Immune Netw. 2025 Apr;25(2):e1
https://doi.org/10.4110/in.2025.25.e1
pISSN 1598-2629·eISSN 2092-6685

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Review Article

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Role of the Aryl Hydrocarbon Receptor in the Self-Renewal, Differentiation, and Immunomodulation of Adult Stem Cells

Myeong-Seong Seo [1,2], **Jiyeon Baek** [1,2], **Myung-Shin Jeon** [1,2,3,4,*]

[1]Translational Research Center, Inha University Hospital, Incheon 22332, Korea
[2]Program in Biomedical Science & Engineering, Inha University, Incheon 22212, Korea
[3]Department of Biomedical Sciences, College of Medicine, Inha University, Incheon 22212, Korea
[4]SCM Lifescience, Incheon 21999, Korea

OPEN ACCESS

Received: Oct 17, 2024
Revised: Dec 11, 2024
Accepted: Dec 13, 2024
Published online: Feb 5, 2025

***Correspondence to**
Myung-Shin Jeon
Translational Research Center, Inha University School of Medicine, B/308 Jungseok Bldg., 366 Seohae-daero, Jung-gu, Incheon 22332, Korea.
Email: msjeon@inha.ac.kr

ORCID iDs
Myeong-Seong Seo
https://orcid.org/0000-0002-1746-9230
Jiyeon Baek
https://orcid.org/0009-0009-5067-4066
Myung-Shin Jeon
https://orcid.org/0000-0003-2681-8735

Conflict of Interest
The authors declare no potential conflicts of interest.

Abbreviations
AhR, aryl hydrocarbon receptor; B[a]P, benzo[a]pyrene; BM, bone marrow; BMPRII, bone morphogenetic protein receptor type II; CA, constitutively active; CFU-E,

ABSTRACT

Adult stem cells are a rare population of undifferentiated cells present in almost all body tissues. Depending on their location, stem cells can differentiate into various tissue types, primarily contributing to maintenance, repair, and immune system regulation. Stem cell therapies have significant potential in regenerative medicine and treatment of inflammatory diseases. However, many factors must be considered for successful clinical commercialization, including enhancing therapeutic potential, ensuring product differentiation, and optimizing the manufacturing process for large-scale production. The development of sophisticated regulatory mechanisms may enhance therapeutic applications. The aryl hydrocarbon receptor (AhR) is expressed in all adult stem cells, and its activation and function are tightly regulated. Understanding the role and regulation of AhR is crucial for developing effective stem cell therapies. This review examines the role of the AhR in regulating the fundamental characteristics of adult stem cells, which may contribute to advancing adult stem cell therapies.

Keywords: Aryl hydrocarbon receptor; Adult stem cells; Cell self-renewal; Cell differentiation

INTRODUCTION

Adult stem cells are present in almost all body tissues and possess 2 essential properties: self-renewal and differentiation. These cells can proliferate and differentiate into various cell types. Depending on their location, stem cells can develop into different tissues, primarily contributing to maintenance and repair (1). For example, hematopoietic stem cells (HSCs) reside in the bone marrow (BM) and produce blood cells (2). Intestinal stem cells (ISCs) are located at the base of the intestinal crypts and differentiate into absorptive and secretory lineages, such as enterocytes, goblet cells, enteroendocrine cells, and Paneth cells, which maintain intestinal homeostasis and facilitate repair after injury (3). Mesenchymal stem cells (MSCs) are multipotent and can be found in almost all tissues, including the BM, adipose tissue, and dental pulp. They can differentiate into mesodermal cells, such as bone, cartilage, fat, and muscle cells, as well as into ectodermal and endodermal lineages, including liver and nerve cells (4,5). Additionally, MSCs possess immunomodulatory properties and can suppress immune responses and reduce inflammation (6).

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erythrocyte colony-forming unit; CFU-GM/M, granulocyte-macrophage colony-forming unit; CLP, common lymphoid progenitor; CMP, common myeloid progenitor; DSS, dextran sulfate sodium; eEF2K, eukaryotic elongation factor-2 kinase; EP, erythrocyte progenitor; FICZ, 6-formylindolo(3,2-b) carbazole; GMP, granulocyte-macrophage progenitor; GVHD, graft-versus-host disease; hBM-MSC, bone marrow-derived human mesenchymal stem cell; hMSC, human mesenchymal stem cell; HSC, hematopoietic stem cell; I3A, indole-3-carboxaldehyde; I3C, indole-3-carbinol; IDO1, indoleamine 2,3-dioxygenase 1; iNOS, inducible nitric oxide synthase; ISC, intestinal stem cell; Kyn, kynurenine; KYNA, kynurenic acid; Lgr5, leucine-rich repeat-containing G protein-coupled receptor 5; MEP, megakaryocyte-erythrocyte progenitor; MPP, multipotent progenitor; MSC, mesenchymal stem cell; OA, osteoarthritis; PPARγ, peroxisome proliferator-activated receptor gamma; SR1, StemRegenin 1; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; Trp, tryptophan; TSG-6, tumor necrosis factor-stimulated gene 6; WT, wild-type; XRE, xenobiotic response element; α-NF, α-naphthoflavone.

Author Contributions

Conceptualization: Jeon MS, Seo MS; Data curation: Jeon MS, Seo MS, Baek J; Formal analysis: Jeon MS; Funding acquisition: Jeon MS; Writing - original draft: Jeon MS, Seo MS, Baek J; Writing - review & editing: Jeon MS, Seo MS.

