Polycyclic Aromatic Hydrocarbons Affect Rheumatoid Arthritis Pathogenesis via Aryl Hydrocarbon Receptor

Rheumatoid arthritis (RA), the most common autoimmune disease, is characterized by symmetrical synovial inflammation of multiple joints with the infiltration of pro-inflammatory immune cells and increased cytokines (CKs) levels. In the past few years, numerous studies have indicated that several factors could affect RA, such as mutations in susceptibility genes, epigenetic modifications, age, and race. Recently, environmental factors, particularly polycyclic aromatic hydrocarbons (PAHs), have attracted increasing attention in RA pathogenesis. Therefore, exploring the specific mechanisms of PAHs in RA is vitally critical. In this review, we summarize the recent progress in understanding the mechanisms of PAHs and aryl hydrocarbon receptors (AHRs), in RA. Additionally, the development of therapeutic drugs that target AHR is also reviewed. Finally, we discuss the challenges and perspectives on AHR application in the future.

Keywords: rheumatoid arthritis, polycyclic aromatic hydrocarbons, particulate matter, aryl hydrocarbon receptor, aryl hydrocarbon receptor repressor

HIGHLIGHTS

- We explored the close relationship between PAHs and RA and summarized previous studies.
- PAHs affect the pathogenesis of RA through the AHR pathway.
- We explored the treatment strategies for RA and current novel strategies based on the AHR pathway.
1 INTRODUCTION

Rheumatoid arthritis (RA) is the most common autoimmune disease characterized by changes in the local inflammatory environment, swollen joints and pain; eventually leads to joint dysfunction or contributes to disability. In recent years, the prevalence and incidence rates of autoimmune diseases such as RA have risen rapidly worldwide (1, 2). Autoimmune diseases are one of the most common diseases in the United States, affecting approximately 8% of the population (3), and they are one of the leading causes of death among young and middle-aged women. Some of the affected individuals also have anxiety or depression because of the failure of medication, substantially affecting quality of life. Additionally, in the late stage of RA, respiratory, circulatory and tumor diseases can occur, and the probability of death is further increased. The high incidence and serious consequences of RA have attracted extensive attention, and the depth of research on RA has been increasing.

At present, the etiology and pathophysiology of RA are mainly related to genetic and environmental factors; genetic inheritance accounts for 30% of all autoimmune diseases, while environmental factors, which account for a large proportion of cases, are the primary factors. Genetic factors mainly include human leukocyte antigen-DRB1 (HLA-DRB1), and the main environmental factor is polycyclic aromatic hydrocarbons (PAHs) (4, 5). PAHs are ubiquitous air pollutants formed by the burning and decomposition of coal, oil, garbage, natural gas and other substances. PAHs are closely related to various diseases. In addition to RA, cardiovascular, cerebrovascular, and respiratory system diseases also exist, and PAHs exposure can also lead to metabolic diseases such as diabetes (6) and carcinogenic effects (7).

Many studies have proven that PAHs play a crucial role in the development of RA through various ways (4, 5), including inducing the changes of immune cells and corresponding cytokines (CKs). Immunoregulatory cells and CKs play a vital role in immune homeostasis and the pathogenesis of RA. Previous studies have shown changes in inflammatory environments, such as the infiltration of inflammatory cells and CKs in the local joint RA patients. Several studies have reported the number and function of T cells and B cells, and the corresponding CKs are closely related to RA (8). In addition to immune cells, changes in autoantibodies are also common markers in RA, mainly including rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) (9–11), which is mainly achieved by activating B cells. These complex alterations are primarily caused via the action of aromatic hydrocarbon receptor (AHR). But assessing the detailed impact of PAHs on RA is a massive challenge because through there are many basic studies on the relationship between PAHs and RA, the specific mechanism of PAHs and AHR in the pathological mechanism of RA remains unclear.
In this review, we mainly summarized recent developments of PAHs in RA studies and the RA mechanism via PAHs of environmental pollution and AHR signaling pathway. Additionally, we discussed the therapeutic potential and application prospects of targeting AHR in RA, providing crucial information for discovering novel and effective RA treatments.

2 SOURCES AND EFFECTS OF PAHs IN RA

2.1 Environmental Pollution and PAHs
The factors causing environmental pollution mainly include two major aspects: factors derived from human influence, such as those derived from barbecued foods, smoking, urban traffic pollution, the burning of oil and the random burning of garbage, and factors derived from natural causes, such as forest fires. Thus, mixed ambient pollutants are produced, such as sulfur dioxide, carbon monoxide, nitrogen dioxide and particulate matter (PM). PM is further classified into several types according to the particle size: PM 10 (<10 mm in diameter), PM 2.5 (<2.5 mm in diameter), PM 1.0 (<1.0 mm in diameter), PM 0.1 (<0.1 mm in diameter) and ultrafine particles (UFPs) (in order from largest to smallest).

