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Review article

The aryl hydrocarbon receptor as a target of environmental stressors – Implications for pollution mediated stress and inflammatory responses

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ABSTRACT

The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor regulating the expression of genes, for instance encoding the monooxygenases cytochrome P450 (CYP) 1A1 and CYP1A2, which are important enzymes in metabolism of xenobiotics. The AHR is activated upon binding of polycyclic aromatic hydrocarbons (PAHs), persistent organic pollutants (POPs), and related ubiquitous environmental chemicals, to mediate their biological and toxic effects. In addition, several endogenous and natural compounds can bind to AHR, thereby modulating a variety of physiological processes. In recent years, ambient particulate matter (PM) associated with traffic related air pollution (TRAP) has been found to contain significant amounts of PAHs. PM containing PAHs are of increasing concern as a class of agonists, which can activate the AHR. Several reports show that PM and AHR-mediated induction of CYP1A1 results in excessive generation of reactive oxygen species (ROS), causing oxidative stress. Furthermore, exposure to PM and PAHs induce inflammatory responses and may lead to chronic inflammatory diseases, including asthma, cardiovascular diseases, and increased cancer risk. In this review, we summarize findings showing the critical role that the AHR plays in mediating effects of environmental pollutants and stressors, which pose a risk of impacting the environment and human health.

1. Introduction

Environmental exposure *via* air pollution and industrial chemicals found as contaminants in food and consumer products are increasing the risk of adverse health outcomes. The exposure to chemicals through ambient particulate matter (PM), consumer and food products may affect multiple cellular and physiological processes in our body including oxidative stress and inflammation. There is strong evidence that chronic inflammation is the basis of many adverse human health effects triggered by PM; especially the exposure to PM generated by combustion and accumulating in urban areas have been found to be associated with inflammatory lung and cardiovascular diseases [1,2]. In addition, evidence is accumulating that PM exposure contributes to the pathogenesis of neurodegenerative diseases, diabetes, and inflammatory skin disorders [3–5]. Traffic-related air pollution (TRAP) is a major source of ambient PM, which is based on the combustion of fossil fuels by motor vehicles and industry [6]. The adverse health effects of PM can result from their particulate characteristics (size, mass, even shape) or from the chemical components they adsorb, such as polycyclic aromatic hydrocarbon (PAHs), heavy metals (HM), or a combination thereof (see graphical abstract). PM derived from combustion contain significant amounts of PAHs compared to other PM sources [7]. PAHs are well-known activators of the aryl hydrocarbon receptor (AHR), a latent transcription factor with numerous roles in physiology. In addition, persistent organic pollutants (POPs), in particular dibenzo-*p*-dioxins, dibenzofurans and non-*ortho* substituted polychlorinated biphenyls (PCBs), are another class of high-affinity AHR ligands that can be found in PM fractions [8,9]. In contrast to PAHs, these organochlorines are metabolically stable and accumulate in body fat over time, thus evoking chronic toxicity [10,11]. In this review, we look at the role of the AHR signaling pathway as an important mechanism of PM mediated adverse health effects, especially regarding the generation of oxidative stress and the modulation of immunity. While obvious and often silently assumed, there is still a paucity of studies demonstrating experimentally

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Abbreviations

AD	atopic dermatitis
AHR	aryl hydrocarbon receptor
AKR	aldo-keto reducatse
ARE	antioxidant response elements
ARNT	aryl hydrocarbon receptor nuclear translocator
ASCVD	atherosclerotic cardiovascular disease
BaP	benzo[*a*]pyrene
COPD	chronic obstructive pulmonary disease
COX	cyclooxygenase
CVD	cardiovascular disease
CYP	cytochrome P450
DC	dendritic cells
GST	glutathione S-transferase
HM	heavy metals
KEAP1	Kelch-like ECH-associated protein
LPS	lipopolysaccharide
3MC	3-methylcholanthrene
MCP-1	monocyte chemotactic protein 1
MMP	matrix metalloproteinases
NF-κB	nuclear factor-κB
NKX2.5	NK2 homeobox 5
NOX	NADPH oxidase
NQO1	NADPH:quinone oxidoreductase-1
NRF2	nuclear factor erythroid 2-related factor 2
PAH	polycyclic aromatic hydrocarbon
PCB	polychlorinated biphenyl
PFP	PAH rich PM
PG	prostaglandin
PM	particulate matter
POP	persistent organic pollutant
ROS	reactive oxygen species
SOD	superoxide dismutase
TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin
TCF21	transcription factor 21
TRAP	traffic-related air pollution
UGT	UDP-glucuronosyltransferase
XRE	xenobiotic-responsive element

the AHR-dependency of PM-mediated immune effects. (see Table 1)

Numerous studies have shown that PM-associated PAHs and POPs are capable of binding to and activating AHR in various test systems [12–14]. The AHR is a ligand-activated transcription factor located in the cytoplasm forming a complex with heat-shock protein 90, AHR interacting protein and p23 [10,11]. After ligand binding, the AHR translocates to the nucleus, dimerizes with AHR nuclear translocator (ARNT) and binds on xenobiotic-responsive elements (XREs; a.k.a. dioxin-responsive elements) in the promoter of AHR target genes (Fig. 1). Targets of the AHR gene battery include xenobiotic-metabolizing phase I enzymes, such as CYP1A1, CYP1A2, CYP1B1, and phase II enzymes, including NADPH:quinone oxidoreductase (NQO1), glutathione S-transferase (GST) A2, and UDP-glucuronosyltransferase (UGT) 1A1 and UGT1A6 [10,11]. In addition to this canonical signaling pathway, AHR frequently interacts with other signaling pathways, such as nuclear factor-κB (NF-κB), nuclear factor erythroid 2-related factor 2 (NRF2) and estrogen receptor signaling [10,11].

POPs, PAHs and related environmental AHR ligands are hazardous substances and may elicit a variety of adverse health effects. Specifically, the chronic exposure to PAHs is associated with the development of atherosclerosis [15,16], allergic inflammatory diseases (e.g. asthma and atopic dermatitis) [17–19], cancer [20], and premature tissue aging [21,22]. Accordingly, the AHR represents a sensor of environmental stimuli and stressors and acts as a mediator of their potential harmful health effects.

It is, however, worth mentioning that apart from environmental chemicals, numerous small molecular weight compounds have been identified to bind to AHR and modulate its activity. The growing list of AHR ligands includes endogenously generated tryptophan metabolites and indole derivatives, plant- and microbiota-derived metabolites as well as several pharmaceutical drugs [11,23]. Importantly, not all of these AHR ligands initiate similar molecular and cellular responses. In fact, numerous studies have reported that AHR modulation affects the expression of a multitude of direct and indirect target genes, not only in a cell- and species-specific fashion but also in a ligand-specific manner. In fact, transcriptome analyses have shown that (i) different AHR ligands induce a different transcriptome profile even within the same cell-type and (ii) the same AHR ligand can induce different transcriptome profiles in different cell-types and tissues [24–27]. The molecular mechanisms underlying this ligand-specificity of AHR signaling are yet poorly understood and may include the induction of different conformational states of the AHR protein, for instance causing altered DNA binding behavior or recruitment of different transcriptional co-factors to AHR, as well as different toxicokinetic parameters of the ligands [28,29]. Ligand-specific modulation of AHR target gene expression may translate to the functional level and affect a multitude of processes, including apoptosis [30] and differentiation of T cell subsets [31,32].

