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# Aryl hydrocarbon receptor: Linking environment to aging process in elderly patients with asthma

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**Abstract**

Aging is a significant risk factor for various diseases, including asthma, and it often leads to poorer clinical outcomes, particularly in elderly individuals. It is recognized that age-related diseases are due to a time-dependent accumulation of cellular damage, resulting in a progressive decline in cellular and physiological functions and an increased susceptibility to chronic diseases. The effects of aging affect not only the elderly but also those of younger ages, posing significant challenges to global healthcare. Thus, understanding the molecular mechanisms associated with aging in different diseases is essential. One intriguing factor is the aryl hydrocarbon receptor (AhR), which serves as a cytoplasmic receptor and ligand-activated transcription factor and has been linked to the aging process. Here, we review the literature on several major hallmarks of aging, including mitochondrial dysfunction, cellular senescence, autophagy, mitophagy, epigenetic alterations, and microbiome disturbances. Moreover, we provide an overview of the impact of AhR on these hallmarks by mediating responses to environmental exposures, particularly in relation to the immune system. Furthermore, we explore how aging hallmarks affect clinical characteristics, inflammatory features, exacerbations, and the treatment of asthma. It is suggested that AhR signaling may potentially play a role in regulating asthma phenotypes in elderly populations as part of the aging process.

**Keywords:** Aging; Environment; Reactive oxygen species; Senescence; Aryl hydrocarbon receptor; Asthma

## Introduction

The global population is increasing in terms of growth in size as well as a rise in the ratio of older people to younger ones.[1] There is a growing recognition that aging itself as a natural consequence of living plays a significant role in the development of multiple chronic diseases, including frailty, stroke, arthritis, neurodegeneration, sarcopenia, cancer, vascular disease, renal failure, dementia, diabetes mellitus, osteoporosis, and macular degeneration.[2] Age-related diseases are due to a time-dependent accumulation of cellular damage that causes a progressive decline in cellular and physiological functions, thereby increasing the risk of diseases and death. The effects of aging are not only on the elderly but also on those of younger ages. Particularly, the increased chronic oxidative stress and inflammation have been shown to accelerate aging even in the younger ages.[2] Thus, age-related diseases represent a substantial challenge to health care and socioeconomics worldwide. Studies on targeting fundamental aging mechanisms have been critical in the gerontology community.[3] Environmental factors, including exposure to pollutants, diet, and sedentary lifestyle, largely influence human health and lifespan by triggering age-associated cellular and molecular events.[4] Aryl hydrocarbon receptor (AhR) is a cytoplasmic receptor and mainly expressed at barrier surfaces, including the skin, respiratory tract, and gastrointestinal tract, linking environmental, microbial, and metabolic cues to biological and pathophysiological changes through regulating complex transcriptional programs.[5–8] In recent years, mounting evidence has revealed that AhR plays an important role in regulating environmental factor-triggered age-associated phenotypes. The human lung is one of the important organs highly impacted by aging and has the largest surface area exposed to environmental pollutants and biological, immunological, and xenobiotic stress.[9,10] Recent advances indicate

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that asthma in the elderly population represents a unique phenotype, highlighting that age is a significant risk factor for the inflammatory features, exacerbations, and poor response to treatment in the elderly population with asthma.[11]

In this review, we discuss the literature pertaining to the hallmarks of aging, including mitochondrial dysfunction, cellular senescence, autophagy/mitophagy, epigenetic alterations, inflammation, and microbiome disturbance. We propose AhR as a ligand-activated transcription factor linking environment to immunity regulating hallmarks of aging. Finally, we evaluate the potential role of AhR in regulating asthma phenotypes in the elderly population linked to the aging process.

## Mechanisms of Aging Processes

Aging appears to be a multi-dimensional, irreversible accumulation of physical, environmental, and social changes with a progressive decline in the physiological functions of an organism.[12] Aging can be accelerated by environmental exposure-induced chronic inflammation and subsequent excessive oxidative stress. Specifically, environmental exposure-induced reactive oxygen species (ROS) within mitochondria can damage the mitochondria, which in turn leads to the overproduction of ROS that causes further damage, and thereby aging. However, studies on the cellular and molecular mechanisms of aging processes associated with age-related diseases are limited. Understanding the mechanisms of the aging process is therefore crucial for the prevention or treatment of multiple age-related diseases. Notably, the current research on the biology of aging is guided by the cellular and molecular hallmarks of aging defined by López-Otín *et al*.[13] These hallmarks of aging include genomic instability, telomere attrition, epigenetic alterations, mitochondrial dysfunction, loss of proteostasis, deregulated nutrient-sensing, cellular senescence, stem cell exhaustion, and altered intercellular communication. Recent advances suggest the role of many new hallmarks of aging, including autophagy, microbiome disturbance, altered mechanical properties, splicing dysregulation, and inflammation.[13,14] The updated hallmarks of aging may provide a better guide and advanced research on the biology of aging, as illustrated in Figure 1.

