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REVIEW

Aryl hydrocarbon receptor antagonism and its role in rheumatoid arthritis

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Abstract: Although rheumatoid arthritis (RA) is the most common autoimmune disease, affecting approximately 1% of the population worldwide, its pathogenic mechanisms are poorly understood. Tobacco smoke, an environmental risk factor for RA, contains several ligands of aryl hydrocarbon receptor (Ahr), also known as dioxin receptor. Ahr plays critical roles in the immune system. We previously demonstrated that Ahr in helper T-cells contributes to development of collagen-induced arthritis, a mouse model of RA. Other studies have shown that cigarette smoke condensate and pure Ahr ligands exacerbate RA by altering bone metabolism and inducing proinflammatory responses in fibroblast-like synoviocytes. Consistent with these findings, several Ahr antagonists such as α-naphthoflavone, resveratrol, and GNF351 reverse the effect of Ahr ligands in RA pathogenesis. In this review, we summarize the current knowledge of Ahr function in the immune system and the potential clinical benefits of Ahr antagonism in treating RA.

Keywords: dioxin receptor, antagonists, autoimmunity

The roles of Ahr in RA

RA pathogenesis

Rheumatoid arthritis (RA) is a systemic and chronic inflammatory disease characterized by synovial inflammation and subsequent joint destruction. Bone damage and cartilage loss triggered by osteoclasts and fibroblast-like synoviocytes (FLS) are also observed in RA patients. Accordingly, the immune system, particularly T-cells, dendritic cells, macrophages, and B-cells as well as proinflammatory cytokines such as IL-6 and TNF-α, is implicated in RA pathogenesis.[1–8] In particular, IL-17A-producing $CD4^+$ T-cells (so-called Th17 cells) have attracted attention in this context because accumulating evidence indicates that this T helper (Th) subset plays critical roles in several autoimmune diseases, including RA.[9–11] Furthermore, neutralizing antibodies against IL-6 and TNF-α are promising therapies for RA.[12–18]

RA is thought to be induced by interactions between environmental and genetic risk factors. Environmental risk factors for this disease include smoking and infection, and the best-known genetic risk factors are HLA-DRB1 alleles that encode a shared epitope (SE).[19–22] Several groups have reported a link between SE and cigarette smoking in relation to RA risk,[23–25] illustrating that disease pathogenesis involves both environmental and genetic factors. Although cigarette smoke contains several aryl hydrocarbon receptor (Ahr) ligands, such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), 3-methyl cholanthrene (3-MC), and benzo[*a*]pyrene (BaP), the precise mechanisms by which these molecules contribute to RA development are not

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yet understood. In this review, we summarize our current knowledge about the roles of Ahr in immune cells, including in Th17 cells, during RA pathogenesis, thereby providing further possibility of its use as a target.

Ahr pathway

Ahr is a ligand-activated transcription factor of the bHLH/PAS family.[26–28] It is expressed abundantly in liver and such barrier tissues as skin, lung, gut, placenta, and mucosal epithelia, but at low levels or not at all in muscle, testis, kidney, and brain, indicating that immune cells express high levels of Ahr.[29] Under steady-state conditions, Ahr localizes in cytoplasm and forms complexes with various proteins including HSP90, AIP, and p23.[30–32] Upon binding to its ligands, Ahr translocates into the nucleus, where it binds Ahr nuclear translocator; the resultant complex activates xenobiotic-responsive elements in the promoters of target genes, such as those encoding cytochrome p450 enzymes.[26,33–35] In addition, Ahr controls degradation of specific targets such as estrogen via its ligand-dependent E3 ubiquitin ligase activity.[36,37] Activated Ahr is itself degraded by the 26S proteasome pathway after being exported from the nucleus to the cytoplasm.[38–40] In addition to the canonical Ahr signaling pathway, as described, Ahr also participates in other signaling pathways, resulting in noncanonical Ahr activities.[41] For instance, TCDD-induced association of Ahr with the NF-κB subunit RelB upregulates inflammatory genes such as *IL-8* via the RelB/Ahr responsive element in macrophages and breast cancer cells.[42,43] However, Ahr-deficient mice exhibit more severe inflammatory symptoms following exposure to lipopolysaccharide or cigarette smoke extract due to destabilization of the RelB protein,[44,45] suggesting that Ahr can function as either a pro- or anti-inflammatory regulator in different situations (eg, in response to different stimuli or in different cell types and diseases). Therefore, further study is necessary to elucidate the molecular mechanisms by which Ahr-binding partners and target genes are determined.

