The aryl hydrocarbon receptor at the forefront of host-microbe interactions in the skin: A perspective on current knowledge gaps and directions for future research and therapeutic applications

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Abstract
The skin is home to a community of skin microbiota including bacteria, viruses and fungi, which are widely accepted to be of importance for skin homeostasis but also associated with skin diseases. Detailed knowledge on the skin microbiota composition and its changes in a number of skin diseases is available. Yet, specific interactions between microbes and the host skin cells or how they communicate with each other are less well understood. To identify, understand and eventually therapeutically exploit causal relationships of microbial dysbiosis with disease, studies are required that address the receptors and mediators involved in host-microbe interactions. In this perspective article, we provide an outlook on one of such receptors, namely the aryl hydrocarbon receptor (AHR). The AHR is well known for being a ligand-activated transcription factor regulating the proliferation, differentiation and function of many cell types present in the skin. Its targeting by anti-inflammatory therapeutics such as coal tar and Tapinarof is effective in atopic dermatitis and psoriasis. AHR signalling is activated upon binding of wide variety of small chemicals or ligands, including microbiota-derived metabolites. New evidence has emerged pointing towards a key role for epidermal AHR signalling through skin microbiota-derived metabolites. In response, AHR-driven expression of antimicrobial peptides and stratum corneum formation may alter the skin microbiota composition. This a self-perpetuating feedback loop calls for novel therapeutic intervention strategies for which we herein discuss the requirements in future mechanistic studies.

KEYWORDS
antimicrobial peptides, aryl hydrocarbon receptor, epidermal differentiation, inflammatory skin diseases, microbiome, nuclear receptor
1 | INTRODUCTION

The skin is continuously challenged by the outside environment and harbours multiple receptors that aid in the communication with the environment and contribute to host defence. The aryl hydrocarbon receptor (AHR) has for many years after its discovery primarily been considered a receptor for xenobiotic pollutants, whose activation results in xenobiotic metabolism and elimination, but also taking part in cellular and tissue toxicity. The principle of AHR activation is well known. In brief, small molecular weight chemicals non-covalently bind to a pocket in the AHR protein, resulting in the release of chaperoning proteins, translocation to the nucleus, dimerization with its partner molecule, aryl hydrocarbon receptor nuclear translocator (ARNT) and ultimately the transcription of target genes. This basic signalling mechanism is fine-tuned by a plethora of cell-specific factors, such as competition for transcription co-factors, possibilities to interact with other signalling pathways such as NFkB and target gene accessibility. Importantly, the role of ligand characteristics (eg affinity, degradability and chemistry) for the dynamics of the signalling outcome needs further research.

Importantly, many natural and physiological AHR ligands and their sources were identified over the years (reviewed by Murray and Perdew). Key physiological events are mediated or co-regulated by AHR signalling, which in the in skin encompass cellular proliferation, differentiation, maturation and migration. Here, we focus on the evidence for AHR activation by skin microbiota as well as potential consequences of this activation for both host and microbiota related to skin health and disease.

2 | HOST AHR SIGNALLING VIA SKIN MICROBIOTA

AHR ligands produced by skin microbiota may permeate through the stratum corneum, epidermis and skin appendages such as hair follicles, sweat and sebum glands, which serve as a port of entry for skin microbiota to colonize the deeper layers of the skin. Most well known and studied microbial metabolites that modulate AHR through direct ligand binding are tryptophan metabolites, like indoles and kynurenines, mostly identified from (murine) gut microbiome studies. The AHR activating potential by tryptophan metabolites is complex as weak agonist (like indole) in the presence of a potent agonist will exhibit antagonist activity. However, the differences in ligand affinity between mouse and human AHR should be taken into consideration here as indole exhibits greater agonist activity towards the human AHR compared to the mouse AHR. Short-chain fatty acids (SCFA) produced by microbes, like butyrate, can enhance AHR activation indirectly when AHR ligands are present. Recently, evidence for quorum sensing by AHR was demonstrated for Pseudomonas aeruginosa whereby the AHR controls infection dynamics and orchestrates host defence. Most studies on the AHR-microbiome axis focus on the gut, where the AHR has been firmly established as a key receptor for gut microbial metabolites and regulator of organ homeostasis through modulating intestinal immunity, enhancing epithelial barrier function and inducing xenobiotic metabolism, a topic recently reviewed by Dong and Perdew. Besides local tissue-specific AHR targeting via microbial metabolites, systemic entry of metabolites formed at barrier organs, resulting in cross-compartment effects of gut microbiota on many organs (eg gut-brain axis, gut-lung axis, gut-skin axis), has far-reaching implications for understanding mechanisms of disease, and for the development of disease therapeutics and prevention strategies. Similar effects could hold true for skin-derived AHR ligands which may enter the bloodstream, although direct evidence is not yet available.

