

The Aryl Hydrocarbon Receptor: A Review of Its Role in the Physiology and Pathology of the Integument and Its Relationship to the Tryptophan Metabolism

Rowland Noakes

Queensland Institute of Dermatology, Holland Park, Queensland, Australia.

ABSTRACT: The aryl hydrocarbon receptor (AHR) is a cytosolic receptor for low molecular weight molecules, of which the most widely recognized ligand is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), and the most widely recognized effect, chloracne. Adverse effects of manipulation were most recently and graphically demonstrated by the poisoning of Viktor Yushchenko during the Ukrainian presidential elections of 2004. However, recent research has revealed a receptor with wide-ranging, and at times, paradoxical actions. It was arguably among the first biological receptors to be utilized by dermatologists, dating from the time of topical tar preparations as a therapeutic agent. I provide a review outlining the role AHR plays in the development, cellular oxidation/antioxidation, responses to ultraviolet light, melanogenesis, epidermal barrier function, and immune regulation and its relationship to tryptophan metabolism. Finally, I will review the role of AHR in diseases of the integument.

KEYWORDS: Aryl hydrocarbon receptor, cellular oxidation/antioxidation, tryptophan metabolism, melanogenesis, UV exposure, epidermal barrier, immune regulation

CITATION: Noakes. The Aryl Hydrocarbon Receptor: A Review of Its Role in the Physiology and Pathology of the Integument and Its Relationship to the Tryptophan Metabolism. *International Journal of Tryptophan Research* 2015;8 7–18 doi: 10.4137/IJTR.S19985.

RECEIVED: September 10, 2014. **RESUBMITTED:** January 04, 2015. **ACCEPTED FOR PUBLICATION:** January 13, 2015.

ACADEMIC EDITOR: Gilles Guillemin, Editor in Chief

TYPE: Review

FUNDING: Author discloses no funding sources.

COMPETING INTERESTS: Author discloses no potential conflicts of interest.

CORRESPONDENCE: ky_n_urenine@hotmail.com

COPYRIGHT: © the authors, publisher and licensee Libertas Academica Limited. This is an open-access article distributed under the terms of the Creative Commons CC-BY-NC 3.0 License.

Paper subject to independent expert blind peer review by minimum of two reviewers. All editorial decisions made by independent academic editor. Upon submission manuscript was subject to anti-plagiarism scanning. Prior to publication all authors have given signed confirmation of agreement to article publication and compliance with all applicable ethical and legal requirements, including the accuracy of author and contributor information, disclosure of competing interests and funding sources, compliance with ethical requirements relating to human and animal study participants, and compliance with any copyright requirements of third parties. This journal is a member of the Committee on Publication Ethics (COPE).

Published by Libertas Academica. Learn more about this journal.

Background

The AHR is a cytosolic receptor for low molecular weight molecules, binding and becoming activated by sterically planar ligands approximately three benzene rings in size.¹ It is maximally expressed in interface tissues including the liver, lungs, skin,² and the gastrointestinal tract.³

In the cytosol, AHR exists in a latent state as part of a multi-protein complex (Fig. 1). Chaperoning proteins include the heat shock protein 90 (hsp90), hsp23, and hepatitis B virus X-associated protein 2 (XAP2).⁴ Pp60^{src} is an associated signaling partner that is released into the cytosol on ligand binding.⁴ This binds to the epidermal growth factor receptor (EGFR) and initiates mitogen-activated protein kinase (MAPK) signaling.^{5,6}

On ligand binding, the receptor complex translocates to the nucleus.⁷ Here it binds to the aryl hydrocarbon receptor nuclear transporter (ARNT). The AHR-ARNT heterodimer interacts with several histone acetyltransferases and chromatin remodeling factors.⁸ This promotes the transcription of genes containing xenobiotic response elements (XRE) in their promoters.

Two feedback loops regulate AHR activity. First, AHR is released to the cytosol and degraded by the 26 S proteasome pathway.⁹ Second, binding to the XREs results in the transcription of the aryl hydrocarbon receptor repressor (AHRR), which regulates the activity of the AHR via a negative feedback loop.¹⁰

There is also crosstalk between the AHR and other pathways. These include the estrogen receptor,¹¹ the retinoblastoma protein (Rb), thus inhibiting cell cycle progression¹² and the retinoic signaling pathways.¹³ AHR can also bind the p65 subunit of nuclear factor kappa light chain enhancer of activated β cells (NF- κ B), thereby either suppressing or activating (depending on cellular context) the expression of NF- κ B-dependent genes.^{14,15}

Tryptophan and the Aryl Hydrocarbon receptor. Many tryptophan-based molecules are AHR ligands. These include 6-formylindolo [3, 2-b] carbazole (FICZ)¹⁶ and 2-(1'Hindole-3'-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE), a tryptophan-cysteine dimer.¹⁷

The kynurenine pathway (Fig. 2) is the metabolic pathway via which L-tryptophan is metabolized to nicotinamide adenine dinucleotide (NAD). In addition to generating endogenous supplies of nicotinamide, it has important immune-regulatory roles.¹⁸ Several metabolites known to act as endogenous ligands of the AHR include kynurenine,¹⁹ kynurenic acid,²⁰ and cinnabarinic acid.²¹

Relationship with tryptophan metabolism. Tryptophan is metabolized by four primary pathways.

The kynurenine pathway. The kynurenine pathway (Fig. 2) is the metabolic pathway via which L-tryptophan is metabolized to NAD. Indoleamine 2,3-dioxygenase (IDO) is the

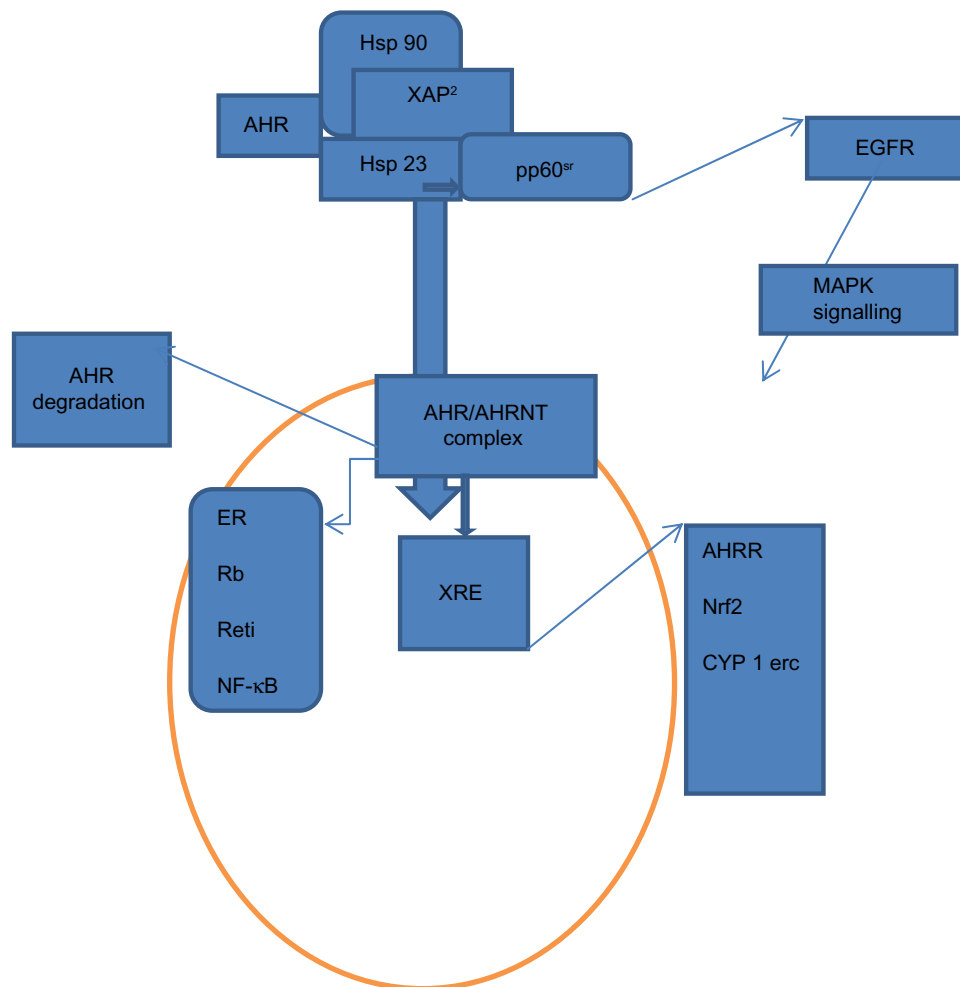


Figure 1. In the cytosol, AHR exists in a latent state as part of a multiprotein complex. Chaperoning proteins includes heat shock protein 90 (hsp90), hsp23, and hepatitis B virus X-associated protein 2 (XAP2). On ligand binding, pp60^{src} is released and binds to the epidermal growth factor receptor (EGFR), initiating MAPK signaling. The remainder of the complex translocates to the nucleus where it binds to the aryl hydrocarbon receptor nuclear transporter (ARNT), promoting the transcription of genes with xenobiotic response elements (XRE) in their promoters. Crosstalk occurs with the estrogen receptor (ER), retinoblastoma protein (Rb), retinoic acid (Reti), and NF-κB pathways. Control is provided by two loops, exportation of the AHR to the cytoplasm with subsequent degradation and transcription of the aryl hydrocarbon receptor repressor (AHRR).

rate-limiting enzyme of the kynurenine pathway (KP). It is induced by several proinflammatory molecules, especially interferon gamma (IFN- γ).²² It is essential that the inflammatory response be controlled and not surprising that one of the downstream KP metabolites, kynurenine,¹⁹ provides a negative feedback loop through AHR to promote the generation of T_{reg} cells.¹⁹ Other downstream AHR ligands include kynurenic,²⁰ cinnabarinic,²¹ and xanthurenic acid.²³

Reflecting the complexity and multilayered nature of the control mechanisms, it has been reported that kynurenic acid promotes the generation of inflammatory cytokines.²⁰ In addition, IDO is upregulated by AHR activation, suggesting that positive feedback loops operate within the microenvironment.²⁴

More recently, it has been demonstrated that the AHR chaperoning protein pp60^{src} can phosphorylate IDO-1, promoting transforming growth factor beta 1 (TGF β 1) production by dendritic cells, leading to disease tolerance.²⁵

TGF β 1 production in dendritic cells in response to the downstream KP metabolite quinolinic acid has also been reported.²⁶

Pleiotropic responses are seen with AHR ligands, with some promoting the generation of T_{reg} cells (regulatory ligands), and others, TH₁₇ expansion (effector ligands).²⁷ The former include TCDD and kynurenine, and the latter, FICZ.²⁸ Effector ligands such as FICZ are rapidly metabolized and produce only transitory stimulation²⁹ of AHR, whereas regulatory ligands such as TCDD are long-lived.