Abundant PAHs are found in barbecued foods, and cigarette smoke also contains many PAHs. A previous study in Bangladesh found that people who were overexposed to urban traffic pollution were exposed to high levels of PAHs (12). This finding suggests that in Dhaka, urban residents who are exposed to traffic pollution are at a higher risk of exposure to carcinogenic PAHs. Not surprisingly, excessive amounts of PAHs are also found in waste incinerators and decomposition products of oil burning. Generally, PAHs are the major components in environmental particulate pollutants and have adverse health effects (that is, they are hazardous to health). Additionally, among the PM types, those that pose the main threat to human health are UFPs (13), which are too small for airway mucous cilia and alveolar macrophages to eliminate and therefore become deposited in the lungs.

Although extensive studies have proven that an increased risk of RA is closely related to environmental pollution (14–18), the exact mechanism between RA and environmental pollution is poorly clear.

2.2 PAHs and RA

2.2.1 General Overview of PAHs
PAHs are the most common pollutants in the environment and are a group of organic compounds comprising two or more aromatic rings in different configurations that are mainly derived from the burning of coal and natural gas, the indiscriminate burning of garbage and other organic compounds such as tobacco and barbecued foods. A few PAHs are used as pharmaceuticals and pesticides and in plastics, while others are included in the asphalt used for road construction. More than 100 PAHs have been identified in the environment, and sixteen of them are listed as primary pollutants by the United States Environmental Protection Agency. PAHs exist primarily as mixtures instead of single compounds. Additionally, they tend to become deposited in the human body and remain within the food chain because of their lipophilic properties (19).

Halogenation of PAHs gives them metabolic and environmental stability. Generally, PAHs are agonists of and have a high affinity for AHR, leading to halogenation of PAHs side rings; PAHs also show distinct affinity for and are easily metabolized by CYP enzymes (20). However, several PAHs have been demonstrated to inhibit the generation of CYP enzymes, inhibiting their metabolism and that of other organic components present in mixtures (21, 22).

Recently, the effects of PAHs on human health have been widely studied, and many experimental studies have recently focused on the link between PAHs and RA (4, 5). Novel studies have demonstrated that high levels of PAHs in urine are significantly related to a high incidence of RA, implying that PAHs exposure may increase the incidence of RA (23, 24).

2.2.2 General Biology of AHR
AHR is a ligand-dependent transcription factor that plays a crucial role in regulating the differentiation, activation and apoptosis of various cells in RA. AHR is best known for its capacities to mediate the toxicity of dioxin and is normally present in the immune cell cytoplasm as a part of a complex of multiple proteins, primarily comprising heat shock protein (HSP) 90, P23, which is a scaffold protein, and activated AHR. According to molecular cloning studies, AHR contains a basic helix-loop-helix (bHLH) domain, which is similar to that found in DNA-binding proteins (25, 26). Additionally, AHR contains a PER-ARNT-SIM (PAS) homology domain, including a PAS A and PAS B domain, similarly found in other regulators of cell and organism responses to the environment (27, 28). Interestingly, the binding of ligands to AHR mainly occurs via the PAS B domain.

Activation of the AHR signaling pathway depends on the ligands, including endogenous and exogenous ligands. These ligands can be present in the environment or produced by metabolism. AHR-mediated signaling pathways may be essential for the immune regulatory response, and previous studies have revealed that AHR signaling not only affects innate immunity but also participates in adaptive immunity in the development of diseases, such as RA.

Recent studies have also suggested that abnormal activation of AHR signaling pathways may be associated with autoimmune diseases, such as RA, multiple sclerosis (MS), systemic lupus erythematosus (SLE), autoimmune uveitis (AU), myasthenia gravis (MG) and Bechet’s disease (BD). Importantly, regulating AHR’s involvement in autoimmune diseases is multidimensional with 3-MC or other ligands, which can disrupt the balance between immune cells, significantly shift the Th1/Th2 balance in favor of a Th1 response, modulate the differentiation of regulatory T (Treg) cells, and increase the proliferation and differentiation of Th17 cells. Not surprisingly, several studies have shown that AHR has opposite effects on Treg cell and Th17 cell differentiation (29, 30). Furthermore, AHR can regulate the
activity of dendritic cells (DCs), natural killer (NK) cells and macrophages. These changes in immune cells eventually lead to and exacerbate autoimmune diseases.

More novel ideas have been confirmed, in addition to Th17 cells being activated in a manner dependent on the AHR pathway, the same is true for Th1, Th2 and Treg cells. In recent years, AHR has been studied in various aspects of immunology, mainly focusing on its effect and regulation of T cell differentiation, maturation and function. AHR is highly expressed in several CD4+ cells; the highest expression is observed on Th17, and FoxP3+ Treg cells, followed by Th1 and Th2 cells (31, 32).

2.2.3 Signal Transduction Pathway of AHR
Numerous studies have indicated that AHR plays a critical role in immunomodulation (33, 34). After activation of AHR, intracellular signaling occurs through genomic and/or nongenomic pathways (Figure 1). In this review, we mainly discuss the activation pathway of AHR from the perspective of genomic pathways.