Herein we review the current concepts of AHR activity concerning the generation of reactive oxygen species (ROS) and its interaction with NRF2, the key player in the cellular antioxidant response. We move on to review the literature regarding PM, AHR, and adverse health effects, which involve the immune system, and may affect the heart, lung, and skin.

2. AHR and the generation of ROS

Exposure to PM and PAHs is well known to cause ROS formation and induce oxidative damage to DNA, lipids and other cellular macromolecules. A study on Asian schoolchildren, for instance, revealed a synergistic positive association between outdoor PM concentration and urinary 1-hydroxypyrene (a biomarker for PAH exposure) on one side and urinary malondialdehyde levels (a biomarker for oxidative stress) on the other side [33]. One pathway through which PAHs may induce ROS formation is the AHR-dependent induction of CYP1 isoforms, including CYP1A1, CYP1A2, and CYP1B1. For instance, a study showed that overexpression of recombinant CYP1A1 and CYP1A2 in human lymphoblast-derived microsomes stimulated the production of ROS, such as superoxide anion radicals [34]. Along the same lines, treatment of murine Hepa1c1c7 hepatoma cells and C57BL/6J mice with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a prototypical ligand of AHR, resulted in an enhanced excretion of 8-hydroxyguanine and 8-hydroxydeoxyguanosine, two biomarkers of oxidative DNA damage [35,36]. Importantly, in the in vitro study, the excretion rate of these markers for oxidative DNA damage could be reduced by AHR antagonism and CYP1A1 inhibition [35]. Indeed, ROS production is tightly linked to the catalytic circle of CYP enzymes, more precisely to a phenomenon called “uncoupling” [37]. Briefly, in the presence of NADPH, CYP monooxygenases reduce molecular oxygen to introduce one oxygen equivalent into the substrate and the second one into water. By analyzing the stoichiometry of this reaction, it became evident that most CYP enzymes expend more oxygen than needed to monooxygenize their substrates and, in fact, small amounts of hydrogen peroxide are frequently formed as a by-product of this catalysis [38–40]. In particular, when compounds that are not oxidizable, such as TCDD, induce the formation of the oxygen-bound CYP complex, the lack of an electron acceptor may

Table 1
Studies showing a link between air pollution, AHR-signaling, and adverse immune effect.

Pollutant/substance	Target organ/cells	Immune effect	Reference	AHR dependency confirmed[a]
Mouse				
Ambient urban dust (SRM1649b)	Murine T cells in vivo	Severity of experimental autoimmune encephalitis; Th17, Th1, Treg cells	[108]	$AHR^{-/-}$ mice; inhibitors
Organic fractions of ambient urban dust	Murine T cell differentiation in vitro	Enhancement of Th17 differentiation	[107]	Induction of CYP1A1
Ambient air $PM_{2.5}$	Murine dendritic cells, T cells, in vitro	Activation dependent upregulation of IL1ß, co-stimulation molecules; IL17 and IL22 production by T cells	[117]	Luciferase reporter assays; *cyp1a1* induction
MCP230 particles	Mouse lung in vivo, dendritic cells in vitro	Increase in Th17 cytokines (IL6, IL17A, IL22, IL1ß, IL33 etc.); oxidative stress	[115]	Inhibitors, *cyp1a1* induction, luciferase reporter assay
Diesel exhaust samples differing in PAH content	Murine T cell differentiation in vitro, EAE in vivo	Effects depended on Diesel sample, i.e. Active PAH components matter	[122]	$AHR^{-/-}$ mice
Air pollutants	Murine skin/skin innervation	Hypersensitivity to pruritus, induction of artemin	[18]	$AHR^{-/-}$ mice
Diesel exhaust (ultrafine particles)	Murine airways in vivo; **human** monocytes, murine dendritic cells in vitro	Promotion of airway inflammation; activation of Jag1-Notch Cascade	[118]	Antagonists; luciferase reporter assay
Ambient Urban dust, diesel exhaust, cigarette smoke	Murine T cells in vitro, in vivo exposure of mice	Enhanced Th17 differentiation, IL17 secretion	[120]	$AHR^{-/-}$ mice
Human				
Diesel exhaust particles	Human primary bronchial epithelial from asthma patients	upregulation of IL-33, IL-25 and TSLP	[12]	Knock-down of *AHR* with siRNA
Ambient particulate matter and diesel exhaust particles	Human primary bronchial epithelial cells	Upregulation of TSLP mRNA and human microRNA (hsa-miR)-375; regulation of mRNA for *AHR*	[128]	Induction of *AHR* and *CYP1A1*

[a] in the studies listed here an involvement of AHR has been demonstrated, e.g. by measuring induction of AHR target genes, inhibition or ablation of AHR in the target cells, or use of AHR-deficient mice. For more details, see the respective publication.

Fig. 1. Scheme of AHR signaling – The AHR resides in the cytosol within a complex of chaperones and other proteins. Lipophilic ligands (e.g. PAH) may cross the cell membrane and bind to the AHR. Due to the ensuing conformational change, the AHR sheds its complexing proteins and translocates to the nucleus, where it dimerizes with ARNT or other partners from other signaling pathways (not shown here). Finally, the AHR:ARNT complex binds to DNA at responsive promoter elements an can initiate transcription. Genes encoding for xenobiotic metabolizing enzymes were among the first AHR target genes described.

lead to autooxidation of the CYP enzyme and the subsequent release of superoxide [35,37]. Superoxide dismutates to form hydrogen peroxide and, by undergoing Fe^{2+}-catalyzed Haber-Weiss and Fenton reactions, both superoxide anions and hydrogen peroxide may be converted to highly reactive hydroxyl radicals [39,41].

Recent studies confirm that AHR-dependent induction of CYP1A is a major source of ROS formation in TCDD-treated hepatocytes [42]. This study also showed that a significant and sustained increase of CYP1A1 expression and 7-ethoxyresorufin-*O*-deethylase enzyme activity over 48 h generates ROS and 8-hydroxydeoxyguanosine in an AHR-dependent manner. In contrast, PM-mediated generation of ROS may involve AHR-independent pathways, which are based on the presence of metals (e.g. iron, nickel, copper), the matrix or other components of PM. The AHR-independent production of ROS is supported by the direct oxidative potential of PM and the rapid generation of ROS, which can be measured in cell free assays [43,44]. It is important to note that the direct oxidative potential of PM is distinctive from the intracellular production of ROS, which can be mediated *via* activation of AHR by PAHs present in PM from urban areas. The importance of ROS generation for the toxicity induced by PM exposure, however, is unclear and seems to be limited based on a literature review [45].