Much research on the kynurenine pathway has focused on its neuro-inflammatory roles. The nervous system, however, expresses only low levels of the AHR compared to the integument,² and it is in the skin that the relationship is likely to be of greatest significance.

AHR is important in the development of the KP. Langerhans cells (LCs) from AHR-null mice display significantly reduced IDO activity³⁰ compared to the wild phenotype. In addition, the archetypical AHR ligand, TCDD has been

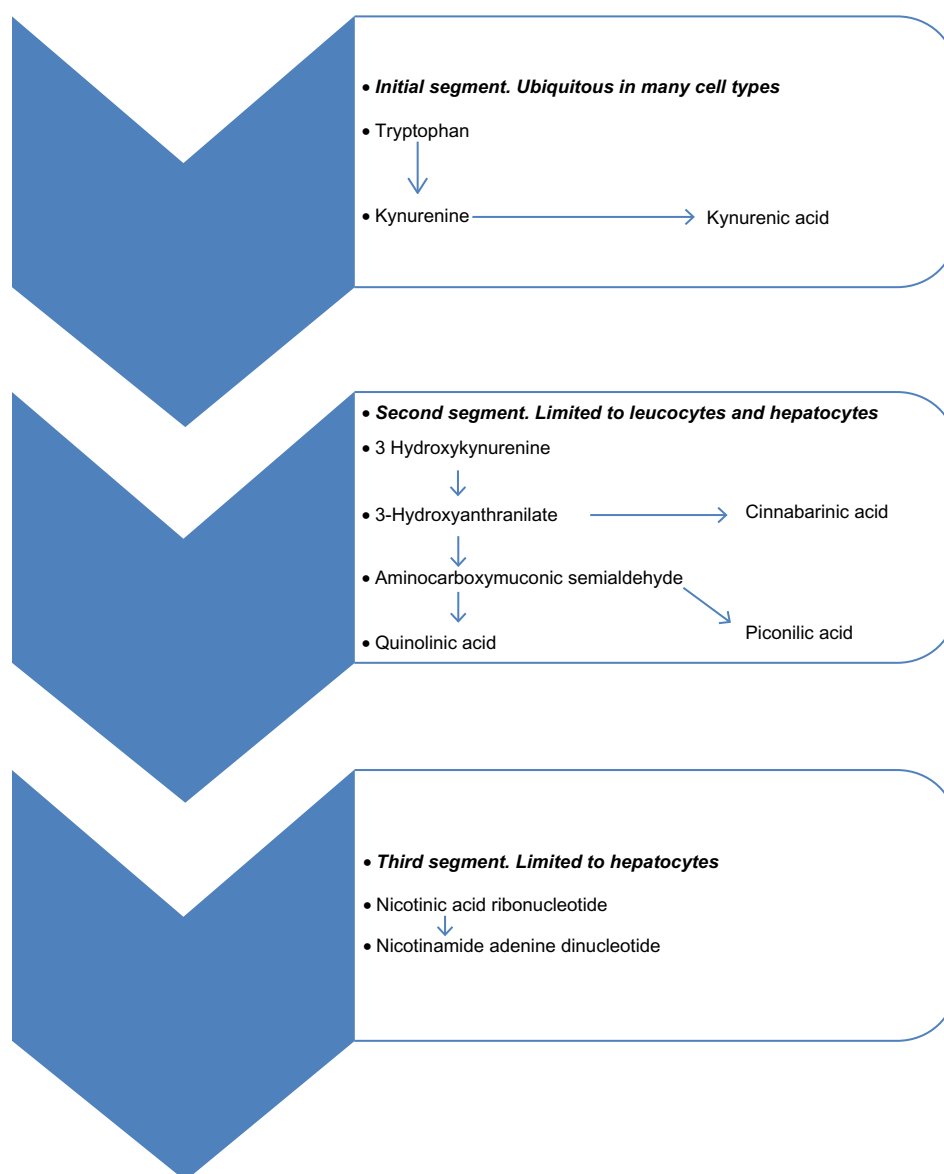


Figure 2. The kynurenine pathway (Reproduced from Noakes, RR, *Int. J. Tryptophan Res.* 2013;6:67–71).

shown to induce IDO in dendritic cells, which promotes T_{reg} generation.^{20,31}

Several pharmacological agents known to modulate the KP are also ligands of AHR. These include tranilast^{32,33} and leflunomide.^{34,35}

The tryptamine pathway. The tryptamine pathway, catalyzed by tryptophan hydroxylase and dopamine decarboxylase, has been implicated in AHR activation. Tryptamine is a potent AHR activator acting either as a direct ligand²⁹ or as a precursor for downstream ligands such as indole acetic acid.²⁹ In addition, shunting through this pathway via carcinoid tumors can result in nicotinamide deficiency (pellagra).

The serotonin pathway. 5-Hydroxy-tryptophan, a proximal metabolite, is an AHR agonist.³⁶

Tryptophan photoproducts. Tryptophan is readily photooxidized by UV light. The products include kynurenine,¹

tryptamine,³⁷ FICZ, and 6,12-di-formylindolo[3,2-*b*]carbazole (dFICZ), the latter two representing high affinity compounds.³⁸

The skin. The structure of the skin is shown in Figure 3. The epidermis is composed principally of keratinocytes and continuously regenerated from the basal layer. It serves as a barrier against the environment. As an interface with the external environment, it contains specialized antigen-processing cells known as LCs. The cells responsible for melanin production, melanocytes, are found in the basal layer of the epidermis and transfer pigment granules containing melanin to neighboring keratinocytes via dendritic processes. In keratinocytes, these localize over the cell nucleus and provide protection for the genetic material against environmental ultraviolet radiation.

The dermis is divided into a finer papillary and a coarser reticular dermis and provides mechanical strength. Fibroblasts produce collagen, elastin, and glycosaminoglycans that

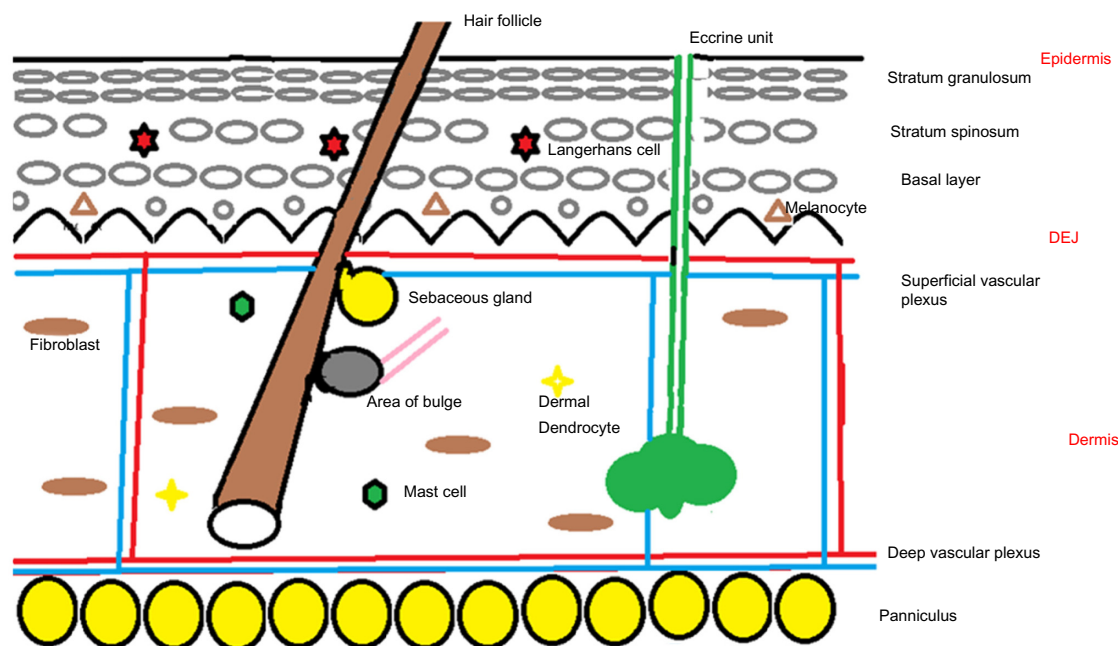


Figure 3. Stylized image of the skin.

