

Review

Epigenetic control of inflammation in Atopic Dermatitis

Sabah Akhtar^{a,1}, Reem Khaled M.E. Alsayed^{a,1}, Fareed Ahmad^{a,b,c}, Ayda AlHammadi^c, Sara Al-Khawaga^c, Sara Mohamed A.M. AlHarami^d, Majid Ali Alam^{a,b,c}, Khalifa Abdulla H.N. Al Naama^c, Joerg Buddenkotte^{a,b,c}, Shahab Uddin^{a,b,e}, Martin Steinhoff^{a,b,c,f,g,*}, Aamir Ahmad^{a,b,c,*}

^a Translational Research Institute, Academic Health System, Hamad Medical Corporation, Doha 3050, Qatar

^b Dermatology Institute, Academic Health System, Hamad Medical Corporation, Doha 3050, Qatar

^c Department of Dermatology and Venereology, Rumailah Hospital, Hamad Medical Corporation, Doha 3050, Qatar

^d Department of Plastic Surgery, Hamad General Hospital, Hamad Medical Corporation, Doha 3050, Qatar

^e Laboratory Animal Research Center, Qatar University, Doha 2713, Qatar

^f Weill Cornell Medicine-Qatar, Medical School, Doha 24144, Qatar

^g Dept. of Dermatology, Weill Cornell Medicine, New York 10065, NY, USA

ARTICLE INFO

Keywords:

Atopic Dermatitis

Inflammation

Epigenetic

Barrier dysfunction

Non-coding RNAs

ABSTRACT

Atopic dermatitis (AD), also known as atopic eczema, is a common but also complex chronic, itchy skin condition with underlying inflammation of the skin. This skin ailment is prevalent worldwide and affects people of all ages, particularly children below five years of age. The itching and resulting rashes in AD patients are often the result of inflammatory signals, thus necessitating a closer look at the inflammation-regulating mechanisms for putative relief, care and therapy. Several chemical- as well as genetically-induced animal models have established the importance of targeting pro-inflammatory AD microenvironment. Epigenetic mechanisms are gaining attention towards a better understanding of the onset as well as the progression of inflammation. Several physiological processes with implications in pathophysiology of AD, such as, barrier dysfunction either due to reduced filaggrin / human β -defensins or altered microbiome, reprogramming of Fc receptors with resulting overexpression of high affinity IgE receptors, elevated eosinophil numbers or the elevated IL-22 production by CD4 + T cells have underlying epigenetic mechanisms that include differential promoter methylation and/or regulation by non-coding RNAs. Reversing these epigenetic changes has been verified to reduce inflammatory burden through altered secretion of cytokines IL-6, IL-4, IL-13, IL-17, IL-22 etc, with benefit against AD progression in experimental models. A thorough understanding of epigenetic remodeling of inflammation in AD has the potential of opening avenues for novel diagnostic, prognostic and therapeutic options.

1. Atopic Dermatitis: an introduction

Atopic dermatitis (AD), commonly referred to as atopic eczema, is an inflammatory chronic skin condition that is characterized by rashes covering several parts of the body [1]. “Dermatitis” refers to a condition of the skin and “atopic” relates to diseases caused by allergic reactions. AD often relapses starting commonly in children five years of age, and occasionally carrying on to adulthood [2]. AD has a very high prevalence compared to other non-fatal skin conditions, where it affects 15–20% of all children and upto 10% of adults, with 95% of those affected experiencing an early onset below the age of five [1,3–5].

During a flare, AD becomes a red, itchy rash. Many different physical and internal factors can trigger an eczema flare-up. The resulting inflammation causes increased blood flow and the urge to itch [6]. Eczema flares are part of the agonizing itch-scratch cycle. It is hard to fight the physical and psychological components that drive the itch-scratch cycle. Scratching provides transient relief but can lead to more inflammation and even skin infections. Clinical management of AD is challenging with no known cure. Prevalence varies across races, genders and geographical regions. Targeting neuroimmune circuits and individual signaling pathways seems to be an option for the control of pruritus in AD [7]. Different environmental factors such as hygiene

* Corresponding authors at: Translational Research Institute, Academic Health System, Hamad Medical Corporation, Doha 3050, Qatar.

E-mail addresses: MSteinhoff@hamad.qa (M. Steinhoff), aahmad9@hamad.qa (A. Ahmad).

¹ Equal contributing authors

<https://doi.org/10.1016/j.semcdb.2023.04.005>

Received 22 February 2023; Received in revised form 12 April 2023; Accepted 16 April 2023

Available online 27 April 2023

1084-9521/© 2023 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

products and pollution can contribute to the acquisition of this disease. In recent years, and with the industrial boom, the incidence of AD has increased many folds [2]. Not only does AD negatively impact the quality of life for both patient and the family, but also the financial burden of treatment has proved to be a problem. Also, the prevalence of AD seems to be on a rise in industrialized nations [4] as well as the developing economies [8,9], which remains a cause for worry. AD onset and progression is further concerning because AD-derived cytokines can potentially lead to systemic inflammatory diseases as well as malignancies [10]. Hence, there is a need to better understand this disease so that novel treatments can be found.

