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The Human Aryl Hydrocarbon Receptor (AHR) and its Role in Skin Homeostasis

Coatmeur R[1], Sauzet C[1], Viton A[1], Piccerelle P[1], Rapetti L[2]* and Villard PH[1]*

[1]*IMBE-UMR CNRS 7263, IRD 237 Aix-Marseille Université Campus Timone, Faculté de Pharmacie, Marseille, France.*

[2]*Alphenyx, Marseille, France.*

*Correspondence:

Coatmeur Raphaël, Aix-Marseille Université, 27 boulevard Jean Moulin, 13005 Marseille, France, Tel: 06-81-29-55-77.

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ABSTRACT

The aryl hydrocarbon receptor (AhR) is a transcription factor activated by the binding of low molecular weight molecules that could be environmental chemicals, molecules of plant origin or endogenous compounds. AhR is strongly expressed in tissue barriers, such as lungs, intestinal gut, and skin. It was identified as the key regulator of certain xenobiotic metabolism enzymes. The signaling pathway regulated by AhR is thus considered an adaptive response to these xenobiotics. More recently, several studies have highlighted the AhR involvement in inflammatory processes, which can lead to the development of chronic inflammatory pathologies and skin cancers. Given the growing importance of environmental pollution, AhR's involvement in xenobiotic metabolism and inflammation gives it a crucial role in skin homeostasis. During this review, we will discuss about different AhR ligands families, its activation/repression mechanisms, and its target genes. Subsequently, we will focus on interactions between AhR and other signaling pathways and its involvement in inflammatory skin pathologies. Taken together, it strongly suggests that AhR is an emerging suitable target to handle inflammatory skin diseases.

Keywords

AhR, Environmental pollution, Inflammation, Cutaneous pathologies.

Introduction

The Aryl Hydrocarbon Receptor (AhR) belongs to the superfamily of basic-helix-loop-helix - Per- ARNT-Sim (bHLH-PAS) transcription factors. These proteins are involved in the control of various physiological processes such as organ development, circadian rhythms, metabolism and in the response towards hypoxia.

AhR activation is triggered by the binding of a wide range of low molecular weight molecules including environmental chemicals (like dioxins or polychlorinated biphenyls), molecules of plant origin (flavonoids or indigo) or endogenous compounds, such as oxidized tryptophan derivatives [1]. In humans, the gene coding for AhR is located on chromosome 7 and its expression is described in 232 tissues [2]. AhR is in particular highly expressed in the barrier tissues including lungs, intestines, colon, and skin. In the skin, several cell types of the epidermis and the dermis express AhR at various levels, such as keratinocytes, Langerhans cells, melanocytes, sebocytes and fibroblasts [3,4].

AhR has been identified as the key regulator of some enzymes in the xenobiotic metabolism, in particular cytochromes P450 (belonging to the CYP1 family), which are involved in the bioactivation of various environmental pro-carcinogens, including polycyclic aromatic hydrocarbons (PAHs) and arylamines. The AhR signaling pathway has thus been considered as an "adaptive" response to these xenobiotics [5] and therefore AhR was initially described as an chemo-sensor to environmental pollutants [3,5]. More recently, several studies have also highlighted its role in the regulation of several genes involved in the inflammation and the immune response. [1,5,6] In addition, it has been shown that the transcription of AhR target genes depends on the ligand nature, the cells type and environment. In any case, it is clear that AhR links the detection of specific chemical signatures to critical body functions

[7,8]. AhR represents thus an interface between the environment and the organism and it could be recognized as an attractive target for the treatment of certain human diseases including cancers and chronic inflammatory syndromes [5].

In this this review, we will first present the different families of AhR ligands. We will then discuss on AhR regulation and its main target genes and functions, before examining its link with other signalling pathways and epigenetic regulation. We will eventually examine the effects of AhR activation by environmental xenobiotics and more specifically the role that AhR plays in inflammation and certain skin pathologies.

AhR ligands

There are three main routes of exposition to exogenous compounds: digestive, pulmonary, and cutaneous. Increased environmental pollution leads mainly to increased dermal and pulmonary absorption of environmental pollutants. In addition, the intensive use of pesticides in agriculture favours the absorption of compounds via the digestive tract. The activation of AhR by various xenobiotics present in our environment, like PAHs and dioxins, has been widely described for 20 years. Evidence of endogenous ligands has more recently emerged.

Polycyclic Aromatic Hydrocarbons

PAHs are mainly formed by pyrolysis (thermal decomposition) and pyro-synthesis (recombination into new products) during the incomplete combustion of organic materials, such as fossil fuels or animal fats. Their sources are essentially anthropogenic, even if natural combustion (forest fires, volcanoes….) can occasionally lead to a large production of PAHs as shown in Table 1 [9]. PAHs bind to AhR with an affinity ranging from nM to µM. For the general population, the ways of exposure to PAHs are essentially digestive or pulmonary. PAHs are produced with the pyrolysis of fats, when cooking and ingested. Pulmonary exposure through smoking and atmospheric pollution (diesel particles, microparticles from combustion processes), is very important in particular in urban and peri-industrial areas [10]. Cutaneous exposure to PAHs is quantitatively less important, but not negligible, especially because of their presence in car exhaust gases or cigarette smoke.

Table 1: Sources of polycyclic aromatic hydrocarbons production from human activities.

Industrial sources	Domestic sources
Tyre manufacturing	**Heating (natural gas, LPG, wood, coal...)**
Steel industry	**Smoking**
Cement works	**Cooking of food (barbecue, frying)**
Combustion engines	
Petrochemical industries	
Household and industrial waste incinerators	
Aluminium production	
Cars (exhaust fumes), trains...	

Dioxins

Dioxins and "dioxin like compounds" (DLC) are compounds of mainly anthropogenic origin, dioxins are generated by industrial thermal processes, such waste dismantling, metal smelting processes, and waste incineration.(11) Dioxins include polychlorinated dibenzo-para-dioxins (PCDDs) and polybrominated dibenzo-para-dioxins (PBDDs). DLC are structurally and chemically related to dioxins and include polychlorinated dibenzofurans (PCDFs) and planar polychlorinated biphenyls, known as dioxin-like PCBs. These molecules are Persistent Organic Pollutants (POPs) which have a very high persistence in the environment and a very high lipophilicity associated to a poor degradation leading to their accumulation all along the food chain, which is called "biomagnification" [11]. The general population is thus mostly exposed through its diet, but cutaneous exposition also occurs notably in urban and industrial sites. Dioxins and DLC have a strong affinity for AhR, ranging from nM to pM [12].

Natural Ligands

AhR also possesses naturally occurring agonist ligands, mainly provided by the diet. Among the high affinity natural ligands described, the indolo-(3,2b)-carbazole (ICZ), results from the degradation in the digestive tract of the indole 3-carbinol (I3C), which is found in plants belonging in particular to the *Brassicaceae* family (formerly known as *Cruciferae*) and include vegetables such as cabbage, horseradish or turnip [13].

However, these naturally occurring ligands also include AhR antagonists. For example, resveratrol (3,5,4' trihydroxystilbene) and Kaempferol [14,15].

In the skin, the absorption of such molecules is rare. However, it can occur through cosmetic products since many of these substances have antioxidant properties. For example resveratrol is able to inhibit the nuclear factor-kappa B (NF-κB) pathway in keratinocytes, but also by degrading the Keap1 protein which leads to an accumulation of NRF2 in the nucleus and protects the cell against oxidative stress [16].

Endogenous Ligands

Although AhR was initially referred as an orphan receptor, it has now been clearly demonstrated that AhR can also modulate cell proliferation in the absence of any xenobiotic or natural exogenous ligand [17]. Indeed, endogenous ligands have been recently described, such as bilirubin or biliverdin [18], but also the oxidized derivatives of tryptophan, which can be released notably during exposure to UV-B radiation [19].

6-formylindolo[3,2-b]carbazole (FICZ), produced during the oxidation of tryptophan by ultraviolet rays and therefore produced naturally in the skin and also by several yeasts from the skin microbiota [20] such as *Malassezia furfur* [21].

AhR Regulation and Functions

The bHLH-PAS proteins, of which AhR belongs, are latent cytoplasmic transcription factors that migrate into the nucleus upon their activation.

Activation Mechanisms

In the absence of any ligand, AhR is maintained inactive in the cytosol, associated in a complex formed by a dimer of the heat shock proteins Hsp90, the XAP2 protein and the co-chaperone protein P23 [5,22]. The composition of this complex is still subject to debate; some studies highlight the presence of one or more other components, but without any real evidence. This complex mask AhR DNA binding domain, while keeping the receptor in a conformation accessible to its ligands [23].

AhR ligands penetrate the cell membrane by passive diffusion, certainly due to their hydrophobic properties [22]. When a ligand binds AhR (Figure 1), the conformation of the complex is then modified, exposing one or more nuclear localization sequences, which are activated by phosphorylation via the P38-MAPK pathway kinases, presumably ERK1 and ERK2 [24]. The complex then translocates into the nucleus, where AhR dimerizes with its nuclear partner Ah receptor nuclear translocator (Arnt). The heterodimerization of AhR with Arnt also leads to the dissociation of the Hsp90, p23 and XAP2 proteins, facilitating AhR/ARNT interaction and the complex [ligand - AhR - ARNT] conversion into a high affinity DNA binding form [25].

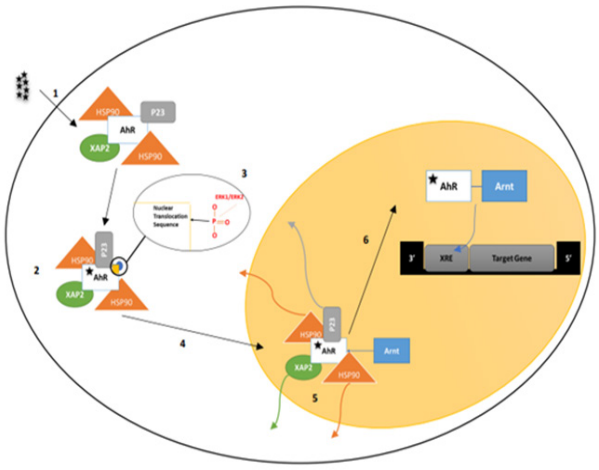

Figure 1: Schematic representation of the AhR activation mechanism: (1) the ligand penetrates the cell by passive diffusion and binds to the complexed AhR binding site (2) modification of the conformation of the AhR inactivation complex, exposure of the nuclear transfer sequence (3) phosphorylation of the AhR nuclear transfer sequence, carried out by a kinase (4) translocation of the [AhR-ligand] complex into the nucleus (5) dimerisation of AhR with Arnt, dissociation of the AhR inactivation complex (6) binding of the [ligand-AhR-Arnt] complex to the DNA at the XREs and transcription of the target genes.

The [Ligand - AhR - ARNT] complex can thus activate the expression of a wide variety of genes containing in their promotors a xenobiotic response element (XRE) sequence, also known as a Dioxin Response Element (DRE). Binding of the [Ligand - AhR - ARNT] complex at the XREs leads to DNA bending, recruitment of co-activators, chromatin and nucleosome disruption, increased the promotor accessibility to general transcription factors and therefore increased levels of gene transcription [19,26]. This mechanism is considerated as the AhR canonical signaling [27,28]. Although the vast majority of toxic effects caused by environmental ligands of AhR are regulated by this canonical AhR-Arnt signaling, several studies have identified a number of AhR target genes that do not contain obvious XRE sites [29,30]. This indicates the existence of non-canonical AhR signaling, which may consist of AhR interacting with other signaling pathways without the intervention of Arnt.