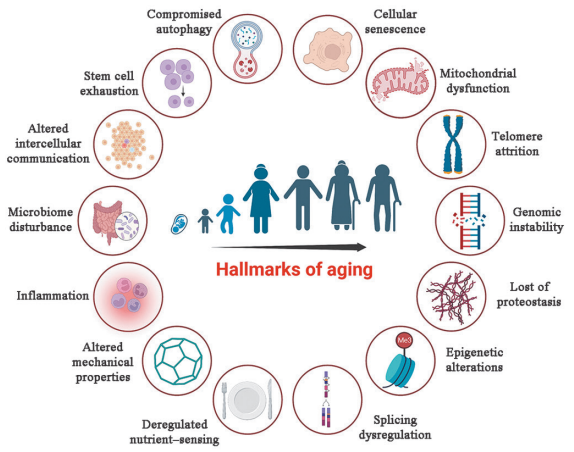


**Figure 1:** Updated hallmarks of aging.

### *Mitochondrial dysfunction*

Mitochondrial dysfunction has been considered a hallmark of environmental injury.[4] The major feature of mitochondrial dysfunction in aging tissues is a decrease in respiratory capacity per mitochondrion and in mitochondrial membrane potential (MMP).[15] During mitochondrial dysfunction, low MMP is mainly linked to the overproduction of ROS.[16] Furthermore, mitochondrial biogenesis declines with age, reducing adenosine triphosphate (ATP) generation and increasing electron transport. These age-dependent abnormalities in mitochondrial biogenesis can contribute to the impairment and weakening of mitochondrial function. With advanced age, mitochondrial DNA (mtDNA) volume, integrity, and functionality can decrease, and mitophagy, an autophagy process that removes dysfunctional mitochondria due to accumulation of oxidative damage induced by ROS, is inhibited.[17] ROS are critical in signaling cellular stress that initially compensates for age-related deterioration, which seems beneficial for mitochondrial homeostasis.[18] As age progresses, excessive ROS can exacerbate age-related mitochondrial oxidative damage, implying ROS's role in aging.[19,20] Several mechanisms cause mitochondrial dysfunction, including mtDNA mutations (genomic instability), mitochondrial turnover as measured by the ratio of mitochondrial biogenesis and mitophagy associated with fusion and fission, nutrient signaling through mammalian target of rapamycin (mTOR) regulated by the mitochondrial sirtuin 3 (SIRT3) and SIRT5, nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide hydrogen ($NAD^+$/NADH) imbalance, and $Ca^{2+}$ fluxes resulting in mitochondrial $Ca^{2+}$ overload [Figure 2].[15] Of these, mtDNA shows an increased susceptibility to ROS,

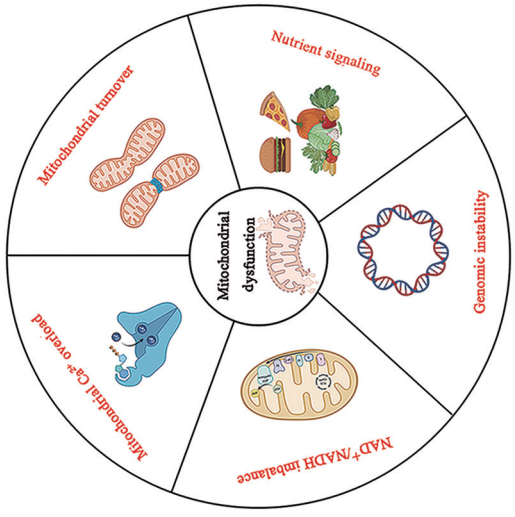


**Figure 2:** Mechanisms that can cause mitochondrial dysfunction. These include mitochondrial $Ca^{2+}$ overload, mitochondrial turnover, nutrient signaling, genomic instability, and $NAD^+$/NADH imbalance. $NAD^+$: Nicotinamide adenine dinucleotide; NADH: Nicotinamide adenine dinucleotide hydrogen.

leading to severe oxidative damage.[21] The mutation rate of mtDNA is 10–17 times higher than that of a nuclear genome (nDNA) because of the lack of histones protection and efficient DNA repair mechanism.[22] mtDNA mutations can cause mtDNA damage, and the accumulation of mtDNA damage with age and impaired mtDNA repair can lead to mitochondrial dysfunction.[23] Thus, mtDNA is a major risk factor that contributes to mitochondrial dysfunction and age-associated multisystemic diseases.

Dysregulation of nutrient cellular signaling is also one of the mechanisms contributing to mitochondrial dysfunction through mTOR, which is modified by the mitochondrial SIRT3 and SIRT5.[15] Particularly, excessive cellular nutrients activate the mTOR pathway and induce anabolic processes, and cause inhibition of autophagy. In contrast, a lack of cellular nutrients activates mitochondrial SIRT3 and SIRT5, resulting in mitochondrial biogenesis and increased autophagy.[24] The imbalance of the $NAD^+$/NADH ratio also causes cellular and mitochondrial dysfunction during aging.[25] $NAD^+$ is a cofactor in several oxidation reduction pathways and a substrate for many redox reactions. While NADH is produced by glycolysis and tricarboxylic acid (TCA) cycle in the mitochondria, $NAD^+$ as a cofactor is required for the production of ATP and maintenance of MMP. Thus, the optimal ratio of $NAD^+$/NADH is required for normal cellular reactions and mitochondrial metabolism, and disruption of $NAD^+$/NADH ratio can affect mitochondrial function, and subsequently aging.

### Cellular senescence

Cellular senescence is defined as a state of permanent cell cycle arrest induced by several factors, including aging, oxidative stress, DNA damage, mitochondrial dysfunction,[26] epigenetic modifications,[27] and telomere shortening.[28] Senescence arrest occurs in the G1 phase of the cell cycle, distinguishing it from G0-arrested quiescent cells, and is mediated by cyclin-dependent kinase inhibitors (CDKis) (e.g., $p21^{CIP1}$, $p16^{INK4a}$) and is also dependent on the tumor protein p53 (TP53) and retinoblastoma protein (pRB) tumor suppressor pathways.[29] Senescent cells can secrete plethoric pro-inflammatory cytokines, chemokines, angiogenic factors, growth modulators, and matrix metalloproteinases (MMPs), termed the senescent associated secretory phenotype (SASP). The SASP can create a feedback loop, further promoting senescence in neighboring cells and contributing to tissue dysfunction.[30] Senescent cells also show increased rates of mitochondrial metabolic activity, including the TCA cycle, oxidative phosphorylation (OXPHOS), and glycolytic pathways, together with increased adenosine monophosphate (AMP) and adenosine diphosphate (ADP) and decreased ATP and $NAD^+$/NADH in senescent cells.[31] Additionally, senescent cells do not proliferate but are resistant to autophagy and apoptosis and are thus long living. Importantly, senescent cells can exacerbate mitochondrial dysfunction, inflammation, and other disease-promoting pathways through SASP.[32] It has been debated whether senescent cells contribute to aging or are simply a protective mechanism against the development of inflammatory diseases. However, it is clear that senescent cells accumulated in tissues with aging may stop cell regeneration and tissue maintenance and are physiologically important drivers of age-associated functional decline, morbidity, and mortality.[33] Deletion of senescent cells from tissues of mouse models can delay or prevent multiple age-related diseases.[34] However, it remains elusive as to how senescent cells contribute to age-related diseases. SASP is emerging as a key driver of inflammation, and persistent inflammation may result in the accumulation of senescent cells in tissues, further contributing to age-related diseases.[35]