Notes: The epidermis consists mainly of keratinocytes (gray), which are continually generated from a basal layer and are progressively compacted as they migrate toward the stratum corneum from which they are shed. The epidermis also contains specialized antigen-presenting cells, Langerhans cells (red), and pigment-producing melanocytes (brown). The dermis provides mechanical strength and principally comprises collagen, elastin, and glycosaminoglycans. Cells found within the dermis include fibroblasts (brown), dermal dendrocytes (yellow), and mast cells (green). The panniculus (yellow) lies below the dermis. Appendageal structures include pilosebaceous units comprising a hair follicle (filled brown), sebaceous glands (filled yellow), and a bulge area from which regeneration of the follicle occurs (filled gray). Sweat is produced by eccrine glands comprising a coil (filled green) and a duct.

act as an intercellular ground substance imparting viscoelastic properties.

The dermis is also home to a population of cells essential in immunological function including mast cells, dermal dendrocytes, and a resident population of CD4, CD8, CD45, memory, and FOXP3-regulatory T cells.

All cells in the skin express AHR. The highest levels of expression are found in the outer layers of the epidermis (stratum spinosum and granulosum), melanocytes, fibroblasts, and LCs.³⁹

Function of the Aryl Hydrocarbon Receptor

In addition to the traditional role of metabolizing environmental toxins, AHR plays a role in the development, cellular oxidation/antioxidation, responses to ultraviolet light, melanogenesis, epidermal barrier function, and immune regulation.

Developmental roles. AHR-null mice display growth retardation, reduced liver size, abnormalities in vascular structure, portal tract fibrosis, dermal fibrosis, and decreased fertility,^{40–43} supportive of a role for the AHR in embryogenesis. Patent ductus venosus is the most consistent abnormality, and the resulting porto-systemic shunt is likely responsible for reduced liver size and portal tract fibrosis.

Oxidant/antioxidant responses. The best known function of AHR is the induction of the cytochrome P450 genes,⁴⁴ which are involved in the metabolism of drugs and the detoxification of environmental toxins. The phase I enzymes, cytochrome P450 (CYP) 1A1, CYP1A2, and CYP1B1, contain

XRE in their promoters and respond to AHR signaling.⁴⁵ These are monooxygenases that introduce functional groups prior to conjugation with water-soluble molecules by phase 2 enzymes. Phase 2 enzymes are under the control of the nuclear factor erythroid derived 2, like 2 transcription factor (Nrf2), which regulates cellular antioxidant responses. Nrf2 promoter sequences are known to contain XRE,⁴⁶ allowing coordination of phase 1 and 2 responses.

Ultraviolet light. Tryptophan is a chromophore for ultraviolet (UV) light in the cellular cytoplasm. The photo-products include FICZ, a potent AHR ligand.¹⁶ On ligation and subsequent dissociation of the AHR complex, the chaperoning protein pp60^{src} binds to the EGFR and initiates MAPK signaling. This increases transcription of cyclooxygenase 2 (COX-2)⁴⁷ and matrix metalloproteinase-1.⁴⁸ The former plays a role in cutaneous carcinogenesis⁴⁹ and the latter in photo-aging.⁵⁰ Thus, AHR-mediated cytoplasmic events influence carcinogenesis and aging independent of DNA damage.

Melanogenesis. The tanning response is vital to protect the skin from harmful UV light. Keratinocytes produce α -MSH in response to UV light, which promotes melanin synthesis in local melanocytes. Melanin is then transferred back to the keratinocytes in small packages (melanosomes) via the dendritic processes. The melanosomes localize over the cell nucleus, providing protection against UV radiation.

Poisoning with toxins known to be powerful AHR ligands has been reported to result in hyperpigmentation.

Mass poisoning with cooking oils contaminated with polychlorinated biphenyl (PCB) was associated with cutaneous hyperpigmentation.⁵¹ Likewise, exposure to TCDD has been reported to result in hyperpigmentation.⁵²

Melanogenesis is also inducible in cultured melanocytes by FICZ.⁵³ In addition, c-kit/stem cell factor system is important in melanocyte hemostasis,⁵⁴ and c-kit has XREs in its promoter.⁵⁵ Thus the AHR plays a role in the tanning response and protection against environmental ultraviolet light.

Epidermal barrier function. An intact epidermal barrier is essential in providing protection against environmental insults and limiting transepidermal water loss. It is most commonly conceptualized as a bricks-and-mortar model. The bricks are compacted keratinocytes containing keratin 1 and 10 filaments. The protein, flaggrin, is responsible for mediating the assembly of the keratin filaments. A cornified cell envelope is synthesized below the plasma membrane comprising cross-linked molecules of envoplakin, periplakin, and involucrin.⁵⁶ Cross-linking is mediated by tissue transglutaminase. The mortar is provided by free fatty acids, cholesterol, and ceramides.

Atopic dermatitis is due to defects in skin barrier function secondary to loss-of-function mutations in the flaggrin gene.⁵⁷ A mouse model with constitutive expression of AHR was reported as displaying itching, skin inflammation, and immunological imbalances resembling atopic dermatitis.⁵⁸ Interestingly, but somewhat counterintuitively, EGFR expression has been reported to be reduced in patients with atopic dermatitis⁵⁹ and EGFR signaling attenuates the development and relapse of atopic dermatitis.⁶⁰ This appears to be at odds with the anticipated increased availability of the chaperoning pp60^{src} protein and associated increased EGFR signaling expected with constitutive expression of AHR. These apparent contraindications may represent species specificity, although it has been reported that EGFR signaling inhibits the AHR-mediated differentiation of human keratinocytes,⁶¹ suggesting that feedback loops are present and that constitutive expression of a receptor may produce different features to one under feedback control.

Immune regulation. *Keratinocytes.* Keratinocytes express an impressive array of cytokines.⁶² Cytokines of keratinocyte origin known to contain XRE in their promoters include IL-1 β ⁶³ and IL-8.⁶⁴

Langerhans cells. LCs are epidermal dendritic cells involved in antigen presentation. More recently, their role in immune regulation and telereogenesis has been recognized.⁶⁵ AHR is expressed in LCs, and AHR-null LCs display evidence of impaired function.³⁰

Interleukins. TH17 T cells are a subgroup of T cells and are important in mediating responses to bacteria and yeast. They play a pivotal role in psoriasis⁶⁶ and are the target for several biological agents used in the management of psoriasis. They also play a role in autoimmune disease.⁶⁷ They produce IL-17 and IL-22.⁶⁸ AHR promotes the expansion of TH17 lymphocytes and is obligatory for IL-22 production.⁶⁸

Reflecting the complexity of the interplay between control systems, AHR has also been found to promote IL-21 and IL-23 production and may display inhibitory effects on TH17 depending on the ligand.¹⁹ In human skin, LCs induce a special subset of T cells, TH-22, which produce IL-22 (but not IL-17, which is under control of AHR).⁶⁹

AHR is also known to crosstalk with NF- κ B¹⁵ and thus is involved in the regulation of inflammatory and immune responses, cell survival, and proliferation.

Dermatopathological Correlations

Archetypical correlations. *Chloracne.* Chloracne (Fig. 4) is the archetypical toxic response of the skin to TCDD. The name is a misnomer, as it is characterized by atrophy of the sebaceous glands, keratinocyte hyperpigmentation, and epidermal hyperplasia. Recently, the skin lesions were recognized as hamartomas⁷⁰ and, in the case of TCDD poisoning, represent a TCDD metabolizing compartment.⁷¹ Curiously, mice (with the exception of the hairless mouse) do not develop chloracne-like lesions on exposure to TCDD,⁷² and there are likely to be significant species differences in the action of the AHR.

TCDD promotes terminal differentiation of keratinocytes,⁷³ possibly mediated by changes in the expression of transforming growth factor alpha (TGF α)⁷⁴ and epidermal growth factor (EGF).⁷⁵

It has been proposed that these altered cytokine profiles and abnormalities in lipid metabolism, which have also been identified,⁷⁶ may play a role in pathogenesis.

Recently, it has been reported that transgenic mice with constitutional activation of nrf-2, which contains XRE in its promoter, develop chloracne-like lesions.⁷⁷ This is reportedly related to the upregulation of the growth factor epigen (*Epgn*), secretory leukocyte peptidase inhibitor (Slpi), and small proline-rich protein 2d (Sprr2d). In hair follicles, the latter three were identified as the likely causes of infundibular acanthosis, hyperkeratosis, and cyst formation.⁷⁷

Cutaneous Carcinogenesis

AHR is involved in cutaneous carcinogenesis. Exposure to tar has long been recognized by dermatologists to cause premalignant lesions, known as tar keratosis. They are considered to be due to polycyclic aromatic hydrocarbons (PAHs), which are components of tar.⁷⁸ PAHs are known ligands of AHR.

Human subjects are less susceptible to the carcinogenic effects of tars compared to mice, as evidenced by the long historical use of tar preparations with few reports of carcinogenesis. Nonetheless, scrotal carcinomas were historically reported amongst London chimney sweepers.