PAHs are ubiquitous pollutants and always exist in the environment as a mixture. Overexposure to PAHs usually activates AHR in immune cells, such as Th1 and Th17 cells, resulting in the promotion of inflammatory CKs production and an increased RA incidence. Additionally, PAHs inhibit the activation of AHR in Th2 and Treg cells and weaken the ability to produce interleukin-10 (IL-10), transforming growth factor-β (TGF-β) and IL-4 to further promote the occurrence of RA (31, 35, 36).

Once agonists (ligands such as PAHs) reach the immunomodulatory cell and bind to the PAS domain of AHR, a conformational change of AHR is induced. This change alters the binding of AHR with other chaperones and leads to the nuclear localization signal being fully exposed. Thus, the ligand-AHR complex is transferred to the nucleus. When the ligand-AHR complex is disassociated from the complex containing HSP90, ARA9 and P23, it forms a heterodimer with another protein, bHLH-PAS, also known as AHR nuclear translocation (ARNT). In the nucleus, the interaction between AHR and ARNT (which forms AHR/ARNT heterodimers) increases their ability to bind to specific sequences of enhancers near the target gene promoter, known as dioxin response elements (DREs) (37, 38); this effect leads to the changing of downstream several genes, among these genes, the most well-studied include cytochrome P (CYP)1A1, CYP1A2, CYP1B1, and aryl hydrocarbon receptor repressor (AHRR), the former three of which encode a phase I enzyme, a heme-mercaptan protein and a key adaptor to metabolic reactions, known as CYP. CYP is involved in the metabolism
of endogenous substances and exogenous substances, including drugs and environmental compounds. Additionally, the CYP enzyme is mainly located in the endoplasmic reticulum, where it is responsible for catalyzing the first stage of exogenous biological oxidation transformation (39) and regulating the activation, differentiation, and apoptosis of various cells (40). This biotransformation reduces the toxicity of compounds, but intermediates can be produced in the case of PAHs (41).

In addition to positive activation of AHR, AHR is also negatively regulated. First, with ligand-induced activation and nuclear output (42, 43), AHR is degraded via the 26S proteasome (44, 45). The second mechanism of reduced activity of the AHR-ARNT complex is the upregulation of a transcriptional repressor called AHRR (46). AHRR is also a bHLH-PAS protein with a sequence with high similarity to the AHR and ARNT sequences (Figure 2); specifically, AHR, AHRR and ARNT are expressed in most cells and tissues, and they show high similarity in their structures (Figure 2).

The three proteins are members of the bHLH-PAS family of transcription factors. The absence of the PAS B domain in the AHRR structure, which is vital for the ligand binding of AHR, contributes to the negative modulation of AHR by AHRR. Additionally, the carboxyl termini of AHR and ARNT include transcriptional activation domains (TADs). The TADs of AHR contain numerous independent active subdomains, while the TAD of ARNT is simpler (Figure 2).

AHRR inhibits the transcriptional activity of AHR mainly by binding to ARNT, and the interaction between ARNT and AHRR inhibits the binding of compounds with DREs (46). Under normal conditions, positive and negative feedback is balanced, however, in the event of diseases, the balance between them is completely disturbed.

To some extent, CYP can promote the metabolism of PAHs in vivo to alleviate the occurrence of diseases, but PAHs exposure can inhibit the activity of CYP and worsen diseases. Several PAHs have been revealed to inhibit the activity of CYP enzymes to alter their own metabolism (21, 47). Specifically, the inhibitory effect of PAHs on CYP enzymes suppresses the production of water-soluble metabolites that is not conducive to the excretion of PAHs. Subsequently, PAHs penetrate the intestinal epithelium and enter the lamina propria and immunomodulatory cells, contributing to the acceleration of autoimmune diseases like RA (48). In recent years, the attention at PAHs has been gradually increasing, while the attention directed at AHR has also increased. An up-to-date summary of the changes caused by activation of the AHR pathway on the levels of immune cells and CKs in vivo when PAHs exposure contributes to RA will be described below.

### 3 PAHs STIMULATION-INDUCED CHANGES IN RA

The effects of PAHs in RA mainly involve the changes of immunomodulatory cells and corresponding CKs (Figure 3).

#### 3.1 Cell Changes

PAHs are currently recognized as the main environmental pollutants causing RA. The pathogenesis of PAHs exposure-induced RA mainly involves regulating immune cells, and studies
have found that PAHs exposure changes the distribution of T cell subtypes. The balance of immune cells is disordered, mainly represented by an increase in pro-inflammatory T cells and a decrease in Treg cells (49, 50). Eventually, the changes in downstream CKs corresponding to these cells are affected, such as promoting an increased number of pro-inflammatory cells and related CKs, inhibiting the production of anti-inflammatory cells and CKs.