Besides CYP1 isoforms, aldo-keto reductases (AKR) are involved in the metabolic activation of PAHs and associated with ROS formation. AKRs are cytosolic NADPH-dependent oxidoreductase that convert carbonyl groups to primary and secondary alcohols [46]. AKRs, in particular human AKR1A1 and AKR1C1 – AKR1C4, can oxidize *trans*-dihydrodiols, intermediates derived from CYP1-mediated oxidation of PAHs, to respective catechols [47,48]. Benzo[*a*]pyrene (BaP), for instance, is oxidized by CYP1A1 to BaP-7,8-epoxide [49]. In a dihydroxylation reaction, microsomal epoxide hydrolase-1 converts this

epoxide to BaP-7,8-*trans*-dihydrodiol, which is either detoxified by phase II enzymes, again oxidized by CYP1 isoforms, or converted by AKR enzymes to BaP-7,8-catechol [46,49]. In the presence of oxygen, BaP-7,8-catechol undergoes a one-electron oxidation to form an *o*-semiquinone anion radical, a reaction which releases hydrogen peroxide [50]. If not detoxified by catechol-*O*-methyltransferases or conjugating phase II enzymes, another one-electron oxidation leads to the formation of BaP-7,8-dione (*o*-quinone) and superoxide anion radicals [50]. BaP-7,8-dione is highly reactive and either forms DNA adducts [51] or undergoes redox-cycling, i.e. in presence of NADPH it is reduced back to BaP-7,8-catechol [52]. Hence, AKR-mediated metabolism of PAHs contributes to oxidative damage and genotoxicity. Notably, the role of AHR in regulating AKR1 gene expression is not clear yet. An increased expression of AKR1C enzymes was observed in BaP-exposed cell-lines, including human hepatoma, colon carcinoma and breast cancer cells [53–55]. Moreover, knockdown of AHR in MDA-MB-231 breast cancer cells dramatically reduced both basal as well as 3-methylcholanthrene (3MC)-induced expression of AKR1C3 [55]. However, the AHR prototype ligand TCDD has been shown to be ineffective in terms of AKR1C induction and the promoter sequences of the human AKR1C-encoding genes do not contain responsive XRE [53,55], arguing against a regulation of these enzymes through the canonical AHR/ARNT signaling pathway.

Further, there is accumulating evidence in the literature that PM and PAHs may stimulate ROS production by NADPH oxidases (NOX), in particular NOX2 and NOX4 [56–61]. These membrane-bound enzyme complexes can be found in the plasma membrane of various cell types, such as phagocytic cells, endothelial and epithelial cells [62]. In its inactive state, the NOX subunits, three cytoplasmic (Rac1, $p47^{phox}$, $p67^{phox}$) and two intrinsic membrane ($p22^{phox}$, $gp91^{phox}$) components, are unassembled [62]. Upon activation by cytokines, opsonized bacteria, bacterial lipopolysaccharides (LPS) or other stimuli, the complex assembles and the catalytic subunit, i.e. the heterodimeric flavocytochrome consisting of $gp91^{phox}$ and $p22^{phox}$, transfers one electron from NADPH to molecular oxygen thereby generating superoxide anions, which then dismutate to hydrogen peroxide [62]. Notably, additional proteins, such as $p40^{phox}$, probably also play a role for NOX activity, in particular for activation of the complex [62]. In the literature, several ways of interaction between NOX and AHR signaling are described. In epidermal keratinocytes, for instance, PM-bound PAHs caused NOX2-mediated ROS formation by stimulating the phosphorylation of $p47^{phox}$ (also known as neutrophil cytosolic factor 1), a signal for NOX2 complex assembly at the plasma membrane, in an AHR-dependent manner [58]. Subsequently generated ROS initiate MAPK signal transduction resulting in the activation of AP-1 and NF-κB transcription factors and downstream pro-inflammatory responses [58]. In human and rat macrophages, BaP treatment led to a transcriptional upregulation of $p47^{phox}$ through direct binding to a responsive XRE in the promoter region of the gene. In addition, BaP facilitated the translocation of the $p47^{phox}$ protein to the cell membrane of the macrophages and potentiated phorbol myristate acetate-induced superoxide anion production [57]. Another study observed a 3MC-induced induction of the NOX subunit $p40^{phox}$ in liver of C57BL/6J mice, which was absent in the hepatic tissue of AHR liver-specific knockout mice [61]. Corresponding mechanistic analyses in Hepa1c1c7 cells revealed the presence of a functional XRE in the promoter of the murine $p40^{phox}$ gene and demonstrated the critical role of $p40^{phox}$ for the 3MC-induced increase in NADPH oxidase activity and ROS formation [61]. Interestingly, activation of NOX4 by thiol-reactive agents, such as cadmium, arsenic, nickel and mercury, was reported to interfere with AHR signaling [63]. Treatment of human HaCaT keratinocytes with arsenic resulted in a NOX4-dependent generation of oxidative stress. Subsequently, ROS inhibited the catalytic activity of CYP1A1, leading to an accumulation of the endogenous AHR ligand 6-formylindolo[3,2-*b*]carbazole and an AHR-dependent transcriptional upregulation of CYP1A1 [63,64], which has been previously observed in arsenic-treated cells and mice, too [65,66]. Notably, an interference of ROS with the metabolic degradation of AHR ligands may also account for the enhanced transcriptional activity of AHR observed in glutathione-depleted normal and malignant mammary cells [67].

Additionally, an alternate enzyme for chemical oxidation exists in form of prostaglandin-endoperoxide synthase-2, also known as