All barrier organs, and, in particular, the skin are continuously challenged by the exposome (or the collection of all environmental factors impacting human health) which also impacts the microbiome in its composition and metabolism, exemplified by dietary intake, environmental pollution and UV exposure. Epidemiological and experimental studies on exposome-associated AHR ligands (eg certain pollutants and dietary compounds, or UV radiation-generated endogenous tryptophan metabolites) and signalling thus need to consider the additional influence of exposome-mediated alterations in the microbiome and changes in microbial-derived AHR ligands thereof.

Studies addressing the AHR activating potential and downstream effects by skin microbiota are mostly performed by exposure of AHR reporter cells or primary skin cells to whole bacteria, bacterial lysates or purified metabolites, after which known AHR ligands with differences in receptor affinity and turnover times, like TCDD or FICZ are used to substantiate findings. Skin microbiota include a substantial fungal community, which is dominated by Malassezia species. Malassezia produce a variety of indole metabolites having AHR activating potential (eg indirubin, Malassezin, FICZ). Although Malassezia dysbiosis is associated with skin diseases (eg seborrheic/ atopic dermatitis), in dept studies on the effects of the metabolites formed by the different Malassezia species in skin or co-cultures of Malassezia isolates with (organotypic) skin are scarce. Evidence from studies on skin commensal bacteria indicate that AHR activation after skin cell exposure to commensal bacteria (eg S. epidermidis, S. warneri and C. aurimucosum) or specific microbial metabolites (eg indole-3-aldehyde) contributes to epidermal skin barrier function, negatively regulates immune cell responses and dampens (experimentally induced) skin inflammation. These effects are generally seen also for non-microbial-derived AHR ligands that are able to activate the AHR which provide a rationale to the therapeutic targeting of AHR for two major inflammatory skin diseases, atopic dermatitis and psoriasis both characterized by skin barrier defects and chronic inflammation. Furthermore, AHR activation upregulates antimicrobial peptides expression in keratinocytes, potentially altering skin microbiota composition and restoring dysbiosis in atopic dermatitis. Recently, also for hidradenitis suppurativa, another severe inflammatory skin condition, AHR therapeutic targeting was proposed. Changes in the skin microbiota are characteristic for the disease, with fewer bacteria present known
to produce beneficial AHR ligands from tryptophan suggesting a loss of AHR-mediated host-microbe communication through altered tryptophan catabolism. Altered tryptophan metabolism is a feature also associated with dysbiosis in atopic dermatitis. Hence, altered levels or composition of microbial-derived AHR ligands may contribute to disease pathophysiology. In other words, due to dysbiosis, ligand availability changes, which normally drive constitutive AHR signalling required for epidermal structural integrity and barrier function, as well as skin immunity. This concept was recently underscored by the finding that high levels of CYP1A1 enzymatic activity lead to exaggerated skin inflammation and phenocopy AHR deficient mice. The authors proposed that CYP1A1 may deplete the AHR natural ligand pool in the skin (eg microbial metabolites or the UV-irradiation generated molecule FICZ) by phase I metabolism and thereby release the break that AHR normally holds on skin inflammation. Unfortunately, metabolomic analysis to determine actual metabolite levels, composition and source were lacking and remain to be further explored. The need for active AHR signalling as protection against overt skin inflammation is further indicated by the vemurafenib-induced inflammatory skin rashes in melanoma patients. Vemurafenib was found to act as an AHR antagonist and elevated pro-inflammatory molecules in keratinocytes in vitro.