Considering that PAHs are diverse, one experiment exposed mice to the 16 most common PAHs. Acenaphthylene (ANY), fluoranthene (FLT), benzo [a] pyrene (B[a]P), benzo [a] anthracene (B[a]A), benzo [b] fluoranthene (B[b]F), benzo [k] fluoranthene (B[k]F), dibenzo (a,h) anthracene (DBA), indeno [1,2,3-cd] pyrene (IPY), and benzo [ghi] perylene (BPE) significantly promoted the differentiation of Th17 and Th1 cells and B[a]P, B[a]A, B[b]F, and B[k]F induced more obvious inhibition of Treg cell differentiation; however, naphthalene (NAP), anthracene (ANT), phenanthrene (PHE), fluorene (FLU) and diphenyl had no significant effect on the differentiation of Th1, Th2, Th17 and Treg cells; interestingly, when AHR is activated by 1-pyrene (PYR), fluorene (FLU) plays a protective role in RA (24). It is speculated that different PAHs show different mechanism.

In addition to the CD4 T cells mentioned above, PAHs also affect the differentiation and maturation of B cells, DCs, macrophages, NK cells, osteoclasts (OCs) and osteoblasts (OBs).

### 3.1.1 Th1 and Th2 Cells

Both Th1 and Th2 cells are CD4+ T cell subsets that participate in the development of autoimmune diseases but their mechanisms are different, the Th1 is pro-inflammatory cells, while Th2 is anti-inflammatory cells (51). Interferon-γ (IFN-γ) is the major CKs secreted by Th1 cells and can promote the differentiation and maturation of CD8+ cytotoxic T lymphocytes (CTLs), improving the phagocytosis ability of macrophages to kill parasitic pathogens in target cells and playing a role in cellular immunity. In contrast to the mechanism of Th1 cells, Th2 cells secrete IL-4, which mainly stimulates the proliferation and differentiation of B lymphocytes, producing antibodies such as IgE to clear extracellular pathogens.
within the normal range and mainly playing a role in humoral immunity. However, excessive IgE production can lead to immune hypersensitivity, as observed in asthma. Therefore, the balance between Th1 and Th2 cells plays a key role in the immune response, and imbalance of these cells leads to immune diseases (52), such as RA. A significant imbalance between Th1 and Th2 cells has been reported in collagen-induced arthritis (CIA) mice and RA patients (53).

As the receptor of PAHs, AHR normally exists within the cytoplasm in Th1 and Th2 cells (36). A study confirmed that when PAHs (3-MC) activate AHR, oxidative stress significantly activates nuclear factor kappaB (NF-κB), which stimulates the airway production of Th1 cells; thus, the balance between Th1 and Th2 cells is biased toward Th1 cells, while Th2 cell production and CKs secretion are inhibited (36), functions that are associated with decreased expression of GATA-3, a critical factor in Th2 cell differentiation, this study suggests that exposure to PAHs results in an imbalance of Th1/Th2 cells and the occurrence of RA and that the intermediary involvement of AHR is even more important. Another RA mouse model showed that the lack of AHR in T cells inhibited the development of arthritis (35).

### 3.1.2 Th17 Cells

Th17 cells are a relatively newly discovered subset of CD4+ T cells. ROR-CT, a transcription factor expressed on the surface of Th17 cells (54), plays a crucial role in the control of extracellular pathogens and plays a critical role in human autoimmunity. Th17 cells secrete key pro-inflammatory CKs, such as IL-17A, IL-17F, and IL-22 (55). Studies have revealed that the upregulation of Th17 cells and relevant pro-inflammatory CKs is closely related to the formation and severity of RA (55).

PAHs are common exogenous AHR ligands, continuous overexposure to PAHs causes a series of pro-inflammatory changes in humans. Adequate experiments have shown that AHR plays a crucial role in the activation and proliferation of Th17 cells (31, 56). Additionally, PAHs in PM act directly on T cells through AHR-dependent and CYP-dependent pathways to promote Th17 cell differentiation and the immune response (49). AHR is expressed in the cytoplasm of Th17 cells (31); and when it is activated by PAHs in PM, the proliferation and differentiation of Th17 cells and their ability to produce pro-inflammatory CKs are enhanced during the development of RA (56). Notably, AHR is not involved in the initial stage of Th17 cell differentiation; instead, it is important for terminal differentiation.

Consistent with this view, the production of IL-17 by Th17 cells is significantly reduced and the IL-22 production is completely inhibited when AHR deficiency (57). Published results recently showed that exposure to PM enhanced the differentiation of naive T cells into a Th17-like phenotype through an AHR-dependent mechanism (49, 58), contributing to the formation RA. However, the diversity of ligands may lead to different effects on Th17 when AHR activated, when other kinds of ligands, such as, tetrachlorodibenzo-p-dioxin (TCDD), stimulates AHR, it can inhibit Th17 differentiation (59). Therefore, it is speculated that AHR on the initial T cells is a target to prevent the transformation into Th17 cells or that targeting AHR on Th17 cells to control RA has promising therapeutic prospects.