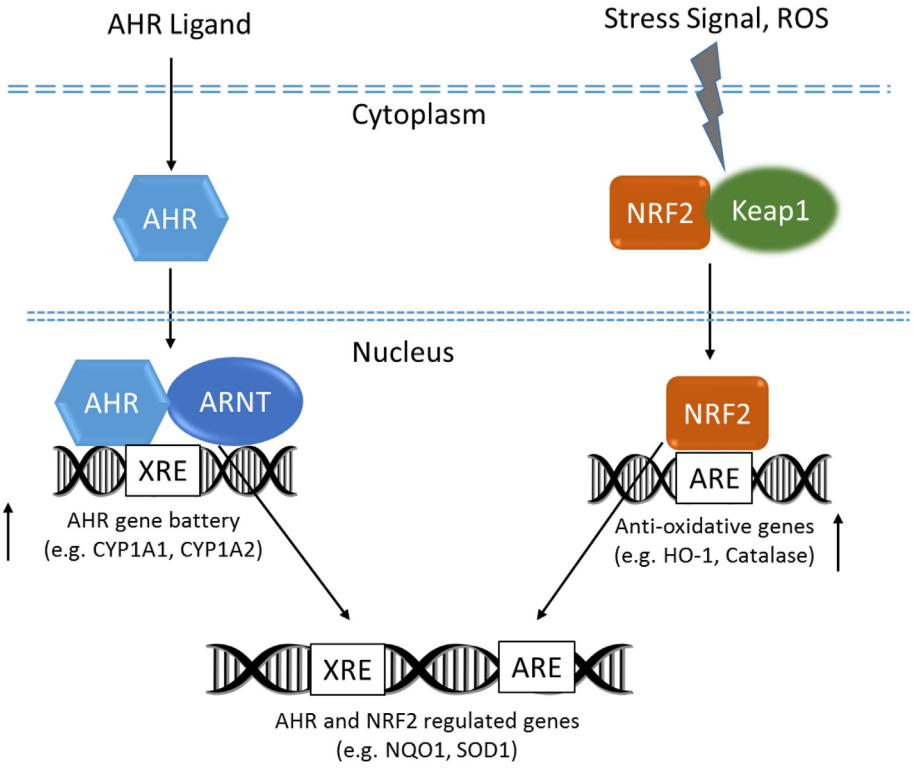

Fig. 2. AHR- and NRF2-mediated regulation of genes of CYP1A genes and anti-oxidant genes, respectively. AHR and NRF2 can interact and regulate the expression of antioxidant genes containing DNA response elements for both pathways. Possible antioxidant mechanisms are triggered by activation of AHR and NRF2 inducing NQO1 and SOD1.

cyclooxygenase (COX)-2. COX-2 may exemplify an alternate enzyme of xenobiotic metabolism in extrahepatic tissues [68,69]. Previously, it has been shown that AHR activation by TCDD induced the expression and activity of COX-2 [70,71]. Unlike COX-1, the expression of COX-2 is inducible by various stimuli, such as growth factors and cytokines [72]. An elevated expression of COX-2 has been found to be associated with chronic inflammation and carcinogenesis [73–75]. COX-2 converts arachidonic acid to prostaglandin (PG) G_2, which undergoes peroxidation to PGH_2. In this two-step enzymatic process, which generates ROS, COX represents the rate-limiting enzyme to produce PGs [76,77]. Whereas TCDD and other AHR ligands mediate the expression of CYP1A1 and CYP1A2 *via* the canonical AHR/ARNT pathway, the TCDD-induced expression of COX-2 involves non-canonical AHR signaling pathways, including activation of c-Src and downstream CCAAT/enhancer binding protein-β [78] and MAPK signal transduction [58,79]. The increased expression of COX-2 may contribute to an enhanced production of ROS. Interestingly, reports demonstrated that elevated levels of COX-2 and ROS cause vasoconstriction and renal endothelial dysfunction [80]. Another study suggested that LPS induces the inhibition of the endothelium-dependent vasodilator response in middle cerebral arteries from normotensive rats [81]. The LPS effect was mediated by the release of superoxide anion generated at least in part *via* the LPS-activated expression of COX-2.

In summary, several enzyme systems including CYP1A, AKR1, NOX, and COX-2 are regulated through the AHR signaling pathway with the ability to generate ROS in various cell types and tissues.

3. AHR mediated antioxidant response and interaction with NRF2

In contrast to AHR-dependent and CYP1A-mediated production of intracellular ROS, the AHR signaling pathway also regulates the expression of genes involved in antioxidant responses. Besides AHR signaling, NRF2 is another important transcription factor regulating genes that are critically involved in the metabolism of xenobiotics as well as endogenous compounds (Fig. 2). Both signaling pathways respond to environmental and endogenous stressors. Even though, AHR and NRF2 are clearly separated signaling pathways, recent reports demonstrate the cross-regulation between these two signaling axes suggesting that a tight connection of the AHR and NRF2 pathways provides an integrated response to environmental stressors [82].

NRF2 is bound to the Kelch-like ECH-associated protein (KEAP1) in the cytoplasm and is activated by stress signals, like electrophilic molecules or free radicals. After dissociation of KEAP1, NRF2 binds to antioxidant response elements (AREs) inducing antioxidative enzymes, such as heme oxygenase-1, NQO1, superoxide dismutase (SOD), catalase, and thioredoxin-1 to protect against oxidative stress. As shown previously, the promoter region of the target genes NQO1 and SOD1 contain XRE as well as ARE elements and are regulated by both the AHR and NRF2 signaling pathways [83–86]. Furthermore, besides generation of ROS *via* CYP1A1, AKR1 and COX-2, other mechanisms exist which may contribute to AHR-mediated induction of NRF2-regulated genes. First, Miao et al. (2005) have shown that the promoter of NRF2 contains several XRE elements [87] and that activation of AHR transcriptionally activates NRF2, leading to increases of NRF2 mRNA and protein [88]. Our recent data show the activation of NRF2 in a luciferase reporter assay after treatment with TCDD and diesel emission samples [14]. However, ligand-dependent activation of AHR by TCDD did not induce NRF2 mRNA expression in primary macrophages derived from mouse or human monocytes (unpublished results), indicating a cell type specific induction of NRF2 mRNA expression *via* AHR. Interestingly, treatment of human epidermal keratinocytes with the antifungal agent ketoconazole has been reported to induce both, the nuclear translocation of NRF2 and downstream NQO1 expression, in an AHR-dependent manner [89], suggesting that non-canonical AHR signaling pathways may activate protein kinases that control KEAP1 stability and thus NRF2 activation [90]. Interestingly, sustained activation of NRF2 in keratinocytes may lead to a chloracne-like skin phenotype in mice [91]. The authors reported that a similar NRF2-dependent mechanism is likely to be involved in dioxin-induced chloracne. Chloracne, a certain type of acne-like skin disease, is a very specific and sensitive biomarker of dioxin exposure in human [92].