The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor that plays crucial roles in drug metabolism, detoxification of xenobiotics, and biosynthesis of various compounds, such as the cytochrome p450 enzyme CYP1A1 (7,8). In addition, the AhR regulates the development and function of different immune cell types, including T, B, and innate immune cells (9,10). Both exogenous ligands, such as environmental toxins like dioxins, and endogenous ligands, including tryptophan (Trp) metabolites, can activate the AhR. Additionally, dietary compounds and microbial products can act as AhR ligands. There are 3 known AhR signaling pathways: i) the canonical pathway involves the translocation of the ligand-activated AhR to the nucleus, where it forms a complex with the AhR nuclear translocator. This complex binds to xenobiotic response elements (XREs) to regulate gene expression; ii) non-canonical pathways, in which AhR interacts with other transcription factors in the nucleus, such as pRb, E2F, and p300; and iii) AhR's role as an E3 ubiquitin ligase, which is involved in the degradation of proteins such as estrogen receptor alpha, peroxisome proliferator-activated receptor gamma (PPARγ), and eukaryotic elongation factor-2 kinase (eEF2K) (11,12).

The AhR is expressed in stem cells and is tightly regulated. Given the growing interest in stem cells for disease treatment, understanding the role and regulation of AhR is crucial for the development of effective cell therapies. We describe 3 types of adult stem cells, focusing on how AhR regulates fundamental properties that may contribute to the advancement of clinical therapies.

HSCs

Hematopoiesis, the process through which blood cells develop from HSCs, is highly regulated. HSCs, rare cells primarily located in the BM and peripheral and umbilical cord blood, possess self-renewal capacity (13). Recent advances in single-cell technologies have highlighted the heterogeneity of HSCs and provided new insights into their differentiation (2). Despite these recent findings, the traditional understanding of HSC differentiation into multipotent progenitor (MPP) cells, which subsequently commit to further maturation along specific pathways, remains the cornerstone of our knowledge (14). MPPs can differentiate into common myeloid progenitor (CMP) and common lymphoid progenitor (CLP) cells. CMPs give rise to megakaryocytes, erythrocytes, granulocytes, and monocytes, whereas CLPs develop into T, B, and NK cells (**Fig. 1**) (14-16).

The *Ahr* gene consists of 11 exons and 3 distinct domains: the basic helix-loop-helix domain (exons 1–2), the Per-Arnt-Sim domain (exons 3–9), and the transactivation domain (exons 10–11). Exon 1 includes a 5'-untranslated region and a nuclear localization signal, exon 2 encodes the DNA-binding domain, and exon 3 encodes the dimerization domain (17). *Ahr* knockout ($Ahr^{-/-}$) mouse models, which lack exons 1, 2, or 3, provide evidence for the role of the AhR in hematopoiesis. These 3 models showed enlarged spleens, increased circulating white blood cells, and hematopoietic cell accumulation in tissues (18-22). $Ahr^{-/-}$ mice with a deletion of exon 1 exhibited myeloid hyperplasia in the red pulp of the spleen, primarily composed of myeloid, erythrocytic, and megakaryocytic cells (20). HSCs from aging $Ahr^{-/-}$ mice with exon 2 deletion exhibited elevated levels of Ki67, ROS, and the DNA damage response gene γ-H2AX (22). Several genes are associated with HSC hyperproliferation, myelogenous leukemia, and accelerated aging. These findings indicate that loss of *Ahr* promotes premature HSC exhaustion and the development of myeloproliferative disorders in aging mice (22).