Carcinogenicity may be dependent upon on whether the induction of cytochrome p 450 enzymes results in the detoxification or generation of potential carcinogens.⁷⁹

Stimulation of AHR leads to MAPK signaling.^{5,6} This can be mediated by tryptophan photoproducts such as FICZ¹⁶ generated on exposure to UV radiation. MAPK signaling

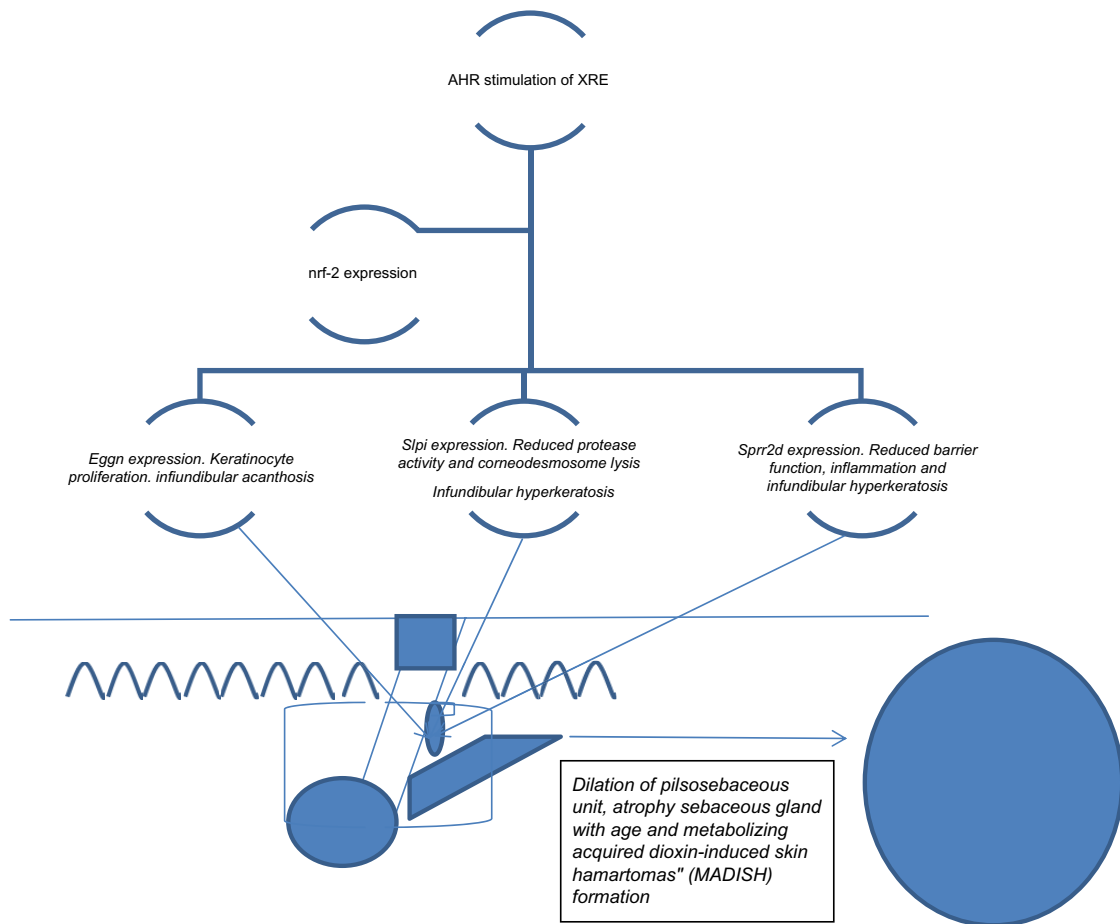


Figure 4. Proposed pathogenesis of chloracne. Ligand binding to the AHR leads to nrf-2-mediated expression of *Eggn*, *Slpi*, and *Sprr2d*. This causes infundibular hyperkeratosis and obstruction of the pilosebaceous unit. With the progress of time, the sebaceous gland undergoes atrophy and a MADISH is formed.

leads to the expression of COX-2,⁴⁷ which plays a role in cutaneous carcinogenesis.⁴⁹

Disorders Involving TH17 Lymphocytes

Psoriasis is the archetypical TH17-mediated disease. TH17 responses are also important in autoimmune diseases.

Psoriasis. Psoriasis (Fig. 5) is a common cutaneous disorder affecting 3% of the population. It is believed to be due to overactivity in the TH17 limb of the immune response and is characterized by well-defined erythro-squamous plaques with a distinctive silvery scale found predominantly on extensor surfaces. Several variants are recognized, including flexural variants, a sebo-psoriatic variant, which overlaps with seborrheic dermatitis, and less common pustular variants. Flexural and sebo-psoriatic variants are likely to be related to TH17 hyper-reactivity to commensal *Candida sp.* and *Malassezia sp.*

The AHR is known to be involved in development of the TH17 subset of T cells and their cytokines, IL-17 and IL-22.⁶⁸ IL-17 is known to be involved in the pathogenesis of psoriasis⁶⁶ and autoimmunity.⁶⁷ Deficiency of the AHR is known to exacerbate psoriasis.⁸⁰

Dermatologists, if unknowingly, have been using AHR modulation in the management of psoriasis since the introduction of coal tar. PAHs, and possibly other components, are known to be active at AHR.⁸¹

Phototherapy is a highly effective treatment for psoriasis. It is notable that one of the known endogenous ligands of AHR, FICZ, is a photoproduct of cutaneous tryptophan.

Scleroderma. Scleroderma (Fig. 6) is a fibrotic disease. It is divided into localized (morphea) and generalized (progressive systemic sclerosis) variants. The latter is distinguished by the presence of Raynaud's phenomenon (transient digital vasospasm usually in response to cold) and pulmonary, esophageal, and renal involvement. The cause is unknown, but it is considered an autoimmune disorder. A congenital form of scleroderma with a poor prognosis, known as infantile stiff skin syndrome, is due to mutations in the fibrillin-1 gene.⁸² Fibrillin-1 is a component of the microfibrils of the extracellular matrix and a binding site for cellular integrins, allowing resident cells to bind to the extracellular matrix. Antibodies to fibrillin-1 have been detected in patients with both morphea⁸³ and scleroderma.⁸⁴

TGF β is a major fibrotic cytokine and displays altered expression in scleroderma.⁸⁵ TGF β is secreted from the cell in

a large latent complex (LLC) that includes the active cytokine, a dimer of its processed N-terminal pro-peptide (latency associated peptide or LAP), and one of three latent TGF β binding proteins (LTBP-1, -3, or -4). As implied by mouse models and confirmed biochemically, fibrillin-1-rich microfibrils contribute to targeting of the LLC to the extracellular matrix by direct interaction with LTBPs. Failed matrix sequestration of the LLC in fibrillin-1-deficient patients and mice promotes increased availability of the TGF β family of cytokines.

The sclerodermoid disorders include eosinophilic fasciitis and eosinophilia-myalgia syndrome, both of which^{86,87} are associated with L-tryptophan ingestion. The majority of L-tryptophan is converted by the KP to NAD, several intermediates of which have been identified as AHR ligands.^{19–21} In addition, agents used in the management of Parkinson's disease, which are inhibitors of kynureninase,⁸⁸ have been reported to have cutaneous sclerosis as a side effect.⁸⁹ This would be consistent with prolonged activation of AHR by the KP metabolite, kynurenine, mediating cutaneous sclerosis.

Noakes et al.²⁶ reported TGF β 1 production in dermal dendritic cells and endothelium in response to quinolinic acid, a KP metabolite, in a human subject. In patients with morphea, KP activation has been identified in infiltrating leucocytes, endothelium, the basal layer of the epidermis, and eccrine units,⁹⁰ suggesting that an ample supply of AHR ligands is present in this condition.

The pro-fibrotic cytokines are TH17-driven in systemic sclerosis,⁹¹ supportive of AHR involvement in view of the central role it plays in TH17 expansion. In addition, pp60^{src} released by AHR on ligand binding has been demonstrated to play a significant role in fibroblast activation.⁹² Fibroblasts from AHR-deficient mice display increased TGF β production⁹³ and marked dermal fibrosis.⁹⁴ Once again, the concept of effector and regulatory ligands is relevant. Long-acting ligands such as TCDD⁹⁵ have been reported to produce cutaneous sclerosis. In these circumstances, long-acting ligands appear to produce an AHR-null effect. Phototherapy is an evidenced-based therapeutic modality used in the management of scleroderma.⁹⁶ It is tempting to postulate that the effects are mediated via AHR. FICZ is a photoproduct of tryptophan, which acts as an effector ligand at AHR and thus may be expected to reduce dermal fibrosis.

Tranilast is an agent marketed in Japan and Korea for the management of both allergies and keloids. It has reported activity at AHR³³ and a modulatory effect on the KP.³² As an antifibrotic agent, tranilast is anticipated to act as an effector ligand at AHR.

Scleroderma, both generalized and localized, is currently considered to be an autoimmune disorder. AHR is important in regulating immune responses. TCDD is potently immunosuppressive,⁹⁷ promoting the development of T_{reg} cells. The endogenous ligand, kynurenine, has also been reported to have the same action.¹⁹ Thus, modulation of AHR may be a means of suppressing autoimmune disorders and promoting T_{reg} cell

differentiation. Nonetheless, the effects of AHR are complicated by the regulatory nature of some ligands and the effector nature of others. FICZ as an effector ligand has been reported to promote TH17 expansion and worsen experimental allergic encephalomyelitis.⁹⁸ The AHR agonist ITE has an inhibitory effect on scarring by inhibition of TGF β 1 myofibroblast differentiation, although this appears to be in a manner independent of the AHR receptor.⁹⁹

The initial precipitating event is thought to be endothelial damage.¹⁰⁰ This may be precipitated by viruses.¹⁰¹ Anti-endothelial antibodies have been found in scleroderma.¹⁰¹ This results in elevated levels of vascular endothelial growth factor (VEGF).¹⁰² VEGF is an inducer of IDO,¹⁰³ allowing the generation of downstream metabolites and activation of the AHR. In addition, TGF β sustains IDO expression,¹⁰⁴ thereby establishing an autocrine loop, which may account for the delayed response traditionally seen with immunosuppressive therapy.