For example, studies have shown that AhR can associate with the retinoblastoma protein (pRB) hypo-phosphorylated form, resulting in growth arrest in the GL/S phase of the cell cycle [31,32]. NF-κβ is another example of a protein that can interact directly with AhR in the ARNT absence; indeed, AhR can associate with the NF-kB factor subunit, RelB, and bind directly to a promoter located in the interleukin-8 gene regulatory region [33]. AhR can interact with a number of signaling pathways, such as retinoid and estrogen receptor or NRF-2, some of which will be presented elsewhere, in both an Arnt-dependent and Arnt-independent manner. However, there is evidence for AhR action via epigenetic mechanisms, such as the methylation. In eukaryotes, methylation of a gene promotor leads to its repression, and inversely for demethylation. The DNA methylation process is catalyzed by DNA methyltransferases (DNMTs) [34] on CpG sites and is strongly influenced by environmental factors, such as smoking, which increases genes methylation levels. Alterations of DNA methylation is involved in the development of several pathologies, including autoimmune diseases and cancers [34], such as Systemic Lupus Erythematosus (SLE). It is an auto-immune disease characterized by uncontrolled lymphocyte autoreactivity that triggers inflammation and tissue damage in many parts of the body. DNA hypomethylation take an important place in this pathology [35]. AhR activation following UV exposure activates the deacetylase SIRT1, which in turn repress the acetylated DNA-methyltransferase DNMT1 and thus to a hypomethylation in T CD4+ lymphocytes from SLE patients [35]. This also links AhR to histone acetylation, another epigenetic mechanism.

Target Genes and Functions

The AhR protein presence in a wide variety of tissues suggests that its biological and toxic effects result from differential alterations in gene expression in susceptible cells depending on their subtypes [3]. The ligand nature and the AhR activation duration also determine the level and spectrum of the genes which are induced. These two parameters are thus essential in the AhR activation outcome, including toxic effects [3].

Several studies, using DNA chips, have revealed a large number of genes that are induced or repressed in an AhR-dependent manner, directly or indirectly [22,36]. XRE sequence-scale analysis has identified a large set of genes, involved in physiological functions and detoxification of environmental pollutants that may respond to AhR. Although many AhR-sensitive genes have been discovered, their number is certainly still underestimated. All the genes mentioned below are summarized in Table 2.

Self-regulation

Several studies show that AhR expression increases following its activation by environmental pollutants [37]. This "self-induction" is certainly an adaptative mechanism to better respond to the presence of exogenous ligands by increasing its own synthesis.

The AhR repressor (AhRR) is also an AhR target gene. Contrary to AhR, AhRR can bind AhR ligands, but cannot bind the DNA due to the absence of the PAS B domain in its N-terminal region [40]. It will therefore compete with AhR both for the ligands and the ARNT binding site and form a transcriptionally inactive complex [64], which stops the transcription of AhR target genes. Several studies show that AhRR expression is induced by the action of a multitude of AhR agonists [65]. Although few studies have investigated the timing of AhRR activation, it is likely that the AhRR gene is transcribed after the others to switch off the signal and avoid its persistence. AhRR plays an important role in AhR repression mechanisms [65], and would thus participate in a mechanism of self-regulation loop which maintains the physiological balance.

Metabolism of Xenobiotics

AhR plays a key role in the organism defense towards xenobiotics by regulating the numerous genes expression of phases I and II of metabolism. Phase I enzymes regulated by AhR include numerous CYPs, such as CYP1A1, CYP1A2 and CYP1B1 [42,44], which metabolize xenobiotics into inactive or active metabolites. Among the phase II enzymes regulated by AhR, UGT family members [46] are responsible of glucuronidation pathway that transforms small lipophilic molecules into water-soluble and so excretable metabolites. AhR also regulates Glutathione S-transferase A1/2 (GSTA-1/2) expression, which is involved in electrophile compounds detoxification and the ATP-binding cassette super-family G member 2 (ABCG-2). ABCG-2 is a cellular efflux transporter involved notably in multidrug resistance and is also called BCRP (breast cancer resistance protein) [47,48].

Even if the primary function of theses enzymes is to detoxified xenobiotic molecule to protect the organism, several of them can also have pathological effects in certain conditions. These pathological effects might result from the ability of some AhR agonists (TCDD and DLC) to persistently activate/repress the expression of key AhR-sensitive genes. For example, the metabolic conversion of procarcinogens into genotoxic reactive intermediates can lead to tumors development [66].

Inflammation and Immunity

Cytokines are produced by a broad range of cells, including immune cells, endothelial cells or keratinocytes, in response to an activating signal [67]. They act through cell surface receptors and have a key role in the immune system, specifically in host immune responses to infection, inflammation, or trauma and cancers. AhR can modulate expression of a large panel of cytokines, including interleukins (ILs), tumor necrosis factors (TNF) or chemokines (CCL, CXCL) and interferons (IFN) in various cells and organs [49]. Most cytokines regulated by AhR are pro-inflammatory cytokines (IL-1β, TNF-α), but some have anti-inflammatory properties like the tumor growth factor β (TGF-β) and IL-10 [49].

Basically, immunity is regulated by a specialized subset of T lymphocytes called regulatory T cells (T_{regs}) [68]. T_{regs} regulate the proliferation of other lymphocyte populations after an immune response and inappropriate responses against non-harmful unself and self. Dysregulation of T_{regs} can cause excessive inflammation, allergy, or autoimmunity. The differentiation and function of T_{regs} are mainly controlled by the transcription factor Foxp3 [69] and mutations in this gene have been linked to immune deregulation and autoimmune syndromes [70,71].

A study using phylogenetic fingerprinting showed that Foxp3 has an AhR-specific XRE site located in its promotor regions [72]. Therefore, AhR activation could directly play an important role in the regulation of Foxp3 expression. In addition, another study show the implication of TGF-β in the differentiation of T_{regs} [73]. TGF-β being an AhR target gene, it is thus probable that AhR activation induces TGF-β expression, which in turn increases T_{regs} differentiation.

T helper 17 cells (Th17) are a specialized subset of T lymphocytes

Table 2: Target genes of AhR with their functions and localization in human organism.

AhR Target Genes	Functions	Localization	References
AhR	**Transcription factor**	Liver, lung, skin, intestinal tract	[37]
AhRR	**Self-Repression**	Liver, lung, skin, intestinal tract	[38-41]
CYP1A1 / CYP 1B1 / CYP1A2	**Phase I enzymes, xenobiotics metabolism**	Liver, lung, kidney, brain, intestinal tract	[42-44]
UGT	**Phase II enzymes, xenobiotics metabolism**	Liver, kidney, digestive tract	[45,46]
GSTA 1/2	**Phase II enzymes, xenobiotics metabolism**	Liver, kidney	[47]
ABCG-2	**Phase II enzymes, xenobiotics metabolism**	Intestinal tract, liver, kidney, mammary glands	[48]
Interleukins: IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IL-17, IL-22	**Inflammation and immune response (chemotaxis, cell activation and differentiation…)**	Macrophages, dendritic cells, T & B lymphocytes	[49-54]
Chemokines: CCL1, CCL2, CCL5, CXCL1, CXCL3, CXCL4, CXCL5, CXCL8 (IL-8), CXCL12, CXCL13	**Inflammation and immune response (chemotaxis, cell activation and differentiation…)**	Macrophages, dendritic cells, T & B lymphocytes	[33,49,50, 54-57]
Other cytokines: TNF-α, BAFF, INF-ϒ, TGF-β	**Inflammation and immune response (chemotaxis, cell activation and differentiation…)**	Macrophages, dendritic cells, T & B lymphocytes	[49,50,58-63]

that are involved in the control of extracellular pathogens and play an important role in the activation of inflammation. Dysregulation of these cells could trigger autoimmunity [74,75]. Since the early 2000s, several studies seemed to indicate that AhR promotes Th17 cell differentiation [76,77]. Indeed, it was shown, that AhR activation by FICZ, an AhR high affinity ligand, in CD4+ T murine and human cells, causes an increase of the Th17 proportion and an significant augmentation of IL-17 and IL-22 production [78]. In addition, another study demonstrated that a combination of TGF-β and IL-6 or IL-21, whose expressions are regulated by AhR, seems to be able to induce Th17 cell differentiation [79]. Several other studies indicate that AhR seems to regulate T $CD4^+$ cells differentiation into T_{regs} or Th17, depending on the ligand which activates it [6,76].

Repression Mechanisms

As explained previously, AhRR induced by AhR itself will inhibit the heterodimerization of AhR with ARNT, the [AhRR-ARNT] complex being transcriptionally inactive [40,64] which is a first mechanism of retro-control.

AhR-dependent genes transcription generally ends with the dissociation of the [Ligand - AhR - ARNT] complex from XREs and the export of AhR from the nucleus into the cytosol, mediated by a N-terminal nuclear export sequence. Once in the cytoplasm, AhR is ubiquitinated and degraded by the 26S proteasome. The proteasome is itself activated following the transcription of target genes by AhR, suggesting a second mechanism of retro-control. The AhR protein degradation by the proteasome leads to a significant decrease in AhR-dependent proteins [80,81].

A last mechanism of AhR repression would be the metabolism of its ligands. AhR ligands present in the cells can be degraded by CYP1 family enzymes [39]. Indeed, It has been shown that CYP1 family enzymes inhibition leads to a preservation of the concentration of extracellular ligands and prolongs the activity of AhR, in particular in keratinocytes [82].

AhR Interaction with other Signaling Pathways

AhR ability to interact with and modulate other signaling pathways following its activation is well known [83,84]. A large majority of the toxic effects induced by "environmental" AhR ligands probably results from a complex interaction with several signaling pathways and key regulatory factors; therefore, these effects involve a combination of direct and indirect AhR-dependent mechanisms [22,85,86]. In this section, we will not present all the signalling pathways with which AhR interacts, but only those most relevant to skin inflammation.

NF-κB

The NF-κB transcription factor is involved in several mechanisms of the immune response, including inflammation. NF-kB is a heterodimer formed by Rel and p50 proteins. In the cytosol, inactive NFκB is bound to its inhibitor, IkB which prevents NF-kB nuclear translocation [87,88]. Various cell signals, such as cellular stress or inflammation, can activate the enzyme IkB Kinase (IKK) which phosphorylates IkB leading to its ubiquitination and its degradation. NF-κB is then released and able to translocate into the nucleus [87]. It binds to a specific sequence, the Response Elements (RE), present in the promotor of certain genes, like B lymphocyte-induced maturation protein-1 (BLIMP-1) [89] or Interferon-ϒ (INF-ϒ) [90], and initiates their transcription.

It had been shown that mutation in the NFκB DNA binding sites or blocking NFκB activation inhibit AhR activation following exposure to phorbol 12-myristate 13-acetate (PMA), in the CACO-2 tumoral epithelial cells [5]. Several in vitro studies suggest that pro-inflammatory conditions induce AhR expression via NFκB. PAHs, such as benzo(a)pyrene activate AhR, which induces the expression of CYP1A1 and CYP1B1. Both enzymes will transform or metabolize PAHs into diol-epoxides, such as benzo(a)pyrene diol-epoxide, resulting in NFκB activation [5,91]. The activation of NFκB promotes an inflammatory loop via IL-1β expression and induces in turn AhR expression suggesting a potentiating effect.