https://doi.org/10.4110/in.2025.25.e1

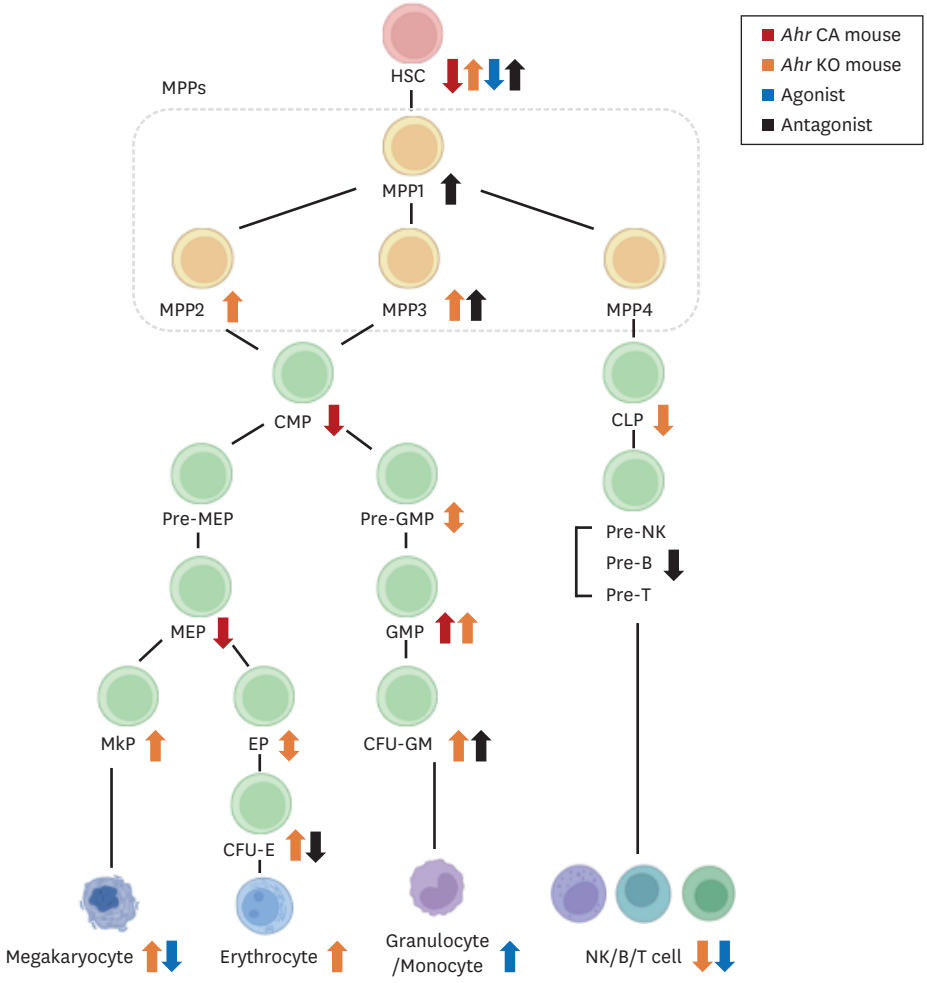

Figure 1. The role of AhR in the proliferation and differentiation of HSCs.
CA, constitutively active; KO, knockout; MEP, megakaryocyte-erythrocyte progenitor; MkP, megakaryocyte progenitor.

Like exon 2 deletion mice, *Ahr*$^{-/-}$ mice with exon 3 deletion exhibited altered proliferation and quiescence of HSCs, enhancing their ability to differentiate into granulocyte-macrophage colony-forming unit (CFU-GM/M) (21).

Recently, Vaughan et al. (23) further analyzed the influence of the AhR on the differentiation of lineage-based progenitor cells in different *Ahr*$^{-/-}$ mice. The number of myeloid-biased HSC and MPP3 increased in exon 2-deleted *Ahr*$^{-/-}$ mice. In tamoxifen-induced *Ahr*$^{-/-}$ mice, the number of MPP2 and MMP3 was increased. The percentages of megakaryocyte progenitor and PreGM increased, whereas those of CLP and erythrocyte progenitor (EP) decreased. Hematopoietic-specific conditional deletion of *Ahr* induces an expanded number of myeloid-biased HSCs and MPP3 cells. The percentages of granulocyte-macrophage progenitor (GMP) and EP cells and colonies of CFU-GM and erythrocyte colony-forming unit (CFU-E) increased, whereas those of PreGM decreased. Antagonism of AhR injection with CH223191 in mice increased MPP1, MMP3, and CFU-GM colonies and decreased CFU-preB and CFU-E. Overall, the deficiency of *Ahr* due to the deletion of genes or antagonism by inhibitors led to an increase in the HSCs and MPP3 population, which develops into the myeloid lineage (23). Murakami et al. (24) observed that transgenic mice with constitutively active *Ahr* driven by the keratin 14 promoter developed chronic dermatitis and splenomegaly. This was accompanied

https://doi.org/10.4110/in.2025.25.e1

by an increase in the percentage of GMPs. In contrast, the percentages of CMPs and megakaryocyte-erythrocyte progenitors decreased, resulting in the skewed differentiation of hematopoietic progenitor cells toward the granulocyte-monocyte lineage. Consequently, there was a reduction in long-term self-renewing HSCs at the early stage of dermatitis (24). Thus, AhR influences the differentiation and proliferation of HSCs, either directly within HSCs or indirectly through non-hematopoietic cells.

AhR plays a crucial role in regulating hematopoiesis through its interaction with various ligands. *In vivo*, the administration of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), an AhR ligand, induces significant changes in the number of hematopoietic progenitor cells in mice. Post-TCDD treatment, the populations of HSCs, $CD34^-$, Lin^-, $Sca\text{-}1^+$, and $c\text{-}Kit^+$ cells increased (25). When these HSCs were isolated and adoptively transferred into irradiated wild-type (WT) mice, the number of HSCs decreased during long-term reconstitution experiments. However, this defect was absent in adoptively transferred HSCs isolated from TCDD-treated *Ahr*$^{-/-}$ mice (25). In contrast, the Gasiewicz group demonstrated that the TCDD-mediated activation of AhR led to a decrease in long-term engraftment, likely due to reduced migration rather than a diminished number of functional HSCs in mice (26). Additionally, they showed through *in vitro* culture that proliferating HSCs downregulated *Ahr* mRNA and that direct exposure of cultured BM cells to TCDD inhibited the growth of immature HSCs (27). This suggests that AhR activation inhibits HSC proliferation and development.

Boitano et al. (28) identified a purine derivative, StemRegenin 1 (SR1), that promotes the *ex vivo* expansion of $CD34^+$ cells from human blood through AhR inhibition. They discovered that SR1 functioned as an AhR antagonist and that other AhR antagonists, such as α-naphthoflavone (α-NF) and CH223191, also enhanced the number of $CD34^+$ cells. Rentas et al. (29) demonstrated that overexpression of the RNA-binding protein Musashi-2, which directly inhibits AhR signaling, resulted in the expansion of human HSCs. Strassel et al. (30) reported that co-culturing peripheral blood $CD34^+$ cells with bone marrow-derived human MSCs (hBM-MSCs) significantly enhanced the production of proplatelet-bearing megakaryocytes and platelet-like elements by inhibiting the AhR pathway. Recently, Khan et al. (31) demonstrated the differentiation of $CD34^+$ human hematopoietic stem and progenitor cells using single-cell methods in an *in vitro* stromal cell-free culture system. They found that AhR activation by TCDD significantly suppressed lymphoid and megakaryocyte populations and increased monocyte and granulocyte populations. A brief overview of these studies is provided in **Table 1**.

The AhR is pivotal in regulating steady-state hematopoiesis and influences HSC and lineage commitment. Thus, modulating AhR activation in human hematopoietic cells is a promising strategy for developing hematopoietic cells suitable for clinical therapies.