### Autophagy/mitophagy

Autophagy, a homeostatic process with multiple effects on immunity, has been recently recognized as a new hallmark of aging.[14] Autophagy is a mechanism in which the eukaryotic cell encapsulates damaged proteins or organelles for lysosomal degradation and recycling.[36] A growing body of evidence suggests that autophagic activity declines with age.[37] Furthermore, autophagy can modulate the major features of aging such as DNA repair and nutrient sensing/metabolism.[38] Autophagy can be initiated by calorie restriction, endoplasmic reticulum (ER) stress, or amino acid depletion through either the autophagy-related (ATG) or vacuolar protein sorting (VPS ) gene.[39] Mechanistically, studies demonstrated that Atg5 transgenic mice displayed anti-aging phenotypes that could extend the lifespan by enhancing autophagic activity.[40] Furthermore, $Becn1^{F121A/F121A}$ knock-in mice showed higher levels of basal autophagic flux and improved lifespan in both male and female mice.[41] In the meantime, human research targeted promoting autophagy to increase lifespan through lifestyle improvement and pharmacological modulation.[42]

Mitophagy is the selective degradation of mitochondria by autophagy. Mitophagy is an evolutionarily conserved homeostatic process by which the cells selectively degrade only dysfunctional or damaged mitochondria.[43] Mitophagy can act either as a response to nutrient starvation and oxidative stress or as a programmed removal of damaged mitochondria.[44] Mitophagy promotes the turnover of mitochondria and prevents the accumulation of dysfunctional mitochondria. Mitophaging was defined as the defective removal of damaged mitochondria through mitophagy resulting in degenerative diseases and aging.[45] There are substantial data on the effects of mitophagy changes on health and lifespan that support a decline in mitophagy and mitophaging in aging.[45]

### Epigenetic modifications

Epigenetic alterations affect all cells and tissues throughout life. Loss of epigenetic information has been considered a cause of mammalian aging.[46] The epigenetic mechanism accompanied by cell senescence during aging has multiple modifications in DNA methylation, histone modification, chromatin remodeling, and non-protein-coding RNA transcripts (ncRNAs) that dictate their cell fate.[47] Endogenous DNA damage has been recognized as a significant causal factor in age-related systematic and stochastic

changes in DNA methylation. DNA methylation can not only upregulate the expression of $p21^{WAF1/Cip1}$ and $p16^{INK4A22}$, but also induce DNA damage.[48] In addition to DNA methylation, epigenetic modifications of histones play an important role in DNA damage and aging. Histone modifications include alterations in phosphorylation, acetylation, and methylation, as well as chromatin remodeling, which change significantly with age. Notably, histone modifications have become a significant regulator and sensitive marker of telomere attrition, such as histone gamma H2A histone family member X (γH2AX).[49] The $NAD^+$-dependent SIRT1, SIRT6, and SIRT7 as anti-aging medicines may catalyze modifications in histone proteins to regulate gene transcription and genome instability.[50] Recent advances have demonstrated that the senescence-associated ncRNAs can regulate cell proliferation and cell cycle arrest by affecting the transcripts of the inhibitor of CDK4/alternative reading frame (INK4/ARF)/very long integenic non-coding RNAs (vlincRNA) VAD/MIR31HG locus to increase $p14^{ARF}$, $p15^{INK4b}$, $p16^{INK4a}$, and B-cell lymphoma-2 (Bcl-2).[51] Furthermore, some ncRNAs can also modulate the expression of SASP genes in senescent cells or directly interact with them. Different epigenetic modifications may interact with each other, coregulate gene expression, and eventually form an intricate network that is associated with aging.

### *Composition and diversity of the microbiota*

Current researchers have focused on the role of the commensal human microbiome in health and disease. Over 10 microorganisms are inhabited in the human gastrointestinal tract and maintain the structure and function of a healthy gut ecosystem.[52] These microorganisms are essential for metabolic homeostasis, immune regulation, and protection against pathogens through different mechanisms, such as inducing interleukin (IL)-10 production, activation of Tregs (transforming growth factor-β [TGFβ]-producing regulatory T cells), T helper 17 (Th17) cells, and innate lymphoid cell type 2 (ILC2).[53,54] While the reason for this remains unclear, the composition of the gut microbiota of elderly humans markedly differs from that of young and middle-aged adults. For example, compared to the young population, the middle-aged adults showed decreased *Actinobacteria* and *Firmicutes* but increased *Proteobacteria*.[55] The compositional shift, together with age-associated loss of structural integrity of the gut, may contribute to the onset of immune dysregulation and manifestation of aging-associated pathologies.[56] In elderly people, the composition of the gut microbiota shows signs of dysbiosis. The decrease of beneficial microbes, particularly supporters of mucin production and producers of short chain fatty acids (SCFAs), appears to induce a chain of pathogenic inflammatory changes, thereby leading to inflammaging and aging-associated morbidities. Thus, gut dysbiosis and leakiness are major causes of increased mortality and premature death in elderly people. Recent advances in next generation sequencing technologies have allowed the identification of notable changes in the gut microbiota's composition and diversity with age.[57]

## AhR and Hallmarks of Aging

AhR has been considered initially as a receptor of polycyclic aromatic hydrocarbons (PAH) or dioxins; a lot of ligands have been recently identified in food or microbiota but are also produced by the human body (endogenous ligands).[58] Upon ligand binding, AhR translocates from the cytosol to the nucleus, leading to changes in target gene transcription (e.g., cytochrome P450 a1 [cyp1a1] and b1 [cyp1b1]) and immunotoxicological effects[59] [Figure 3]. AhR is featured not only in mediating the toxicity of dioxins, dioxin-like compounds (DLCs), and PAHs, but also in regulating a series of physiological functions.[60] Interestingly, the ligands of AhR from environmental (e.g., pollutants and other toxicants) and nutritional (e.g., flavonoids, carotenoids) factors influence aging and mitochondrial functions directly or indirectly.[61] Furthermore, expression of the AhR protein decreases with age, and lack of AhR has been associated with premature aging processes involved in increased cellular senescence and inflammaging features.[62] Additionally, we performed bioinformatical analyses on public datasets from the Gene Expression Omnibus (GEO) database GSE40732 with microarray data from peripheral blood mononuclear cells (PBMCs) of asthmatic patients and healthy controls. We found that AhR expression is highly correlated with several major hallmarks of aging, including epigenetic regulation, autophagy, immune response, DNA damage, protein destabilization, telomere maintenance, and defense against the bacterium [Figure 4]. Here, we review the existing literature on the role of AhR in regulating some of the hallmarks of aging: mitochondrial dysfunction, cellular senescence, autophagy/mitophagy, epigenetic regulation, and microbiome disturbance.