2. Inflammation in Atopic Dermatitis

AD is an important chronic or relapsing inflammatory skin disease that often precedes asthma and allergic disorders [11]. Underlying chronic inflammation is a source of lesions and itch; the primary signs and symptoms of atopic dermatitis [12,13]. Thus, the process of inflammation is intricately linked with onset and progression of AD. The immune system protects human body from pathogens. When the body encounters foreign bodies such as toxic compounds, pathogens, damaged cells etc., immune system triggers the initiation of healing axis [14]. Such a trigger to the immune system could be beneficial or even harmful. Acute inflammation heals injuries and reduces infection, but chronic inflammation has the potential to damage cells and organs. The physical manifestation of the underlying effects of vascular and immune cell responses includes heat, redness, pain, and swelling. Additionally, nature of inflammatory diseases causes them to be associated with comorbidities [15].

In AD, not only is immune system dysfunctional, the main factor leading to pathogenesis of this disease, but it causes further complications after the disease manifests [16]. Many pro-inflammatory factors, such as IL-17 and IL-2, facilitate the immune reaction in AD. These factors impair the skin barrier, which makes it more sensitive to allergens and inflammation, and this initiates disease acquisition. Comorbidities associated with AD are digestive complications, and these occur due to the excessive growth of pathogenic bacteria in the gut [16] which is marked by the loss of immune tolerance, and a decrease in the stimulation of regulatory T (Treg) cells. The effects of AD on the immune system also include elevated levels of serum immunoglobulin E (IgE), an increase in Th2 cytokines and thymic stromal lymphopoietin (TSLP) and increase in T cells expressing cutaneous lymphocyte-associated antigen [16]. Genetic mutations related to inflammations have been noticed to be specific to patients with AD. These include mutations in the genes *SPINK5*, *SPINK5*, IgE receptor *FcεRb*, *NOD1*, *NOD2*, *IL-4*, *-5*, *-9*, *-10*, *-12*, *-13*, *-18*, *-31*, *TSLP*, *TLR24* and *TLR29* [16]. It would be important to mention here that our recent clinical study suggests that targeting IL-12/23 pathway does not provide any benefit to AD patients [17]. Clinical verification such as this is important to make an impact on patient outcome. Many other inflammation related cytokines are being suggested for their putative role in AD-associated inflammation. IL-33 inhibition has been associated with triggering the initial immune response in AD inflammation [18]. IL-1 family cytokines induced by NLRP1 inflammasome play a role in AD pathogenesis [19]. IL-4 and IL-13 remain the cornerstones of inflammation in AD [20,21] and the role of a Q576->R576 polymorphism in the IL-4 receptor alpha has been shown to predispose to significantly increased inflammation and severe AD [22]. In the context of inflammation, even the use of certain nanoparticles, the delivery components of several medications, can induce inflammation [23] thus necessitating the need to fully understand inflammation in drug design and delivery.

Being an inflammatory skin disease, the inflammation in AD has been a central point for discussion in hundreds of publications, if not more. It is beyond the scope of this review to provide a detailed background information on the inflammation in AD and the various mechanistic details. A number of review articles are available on the subject

that the readers can refer to [6,10,24–29]. The investigations on inflammation in AD keep being reported and we provide a very brief overview of literature that has emerged on the topic in last couple of months that is probably not yet covered in any review article on the subject. In particular, recent research on AD is tending towards testing the effectiveness of several putative agents/drugs for the control / treatment of AD, all with the central premise that these agents modulate inflammation and could therefore be protective against AD. A lot of in vitro laboratory work has been published but there also are studies that have employed in vivo models to study inflammation in AD, and the protective effects of novel therapeutic agents. Some examples that have been recently reported (Table 1) are *Lycium barbarum* extract [30], a component of tea from oriental eastern medicine, edible bird's nest [31], an east Asian delicacy, ethanol extract of *Grewia tomentosa* Juss. [32], a shrub from Asia, Angelica Yinzi [33], a component of traditional medicine, β -caryophyllene [34], a naturally occurring agonist of cannabinoid receptor 2, bisdemethoxycurcumin [35], a component of turmeric spice, wheatgrass (*Triticum aestivum* L.) and aronia (*Aronia melanocarpa*) extracts [36], hot water extract of seaweed *Sargassum horneri* [37], ethanol extract of herbal medicine component *Vigna angularis* [38] and D-mannose [39] that inhibit proinflammatory cytokines produced by 2, 4-dinitrochlorobenzene (DNCB) in an experimental mouse model of AD; the calcium-based antimicrobial peptide compounds [40] and Cortex Dictamni [41], a traditional Chinese medication, that suppress inflammatory mediators and inflammatory cytokines in dinitrofluorobenzene (DNFB)-induced AD mouse model; flavone oroxylin A [42], from flowering plant *Scutellaria baicalensis* that protects against proinflammatory cytokines in a 1-chloro-2,4-dinitrobenzene (CDNB)-induced in vivo AD model; orismilast [43], a phosphodiesterase 4 (PDE4) inhibitor, that suppresses pro-inflammatory cytokines in a chronic oxazolone-induced in vivo ear skin inflammation model; oxymatrine that inhibits JAK-STAT3 pathway and reduces inflammation in a carbatriol-induced mouse AD model [44] and nuclear transport checkpoint inhibitor [45] and IRAK4 inhibitors [46] that suppresses inflammation in calcipotriol-induced AD model. These reports, in addition to exploring the AD-suppressing potential of novel formulations, also suggest an important role of chemicals-induced animal models. But such models are not the only models available for AD research as a number of alternate models are also being investigated to 'more accurately' mimic AD. For example, *Torilis japonica* extract [47] has been shown to protect against pro-inflammatory cytokines and matrix metalloproteinases in a 3D skin model and chestnut family *Castanea sativa* [48] has been shown to restore membrane integrity and decrease *Staphylococcus aureus*-induced effects in a reconstructed human skin AD model. Additionally, genetically modified mouse models are also being studied to understand inflammation in AD. Examples include mice with keratinocyte-specific deletion of Ddx5 that makes them more susceptible to skin inflammation [49] and the FADS mice [50] that have Ikk2 deleted in facial skin fibroblasts leading to AD-like facial skin inflammation and scratching behavior i.e. 'facial AD with scratching' or FADS.