ISCs

Maintaining intestinal homeostasis involves the integration of immunological and molecular processes with environmental, dietary, metabolic, and microbial cues, all of which rely on the proper functioning of epithelial cells. The small intestinal epithelium consists of proliferative crypts and terminally differentiated cells along the villi. ISCs are located at the base of each crypt. They are believed to comprise actively cycling leucine-rich repeat-containing G protein-coupled receptor 5 $(Lgr5)^+$ crypt base columnar cells interspersed with Paneth cells, as well as quiescent label-retaining cells that reside approximately at the "+4" cell positions

Table 1. Functions of AhR in HSC

Variables	Type	Function	Ref.
Mouse model			
Ahr KO	Exon 1 deletion	- Splenomegaly, decreased in T and B cells - Myeloid hyperplasia	(20)
	Exon 2 deletion	- Splenomegaly	(18)
		- Promoted premature HSC exhaustion	(19)
		- Myeloproliferative disorder	(22)
		- Increased myeloid-biased HSC and MPP3	(23)
	Exon 3 deletion	- Splenomegaly - Increased CFU-GM/M	(21)
	Tamoxifen-induced $Ahr^{CreERT2}$ KO	- Increased MPP2/3, MkP, and preGMP - Decreased CLP and EP	(23)
	Hematopoietic-specific conditional Ahr^{vav1} KO	- Increased myeloid-biased HSC and MPP3 - Increased GMP, EP, CFU-GM, and CFU-E - Decreased preGMP	(23)
Ahr Tg	*Ahr* CA mouse	- Increased GMP - Decreased long-term self-renewing HSC - Decreased CMP and MEP	(24)
AhR ligand			
Agonist	TCDD	- Increased $CD34^-$ Lin^- $Sca\text{-}1^+$ $c\text{-}Kit^+$ HSCs	(25)
		- Inhibited the growth of immature HSCs	(27)
		- Decreased lymphocyte and megakaryocytes	(31)
		- Increased monocytes and granulocytes	(31)
Antagonist	CH223191	- Increased HSC, MPP1/3, and CFU-GM	(23)
		- Decreased CFU-preB and CFU-E	(23)
		- Increased $CD34^+$ cells	(28)
	SR1/α-NF	- Promoted the *ex vivo* expansion of $CD34^+$ cells	(28)

CA, constitutively active; KO, knockout; MEP, megakaryocyte-erythrocyte progenitor; MkP, megakaryocyte progenitor; Tg, thyroglobulin.

above the crypt base. Lgr5 is recognized as the most reliable marker for ISCs (32). These $Lgr5^+$ ISCs continuously generate rapidly proliferating transit-amplifying cells, which subsequently differentiate into functional cells in the villi, including goblet, enteroendocrine, tuft, and enterocyte cells (**Fig. 2**) (3,33).

The AhR is highly expressed in $Lgr5^+$ ISCs, suggesting that AhR activation plays a regulatory role in the development of mouse intestinal epithelial cells (34). The role of AhR in the proliferation and differentiation of ISCs varies depending on the health status of mice and the types of ligands to which they are exposed. Park et al. (34,35) demonstrated that treatment with TCDD, 6-formylindolo(3,2-b)carbazole (FICZ), and indole-3-carbinol (I3C) inhibited the development of intestinal organoids derived from the crypts of $Lgr5^+$ ISCs *in vitro*. *In vivo*, a single oral administration of TCDD in steady-state mice induced changes in the villous structure of intestinal epithelial cells, resulting in functional alterations (36). Administration of FICZ to mice reduced the length of intestinal crypts and the number of Paneth cells, whereas I3C treatment increased the number of goblet cells (34,35). HT-29 human epithelial cells differentiate into goblet cells; 1-methyltryptophan inhibits this process, whereas Trp and kynurenine (Kyn) promote goblet cell differentiation *in vitro* (37). Loss of the Trp-metabolizing enzyme indoleamine 2,3-dioxygenase 1 (IDO1) in mice reduced proliferation in the crypts and the number of goblet cells, whereas IDO1 overexpression increased the number of proliferating cells in the crypt, goblet, and Paneth cells by inhibiting NOTCH1 signaling in an AhR-dependent manner. Inhibition of Notch signaling skews goblet cell differentiation (38). AhR ligands differentially regulate the proliferation and differentiation of ISCs by inhibiting Notch signaling pathways.