AhR can also be found dimerized with several NFκB sub-units, in particular RelA [5,92] and RelB [5] leading to distinct effects. Indeed, the consequence of RelA/AhR interaction appears to be mainly antagonistic, with, for example, the downregulation of the expression of several genes such as CYP1A1 or IL-6 [92]. On the other hand, AhR/RelB interaction improves CYP1A1 activity and the transcription of several target genes of NFκB, such as IL-8 [91,93]. To explain these opposite effects it was hypothesized that AhR promotes the function of RelB both to trigger chronic inflammation and then to resolve inflammation via a negative feedback mechanism [94,95]. To the contrary, AhR may antagonize RelA action to moderate cellular inflammation after stimulation by potent inflammation inducing agents (LPS). This hypothesis could explain antagonist effects between RelA and AhR and synergetic effects between RelB and AhR [91].

PPAR-α

Peroxisome proliferator-activated receptor alpha (PPAR-α) is a transcription factor expressed by several tissues including adipose tissue, liver, and colon. It is a major regulator of lipid and carbohydrate metabolisms. PPAR-α is activated under conditions of energy deprivation and is necessary for ketogenesis, a key adaptive response to prolonged fasting in adipose tissues and liver. In addition, PPAR-α is also expressed in several immune cells, like macrophages and is involved in the anti-inflammatory response [96].

PPAR-α binds DNA on PPAR Response Elements (PPRE) promotor sites. Analysis of human AhR promotor revealed one PPRE site and that PPAR regulates its own expression by increasing AhR expression [97]. This PPRE seems to play an important role in AhR expression, as its mutation led to the suppression of AhR activation by PPAR-α agonist. PPAR-α could also regulate the expression of CYP1A1; indeed, two PPRE sites were identified at the CYP1A1 promotor [98]. This explains the observed potentiation of CYP1A1 activity with a co-exposure to an AhR agonist and a PPAR-α agonist in Caco2 cells [99], demonstrating the interaction between AhR and PPAR-α signaling pathway.

NRF2

The ubiquitary transcription factor nuclear factor (erythroid-derived 2-like 2 (NRF2) is a main switch for inducing antioxidant enzymes, like NAD(P)H dehydrogenase [quinone] 1 (NQO1) or electrophilic species detoxification enzymes, such as glutathione S-transferases. NRF2 forms an inactive complex with Kelch-like ECH-associated protein 1 (KEAP1) and Cullin 3 (CUL3). The cell oxidative state, i-e an imbalance between the production of free radicals and the antioxidant response, leads to the oxidation of the cysteine residues in the KEAP1 molecule, modifying its conformation and causing the dissociation of NRF2 from the complex [100,101]. Once free and activated, NRF2 enters into the nucleus and triggers the transcription of anti-oxidant genes.

Some studies have shown that AhR activation by certain types of ligands, such as flavonoids or azoles can initiate the activation of NRF2 signaling pathway, and thus participate to the antioxidant responses without initial production of ROS [101-103]. On the other hand, oxidative stress, caused by AhR agonists, like dioxines or PAHs, also leads to NRF-2 activation in response to AhR.

NFR2 agonists can also influence AhR signaling pathway, but with different effects. They can be differentiated into three categories. The first category consists of NRF2 agonists with AhR-agonist activity, like cynaropicrin, soybean tar glyteer or *Opuntia ficus-india*. They inhibit the ROS production caused by BaP, TCDD and TNF-α, by increasing the expression of NQO1 [103-105]. The second group is composed of NRF2 agonists with AhR-antagonist activity, like cinnamaldehyde or epigallocatechin gallate. They inhibit the AhR action and increase the heme oxygenase 1 (HO-1) expression [101]. For example, it has been showed that cinnamaldehyde, besides upregulating HO-1 expression via the regulation of NRF2 translocation, downregulates the oxidative stress caused by HAPs and reduced the AhR nuclear translocation in human keratinocytes [106]. The third group comprises NRF2 agonists with an indirect agonist effect on AhR signaling pathway, like Z-Ligustilide, quercetin, kaempferol or resveratrol. They act by inhibiting CYP1A1 activity. An activation of NRF2/HO-1 pathway leads to the inhibition of both NF-κB pathway and CYP1A1 expression [101,107,108]. By decreasing the expression of CYP1A1, they inhibit the degradation of endogenous AhR ligand such as FICZ, which leads to AhR activation.

AhR and Skin Diseases

The skin performs several functions including body protection (skin barrier), thermoregulation and sensitivity [109]. The skin is indeed the body first line of defense against aggressions such as pathogens, toxins, radiation and harmful pollutants.

For many years, the involvement of AhR in chloracne has been demonstrated and well documented. More recently, the role of AhR in several skin diseases, such as certain skin cancers or autoimmune disorders, has emerged.

Chloracne

Acneiform lesions and cysts were first described in 1899 and called "chloracne" by the dermatologist Karl Herxheimer. Chloracne is the most likely toxic phenomenon occurring after acute or chronic exposure to high doses of dioxins [110]. Its gravity being correlated to the blood level of dioxin [111]. This pathology is characterized by a interfollicular epidermis hyperkeratinization and a sebaceous glands metaplastic response [112,113]. A hyperproliferation and hyper-keratinization of the hair follicle cells are observed and a sebocytes progressive loss with narrowing of the sebaceous glands and infundibular dilatation, possibly leading to the formation of blackheads [114,115]. These cell alterations coincide with the pathological characteristics of chloracne [110,113].

As mentioned previously, chloracne lesions are caused by exposure to dioxins, but also furans [110,116]. In addition, it is known that AhR is abundantly expressed in keratinocytes and sebocytes [114,117]. Upon activation of AhR by dioxin, sebocytes first start to loose keratin 7 and epithelial membrane antigen (MUC1) expressions and their ability to produce sebum by lipogenesis. Then, they progressively convert into a keratinocyte phenotype, expressing keratin 10 and PPARδ [117]. A study conducted on a man who was exposed to a very high dose of TCDD (more than 5 million times the daily dose) for 5 years showed that certain AhR target genes, including those coding for CYP1A1, 1B1 and 1A2, were overexpressed in skin lesions [118]. Several genes coding for the main enzymes of sebaceous lipid synthesis, containing XREs in their promotors, have also been strongly repressed: ELOVL3, AWAT1, ALOX15B, FADS2, SOAT1 [118]. The transcriptional repression of lipid metabolism, induced by dioxins, may be the mechanism leading to the sebaceous glands atrophy. This would also be consistent with the previously reported negative effect of AhR signaling in adipogenesis [18].

AhR and Skin Cancers

It has been clearly established that skin chronic exposure to factors such as UV radiation, airborne pollutants (tobacco smoke, diesel particles…) leads to damaged macromolecules accumulation and the loss of cell and tissue integrity. Occupational diseases, has been observed, for example in workers handling creosote (tar used as a wood preservative biocide) or farmers using pesticides without Personal Protection Equipment [119]. Over time, this exposure can facilitate the aging process and the development of malignant tumors that are partly related to aging [120]. These elements clearly indicate an important role for AhR in the development of environmentally-induced cancers have been reviewed [121-123].

Bioactivated Molecules

AhR and downstream cytochromes P450 (CYPs) have been shown to be essential for PAHs and associated environmental pollutants bioactivation in skin carcinogenesis. PAHs are bioactivated into electrophilic metabolites by CYP1 enzymes. However, some generated epoxides cannot be detoxified by epoxide hydrolases. They can further bind to DNA and cause alterations leading to cancer [10,124]. In addition, reactions induced by CYPs may

cause a higher production of ROS, resulting in additional oxidative damages to DNA and other macromolecules [124,125].

Currently, it is widely accepted that dermal exposure to environmental PAHs or PAH-containing formulations may result in squamous cell carcinomas. Concerning cosmetic products, the use of PAHs in formulation has been forbidden by the European Parliament since 2009, but some treatments for skin diseases could still contain members of this family. For example, the Goeckerman regimen for the treatment of severe psoriasis consists of a combination of UV-B exposure and topical application of coal tar, a substance containing various PAHs [126].

Squamous Cell Carcinomas (SCC)

Skin squamous cell carcinoma (SCC), also known as spin-cell carcinoma, is the second most common skin cancer after basal cell carcinoma (BCC). In the United States, for example, it is estimated that 50 000 new cases of SCC occur each year [127]. This type of skin cancer develops from keratinocytes composing the spinous layer of the epidermis. SCC can affect all body parts, including the oral and genital mucosa, but are most common on areas of skin exposed to the sun, such as the face, ears, lower lip, bald scalp, neck, back of hands, arms and legs. Often, these areas of skin show signs of sun damage, such as wrinkles, brown spots or loss of elasticity [128,129]. Indeed, exposure to ultraviolet B rays (UV-B) is the main risk factor for SCC. During exposition to solar radiation, UV-B rays penetrate the epidermis and are absorbed by the keratinocyte chromophores, mainly by the DNA and can alter the skin integrity [129,130]. The resulting DNA photoproducts, in particular pyrimidine dimers (the formation of covalent bonds between the two DNA strands), such as cyclobutan pyrimidine dimers (CPD) and pyrimidine (6-4) pyrimidine, are highly mutagenic and play a critical role in the development of SCC [129,131]. In addition to UV-B, exposure to environmental, occupational and/or lifestyle chemicals, particularly PAHs, may contribute to the genesis of this type of cancer [132]. The development of SCC is a multi-step process, involving DNA damage, failure of appropriate cell rescue (DNA repair) or cell death (apoptosis) responses, suppression of anti-tumor immune responses and clonal expansion of malignant cells [133]. Unlike BCC, it can invade other parts of the body (metastasis) [127].

There is strong evidence that AhR-dependent processes contribute to UV-B-induced photo-carcinogenesis in three different ways (Figure 2).

In epidermal keratinocytes, an induction of the xenobiotics metabolism enzymes expression, in particular CYP1A1 and CYP1B1 is observed [134-136]. CYP1 can bioactivate PAHs into mutagenic electrophile metabolites, and induces some pro-inflammatory chemokines like CXCL5 and associated chemotactic factors [134,137]. Induction of CYP1 isoforms results in rapid metabolism of FICZ, [138], which would probably attenuate the AhR signaling when the UV-B irradiation ends and minimizes the negative effects of AhR activation. Moreover, in cases where exposure to UV-B radiation would be too intense, activation of CYP1 may also lead to the formation of ROS and to associated oxidative damage of macromolecules [86,139].

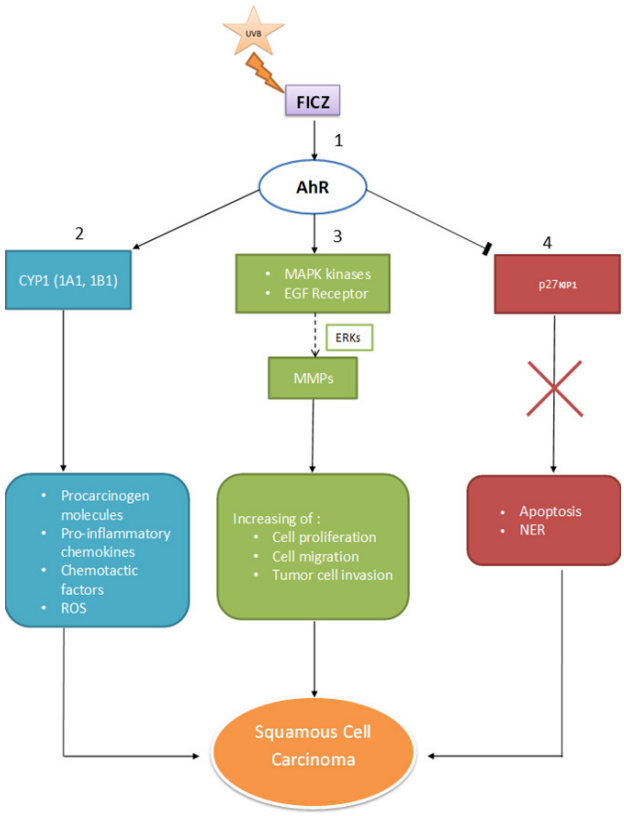

Figure 2: Schematic representation of Spin Cells Carcinoma development mechanisms: (1) AhR activation by the agonist FICZ leads to (2) the transcription of CYP1 isoforms, causing the activation of pro-carcinogen molecules and ROS, chemokines and chemotactic factors productions, (3) the induction of MMPs, via a MAPK kinases and EGF receptor signaling pathways activation, causing a proliferation increase, cell migration and invasion of tumor cells and (4) the inhibition of p27kip1 by forced proteolysis , leading to the repression of nucleotide excision repair (NER) and apoptosis. These three mechanisms contribute to the development to spin cell carcinoma.

