Review

Possible mechanism of benvitimod in atopic dermatitis and psoriasis

Jin Hu[1*], Jiajun Xue[1], Juan Shen[2]

1. Beijing Wenfeng Tianji Pharm, Ltd. Changping 102200, Beijing, China
2. Zhonghao Pharmaceutical, Zhongshan 538427, Guangdong, China

Abstract: Atopic dermatitis (AD) and psoriasis are common chronic and relapsing inflammatory skin diseases mainly mediated by T cells. Type 2 and 17 inflammations are essential in the pathogenesis of AD and psoriasis, respectively. Clinical evidence suggests that benvitimod, a natural metabolite produced by bacterial symbionts, plays a therapeutic role in the development and progression of both AD and psoriasis. Mechanistically, the two most potent interactions with benvitimod are observed in the aryl hydrocarbon receptor (AhR) and nuclear factor-erythroid 2-related factor-2 (Nrf2) pathways. However, it remains largely unknown how is the local interplay among benvitimod, AhR, and Nrf2, and how the epithelial microenvironment contributes to the complex inflammatory context that results in the treatment of AD and psoriasis. In the present study, the modulatory effects of benvitimod on treating AD and psoriasis.

Keywords: Benvitimod; Atopic dermatitis; Psoriasis; Tapinarof; AhR; Nrf2

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Contents

1. Introduction

Atopic dermatitis (AD) and psoriasis are common chronic inflammatory skin diseases mediated by T cells. Although their pathogeneses are different, both diseases share barrier abnormalities and local inflammation. Evidence has shown that topical application of benvitimod can maintain barrier homeostasis and reduce local inflammation in the epithelial immune microenvironment. This marvelous medical function is inseparable from AhR-Nrf2 anti-oxidative system. In the present work, we reviewed the functions of AhR-Nrf2 in the pathogenesis of AD and psoriasis.

2. Inflammatory events in the epithelial micro-environment in the pathogenesis of AD and psoriasis

As the human body's largest organ, the skin functions as a physical and immune barrier between external

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*Corresponding author. Tel.: +86-15701317056;
E-mail: hujinpumc@163.com

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environments and internal tissues. Anatomically, the outermost layer of the skin is the epidermis, in which professional antigen-presenting cells (APCs), including dendritic cells (DCs), Langerhans cells (LCs), macrophages, mast cells, innate lymphoid cells (ILCs), and γδ T cells, reside permanently[1-4]. In response to inflammatory stimuli, cutaneous APCs induce the differentiation of effector T cells[5,6]. As a result, cytokines, chemokines, and other inflammatory mediators produced by immune cells in this micro-environment affect the proliferation and activation of keratinocytes, which not merely function as a progenitor of the skin barrier but also initiate a complex network that results in inflammatory skin diseases[7,8]. In addition, activations of distinct subsets of lymphocytes induce characteristic diseases. For example, Th2 cell activation mediates IL-4 and IL-13 release, which subsequently leads to AD, while Th17 cell activation is critically involved in psoriasis by inducing the production of IL-17, IL-23, and tumor necrosis factor-α (TNF-α)[9,10]. Besides the dysfunction of the epithelial micro-environment related to AD and psoriasis closely, accumulating evidence suggests that an altered microbiome is another crucial event in the development of skin inflammation[11,12].

3. Introduction of benvitimod

Both AD and psoriasis are common and relapsing[13]. Current topical therapies for AD include various topical corticosteroids (TCSs), topical calcineurin inhibitors (TCIs), and inhibitors of PDE-4[14]. TCSs and TCIs can also be used to treat psoriasis[15]. Besides, vitamin D3 derivatives, retinoids, and some compound prescriptions are also considered to treat psoriasis[15].