### *AhR and mitochondrial dysfunction*

Both environmental and nutritional factors can bind AhR and trigger the transcriptional activity of AhR, suggesting a possible link between AhR and mitochondrial dysfunction. Indeed, AhR signaling activated by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) could cause oxidative stress and disrupt mitochondrial metabolism, leading to mitochondrial dysfunction. Similarly, benzo[α]pyrene can also promote mitochondrial dysfunction and inhibit the MMP, leading to the depletion of ATP levels and reduction of the oxygen consumption (OC) rate.[63] Our recent studies suggest that increased mitochondrial reactive oxygen species (mtROS) generation induced by allergens can promote mitochondrial dysfunction with decreased basal and maximal respiration and ATP turnover rate.[64] It is well recognized that elevated levels of mtROS may lead to mitochondrial dysfunction.[19] We have previously suggested that AhR signaling is critical in regulating mtROS generation that contributes to different inflammation-associated phenotypes, including mast cell degranulation and activation,[65] epithelial cytokine release,[66] and NLR family pyrin domain containing 3 protein (NLRP3) inflammasome formation.[67] Other studies also suggest a possible involvement of mitochondrial dysfunction and ROS generation in an AhR activation-dependent manner in a cellular model of non-alcoholic fatty liver progression induced by 6-benzylaminopurine/benzyl adenine (BaP)/

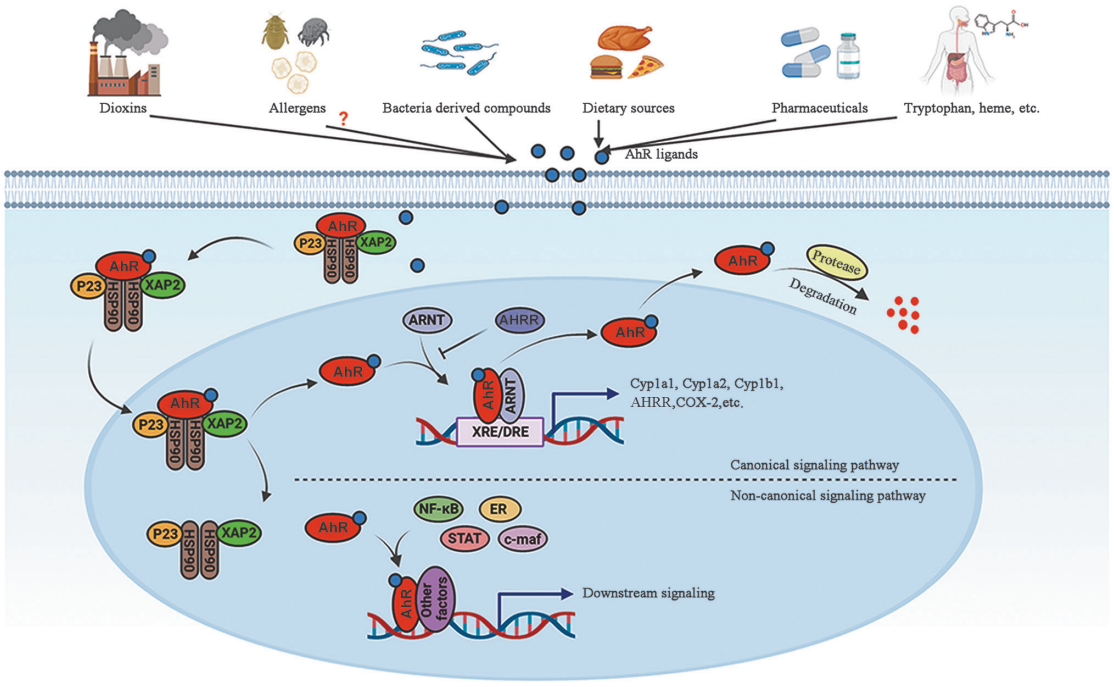


**Figure 3:** Model of the AhR signaling pathways. Upon binding to ligands from dioxins, allergens, bacterial-derived compounds, dietary sources, and pharmaceuticals, the AhR is activated and then translocated into nucleus. On one hand, AhR in the nucleus forms a heterodimeric complex with the ARNT and binds to a DRE consensus. This induces the expression of the AhR target genes, such as *CYP1A1, CYP1A2, CYP1B1, AHRR*, and *COX-2*, which are involved in a canonical signaling pathway. AhR can also be controlled via nuclear export and subsequent AhR degradation through the ubiquitin–proteasome signaling pathway. On the other hand, AhR in the nucleus can directly interact with other proteins such as the members of the NF-κB protein family or participate in the cross-talk with ER, which is involved in a non-canonical signaling pathway. AhR: Aryl hydrocarbon receptor; *AHRR:* Aryl hydrocarbon receptor repressor; ARNT: Aryl hydrocarbon receptor nuclear translocator; *COX-2:* Cyclooxygenase-2; *CYP1A1/2*: Cytochrome P450 1A1/2; *CYP1B1*: Cytochrome P450 1B1; DRE: Dioxin responsive elements; ER: Estrogen receptor; HSP90: Heat shock protein 90; NF-κB: Nuclear factor-κB; STAT: Signal transducer and activator of transcription; XAP2: Aryl hydrocarbon receptor interacting protein; XRE: Xenobiotic responsive element.