In addition, UV-B absorption by tryptophan leads to the formation of FICZ and associated photoproducts, which bind to AhR and activate certain downstream signaling pathways. Among them, MAPK kinases, EGF receptor, ERK1 and ERK2, [134,140] activation results in the induction of the metalloproteases, involving in modification of extra cell matrix, that contribute to cancer progression by promoting processes such as cell proliferation, migration and invasion of tumor cells [141].

These two cascades of events are part of the inflammatory process and remain inseparable from each other, but the development of tumors also result of inhibition of cell defense mechanisms. Depending on the extent of DNA damage, the keratinocytes can initiate nucleotide excision repair (NER), a mechanism common to many mammalian species. If DNA damage is too severe or NER fails, they can alternatively trigger apoptosis, to maintain tissue integrity and avoid mutagenesis [142,143]. Failure (or blockage)

of these early defense mechanisms may result in accumulation of damaged cells, and further facilitate proliferation, resistance to apoptosis, and altered host immune responses [133,135,143].

AhR activation can also induce forced proteolysis of p27KIP1. p27KIP1 is a cell cycle inhibitor that can lead cell proliferation arrest and critically contributes to the repression of the two cellular defense mechanisms above. Its proteolysis is associated with the proliferation of "damaged" keratinocytes and carcinogenesis [144,145]. Indeed, several studies show that AhR inhibits both the elimination of CPDs by NER and the induction of apoptosis in UV-B irradiated epidermal keratinocytes [135,144,146]. A study in hairless SKH-1 mice confirmed AhR role in p27KIP1 degradation: AhR inhibition stabilized p27KIP1 protein levels in damaged keratinocytes, increased their apoptosis and reduced UV-B-induced SCC formation by about 50%. Taken together, these data strongly suggest that AhR contributes to the development of SCC.

Basal cell carcinoma

Basal cell carcinoma (BCC) is the most common skin cancer observed in humans (nearly 70% of skin cancers), but the less aggressive contrary to melanoma. For example, there are almost 3 million new cases in USA each year [127]. This cancer starts in the basal cell layer, which is the deepest part of the epidermis. These tumors are only locally malignant and do not metastasize, neither in the draining lymph nodes, nor at a distance in another tissue. If left untreated for a long time, they can eventually develop deep down and invade the tissue under the skin, a muscle, a bone or even the organ under the skin lesion [147].

The Sonic Hedgehog (SHh) signaling pathway is one of the most fundamental signal transduction pathways in embryonic development. In the skin, the SHh pathway is crucial for maintaining stem cell population, and for regulating hair follicle and sebaceous gland development. Alterations of this pathway are involved in the development of basal cell carcinoma [120,148]. A potential interaction between AhR and SHh has been reported in the literature. The indirubin, an AhR ligand produced by the skin yeast microbiota *Malassezia furfur*, down-regulates glycogen synthase kinase 3 (GSK3) [149], belonging to SHh pathway [150-152]. It is not clear though, if GSK3 repression by indirubin causes an up- or a downregulation of SHh signaling pathway, a crosstalk with AhR signaling pathway is demonstrated, suggesting that AhR may play a key role in the alteration of SHh pathway and thus in BCC pathogenesis.

Other studies have preliminarily established that the exposure to fine particles with a diameter less than 2.5 μm (PM2.5) such as AhR ligands PAHs, correlates with the initiation of the epithelial-mesenchymal transition (EMT). EMT is a pathological process that corresponds to the conversion of epithelial cells to the mesenchymal phenotype, which confers to epithelial cells enhanced capacities for migration, invasion, and extracellular matrix production. These characteristics thus link EMT to the pathogenesis of tissular fibrosis and cancer progression [153]. PM2.5 particles, and their derived species, such as ROS, seem to be involved as potential mediators of EMT and would be linked to the activation of different signaling pathways such as TGF-β/SMADs, NF-κB, ERK, phosphatidylinositol 3-kinase (PI3K) or Wnt/β-catenin [153,154]. AhR crosstalks with these signaling pathways could suggest that AhR plays a role in EMT initiation; however, the mechanisms involved are not yet known or defined.

These data indicate that, although several information emerged regarding the involvement of AhR in the pathogenesis of BCC, further works are thus needed to clarify its role in this disease.

AhR and Autoimmunity

Psoriasis

Psoriasis vulgaris is an inflammatory autoimmune disease affecting the skin. Psoriasis results from interactions between environmental factors and several genetic factors (this pathology is frequently observed in family groups) [155]. It affects nearly 2% of the world population [156]. Innate and adaptative immune systems disturbances are involved in the pathogenesis of this disease, causing aberrant cellular infiltrates, inflammatory mediators production and hyper-keratinization (epidermis thickening) [156,157]. The lesions are potentially distributed all over the body: arms, legs, torso, scalp, back....

The comparison of lesional and non-lesional skin samples from biopsies of psoriasis patients shows that psoriasis-related genes are regulated differently [158]. Following AhR activation by an agonist (FICZ), 41 AhR-regulated genes, are over-expressed in lesional skin, but not in non-lesional samples (Table 3). Conversely, nearly 70% of them were suppressed after AhR inhibition by an antagonist [158]. This inhibition was more pronounced in lesional skin samples.

Psoriatic lesions contain high amounts of pro-inflammatory cytokines such as interleukin 17 (IL-17), IL-21 and IL-22, produced by Th17 cells, leading to the classification of psoriasis as a Th17-regulated disease [156-158]. As discussed previously, AhR ability to modulate Th17 differentiation and activation has been confirmed, suggesting an important role in the pathogenesis of this disease [159-161]. It is also known that cytokine IL-23, produced by dermal dendritic cells, is involved in the expansion and the differentiation of Th17 cells [162,163]. Synergistic effects between AhR and IL-23 in the production of Th17 cytokines, which will act on the keratinocytes in the pathology of psoriasis, appears coherent and probable [78,159] (Figure 3).

IL-22 acts as a major regulator of psoriasis, [164,165] its expression being massively increased in psoriatic lesions [166]. Several studies show that IL-22 treatment on keratinocytes culture *in vitro* induces changes similar to psoriasis lesions such as acanthosis, loss of granular layer and a compact cornified layer [167,168]. In addition, certain genetic polymorphisms in IL-22 gene significantly increase the likelihood of developing psoriasis [158,164,169]. IL-22 induces the production of other pro-inflammatory molecules,

such as CXCL8 (IL-8) [170], but also keratin 17 (K17) [171]. K17 is a protein, non-commonly expressed in epidermis under physiological conditions, but strongly induced in psoriatic lesions [172]. K17 is an important regulator of keratinocytes hyper-proliferation in psoriasis [173,174]. It also modulates keratinocytes immunocompetent activity by increasing the production of pro-inflammatory cytokines, such as CXCL1 and CCL20, and antimicrobial peptides (AMPs) [172,175]. Psoriatic lesions highly express indeed AMPs such as cathelicidin or S100 proteins [176]. AMPs participate to the skin immunity, enabling epithelial surface to defend against a large spectrum of microbial exposure. AMPs modify host inflammatory responses by acting as chemokines or by inducing pro-inflammatory cytokines production and modulating the responses of dendritic cells or T cells of the adaptive immune response [177]. S100A7 in particular has a chemotactic activity for neutrophils and CD4+ T lymphocytes [178].

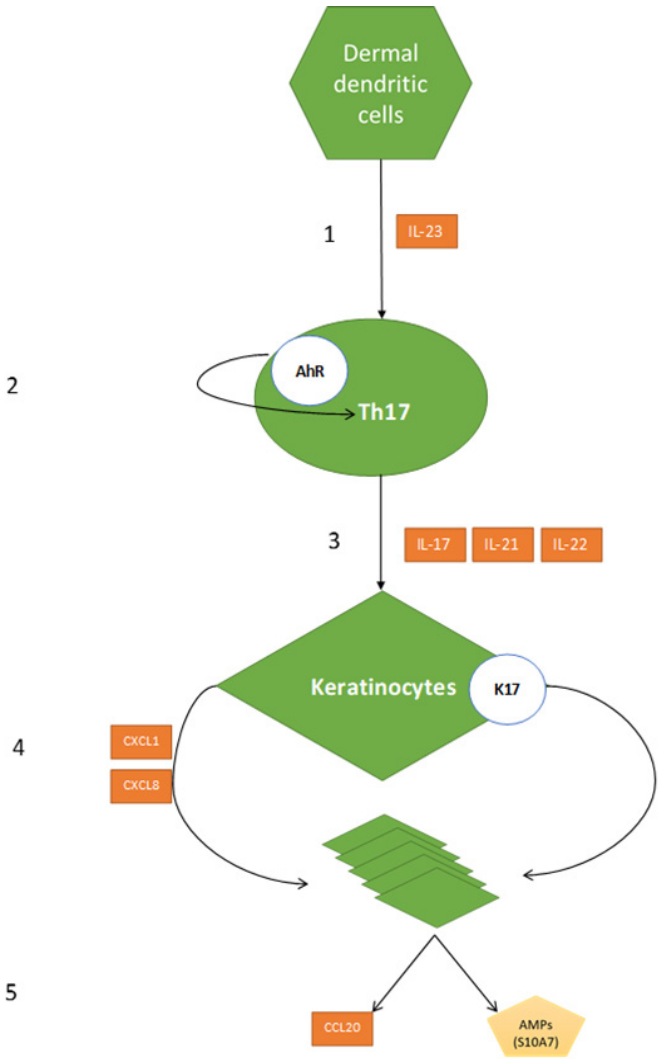

Figure 3: Schematic representation of *Psoriasis Vulagaris* development mechanisms: inflammatory dermal DCs (1) produce IL-23 causing (2) Th17 cells activation and differentiation, probably via a synergetic effect with AhR. (3) Th17 cells produce IL-17 and IL-22 which increase (4) keratinocytes proliferation and chemokines production such as CXCL1 or CXCL8. (5) In addition, Il-22 induces K17 expression which also contributes to the keratinocytes proliferation and the production of inflammatory molecules like CCL20 or antimicrobial peptides (AMPs).

Keratinocytes exposition to IL-17 increases their proliferation and induces the production of inflammatory molecules, which in turn increases skin immune responses. Indeed the chemokines have the ability to feedback on immune cells, therefore chronic T cell activation will persist. They attract more T cells and other immune effector cells, on the site of inflammation, which will produce themselves more chemokines, thus maintaining an inflammatory loop [179,180].