3 | MECHANISTIC INSIGHTS AND THE CHALLENGES OF EXPERIMENTAL APPROACHES

Overall, mechanistic insights into the molecular signalling events that drive AHR-mediated effects in skin are still under-explored. This is of particular interest given the promiscuity of the AHR towards various ligands and its canonical (through dimerization with ARNT) and non-canonical signalling pathways, as mentioned before. Up or downstream interaction of AHR with signalling pathways important for skin structure and function demonstrate the need for in depth molecular analysis to pinpoint AHR’s mode of action in host-microbe interactions. Herein, the setup of studies is a crucial factor in providing key evidence for microbiota-driven AHR activation contributing to skin homeostasis. The interspecies differences in receptor affinity known for the murine and human AHR should be taken into consideration when extrapolating study findings from mouse to human. Alternatively, humanized AHR mice or low affinity (human) variant (Ahr<sup>ld/d</sup>) may better predict AHR activation from host-microbe interactions and its consequences for human health and disease. In addition, human organotypic skin models for microbiome research emerge as alternatives to mouse models. Studies using purified metabolites at artificial concentrations and specific time of dosage indeed provide proof-of-concept on the potential for AHR activation. However, the resulting effects may not reflect the actual mode of action as metabolite concentration, turnover, bioavailability and interaction with other microbial metabolites and host proteins are not captured. In addition, studies on single bacterial (laboratory) strains or mixtures thereof may be less representative as bacterial transcriptomes are influenced by the host environment and tissue state. Indeed, individual clinical isolates may differ, and reflect interpersonal differences regarding the production of metabolites capable of AHR activation.

To date, only few studies exist addressing AHR signalling in skin investigated patient cohorts from a microbiome perspective. Because these had only small sample numbers (<20 per group), there is a need for integrated multi-omics approaches to investigate and correlate microbiome composition (16S rRNA gene sequencing or ideally metagenomics) with microbial metabolome and host transcriptome/epigenome. Given the wide expression of AHR in a multitude of cell types in skin, conventional transcriptomics studies using bulk RNA from full skin biopsies may mask potential cell type-specific effects hence favouring single-cell approaches. Functional analysis of in vivo host-microbe signatures in organotypic models of human skin can provide proof-of-principle data to pinpoint the role of the AHR using genome editing strategies or selective AHR inhibition. The first would be preferred given potential unspecific targeting by pharmacological inhibitors that might mask the actual AHR-mediated signalling events and its downstream cellular effects.

4 | SELF-PERPETUATING FEEDBACK LOOP FROM AHR ACTIVATION TO MICROBIOME COMPOSITION

Besides the above-discussed function of the AHR in communicating signals from the microbiome to the host, the known downstream effects of AHR activation on the epidermis and stratum corneum formation could provide a feedback mechanism controlling the skin microbiome composition. Although ligand promiscuity of microbial metabolites may also be a factor to consider, AHR activation is involved in the transcription of genes for epidermal differentiation proteins, lipid synthesis and sebocyte differentiation. Expression of these genes may change stratum corneum structure, lipid and amino acid content, skin surface pH and sebum levels. Of note, these are all processes, which ultimately can affect the skin microbiome composition. Specifically, the induction of filaggrin may be of importance considering the key functions of this protein in generating natural moisturizing factor (NMF) by its proteolytic cleavage and deamination during keratinocyte terminal differentiation. NMF is important for skin barrier function and NMF levels inversely correlate to AD disease severity. Recently, adhesion of <em>Staphylococcus aureus</em> to the stratum corneum was found to correlate to NMF levels. Low levels of NMF are found in skin of atopic dermatitis (AD) and ichthyosis vulgaris (IV) patients which harbour loss-of-function mutations in the <em>filagrin</em> gene or have downregulated filaggrin levels due to the local inflammatory milieu. Skin microbiome dysbiosis in IV patients is characterized by a low abundance of specific bacteria, called gram-positive anaerobic cocci (GPAC). GPAC abundance correlated to NMF levels in a dose-dependent manner, possibly due to their nutrient requirement for histidine, one major constituent of NMF. Also in AD, GPAC
are less abundant. It would be highly interesting to investigate if AHR targeting drugs in AD, like in the Tapinarof trials, restore microbial dysbiosis, whether GPAC levels return to normal, and if this coincides with normalized filaggrin expression and NMF levels in the stratum corneum. The study on the effects of coal tar treatment (and AHR activation) on the microbiome of AD patients and healthy volunteers did not detect differences in GPAC before or after treatment, albeit this study was underpowered to detect such differences and the time period of treatment may have been too short. Of note, therapeutic AHR ligands like polycyclic hydrocarbons in coal tar and Tapinarof may also exert direct effects on the microbiome by their antimicrobial activity, adding even more complexity to the various modes of AHR-directed host-microbe interplay, its involvement in disease pathophysiology and therapeutic potential (Figure 1).