### 3.1.3 Treg Cells

Treg cells, like Th17 cells, are also a novel type of CD4+ T cell; however, in contrast to Th17 cells, Treg cells secrete anti-inflammatory CKs, such as IL-10 and transforming growth factor-β (TGF-β), which inhibit the progression of autoimmune diseases (53). Treg cells are mainly characterized by cell surface expression of the FoxP3 transcription factor (51). Foxp3 encodes a transcription factor that participates in inflammatory and autoimmune diseases in mice and humans and is specifically expressed in CD4+ Treg cells. Furthermore, retrovirus transfer of the Foxp3 gene induced increased differentiation of naive T cells into Treg cells. Thus, Foxp3 is a crucial regulatory gene for Treg cell differentiation; in other words, the differentiation, maturation and function of Treg cells are induced by Foxp3 (60). An increasing number of studies have shown that a decreased frequency of Foxp3+ T cells (Treg cells) is closely associated with increased disease activity in RA (61). Several studies have shown that Treg cells are significantly reduced in RA patients and CIA model mice (53).

Relationships exist between impairments of Treg and PAHs exposure. A study found substantial increases in PAHs exposure specifically in winter, which was significantly related to the ability and function of Treg cells (62), but the specific mechanism has not been fully characterized.

As receptor of PAHs, AHR is a transcription factor in the cytoplasm of Treg cells and is ligand-dependent (63). In contrast to the low levels of endogenous AHR in naïve T cells, AHR expression was increased in CD4+Foxp3+ cells (63). Recent studies have demonstrated a clear link between Treg cell differentiation and the signaling pathway of AHR, providing a possible mechanism for TCDD mediated immune suppression (30). In support of this conjecture, when AHR was activated with TCDD, Treg cell differentiation was accordingly improved (30). Research has demonstrated a link between Foxp3 and AHR; surprisingly, AHR was found to directly control Foxp3 expression (30) and play a role in Treg cell differentiation. Consistent with this idea, AHR activation by TCDD increased the binding of AHR to the Foxp3 promoter and upregulated the expression of the Foxp3 gene to increase the differentiation of Treg cells involved in immunity (30). Conversely, when the mice were exposed to PAHs, Treg cell differentiation was significantly reduced by inhibiting the binding of AHR and the Fox3P promoter to induce the RA (30).

The balance of Treg/Th17 cells is maintained under normal conditions; however, when RA occurs, the balance is broken (53). Experiments have found that AHR affects the differentiation of Th17 cells and Treg cells in opposite ways (30). Although inhibition of Treg cell function and/or hyperfunction of Th17 cells are considered important causes of RA, the specific physiological pathways is known about poorly. Nothing more than, the ability of AHR to selectively modulate the differentiation of Treg cells versus Th17 cells can be exploited, making it a unique target to treat immune diseases.
3.1.4 B Cells
B cells are the only cell type to express immunoglobulin (Ig) on their surface and secrete antibodies after activation. These cells mainly function in humoral immunity, and the humoral response plays a crucial role in the pathogenesis of RA (64, 65). Thus, the activation of B cells plays a key role in the pathogenesis of RA (64). And many studies have shown that the number and activity of B cells are significantly increased in patients with RA (64, 66). One of the main characteristics of RA is the activation of B cells that produce RF and ACPAs. Additionally, some studies have shown that continuous expression of RF increases the activation of B cells and monocytes (65) to aggravate RA. ACPAs enhance NF-κB activity and tumor necrosis factor-α (TNF-α) production by binding to citrullinated Grp78 expressed on macrophages (67). Grp78 protein (72 kD) is a homologous antigen of ACPA, but the mechanism by which the tolerance of B cells is broken remains incompletely understood.

AHR is expressed in B cells cytoplasm in the absence of a ligand (68), which are known targets of PAHs. A study showed that AHR-deficient B cells are less proliferative and less likely to enter the S stage of the cell cycle and remain in the G0/G1 phase of the cell cycle (69), this finding suggests that AHR activated by PAHs might indirectly promote B cell proliferation and activation, aggravating RA and other immune diseases, but enough evidence is needed to support this conjecture. Targeting AHR on B cells also will be a promising treatment in RA.

3.1.5 DCs
DCs are specialized antigen-presenting cells (APCs) that link innate and adaptive immune responses and promote the activation and differentiation of naïve T cells into effector T cells.

DCs are mainly divided into two key distinct functional subsets (conventional myeloid dendritic cells (cDCs) and plasmacytoid dendritic cells (pDCs)), induce initial effector differentiation of CD4+ T cells, activate CD8+ T cells, and promote B cell antibody responses, suggesting that DCs may play a crucial role in the initiation of joint inflammation. The interaction between pDCs and T cells (pDCs induce T cell differentiation) induces the autoimmune response in RA, DCs and secreted inflammatory CKs are significantly increased in arthritis model mice (70), and the number of DCs in synovial joint tissues is dramatically increased in RA patients (71). And there was study have shown that DCs are increased in the articular cavity of RA patients (72).