Taken together, these data suggest that AhR play an important role in the pathogenesis of *Psoriasis* and may constitute an essential element in the treatment of this disease. Some studies have been carried out on the use of ahr agonists in the treatment of this condition [181].

Atopic Dermatitis

Atopic dermatitis (AD) is a chronic inflammatory autoimmune skin disease, that can trigger other types of atopic diseases [182], including bronchial asthma, allergic rhinitis and allergic conjunctivitis [183]. AD develops preferentially in infants and children, but can persist and sometimes appears in adolescents and adults. The pathogenesis involves abnormal epidermal differentiation and aberrant immune responses from skin-induced lymphoid tissue [184]. Genetic polymorphisms are involved in the pathogenesis. For example, genetic mutations in fillagrin, a major epidermal differentiation molecule, have been observed in a significant proportion of AD patients [182,185]. In addition to genetic factors, environmental factors and immune adaptations to these factors can contribute significantly to the onset of AD, as well as the severity and progression of the disease [183,186].

Several evidence show a role for AhR in the pathogenesis of atopic dermatitis. Skin tissue analysis has shown a significant increase in both AhR and ARNT expressions, in the keratinocytes of patients suffering of AD. In addition, a study using an "Ova-patched" mouse model showed that percutaneous sensitization, a key step in the development of AD, by BaP (AhR high affinity agonist) causes increased migration of Langerhans cells to the lymph nodes and increased proliferation of Th2 and Th17 [182]. Conversely, the proliferation of Th2 and Th17 cells is significantly reduced in "AhR-deficient" mice [189]. These data therefore strongly suggest that AhR is involved in the immune response deregulation at the origin of the development of AD.

AhR also appears to be involved in the treatment of this disease since the coal tar, an emollient considered as the “classic” treatment of AD is an agonist of AhR. It has been shown in an 3D-skin model that use of coal tar, by activating AhR, leads to the induction of epidermal differentiation and repair of skin barrier functions [182,187]. Coal tar reduces the cutaneous inflammatory processes of psoriasis and atopic dermatitis without the genotoxicity associated with this family of molecules [182]. In addition, an interaction between coal tar and the signaling of Th2 cytokines

via STAT6 dephosphorylation has been demonstrated [187]. This interaction is probably due to the activation of the NRF2 [182,187], a major switch in the induction of antioxidant enzymes, which is strongly expressed in keratinocytes. As discussed previously, synergistic interactions between AhR and NRF2 have been shown [105,188,189]. It seems that AhR is therefore involved in both the development and treatment of AD.

In a 2015 review, Thomas Haarmann-Stemmann, Charlotte Esser and Jean Krutmann noted this paradox and hypothesized that the effects of skin exposure to environmental pollutants differ from those of inflammatory skin, as is the case for AD or psoriasis vulgaris [27]. The latter case thus seems to be characterized by a high presence of AhR non-canonical signaling molecules, which causes an imbalance in this signaling, thus tilting towards pro-inflammatory target genes. The authors also indicate that administration of one or more strong AhR agonists would restore canonical signaling [27], which would explain the role of AhR in the treatment of these diseases.

Conclusion

Discovered 40 years ago, AhR was first considered as a new class of proteins, an orphan receptor acting as a transcription factor and regulating the toxicity of environmental chemicals. Indeed, this transcription factor was identified as the key regulator of certain xenobiotic metabolism enzymes, notably the cytochrome P450s belonging to the CYP1 family. The regulation of the expression of xenobiotic metabolism enzymes is thus the best-known function of AhR and seems to represent an "adaptive" protective response against harmful pollutants. Several genetic studies suggest a strong involvement of AhR in endogenous functions, independent of xenobiotic metabolism. The metabolic function of AhR in the response to environmental toxins could thus have been acquired late in evolution.

Recent years have seen a significant increase in the understanding of AhR mechanisms network. However, in finding the answers to the questions that have arisen, new questions have emerged, including its various endogenous functions. Indeed, some researchers who have carried out studies on AhR have hypothesized that the activation of AhR by exogenous compounds is merely a disruption of normal AhR function. This needs to be demonstrated, and for this reason further studies are required to deepen our knowledge on AhR. Traditionally considered as a critical intermediate in the toxic and carcinogenic response to dioxins, PAHs and other environmental pollutants, AhR is thus proving to be an important regulator of cell physiology and organ homeostasis.

Moreover, for about ten years now, several studies have highlighted AhR involvement in the regulation of genes related to inflammation and immune responses. Indeed, AhR seems to regulate the expression of several pro- and anti-inflammatory cytokines but above all it plays a crucial role in the differentiation and activation of Th17 cells, considered as the driving cells of the inflammatory process.

AhR therefore represents a bridge between the environment and the human body; consequently, it constitutes an innovative therapeutic target for a certain number of inflammatory pathologies. Several research teams have shown that this transcription factor plays a central role in many autoimmune diseases affecting the skin (atopic dermatitis, psoriasis) but not only: atherosclerosis, Crohn's disease... In addition, AhR involvement in various several skin cancers such as squamous and basal cell carcinomas but not only (lung cancers) is known even if mechanisms are not fully identified, at least proven. Therapeutic potential of AhR agonists or antagonists has also been demonstrated.

Nevertheless, the gaps in knowledge about the extent of its functions and the context-specific effects (organ, ligand) call for caution in the use of AhR agonists or antagonists because of potential side effects. This can be explained on the one hand by the potential occurrence of side effects due to the large number of signaling pathways with which AhR interacts. On the other hand, the development of an active ingredient combining a good efficiency and a necessary selectivity minimizing side effects to modulate a target remains complex even for protein families better studied than AhR. Furthermore, the fact that AhR has not been crystallized to date constitutes a major gap in the study of AhR/ligand interactions and thus in the development of an active ingredient to modulate its activity.

However, the last two decades saw a strong increase of strokes, heart diseases, lung cancers, chronic and acute respiratory diseases or skin disorders caused by environmental pollution. In the coming years, considering the involvement of AhR in skin but also lung pathologies in response to xenobiotics, it can therefore be expected that the number of studies on AhR will continue to speed up, allowing the elucidation of many of its mechanisms and thus a better understanding of its functions. An increase in the search for active ingredients specifically targeting AhR or modulating its activity is also to be expected in the context of the prevention or treatment of several inflammatory pathologies. This growing interest for AhR is even beyond therapeutic potential and reaches the field of cosmetics in their quest of anti-pollutant new products. Indeed, there is a modulation of the effects of active principle, which can be relatively marked depending on the type of formulation such as a nano or microemulsion and nano lipid matrix. In addition, certain types of formulations used for medical treatments, have the capacity to act on a specific target. This selectivity could be adapted to a cosmetic use to act on the AhR and thus constitute an innovative alternative in the prevention of pollution induced skin damages.

References

1. Esser C, Lawrence P. Old Receptor, New Tricks -The Ever-Expanding Universe of Aryl Hydrocarbon Receptor Functions. Int J Mol Sci. 2018.
2. Le Beau MM, Carver LA, Espinosa R, et al. Chromosomal localization of the human AHR locus encoding the structural gene for the Ah receptor to 7p21-->p15. Cytogenet Cell Genet. 1994; 66: 172-176.

3. Esser C, Bargen I, Weighardt H, et al. Functions of the aryl hydrocarbon receptor in the skin. Semin Immunopathol. 2013; 35: 677-691.
4. Fernández-Gallego N, Sánchez-Madrid F, Cibrian D. Role of AHR Ligands in Skin Homeostasis and Cutaneous Inflammation. Cells. 2021; 10: 3176.
5. Champion S, Sauzet C, Bremond P, et al. Activation of the NF κ B Pathway Enhances AhR Expression in Intestinal Caco-2 Cells. ISRN Toxicol. 2013; 2013: 792452.
6. Marshall NB, Kerkvliet NI. Dioxin and immune regulation. Ann N Y Acad Sci. 2010; 1183: 25-37.
7. Denison MS, Nagy SR. Activation of the Aryl Hydrocarbon Receptor by Structurally Diverse Exogenous and Endogenous Chemicals. Annu Rev Pharmacol Toxicol. 2003; 43: 309-334.
8. Sun VY, Boverhof DR, Burgoon LD, et al. Comparative analysis of dioxin response elements in human, mouse and rat genomic sequences. Nucleic Acids Res. 2004; 15: 4512-4523.
9. Nguyen LP, Bradfield CA. The search for endogenous activators of the aryl hydrocarbon receptor. Chem Res Toxicol. 2008; 21: 102-116.
10. Tarantini A. Modulation of the genotoxicity of polycyclic aromatic hydrocarbons (PAH) in mixtures . 2009.
11. Zhou Y, Liu J. Emissions, environmental levels, sources, formation pathways, and analysis of polybrominated dibenzo-p-dioxins and dibenzofurans: a review. Environ Sci Pollut Res Int. 2018; 25: 33082-33102.
12. Bock KW. Toward elucidation of dioxin-mediated chloracne and Ah receptor functions. Biochem Pharmacol. 2016; 112: 1-5.
13. Wang S qi, Cheng L sha, Liu Y, et al. Indole-3-Carbinol (I3C) and its Major Derivatives: Their Pharmacokinetics and Important Roles in Hepatic Protection. Curr Drug Metab. 2016; 17: 401-409.
14. Puppala D, Gairola CG, Swanson HI. Identification of kaempferol as an inhibitor of cigarette smoke-induced activation of the aryl hydrocarbon receptor and cell transformation. Carcinogenesis. 2007; 28: 639-647.
15. Assefa EG, Yan Q, Gezahegn SB, et al. Role of Resveratrol on Indoxyl Sulfate-Induced Endothelial Hyperpermeability via Aryl Hydrocarbon Receptor (AHR)/Src-Dependent Pathway. Oxid Med Cell Longev. 2019; 2019: 5847040.
16. Liu Y, Chan F, Sun H, et al. Resveratrol protects human keratinocytes HaCaT cells from UVA-induced oxidative stress damage by downregulating Keap1 expression. Eur J Pharmacol. 2011; 650: 130-137.
17. Barouki R, Coumoul X, Fernandez-Salguero PM. The aryl hydrocarbon receptor, more than a xenobiotic-interacting protein. FEBS Lett. 2007; 581: 3608-3615.
18. Phelan D, Winter GM, Rogers WJ, et al. Activation of the Ah receptor signal transduction pathway by bilirubin and biliverdin. Arch Biochem Biophys. 1998; 357: 155-163.
19. Beischlag TV, Luis Morales J, Hollingshead BD, et al. The aryl hydrocarbon receptor complex and the control of gene expression. Crit Rev Eukaryot Gene Expr. 2008; 18: 207-250.
20. Smirnova A, Wincent E, Vikström Bergander L, et al. Evidence for New Light-Independent Pathways for Generation of the Endogenous Aryl Hydrocarbon Receptor Agonist FICZ. Chem Res Toxicol. 2016; 29: 75-86.
21. Mexia N, Gaitanis G, Velegraki A, et al. Pityriazepin and other potent AhR ligands isolated from Malassezia furfur yeast. Arch Biochem Biophys. 2015; 571: 16-20.
22. Denison M, Soshilov AA, Zhao B, et al. Exactly the Same but Different: Promiscuity and Diversity in the Molecular Mechanisms of Action of the Aryl Hydrocarbon (Dioxin) Receptor. Toxicol Sci. 2011; 124: 1-22.
23. Pongratz I, Mason GG, Poellinger L. Dual roles of the 90-kDa heat shock protein hsp90 in modulating functional activities of the dioxin receptor. Evidence that the dioxin receptor functionally belongs to a subclass of nuclear receptors which require hsp90 both for ligand binding activity and repression of intrinsic DNA binding activity. J Biol Chem. 1992; 267: 13728-13734.
24. Tan Z, Chang X, Puga A, et al. Activation of mitogen-activated protein kinases (MAPKs) by aromatic hydrocarbons: role in the regulation of aryl hydrocarbon receptor (AHR) function. Biochem Pharmacol. 2002; 64: 771-780.
25. Denison M, Soshilov AA. Role of the Per/Arnt/Sim Domains in Ligand-dependent Transformation of the Aryl Hydrocarbon Receptor. J Biol Chem. 2008; 283: 32995-33005.
26. Hankinson O. Role of coactivators in transcriptional activation by the aryl hydrocarbon receptor. Arch Biochem Biophys. 2005; 433: 379-386.
27. Haarmann-Stemmann T, Esser C, Krutmann J. The Janus-Faced Role of Aryl Hydrocarbon Receptor Signaling in the Skin: Consequences for Prevention and Treatment of Skin Disorders. J Invest Dermatol. 2015; 135: 2572-2576.
28. Napolitano M, Patruno C. Aryl hydrocarbon receptor (AhR) a possible target for the treatment of skin disease. Med Hypotheses. 2018; 116: 96-100.
29. Tijet N, Boutros PC, Moffat ID, et al. Aryl hydrocarbon receptor regulates distinct dioxin-dependent and dioxin-independent gene batteries. Mol Pharmacol. 2006; 69: 140-153.
30. Boverhof DR, Burgoon LD, Tashiro C, et al. Temporal and dose-dependent hepatic gene expression patterns in mice provide new insights into TCDD-Mediated hepatotoxicity. Toxicol Sci. 2005; 85: 1048-1063.
31. Esser C, Rannug A, Stockinger B. The aryl hydrocarbon receptor in immunity. Trends Immunol. 2009; 30: 447-454.
32. Levine-Fridman A, Chen L, Elferink CJ. Cytochrome P4501A1 promotes G1 phase cell cycle progression by controlling aryl hydrocarbon receptor activity. Mol Pharmacol. 2004; 65: 461-469.
33. Vogel CFA, Sciullo E, Matsumura F. Involvement of RelB in aryl hydrocarbon receptor-mediated induction of chemokines. Biochem Biophys Res Commun. 2007; 363: 722-726.