4. Activation of AHR *via* PM, PAHs and POPs associated with adverse health effects and the immune system

Inflammation is a major defense mechanism of the immune system, but if inflammation gets chronic or somehow awry it can become a major cause of adverse health issues. Very early work on AHR and the immune system, mostly using TCDD as a ligand, described the AHR-dependent expression of pro-inflammatory cytokines, such as IL-1β or transforming growth factor-β [93–95], which later expanded to other cytokines, such as IL-6 or IL-22, as well [96,97]. At that time, research on AHR and immunity largely studied TCDD's immunosuppressive effects. Only much later, research on AHR and cytokine induction, and more generally AHR's role in the physiology of the immune system took off. This was due to the initial discovery that AHR is necessary for the differentiation and function of Th17 cells and expression of their signatory cytokine, the pro-inflammatory IL-22. Consequently, induction of AHR signaling by a high-affinity ligand 6-formylindolo[3,2-*b*]carbazole could exacerbate autoimmunity [31,98]. Other reports demonstrated that AHR-signaling balances the Th17 *vs.* regulatory T cell differentiation [31,99,100]. Moreover, the concept gained traction that, beyond being a mediator of toxicity, AHR is critical for a meaningful immune response against pathogens and in the context of barrier integrity of, e.g., the skin, gut, or lungs and also for the brain (reviewed in Ref. [11,101,102]). A major discussion point has been which parameters are critical for a beneficial *vs.* adverse outcome for AHR ligand exposure: source, chemistry, dose, exposure routes, cellular context or a combination thereof. This important issue has not yet been satisfactorily resolved, albeit the Janus-faced role of AHR signaling is an accepted concept by now, including regarding its role mediating effects of air pollution [103,104]. Halogenated aromatic hydrocarbons and PAHs adsorb to airborne particulate matter and thereby become a relevant source of environmental AHR ligands to which humans are exposed [105,106]. By now, an increasing body of research addresses the effects of PM on the immune system, and thereby involve a range of diseases, from cardiovascular diseases, airway diseases, especially regarding Th2 driven asthma/lung damage and skin eczemas, and Th17 driven autoimmunity [107–109]. They are discussed in several sections of this review. Both direct immunological inflammatory effects of airborne particles and indirect exacerbation of particle-induced damage have been reported, with oxidative stress and induction of a range of cytokines, which affect the lung epithelium appearing to be an important mechanism [110–112]. Moreover, insoluble material in the lungs as such can cause oxidative burst in inflammatory cells, e.g., macrophages or neutrophils [111]. However, whether or not AHR signaling is somehow involved in such immune effects, for instance by its regulation of cytokines, is not always clear or has not been explicitly analyzed or even considered. It is noteworthy that after the Seveso-Incident in 1976 – i.e., upon primarily TCDD exposure - the incidence of chronic obstructive pulmonary diseases (COPD) was doubled [113]; in general, PAH-bearing particles are considered causative for COPD [114], suggesting a link between AHR-agonists on air pollution particles with this disease.

A recent study reported, that persistent free radicals associated with combustion-generated particles may activate AHR and induce Th17 related cytokines (IL-1ß, IL-22, IL-33, keratinocyte-derived chemokine) leading to Th17 polarization and IL-17-dependent pulmonary inflammation [115]. The authors concluded that the ROS-mediated effects on Th17 polarization depends at least in part on activation of AHR. The mechanism of ROS-mediated activation of AHR is unclear. Previously, we have shown that the expression of AHR is regulated through

a distal NF-κB-binding element located on the promoter of the human AHR gene [116]. Based on this finding, it is possible that ROS induces the expression of AHR *via* NF-κB signaling. We could also show that ambient urban $PM_{2.5}$ collected in Sacramento (CA, USA) triggers polarization of Th17 cells mediated by activation of dendritic cells (DC) [117]. We found that PAH-containing $PM_{2.5}$ directly activate AHR and induce inflammatory markers associated with an enhanced activation of DC responsible for differentiation of naive T cells towards a Th17-like phenotype. The important role of DC mediating elevated IL-17 responses and allergic responses has been confirmed in mice after treatment with vehicular ultrafine PM [118]. The deletion of AHR in $CD11c^+$ cells protected against PM-mediated exacerbation of the allergic responses and PM-mediated IL-17 increase, underlining the key role of DC and AHR. Interestingly, the impact of AHR activation modulating the function of DC during development in mice suggested long-lasting consequences on immune function through environmental exposure in early life [119]. The findings of Joshua Mezrich's group [120] revealed that PAHs are a critical component in PM promoting Th17-polarization and secretion of IL-17A from T cells in vitro. More recently, studies by the same group showed that the PM matrix and chemical components other than PAHs in the organic fraction are also contributing to the observed IL-17 responses in vivo and the associated adverse health effects, including autoimmune diseases [107,121,122].

The skin offers another major interface to air pollution, and studies have looked at the immunological response in skin. Activation of AHR by either diesel exhaust particles or 7,12-dimethylbenz[*a*]anthracene induced expression of artemin, epidermal hyper-innervation and inflammation in mice. AHR activation and artemin expression positively correlated in the epidermis of patients with atopic dermatitis, an inflammatory condition of the skin, and induced both inflammatory genes, and genes related to skin innervation, leading to hypersensitivity to pruritus [18]. Inhaled PM, and thus the POPs and PAHs adsorbed on them, ultimately reach the gut and indeed can adversely affect the immune system there. Feeding PAH-containing fine air particles to mice resulted in gut inflammation and dysbiosis [123]. PM, POPs and PAHs can be obesogenic or exacerbate obesogenicity *via* their inflammatory potential in an AHR-dependent manner, which may be used for preventive approaches [124–127]. Future studies are needed to clearly identify the most critical components of PM and their inflammatory potential and effectiveness to induce chronic inflammatory diseases.

5. Impact of chemicals and PM on the lung, ROS and inflammation mediated effects, and possible role of AHR

The lung is at the interface with both the internal and external environment and is susceptible to perturbation by air pollution and chemical exposures both systemically or by inhalation. Further, the lung is a high oxygen environment resulting in susceptibility to oxidant stress. Fortunately, the respiratory system has developed a number of defense mechanisms to resist chemical and particulate injury including abundant innate immune cells (alveolar macrophages) to remove particulates, a mucociliary escalator to remove detritus and metabolizing and antioxidant systems to resist chemical stressors. There is abundant evidence that the lung also contains numerous cells in which the AHR system plays a major role in regulating lung function, particularly in relation to environmental exposures. Lung cells with well studied AHR responses include a number of cell types that also have CYP monooxygenase activity, such as macrophages [129,130] and conducting airway and alveolar epithelial cells [131–133], particularly Club cells and alveolar type II cells. TRAP contains abundant PAHs in both the vapor and particulate phases. A series of studies using laboratory-generated combustion PM that was PAH rich *vs.* a similar PM that was not PAH rich found that PAH-rich PM was more impactful on lung antioxidant enzymes and caused more injury in the lung [134]. Further, PAH-rich particles alone were capable of stimulating AHR activity and an increase of CYP1A1 and CYP1B1 expression in vivo [133]. This PAH-rich PM exposure system is useful for teasing out the effects of carbonaceous PM associated with combustion generated PAHs, approximating near roadway exhaust, and this type of exposure disrupts postnatal lung development [135]. Work in 7 day old neonatal rats has shown that PAH-rich PM can activate the AHR in both the airways and the alveoli [133,134]. Further, neonates are more susceptible to inhaled PAH-rich PM lung toxicity than adults [134] and this exposure changes how the lung grows [136]. Other studies of combustion-generated soot have found that particles activate both AHR and NRF2 as well as inflammation related genes (see prior discussion in this manuscript of these responses and their interaction with AHR) [137–140].