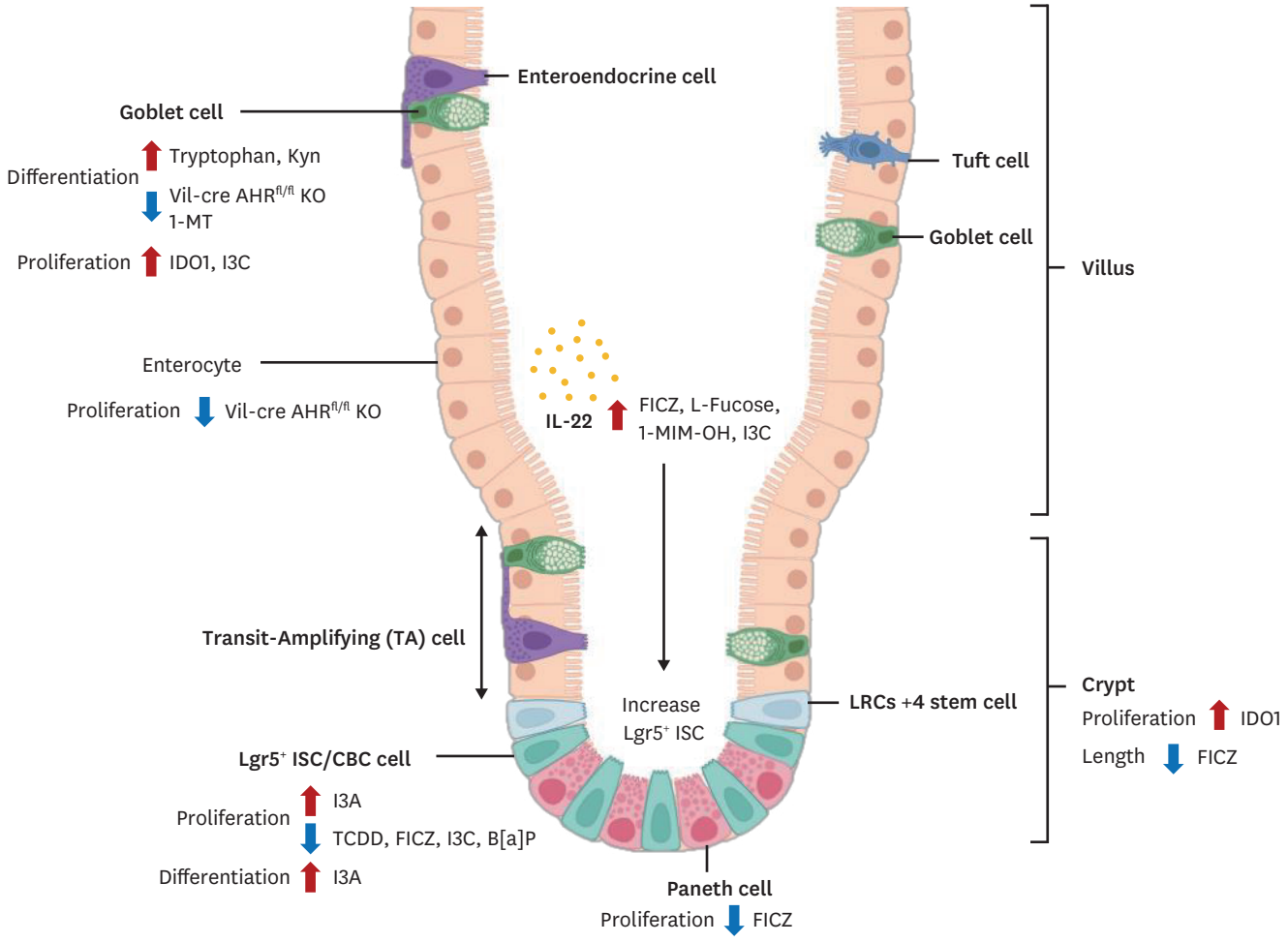

Figure 2. The role of AhR in the proliferation and differentiation of ISCs.
KO, knockout; CBC, crypt base columnar; LRC, label-retaining cell; 1-MT, 1-methyltryptophan; 1-MIM-OH, 1-methoxy-3-indolyl methyl alcohol.

Intestinal *Ahr*$^{-/-}$ was shown to increase basal stem cell proliferation and enhance crypt injury-induced cell proliferation by upregulating FoxM1 signaling. This cell cycle-associated transcription factor is a direct target of AhR and is suppressed by it (39,40). The role of AhR in epithelial maintenance has been elucidated in studies involving a dextran sulfate sodium (DSS)-induced injury mouse model and *Citrobacter rodentium* infection in Vil-cre AHR$^{fl/fl}$ mice (41,42). DSS treatment compromised epithelial barrier function in both WT and Vil-cre AHR$^{fl/fl}$ mice. Sca-1 expression, a regeneration marker, peaked on day 12 after DSS treatment in WT mice and then gradually decreased, whereas Sca-1 expression remained elevated in Vil-cre AHR$^{fl/fl}$ mice (41). Under DSS-induced injury conditions, the loss of *Ahr* led to increased ISC proliferation and reduced differentiation of epithelial cells, such as goblet cells (41,43). The activation of the AhR by FICZ can decrease the expression of stemness markers such as *Sox9* while increasing differentiation markers such as *Cdx2*, both of which are target genes of AhR in epithelial cells (41). These findings suggest that cell-intrinsic AhR signaling is essential for terminating injury-induced regenerative responses in colonic stem cells (41). In a study involving *C. rodentium*-infected Vil-cre AHR$^{fl/fl}$ mice, Metidji et al. (42) demonstrated that the loss of *Ahr* resulted in a rapid onset of mortality and a significant reduction in goblet cells within the crypts. *Ahr*-deficient colon organoids exhibited increased proliferation along with a decrease in goblet cells and enterocytes, indicating impaired proliferation and

differentiation of ISCs. Furthermore, the researchers found that ligand-activated AhR directly promoted the expression of RNF43, an E3 ubiquitin ligase expressed in $Lgr5^+$ stem cells, which restricts ISC proliferation (44). Another ISC marker, Smoc2, is expressed in ISCs and enhances growth factor-induced cyclin D1 expression and DNA synthesis (45,46). However, it can be suppressed by AhR ligands such as benzo[a]pyrene (B[a]P) and TCDD (47). This indicates that active AhR can directly inhibit ISC proliferation by regulating ISC markers, such as RNF43 and Smoc2.

Many other cells, such as immune cells, are present in the intestine and may indirectly regulate ISCs. Lindemans et al. (48) reported that the IL-22 receptor is expressed in $Lgr5^+$ ISCs. Treatment with IL-22 directly enhances the growth of intestinal organoids and promotes the expansion of $Lgr5^+$ ISCs via STAT3 phosphorylation. Since IL-22 is produced by immune cells, including ILC3, γδT, and regulatory T cells (49), it has been suggested that the immune system can activate ISCs to facilitate regeneration (48). AhR activation by FICZ treatment partially alleviates DSS-induced colitis by upregulating IL-22 (50). AhR ligands, such as I3C, indole-3-carboxaldehyde (I3A), L-fucose, and 1-methoxy-3-indolyl methyl alcohol, activate AhR to induce and promote IL-22 production (51-53). In immune cells, AhR directly regulates the expression of IL-22 by binding to XREs in the promoter region of the IL-22 gene (54).