34. Hewagama A, Richardson B. The genetics and epigenetics of autoimmune diseases. J Autoimmun. 2009; 33: 3-11.
35. Wu Z, Mei X, Ying Z, et al. Ultraviolet B inhibition of DNMT1 activity via AhR activation dependent SIRT1 suppression in CD4+ T cells from systemic lupus erythematosus patients. J Dermatol Sci. 2017; 86: 230-237.
36. Dere E, Forgacs A, Zacharewski TR, et al. Genome-wide computational analysis of dioxin response element location and distribution in the human, mouse, and rat genomes. Chem Res Toxicol. 2011; 24: 494-504.
37. Madaniyazi L, Li S, Li S, et al. Candidate gene expression in response to low-level air pollution. Environ Int. 2020; 140: 105610.
38. Karchner SI, Franks DG, Powell WH, et al. Regulatory interactions among three members of the vertebrate aryl hydrocarbon receptor family: AHR repressor, AHR1, and AHR2. J Biol Chem. 2002; 277: 6949-6959.
39. Peres AG, Zamboni R, King IL, et al. Suppression of CYP1 members of the AHR response by pathogen-associated molecular patterns. J Leukoc Biol. 2017; 102: 1471-1480.
40. Larigot L, Juricek L, Dairou J, et al. AhR signaling pathways and regulatory functions. Biochim Open. 2018; 7: 1-9.
41. Mimura J, Ema M, Sogawa K, et al. Identification of a novel mechanism of regulation of Ah (dioxin) receptor function. Genes Dev. 1999; 13: 20-25.
42. Kress S, Greenlee WF. Cell-specific regulation of human CYP1A1 and CYP1B1 genes. Cancer Res. 1997; 57: 1264-1269.
43. Kress S, Reichert J, Schwarz M. Functional analysis of the human cytochrome P4501A1 (CYP1A1) gene enhancer. Eur J Biochem. 1998; 258: 803-812.
44. Ueda R, Iketaki H, Nagata K, et al. A common regulatory region functions bidirectionally in transcriptional activation of the human CYP1A1 and CYP1A2 genes. Mol Pharmacol. 2006; 69: 1924-1930.
45. Münzel PA, Lehmköster T, Brück M, et al. Aryl hydrocarbon receptor-inducible or constitutive expression of human UDP glucuronosyltransferase UGT1A6. Arch Biochem Biophys. 1998; 350: 72-78.
46. Yueh MF, Huang YH, Hiller A, et al. Involvement of the Xenobiotic Response Element (XRE) in Ah Receptor-mediated Induction of Human UDP-glucuronosyltransferase 1A1. J Biol Chem. 2003; 278: 15001-15006.
47. Hayes JD, Flanagan JU, Jowsey IR. Glutathione transferases. Annu Rev Pharmacol Toxicol. 2004; 45: 51-88.
48. Tan KP, Wang B, Yang M, et al. Aryl Hydrocarbon Receptor Is a Transcriptional Activator of the Human Breast Cancer Resistance Protein (BCRP/ABCG2). Mol Pharmacol. 2010; 78: 175-185.
49. Fardel O. Cytokines as molecular targets for aryl hydrocarbon receptor ligands: implications for toxicity and xenobiotic detoxification. Expert Opin Drug Metab Toxicol. 2013; 9: 141-152.
50. Haarmann-Stemmann T, Bothe H, Abel J. Growth factors, cytokines and their receptors as downstream targets of arylhydrocarbon receptor (AhR) signaling pathways. Biochem Pharmacol. 2009; 77: 508-520.
51. de Waal Malefyt R. Inteleurkin-10. Curr Opin Immunol. 1992; 4: 314-320.
52. Veldhoen M, Duarte JH. The aryl hydrocarbon receptor: fine-tuning the immune-response. Curr Opin Immunol. 2010; 22: 747-752.
53. Trifunović J, Miller L, Debeljak Ž, et al. Pathologic patterns of interleukin 10 expression--a review. Biochem Med. 2015; 25: 36-48.
54. Wagner S, Lang S, Popp T, et al. Evaluation of selective and non-selective cyclooxygenase inhibitors on sulfur mustard-induced pro-inflammatory cytokine formation in normal human epidermal keratinocytes. Toxicol Lett. 2019; 312: 109-117.
55. N'Diaye M, Le Ferrec E, Lagadic-Gossmann D, et al. Aryl hydrocarbon receptor- and calcium-dependent induction of the chemokine CCL1 by the environmental contaminant benzo[a]pyrene. J Biol Chem. 2006; 281: 19906-19915.
56. Sparfel L, Pinel-Marie ML, Boize M, et al. Transcriptional signature of human macrophages exposed to the environmental contaminant benzo(a)pyrene. Toxicol Sci. 2010; 114: 247-259.
57. Vogel CFA, Nishimura N, Sciullo E, et al. Modulation of the chemokines KC and MCP-1 by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in mice. Arch Biochem Biophys. 2007; 461: 169-175.
58. Chen G, Goeddel DV. TNF-R1 Signaling: A Beautiful Pathway. Science. 2002; 296: 1634-1635.
59. Rozières A. Le TNF-D dans la physiopathologie du psoriasis. Ann Dermatol Venereol. 2006.
60. Benson JM, Shepherd DM. Aryl Hydrocarbon Receptor Activation by TCDD Reduces Inflammation Associated with Crohn's Disease. Toxicol Sci. 2011; 120: 68-78.
61. Li W, Vogel CFA, Wu D, et al. Non-genomic action of TCDD to induce inflammatory responses in HepG2 human hepatoma cells and in liver of C57BL/6J mice. Biol Chem. 2010; 391: 1205-1219.
62. Monteleone I, Rizzo A, Sarra M, et al. Aryl Hydrocarbon Receptor-Induced Signals Up-regulate IL-22 Production and Inhibit Inflammation in the Gastrointestinal Tract. Gastroenterology. 2011; 141: 237-248.
63. Negishi T, Kato Y, Ooneda O, et al. Effects of aryl hydrocarbon receptor signaling on the modulation of TH1/TH2 balance. J Immunol. 2005; 175: 7348-7356.
64. Chernyak YI, Grassman JA. Impact of AhRR (565C > G) polymorphism on dioxin dependent CYP1A2 induction. Toxicol Lett. 2020; 320: 58-63.
65. Mimura J, Ema M, Sogawa K, et al. Identification of a novel mechanism of regulation of Ah (dioxin) receptor function. Genes Dev. 1999; 13: 20-25.

