Frontal Fibrosing Alopecia. An Example of Disrupted Aryl Hydrocarbon Receptor-Mediated Immunological Homeostasis in the Skin?

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Abstract: Sun protection has been recommended by public health authorities to reduce the risk of keratinocyte and melanocyte tumors, yet some sun exposure is required for vitamin D synthesis. Frontal fibrosing alopecia (FFA) is a cicatricial alopecia that has been reported to have an association with facial photoprotection. The brief review proposes the hypothesis that FFA arises as a result of excessive facial photo-protection with a resultant disturbance in immunological homeostasis mediated via the aryl hydrocarbon receptor-kynurenine pathway axis (AHR/KP) leading to the collapse of immune privilege at the hair bulge.

Keywords: sun exposure, aryl hydrocarbon receptor, frontal fibrosing alopecia, 6-formylindolo [3, 2-*b*]carbazole

Introduction

Frontal fibrosing alopecia is a cicatricial alopecia seen most commonly in post-menopausal women which involves the anterior hairline and eyebrows. First described by Kossard,¹ it is considered a variant of lichen planopilaris. The incidence is reported to be rising suggesting a role for environmental factors. Recent attention has focused on the role played by sunscreens and facial care products² and this was supported in a recent multivariate analysis.³ More recently the role of sun exposure in immunological homeostasis has been explored.⁴

The aryl hydrocarbon receptor (AHR) is a cytosolic receptor for low molecular weight molecules, the most widely recognized ligand being 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), which plays an important role in immunological homeostasis in the skin.⁵ 6-formylindolo[3,2-*b*] carbazole (FICZ) is a potent endogenous ligand of the AHR produced by photo-oxidation of the essential amino acid L tryptophan which displays pro-inflammatory properties at lower concentrations and anti-inflammatory properties at higher concentrations.⁶

The hair follicle is a cutaneous appendage that displays immunological privilege,⁷ collapse of which results in TH1 mediated immune destruction of the epithelial hair follicle stem cells (eHFSC)⁸ and permanent hair loss. This article will review our current understanding of the pathogenesis of frontal fibrosing alopecia and the potential role the AHR may play. It postulates that a certain level of sun exposure is required to maintain immunological homeostasis within the skin and frontal fibrosing alopecia arises due to a disruption immunological homeostasis mediated via the AHR/KP axis.

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Discussion

The Pathogenesis of Frontal Fibrosing Alopecia

The hair follicle is a site of immunological privilege. Several mechanisms are at play in the maintenance of immunological privilege.

1. There is reduced or absent expression of the major histocompatibility complex 1 (MHC 1) beta 2 microglobulin complex rendering expression of endogenous peptides ineffectual or impossible.⁹
2. There is a downregulation of MHC class 2 in antigen-presenting cells (APC).⁹ This has been reported to be mediated by AHR agonists.¹⁰
3. A local immunoinhibitory medium is established by the secretion of immunoinhibitory molecules. These include alpha melanocyte-stimulating hormone (α -MSH), transforming growth factor-beta 1 and 2 (TGF- β 1,2), interleukin 10 (IL-10), cortisol and enhanced indoleamine 2,3 di-oxygenase expression (IDO) which depletes the micro-environment of the essential amino acid L tryptophan limiting T cell proliferation.¹¹ A breach of immune privilege leads to TH1-mediated destruction of the eHFSC and permanent destruction of the hair follicle.
4. Expression of peroxisome proliferator-activated receptor-gamma (PPAR- γ) is down-regulated in lichen planopilaris.¹²
5. CD200 is a membrane glycoprotein highly expressed in human follicular stem cells which represents a “no danger signal” to immunosurveillance systems.¹³ Interaction with the CD200 receptor (CD200R) attenuates inflammatory responses and protects eHFSC. CD200 expression has been reported to be a factor in the maintenance of hair follicle immune privilege.¹³

A loss of immunological privilege leads to a CD8 mediated immune destruction, Epithelial–mesenchymal transition (EMT) is involved in the loss of follicles.¹⁴ TGF- β 1, epidermal growth factor (EGF) and interferon-gamma (IFN- λ) are involved in this process.¹⁵

The Aryl Hydrocarbon Receptor

The aryl hydrocarbon receptor (AHR) is a cellular receptor for low molecular weight molecules which plays an important role in cellular oxidation/antioxidation reactions, response to ultraviolet light, pigmentation, and immune regulation.