The AHR is now drawing much attention in the field of chronic lung diseases. It is becoming clear that AHR amplifies the adverse effect of tobacco smoke on ciliated cells, Club cells, and alveolar macrophages in mediating the pathogenesis of COPD as well as lung cancers [141,142]. Tobacco smoke and PM therein contain dioxins and PAHs that activate the AHR and mediate at least part of their toxicity through AHR signaling. Many PAHs are ligands of the AHR and are known to irritate the developing lung, predisposing to infections, reduced lung function, and increasing asthma. PAHs, including BaP, PCBs and dioxin-like compounds in tobacco smoke have the potential to induce inflammation and exacerbate chronic bronchitis, asthma, COPD, and lung cancer [143,144]. Furthermore, Kim et al. (2004) demonstrated that AHR promotes induction of CYP1A1 and CYP1B1, particularly among smokers [145]. Recent studies show that exposure to tobacco products, such as electronic cigarette aerosol, also activates the AHR pathway and induces CYP1A1, thus confirming the critical role of AHR to mediate toxicity of smoke from traditional tobacco cigarettes as well as from electronic cigarettes [146]. Lin et al. (2003) have shown that expression of AHR among human lung cancer patients is more intense in adenocarcinoma than in squamous cell carcinomas or matched normal cells [147]. As for potential biomarkers, obvious candidates are inflammatory markers, CYP1A1, and, as discussed below, lung-specific genes, such as cyclin O and mucin 5AC. The AHR-dependent up-regulation of inflammatory genes and mucin 5AC production by tobacco smoke has been shown in lung epithelial cells [148]. Together these studies show that the AHR is critical for pulmonary responses induced by tobacco smoke and PM and it will be important to define how the AHR amplifies the adverse effects and thereby promotes pathogenesis of chronic lung diseases.

Recently, it became evident that the AHR is involved in normal physiological processes of the lung and may affect lung growth and development. AHR regulates Muc5AC expression [148–150] and disordered AHR can affect alveolar growth [151]. Additionally, cyclin O, a factor required for multiciliogenesis, has been identified as a direct target of AHR in mouse tracheal epithelial cells [152]. There have been studies of hyperoxia related bronchopulmonary dysplasia. In this model, the genome-wide transcriptional profile in newborn C57BL6 mice shows that AHR has a critical regulatory role in lung development [153], which is correlated by studies of human fetal lung and hyperoxia [154] lending credence to the concept that AHR is involved in lung growth, development and response to injury. Studies of hyperoxia in AHR dysfunctional mice found that a decrease in pulmonary AHR activation in newborn mice increased hyperoxia-induced alveolar simplification and lung inflammation [151], supporting the hypothesis that a lack of AHR signaling changes normal lung development. While developmental roles for AHR have been most studied in animal models of bronchopulmonary dysplasia, it has been increasingly recognized to play a crucial role in normal physiological homeostasis of the lung [155], including ciliogenesis [152,156], mucin production [149], immune function [141] and traffic PM-mediated airways hyperresponsiveness [118]. AHR has a well-established role in regulation of inflammation in the lung, and DC and macrophages are key players in this response [141]. AHR in the lung promotes induction of CYP1A1 and CYP1B1, particularly among smokers or after PM exposure in human alveolar type I and II cells, Club cells and ciliated columnar epithelial

cells lining airways. Furthermore, AHR-dependent regulation of antioxidant enzymes, such as NQO1, SOD, GSTs and UGTs, have been described above, indicating that deficiency or changes in AHR activity may lead to complex changes in enzymes of oxidative stress in the lung [157]. Whereas, activation of AHR by high doses of TCDD leads to significant induction of CYP1A1 and increased levels of ROS and inflammatory markers in the lung [158], low-dose and transient activation of AHR (e.g. natural and endogenous AHR ligands) may maintain the expression of antioxidative genes to protect from cell damage and tissue injury. While it is obvious that there are complex mechanisms involved in the activation of the AHR signaling pathway in the lung, the role of AHR implicated in molecular mechanisms of lung development and remodeling are only little understood.

6. Impact of environmental pollutants and PM on the cardiovascular system: ROS and inflammation mediated effects, and possible role of AHR

The following chapter focuses on the role of AHR mediating the effects of environmental pollutants including ambient PM leading to adverse health effects of the cardiovascular system. The correlation between exposure to POPs and the development of cardiovascular diseases (CVD) in humans, including acute myocardial infarction, has been described in several studies [159–161]. Epidemiologic studies also showed that occupational exposure to high doses of dioxin is associated with ischemic heart disease [162]. Further, a study examining U.S. Army veterans exposed to Agent Orange, a defoliant contaminated with dioxin, found a higher incidence of hypertension, stroke, and coronary heart disease in Vietnam and Korean veterans [163,164]. Another study including 12 cohorts also suggested that dioxin exposure is associated with mortality from ischemic heart disease [165]. These studies strongly suggest that exposure to POPs, such as dioxins, increase the risk of CVD.

Atherosclerosis is a chronic inflammatory condition and the primary cause of ischemic heart disease and stroke, leading to about 50% of all deaths in Western countries [166,167]. There is increasing evidence that exposure to air pollutants and ambient PM contribute to atherosclerotic cardiovascular disease (ASCVD) and the incidence of CVD [168–170]. Recent studies support the conclusion that exposure to air pollution causes an even higher acute risk for mortality from CVD than from pulmonary diseases [171]. Thus, the impact of air pollution on CVD represents a serious public health problem [172]. Air pollution and PM contain a complex mixture of compounds, such as PAHs and various metals (e.g. iron, nickel, copper), which may induce inflammatory responses [173,174]. Numerous studies implicate inflammatory pathways in early atherogenesis and the progression of the lesions [167]. A major source of ambient PM, especially in industrialized areas, is the combustion of fossil fuels by motor vehicles and industry, including power generation [6]. TRAP in urban areas is a main contributor to unhealthy ambient air quality, and is associated with increased cardiac and pulmonary mortality [175,176]. A recent study also showed a clearly stronger association of subclinical atherosclerosis with exposure to vehicular-specific PM as compared to the crustal source PM [177]. About 15% of the total U.S. population lives and works near major highways and thus have an increased risk to develop cardiovascular and pulmonary health problems [178]. The mechanisms by which PM, including TRAP emissions, is recognized on a cellular level and how chronic inflammatory responses lead to atherosclerosis are poorly understood. In recent years, PM generated by combustion from heavy-duty vehicles has been found to contain significant amounts of PAHs compared to light-duty vehicles and other PM sources [7,179]. AHR-dependent activation of CYP1A1 and inflammatory cytokines, including IL-8 and IL-1β, after exposure to PAH-containing PM has been shown in different cell types as well as in vivo [13,130,180–184]. Recent studies indicate that PAHs are major contributors to PM-mediated atherogenesis and AHR-induced toxicity [105,118,185–188]. Despite evidence for a role of inflammatory mediators in atherosclerosis, less is known about how the expression of these inflammatory mediators are regulated through exposure to air pollutants. Recent studies implicate the interaction of PM and its components with AHR as a key event leading to elevated levels of pro-inflammatory cytokines, such as IL-1β, IL-8, monocyte chemotactic protein 1 (MCP-1; a.k.a. CCL2), CXCL2 and the promotion of Th17-immune responses [120,130,180]. Using an in vitro bioassay consisting of human macrophages, we found that activation of AHR leads to accumulation of lipids and foam cell formation [189]. Foam cell formation is an early indication of the development of atherosclerotic lesions. In the apolipoprotein E-deficient mouse model treatment with TCDD caused the progression of atherosclerosis, which was associated with induction of inflammatory markers and accumulation of foam cells [190]. Interestingly treatment with an inhibitor of CXCR2, a chemokine receptor for CXCL2 and IL-8, reduced the dioxin-induced and AHR-dependent progression of atherosclerotic lesions. The AHR-mediated foam cell formation in vivo was associated with increased expression of IL-1β and matrix metalloproteinases (MMP) in atherosclerotic plaques [190]. MMPs and IL-1β are critical players in atherogenesis and plaque disruption [191].