66. Chen S, Operaña T, Bonzo J, et al. ERK kinase inhibition stabilizes the aryl hydrocarbon receptor: implications for transcriptional activation and protein degradation. J Biol Chem. 2005; 280: 4350-4359.
67. Holtmann H, Resch K. Cytokines. Naturwissenschaften. 1995; 82: 178-187.
68. Sakaguchi S. Naturally Arising CD4+ Regulatory T Cells for Immunologic Self-Tolerance and Negative Control of Immune Responses. Annu Rev Immunol. 2004; 22: 531-562.
69. Fontenot JD, Gavin MA, Rudensky AY. Foxp3 programs the development and function of CD4 + CD25 + regulatory T cells. Nat Immunol. 2003; 4: 330-336.
70. Chatila TA, Blaeser F, Ho N, et al. JM2, encoding a fork head–related protein, is mutated in X-linked autoimmunity–allergic disregulation syndrome. J Clin Invest. 2000; 106: R75-R81.
71. Gavin MA, Torgerson TR, Houston E, et al. Single-cell analysis of normal and FOXP3-mutant human T cells: FOXP3 expression without regulatory T cell development. Proc Natl Acad Sci. 2006; 103: 6659-6664.
72. Quintana FJ, Basso AS, Iglesias AH, et al. Control of T(reg) and T(H)17 cell differentiation by the aryl hydrocarbon receptor. Nature. 2008; 453: 65-71.
73. Chen W, Jin W, Hardegen N, et al. Conversion of Peripheral CD4+CD25− Naive T Cells to CD4+CD25+ Regulatory T Cells by TGF-β Induction of Transcription Factor Foxp3. J Exp Med. 2003; 198: 1875-1886.
74. Singh RP, Hasan S, Sharma S, et al. Th17 cells in inflammation and autoimmunity. Autoimmun Rev. 2014; 13: 1174-1181.
75. Bettelli E, Oukka M, Kuchroo VK. T H -17 cells in the circle of immunity and autoimmunity. Nat Immunol. 2007; 8: 345-350.
76. Liu X, Hu H, Fan H, et al. The role of STAT3 and AhR in the differentiation of CD4+ T cells into Th17 and Treg cells. Medicine (Baltimore). 2017; 96: e6615.
77. Veldhoen M, Hirota K, Christensen J, et al. Natural agonists for aryl hydrocarbon receptor in culture medium are essential for optimal differentiation of Th17 T cells. J Exp Med. 2009; 206: 43-49.
78. Veldhoen M, Hirota K, Westendorf AM, et al. The aryl hydrocarbon receptor links TH17-cell-mediated autoimmunity to environmental toxins. Nature. 2008; 453: 106-109.
79. Korn T, Bettelli E, Gao W, et al. IL-21 initiates an alternative pathway to induce proinflammatory T H 17 cells. Nature. 2007; 448: 484-487.
80. Pollenz RS, Necela B, Marks-Sojka K. Analysis of rainbow trout Ah receptor protein isoforms in cell culture reveals conservation of function in Ah receptor-mediated signal transduction. Biochem Pharmacol. 2002; 64: 49-60.
81. Wentworth JN, Buzzeo R, Pollenz RS. Functional characterization of aryl hydrocarbon receptor (zfAHR2) localization and degradation in zebrafish (Danio rerio). Biochem Pharmacol. 2004; 67: 1363-1372.
82. Wincent E, Amini N, Luecke S, et al. The suggested physiologic aryl hydrocarbon receptor activator and cytochrome P4501 substrate 6-formylindolo[3,2-b]carbazole is present in humans. J Biol Chem. 2009; 284: 2690-2696.
83. Rothhammer V, Quintana FJ. The aryl hydrocarbon receptor: an environmental sensor integrating immune responses in health and disease. Nat Rev Immunol. 2019; 19: 184-197.
84. Schneider AJ, Branam AM, Peterson RE. Intersection of AHR and Wnt Signaling in Development, Health, and Disease. Int J Mol Sci. 2014; 15: 17852-17885.
85. Kopf P, Scott JA, Agbor L, et al. Cytochrome P4501A1 Is Required for Vascular Dysfunction and Hypertension Induced by 2,3,7,8-Tetrachlorodibenzo-p-Dioxin. Toxicol Sci. 2010; 117: 537-546.
86. Park JY, Shigenaga MK, Ames BN. Induction of cytochrome P4501A1 by 2,3,7,8-tetrachlorodibenzo-p-dioxin or indolo(3,2-b)carbazole is associated with oxidative DNA damage. Proc Natl Acad Sci U S A. 1996; 93: 2322-2327.
87. Manna SK, Aggarwal BB. Wortmannin inhibits activation of nuclear transcription factors NF-κB and activated protein-1 induced by lipopolysaccharide and phorbol ester. FEBS Lett. 2000; 473: 113-118.
88. Baldwin AS. The NF-kappa B and I kappa B proteins: new discoveries and insights. Annu Rev Immunol. 1996; 14: 649-683.
89. Calame K. Activation-dependent induction of Blimp-1. Curr Opin Immunol. 2008; 20: 259-264.
90. Sica A, Dorman L, Viggiano V, et al. Interaction of NF-kappaB and NFAT with the interferon-gamma promoter. J Biol Chem. 1997; 272: 30412-30420.
91. Vogel CFA, Matsumura F. A new cross-talk between the Aryl hydrocarbon receptor and RelB, a member of the NF-κB family. Biochem Pharmacol. 2009; 77: 734-745.
92. Tian Y, Ke S, Denison MS, et al. Ah Receptor and NF-κB Interactions, a Potential Mechanism for Dioxin Toxicity. J Biol Chem. 1999; 274: 510-515.
93. Vogel CFA, Sciullo E, Li W, et al. RelB, a new partner of aryl hydrocarbon receptor-mediated transcription. Mol Endocrinol. 2007; 21: 2941-2955.
94. Pereira SG, Oakley F. Nuclear factor-kappaB1: regulation and function. Int J Biochem Cell Biol. 2008; 40: 1425-1430.
95. Xia Y, Pauza ME, Feng L, et al. RelB regulation of chemokine expression modulates local inflammation. Am J Pathol. 1997; 151: 375-387.
96. Delerive P, Bosscher KD, Besnard S, et al. Peroxisome Proliferator-activated Receptor α Negatively Regulates the Vascular Inflammatory Gene Response by Negative Cross-talk with Transcription Factors NF-κB and AP-1. J Biol Chem. 1999; 274: 32048-32054.
97. Villard PH, Caverni S, Baanannou A, et al. PPARα transcriptionally induces AhR expression in Caco-2, but represses AhR pro-inflammatory effects. Biochem Biophys Res Commun. 2007; 364: 896-901.

98. Sérée E, Villard PH, Pascussi JM, et al. Evidence for a new human CYP1A1 regulation pathway involving PPAR-α and 2 PPRE sites. Gastroenterology. 2004; 127: 1436-1445.

99. Fallone F, Villard PH, Decome L, et al. PPARα activation potentiates AhR-induced CYP1A1 expression. Toxicology. 2005; 216: 122-128.

100. Gęgotek A, Skrzydlewska E. The role of transcription factor Nrf2 in skin cells metabolism. Arch Dermatol Res. 2015; 307: 385-396.

101. Furue M, Uchi H, Mitoma C, et al. Antioxidants for Healthy Skin: The Emerging Role of Aryl Hydrocarbon Receptors and Nuclear Factor-Erythroid 2-Related Factor-2. Nutrients. 2017; 9: E223.

102. Tsuji G, Takahara M, Uchi H, et al. Identification of ketoconazole as an AhR-Nrf2 activator in cultured human keratinocytes: the basis of its anti-inflammatory effect. J Invest Dermatol. 2012; 132: 59-68.

103. Nakahara T, Mitoma C, Hashimoto-Hachiya A, et al. Antioxidant Opuntia ficus-indica Extract Activates AHR-NRF2 Signaling and Upregulates Filaggrin and Loricrin Expression in Human Keratinocytes. J Med Food. 2015; 18: 1143-1149.

104. Takei K, Mitoma C, Hashimoto-Hachiya A, et al. Antioxidant soybean tar Glyteer rescues T-helper-mediated downregulation of filaggrin expression via aryl hydrocarbon receptor. J Dermatol. 2015; 42: 171-180.

105. Takei K, Hashimoto-Hachiya A, Takahara M, et al. Cynaropicrin attenuates UVB-induced oxidative stress via the AhR-Nrf2-Nqo1 pathway. Toxicol Lett. 2015; 234: 74-80.

106. Uchi H, Yasumatsu M, Morino-Koga S, et al. Inhibition of aryl hydrocarbon receptor signaling and induction of NRF2-mediated antioxidant activity by cinnamaldehyde in human keratinocytes. J Dermatol Sci. 2017; 85: 36-43.

107. Tamaki N, Cristina Orihuela-Campos R, Inagaki Y, et al. Resveratrol improves oxidative stress and prevents the progression of periodontitis via the activation of the Sirt1/AMPK and the Nrf2/antioxidant defense pathways in a rat periodontitis model. Free Radic Biol Med. 2014; 75: 222-229.

108. Wu Z, Uchi H, Morino-Koga S, et al. Z-ligustilide ameliorated ultraviolet B-induced oxidative stress and inflammatory cytokine production in human keratinocytes through upregulation of Nrf2/HO-1 and suppression of NF-κB pathway. Exp Dermatol. 2015; 24: 703-708.

109. Agache P. Physiologie de la peau et explorations fonctionnelles cutanées. Editions Médicales Internationales. Cachan. 2000.

110. Suskind RR. Chloracne, the hallmark of dioxin intoxication. Scand J Work Environ Health. 1985; 11: 165-171.

111. Furue M, Fuyuno Y, Mitoma C, et al. Therapeutic Agents with AHR Inhibiting and NRF2 Activating Activity for Managing Chloracne. Antioxidants (Basel). 2018; 7: E90.

112. Ramot Y, Nyska A, Lieuallen W, et al. Inflammatory and chloracne-like skin lesions in B6C3F1 mice exposed to 3,3′,4,4′-tetrachloroazobenzene for 2 years. Toxicology. 2009; 265: 1-9.

113. Panteleyev AA, Bickers DR. Dioxin-induced chloracne--reconstructing the cellular and molecular mechanisms of a classic environmental disease. Exp Dermatol. 2006; 15: 705-730.

114. Furue M, Takahara M, Nakahara T, et al. Role of AhR/ARNT system in skin homeostasis. Arch Dermatol Res. 2014; 306: 769-779.

115. Mitoma C, Mine Y, Utani A, et al. Current skin symptoms of Yusho patients exposed to high levels of 2,3,4,7,8-pentachlorinated dibenzofuran and polychlorinated biphenyls in 1968. Chemosphere. 2015; 137: 45-51.

116. Sorg O, Zennegg M, Schmid P, et al. 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) poisoning in Victor Yushchenko: identification and measurement of TCDD metabolites. Lancet. 2009; 374: 1179-1185.

117. Ju Q, Fimmel S, Hinz N, et al. 2,3,7,8-Tetrachlorodibenzo-p-dioxin alters sebaceous gland cell differentiation in vitro. Exp Dermatol. 2011; 20: 320-325.

118. Saurat JH, Kaya G, Saxer-Sekulic N, et al. The cutaneous lesions of dioxin exposure: lessons from the poisoning of Victor Yushchenko. Toxicol Sci. 2012; 125: 310-317.

119. Dich J, Zahm SH, Hanberg A, et al. Pesticides and cancer. Cancer Causes Control. 1997; 8: 420-443.

120. Vogeley C, Esser C, Tüting T, et al. Role of the Aryl Hydrocarbon Receptor in Environmentally Induced Skin Aging and Skin Carcinogenesis. Int J Mol Sci. 2019; 20: 6005.

121. Hidaka T, Fujimura T, Aiba S. Aryl Hydrocarbon Receptor Modulates Carcinogenesis and Maintenance of Skin Cancers. Front Med. 2019; 6: 194.

122. Vogeley C, Rolfes KM, Krutmann J, et al. The Aryl Hydrocarbon Receptor in the Pathogenesis of Environmentally-Induced Squamous Cell Carcinomas of the Skin. Front Oncol. 2022; 12: 841721.

123. Esser C. Trajectory Shifts in Interdisciplinary Research of the Aryl Hydrocarbon Receptor—A Personal Perspective on Thymus and Skin. Int J Mol Sci. 2021; 22: 1844.

124. Xue W, Warshawsky D. Metabolic activation of polycyclic and heterocyclic aromatic hydrocarbons and DNA damage: a review. Toxicol Appl Pharmacol. 2005; 206: 73-93.

125. Bourgart E, Persoons R, Marques M, et al. Influence of exposure dose, complex mixture, and ultraviolet radiation on skin absorption and bioactivation of polycyclic aromatic hydrocarbons ex vivo. Arch Toxicol. 2019; 93: 2165-2184.

126. Gupta R, Debbaneh M, Butler D, et al. The Goeckerman Regimen for the Treatment of Moderate to Severe Psoriasis. JoVE J Vis Exp. 2013; 77: e50509.

127. https://www.cancer.org/

128. https://www.skincancer.org/international/le-carcinome-epidermoide-cutane/

129. Cadet J, Douki T. Formation of UV-induced DNA damage contributing to skin cancer development. Photochem Photobiol Sci. 2018; 17: 1816-1841.

130. Herrlich P, Karin M, Weiss C. Supreme EnLIGHTenment: damage recognition and signaling in the mammalian UV response. Mol Cell. 2008; 29: 279-290.

131. Whitmore SE, Potten CS, Chadwick CA, et al. Effect of photoreactivating light on UV radiation-induced alterations in human skin. Photodermatol Photoimmunol Photomed. 2001; 17: 213-217.

132. Baudoin C, Charveron M, Tarroux R. Environmental Pollutants and Skin Cancer. Cell BiolTox. 2002; 18: 341-348.

133. Ratushny V, Gober M, Hick R, et al. From Keratinocyte to Cancer: The Pathogenesis and Modeling of Cutaneous Squamous Cell Carcinoma. J Clin Invst. 2012; 122: 464-472.