PAHs in the environmental pollutants promote the maturation and differentiation of DCs in an AHR-dependent manner (49). These results imply that PAHs in environmental pollution can induce RA in an AHR-dependent manner by affecting DCs (73).

Additionally, AHR regulates the production of tolerance-related metabolites in a subset of DCs, regulatory DCs (DCregs). This signaling induces the expression of enzymes responsible for tryptophan metabolism, such as indoleamine 2,3-dioxygenases (IDO1 and IDO2). Both IDO1 and IDO2 are immunosuppressive enzymes that participate in kynurenine metabolism to induce the production of Treg cells, which regulate the role of immune suppression by activating AHR (74). Kynurenine inhibits the ability of DCs to initiate T cell responses (73) and contributes to the apoptosis of Th cells, particularly Th1 cells (75). Under normal circumstances, the immune inflammatory and immune tolerance effects of AHR in DCs are balanced; however, in RA patients, a significant bias exists toward the immune inflammatory effect. Currently, strategies targeting immune inflammatory DCs for RA treatment have attracted extensive attention (70), and DCreg therapy for RA is gradually becoming common (76).

3.1.6 Macrophages
Macrophages are also central inflammatory immune cells that play a crucial role in the innate immune function involved in RA and become polarized into different cell phenotypes to mediate inflammatory/immune responses. Studies on the role of macrophages in inflammation have identified two different states of polarization (77), after stimulation, macrophages can mainly become polarized into M1 and M2 macrophages. M1 are pro-inflammatory macrophages, and M2 are anti-inflammatory macrophages. Classically activated macrophages (M1, CD68+CD192+) lead to joint damage with the production of pro-inflammatory CKs, such as TNF-α and IL-1β. Alternatively activated macrophages (M2, CX3CR1+CD163+) produce anti-inflammatory CKs (mainly IL-10 and TGF-β), contributing to tissue remodeling and repair. Recent studies have found that destruction of the balance between M1 and M2 macrophages—that is, a bias toward M1 macrophages, is one of the main reasons for RA (78, 79). The levels of M1 macrophages in RA inflammatory and synovial tissue are increased compared with healthy joints (80).

PAHs are involved in the formation of RA by affecting the maturation and differentiation of macrophages through AHR, which is expressed in both M1 and M2 macrophages cytoplasm, and the expression of AHR is upregulated by PAHs in M1 macrophages, however, down-regulated in M2 macrophages, contributing the increased pro-inflammatory CKs and decreased anti-inflammatory CKs to promote osteoclastogenesis to induce RA (81). Therefore, targeting AHR on different types of macrophages can be developed as a treatment for RA.

3.1.7 NK cells
NK cells also play a crucial role in the pathogenesis of autoimmune diseases (82), they are generally defined by the expression of CD56 and lack of CD3 expression (CD56+CD3−), and CD56− is another NK cell subtype. These two subtypes differ in maturity, function, and distribution. The main type related to immunoregulatory effects is the CD56− subtype (83), which can produce many CKs after stimulation and exert immunomodulatory functions. Some reports suggest that NK cells markedly expand in the joints and blood of RA patients (82, 84).

Similar to other immune cells, NK cells also have AHR (85), particularly immature CD56− cells (83). After exposure to PAHs, NK cell signal pathway is activated, inflammation may occur, and the number of NK cells in inflammatory joints increases (82, 83). AHR activation by PAHs significantly upregulates the expression
of the CYP1A1 enzyme (83, 86) in CD56+ NK cells, and CYP1A1 promotes the metabolism of PAHs and alleviates the occurrence of disease. However, PAHs inhibit the function of CYP1A1, leading to the accumulation of PAHs in inflamed joints and aggravation of joint inflammation. Therefore, regulation of AHR-targeted CYP1 enzyme activity may be a potential treatment for RA in the future.

3.1.8 OCs
OCs are multinucleated bone cells and responsible for the bone erosion of RA synovial joints, it is the only bone-resorptive cell type (86). OCs are also indispensable for physiological bone remodeling; however, excessive local OCs activity leads to periarticular bone destruction, which is a typical symptom of patients with RA. OCs are mainly derived from mononuclear precursor cells via receptor activator of NF-κB ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) signaling. Both RANKL and M-CSF are expressed on NK cells, and NK cells and mononuclear cells are abundant in the inflammatory joints of RA patients. When synovial NK and mononuclear cells are cocultured in vitro, mononuclear cells are triggered to differentiate into OCs, and the process relies on RANKL and M-CSF (84). A study found that the number of OCs was increased in RA patients (86).