It is a cytoplasmic receptor that forms part of a multiprotein complex. Chaperoning proteins include heat shock protein 90 (hsp90), hsp23, and hepatitis B virus X-associated protein 2 (XAP2). Pp60^{src} is an associated signaling partner that is released into the cytosol on ligand binding. On ligand binding, the AHR translocates to the nuclear membrane where it binds to the aryl hydrocarbon receptor nuclear transporter (AHRNT). This promotes the expression of genes containing xenobiotic response elements (XRE) in their promoters. Principal amongst these are the cytochrome P450 1A1, 1A2, 1B1 monooxygenases which introduce functional groups prior to conjugation with water-soluble molecules by the Phase 2 detoxification enzymes.

Phase 2 enzyme regulation is via the nuclear factor erythroid derived 2, like 2 transcription factor (Nrf2) which also contains XRE in its promoter allowing the co-ordination of Phase 1 and 2 detoxification reactions. Control is provided firstly by the synthesis of the repressor protein, the aryl hydrocarbon receptor repressor (AHRR) and export of the AHR for cytosolic degradation via the 26S proteasome pathway.

Cross talk exists with the retinoblastoma protein, the estrogen receptor (ER), the retinoic acid signaling pathway and nuclear factor kappa light chain enhancer of activated β cells (NF- κ B) pathway. In addition, Pp60^{src} binds to the EGF receptor initiating mitogen-activated protein kinase (MAPK) signaling. Thus, the AHR can modify multiple signaling pathways.¹⁶

AHR Involvement in the Pathogenesis of Frontal Fibrosing Alopecia

Factors mediating immune privilege at the hair follicle are illustrated in Figure 1.

The KP/AHR Axis

The KP is the metabolic pathway by which L tryptophan is metabolized to nicotinamide. In addition to providing an endogenous supply of nicotinamide, it serves important immunoregulatory roles. The rate-limiting enzyme is indoleamine 2, 3-dioxygenase (IDO). Although the best recognized inducer of this enzyme is interferon-gamma (IFN- λ), it is also induced by the AHR. In addition, a metabolic intermediate of the KP, kynurenine is an AHR agonist.¹⁷ As well as depleting the micro-environment of the essential amino acid L tryptophan thereby inhibiting immune proliferation, many of the intermediates display immunoregulatory properties.

Figure 1 Factors mediating immune privilege at the hair follicle are illustrated on the left of the diagram with the role of the aryl hydrocarbon receptor (AHR) on the right. Cells which do not express MHC 1 are normally subject to natural killer (NK) attack. AHR activity stimulates indoleamine 2,3 di-oxygenase (IDO) and thus the kynurenine pathway (KP), metabolites of which inhibit NK activity. MHC class 2 expression is also downregulated by the AHR. In addition, AHR agonists facilitate the development of regulatory T cells (Treg) and IL-10 secreting TR1 cells which secrete TGF β and IL-10. These in combination with α -MSH create a local immunoinhibitory medium. Finally, the AHR promotes the conversion of extracellular ATP to adenosine which has immune-inhibitory activity. CD200 expression requires an adequate supply of vitamin D which is also dependent on sun exposure.

Natural killer (NK) cells are a component of the innate lymphoid system which preferentially target cells that lack the surface expression of MHC class 1 molecules. Inhibition of NK activity is thus required for the maintenance of immune privilege at the follicular unit. KP metabolites that inhibit NK activity include anthranilic acid, 3-hydroxykynurenine, 3-hydroxyanthranilic acid, quinolinic acid and picolinic acid.¹⁸

Alpha MSH

Alpha MSH displays immunosuppressive properties in the skin¹⁹ and is influenced by AHR activity.²⁰

Regulatory T Cells and TGF β 1,2 and IL-10

FoxP3 T regulatory cells (Treg) and IL-10 secreting type 1 regulatory T cells (TR1) are best recognized regulatory T cell groups. AHR activation increases Treg cells and is important in

the differentiation of TR1 cells.²¹ TGF β is utilized by Treg to suppress cytotoxic tumor responses²² and latent TGF β is carried on the surface of Treg cells linked to the transmembrane protein Glycoprotein A repetitions predominant protein (GARP), via disulfide bonds.²³ Activation is via α V class integrins.