3. The epigenetics of Atopic Dermatitis

Molecular and genetic markers of inflammation have traditionally been the focus of research. Recently, the role of epigenetics as the basis of inflammation has been recognized [51]. The research on epigenetics has now moved from pre-clinical biomarker discoveries to translational studies as well as clinical trials [52,53] and epigenetic changes are now being targeted even in the personalized/precision medicine strategies [54]. Epigenetics is the study of changes in gene expression that are heritable and caused by events other than the change in DNA/gene sequence [55]. The incidence of skin related diseases has increased with industrialization and pollution because these environmental factors alter epigenetic regulation [56]. Gene expression is controlled by non-coding RNAs, DNA methylation and histone modification [57–59]. In AD, there has been evidence of altered genetic and epigenetic

Table 1
Recent reports on regulation of AD-associated inflammation: evidence from in vivo studies.

Agent	Origin	Model Tested	Major Findings	Reference
<i>Lycium barbarum</i> extract	Tea component from oriental eastern medicine	DNCB-treated BALB/c mice	Oral administration reduced inflammatory cytokines and chemokines	Bak et al.[30]
Edible bird's nest	Chinese delicacy	DNCB-treated C57BL mice	Topical application reversed DNCB-induced skin damage and scratching behavior	Lai et al.[31]
Ethanol extract of <i>Grewia tomentosa</i> Juss.	An Asian shrub	DNCB-treated BALB/c mice	Topical administration reduced mRNA levels of inflammatory cytokines and inhibited NF-κB signaling	Lee et al.[32]
Angelica Yinzi	Component of traditional Chinese medicine	DNCB-treated C57BL mice	Oral administration reduced AD lesions and infiltration of mast cells	Liu et al.[33]
β-caryophyllene	Plants-derived agonist of cannabinoid receptor 2	DNCB-treated BALB/c mice	Topical administration reduced skin inflammation	Ahn et al.[34]
Bisdemethoxy-curcumin	Component of turmeric spcie	DNCB-treated BALB/c mice	Oral administration reduced inflammation and inhibited NF-κB signaling	Wang et al. [35]
Wheatgrass (<i>Triticum aestivum</i> L.) and Aronia (<i>Aronia melanocarpa</i>) extracts	Belong to Poaceae and Rosaceae families of plants, respectively	DNCB-treated BALB/c mice	Oral administration restored barrier function and suppressed IgE and IL-4	Lee et al.[36]
<i>Sargassum horneri</i>	A Seaweed	DNCB-treated BALB/c mice	Hot water extracts reduced IL-4, IL-5 and IgE	Woo et al.[37]
<i>Vigna angularis</i>	Herb component of traditional Asian medicine	DNCB-treated BALB/c mice	Oral administration inhibited pro-inflammatory cytokines and chemokines	Bak et al.[38]
Calcium-based antimicrobial peptide compounds	Combination of calcium extracted from marine shellfish and antimicrobial peptides	DNFB-treated BALB/c mice	Topical administration reduced scratching behavior and inflammatory cytokines	Liu et al.[40]
Cortex Dictamni	Dried root bark herb of <i>Dictamnus dasycarpus</i> Turcz from traditional Chinese medicine	DNFB-treated mice	Reduced skin lesions and inflammatory cytokines	Yang et al. [41]
Flavone oroxylin A	Component of <i>Scutellaria baicalensis</i> from Asian traditional medicine	CDNB-treated BALB/c mice	Reduced inflammatory cytokines and chemokines	Lee et al.[42]
Orismilast	A high-potency PDE4 inhibitor	Oxazolone-treated BALB/c mice	Oral administration inhibited secretion of inflammatory cytokines	Silverberg et al.[43]
Oxymatrine	Component of herbs <i>Sophora flavescens</i> Alt., <i>Sophora tonkinensis</i> Gagnep and <i>Sophora alopecuroides</i>	Carbotriol-treated C57BL mice	Intragastric administration reduced inflammatory cytokines	Han et al.[44]
Nuclear transport checkpoint inhibitor	Anti-inflammatory cell-penetrating peptide	Calcipotriol-treated C57BL mice	Topical administration inhibited skin inflammation	Liu et al.[45]

AD: Atopic Dermatitis, CDNB: 1-chloro-2,4-dinitrobenzene, DNCB: 2,4-dinitrochlorobenzene, DNFB: Dinitrofluorobenzene, IL-4: Interleukin-4, IL-5: Interleukin-5, PDE4: Phosphodiesterase-4
Legends to Figures

expression in immune cells, which contributes to disease pathogenesis [56,60]. It has been observed that infants expressing low levels of Treg cells have a higher risk of developing AD [56]. Reduced expression of Treg cells can be caused by exposure to tobacco smoke, which correlates with increased expression of miR-223, and increased methylation of FOXP3 gene [56,61,62].