These data are in line with a previous study finding earlier and more severe atherosclerotic lesions in descending aortas associated with an increase in blood pressure and lipids after sub-chronic exposure to dioxin in apolipoprotein E-deficient mice [192]. These reports show that the atherogenic activity of environmental pollutants, such as dioxins and dioxin-like compounds contribute to the development of atherosclerosis through the induction of a vascular inflammatory response by activating the AHR-signaling pathway. There was also evidence that exposure to $PM_{2.5}$ impairs the function of endothelial progenitor cells leading to vascular injury [193]. The authors concluded that pulmonary oxidative stress induced by $PM_{2.5}$ exposure significantly contributed to the dysfunction of endothelial progenitor cells. These studies indicate that environmental pollutants, in particular ambient PM and their

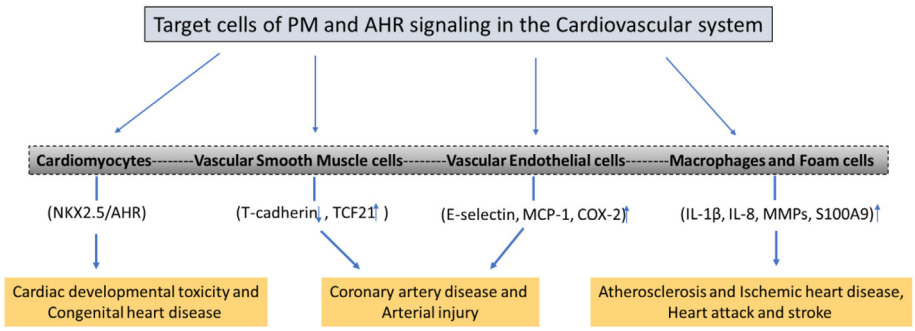

Fig. 3. PM and AHR mediated effects on target cells and markers of the cardiovascular system and potential outcomes of CVD. NK2 homeobox 5 (NKX2.5); transcription factor 21 (TCF21), monocyte chemotactic protein 1 (MCP-1); matrix metalloproteinases (MMPs); S100 calcium-binding protein A9 (S100A9).

chemical components, may induce oxidative stress as well as inflammatory mediators leading to vascular injury and ASCVD.

As shown in Fig. 3, activation or deficiency of AHR signaling can affect several cell types of the cardiovascular system, including cardiomyocytes [194], endothelial cells [21,180], and smooth muscle cells [195–197]. Consequently, the AHR may affect the function and development of the heart directly or target the cells, which are important to maintain function and homeostasis of the cardiovascular system. For instance, in vascular smooth muscle cells ligands of the AHR repressed T-cadherin expression [195]. T-cadherin is a highly expressed adhesion protein in cardiac and vascular tissues. In a different study with coronary artery smooth muscle cells, the interaction of transcription factor 21 (TCF21) and AHR has been described leading to the activation of pro-inflammatory gene expression [197]. Aung et al. (2011) investigated the effects of fine and ultrafine PM in human aortic endothelial cells [180]. The authors found that PM activated the AHR signaling pathway and induces the expression of inflammatory response genes, including E-selectin, CXCL2, MCP-1 and COX-2, in human aortic endothelial cells. Further, the importance of immune cells and inflammation in atherosclerosis is well established [198] and activation of AHR by POPs, including dioxins and PCBs, may affect the function and differentiation of macrophages, dendritic cells, and T lymphocytes [11]. Therefore, changes in inflammatory responses (e.g. expression of pro-inflammatory cytokines, MMPs, and S100 calcium-binding protein A9) induced by AHR ligands in immune cells have to be considered as an important step in the development of vascular lesions and ASCVD.

Lanham et al. (2014) reported that TCDD exposure in zebrafish leads to cardiovascular toxicity [199]. In this study, the authors found that a constitutively active AHR in cardiomyocytes of zebrafish would lead to cardiac malformations, loss of circulation, and pericardial edema. In earlier studies Rick Peterson's group [200] demonstrated that TCDD significantly reduced the development of the common cardinal vein in zebrafish embryos, resulting in alterations of vascular growth and remodeling in an AHR-dependent manner. More recently, Alvaro Puga's group [194] performed a similar study with mice using mouse strains with cardiomyocyte-specific AHR gene knockout. The results showed that AHR ablation protected haploinsufficient male mice from cardiac dysfunction. Interestingly, the effects were almost absent in female mice and suggested the interaction of AHR with the cardiomyocyte-specific NK2 homeobox 5 (NKX2.5) gene (Fig. 3). NKX2.5 is a homeobox-containing transcription factor and functions in heart formation and development. Furthermore, it has been shown that PM exposure may cause cardiac developmental toxicity in a zebrafish model [201]. Using the AHR antagonist CH223191 and the ROS scavenger N-acetyl-L-cysteine the authors concluded that PM and AHR-mediated generation of ROS contribute to DNA damage and apoptosis, causing cardiac developmental toxicity in zebrafish embryos. On the other hand, the organic fraction containing PAHs of $PM_{2.5}$ extracts inhibited cardiac differentiation in an AHR-dependent using a mouse embryonic carcinoma stem cell model (186).

Future studies need to identify the mechanisms how and to what extent ROS and chronic inflammation contribute to cardiac developmental toxicity mediated by PM and AHR signaling.