After stimulation by PAHs, AHR activation plays a crucial role in bone remodeling by altering the interaction between OBs and OCs, and. AHR is expressed in osteocytes, including OBs and OCs (87, 88). There was a study demonstrated that the activation of AHR by B[a]P-mediated (a type of PAHs) stimulates RANKL-induced OCs generation and OCs function in wild-type mice (89) by CYP1A1 enzyme to lead to the formation of arthritis (86, 89).

These findings imply that the AHR, RANKL and CYP1 enzymes may play critical roles in OCs formation. And in the future treatment of RA, AHR-RANKL-CYP1-OCs will be used as an effective therapeutic axis.

3.1.9 OBs
OBs also play an important role in bone remodeling and are involved in bone formation. B cells play a crucial role in OBs dysfunction. In CIA mice, B cells are enriched in subchondral bone marrow and express high levels of genes encoding possible OBs inhibitors such as CCL3 (also called macrophage inflammatory protein 1-α) and TNF-α, which can inhibit OBs differentiation by activating the ERK and NF-κB pathways. CCL3 activates the ERK signaling pathway (90) and TNF-α activates the NF-κB signaling pathway (91). TNF-α is a crucial inflammatory CKs in RA; it not only inhibits OBs bone formation but also triggers OCs bone erosion through the RANK-RANKL pathway by inducing overexpression of Dickkopf-related protein 1 (DKK1), a strong inhibitor of the Wnt signaling pathway for bone synthesis. The regulation of typical Wnt pathways is mainly driven by the production of receptor inhibitors such as DKK1 (92). Additionally, the Wnt pathway plays an important role in the formation of OBs, and increased Wnt signaling pathway activation may lead to decreased OCs formation and bone resorption (93) through upregulating osteoprotegerin (OPG) expression of OBs. The differentiation of OBs is significantly reduced in RA patients (91).

Similar to OCs, AHR also exists in OBs cytoplasm (88), and AHR stimulation has a dose-dependent effect on OBs: overactivation and under-activation inhibit and promote bone formation, respectively. When stimulated by extensive PAHs in the environment, AHR is activated in OBs, causing a series of changes, such as transcriptional activation of CYP1A1 and CYP1B1 (88). CYP1A1 and CYP1B1 polymorphisms alter bone mineral density (BMD) (94, 95) to induce RA disease. A study suggested that women carrying the CYP1B1 gene had increased estrogen catabolism and showed higher urinary estrogen metabolites, the effect may result in relatively low levels of estrogen and low BMD in the lumbar spine and femoral neck of these women (94).

Therefore, for OBs, AHR is the target to regulate the generation of downstream gene CYP1, so as to reduce the catabolism of estrogen to upregulate BMD, which can be a prospective treatment for RA.

4 AHR AS A POSSIBLE THERAPEUTIC TARGET IN RA
AHR is considered an essential factor in immune responses, and many AHR-induced immune mechanisms have been identified, enhancing the understanding of the pathogenesis of immunological inflammatory diseases, including RA, at the molecular level.

Targeting AHR is considered a novel therapeutic target in RA, because it can avoid the long-term use of previous compounds contributing to serious side effects, such as high embryonic mortality (96), recurrent hepatotoxicity (97) and carcinogenicity (98). AHR ligands with fewer side effects and other novel drugs have regards as potential candidates to treat RA and other autoimmune diseases (Table 1). Recently, novel drugs targeting AHR are widely used to treat immune-related diseases, however,
AHR ligands have yet to be developed for clinical use. Therefore, we should study the treatment of RA with AHR ligand overall in order to make this therapy more practical in the future.

4.1 Traditional Chinese Medicine Monomer Therapy

4.1.1 Tetrandrine
Tetrandrine is a dibenzyl isoquinoline alkaloid isolated from tetrandrine roots and is clinically used to relieve rheumatic pain and joint pain. As an agonist of AHR, tetrandrine ameliorates CIA in mice by inhibiting Th17 cell differentiation and inducing Treg cell formation to restore the balance between Th17 cells and Treg cells, and the primary mechanism of the effect occurs by promoting the expression of the AHR target gene cytochrome P4501A1 (CYP1A1) (99).

4.1.2 Norisoboldine
Norisoboldine (NOR) is the main isoquinoline alkaloid component of polylindera roots that attenuates OCs differentiation to alleviate RA. As an AHR agonist, NOR can promote AHR/Hsp90 dissociation and AHR nuclear function of Treg cells in an AHR-dependent manner, inducing protein expression (24).

4.1.3 Sinomenine
Sinomenine (SIN) is an alkaloid isolated from the root of sinomenine acutum that has been used to treat RA for decades (102). It alleviates arthritis by promoting the production and function of Treg cells in an AHR-dependent manner, inducing the expression of the AHR-targeted gene CYP1A1, and promoting AHR/Hsp90 dissociation and AHR nuclear translocation (101).