Patients undergoing abdominal radiation therapy often develop enteritis because radiation can cause intestinal damage (55). Recently, Xie et al. (56) reported that microbiota-derived I3A protects the intestine against radiation by activating AhR/IL-10/Wnt signaling. I3A promotes the proliferation and differentiation of $Lgr5^+$ ISCs through the Wnt/β-catenin signaling pathway, which enhances survival rates and modifies the gut microbiota. Treatment with I3A in irradiated mice reduced pathogenic bacteria such as *Desulfovibrio* and *Escherichia-Shigella* while simultaneously increasing beneficial bacteria like *Lactobacillus*, *Bifidobacterium*, *Alloprevotella*, and *Lachnospiraceae_NK4A136* (56). A brief overview of these studies is provided in **Table 2**.

These findings indicate that intrinsic and extrinsic AhR signaling plays a significant role in the proliferation, differentiation, regeneration, and regulation of inflammation in ISCs, thereby preserving the health and integrity of the intestine.

MSCs

MSCs represent a significant advancement in regenerative medicine owing to their unique self-renewal capabilities and ability to differentiate into osteogenic (bone), chondrogenic (cartilage), and adipogenic (fat) cells (**Fig. 3**). Their ability to be sourced from various adult tissues and their potential for treating several diseases make them ideal candidates for stem cell therapies. Furthermore, the low immunogenicity and immunomodulatory functions of these cells open new avenues for addressing graft-versus-host disease (GVHD), cardiovascular diseases, allergies, and autoimmune disorders (4,57-59).

The AhR is expressed in MSCs. Treatment with B[a]P reduced the self-renewal capacity of hBM-MSCs and placenta-derived MSCs (PD-MSCs) via inhibiting TGF-β1/SMAD4 and TGF-β1/ERK/AKT signaling pathways (60,61). Resveratrol, a natural antagonist, abolished the effects of B[a]P (60). Kyn activated AhR, reduced BM-MSC proliferation, and decreased L-lactate concentration while simultaneously enhancing mitochondrial function (62).

Table 2. Functions of AhR in ISC

Variables	Type	Function	Ref.
Mouse model			
DSS-induced	Vil-cre AhR$^{fl/fl}$ KO	- Promoted cell proliferation in the TA region	(39)
		- Increased Sca-1 expression and ISC proliferation	(41)
		- Reduced goblet cell differentiation	(41)
C. rodentium-induced		- Increased mortality	(42)
		- Increased ISC proliferation	
		- Reduced goblet cells and enterocytes	
IDO	IDO1-KO	- Reduced the proliferation in the crypt and goblet cells	(38)
	IDO1-Tg	- Increased stem cells, goblet, and Paneth cells	(38)
		- Decreased enterocytes	
AhR ligand			
Agonist	B[a]P	- Inhibited cyclin D1 expression and DNA synthesis	(47)
	FICZ	- Inhibited the development of intestinal organoids	(34)
		- Decreased length of the crypt and Paneth cells	(34)
		- Decreased expression of stemness marker, Sox9	(41)
		- Increased expression of differentiation marker, Cdx2	(41)
		- Increased the expression of IL-22	(50)
	L-Fucose	- Increased IL-22 expression	(52)
	I3A	- Increased IL-22 expression	(51)
		- Increased Lgr5^{+} ISC proliferation and differentiation	(56)
	I3C	- Inhibited the development of intestinal organoids	(35)
		- Increased goblet cells	(35)
		- Increased IL-22 expression	(53)
	Trp/Kyn	- Increased goblet cell differentiation	(37)
	TCDD	- Inhibited the development of intestinal organoids	(34)
		- Altered villous structure in intestinal epithelial cells	(36)
		- Inhibited cyclin D1 expression and DNA synthesis	(47)
	1-MIM-OH	- Increased IL-22 expression	(53)
Antagonist	1-MT	- Decreased the differentiation into goblet cells	(37)

KO, knockout; Tg, thyroglobulin; TA, transit-amplifying; 1-MIM-OH, 1-methoxy-3-indolyl methyl alcohol; 1-MT, 1-methyltryptophan.

Conversely, the inhibition of AhR activation by SR1 produced the opposite effect (62). Tao et al. (63) reported that TCDD may induce cleft palate by inhibiting the proliferation of palatal MSCs through suppression of Oct4, a transcription factor associated with pluripotent stem cells. These findings suggest that AhR activation negatively affects the proliferation of MSCs.

B[a]P and TCDD suppress the osteogenic differentiation of MSCs (60). B[a]P activates the AhR, which inhibits TGFβ1/SMAD-dependent signaling pathways (60). It reduces the expression of bone morphogenetic protein receptor type II (BMPRII) during BMP2/BMPRII-induced osteogenic differentiation, thereby impairing the BMP/Smad pathway (64). TCDD-activated AhR suppresses osteogenesis by inhibiting β-catenin expression and related transcription factors, such as DLX5 (65-68). In addition, Kyn accumulates in the plasma with age, leading to bone loss and osteoporosis. It inhibits autophagy and induces senescence in MSCs through AhR signaling (69-71). The high bone mass observed in *Ahr*$^{-/-}$ male mice has been consistently attributed to a reduction in Cyp1 enzyme-mediated bone resorption (72). In contrast, Huang et al. (73) demonstrated that the AhR ligand FICZ positively influences the regenerative potential of BM-MSCs in rats and enhances primed cartilage templates. FICZ reduces the expression of inflammatory cytokines, including IL-1β, IL-6, and TNF-α, while enhancing the osteogenic differentiation and polarizing macrophages to an anti-inflammatory M2 phenotype. The authors reported that FICZ is crucial in reducing inflammation and promoting the regeneration of BM-MSCs and cartilage templates by inducing sphingomyelin phosphodiesterase 2 (Smpd3) (73). Different AhR ligands influence osteogenic differentiation in various ways. Kyn levels are elevated in the synovial fluid