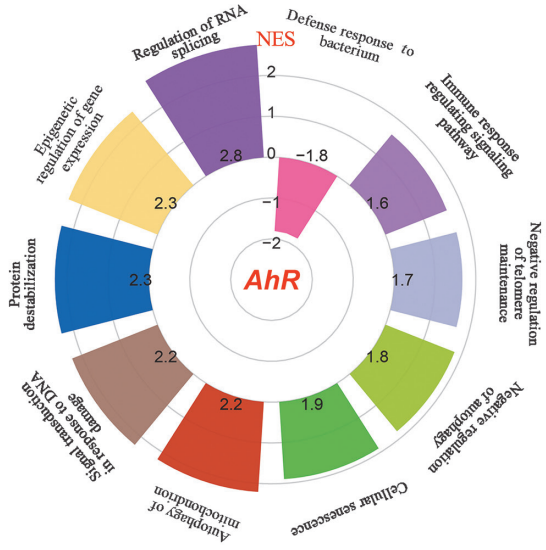


**Figure 4:** Association of AhR expression with hallmarks of aging. Bioinformatical analyses were performed on public datasets from GEO databases GSE40732 with microarray data from PBMCs of asthmatic patients and healthy controls. The samples are divided into AhR-High and AhR-Low groups based on the median expression value of AhR. GSEA analysis is performed with DEGs in a ranked manner. The NES are listed on the bottom of each bar. Only those biological processes with statistical significance (adjusted *P*-value <0.05) were illustrated, including epigenetic regulation, autophagy, immune response, DNA damage, protein destabilization, telomere maintenance, and defense to the bacterium. AhR: Aryl hydrocarbon receptor; DEGs: Differential expressed genes; GEO: Gene expression omnibus; GSEA: Gene set enrichment analysis; NES: Normalized enrichment scores; PBMCs: Peripheral blood mononuclear cells.

ethanol co-exposure.[68] Mechanistically, particulate matter (PM) exposure can induce increased ROS production and reduced MMP with a lower expression of SIRT1, and the SIRT1 activator, SRT1720, can effectively inhibit ROS production and reverse PM-induced mitochondrial dysfunction.[69] SIRT1 and SIRT3 belong to NAD+ dependent deacetylases, are key to the control of metabolic processes and are localized to the nucleus and mitochondria, respectively.[70] Thus, this finding implicates that there might be a cross talk between AhR, Sirt1, and mitochondria that are essential for aging process.

### *AhR controls the balance of cellular senescence and reprograming*

Mitochondrial dysfunction has been associated with age-associated cell and tissue changes via different signaling pathways, thereby contributing to senescent phenotypes. Given that AhR signaling is critical in regulating mitochondrial function, it is possible that AhR also modulates cellular senescence. Indeed, kynurenine, as a tryptophan metabolite and an endogenous AhR agonist, has been reported to inhibit autophagy and promote senescence in aged bone marrow mesenchymal stem cells via AhR signaling.[71] This study suggests that AhR is a novel target to prevent or reduce age-associated bone loss and osteoporosis. In contrast, mouse embryo fibroblasts from AhR$^{-/-}$ mice showed earlier senescence than WT mice during adipogenic differentiation.[72] Further studies

indicate that aged AhR$^{-/-}$ mice had exacerbated cellular senescence.[73] AhR signaling can also inhibit the proliferation of stem cells by repressing cell-cycle progression. Mechanistically, activated AhR can increase the expression of the p21$^{Cip1}$ and p27$^{Kip1}$ proteins and thus arrest cell proliferation. Moreover, AhR can bind elongation factor 2-promoter-binding factor (E2F) transcription factors and subsequently inhibit the transcription of many E2F-regulated genes, thereby controlling cellular senescence and aging. Collectively, the role of AhR in regulating senescence likely varies depending on different cellular and environmental contexts. Although both AhR and senescence have been shown to have beneficial effects in immune regulation and tolerance, they can also be detrimental when they lead to oxidative stress and DNA damage. Studies are clearly needed to uncover the diverse effects of AhR activation and its implications for cellular senescence and overall health.

### AhR and autophagy/mitophagy

There is growing evidence that AhR could suppress autophagic activity in different cells through multiple mechanisms. For example, TCDD treatment can not only downregulate the expression of several autophagy-related genes in human keratinocytes, such as microtubule-associated protein 1A/1B light chain 3 (IC3), ATG5, and Beclin 1, but also suppress the formation of autophagosomes preventing autophagy-mediated cell death in the psoriasis pathogenesis.[74] In addition, the AhR agonist kynurenic acid (Kyn) has been shown to accumulate in plasma and tissues with age.[75] Kyn treatment can induce AhR nuclear translocation and disrupt autophagy, and inhibition of the AhR pathway prevented the kynurenine-induced increase of senescence and preserved autophagy in BMSCs in aged mice.[76] Of interest, the inhibition of autophagy can also increase the level of the AhR protein in different cell types (e.g., keratinocytes, HeLa cells). While the mechanisms remain unclear, recent studies suggest that glycogen synthase kinase 3β (GSK3β)-induced phosphorylation can promote the degradation of AhR protein via the autophagy-lysosomal pathway.[77] Several other studies have demonstrated that the ligand-induced activation of AhR factor stimulates the proteasome-dependent pathway, whereas the non-activated turnover of AhR protein is under physiological regulation via autophagy.[76] We have demonstrated a functional axis of AhR-ROS-NLRP3 inflammasome in regulating allergic airway inflammation.[67] The NLRP3 inflammasome has been associated with mitophagy-mediated maintenance of mitochondrial homeostasis. Thus, AhR signaling may be involved in regulating autophagy/mitophagy, which could be one of the possible mechanisms driving the aging process.

### AhR and epigenetic regulation

AhR can selectively bind to the unmethylated form of a specific sequence called the xenobiotic responsive element (XRE). The ligand-specific transcriptional response depends on AhR-DNA binding to XREs located in the regulatory regions of each gene. Studies have suggested that AhR is a novel DNA methylation reader, unlike classical methylation readers, such as methyl-CpG-binding protein 2, which binds to methylated sequences.[78] With exposure to endogenous AhR ligands, such as Kyn, methylation states of the individual target XREs are regulated to coordinate the expression of downstream genes that maintain homeostasis in a tissue-specific manner. However, continuous exposure to AhR ligands can cause changes in the methylation patterns around the XRE sequence and lead to different immune responses. Thus, it is likely that these environmental (e.g., pollutants and other toxicants) factors may induce DNA methylation through AhR-dependent mechanisms. In addition to DNA methylation, AhR impacts histone hyperacetylation and methylation through interactions with coactivators or by displacing histone deacetylase (HDAC) complexes. In turn, histone acetylation was found to be critical in the activation of the AhR promoter. Metastasis tumor-associated protein 2 (MTA2) was identified as a cofactor recruited by the AhR–aryl hydrocarbon receptor nuclear translocator (ARNT) complex exclusively in response to cinnabarinic acid (CA), an AhR agonist.[79] MTA2 is a chromatin-modifying protein and a component of the nucleosome remodeling and deacetylation complex with the capacity to repress and activate gene expression. A recent study demonstrated that CA-specific recruitment of the MTA2-AhR complex to XREs in the promoter of AhR target gene stanniocalcin 2 (Stc2) with concomitant acetylation of lysine 5 on histone H4 (H4K5Ac) at the Stc2 promoter leads to the transcriptional activation of target genes.[80] Additionally, activation of AhR is tissue-specific and depends on chromatin-accessible regions. These findings indicate that AhR is a pivotal player in epigenetic regulation in response to age-associated environmental and nutritional factors.