IL-10 is secreted by TR1 cells. The AHR interacts with the transcription factor c-Maf to promote the secretion of IL-10 and IL-21.²⁴ In addition, the AHR and Stat 3 combine to deplete the extracellular environment of Adenosine Triphosphate (ATP) via CD39 generating immunosuppressive adenosine.²⁵

Epithelial–Mesenchymal Transition

AHR activity has been reported both to promote and to inhibit EMT depending on the system and cell type being

investigated. As the AHR promotes the differentiation of Treg which promotes a TGF β enhanced environment,²¹ an expectation of enhanced EMT would not be unexpected. As expected, however, a balance of factors is at play. In a mouse model, the AHR agonist of relevance FICZ inhibited TGF β -induced EMT.²⁶

Additionally, IFN- λ expression, which plays a role in EMT,¹⁴ is influenced by the AHR. IFN- λ signals through the Janus kinases, Jak 1 and 2 activating Stat 1. Stat 1 is inhibited via the AHR.²⁰

Peroxisome Proliferator-activated Receptor Gamma (PPAR- γ)

PPAR- γ is one of the three members of the PPAR group with important roles in fatty acid metabolism as well as insulin secretion and sensitivity. Disturbances in PPAR- λ are considered to play an essential role in cicatricial alopecia.²⁷ The AHR agonist TCDD inhibits PPAR- λ mRNA synthesis²⁸ yet this is a long-acting and slowly metabolized agonist. The actions of physiological agonists such as FICZ which are rapidly metabolized by the inducible cytochrome P450 system remain to be elucidated and are likely to be far more dynamic.

The AHR is also active at many sites within the follicular unit and the net effect on PPAR- λ is likely to be the result of the interplay of several factors. The AHR increases Treg cells²⁰ which have been demonstrated to augment the proliferation and differentiation of eHFSC.²⁹

CD200/CD200R Axis

Although there is a paucity of published reports for the role of the AHR in CD200/CD200R expression, CD 200 expression is upregulated by vitamin D³⁰ which is synthesized by the skin on light exposure.

The CD200/CD200R axis however does exert influence by modulation of the KP with CD200 induction of IDO in dendritic cells.³¹

Endocrine Factors

Frontal fibrosing alopecia is seen predominantly in post-menopausal women. There is cross-talk between the ER and the AHR. Activation of the AHR inhibits estrogen signaling whereas ER- α has a positive role in AHR signaling supportive of the view that AHR signaling decreases in the post-menopausal state.³²

The 5 α -reductase inhibitors finasteride and dutasteride which inhibit the conversion of testosterone to dihydrotestosterone (DHT) have been reported to be efficacious in the management of frontal fibrosing

alopecia. Of interest, FICZ has been reported to inhibit the formation of DHT in the prostatic adenocarcinoma cell line LNCaP.³³

Immunological Attack

CD8 cells are prominent in the inflammatory infiltrate.^{8,34} AHR activation by TCDD inhibits CD8 function.³⁵

AHR Expression

After binding to the XRE, the AHR is exported to the cytoplasm for degradation by the 26S proteasome pathway. After exposure to a ligand, the level of the AHR protein has been found to decrease.³⁶ Increased levels of AHR expression have been reported in frontal fibrosing alopecia suggesting that AHR cycling may be reduced.³⁷

Conclusion

A possible association between low levels of photo-exposure and a loss of immune tolerance first appeared when the association between vitamin D and multiple sclerosis was documented.³⁸ Although vitamin D does have immunoregulatory properties,³⁹ other immunoregulatory molecules are generated on light exposure. In this hypothesis, we propose and review the evidence that FFA arises due to the collapse of immune privilege at the hair bulb because photo-protection provided by many facial care products reduces the synthesis of the tryptophan photoproduct FICZ. Of relevance, FICZ is generated most efficiently by UVB but is also capable of being generated by UVA and visible light.⁵ Low levels of FICZ are immunostimulatory with higher levels being immunosuppressive⁶ which would support the proposition that UV protective facial products which allow the transmission of visible light but block UV light may have immunostimulatory properties.

An association between FFA and exposure to alkylphenolic compounds has also been reported. These are environmental toxins with both an endocrine disruption potential and activity at the AHR⁴⁰ which have been shown to interfere with PPAR- γ .

The role of genetic factors was explored in a recent genome-wide association study.⁴¹ Reported associations were with HLA-B*07:02, Cytochrome P450 1B1 (CYP1B1), the ST3GAL1 gene encoding the galactoside sialyltransferase enzyme and possibly the gene SEMA4B. CYPB1 is an AHR dependent monooxygenase supporting the proposal that the AHR plays a significant role in this disorder. ST3GAL1 is reported to play a role in T cell homeostasis consistent with the role played by T cells in

eHFSC destruction. Class 1 HLA antigens are normally absent or expressed only at lower levels in the hair follicle permissive of immune privilege; however, an HLA association may assume significance in the event of immune privilege collapse, mediating ongoing destruction. These reported genetic associations are consistent with the hypothesis outlined.

Disclosure

The author reports no conflicts of interest in this work.

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