. *Toxicol Appl Pharmacol* 2007, **220**:320-332.

5. Perdew GH: **Association of the Ah receptor with the 90-kDa heat shock protein**. *J Biol Chem* 1988, **263**:13802-13805.

6. Carver LA, Bradfield CA: **Ligand-dependent interaction of the aryl hydrocarbon receptor with a novel immunophilin homolog in vivo**. *J Biol Chem* 1997, **272**:11452-11456.

7. Meyer BK, Pray-Grant MG, Vanden Heuvel JP, Perdew GH: **Hepatitis B virus X-associated protein 2 is a subunit of the unliganded aryl hydrocarbon receptor core complex and exhibits transcriptional enhancer activity**. *Mol Cell Biol* 1998, **18**:978-988.

8. Nair SC *et al.*: **A pathway of multi-chaperone interactions common to diverse regulatory proteins: estrogen receptor, Fes tyrosine kinase, heat shock transcription factor Hsf1, and the aryl hydrocarbon receptor**. *Cell Stress Chaperones* 1996, **1**:237-250.

9. McGuire J, Whitelaw ML, Pongratz I, Gustafsson JA, Poellinger L: **A cellular factor stimulates ligand-dependent release of hsp90 from the basic helix-loop-helix dioxin receptor**. *Mol Cell Biol* 1994, **14**:2438-2446.

10. Fukunaga BN, Probst MR, Reisz-Porszasz S, Hankinson O: **Identification of functional domains of the aryl hydrocarbon receptor**. *J Biol Chem* 1995, **270**:29270-29278.

11. Stockinger B, Di Meglio P, Gialitakis M, Duarte JH: **The aryl hydrocarbon receptor: multitasking in the immune system**. *Annu Rev Immunol* 2014, **32**:403-432.

12. Mandal PK: **Dioxin: a review of its environmental effects and its aryl hydrocarbon receptor biology**. *J Comp Physiol B* 2005, **175**:221-230.

13. Nguyen LP, Bradfield CA: **The search for endogenous activators of the aryl hydrocarbon receptor**. *Chem Res Toxicol* 2008, **21**:102-116.

14. Denison MS, Nagy SR: **Activation of the aryl hydrocarbon receptor by structurally diverse exogenous and endogenous chemicals**. *Annu Rev Pharmacol Toxicol* 2003, **43**:309-334.

15. Bjeldanes LF, Kim JY, Grose KR, Bartholomew JC, Bradfield CA: **Aromatic hydrocarbon responsiveness-receptor agonists generated from indole-3-carbinol in vitro and in vivo: comparisons with 2,3,7,8-tetrachlorodibenzo-p-dioxin**. *Proc Natl Acad Sci U S A* 1991, **88**:9543-9547.

16. Zhang S, Qin C, Safe SH: **Flavonoids as aryl hydrocarbon receptor agonists/antagonists: effects of structure and cell context**. *Environ Health Perspect* 2003, **111**:1877-1882.

17. Sonowal R *et al.*: **Indoles from commensal bacteria extend healthspan**. *Proc Natl Acad Sci U S A* 2017, **114**:E7506-E7515.

18. Takamura T *et al.*: ***Lactobacillus bulgaricus* OLL1181 activates the aryl hydrocarbon receptor pathway and inhibits colitis**. *Immunol Cell Biol* 2011, **89**:817-822.

19. Zelante T *et al.*: **Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22**. *Immunity* 2013, **39**:372-385.

20. •• Cervantes-Barragan L *et al.*: ***Lactobacillus reuteri* induces gut intraepithelial CD4+CD8αα+ T cells**. *Science* 2017, **357**:806-810.
This manuscript shows that indole derivatives like indole-3-lactic acid produced by *Lactobacillus reuteri* induce the development of intraepithelial CD4+CD8αα+ T cells in the small intestine of mice after binding of the AHR in T cells.

21. Lamas B *et al.*: **CARD9 impacts colitis by altering gut microbiota metabolism of tryptophan into aryl hydrocarbon receptor ligands**. *Nat Med* 2016, **22**:598-605.

22. Moura-Alves P *et al.*: **AhR sensing of bacterial pigments regulates antibacterial defence**. *Nature* 2014, **512**:387-392.