7. AHR, ROS and inflammation: effects on skin

The epidermal barrier is essential to protect the underneath tissues and structures. Originating from epidermal stem cells in the basal layer, keratinocytes differentiate towards their way through the epidermal layers to the skin surface and finally transform to dead corneocytes. During this process of terminal differentiation, the plasma membrane of the keratinocytes is replaced by lipids, such as ceramides, fatty acids, and cholesterol, which interact with filaggrin, involucrin, loricrin and related proteins to build a compact lipid-protein complex called cornified envelope. In concert with other epidermal structures, e.g., tight junctions located in the *stratum granulosum*, the cornified envelope protects the skin against microbial insults, chemical exposure, ultraviolet radiation, mechanical stress, and dehydration. Disturbance of the epidermal barrier occurs in the majority of inflammatory skin diseases, including atopic dermatitis (AD), contact dermatitis and psoriasis [202,203]. As discussed above, cutaneous exposure to airborne PM and PAHs causes the formation of ROS, which may contribute to the development and/or aggravation of inflammatory skin diseases. Oxidative stress may either directly disturb keratinocyte differentiation and associated epidermal barrier function or stimulate MAPK signal transduction and downstream NF-κB and AP-1 transcription factors in keratinocytes to induce the expression of proinflammatory enzymes and cytokines, such as COX-2, tumor necrosis factor-α, and IL-4. COX-2, for instance, produces PGE_2, which downregulates filaggrin expression in keratinocytes and thereby attenuates skin barrier function [58,204]. Likewise, IL-4, IL-13 and related Th2-derived cytokines are known to activate signal transducer and activator of transcription-6 and repress the expression of loricrin and involucrin in the epidermis from AD patients [205,206]. ROS originating from AHR-related processes may have also contributed to the degranulation of mast cells and the associated release of histamine and IL-4 observed in the nasal epithelium of human individuals challenged with house dust mite and diesel exhaust particles [207]. Another cytokine frequently present in chronic inflammatory skin diseases is IL-17, which also decreases filaggrin expression in keratinocytes [208] and is under transcriptional control of AHR [31,98].

In fact, several studies provided evidence for an involvement of AHR in the pathogenesis of AD [18,209], psoriasis [210], and vitiligo [211]. AD, for instance, results from a complex interplay between environmental and genetic factors and is characterized by skin barrier dysfunction, overexpression of proinflammatory cytokines and activation of Th2 cell-driven immune responses [212]. Interestingly, exposure to air pollution [3], in particular PAH-rich pollutants, such as tobacco smoke and TRAP [17,18,213–215], is positively associated with the development and worsening of AD in humans. In addition, a recent epidemiological study found a positive correlation between eczema in elderly women, exposure to TRAP and a single nucleotide polymorphism (rs2066853) in the AHR gene locus [216]. In contrast to these findings, exposure to dioxin-like AHR agonists seems to lower the risk of developing AD [217–219]. The underlying causes for this difference are quite enigmatic but may involve a ligand-specific modulation of proinflammatory and/or immunosuppressive responses. However, in contrast to an exposure to PAHs, TCDD treatment even accelerates keratinocyte differentiation and cornification in a ROS- and sirtuin 1-dependent manner [220,221]. On the other hand, these halogenated aromatic hydrocarbons also induce immunosuppressive regulatory T cells [31,99], which may alleviate the contribution of Th2 and Th17 lymphocytes to the pathogenesis of the disease. Even more surprisingly, PAH-rich crude coal tar is being used since decades to treat AD [209]. Topical application of the bacterial-derived AHR agonist tapinarof was also found to attenuate the clinical symptoms of AD [222]. Tapinarof as well as several other natural AHR agonists accelerate keratinocyte differentiation in vitro, which, at least in part, is triggered by an NRF2-mediated induction of antioxidative enzymes and the associated neutralization of oxidative stress [223–225]. However, the obvious discrepancy between PAHs as both risk factor and remedy for AD may be due to alterations in the microenvironment of healthy *vs.* inflamed skin and respective differences in skin-residing immune cell populations or epidermal barrier function at the time of exposure [103]. A recent study showed that the anti-inflammatory effect of medicinal coal tar is largely based on AHR-dependent induction of anti-microbial peptides [226] and, interestingly, tapinarof has antibiotic properties as well [227]. Hence, the beneficial effect of these AHR agonists may depend on a modulation of the skin microbiome, which significantly differs between AD patients and healthy individuals [228,229]. Lesional skin of AD patients exhibits a decreased microbial diversity together with an increased colonialization with *Staphylococcus aureus*

[228]. Other bacteria, such as *Cutibacterium acnes* (formerly *Propionibacterium acnes*), are lower in abundance in AD as compared to healthy skin [229]. A small clinical study assessing the alterations of the skin microbiome in AD patients and healthy controls revealed that under topical coal tar treatment, the abundance of *Staphylococcus aureus* decreased while the *Cutibacterium acnes* abundance increased [226]. Interestingly, even though exhibiting proinflammatory properties when dominating in acne vulgaris [230], *Cutibacterium acnes* was recently shown to protect skin against oxidative stress by secreting antioxidant proteins, such as RoxP [231]. Hence, treatment of inflamed skin with certain AHR ligands partially restores the microbiome of healthy skin, which may be associated with a production of bacterial antioxidants and a neutralization of ROS, one of the driving forces in the pathogenesis of AD [209,212]. Further mechanistic studies, in particular considering the skin condition and the associated composition of the microbiome at the time of PM/PAH exposure, are needed to better understand the Janus-faced role of AHR in inflammatory skin diseases.

8. Conclusion and outlook

In industrialized countries, the prevalence of non-communicable diseases, including allergic, cardiovascular, respiratory and metabolic diseases, as well as cancer, is rapidly rising and poses not only a major threat to the health of the general population but also a tremendous economic challenge for health care systems. There is broad consensus that chronic exposure to air pollution, i.e. PM and associated PAHs, POPs and HMs, significantly contributes to this steep increase.

However, there are still many gaps in our knowledge how exactly particulate matter drives diseases. We here focus on the AHR as a sensor of PAHs and POPs adsorbed to particulate matter. Much data exist that show how AHR-activation by PAHs/POPs and the associated modulation of metabolic reactions, cytokine patterns and immune responses, results in oxidative stress, tissue damage and proinflammatory conditions in various target tissues, such as the lung, the skin, and the cardiovascular system. However, only recently, studies directly began to analyze the link “PM-PAH-AHR”, i.e. showed that PM adsorbed PAHs trigger AHR-dependent cellular changes. This development is welcome and will give important insights into the differing toxicity of PM whose PAH content changes depending on the geographical location or source of PM. Another important consideration regarding predictions of adverse health effects is the complexity of interactions of air pollution with AHR signaling in the target tissue and the potential pathophysiological responses. Both the properties of the particles and the context-dependent outcome of AHR-signaling in the particular tissues are relevant, as has been detailed in the above review. An interplay of these variables ultimately defines the toxicodynamic and toxicokinetic properties of the respective pollutants. Understanding this is necessary for proper risk assessment and for possible therapeutic interventions (notwithstanding the priority of reducing pollution). Accordingly, there is a clear and urgent need for further research aiming to unravel functional relevance of AHR for air pollution-associated adverse health effects and to assess its suitability as a target for molecular prevention.

We, the authors, are enthusiastic that the fast evolution of modern genome editing techniques, tailored experimental models, and Omics technologies, along with the ongoing developments in the areas of exposure assessment and gene-environment interaction studies will help to clarify these issues of global health relevance within the next years.

Declaration of competing interest

The authors declare that they have no competing interests.

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