### AhR as a mediator of host–microbiota interplay

The cumulated evidence demonstrated that the activation of AhR could be either beneficial or detrimental to aging.[81] For example, AhR can be predominantly activated by ligands produced from gut microbes metabolizing diet-derived tryptophan. The gut microbiota can metabolize tryptophan to activate AhR signaling, which participates in varying physiological processes rather than pathophysiological events associated with aging.[82] However, aberrant tryptophan metabolism and dysbiosis of gut microbiota may lead to changes in AhR activity during aging that might contribute to the acceleration of the aging processes.[83] Similar to the "imbalance" in the gut microbial community, dysbiosis of the microbiota in the gut, "dysbiosis" of the skin microbiota is equally important by affecting skin homeostasis, exacerbating a variety of skin diseases, and affecting disease diagnosis and treatment. For example, *Staphylococcus aureus* (SA) was found on the skin of patients with atopic dermatitis (AD) at the site of lesions caused by AD that can impede the function of the skin barrier or activate the inflammatory response.[84] A recent study demonstrated that SA could activate the AhR–ARNT system and enhance the terminal differentiation of epidermal keratinocytes.[85] However, the metabolites that served as AhR ligands remain unidentified. Further, AhR activation could upregulate the

expression of antimicrobial peptides in keratinocytes, contribute to the changes in skin microbiota composition, and restore dysbiosis in AD.[86] Thus, AhR and tryptophan metabolites are important regulators in the "microbiota–AhR–skin" axis.

## AhR signaling, Hallmarks of Aging, and Asthma

Asthma is recognized as a comorbidity of aging because aging can influence the occurrence and development of asthma.[87] Intriguingly, the hallmarks of aging, such as mitochondrial dysfunction, telomere shortening, epigenetic alterations, and altered intercellular communication, have been observed in patients with asthma.[88] We also performed bioinformatical analyses on the gene expression omnibus (GEO) database GSE69683 for the relationships between asthma and the hallmarks of aging [Figure 5]. Our analyses provided supporting evidence that asthma is associated with these hallmarks of aging. Here we provide an overview of the impact of aging hallmarks on asthma phenotypes (e.g., airway inflammation, remodeling, airway hyper-responsiveness, asthma exacerbation, and therapeutic response).

"Elderly" was defined as the chronological age of 65 years or more. Elderly patients with asthma not only had a higher prevalence but also had the highest death rate at 5.8 deaths per 10,000 people.[89] For those elderly patients, there are significant changes in the innate and adaptive immune responses to environmental exposures that contribute to an increased chronic systemic inflammation, termed inflammaging, with increased interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α).[90] To understand the importance of aging in asthma, Wang *et al*[11] have performed an interesting study with the goal of exploring the age-associated clinical characteristics, inflammatory features, and treatment response in young (18–39 years), middle-aged (40–64 years), and elderly (≥65 years) patients with asthma. As expected, elderly patients had worse airway obstruction, more comorbidities, lower levels of immunoglobulin E (IgE) and fractional exhaled nitric oxide (FeNO), elevated Th1 and Th17 inflammation, decreased odds of T2-profile asthma, and a higher risk for future exacerbations. This study provided strong evidence to support the hypothesis that asthma in the elderly population represents a specific phenotype and that aging can influence the pathophysiology of asthma.

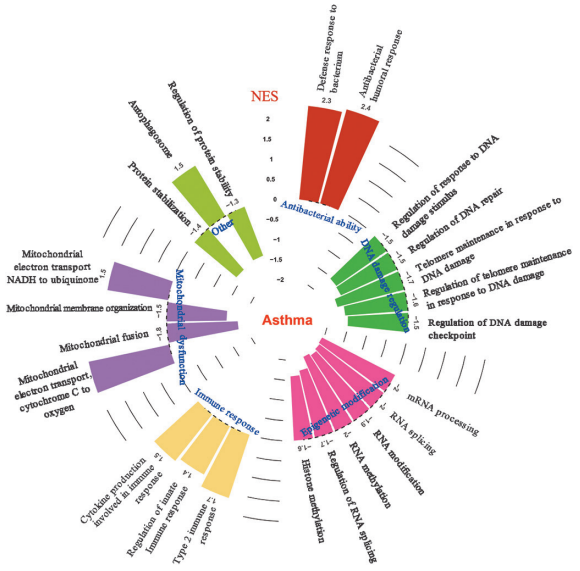


**Figure 5:** Association of asthma with hallmarks of aging. Bioinformatical analyses were performed on public datasets from GEO databases GSE69683 with microarray data from PBMCs of asthmatic patients and healthy controls. The comparison is performed between asthma patients and relative normal control. GSEA is performed with DEGs in a ranked manner. The NES are listed on the bottom of each bar. Only those biological processes with statistical significance (adjusted *P*-value <0.05) were illustrated, including immune response, DNA damage, epigenetic modification, mitochondria, protein stabilization, and autophagy in asthmatic patients. DEGs: Differential expressed genes; GEO: Gene expression omnibus; GSEA: Gene set enrichment analysis; mRNA: Messenger RNA; NADH: Nicotinamide adenine dinucleotide hydrogen; NES: Normalized enrichment scores; PBMCs: Peripheral blood mononuclear cells.