Benvitimod (3,5-dihydroxy-4-isopropylstilbene, also known as tapinarof and GSK2894512, previously known as WBI-1001) is a non-steroid small molecule isolated from symbiotic bacteria of entomopathogenic nematode[16]. In 2013, a phase 3 double-blind, randomized, placebo- and positive-controlled trial evaluated the use of 1% benvitimod cream twice daily for 12 weeks in 732 adults with mild-to-moderate plaque psoriasis. The primary efficacy endpoints was the percentage of patients with a 75% or greater reduction from baseline in the Psoriasis Area and Severity Index (PASI) score (higher scores indicated more severity of psoriasis) and with a score of 0 or 1 (clear or minimal) in static Physician's Global Assessment (PGA) at week 12. As a result, 50.4% of patients achieved PASI 75 at week 12 in the benvitimod group, which was significantly higher compared with either the calcipotriol group (38.5%, $P < 0.05$) or placebo group (13.9%, $P < 0.05$). In addition, the PGA score of 0 or 1 was achieved in 66.3% of the benvitimod group and 63.9% of the calcipotriol group; both were significantly higher than the placebo group (33.5%, $P < 0.05$, respectively)[17]. After 12 weeks of treatment with benvitimod and 8 weeks of follow-up, 59 patients were screened for the long-term follow-up study. Among them, 29 patients had maintained the resolution of psoriasis plaques until week 52. The median relapse time was 36 weeks. No systemic side effects were reported.

Two identical Phase 3 randomized trials have evaluated the use of tapinarof cream, the same active pharmaceutical ingredient as the benvitimod cream, once daily for 12 weeks in 692 and 674 patients. Adults with a baseline PGA score of 2 to 4 were randomly assigned in a 2:1 ratio to use tapinarof 1% cream or vehicle cream. The primary endpoint was the PGA response. A total of 510 and 515 patients were enrolled. PGA response occurred in 35.4% of the patients in the tapinarof group and in 6.0% of those in the vehicle group in trial 1, respectively, and such number became 40.2% and 6.3% in trial 2 ($P < 0.001$ for both comparisons)[18].

In addition, tapinarof is also efficacious and tolerated in adolescents and adults with AD. A phase 2b, double-blind, vehicle-controlled study has evaluated the use of tapinarof cream for 12 weeks in 247 adolescents and adults with AD in Canada[19]. Briefly, 247 patients with AD were randomly assigned in a 1:1:1:1:1:1 ratio to receive tapinarof cream 0.5%, 1%, or vehicle, once or twice daily. Outcomes include Investigator Global Assessment (IGA), Eczema Area and Severity Index (EASI), body surface area affected, pruritus numeric rating scale scores, patients' impressions of AD and pruritus symptom severity, and Patient-Oriented Eczema Measure (POEM) scores. At week 12, results showed that both IGA responses and EASI scores were significantly higher in the 1% tapinarof group compared with the vehicle group, and body surface area affected was significantly reduced in the tapinarof groups. Most adverse events were mild or moderate.

Mechanism studies show several lines in which benvitimod plays a role, including the aryl hydrocarbon receptor (AhR) and the nuclear factor-erythroid 2-related factor-2 (Nrf2) signaling pathway, and the alteration of the skin microbiome, as described below[20,21].

4. Modulatory effects of AhR in the epithelial micro-environment

AhR is a ligand-activated transcription factor with numerous biological roles[22]. In murine and human epithelial micro-environment, functional AhR can be expressed in keratinocytes, LCs, fibroblasts, melanocytes, and dermal DCs[23–26]. In the absence of ligand, AhR located in the cytoplasm forms a protein complex with heat-shock protein 90 (HSP90), hepatitis B virus X-associated protein 2 (XAP-2), c-Src protein kinase, and p23[27–31]. After ligand binding, the AhR translocates to the nucleus and dimerizes with AhR nuclear translocator (ARNT)[32]. The AhR/ARNT complex then binds to xenobiotic responsive elements (XRE) in the promoter of the target genes, such as cytochrome P450 (CYP) 1A1, CYP1A2, and CYP1B1, which are essential monooxygenases in the metabolism of xenobiotics[33,34]. CYP1A2 and CYP1B1 are expressed far less than CYP1A1 in human keratinocytes[35]. It is well known that CYP1A1 induction causes reactive oxygen species (ROS) formation and induces oxidative damage to DNA[36,37]. In the *in vitro* study, the markers for oxidative DNA damage can be reduced by AhR antagonism and CYP1A1 inhibition[38,39]. Besides, very early studies have described that AhR ligands, such as formylindolo [3,2-b] carbazole (FICZ), 2,3,7,8,-tetrachlorodibenzo-p-dioxin (TCDD), and benzo[a]pyrene (BaP), can not only significantly stimulate the production of ROS but also increase the expressions of pro-inflammatory cytokines, such as IL-1β or transforming growth factor-β, which are then expanded to other cytokines, such as IL-6 or IL-22[40–42]. Thus far, although the anti-IL-22 antibody Fezakinumab plays a weak therapeutic role in treating patients with AD or psoriasis in clinical trials, IL-22 is shown to be responsible for keratinocyte proliferation and down-regulation of IVL, LOR, and FLG in *in vitro* studies[43,44].