Disorders of Cutaneous Barrier Function

Atopic dermatitis. Atopic dermatitis is a common skin condition affecting up to 20% of children and 3% of adults. It is characterized by a poorly defined pruritic eruption, which histologically displays spongiosis. As previously noted, loss of function in the filaggrin gene is thought to be responsible.

EGFR signaling is known to attenuate the development and relapse of atopic dermatitis.⁶⁰ EGF/EGFR signals through the MAPK pathway, which is activated by pp60^{src} released on AHR ligand binding.⁴ The use of EGFR inhibitors in cancer patients is associated with cutaneous eruptions, which share¹⁰⁵ many features with atopic dermatitis.

Coal tar is a traditional treatment for atopic dermatitis. Van den Bogaard et al.⁸¹ demonstrated AHR-mediated skin barrier repair in atopic dermatitis patients with tar preparations. Counterintuitively, however, TCDD has been reported to exacerbate atopic dermatitis,¹⁰⁶ representative of the pleotropic regulatory and effector responses seen with AHR.

Phototherapy is the therapeutic modality used in atopic dermatitis.¹⁰⁷ It would be tempting to postulate that its effects are mediated by FICZ.

Disorders of Pigmentation

Vitiligo. Vitiligo (Fig. 7) is a de-pigmenting disease characterized by an autoimmune attack on, and subsequent loss of, melanocytes. Vitiligo is a partly understood condition. Current models would suggest that a primary abnormality is present in melanocytes.¹⁰⁸ Oxidative stress leads to melanocyte death,¹⁰⁹ and the subsequent autoimmune response, which develops against liberated melanocyte antigens, results in the perpetuation of the condition.

AHR plays a central role in cellular antioxidant responses via Nrf2 signaling. In addition, TH17 responses, in which

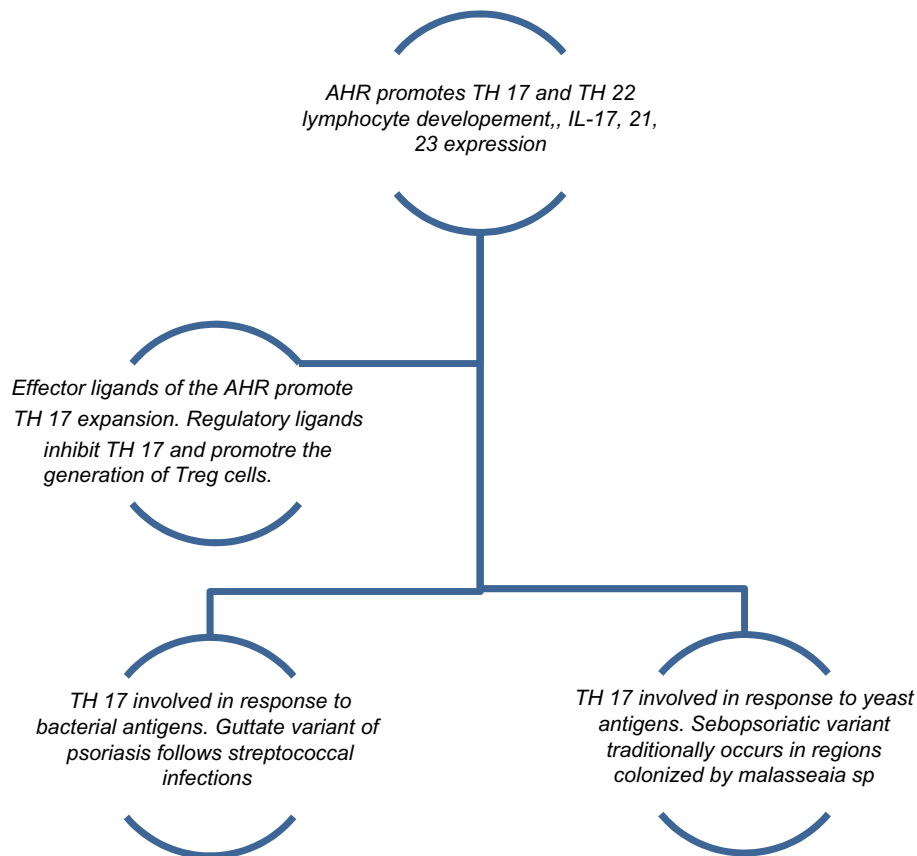


Figure 5. Proposed involvement of the AHR in the pathogenesis of psoriasis. Enhanced TH 17 responsiveness to bacterial antigens likely explains the guttate variant seen after streptococcal infections. The sebo-psoriatic and flexural variants are probably due to enhanced responsiveness to *Malassezia* and *Candida sp.*, respectively.

AHR is known to play a role, are involved in the autoimmune responses in vitiligo.¹¹⁰ Importantly, polymorphisms in AHR have been reported as a susceptibility factor for vitiligo.¹¹¹

In addition, AHR is involved in the tanning response. It has also been demonstrated that hyperpigmentation induced by cigarette smoking is mediated via AHR.¹¹² The *c-kit*/stem cell factor system is involved in melanocyte homeostasis,¹¹³ and both contain XREs that respond to the AHR.

Malassezia-Associated Diseases

Malassezia species, especially *M. furfur* and *M. globosa*, generate a number of potent AHR ligands including indirubin, FICZ, indolo[3,2-*b*]carbazole (ICZ), malassezin, and pityriacitrin.¹¹⁴ These organisms are normal commensals of the human integument and are known to play a role in a number of dermatological conditions. Tryptophan is excreted in human sweat¹¹⁵ and is the source of these metabolites.¹¹⁶

Pityriasis versicolor. Pityriasis versicolor is a pityriasi-form eruption predominantly involving sebaceous areas of the skin. Its presentation varies from hypopigmented macules in tanned skin to erythematous or brown macules depending on the species of *Malassezia sp.* involved.

Pityriasis versicolor is due to the overgrowth of *Malassezia* species, most commonly *M. furfur* and *M. globosa*. Impairment

of the tanning response is characteristic of colonization, and depigmentation persists long after mycological clearance. Many species produce malassezin, an AHR agonist that has been reported to cause apoptosis of melanocytes.¹¹⁷

Seborrhoeic dermatitis. Seborrhoeic dermatitis is a pruritic eruption involving the seborrhoeic regions of the skin classically displaying a greasy scale. It is currently considered to be mediated by *Malassezia sp.* based on the known response to agents directed against *Malassezia*. The AHR ligands Malassezin and ICZ are selectively produced by *Malassezia* yeast isolated from the scalps of patients with seborrhoeic dermatitis¹¹⁸ compared to healthy individuals.

Cutaneous Disease known to Have an Association with Smoking

Tobacco smoke is a source of PAH,¹¹⁹ a known AHR ligand. Smoking has a reported association with palmoplantar pustulosis, a localized version pustular psoriasis.¹²⁰ AHR is known to be involved in the development of the TH17 subset of T cells and their cytokines IL-17 and IL 22.⁶⁸ Increased levels of IL-17 have been reported in both the serum and lesions of patients with palmoplantar pustulosis.¹²¹

Hidradenitis suppurativa, a chronic noninfectious suppurative eruption arising in apocrine-bearing skin, has also been

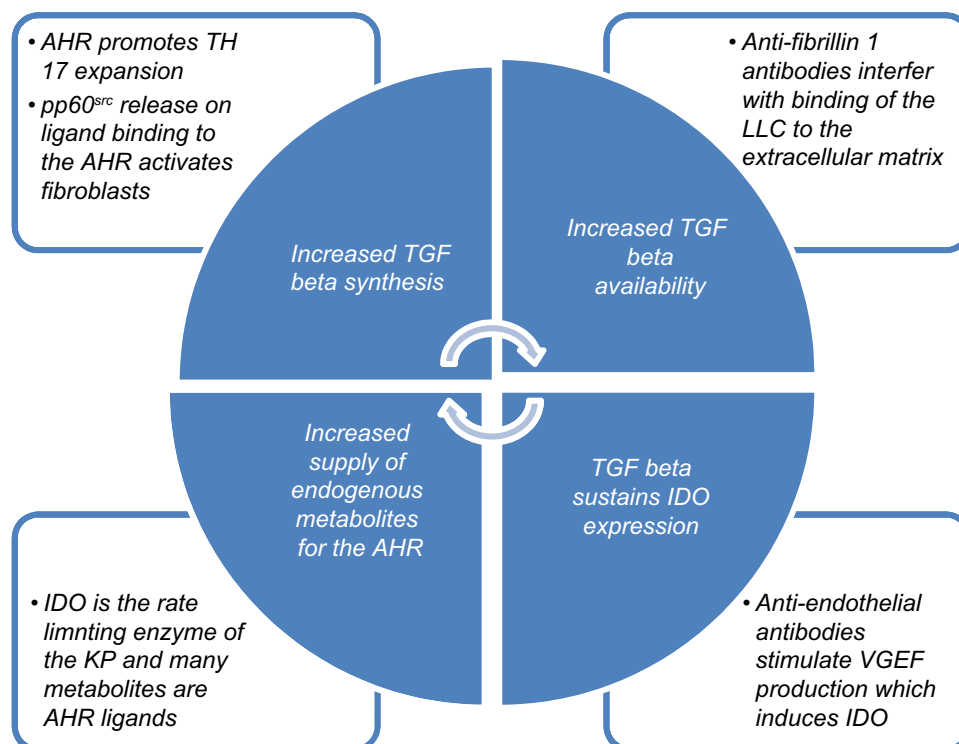


Figure 6. Proposed involvement of the AHR in scleroderma. A complex interplay involving anti-endothelial and fibrillin-1 antibodies, enhanced TH 17 responsiveness, and kynurenine metabolites are likely to be involved. AHR is involved in the mediation of several of these processes.