Methylation is an important epigenetic event that determines the expression of genes [63,64]. Several attempts have been made to look at differential DNA methylation in AD patients, as compared to healthy controls. In one such study that performed genome-wide methylation profiling to compare DNA methylation in 12 AD patients and 6 healthy volunteers, a significantly different methylation profile was observed for the AD patients, when compared to healthy controls [65]. In peripheral blood mononuclear cells, there is an increased expression of *FcεRI* and *IgE* genes (through reduction in DNA methylation), and this alters the sensitivity to allergens. In one of the early studies providing an epigenetic basis of AD, demethylation of FCER1G promoter was reported when DNA methylation of monocytes from 10 AD patients and 10 healthy controls was evaluated [66]. Global DNA methylation analysis showed a global hypomethylation, in general, as well as a local hypomethylation of FCER1G promoter in AD patients leading to increased expression of the high affinity IgE receptor, FcεRI, on monocytes (Fig. 1). This study provided the epigenetic basis of increased IgE levels in AD patients, as there is a positive correlation between higher levels of IgE and the severity of AD [67], leading to the evaluation of IgE-targeting omalizumab in several clinical studies [3]. The mechanism of FCER1G demethylation was studied in a later study as well [68]. As a further proof of differential methylation and epigenetics in AD, significantly different methylation patterns were observed for various CpG sites in lesional epidermis from AD patients, compared to epidermis from healthy controls [69]. These differentially methylated CpGs partly

correlated with differentially regulated genes involved in epidermal differentiation and innate immune response. Differential methylation brings to forefront the role of DNA methyltransferases, the enzymes that catalyze methylation of genes by adding methyl groups. In a study that evaluated human as well as mice models of AD, reduced DNA methyltransferase 1 (DNMT1) levels were observed in AD and the low DNMT1 expressing AD patients exhibited higher itch, compared to AD patients with relatively higher DNMT1 [70].

Integrity of skin is critical and the skin barrier dysfunction is an initial step and a pathological feature in the development of AD (Fig. 2) [5,71]. Skin barrier is subjected to regulation by environmental and exogenous factors thus raising the possibility of being regulated epigenetically [72]. Among the many factors responsible for the integrity of skin barrier, a role of human β-defensins has been suggested as they are localized in epithelium and act as protective barriers [73]. Reduced expression of these human β-defensins can, therefore, have a deleterious effect resulting in AD. In support of an epigenetic regulation, specifically the promoter methylation, methylation frequencies at CpG3 and CpG4 in lesional vs. non-lesional skin samples of patients with severe AD and the same methylation frequencies between these paired tissues and control skins from healthy volunteers without AD history were compared [74]. Significantly higher methylation was observed in AD lesional skins, as compared to both non-lesional as well as control skins. Further, in vitro investigations within this study established that methylation of CpG sites with the promoter of human β-defensin-1 led to approximately 86% reduced promoter activity, thus resulting in reduced expression.

Another factor that has attracted a lot of attention for its role in barrier function of AD is filaggrin (FLG) [75,76]. FLG is important for the maintenance of membrane function and therefore its reduced expression is seen in AD [77]. An epigenetic reason for the