134. Fritsche E, Schäfer C, Calles C, et al. Lightening up the UV response by identification of the arylhydrocarbon receptor as a cytoplasmatic target for ultraviolet B radiation. Proc Natl Acad Sci U S A. 2007; 104: 8851-8856.

135. Vogeley C, Esser C, Tüting T, et al. Role of the Aryl Hydrocarbon Receptor in Environmentally Induced Skin Aging and Skin Carcinogenesis. Int J Mol Sci. 2019; 20: E6005.

136. Smith KJ, Murray IA, Boyer JA, et al. Allelic variants of the aryl hydrocarbon receptor differentially influence UVB-mediated skin inflammatory responses in SKH1 mice. Toxicology. 2018; 394: 27-34.

137. Villard PH, Sampol E, Elkaim JL, et al. Increase of CYP1B1 transcription in human keratinocytes and HaCaT cells after UV-B exposure. Toxicol Appl Pharmacol. 2002; 178: 137-143.

138. Bergander L, Wincent E, Rannug A, et al. Metabolic fate of the Ah receptor ligand 6-formylindolo[3,2-b]carbazole. Chem Biol Interact. 2004; 149: 151-164.

139. Costa C, Catania S, De Pasquale R, et al. Exposure of human skin to benzo[a]pyrene: role of CYP1A1 and aryl hydrocarbon receptor in oxidative stress generation. Toxicology. 2010; 271: 83-86.

140. Rannug A, Rannug U, Rosenkranz HS, et al. Certain photooxidized derivatives of tryptophan bind with very high affinity to the Ah receptor and are likely to be endogenous signal substances. J Biol Chem. 1987; 262: 15422-15427.

141. Pittayapruek P, Meephansan J, Prapapan O, et al. Role of Matrix Metalloproteinases in Photoaging and Photocarcinogenesis. Int J Mol Sci. 2016;17: 868.

142. Marteijn JA, Lans H, Vermeulen W, et al. Understanding nucleotide excision repair and its roles in cancer and ageing. Nat Rev Mol Cell Biol. 2014; 15: 465-481.

143. Roos WP, Thomas AD, Kaina B. DNA damage and the balance between survival and death in cancer biology. Nat Rev Cancer. 2016; 16: 20-33.

144. Frauenstein K, Sydlik U, Tigges J, et al. Evidence for a novel anti-apoptotic pathway in human keratinocytes involving the aryl hydrocarbon receptor, E2F1, and checkpoint kinase 1. Cell Death Differ. 2013; 20: 1425-1434.

145. Kalmes M, Hennen J, Clemens J, et al. Impact of aryl hydrocarbon receptor (AhR) knockdown on cell cycle progression in human HaCaT keratinocytes. Biol Chem. 2011; 392: 643-651.

146. Pollet M, Shaik S, Mescher M, et al. The AHR represses nucleotide excision repair and apoptosis and contributes to UV-induced skin carcinogenesis. Cell Death Differ. 2018; 25: 1823-1836.

147. Lok C, Vabres P. Tumeurs cutanées épithéliales et mélaniques. In: Dermatologie. Elsevier-Masson. 2018; 295-335.

148. Madan V, Lear JT, Szeimies RM. Non-melanoma skin cancer. Lancet Lond Engl. 2010; 375: 673-685.

149. Gaitanis G, Velegraki A, Magiatis P, et al. Could Malassezia yeasts be implicated in skin carcinogenesis through the production of aryl-hydrocarbon receptor ligands? Med Hypotheses. 2011; 77: 47-51.

150. Takenaka K, Kise Y, Miki H. GSK3beta positively regulates Hedgehog signaling through Sufu in mammalian cells. Biochem Biophys Res Commun. 2007; 353: 501-508.

151. Athar M, Tang X, Lee JL, et al. Hedgehog signalling in skin development and cancer. Exp Dermatol. 2006; 15: 667-677.

152. Meijer L, Skaltsounis AL, Magiatis P, et al. GSK-3-selective inhibitors derived from Tyrian purple indirubins. Chem Biol. 2003; 10: 1255-1266.

153. Xu Z, Ding W, Deng X. PM2.5, Fine Particulate Matter: A Novel Player in the Epithelial-Mesenchymal Transition? Front Physiol. 2019; 10: 1404.

154. Gualtieri M, Ovrevik J, Mollerup S, et al. Airborne urban particles (Milan winter-PM2.5) cause mitotic arrest and cell death: Effects on DNA, mitochondria, AhR binding and spindle organization. Mutat Res. 2011; 713: 18-31.

155. Farber EM, Nall ML, Watson W. Natural history of psoriasis in 61 twin pairs. Arch Dermatol. 1974; 109: 207-211.

156. Cibrian D, Saiz ML, de la Fuente H, et al. CD69 controls the uptake of L-tryptophan through LAT1-CD98 and AhR-dependent secretion of IL-22 in psoriasis. Nat Immunol. 2016; 17: 985-996.

157. Smith SH, Jayawickreme C, Rickard DJ, et al. Tapinarof Is a Natural AhR Agonist that Resolves Skin Inflammation in Mice and Humans. J Invest Dermatol. 2017; 137: 2110-2119.

158. Di Meglio P, Duarte JH, Ahlfors H, et al. Activation of the aryl hydrocarbon receptor dampens the severity of inflammatory skin conditions. Immunity. 2014; 40: 989-1001.

159. Schiering C, Vonk A, Das S, et al. Cytochrome P4501-inhibiting chemicals amplify aryl hydrocarbon receptor activation and IL-22 production in T helper 17 cells. Biochem Pharmacol. 2018; 151: 47-58.

160. Furue M, Hashimoto-Hachiya A, Tsuji G. Aryl Hydrocarbon Receptor in Atopic Dermatitis and Psoriasis. Int J Mol Sci. 2019; 20: E5424.

161. Cochez PM, Michiels C, Hendrickx E, et al. AhR modulates the IL-22-producing cell proliferation/recruitment in imiquimod-induced psoriasis mouse model. Eur J Immunol. 2016; 46: 1449-1459.

162. Wilson NJ, Boniface K, Chan JR, et al. Development, cytokine profile and function of human interleukin 17–producing helper T cells. Nat Immunol. 2007; 8: 950-957.

163. Langrish CL, Chen Y, Blumenschein WM, et al. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. J Exp Med. 2005; 201: 233-240.

164. Owczarczyk-Saczonek A, Placek W. Interleukin-17 as a factor linking the pathogenesis of psoriasis with metabolic disorders. Int J Dermatol. 2017; 56: 260-268.

165. Hack K, Reilly L, Palmer C, et al. Skin-targeted inhibition of PPAR β/δ by selective antagonists to treat PPAR β/δ-mediated psoriasis-like skin disease in vivo. PloS One. 2012; 7: e37097.

166. Wolk K, Kunz S, Witte E, et al. IL-22 Increases the Innate Immunity of Tissues. Immunity. 2004; 21: 241-254.

167. Boniface K, Bernard FX, Garcia M, et al. IL-22 inhibits epidermal differentiation and induces proinflammatory gene expression and migration of human keratinocytes. J Immunol. 2005; 174: 3695-3702.

168. Sa SM, Valdez PA, Wu J, et al. The effects of IL-20 subfamily cytokines on reconstituted human epidermis suggest potential roles in cutaneous innate defense and pathogenic adaptive immunity in psoriasis. J Immunol. 2007; 178: 2229-2240.

169. Hawkes JE, Chan TC, Krueger JG. Psoriasis pathogenesis and the development of novel targeted immune therapies. J Allergy Clin Immunol. 2017; 140: 645-653.

170. Wolk K, Haugen HS, Xu W, et al. IL-22 and IL-20 are key mediators of the epidermal alterations in psoriasis while IL-17 and IFN-gamma are not. J Mol Med Berl Ger. 2009; 87: 523-536.

171. Jin L, Wang G. Keratin 17: a critical player in the pathogenesis of psoriasis. Med Res Rev. 2014; 34: 438-454.

172. Lin Y, Zhang W, Li B, et al. Keratin 17 in psoriasis: Current understanding and future perspectives. Semin Cell Dev Biol. 2022; 128: 112-119.

173. Zhang X, Yin M, Zhang L juan. Keratin 6, 16 and 17—Critical Barrier Alarmin Molecules in Skin Wounds and Psoriasis. Cells. 2019; 8: 807.

174. Yu T, An Q, Cao XL, et al. GOLPH3 inhibition reverses oxaliplatin resistance of colon cancer cells via suppression of PI3K/AKT/mTOR pathway. Life Sci. 2020; 260: 118294.

175. Wolk K, Witte E, Wallace E, et al. IL-22 regulates the expression of genes responsible for antimicrobial defense, cellular differentiation, and mobility in keratinocytes: a potential role in psoriasis. Eur J Immunol. 2006; 36: 1309-1323.

176. Büchau AS, Gallo RL. Innate Immunity and antimicrobial defense systems in psoriasis. Clin Dermatol. 2007; 25: 616-624.

177. Lai Y, Gallo RL. AMPed up immunity: how antimicrobial peptides have multiple roles in immune defense. Trends Immunol. 2009; 30: 131-141.

178. Takahashi T, Yamasaki K. Psoriasis and Antimicrobial Peptides. Int J Mol Sci. 2020; 21: E6791.

179. Lowes MA, Suárez-Fariñas M, Krueger JG. Immunology of Psoriasis. Annu Rev Immunol. 2014; 32: 227-255.

180. Lowes MA, Russell CB, Martin DA, et al. The IL-23/T17 pathogenic axis in psoriasis is amplified by keratinocyte responses. Trends Immunol. 2013; 34: 174-181.

181. Sabnis RW. Novel Aryl Hydrocarbon Receptor Agonists for Treating Psoriasis. ACS Med Chem Lett. 2023; 14: 696-697.

182. Hong CH, Lee CH, Yu HS, et al. Benzopyrene, a major polyaromatic hydrocarbon in smoke fume, mobilizes Langerhans cells and polarizes Th2/17 responses in epicutaneous protein sensitization through the aryl hydrocarbon receptor. Int Immunopharmacol. 2016; 36: 111-117.

183. Lee CH, Chuang HY, Shih CC, et al. Correlation of Serum Total IgE, Eosinophil Granule Cationic Proteins, Sensitized Allergens and Family Aggregation in Atopic Dermatitis Patients with or without Rhinitis. J Dermatol. 2004; 31: 784-793.

184. Kabashima K. New concept of the pathogenesis of atopic dermatitis: Interplay among the barrier, allergy, and pruritus as a trinity. J Dermatol Sci. 2013; 70: 3-11.

185. Palmer CNA, Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat Genet. 2006; 38: 441-446.

186. Lee CH, Yu HS. Biomarkers for Itch and Disease Severity in Atopic Dermatitis. Pathog Manag Atopic Dermat. 2011; 41: 136-148.

187. van den Bogaard EH, Bergboer JGM, Vonk-Bergers M, et al. Coal tar induces AHR-dependent skin barrier repair in atopic dermatitis. J Clin Invest. 2013; 123: 917-927.

188. Doi K, Mitoma C, Nakahara T, et al. Antioxidant Houttuynia cordata extract upregulates filaggrin expression in an aryl hydrocarbon-dependent manner. Fukuoka Igaku Zasshi. 2014; 105: 205-213.

189. Haarmann-Stemmann T, Abel J, Fritsche E, et al. The AhR-Nrf2 pathway in keratinocytes: on the road to chemoprevention?. J Invest Dermatol. 2012; 132: 7-9.