Ahr in RA

Because Ahr acts as an important mediator of xenobiotic metabolism by inducing cytochrome p450 enzymes such as CYP1A1, over the past 3 decades it was primarily studied in the field of toxicology and pharmacology. However, two different groups reported that Ahr controls generation of Th17, a recently identified Th cell subset,[46,47] leading many immunologists to study Ahr in the immune system. Th17 cells, which are induced by IL-6 and TGF-β via RORγt transcription, are believed to play a key role in the progression of several autoimmune diseases, including RA and multiple sclerosis (MS).[9–11,48] One of the two groups demonstrated ligand-specific Ahr action in T-cells: the endogenous ligand FICZ exacerbates experimental autoimmune encephalomyelitis, a mouse model of MS, by promoting generation of Th17 cells, whereas the exogenous ligand TCDD suppresses disease progression by inducing production of regulatory T (Treg) cells.[47] It remains unclear how Ahr causes opposite outcomes when activated by FICZ or TCDD; however, several studies have demonstrated mechanisms by which Ahr contributes to Th17 differentiation through various intracellular signaling pathways (eg, inhibition of STAT1/STAT5, Aiolos-mediated transcription, and direct interaction with the IL-17 promoter).[49–52] In addition, several microRNAs (miRNAs) are regulated by Ahr under pathological conditions such as immune disorders and cancers. miRNAs are short (20–22 nucleotide) noncoding RNAs that negatively regulate gene expression by base-pairing with binding sites in the 3′-UTR regions of target mRNAs.[53–56] miR-132/212 is induced in an Ahr-dependent manner under Th17-polarizing conditions, and enhances the development of experimental autoimmune encephalomyelitis and dextran sulfate sodium-induced colitis.[57,58] Several miRNAs form positive or negative feedback loops. For instance, although miR-132/212 expression in neurons is controlled by CREB, CREB itself can be upregulated by miR-132.[59,60] Therefore, identification of Ahr-regulated miRNAs and their targets may contribute to understanding of the Ahr signaling network.[61]

As already mentioned, tobacco smoke is a major environmental risk factor of RA and contains several kinds of Ahr ligands such as TCDD, 3-MC, and BaP. In addition, Ahr expression in synovial tissue is significantly higher in RA patients than in osteoarthritis patients.[62] Several studies have reported that when FLS cell lines or synoviocytes from RA patients are stimulated by Ahr ligands or cigarette smoke condensate, they upregulate proinflammatory cytokines such as IL-1β.[63–66] Moreover, Ahr-knockout (KO) mice exhibited significantly reduced severity of collagen-induced arthritis (CIA), the most widely used mouse model of RA.[67] More importantly, the same study also demonstrated that Ahr deletion in T-cells inhibits CIA development as efficiently as Ahr-KO, with reduced numbers of Th17 cells in draining lymph nodes. In another context, Ahr may contribute to pathogenesis of RA via its effects on bone metabolism. For instance, osteoblasts isolated from CIA-treated mice express high levels of Ahr, and TCDD negatively regulates osteoblast proliferation and differentiation via activation of the

ERK-signaling pathway.[68] Moreover, Ahr ligand promotes osteoclast formation in vitro and bone resorption in vivo.[69] These findings raise the possibility that Ahr in other cell types may affect disease progression. Indeed, several lines of evidence have shown that Ahr plays various roles in immune cells including macrophages, dendritic cells, and B-cells, as well as in T-cells.[70–72] Taken together, these findings indicate that Ahr expression is important for RA pathogenesis in several ways: by inducing proinflammatory cytokine production in FLSs, by influencing bone metabolism via modulating the balance between osteoblasts and osteoclasts, and by regulating Th17 generation. The roles of Ahr in RA pathogenesis are summarized in Figure 1.

Treatment of RA via antagonizing Ahr signaling

Ahr activation by ligands such as TCDD can induce the production of inflammatory cytokines, including IL-1β and IL-6, in human FLS cell lines and RA synoviocytes.[62,63] Researchers have used both Ahr-KO mice and Ahr antagonists to investigate the functions of Ahr in RA development.[62,66,67] In Ahr-KO mice, serum levels of proinflammatory cytokines such as IL-1β and IL-6 are reduced in the CIA model.[67] Interestingly, T-cell-specific deficiency of Ahr suppresses CIA development by inhibiting production of IL-1β and IL-6 and generation of Th17 cells.[67] The functions of several Ahr antagonists in RA are discussed further.