A defect in the mitochondria plays a critical role in lung injury by generating ROS and activating pro-inflammatory signaling pathways. Particularly, ROS generated from mitochondria have been shown to play a significant role in the pathogenesis of allergic airway inflammation through modulating NLRP3 inflammasome activation.[91] Additionally, mitochondrial genetic background is critical in the pathogenesis of asthma.[92] For example, mitochondrial haplogroups have been associated with increased levels of serum IgE, and mutations in the mitochondrial genome sequences encoding mtRNAs have been associated with the risk of asthma. Asthma is also associated with enhanced mitochondrial biogenesis, enhanced dynamin-related protein 1 (Drp1), and decreased mitofusin-1 (Mfn1).[93] Of these, Mfn1, a physical linker between the ER and mitochondria, regulates the mitochondrial buffering of $[Ca^{2+}]_{cyt}$ in ER microdomains, creating for mitochondria a $Ca^{2+}$ reserve. All these studies support the rationale that mitochondrial dysfunction plays a critical role in the pathophysiology of asthma. Thus, given the role of AhR in regulating mitochondrial dysfunction induced by environmental factors, future studies are warranted to explore the connection between AhR signaling and the aging process in asthma.

Several stimuli causing cellular senescence have been associated with asthma, such as telomere shortening, oxidative stress, inflammation, and autophagy/mitophagy.[31] These stimuli and their downstream signaling create an intricate network that causes cell cycle arrest and the release of SASPs from asthma-associated target cells. Of these stimuli, telomere shortening was observed in chronic asthmatic patients, and asthma chronicity is correlated with telomere length even at an early age. Further studies suggested that telomere shortening is also associated with airway hyper-responsiveness and can induce senescence of bronchial fibroblasts in patients with asthma. Thymic stromal lymphoprotein (TSLP) can trigger cellular senescence with higher levels of p21 and p16 in human epithelial cells, which are essential for airway remodeling. Expression of p16 has also been associated with cell sensitivity to dexamethasone treatment,[94] suggesting the possible involvement of cellular senescence in glucocorticoid resistance in asthma. Additionally, persistent accumulation of senescent cells in elderly patients with asthma increases inflammation through SASP (e.g., IL-6, TNF-α) and impairs cellular function.

Of these, IL-6 was increased in patients with asthma and has been shown to trigger or reinforce premature cellular senescence. Collectively, these studies have linked several stimuli associated with cellular senescence to asthma. Additionally, AhR signaling has been suggested to play a role in mediating the effects of these stimuli on cellular senescence. Thus, further research is needed to elucidate the specific mechanisms connecting cellular senescence and asthma, with a focus on AhR involvement.

Autophagy also participates in inflammatory diseases, including asthma. Increased autophagy was observed in sputum granulocytes and peripheral blood cells (e.g., eosinophils) from patients with severe asthma. Autophagy has been linked to asthma immune mechanisms, extracellular matrix deposition, and airway remodeling.[95] However, it still remains vague whether autophagy serves a promoting or protective role in the pathophysiology of asthma. We found that cockroach allergen can induce autophagy in cultured airway epithelial cells and lung tissues from asthmatic patients and mice. Inhibition of autophagy significantly attenuated Th2-associated lung inflammation and ROS generation, suggesting the role of autophagy in promoting asthma development.[64] Mechanistically, we demonstrated a pathological feedforward circuit between cockroach allergen-induced ROS and autophagy that is mediated through calmodulin-dependent protein kinase II (CaMKII) oxidation. In contrast to autophagy, there are limited studies on mitophagy in asthma, which have demonstrated a significant role in COPD and lung fibrosis.[96] Recent studies have shown that $PM_{2.5}$ exposure can induce ROS generation and mitochondrial dysfunction that triggers mitophagy through the PTEN-induced putative kinase 1 (PINK)/Parkin pathway.[97] Further study suggests that hypoxia-inducible factor-1 (HIF-1), forkhead box O3 (FOXO3), and nuclear factor erythroid 2-related factor 2 (NRF2) activated by excessive ROS can promote the transcription of BCL2/adenovirus E1B 19-kDa-interacting protein 3-like (BNIP3/NIX), light chain 3 (LC3)/BNIP3, and p62 and activate mitophagy. We have recently suggested a novel mechanism by which CaMKII modulates mitophagy by regulating optineurin (OPN), a ubiquitin-binding autophagy receptor. OPN can bind both ubiquitin and LC3 to target ubiquitinated substrates to newly forming autophagosomes for the autophagic clearance of damaged mitochondria.[64] We are exploring the relationship between ROS, oxidized CaMKII, OPTN, and mitophagy in asthma and the potential mechanisms. Together, these studies suggest that autophagy/mitophagy plays a crucial role in asthma's development or pathophysiology. Given that AhR signaling is linked to the regulation of autophagy/mitophagy, it is reasonable to hypothesize that AhR signaling influences aging-related autophagy/mitophagy and, consequently, asthma.

Epigenetic alterations have also been associated with asthmatic phenotypes. Particularly, the alterations of DNA methylation throughout the life span have been defined as a biological clock or biomarker for different diseases, including asthma.[98] DNA methylation has been demonstrated to be involved in the persistence and remission of asthma.[99] Of these, there are 4 CpG sites and 42 differentially methylated regions that were identified in bronchial biopsies of patients with asthma remission and persistence. Legaki *et al*[100] have recently reviewed the literature on DNA methylation patterns across different tissues in asthma. They found that the most differentially methylated loci in both blood and nasal samples were annotated to *ACOT7, EPX, KCNH2, SIGLEC8, TNIK, FOXP1, ATPAF2, ZNF862, ADORA3, ARID3A, IL5RA, METRNL,* and *ZFPM1*, suggesting that these may be candidates for allergic respiratory disease biomarkers. However, it is unclear whether age affects the status of methylation that has an impact on asthma in elderly patients with asthma. In fact, one of the most prominent external factors that trigger DNA methylation changes is aging. Recent evidence suggested a correlation of age with methylation changes and the occurrence of asthma. The increase in age was concordant with higher levels of serum IgE and the risk of allergy and asthma.[101] Additional evidence suggests the differentially expressed messenger RNA (mRNA) and aberrant levels of DNA methylation in aging-related genes in asthma patients. These findings indicate that epigenetic changes may play a role in the development of asthmatic traits. Moreover, AhR is a key regulator of epigenetic processes in response to environmental factors. It's plausible that AhR signaling connects the epigenetic changes induced by environmental factors to the development of asthma.