Figure 7. Proposed involvement of AHR in the pathogenesis of vitiligo. TH 17-mediated autoimmunity and a reduced capacity of melanocytes to manage oxidative stress are AHR mediated.

reported to be precipitated by smoking.¹²² Interestingly, reduced numbers of sebaceous glands have been reported in patients with hidradenitis suppurativa.¹²³ This may be relevant considering that chloracne is characterized by sebaceous gland atrophy.

Conclusion

AHR is potentially involved in a range of cutaneous disorders, and successful manipulation of this receptor is likely to offer significant therapeutic benefits. Yet, the recognition that both effector and regulatory ligands exist means the results of manipulation can be both paradoxical and unpredictable. This paradox, however, is well known in clinical practice. Psoriasis, a TH17-mediated disorder, may occasionally destabilize into the more dangerous pustular variants in response to treatment with tar preparations or phototherapy, which are active at AHR. A better understanding of the role of AHR would likely reduce these adverse reactions.

It would be tempting to postulate that the effects of phototherapy are mediated via AHR, thus raising the possibility that appropriate agonists may achieve the same therapeutic response without patient inconvenience, cost of equipment, and use of potentially carcinogenic ultraviolet light. This would represent a significant advance in the management.

The sclerodermoid disorders remain poorly understood, and treatments are suboptimal. Involvement of the kynurenine metabolites and their interactions with AHR has long been suspected based on the documented activity of this pathway in several of these disorders. A better understanding of these interactions would allow the development of improved management strategies.

Malassezia sp. have long remained a quandary. The normal skin commensal produces no disease in the majority



of the population, yet is responsible for a range of common problematic disorders in a significant minority. Why it produces different disease patterns in different individuals is also unknown. An understanding of the interactions it has with the AHR may help to clarify this and lead to improvements in treatment.

There remain many unwritten chapters in the saga of AHR, which is part of a complex and multilayered regulatory system within the skin. Its manipulation in the management of cutaneous disorders dates from the earliest days of dermatology; yet its potential remains to be fully realized. Over the last several decades, it has held a prominent place in the field of toxicology, yet this may be a receptor whose time has come.

Author Contributions

Conceived the concepts: RN. Wrote the first draft of the manuscript: RN. Made critical revisions: RN. The author reviewed and approved of the final manuscript.

REFERENCES

- Denison MS, Nagy SR. Activation of the aryl hydrocarbon receptor by structurally diverse exogenous and endogenous chemicals. *Annu Rev Pharmacol Toxicol.* 2003;43(1):309–34.
- Carlstedt-Duke JM. Tissue distribution of the receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin in the rat. *Cancer Res.* 1979;39(8):3172–6.
- Johansson G, Gillner M, Högberg B, Gustafsson JA. The TCDD receptor in rat intestinal mucosa and its possible dietary ligands. *Nutr Cancer.* 1981;3(3):134–44.
- Agostinis P, Garmyn M, Van Laethem A. The Aryl hydrocarbon receptor: an illuminating effector of the UVB response. *Sci Signal.* 2007;2007(403):e49.
- Enan E, Matsumura F. Identification of c-Src as the integral component of the cytosolic Ah receptor complex, transducing the signal of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) through the protein phosphorylation pathway. *Biochem Pharmacol.* 1996;52(10):1599–612.
- Fritsche E, Schafer 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(21):8851–6.
- Furue M, Takahara M, Nakahara T, Uchi H. Role of AhR/ARNT system in skin homeostasis. *Arch Dermatol Res.* 2014;306(9):769–79.
- Schnekenburger M, Peng L, Puga A. HDAC1 bound to the Cyp1a1 promoter blocks histone acetylation associated with Ah receptor-mediated trans-activation. *Biochim Biophys Acta.* 2007;1769:569–78.
- Pollenz RS. The mechanism of AH receptor protein down-regulation (degradation) and its impact on AH receptor-mediated gene regulation. *Chem Biol Interact.* 2002;141:41–61.
- Mimura J, Ema M, Sogawa K, Fujii-Kuriyama Y. Identification of a novel mechanism of regulation of Ah (dioxin) receptor function. *Genes Dev.* 1999;13(1):20–5.
- Matthews J, Gustafsson JA. Estrogen receptor and aryl hydrocarbon receptor signaling pathways. *Nucl Recept Signal.* 2006;4:e016.
- Puga A, Ma C, Marlowe JL. The aryl hydrocarbon receptor cross-talks with multiple signal transduction pathways. *Biochem Pharmacol.* 2009;77:713–22.
- Murphy KA, Quadro L, White LA. The intersection between the Aryl hydrocarbon receptor (AhR)- and retinoic acid-signaling pathways. *Vitam Horm.* 2007;75:33–67.
- Tian Y. Ah receptor and NF- κ B interplay on the stage of epigenome. *Biochem Pharmacol.* 2009;77:670–80.
- Vogel CF, Khan EM, Leung PS, et al. Cross-talk between Aryl hydrocarbon receptor and the inflammatory response a role for nuclear factor- κ B. *J Biol Chem.* 2014;289(3):1866–75.
- Rannug U, Rannug A, Sjöberg U, Li H, Westerholm R, Bergman J. Structure elucidation of two tryptophan-derived, high affinity Ah receptor ligands. *Chem Biol.* 1995;2(12):841–5.
- Wang C, Ye Z, Kijlstra A, Zhou Y, Yang P. Activation of the aryl hydrocarbon receptor affects activation and function of human monocyte-derived dendritic cells. *Clin Exp Immunol.* 2014;177(2):521–30.
- Mándi Y, Vécsei L. The kynurenine system and immunoregulation. *J Neural Transm.* 2012;119(2):197–209.
- Mezrich JD, Fechner JH, Zhang X, Johnson BP, Burlingham WJ, Bradfield CA. An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells. *J Immunol.* 2010;185(6):3190–8.
- DiNatale BC, Murray IA, Schroeder JC, et al. Kynurenic acid is a potent endogenous aryl hydrocarbon receptor ligand that synergistically induces interleukin-6 in the presence of inflammatory signaling. *Toxicol Sci.* 2010;115(1):89–97.
- Lowe MM, Mold JE, Kanwar B, et al. Identification of cinnabarinic acid as a novel endogenous Aryl hydrocarbon receptor ligand that drives IL-22 production. *PLoS One.* 2014;9(2):e87877.
- Widner B, Werner ER, Schennach H, Wachter H, Fuchs D. Simultaneous measurement of serum tryptophan and kynurenine by HPLC. *Clin Chem.* 1997;43(12):2424–6.
- Heath-Pagliuso S, Rogers WJ, Tullis K, et al. Activation of the Ah receptor by tryptophan and tryptophan metabolites. *Biochemistry.* 1998;37:11508–15.
- Bankoti J, Rase B, Simones T, Shepherd DM. Functional and phenotypic effects of AhR activation in inflammatory dendritic cells. *Toxicol Appl Pharmacol.* 2010;246:18–28.
- Quintana FJ. LeA(H)Rning self-control. *Cell Res.* 2014;24(10):1155–6.
- Noakes R, Spelman L, Williamson R. Is the L-tryptophan metabolite quinolinic acid responsible for eosinophilic fasciitis? *Clin Exp Med.* 2006;6(2):60–4.
- Van Voorhis M, Fechner JH, Zhang X, Mezrich JD. The Aryl hydrocarbon receptor: a novel target for immunomodulation in organ transplantation. *Transplantation.* 2013;95(8):983.
- Quintana FJ, Basso AS, Iglesias AH, et al. Control of Treg and TH17 cell differentiation by the aryl hydrocarbon receptor. *Nature.* 2008;453(7191):65–71.
- Duarte JH, Di Meglio P, Hirota K, Ahlfors H, Stockinger B. Differential influences of the Aryl hydrocarbon receptor on Th17 mediated responses in vitro and in vivo. *PLoS One.* 2013;8(11):e79819.
- Jux B, Kadow S, Esser C. Langerhans cell maturation and contact hypersensitivity are impaired in aryl hydrocarbon receptor null mice. *J Immunol.* 2009;182(11):6709–17.
- Nguyen NT, Kimura A, Nakahama T, et al. Aryl hydrocarbon receptor negatively regulates dendritic cell immunogenicity via a kynurenine-dependent mechanism. *Proc Natl Acad Sci U S A.* 2010;107(46):19961–6.
- Noakes RR. Effects of tranilast on the urinary excretion of kynurenine and quinolinic acid under conditions of L tryptophan loading. *Int J Tryptophan Res.* 2013;6:67–71.
- Hu W, Zhao J, Pei G. Activation of aryl hydrocarbon receptor (ahr) by tranilast, an anti-allergy drug, promotes miR-302 expression and cell reprogramming. *J Biol Chem.* 2013;288(32):22972–84.
- O'Donnell EF, Saili KS, Koch DC, et al. The anti-inflammatory drug leflunomide is an agonist of the aryl hydrocarbon receptor. *PLoS One.* 2010;5(10):e13128.
- Chen Y, Guillemin GJ. Kynurenine pathway metabolites in humans: disease and healthy states. *Int J Tryptophan Res.* 2009;2:1–19.
- Bittinger MA, Nguyen LP, Bradfield CA. Aspartate aminotransferase generates proagonists of the aryl hydrocarbon receptor. *Mol Pharmacol.* 2003;64:550–556.
- Creed D. The photophysics and photochemistry of the near-UV absorbing amino acids-I. Tryptophan and its simple derivatives. *Photochem Photobiol.* 1984;39(4):537–62.
- Diani-Moore S, Labitzke E, Brown R, Garvin A, Wong L, Rifkind AB. Sunlight generates multiple tryptophan photoproducts eliciting high efficacy CYP1A induction in chick hepatocytes and in vivo. *Toxicol Sci.* 2006;90(1):96–110.
- Esser C, Barga I, Weighardt H, Haarmann-Stemann T, Krutmann J. Functions of the aryl hydrocarbon receptor in the skin. *Semin Immunopathol.* 2013;35(6):677–91.
- Mimura J, Yamashita K, Nakamura K, et al. Loss of teratogenic response to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in mice lacking the Ah (dioxin) receptor. *Genes Cells.* 1997;2(10):645–54.
- Schmidt JV, Su GH, Reddy JK, Simon MC, Bradfield CA. Characterization of a murine AhR null allele: involvement of the Ah receptor in hepatic growth and development. *Proc Natl Acad Sci U S A.* 1996;93(13):6731–6.
- Gonzalez FJ, Fernandez-Salguero P. The aryl hydrocarbon receptor studies using the AHR-null mice. *Drug Metab Dispos.* 1998;26(12):1194–8.
- Barouki R, Coumoul X, Fernandez-Salguero PM. The aryl hydrocarbon receptor, more than a xenobiotic-interacting protein. *FEBS Lett.* 2007;581:3608–15.
- Denison MS, Whitlock JP. Xenobiotic-inducible transcription of cytochrome P450 genes. *J Biol Chem.* 1995;270(31):18175–8.
- 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.* 2011;132(1):59–68.
- Miao W, Hu L, Scrivens PJ, Batist G. Transcriptional regulation of NF-E2 p45-related factor (NRF2) expression by the aryl hydrocarbon receptor-xenobiotic response element signaling pathway: direct cross-talk between phase I and II drug-metabolizing enzymes. *J Biol Chem.* 2005;280(21):20340–8.