23. Gaitanis G *et al.*: **AhR ligands, malassezin, and indolo[3,2-b] carbazole are selectively produced by *Malassezia furfur* strains isolated from seborrheic dermatitis**. *J Invest Dermatol* 2008, **128**:1620-1625.

24. Magiatis P *et al.*: **Malassezia yeasts produce a collection of exceptionally potent activators of the Ah (dioxin) receptor detected in diseased human skin**. *J Invest Dermatol* 2013, **133**:2023-2030.

25. Mezrich JD *et al.*: **An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells**. *J Immunol* 2010, **185**:3190-3198.

26. • Seok SH *et al.*: **Trace derivatives of kynurenine potently activate the aryl hydrocarbon receptor (AHR)**. *J Biol Chem* 2017.
This manuscript shows that kynurenine can be metabolized into higher affinity AHR ligands.

27. Rannug U *et al.*: **Structure elucidation of two tryptophan-derived, high affinity Ah receptor ligands**. *Chem Biol* 1995, **2**:841-845.

28. •• Schiering C *et al.*: **Feedback control of AHR signalling regulates intestinal immunity**. *Nature* 2017, **542**:242-245.
This manuscript shows that AHR ligands are constantly being sensed and also metabolized in the intestine and have an impact on the homeostasis of the intestinal immune system.

29. Diefenbach A, Colonna M, Koyasu S: **Development, differentiation, and diversity of innate lymphoid cells**. *Immunity* 2014, **41**:354-365.

30. Diefenbach A, Colonna M, Romagnani C: **The ILC world revisited**. *Immunity* 2017, **46**:327-332.

31. Lee JS *et al.*: **AHR drives the development of gut ILC22 cells and postnatal lymphoid tissues via pathways dependent on and independent of Notch**. *Nat Immunol* 2011, **13**:144-151.

32. Ebihara T *et al.*: **Runx3 specifies lineage commitment of innate lymphoid cells**. *Nat Immunol* 2015, **16**:1124-1133.

33. Li S *et al.*: **Ikaros inhibits group 3 innate lymphoid cell development and function by suppressing the aryl hydrocarbon receptor pathway**. *Immunity* 2016, **45**:185-197.

34. Kiss EA *et al.*: **Natural aryl hydrocarbon receptor ligands control organogenesis of intestinal lymphoid follicles**. *Science* 2011, **334**:1561-1565.

35. Qiu J *et al.*: **The aryl hydrocarbon receptor regulates gut immunity through modulation of innate lymphoid cells**. *Immunity* 2012, **36**:92-104.

36. Qiu J *et al.*: **Group 3 innate lymphoid cells inhibit T-cell-mediated intestinal inflammation through aryl hydrocarbon receptor signaling and regulation of microflora**. *Immunity* 2013, **39**:386-399.

37. Wagage S *et al.*: **The group 3 innate lymphoid cell defect in aryl hydrocarbon receptor deficient mice is associated with T cell hyperactivation during intestinal infection**. *PLOS ONE* 2015, **10**: e0128335.

38. Hughes T *et al.*: **The transcription factor AHR prevents the differentiation of a stage 3 innate lymphoid cell subset to natural killer cells**. *Cell Rep* 2014, **8**:150-162.

39. Shin JH *et al.*: **Modulation of natural killer cell antitumor activity by the aryl hydrocarbon receptor**. *Proc Natl Acad Sci U S A* 2013, **110**:12391-12396.

40. Wagage S *et al.*: **The aryl hydrocarbon receptor promotes IL-10 production by NK cells**. *J Immunol* 2014, **192**:1661-1670.

41. Funatake CJ, Marshall NB, Steppan LB, Mourich DV, Kerkvliet NI: **Cutting edge: activation of the aryl hydrocarbon receptor by 2,3,7,8-tetrachlorodibenzo-p-dioxin generates a population of CD4+ CD25+ cells with characteristics of regulatory T cells**. *J Immunol* 2005, **175**:4184-4188.

42. Veldhoen M *et al.*: **The aryl hydrocarbon receptor links TH17-cell-mediated autoimmunity to environmental toxins**. *Nature* 2008, **453**:106-109.

43. Quintana FJ *et al.*: **Control of T(reg) and T(H)17 cell differentiation by the aryl hydrocarbon receptor**. *Nature* 2008, **453**:65-71.