Recent studies have also shown the intersecting role of microbiome–immune interactions in shaping chronic lung diseases, including asthma.[102] However, most of the studies on the microbiota–immune interactions are limited to childhood-onset asthma, and fewer studies have focused on how the microbiota–immune interactions in later life impact asthma phenotypes. The airway microbiota in induced sputum or bronchial epithelial brushings differs not just by asthma status or severity but also between the T2-low and T2-high phenotypes. Of interest, asthma control (Asthma Control Questionnaire [ACQ] score) levels correlate with differences in airway prevalence of specific bacterial groups.[103] Particularly, worsening ACQ score is correlated with a greater abundance of *Proteobacteria*, a class inclusive of many potential respiratory pathogens, in adults with severe asthma. In contrast, better asthma control is associated with a greater prevalence of *Actinobacteria*, a phylogenetically distinct group. Furthermore, the microbiome–immune interactions may also influence asthma control and response to therapies that have been found in other diseases like cancer. Although studies on lower airway microbiome are limited because of the difficulty in obtaining samples, the role of the lower airway microbiome has been increasingly appreciated. In addition to lung microbiota, gut microbiota also impacts asthma phenotype and severity, termed the "gut–lung" axis.[104] While the cellular and molecular mechanisms underlying the gut microbiota's influence on asthma are poorly understood, microbiota-derived metabolites like short-chain fatty acids[105] and 12,13-dihydroxy-9Z-octadecenoic acid (12,13-diHOME)[106] are recognized to impact the systemic immune system, leading to lifelong susceptibility to allergy and asthma. However, limited studies were performed to determine the effects of the gut microbiota on airway inflammation in elderly patients with asthma. In a study of immunological and microbiome alterations in obese asthmatics aged 45 years, asthma severity was negatively correlated with levels of the gut commensal, *Akkermansia muciniphila*. Mice treated with *Akkermansia muciniphila* showed

a significant reduction in the allergen-induced airway hyper-reactivity and airway inflammation.[106] Furthermore, enterotoxigenic *Bacteroides fragilis* 23 (ETBF) is associated with increased gut permeability, oxidative stress, and markers of Th17-mediated inflammation in the lungs of mice following ovalbumin sensitization and challenge.[107] Importantly, ETBF has the potential to alter the phenotype of airway inflammation in patients with asthma. Thus, additional analyses using currently available DNA and RNA sequencing methods will allow us to understand how the microbial dysbiosis of the gut and lungs influences asthmatic disease predisposition and severity, particularly in elderly patients. Crucially, as AhR signaling is thought to be a significant regulator of gut microbiota and their associated physiological functions, it is essential to conduct further research to investigate the connection between gut microbiota and asthma, with particular attention to the role of AhR.

## Conclusion

In this review, we summarized the current evidence regarding several major hallmarks of aging associated with environmental exposures and pushed forward research on the biology of aging in asthma. Environmental factors, including exposure to pollutants, diet, and a sedentary lifestyle, are tightly associated with age-associated cellular and molecular events and the hallmarks of aging. ROS, as a central player in the mediation of environmental exposures, can induce mitochondrial damage, leading to mitochondrial dysfunction and the corresponding aging process. Not surprisingly, all these hallmarks of aging are closely interconnected. For example, there are significant reductions with advanced age in mtDNA volume, integrity, and functionality, as well as reductions in autophagy and mitophagy that impact the clearance of the damaged mitochondria caused by ROS overproduction. Deletion of mitochondria from senescent cells led to a significant reduction in senescence and key components of SASP caused by Parkin-mediated autophagy,[54] suggesting that mitochondrial dysfunction, cellular senescence, and autophagy/mitophagy are also interconnected. Moreover, we provide an overview of the impact of AhR on the hallmarks of aging since AhR signaling could be a potential mechanism for regulating the hallmarks of aging, and subsequently, asthma. Furthermore, we explore the associations of aging hallmarks with asthma clinical characteristics, inflammatory features, exacerbations, and treatment. Although tremendous progress has been made, a unified theory of aging that can affect the pathophysiology of asthma is still lacking. Underlying mechanisms of how age affects immune responses and pathophysiologic changes is clearly essential in asthma. Additionally, we and others have shown that AhR mediates allergic airway inflammation by regulating environmental pollutant/allergen-induced ROS generation, NLRP inflammasome activation, autophagy, and cytokine release in asthma. These studies shed new light on AhR, which may be involved in regulating the aging process in asthma, particularly in elderly patients with asthma. AhR signaling might serve as a potential and critical mechanism in regulating asthma phenotypes that are linked to the aging process [Figure 6]. However, the interesting perspective on the complex relationship between aging, AhR, and asthma would require extensive research to elucidate the specific mechanisms and interactions involved. We believe that with the continuous deepening of aging research in asthma, anti-aging strategies focusing on AhR signaling will offer great promise for the treatment of asthma, particularly for those elderly patients with asthma.

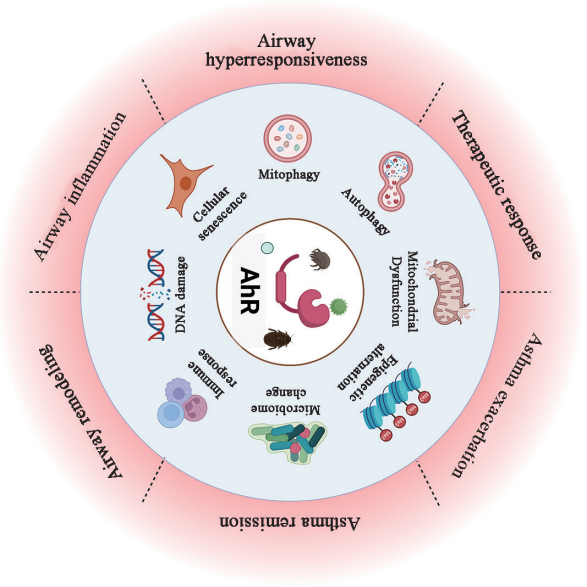


**Figure 6:** Overview of AhR signaling, hallmarks of aging, and asthma. AhR signaling as a mechanism regulates hallmarks of aging and subsequently a variety of asthma clinical phenotypes. AhR: Aryl hydrocarbon receptor.


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## Conflicts of interest

None.

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