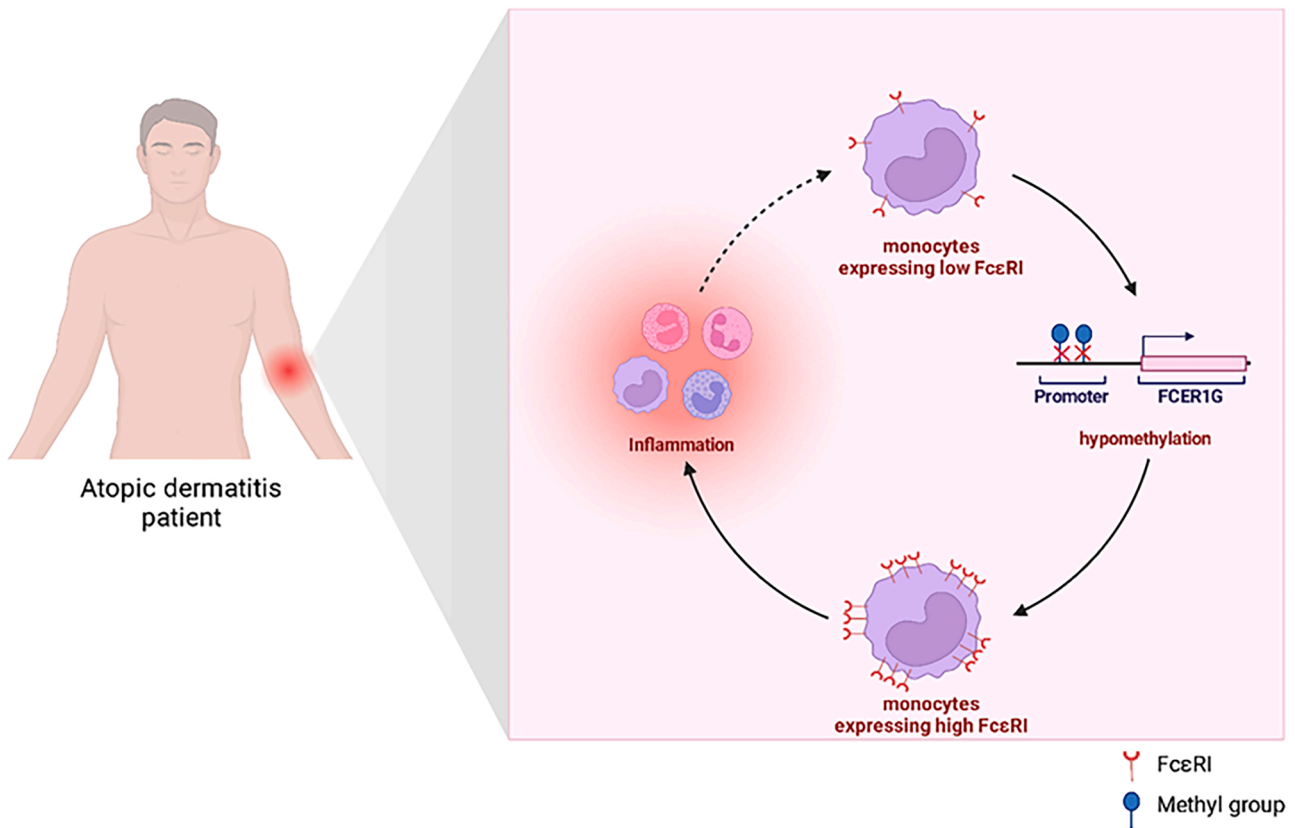


Fig. 1. Demethylation of FCER1G promoter in monocytes of AD patients leads to increased expression of IgE receptor FcεRI, which plays an important role in allergic inflammation.

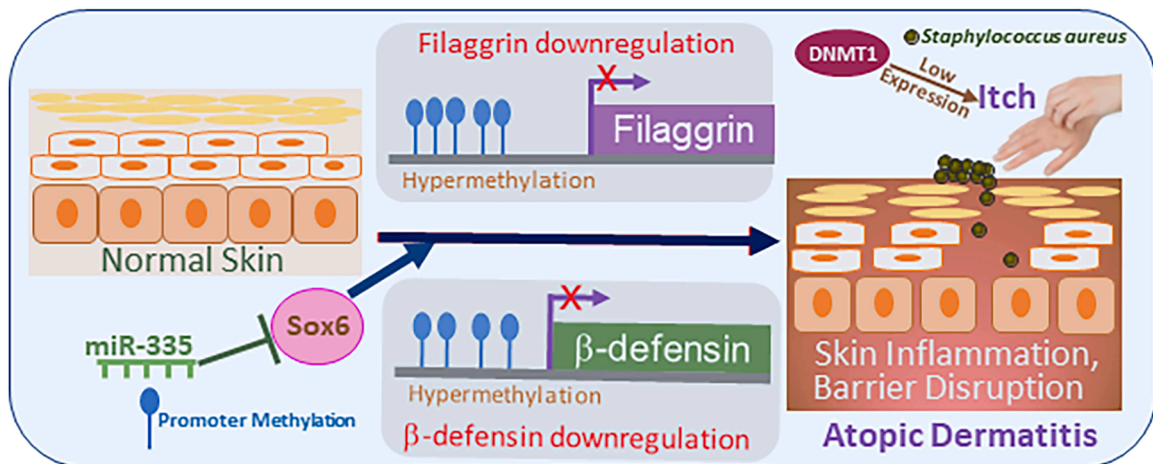


Fig. 2. : Epigenetic basis of Skin Barrier Disruption. A number of events leading to skin barrier disruption and dysfunction in AD patients have epigenetic basis. For example, promoter hypermethylation of Filaggrin and β-defensins results in their downregulation, as observed in skin lesions of AD patients that are inflamed and itchy. Low DNA methyltransferase1 (DNMT1) expression also correlates with itch. Additionally, miR-335 is high in normal skin, and its low expression, resulting in de-repression of its target Sox6 leads to disruption of skin barrier. AD skin lesions are also often marked by *Staphylococcus aureus* colonization.

downregulation of FLG has also been determined to be the increased DNA methylation in the critical CpG sites relevant to its expression in AD lesional epidermis, as compared to matched non-lesional epidermis of patients with severe AD [78]. Thus, differential methylation dictates the differential expression of specific genes that play a role in AD. Differential methylation seems to be of relevance to childhood AD [79] as well as the increased likelihood of AD diagnosis in infants of atopic mothers [80].