α-naphthoflavone

α-naphthoflavone inhibits TCDD-induced upregulation of IL-1β in FLS via the NF-κB and ERK signaling pathways.[62] In addition, in the synovial fibroblast cell line MH7A, isolated from RA patients, α-naphthoflavone inhibits the induction of IL-1β and CYP1A1 by cigarette smoke, which contains such Ahr ligands as TCDD.[66] IL-1, and in particular IL-1β, is a key mediator of the pathogenesis of RA, and blocking of IL-1/IL-1 receptor alleviates RA symptoms in both animal models and clinical studies.[73–79] In the CIA model, IL-1-KO mice develop less arthritis than controls.[80] Moreover, IL-1 can promote Th17 cell development, thereby increasing the level of IL-17 during the onset of spontaneous arthritis in IL-1 antagonist KO mice.[81] Together, these results raise the possibility that α-naphthoflavone can suppress IL-1β production and subsequent Th17 cell generation induced by cigarette smoke or Ahr ligands such as TCDD in patients with RA.

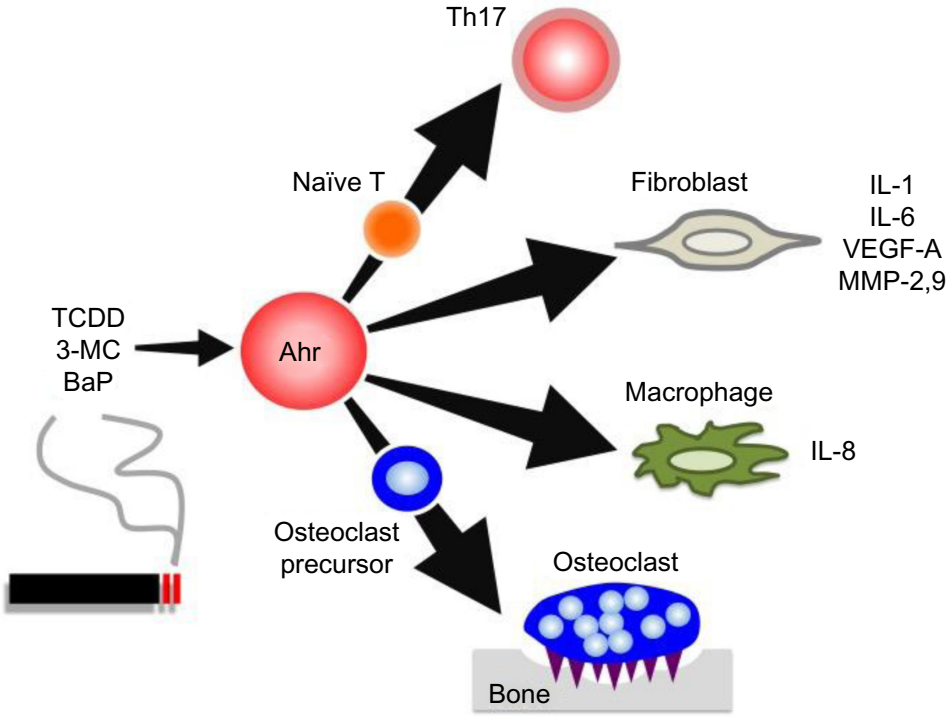

Figure 1 Ahr roles in RA pathogenesis.
Notes: Cigarette smoke contains several Ahr ligands such as TCDD, 3-MC, and BaP. Ahr activation contributes several aspects of RA pathogenesis: differentiation into Th17 cells from naïve T-cells; inflammation, angiogenesis, and cartilage destruction by producing IL-1, IL-6, VEGF, and MMPs in fibroblasts; production of proinflammatory cytokines such as IL-8 in macrophages; and osteoclastogenesis.
Abbreviations: Ahr, aryl hydrocarbon receptor; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; 3-MC, 3-methylcholanthrene; BaP, benzo[*a*]pyrene; VEGF, vascular endothelial growth factor; MMPs, matrix metalloproteinases; RA, rheumatoid arthritis; IL, interleukin.

Resveratrol (3,5,49-trihydroxystilbene)

Resveratrol, a molecule found in red wine, blocks TCDD-mediated effects such as induction of CYP1A1 and IL-1β in the cancer cell lines T-47D and RL95-2, respectively.[82] In rats, resveratrol treatment inhibits induction of CYP1A1 by pure Ahr ligands such as BaP and 7,12-dimethylbenz[*a*] anthracene, compounds found in cigarette smoke, in cells of many organs including lung, kidney, liver, spleen, bone, and testis.[82] Recent work showed that resveratrol inhibits CIA development by decreasing the IL-6 level in serum and reducing the frequency of Th17 in draining lymph nodes.[83] Importantly, resveratrol decreases TCDD-mediated induction of IL-17 under Th17-polarizing conditions in vitro.[83] Therefore, resveratrol may suppress Th17 generation. Another study showed that resveratrol induces apoptosis via sirtuin-1-mediated mitochondrial corruption in MH7A human RA synovial cells.[84] Consistent with these results, resveratrol induces apoptosis via activation of caspase-8 in RA-derived FLS,[85] or caspase-3/-9 in MH7A human RA synovial cells.[86] Collectively, these findings suggest that resveratrol inhibits Ahr signaling to reduce the induction of CYP1A1, suppresses the function of Th17 cells, and induces apoptosis in RA synovial cells, contributing to control Ahr-mediated inflammatory diseases such as autoimmune arthritis.