4.2 Biological Therapy
Our previous studies have shown that human umbilical mesenchymal stem cells (HUMMSCs) play a therapeutic role in CIA rats by mediating the interaction between host immunity and gut microbiota through AHR, and this specific mechanism mainly involves increasing AHR target gene and corresponding protein expression (24).

4.3 Other Therapeutic Drugs
Various types of dietary phytochemicals, the most typical of which are dietary flavonoids such as quercetin and indigo, may be promising drugs to treat nonalcoholic fatty liver disease (NAFLD) (103) because they inhibit hepatic CD38 and affect AHR (104). Considering its effect on AHR, it can be used as a possible drug to treat RA.

Dietary flavonoids control joint inflammation and reduce arthritis symptoms in both RA patients and CIA animal. Although these substances have powerful anti-inflammatory effects, they are associated with few clinical applications and little scientific evidence regarding their mechanism of action in RA has been reported. Therefore, we should strengthen the research in the area so that the treatment is likely to be promising therapeutic agents for RA in the future.

Although many significant advances have been made in the molecular understanding of biological responses and AHR activation, several crucial questions persist. As Sulire and Kaminski pointed out in their paper, most of the literature on AHR to date has investigated mouse AHR (105). Although mouse and human AHR are interchangeable in most in vitro systems, a dramatic difference exists in the binding affinity between the two AHRs to ligands in vivo: the mouse AHR binding affinity is 10-fold higher than that of human AHR (106). Thus, the applicability of the results from mouse AHR experiments in human immunity is unclear. A current challenge is that most effects observed in mouse models have yet to be demonstrated in human cells.

5 DISCUSSION AND PROSPECTS

RA is a chronic autoimmune disease characterized by immune disorder, inflammatory infiltration, articular cartilage damage and joint deformity. The inflammatory infiltration is mainly caused by the increased secretion of inflammatory cells, such as, Th1 (53), Th17 (55), B cells (64, 66), DCs (72), M1 (80), NK cells (82, 84), OCs (86), and corresponding inflammatory CKs, such as, IFN-γ, IL-17, IL-22, TNF-α. Additionally, the decreased Th2 (53), Tregs (53), M2 (79), OBs (91) and IL-10, TGF-β further aggravate the formation of RA.

PAHs in environmental exposure plays a crucial role in the pathogenesis of RA, primarily by influencing the changes in diversity cells and corresponding downstream CKs, and the main pathway of these effects is through the AHR signaling pathway. Interestingly, in these cells, the effects of AHR activation showed an opposite trend. For example, in Th1, Th17, B cells, DCs, M1, NK, and OCs cells, AHR activation had a pathogenic effect on RA (35, 49, 69, 81, 86, 89), however, the activation of Th2 (35), Treg cells (30), DCreg (76), M2 (81) and OBs (88) cells is protective. And the number of these protective cells decreases, the pathogenic effected cells increase, further promoting the occurrence of RA. But, the different types or doses of PAHs mentioned above may produce diverse results in RA. In conclusion, the activation of AHR in RA patients may be either a pathogenic factor or a therapeutic effect, and the specific effect after AHR activation may be related to the type and even the dose of ligands (24).

Although substantial progress has been achieved in the treatment of RA, the current clinical treatment mainly includes nonsteroidal anti-inflammatory drugs, corticosteroids, and disease-modifying antirheumatic drugs (DMARDs). The former two drug classes have an anti-inflammatory analgesic effect soon after administration but do not fundamentally treat RA. DMARDs such as leflunomide (LEF) work slowly but can continuously alleviate disease activity in patients to suppress progressive joint damage and delay the development of RA. Because of their outstanding advantages, DMARDs (particularly new drugs that
HUMSCs therapy for RA targets AHR is also a potential treatment that relieves the differentiation of OCs and erosion of bone by activating AHR (100); SIN mainly plays a role in the treatment of RA by promoting the generation of Treg cells (101). In addition, HUMSCs therapy for RA targets AHR is also a potential treatment (24). Furthermore, the dietary flavonoid in the treatment of liver disease have been reported to relieve joint inflammation and control arthritis symptoms in RA patients and CIA animal models. However, scientific evidence about their mechanism in RA has been poorly studied. The relevant experiments should be carried out and this kind of drugs are likely to be promising therapeutic prescription for RA in the future.

The main purpose of this review was to summarize the possible factors athering RA and the pathogenesis of RA based on AHR and AHR-targeted drugs for RA treatment, as well as propose novel therapeutic drugs. Although many basic studies have been carried out on PAHs-AHR-RA, clinic studies on PAHs-AHR-Ra, clinic studies on the development of novel drugs from the AHR pathway are insufficient currently, and further investigations are needed. The development of novel drugs from the laboratory to the clinic through convincing studies are promising probably.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary files. Further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

XX and QY contributed equally to this paper. YX and CX designed the manuscript. XX and QY wrote the manuscript. DF, XC, QW, XW and MZ participated in discussions associated with the manuscript. DF, XC and CX revised the manuscript. All the authors read and approved the final manuscript.

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