The barrier dysfunction can be a manifestation of another epigenetic

event as well; deregulation of microRNAs (miRNAs). A study, that focused on miRNA-mediated barrier function, found loss of miR-335 in AD lesional skins, compared to healthy skins [81]. The loss of miR-335 resulted in increased expression of its target SOX6 which mediated the disruption of skin barrier. This study also suggested a benefit of using belinostat to treat AD, as belinostat could restore miR-335. Incidentally, belinostat is a histone deacetylase (HDAC) inhibitor [82] which further indicates an involvement of even acetylation, another epigenetic event in AD pathogenesis. For few years now, a role of miRNAs in AD has been

realized [83]. MicroRNA, miR-155, contributes to a constant inflammatory state and AD aggressiveness, as it is aberrant overexpression eventually increases T cell proliferation and T helper type 17 (Th17) cells differentiation respectively [84]. Regulation through miRNAs represents a type of epigenetic regulation.

Based on the available literature, there is ample evidence to support epigenetic mechanisms for the underlying disease onset and disease progression of AD [56,85–93], including some recent reports on immune-related epigenetic changes that perturb NF- κ B signaling [94] and also impact cytokine secretion, particularly IL-22 [95,96].

4. Inflammation-epigenetics connection in Atopic Dermatitis

At this point in the discussion, it is clear that inflammation is integral part of AD pathophysiology. Additionally, a role of epigenetic events in AD is increasingly being realized which begs the question if there is any connection between inflammation and epigenetics in AD, or, simply speaking, is there evidence for epigenetic regulation of inflammation in AD. As discussed above, promoter hypomethylation i.e. an epigenetic event, of FCER1G has been shown to be the mechanism for the overexpression of high affinity IgE receptor, Fc ϵ RI, on monocytes of AD patients [66]. The receptor Fc ϵ RI plays an important role in allergic inflammation [97] and its deficiency [98] or specific targeting [99] can impact inflammation thus establishing this receptor's role in inflammation. Further, its own regulation through methylation in AD patients provides a clue for epigenetic regulation of inflammation in AD. Demethylation and overexpression of FCER1G also results in overexpression of related Fc receptor γ subunit (FcR γ)-related receptors in human monocytes [68]. The role of FcR γ in inflammation is also known [100], as is in general for Fc receptors [101]. Thus, epigenetic overexpression of Fc family receptor mediates inflammation in AD patients.

Within the area of inflammation and epigenetics in AD, an interesting concept that has come up recently is that of the involvement of microbiome in AD [102,103]. Numerous microbial species inhabit human body and affect normal human health as well as several diseases [104–106]. Microbiome affects inflammation and the presence of certain bacteria correlates with inflammatory molecules that can mediate inflammation in different body tissues [107]. Microbes that comprise human microbiome affect mucosal immunity and distal inflammation [108]. In AD, microbes on both skin as well as in gut have the potential of determining the course of AD [102]. Skin microbiome can also play an important role in maintaining barrier function by inhibiting pathogenic *Staphylococcus aureus* colonization and, moreover, application of commensal organisms, such as *Staphylococcus hominis* or *Roseomonas mucosa* can help reduce AD severity [109]. In AD, a reduced microbiome diversity correlates with disease severity and the flares of AD correlate with expansion of pathogenic microbes [110]. In addition to its effect on inflammatory diseases, including AD, microbiome affects epigenetic reprogramming within the human body as well, with microbiome-sensitive changes affecting the major epigenetic events such as DNA/histone modifications as well as regulation through non-coding RNAs [111]. It is, therefore, not surprising that a role of microbiome in epigenetic regulation of AD has been suggested [112].

Eosinophils numbers are elevated in AD patients [113,114]. Additionally, eosinophil granule protein levels are elevated in peripheral blood and also deposited in the skin lesions, with these elevated levels correlating with disease [113]. Eosinophils affect inflammation through multiple mechanisms [115,116] and this connects eosinophils with an inflammatory disease such as AD. In addition, recent evidence suggests eosinophilia under conditions of barrier dysfunction and reduced epithelial integrity [117], a correlation that still needs to be more carefully examined in AD patients. In a study that sought to evaluate the epigenetic changes within eosinophils of AD patients, next-generation sequencing-based miRNA profiling was performed using RNA that was extracted from eosinophils of AD patients [118]. The evaluation included a total of 145 individuals of which 75 presented with AD. A

number of these individuals were also diagnosed with allergic asthma and/or allergic rhinitis leaving 15 individuals with a diagnosis just for AD. A total of 18 miRNAs from eosinophils were found to be significantly different and specific to different conditions, with miR-614 found to be specific for AD patients. Incidentally, nothing much is known about miR-614 in inflammation or in AD, except for some reports for this miRNA in different human cancers, and thus more detailed studies on this miRNA might be of interest.