44. Veldhoen M, Hirota K, Christensen J, O'Garra A, Stockinger B: **Natural agonists for aryl hydrocarbon receptor in culture medium are essential for optimal differentiation of Th17 T cells**. *J Exp Med* 2009, **206**:43-49.

45. Kimura A *et al.*: **Aryl hydrocarbon receptor in combination with Stat1 regulates LPS-induced inflammatory responses**. *J Exp Med* 2009, **206**:2027-2035.

46. Rutz S *et al.*: **Transcription factor c-Maf mediates the TGF-β-dependent suppression of IL-22 production in T(H)17 cells**. *Nat Immunol* 2011, **12**:1238-1245.

47. •• Ehrlich AK, Pennington JM, Bisson WH, Kolluri SK, Kerkvliet NI: **TCDD, FICZ, and other high affinity AhR ligands dose-dependently determine the fate of CD4+ T cell differentiation**. *Toxicol Sci* 2017.
This manuscript demonstrates that the amount of time a ligand is bound to AHR and its susceptibility to degradation determines the outcome of the T cell response.

48. • Apetoh L *et al.*: **The aryl hydrocarbon receptor interacts with c-Maf to promote the differentiation of type 1 regulatory T cells induced by IL-27**. *Nat Immunol* 2010, **11**:854-861.
This manuscript shows that activation of AHR in T cells with different AHR ligands has different outcomes. Stimulation of naïve T cells with TCDD induces Tregs, as well as treatment of mice with TCDD reduces the intensity of EAE, while treatment of naïve T cells with FICZ results in Th17 induction and enhanced EAE.

49. Mascanfroni ID *et al.*: **Metabolic control of type 1 regulatory T cell differentiation by AHR and HIF1-α**. *Nat Med* 2015, **21**:638-646.

50. Ehrlich AK *et al.*: **AhR activation increases IL-2 production by alloreactive CD4+ T cells initiating the differentiation of mucosal-homing Tim3+ Lag3+ Tr1 cells**. *Eur J Immunol* 2017, **47**:1989-2001.

51. Li Y *et al.*: **Exogenous stimuli maintain intraepithelial lymphocytes via aryl hydrocarbon receptor activation**. *Cell* 2011, **147**:629-640.

52. Konkel JE *et al.*: **Control of the development of CD8αα+ intestinal intraepithelial lymphocytes by TGF-β**. *Nat Immunol* 2011, **12**:312-319.

53. Mucida D *et al.*: **Transcriptional reprogramming of mature CD4$^+$ helper T cells generates distinct MHC class II-restricted cytotoxic T lymphocytes**. *Nat Immunol* 2013, **14**:281-289.

54. Sulentic CE, Kaminski NE: **The long winding road toward understanding the molecular mechanisms for B-cell suppression by 2,3,7,8-tetrachlorodibenzo-p-dioxin**. *Toxicol Sci* 2011, **120(Suppl. 1)**:S171-S191.

55. Tanaka G *et al.*: **Induction and activation of the aryl hydrocarbon receptor by IL-4 in B cells**. *Int Immunol* 2005, **17**:797-805.

56. •• Villa M *et al.*: **Aryl hydrocarbon receptor is required for optimal B-cell proliferation**. *EMBO J* 2017, **36**:116-128.
This manuscript shows that B cell proliferation is impaired in the absence of ahr signaling.

57. Inoue H *et al.*: **Aryl hydrocarbon receptor-mediated induction of EBV reactivation as a risk factor for Sjögren's syndrome**. *J Immunol* 2012, **188**:4654-4662.

58. Yoshida T *et al.*: **Effects of AhR ligands on the production of immunoglobulins in purified mouse B cells**. *Biomed Res* 2012, **33**:67-74.

59. Phadnis-Moghe AS, Li J, Crawford RB, Kaminski NE: **SHP-1 is directly activated by the aryl hydrocarbon receptor and regulates BCL-6 in the presence of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)**. *Toxicol Appl Pharmacol* 2016, **310**:41-50.

60. Kovalova N, Manzan M, Crawford R, Kaminski N: **Role of aryl hydrocarbon receptor polymorphisms on TCDD-mediated CYP1B1 induction and IgM suppression by human B cells**. *Toxicol Appl Pharmacol* 2016, **309**:15-23.