However, the friend or foe outcome of AhR ligands exposure depends on several parameters, for instance, the affinity, degradability, or cellular context of ligands or a combination[45]. A recent study has identified the protective role of FICZ in skin barrier integrity by using an AD-like NC/Nga murine model[46]. Counterintuitively, a decreased expression of IL-22 in the FICZ-treated dermatitis-affected skin is also reported, consistent with that in an imiquimod-induced psoriasis model[47]. Despite the effect of AhR on IL-22 and its influence on AD and psoriasis remains enigmatic, published studies have shown that IL-22, as well as IL-17 and IL-23, which compose primary inflammatory receptors for psoriasis, is inhibited by benvitimod in the imiquimod model, indicative of a simultaneous role for signaling *via* IL-22 in the mechanism of benvitimod[20].

However, direct evidence that benvitimod is critical to Th1/Th2 balance in AD has not been identified, and present studies have suggested a potential contribution of LCs and DCs in the therapeutic mechanism of AhR activation to AD[48,49]. Both LCs and DCs initially chemoattract Th2 cells in the epidermis of patients with AD by the IL-4/STAT6 signaling pathway[50]. A recent study has found that Glyteer, an AhR agonist used clinically as an alternative to coal tar, is available to impair this IL-4-mediated inflammation *via* inhibition of Ccl17 and Ccl22 production in murine bone marrow-derived DCs[51,52]. Consistent with that, one of the multiple mechanisms of the AhR agonist is the attenuation of the phosphorylation of STAT6 in keratinocytes[53]. Besides, FICZ may also contribute to the immunosuppressive action through the induction of FcεRI and upregulation of IDO1 in LCs[54]. These results consistently suggest the fundamental role of AhR activation in the homeostasis of the epithelial microenvironment.

5. Modulatory effects of Nrf2 in the epithelial microenvironment

Benvitimod also plays a role in activating transcription factor Nrf2, which is a master regulator and widely and constitutively expressed in cells to ensure the protective response to oxidative inflammation. Under normal physiological conditions, synthesized Nrf2 is associated with a homodimer protein, Kelch-like ECH-associated protein 1 (KEAP1), which constantly facilitates its degradation in the cytosol through ubiquitination modification[55,56]. Exposure of oxidants allows Nrf2 to translocate into the nucleus and then initiate the transcription through antioxidant response elements (AREs)[55,56]. Nrf2 regulates the expressions of genes involved in the generation of several critical enzymes, such as NAD(P)H dehydrogenase, quinone-1 (NQO-1), and Heme oxygenase-1 (HO-1), many of which are critical cofactors that directly participate in antioxidant reactions[57]. This canonical mechanism of Nrf2 activation has been extensively studied. In addition, other non-canonical Nrf2 activation pathways have been described. The implementation in non-canonical pathways includes a set of proteins that can disrupt the Keap1-Nrf2 complex, such as p62, p21, DPP3, BRCA1, and WTX[58–62]. It is worth noting that the p21-dependent non-canonical Nrf2 activation prevents skin carcinogenesis and the inflammatory response[63]. It remains elusive whether the other non-canonical Nrf2 activation pathways play a role in skin inflammation.

Although previously it was thought to be involved in a distinct pathway, increasing evidence suggests that AhR and Nrf2 have functional crosstalk[64]. In 2005, AhR was first reported to bind to both XRE and ARE consensus sequences by gel shift assays[65]. The Nrf2-controlled genes have been further proved to have three XRE-like element regions (position -712, +755, and +850, respectively)[66]. Likewise, direct and specific AhR binding to XRE-like regions located in the Nrf2 promoter region has been confirmed by a chromatin immunoprecipitation analysis, suggesting that Nrf2 expression is as least partly regulated by AhR agonists by activating XRE-like elements in its promoter[67].