Next to the potential AHR-mediated changes on the feeding ground of skin microbiota, the innate host defence mechanisms by means of the skin AMP repertoire can be modulated by AHR signalling. Major epidermal AMPs like beta-defensins, S100 proteins and SKALP/elafin are inducible by AHR ligands, although this induction could coincide with the driving forces of AHR agonist on keratinocyte terminal differentiation. This AHR-mediated expression of genes within the epidermal differentiation complex (EDC) locus on chromosome 1 including filaggrin, hornerin and late cornified envelope proteins further aids in the antimicrobial defence. For long, these proteins were considered classical terminal differentiation proteins, involved in structural integrity of the epidermis and formation of cornified envelopes. Recent findings highlight their antimicrobial activity and classifying them as so-called cationic intrinsically disordered AMPs or CIDAMPs.

These studies clearly point towards a concept where the AHR provides the skin with a communication hub for bi-directional interactions with its microbiota. Considering that the AHR is utilized as a target for intervention, mostly using specific agonists for dampening skin inflammation, we must consider the additional effects of this new drug class on the microbiome, which could feed into a self-perpetuating feedback loop—either beneficial or like a vicious circle. Therapeutic approaches can be topically, or via the diet, exploiting the gut-skin axis. Beyond using AHR agonists, probiotic bacteria (with known potential for AHR metabolite formation) might be useful in manipulating the microbiome-AHR-skin health axis. Alternatively, prebiotic strategies steering the growth of skin microbes, which produce desirable AHR-modulating metabolites may provide new therapeutic modalities for the dermatology field. Herein, it is of importance to critically address the characteristics of the induced ligand-activated AHR signalling considering the adverse effects of uncontrolled AHR activation in the skin. Finally, several lines of evidence provide a mechanistic and therapeutic rationale for specific lifestyle interventions in patients with chronic inflammatory skin conditions. These are (i) anti-inflammatory effects...
of dietary intervention studies with AHR ligands, (ii) the ability to modulate AHR ligand production in the gut by dietary intake and (iii) the known systemic entry of AHR ligands produced in the gut (or via second-pass effects in the liver) and beneficial effects on skin function.

5 | CONCLUSION

The ligand-activated transcription factor AHR is a sensor for parts of the exposome, and intrinsically important for skin health and homeostasis, but may also mediate adverse functions depending on the context, for example chronic exposure to xenobiotic ligands. Evidence emerges that microbes of the skin are a relevant source of AHR ligands, thereby ensuring that their own habitat remains stable. In inflammatory skin diseases with characteristic dysbiosis, such as atopic dermatitis or psoriasis, this balance is perturbed. Understanding that the relationship between AHR and the skin microbiota is reciprocal will help define future experiments and research. Ultimately, therapeutic approaches might seek to balance the skin microbiome and re-balance its AHR-beneficial signature.

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CONFLICT OF INTEREST

Authors have no conflict of interest.

AUTHOR CONTRIBUTIONS

EB conceived and wrote the manuscript. CE and GP critically reviewed and edited the manuscript. CE and EB designed the figure.

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