47. Degner SC, Papoutsis AJ, Selmin O, Romagnolo DF. Targeting of aryl hydrocarbon receptor-mediated activation of cyclooxygenase-2 expression by the indole-3-carbinol metabolite 3, 3'-diindolylmethane in breast cancer cells. *J Nutr*. 2009;139(1):26–32.
48. Ono Y, Torii K, Fritsche E, et al. Role of the aryl hydrocarbon receptor in tobacco smoke extract-induced matrix metalloproteinase-1 expression. *Exp Dermatol*. 2013;22(5):349–53.
49. Escuin-Ordinas H, Atefi M, Fu Y, et al. COX-2 inhibition prevents the appearance of cutaneous squamous cell carcinomas accelerated by BRAF inhibitors. *Mol Oncol*. 2014;8(2):250–60.
50. Quan T, Little E, Quan H, Qin Z, Voorhees JJ, Fisher GJ. Elevated matrix metalloproteinases and collagen fragmentation in photodamaged human skin: impact of altered extracellular matrix microenvironment on dermal fibroblast function. *J Invest Dermatol*. 2013;133(5):1362.
51. Kanagawa Y, Matsumoto S, Koike S, et al. Association of clinical findings in Yusho patients with serum concentrations of polychlorinated biphenyls, polychlorinated quarterphenyls and 2,3,4,7,8-pentachlorodibenzofuran more than 30 years after the poisoning event. *Environ Health*. 2008;7(1):47.
52. Dunagin WG. Cutaneous signs of systemic toxicity due to dioxins and related chemicals. *J Am Acad Dermatol*. 1984;10(4):688–700.
53. Luecke S, Backlund M, Jux B, Esser C, Krutmann J, Rannug A. The aryl hydrocarbon receptor (AHR), a novel regulator of human melanogenesis. *Pigment Cell Melanoma Res*. 2010;23(6):828–33.
54. Lennartsson J, Rönstrand L. Stem cell factor receptor/c-Kit: from basic science to clinical implications. *Physiol Rev*. 2012;92(4):1619–49.
55. Jux B, Kadow S, Luecke S, Rannug A, Krutmann J, Esser C. The Aryl hydrocarbon receptor mediates UVB radiation-induced skin tanning. *J Invest Dermatol*. 2010;131(1):203–10.
56. Kalinin A, Marekov LN, Steinert PM. Assembly of the epidermal cornified cell envelope. *J Cell Sci*. 2001;114(17):3069–70.
57. Weidinger S, Illig T, Baurecht H, et al. Loss-of-function variations within the flaggrin gene predispose for atopic dermatitis with allergic sensitizations. *J Allergy Clin Immunol*. 2006;118(1):214–9.
58. Tauchi M, Hida A, Negishi T, et al. Constitutive expression of aryl hydrocarbon receptor in keratinocytes causes inflammatory skin lesions. *Mol Cell Biol*. 2005;25(21):9360–8.
59. Sääf A, Pivarsci A, Winge MC, et al. Characterization of EGFR and ErbB2 expression in atopic dermatitis patients. *Arch Dermatol Res*. 2012;304(10):773–80.
60. Zhang Z, Xiao C, Gibson AM, Bass SA, Khurana Hershey GK. EGFR signaling blunts allergen-induced IL-6 production and Th17 responses in the skin and attenuates development and relapse of atopic dermatitis. *J Immunol*. 2014;192(3):859–66.
61. Sutter CH, Yin H, Li Y, et al. EGF receptor signaling blocks aryl hydrocarbon-receptor-mediated transcription and cell differentiation in human epidermal keratinocytes. *Proc Natl Acad Sci U S A*. 2009;106(11):4266–71.
62. Matsue H, Cruz PD Jr, Bergstresser PR, Takashima A. Cytokine expression by epidermal cell subpopulations. *J Invest Dermatol*. 1992;99:42S–5S.
63. Henley DV, Bellone CJ, Williams DA, Ruh MF. MAPK signaling pathways modulate IL-1beta expression in human keratinocytes. *Arch Biochem Biophys*. 2004;424(1):112–8.
64. Podechard N, Lecureur V, Le Ferrec E, et al. Interleukin-8 induction by the environmental contaminant benzo (a) pyrene is aryl hydrocarbon receptor-dependent and leads to lung inflammation. *Toxicol Lett*. 2008;177(2):130–7.
65. Bennett CL, van Rijn E, Jung S, et al. Inducible ablation of mouse Langerhans cells diminishes but fails to abrogate contact hypersensitivity. *J Cell Biol*. 2005;169(4):569–76.
66. Lowes MA, Kikuchi T, Fuentes-Duculan J, et al. Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. *J Invest Dermatol*. 2008;128(5):1207–11.
67. Bettelli E, Oukka M, Kuchroo VK. TH-17 cells in the circle of immunity and autoimmunity. *Nat Immunol*. 2007;8(4):345–50.
68. Veldhoen M, Hirota K, Westendorf AM, et al. The aryl hydrocarbon receptor links TH17-cell-mediated autoimmunity to environmental toxins. *Nature*. 2008;453(7191):106–9.
69. Fujita H, Nograla KE, Kikuchi T, Gonzalez J, Carucci JA, Krueger JG. Human Langerhans cells induce distinct IL-22-producing CD4+ T cells lacking IL-17 production. *Proc Natl Acad Sci U S A*. 2009;106(51):21795–800.
70. Tan NS, Wahli W. The emerging role of Nrf2 in dermatotoxicology. *EMBO Mol Med*. 2014;6(4):431–3.
71. 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(1):310–7.
72. Panteleyev AA, Bickers DR. Dioxin-induced chloracne-reconstructing the cellular and molecular mechanisms of a classic environmental disease. *Exp Dermatol*. 2006;15(9):705–30.
73. Osborne R, Greenlee WF. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) enhances terminal differentiation of cultured human epidermal cells. *Toxicol Appl Pharmacol*. 1985;77(3):434–43.
74. Gaido KW, Maness SC, Leonard LS, Greenlee WF. 2,3,7,8-Tetrachlorodibenzo-p-dioxin-dependent regulation of transforming growth factors-alpha and-beta 2 expression in a human keratinocyte cell line involves both transcriptional and post-transcriptional control. *J Biol Chem*. 1992;267(34):24591–95.
75. Greenlee WF, Dold KM, Osborne R. Actions of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on human epidermal keratinocytes in culture. *In Vitro Cell Dev Biol*. 1985;21(9):509–12.
76. Cunliffe WJ, Williams M, Edwards JC, et al. An explanation for chloracne – an industrial hazard. *Acta Derm Venereol*. 1974;55(3):211–4.
77. Schäfer M, Willrodt AH, Kurinna S, et al. Activation of Nrf2 in keratinocytes causes chloracne (MADISH)-like skin disease in mice. *EMBO Mol Med*. 2014;6(4):442–57.
78. Gawkrödger DJ. Occupational skin cancers. *Occup Med*. 2004;54(7):458–63.
79. Shimizu Y, Nakatsuru Y, Ichinose M, et al. Benzo[a]pyrene carcinogenicity is lost in mice lacking the aryl hydrocarbon receptor. *Proc Natl Acad Sci U S A*. 2000;97(2):779–82.
80. 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(6):989–1001.
81. van den Bogaard EH, Bergboer JG, Vonk-Bergers M, et al. Coal tar induces AHR-dependent skin barrier repair in atopic dermatitis. *J Clin Invest*. 2013;123(2):917–27.
82. Loeyls BL, Gerber EE, Riegert-Johnson D, et al. Mutations in fibrillin-1 cause congenital scleroderma: stiff skin syndrome. *Sci Transl Med*. 2010;2(23):23ra20.
83. Arnett FC, Tan FK, Uziel Y, et al. Autoantibodies to the extracellular matrix microfibrillar protein, fibrillin 1, in patients with localized scleroderma. *Arthritis Rheum*. 1999;42:2656–9.
84. Tan FK, Arnett FC, Antohi S, et al. Autoantibodies to the extracellular matrix microfibrillar protein, fibrillin-1, in patients with scleroderma and other connective tissue diseases. *J Immunol*. 1999;163(2):1066–72.
85. Denton CP, Abraham DJ. Transforming growth factor-β and connective tissue growth factor: key cytokines in scleroderma pathogenesis. *Curr Opin Rheumatol*. 2001;13(6):505–11.
86. Freundlich B, Werth VP, Rook AH, et al. L-tryptophan ingestion associated with eosinophilic fasciitis but not progressive systemic sclerosis. *Ann Intern Med*. 1990;112:758–62.
87. Martin RW, Duffy J, Engel AG, et al. The clinical spectrum of the eosinophilia-myalgia syndrome associated with L-tryptophan ingestion. *Ann Intern Med*. 1990;113:124–34.
88. Smith SA, Pogson CI. Effects of benserazide and carbidopa on the metabolism of L-tryptophan by isolated rat liver cells. *Biochem Pharmacol*. 1981;30(6):623–8.
89. Perez MI, Kohn SR. Systemic sclerosis. *J Am Acad Dermatol*. 1993;28(4):525–47.
90. Noakes R, Mellick N. Immunohistochemical studies of the kynurenine pathway in morphea. *Int J Tryptophan Res*. 2013;6:97.
91. Yang X, Yang J, Xing X, Wan L, Li M. Increased frequency of Th17 cells in systemic sclerosis is related to disease activity and collagen overproduction. *Arthritis Res Ther*. 2014;16(1):R4.
92. Skhirtladze G, Distler O, Dees C, et al. Src kinases in systemic sclerosis: central roles in fibroblast activation and in skin fibrosis. *Arthritis Rheum*. 2008;50(5):1475–84.
93. Elizondo G, Fernandez-Salguero P, Sheikh MS, et al. Altered cell cycle control at the G(2)/M phases in aryl hydrocarbon receptor-null embryo fibroblast. *Mol Pharmacol*. 2000;57(5):1056–63.
94. Fernandez-Salguero PM, Ward JM, Sundberg JP, Gonzalez FJ. Lesions of Aryl-hydrocarbon receptor-deficient mice. *Vet Pathol*. 1997;34(6):605–14.
95. Poskitt LB, Duffill MB, Rademaker M. Chloracne, palmoplantar keratoderma and localized scleroderma in a weed sprayer. *Clin Exp Dermatol*. 1994;19(3):264–7.
96. Kreuter A, Hyun J, Stücker M, Sommer A, Altmeyer P, Gambichler T. A randomized controlled study of low-dose UVA1, medium-dose UVA1, and narrowband UVB phototherapy in the treatment of localized scleroderma. *J Am Acad Dermatol*. 2006;54(3):440–7.
97. Kerkvliet NI. AHR-mediated immunomodulation: the role of altered gene transcription. *Biochem Pharmacol*. 2009;77(4):746–60.
98. Ho PP, Steinman L. The aryl hydrocarbon receptor: a regulator of Th17 and Treg cell development in disease. *Cell Res*. 2008;18(6):605–8.
99. Lehmann GM, Xi X, Kulkarni AA, et al. The aryl hydrocarbon receptor ligand ITE inhibits TGFβ1-induced human myofibroblast differentiation. *Am J Pathol*. 2011;178(4):1556–67.
100. Sartori-Valinotti JC, Tollefson MM, Reed AM. Reed review article updates on morphea: role of vascular injury and advances in treatment. *Autoimmune Dis*. 2013;2013:8.
101. Yves R, Revelen R, Levy Y, et al. Anti-endothelial cell antibodies in systemic sclerosis. *Clin Diagn Lab Immunol*. 1999;6(2):156–60.
102. Dzikankowski-Bartkowiak B, Zebrowska A, Wagerowski-Danielewicz M, Kobos J, Waszczykowska E. Systemic sclerosis and scleroderma circumscripta – disturbances of selected serum parameters which are responsible for vascular changes and CD34 expression in involved skin. *Przegl Lek*. 2009;66(12):1040–5.