A recent report has provided further proof for non-coding RNA's-mediated regulation of inflammation in AD. This study focused on finding differentially expressed circRNAs (circular RNAs) in PMBCs from AD patients, as compared to those from age- and gender-matched healthy controls [119]. Among a total of 88750 circRNAs, circRNA hsa_circ_0004287 was found to be upregulated in the initial microarray analysis comprising of a comparison between 4 AD patients and 4 healthy controls, followed by validation in 36 AD patients vs. 18 healthy controls. The differential hsa_circ_0004287 levels in PBMCs were able to discriminate between AD patients and healthy controls, and hsa_circ_0004287 upregulation was observed in skin lesions from AD patients. However, mechanistically, hsa_circ_0004287 was found to be anti-inflammatory in nature and thus its overexpression in AD patients might be a feedback response. hsa_circ_0004287 inhibited M1 macrophage activation which is known to be involved in immune response [120] and its overexpression in macrophages reduced skin inflammation in an inflammatory skin mice model. hsa_circ_0004287 expression negatively correlated with that of IL-6, a well characterized pro-inflammatory cytokine [121,122] as well as with long non-coding RNA (lncRNA), MALAT1, which has also been associated with inflammation [123], thus leading to realization that even though this anti-inflammatory circRNA is upregulated in AD, its endogenous levels are not enough to reverse AD progression and future investigations should focus on further elevating the levels of this circRNA so as to be therapeutically relevant in AD. In addition to circRNA, this study thus also identified a lncRNA in the regulation of AD-associated inflammation, thus establishing multiple layers of non-coding RNAs mediated epigenetic regulation of inflammation in AD. As a validation of these findings, MALAT1 downregulation has shown to be the mechanism by which inflammation and associated AD can be attenuated in an AD mouse model [124].

In a more direct evidence of epigenetic regulation of inflammation in AD, albeit in a canine model, where canine epidermal keratinocyte progenitors cells, CPEK, were pre-stimulated by exposure to interferon gamma, followed by inflammatory stimulation by exposing the cells to a cocktail of IL-4, IL-13 and IL-31, a number of genes were found deregulated [125]. The primary aim of this study was to evaluate possible effect of a nutraceutical mixture consisting of luteolin, piceatannol and cannabidiol (representing flavonoids, stilbenes and cannabinoids) on the inflammation in AD. It was reported that the nutraceutical mix downregulated *ccl2*, *ccl17* and *tslp* genes in the inflamed canine keratinocytes. To find an epigenetic basis of these altered gene expression, methylation at different CpG sites was evaluated for all of these genes and a significantly increased methylation, thus explaining the reduced gene expression, was only found at one site for *tslp*. Similar investigations in canine monocyte-macrophages DH82 reported a similar effect of nutraceutical mix on *ccl2*, *ccl17* and *il31ra* genes but not the *tslp* gene. Further, in these cells, an increased methylation of at least one CpG site of each of the genes was found. *Ccl2* [126], *ccl17* [127], *tslp* [128], *il31ra* [129] have all been linked to inflammation and, thus, these results provide a direct evidence for epigenetic regulation of inflammation in an AD model.

Dysregulation of immune system is associated with AD progression [11]. In particular, the involvement of Th2 cytokines such as IL-4 and IL-13 is well known [130,131]. The neonatal thymic T cells, from newborns without AD, have been shown to exhibit increased expression of IL-17 and IL-10 when exposed to IgG from adult AD patients [132, 133]. Similarly, the IgG from adult AD patients can also induce

production of IL-22 by thymus through its effect on maturation of IL-22-producing T cells [96]. IL-22 is emerging as an important target for therapy in AD patients as its targeted blockade through fezakinumab has shown promise [134,135]. The favorable response to anti-IL-22 monoclonal antibody makes sense given that IL-22 levels are high in AD patients because of the significant increase in IL-22 producing CD4 + and CD8 + T cells in AD patients [136]. Further, in addition to its increased expression in AD, IL-22 is known to modulate inflammation [137], thus making a case for this cytokine in AD and associated inflammation. An epigenetic basis of this increased frequency of IL-22 producing CD4 + cells, through dysregulated miRNAs, has been recently reported [96]. Small RNA-seq resulted in the identification of five miRNAs (miR-181b-5p, miR-4497, let-7i-5p, miR-342-3p and miR-4492) that were upregulated and two miRNAs (miR-130b-3p and miR-26a-5p) that were downregulated and could distinguish between AD and mock control. miR-181b-5p, with 6.17 folds change was the most upregulated miRNA while miR-130b-3p with – 4.5 folds change was the most downregulated miRNA. Further, an miRNA-based epigenetic signature of neonatal thymic gamma-delta T cells-secretion of IL-22, in response to AD patients' IgG, has also been evaluated with miR-4497 being reported as the most upregulated miRNA and miR-130b-3p being the most downregulated miRNA [95]. The modulation of these top deregulated miRNAs is important because of their reported role in inflammation [138–140].