In the micro-environment of AD and psoriasis, Nrf2 is activated in response to oxidative stress. *In vitro* studies have demonstrated that Nrf2 improves keratinocyte differentiation through the upregulation of keratins (KRT6, KRT16, Krt17, and KRT10)[68,69]. In addition, Nrf2 activation increases the IL-36γ level in keratinocytes, which leads to autocrine and paracrine regulation of keratinocyte proliferation[70]. Pharmacological Nrf2 activation has shown efficacy in both AD and psoriasis animal models and clinical trials[71,72]. Classic examples of Nrf2 activators are benvitimod, bixin, astaxanthin, dimethyl fumarate, and sulforaphane, among many others[73,74].

Altogether, Nrf2 plays an indispensable role in the anti-inflammation mechanism of benvitimod in AD and psoriasis. Consistent with that in the skin micro-environment, Nrf2 is also a major regulator of redox balance in other inflammatory responses, such as gastrointestinal disorders and related intestinal diseases[75,76]. Combined with its low toxicity in topical use, further investigation can be profitable to test the efficacy of benvitimod against other inflammatory diseases.

6. Modulatory effects of AhR and Nrf2 in microbiota

Several pieces of evidence have shown the pivotal role of bacteria in the development and persistence of AD and psoriasis. In most individuals affected by AD, *S. aureus* has long been known as a demolisher of skin barriers[77]. In contrast, lesions on psoriasis are often associated with beta-hemolytic streptococcal (GAS) infection[78]. These may lead to a lack of immune system stimulation, which is associated with the dysfunction of the skin barrier. Coal tar treatment results in a shift of microbiota composition *via* the AhR pathway[79]. Moreover, there is a bidirectional link between skin microbial metabolisms and the epithelial immune microenvironment. For instance, the activation is also involved in the transcription of genes for epidermal lipid synthesis and sebocyte differentiation[80]. The expressions of these genes may change the stratum corneum physicochemical environment and ultimately may affect the skin microbiome context.

7. Conclusions

Both AD and psoriasis are common chronic inflammatory skin diseases that are mediated by T cells. Biologics that target specific T cell cytokines are clinically effective for psoriases, such as TNF-α inhibitors, IL-17A inhibitors, and IL-23 inhibitors[81]. However, few biologics are shown to have utility in treating AD. Even worse, several IL-17A or IL-12/23 inhibitors may exacerbate AD symptoms[82].

Despite the pathogenesis being different, both diseases share barrier abnormalities and local inflammation. Evidence has shown that topical application of benvitimod can maintain barrier homeostasis and reduce local inflammation in the epithelial immune microenvironment. This marvelous medical function is inseparable from AhR-Nrf2 anti-oxidative system. Collectively, our review presented the interplay of the AhR signaling pathway and Nrf2 pathway in AD and psoriasis. The features of benvitimod in AD and psoriasis are together expected to lead to the development of other therapies that target on AhR or Nrf2 pathway. In addition, further studies will clarify whether benvitimod plays a protective role in other inflammatory diseases.

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本维莫德治疗特应性皮炎及银屑病作用机制的研究进展

胡金[1*], 薛佳俊[1], 申娟[2]

1. 北京文丰天济医药科技有限公司, 北京 昌平 102200
2. 广东中昊药业有限公司, 广东 中山 528437

摘要: 特应性皮炎(atopic dermatitis, AD)和银屑病是常见的慢性、复发性、炎症性皮肤病。Th2和Th17细胞介导的细胞免疫分别被认为是AD和银屑病发病机制中必不可少的环节。本维莫德是一种芪类小分子化合物, 自从1965年被发现至今, 已成为国家一类新药, 在临床上用于成人轻中度银屑病的治疗。临床研究表明, 本维莫德对特应性皮炎也有积极的治疗作用。尽管目前对本维莫德作用机制的研究还处于探索阶段, 但是越来越多的证据显示, 本维莫德对皮肤中的芳香烃受体(aryl hydrocarbon receptor, AhR)和核转录因子Nrf2起着重要的调控作用。近年来发现本维莫德调节相关免疫因子的同时, 也广泛参与皮肤微环境中抗氧化途径的激活与皮肤屏障的修复。本文就本维莫德治疗AD和银屑病作用机制的相关研究进展做综述。

关键词: 本维莫德; 特应性皮炎; 银屑病; Tapinarof; AhR; Nrf2