103. Marti LC, Pavon L, Severino P, Sibov T, Guilhen D, Moreira-Filho CA. Vascular endothelial growth factor-A enhances indoleamine 2, 3-dioxygenase expression by dendritic cells and subsequently impacts lymphocyte proliferation. *Mem Inst Oswaldo Cruz.* 2014;109(1):70–9.
104. Belladonna ML, Volpi C, Bianchi R, et al. Cutting edge: autocrine TGF-beta sustains default tolerogenesis by IDO-competent dendritic cells. *J Immunol.* 2008;181(8):5194–8.
105. Lacouture ME, Maitland ML, Segaert S, et al. A proposed EGFR inhibitor dermatologic adverse event-specific grading scale from the MASCC skin toxicity study group. *Supportive Care Cancer.* 2010;18(4):509–22.
106. Ito T, Inouye K, Nohara K, Tohyama C, Fujimaki H. TCDD exposure exacerbates atopic dermatitis-related inflammation in NC/Nga mice. *Toxicol Lett.* 2008;177(1):31–7.
107. Krutmann J. Phototherapy for atopic dermatitis. *Clin Exp Dermatol.* 2000;25(7):552–8.
108. Kitamura R, Tsukamoto K, Harada K, et al. Mechanisms underlying the dysfunction of melanocytes in vitiligo epidermis: role of SCF/KIT protein interactions and the downstream effector, MITF-M. *J Pathol.* 2004;202(4):463–75.
109. Passi S, Grandinetti M, Maggio F, Stancato A, De Luca C. Epidermal oxidative stress in vitiligo. *Pigment Cell Res.* 1998;11(2):81–5.
110. Bassiouny DA, Shaker O. Role of interleukin-17 in the pathogenesis of vitiligo. *Clin Exp Dermatol.* 2011;36(3):292–7.
111. Wang XW, Li K, Guo S, et al. The association of functional polymorphisms in the aryl hydrocarbon receptor (AHR) gene with the risk of vitiligo in Han Chinese populations. *Br J Dermatol.* 2012;166(5):1081–7.
112. Nakamura M, Ueda Y, Hayashi M, Kato H, Furuhashi T, Morita A. Tobacco smoke-induced skin pigmentation is mediated by the aryl hydrocarbon receptor. *Exp Dermatol.* 2013;22(8):556–8.
113. Grichnik JM, Burch JA, Burchette J, Shea CR. The SCF/KIT pathway plays a critical role in the control of normal human melanocyte homeostasis. *J Invest Dermatol.* 1998;111(2):233–8.
114. Magiatis P, Pappas P, Gaitanis G, et al. *Malassezia* yeasts produce a collection of exceptionally potent activators of the Ah (dioxin) receptor detected in diseased human skin. *J Invest Dermatol.* 2013;133(8):2023–30.
115. Coltman CA, Rowe NJ, Atwell RJ. The amino acid content of sweat in normal adults. *Am J Clin Nutr.* 1966;18(5):373–8.
116. Magiatis P, Mexia N, Galanou M, et al. *Malassezia* spp. extracts and metabolites induce the AhR dependent genes in HaCaT cells. *Planta Med.* 2009;75(9):A33.
117. Krämer HJ, Podobinska M, Bartsch A, et al. Malassezin, a novel agonist of the aryl hydrocarbon receptor from the yeast *Malassezia furfur*, induces apoptosis in primary human melanocytes. *Chembiochem.* 2005;6(5):860–5.
118. Gaitanis G, Magiatis P, Stathopoulou K, et al. AhR ligands, malassezin, and indolo[3,2-b]carbazole are selectively produced by *Malassezia furfur* strains isolated from seborrheic dermatitis. *J Invest Dermatol.* 2008;128(7):1620–5.
119. Hankinson O. The aryl hydrocarbon receptor complex. *Annu Rev Pharmacol Toxicol.* 1995;35(1):307–40.
120. Giménez-García R, Sánchez-Ramón SS, Cuellar-Olmedo LA. Palmoplantar pustulosis: a clinicoepidemiological study. The relationship between tobacco use and thyroid function. *J Eur Acad Dermatol Venereol.* 2003;17(3):276–9.
121. Murakami M, Hagforsen E, Morhenn V, Ishida-Yamamoto A, Iizuka H. Patients with palmoplantar pustulosis have increased IL-17 and IL-22 levels both in the lesion and serum. *Exp Dermatol.* 2011;20(10):845–7.
122. Simonart T. Hidradenitis suppurativa and smoking. *J Am Acad Dermatol.* 2010;62(1):149–50.
123. Kamp S, Fiehn AM, Stenderup K, et al. Hidradenitis suppurativa: a disease of the absent sebaceous gland? Sebaceous gland number and volume are significantly reduced in uninvolved hair follicles from patients with hidradenitis suppurativa. *Br J Dermatol.* 2011;164(5):1017–22.