GNF351 (N-(2-(1H-indol-3-yl)ethyl)-9-isopropyl-2-(5-methylpyridin-3-yl)-9H-purin-6-amine)

GNF351 is a high-affinity Ahr antagonist.[65,87–90] In human FLS isolated from RA patients, IL-1β production is suppressed by GNF351, and this suppression is rendered by pretreatment of human FLS with the Ahr antagonist CH223191 or by small interfering RNA targeting Ahr.[65] Furthermore, GNF351 reduces IL-1β-induced production of growth factors such as vascular endothelia growth factor A (VEGF-A) in FLS of RA patients via an Ahr-dependent mechanism.[88] Growth factors such as VEGF play important roles in FLS activation, leading to hyperplasia and increased angiogenesis, thereby promoting RA development.[91] In addition, GNF351 reduces IL-1β-induced mRNA expression of matrix metalloproteinases (MMP)-2 and -9 in FLS of RA patients.[65] MMPs are elevated in FLS of RA patients, resulting in cartilage loss and are therefore considered to be promising targets for treatment of RA.[92–96] In summary, GNF351 inhibits RA development by targeting IL-1β and IL-1β-induced VEGF and MMPs. Moreover, GNF351 can bind with high affinity to the ligand-binding pocket of AhR and is a more potent Ahr antagonist than compounds such as α-naphthoflavone and resveratrol.[87]

Potentially antagonistic plant-derived compounds

Previous studies have reported that plants contain secondary compounds such as β-carboline alkaloids that may exert various pharmacological activities.[97–102] Several kinds of plant-derived alkaloids have antagonistic effects on dioxin-mediated CYP1A1 induction in mouse and human cell lines.[98,99] Recently, our group showed that 7-methoxy-(9H-β-carbolin-1-il)-(*E*)-2-propenoic acid, a novel β-carboline alkaloid isolated from hairy-root cultures of the Vietnamese plant *Eurycoma longifolia*, has anti-inflammatory activity.[103] Consistent with this, extract of *E. longifolia* is used in Vietnam and requires further study to establish its effectiveness to treat rheumatic disorders.[104] This alkaloid is currently being investigated as a novel Ahr antagonist to treat inflammatory diseases including RA. The functions of several Ahr antagonists in RA are summarized in Table 1.

Table 1 The functions of several Ahr antagonists in RA

No	Compound	Main functions	References
1	α-naphthoflavone	Inhibits IL-1β production	Kobayashi et al[62]
		Inhibits induction of IL-1β and CYP1A1	Adachi et al[66]
2	Resveratrol	Inhibits IL-1β and CYP1A1	Casper et al[82]
		Suppresses Th17 generation	Xuzhu et al[83]
		Activates caspase-8	Byun et al[85]
		Activates caspase-3/-9	Nakayama et al[86]
3	GNF351	Suppresses IL-1β production	Lahoti et al[65]
		Decreases IL-1β-induced production of VEGF-A	Lahoti et al[88]
		Reduces IL-1β-induced MMP-2 and MMP-9	Lahoti et al[65]
4	Plant-derived alkaloids	Inhibits dioxin-mediated CYP1A1 induction	El Gendy and El-Kadi[98]
			El Gendy et al[99]

Abbreviations: Ahr, aryl hydrocarbon receptor; RA, rheumatoid arthritis; CYP1A1, cytochrome P450, family 1, subfamily A, polypeptide 1; VEGF, vascular endothelial growth factor; MMPs, matrix metalloproteinases.

Conclusion and future work

Research on the function of Ahr in RA pathogenesis has made significant progress. However, further study will be necessary to elucidate the precise molecular mechanisms by which deficiency of Ahr or Ahr antagonists such as α-naphthoflavone, resveratrol, and GNF351 suppress CIA development in mice and attenuate cells isolated from RA patients. Recently, we found that dioxin-exposed patients suffer from various inflammatory diseases, including rheumatoid disorders (our unpublished data). Furthermore, expression of Ahr, CYP1A1, and inflammatory cytokines including IL-1β and IL-6 was highly upregulated in peripheral blood of these patients (our unpublished data). In future work, we will seek to characterize novel potential Ahr antagonists with strong anti-inflammatory properties, with the goal of alleviating the signs and symptoms of RA in dioxin-exposed patients.

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Disclosure

The authors report no conflicts of interest in this work.

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