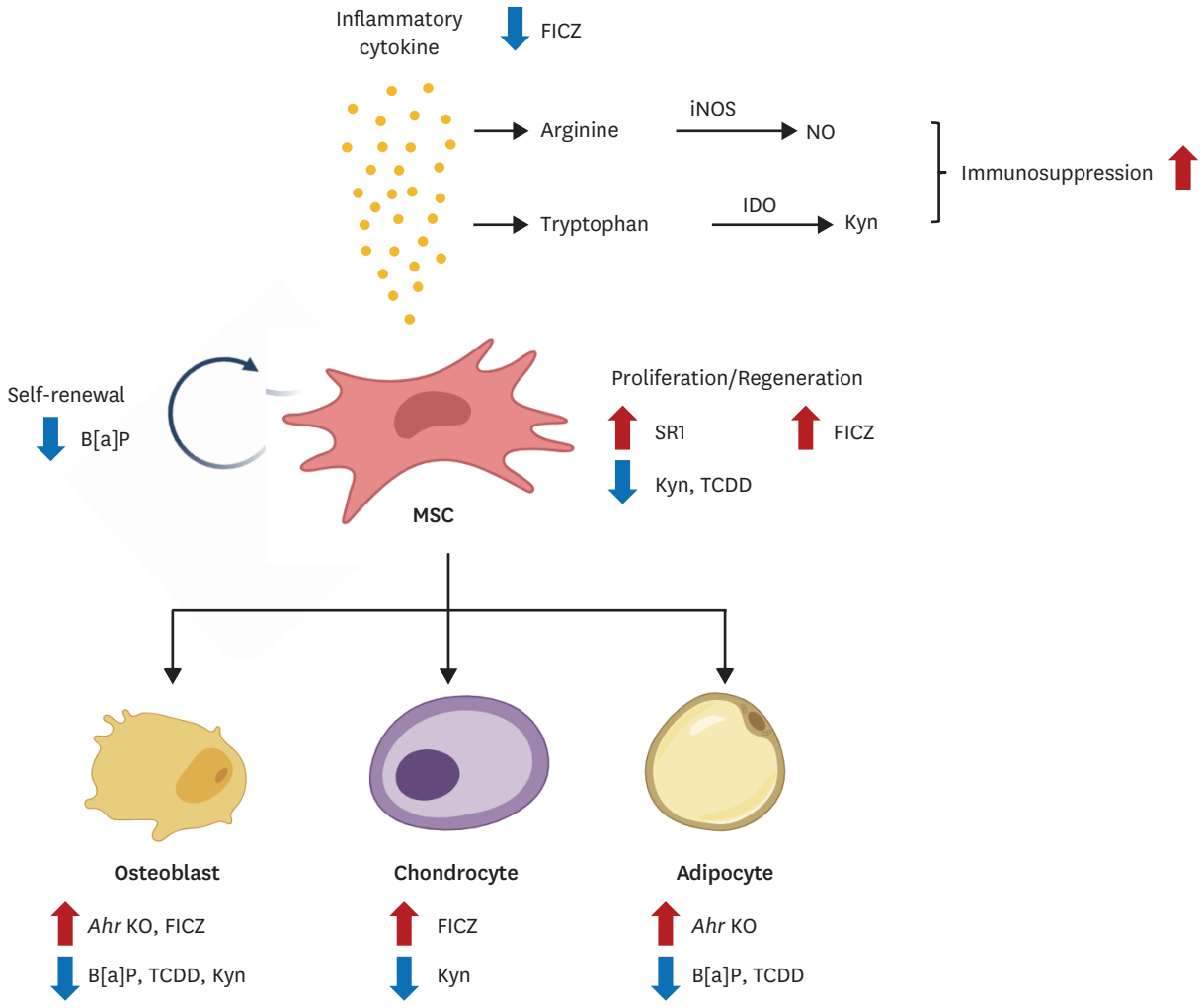

Figure 3. The role of AhR in the proliferation and differentiation of MSCs.
NO, nitric oxide; KO, knockout.

of patients with osteoarthritis (OA) and rheumatoid arthritis, inhibiting chondrogenic differentiation of hUC-MSCs through the activation of AhR (74). B[a]P and TCDD inhibit adipogenesis in hBM-MSCs by downregulating adipogenic markers such as PPARγ and C/EBP isoforms (75,76). Thus, AhR may serve as a promising target for enhancing the therapeutic efficacy of hUC-MSCs in treating cartilage-related diseases, including OA. Consistently, we observed that *Ahr*$^{-/-}$ mouse MSCs exhibited increased adipogenic and osteogenic differentiation (12).

MSCs possess immunosuppressive properties, leading to numerous studies investigating their potential to prevent and treat various immune disorders, including GVHD, organ transplant rejection, and autoimmune diseases (77). However, the role of the AhR in the immunomodulatory function of MSCs has yet to be thoroughly explored. A key immunomodulatory factor in human mesenchymal stem cell (hMSCs) is the induction of IDO by inflammatory cytokines such as IFN-γ (78,79). IDO catalyzes the conversion of Trp to Kyn, which acts as an endogenous AhR ligand. MSCs pretreated with IFN-γ, TGF-β, and Kyn demonstrated reduced levels of IL-6 and increased levels of leukemia inhibitory factor compared to MSCs stimulated solely with IFN-γ and TGF-β. These triple-stimulated MSCs

https://doi.org/10.4110/in.2025.25.e1

also inhibited IL-17 production in activated T cells. Furthermore, injection of these stimulated MSCs significantly improved the survival rate of mice in a GVHD model (80). These results suggest that AhR-ligand-activated MSCs enhance the immunomodulatory functions of MSCs. In addition to IDO, tumor necrosis factor-stimulated gene 6 (TSG-6) is known to be induced by TNF-α in MSCs, thereby improving the therapeutic efficacy of hMSCs (81). Kynurenic acid (KYNA)-pretreated hMSCs demonstrated an enhanced therapeutic effect on LPS-induced acute lung injury through increased TSG-6 expression. KYNA activates the AhR, which directly regulates TSG-6 expression by binding to its promoter (82). Similar results have been observed in human muscle stem cells treated with inflammatory cytokines, which alleviated DSS-induced colitis via IDO-mediated TSG-6 production (83). *Ido*$^{-/-}$ murine endometrial-derived MSCs did not suppress experimental autoimmune encephalomyelitis compared to WT-MSCs. Overall, the IDO/KYN/AhR axis plays a crucial role in the immunomodulatory function of MSCs. Unlike human MSCs, the primary immunomodulatory factor in mouse MSCs is nitric oxide, which is synthesized from L-arginine through the inducible nitric oxide synthase (iNOS) enzyme (84). Recently, we isolated murine MSCs from the BM of *Ahr*$^{-/-}$ mice and observed a decrease in their immunosuppressive function, which was attributed to reduced levels of iNOS and increased expression of eEF2K, an inhibitor of the elongation phase of protein synthesis (12). *Ahr* deficiency increased eEF2K, which inhibited the mRNA translation of iNOS. Consistently, CH223191, an AhR antagonist, increased eEFk2 expression by inhibiting the ubiquitination of eEF2K and consequently reduced iNOS expression. Therefore, we found that AhR, functioning as an E3 ligase, serves as an immunomodulatory regulator of MSCs by targeting the ubiquitination of eEF2K. A brief overview of these studies is provided in **Table 3**.

MSCs derived from various tissues exhibit diverse immunomodulatory and tissue regeneration functions that are mediated by AhR.

Table 3. Functions of AhR in MSC

Variables	Type	Function	Ref.
Mouse			
Ahr KO		- Reduced Cyp1 enzyme-mediated bone resorption	(72)
		- Increased adipogenic and osteogenic differentiation	(12)
AhR ligand			
Agonist	B[a]P	- Reduced self-renewal	(60,61)
		- Inhibited osteogenic differentiation	(60,61)
		- Inhibited adipogenic differentiation	(76)
	FICZ	- Promoted osteogenic differentiation and cartilage templates	(73)
		- Reduced expression of inflammatory cytokines	
	Kyn	- Reduced proliferation and L-lactate concentration	(62)
		- Enhanced mitochondrial function	(62)
		- Inhibited autophagy and induced senescence	(69)
		- Induced bone loss and osteoporosis	(70,71)
		- Inhibited chondrogenic differentiation	(74)
	TCDD	- Inhibited Oct4	(63)
		- Inhibited palate MSC proliferation	(63)
		- Inhibited osteogenic differentiation	(65-68)
		- Inhibited adipogenic differentiation	(75)
Antagonist	CH223191	- Reduced iNOS expression and NO production	(12)
		- Increased expression of eEF2K	
	SR1	- Increased proliferation and L-lactate concentration	(62)
		- Reduced mitochondrial function	

KO, knockout; NO, nitric oxide.

https://doi.org/10.4110/in.2025.25.e1

CONCLUSION AND PERSPECTIVES

Stem cells possess 2 fundamental properties: self-renewal and differentiation. Various types of stem cells have been used to treat various diseases and have therapeutic applications. Inhibition of AhR activation appears to enhance self-renewal, whereas differentiation into specific cell types depends on various AhR ligands. Precise regulation of AhR activity is essential for improving therapeutic efficacy and optimizing the manufacturing process for the large-scale production of stem cells. HSCs are used in transplantation therapies to treat blood disorders, including GVHD, leukemia, and lymphoma. Notably, AhR antagonists (e.g., SR1, α-NF, CH-223191) have been reported to promote HSC expansion. ISCs are essential for maintaining intestinal homeostasis and regenerating damaged epithelium. The modulation of AhR signaling is a promising strategy for the treatment of inflammatory bowel diseases. For instance, studies have suggested that enhancing IL-22 expression or altering the composition of the gut microbiota through AhR activation can suppress inflammation and promote epithelial regeneration. Kyn, an AhR ligand, serves as a crucial regulator of the immunomodulatory functions of MSCs, enhancing the therapeutic potential of MSC-based treatments and playing a vital role in the management of various inflammatory and autoimmune diseases.

Understanding the characteristics and regulatory mechanisms of AhR signaling and ligand-derived lineage commitment in various types of stem cells is essential for developing effective therapeutic strategies and enhancing the efficacy and safety of stem cell-based therapies. Therefore, selecting appropriate ligands and investigating their mechanisms for regulating AhR signaling may be crucial for improving the tailored therapeutic efficacy of stem cells in the future.

ACKNOWLEDGEMENTS

Jung JH supported reference collection. Inha University funded this research (67936-1). Graphics were created using a subscription from BioRender.com.

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