5. Conclusions and future perspectives

AD is an inflammatory skin disease that affects quality of life. Though the contribution of inflammation to its pathophysiology is established, research in recent years has begun to unveil underlying epigenetic events that affect AD-associated inflammation. Given this newly realized importance of epigenetic events in pathophysiology of AD, it makes sense to turn to therapies that have the potential of modifying epigenome [141]. We hope that with the advancements in our understanding of the epigenetic regulation of AD, therapies that target specific epigenetic events, such as the HDAC inhibitors [142] can find a use in AD therapy. Use of some of these inhibitors, such as, HDAC inhibitor belinostat, might provide a unique opportunity to address two different epigenetic events, acetylation and regulation through non-coding RNAs, in the treatment of AD. The research involving microbiome in AD is surely something to look forward to in the future because of the connection of microbiome with barrier dysfunction, inflammation as well as epigenetics [143]. Clearly, epigenetic events can be exploited as possible diagnostic, prognostic or therapeutic biomarkers. As an example, hsa_circ_0004287 is elevated in AD patients even though it is anti-inflammatory, which would suggest a feedback mechanism or even the initiation of a physiological defense against AD. One glaring gap in the knowledge is the understanding of epigenetic mechanisms, if any, that regulate inflammation in correlation to JAK-STAT pathway. JAK-STAT signaling has been the focus of AD research for a long time [144,145] and, moreover, this signaling also influences inflammation in AD [145,146], but how, if at all, this JAK-STAT-mediated inflammation in AD is epigenetically controlled, is not known. The challenge for future research would be to benefit from the emerging cues and develop strategies to potentiate mechanisms by which the various inflammation-regulating epigenetic events can be regulated to improve the prognosis and outcomes for AD patients.

Funding

This work is supported by the Medical Research Center (MRC) routine grants (MRC-01–22–086 to AA, MRC-01–20–829 to MAA) and Internal Research Grant Competition grant (IRGC-04-SI-17–151) from MRC, Hamad Medical Corporation, Qatar. Open Access funding for this article has been provided by the Qatar National Library.

CRediT authorship contribution statement

AAh: Conceptualization and Supervision; SAK, RA and AAh: Writing - original draft; FA, AAI, SAI-K, SAL, MA, KA, JB, SU, MS and AAh: Writing - review & editing.

Conflict of Interest

Dr. Steinhoff has performed consultancy services for which he received compensation from Pfizer, Sanofi, Regeneron, Lilly, Novartis, Galderma, Leo, Merck, Avon, Pierre-Fabre, L'Oreal, BMS, Maruho, Toray, Mitsubishi, Maruho, Kiniksa, ZymoGenetics, Almirall; he served on advisory board for Pfizer, Novartis, Galderma, Leo, Avon, Pierre-Fabre, L'Oreal, BMS, Maruho, Toray, Mitsubishi, Maruho, ZymoGenetics, Almirall; his research was supported by Pfizer, Novartis, Galderma, Leo, Avon, Pierre-Fabre, L'Oreal, BMS, Maruho, Toray, Mitsubishi, Maruho, ZymoGenetics, Almirall. None of the other authors have any other conflicts of interest to report.

References

- [1] S. Ständer, Atopic Dermatitis, *N. Engl. J. Med.* 384 (12) (2021) 1136–1143.
- [2] C. Avena-Woods, Overview of atopic dermatitis, *Am. J. Manag. Care* 23 (8 Suppl) (2017) S115–S123.
- [3] A. Wollenberg, S.F. Thomsen, J.P. Lacour, X. Jaumont, S. Lazarewicz, Targeting immunoglobulin E in atopic dermatitis: a review of the existing evidence, *World Allergy Organ. J.* 14 (3) (2021), 100519.
- [4] S. Nutton, Atopic dermatitis: global epidemiology and risk factors, *Ann. Nutr. Metab.* 66 (Suppl 1) (2015) 8–16.
- [5] T. Tsakok, R. Woolf, C.H. Smith, S. Weidinger, C. Flohr, Atopic dermatitis: the skin barrier and beyond, *Br. J. Dermatol.* 180 (3) (2019) 464–474.
- [6] S.G. Kwatra, L. Misery, C. Clibborn, M. Steinhoff, Molecular and cellular mechanisms of itch and pain in atopic dermatitis and implications for novel therapeutics, *Clin. Transl. Immunol.* 11 (5) (2022), e1390.
- [7] M. Steinhoff, F. Ahmad, A. Pandey, A. Datsi, A. AlHammadi, S. Al-Khawaga, A. Al-Malki, J. Meng, M. Alam, J. Buddenkotte, Neuroimmune communication regulating pruritus in atopic dermatitis, *J. Allergy Clin. Immunol.* 149 (6) (2022) 1875–1898.
- [8] T.F. Tsai, M. Rajagopalan, C.Y. Chu, L. Encarnacion, R.A. Gerber, P. Santos-Estrella, L.J.Q. Llamado, A.M. Tallman, Burden of atopic dermatitis in Asia, *J. Dermatol.* 46 (10) (2019) 825–834.
- [9] C.Y. Chu, T.C. Yao, I.H. Shih, C.Y. Yang, C.L. Chin, S. Ibrahim, S. Thevarajah, L. K. Fon, M.H. Ho, C.C. Mo, C.P. Yu, S.K. Loo, T. Luger, Pimecrolimus for the treatment of atopic dermatitis in infants: an Asian perspective, *Dermatol. Ther. (Heide)* (2023).
- [10] M. Itamura, Y. Sawada, Involvement of Atopic Dermatitis in the development of systemic inflammatory diseases, *Int. J. Mol. Sci.* 23 (21) (2022).
- [11] M. Boguniewicz, D.Y. Leung, Atopic dermatitis: a disease of altered skin barrier and immune dysregulation, *Immunol. Rev.* 242 (1) (2011) 233–246.
- [12] D.Y. Leung, M. Boguniewicz, M.D. Howell, I. Nomura, Q.A. Hamid, New insights into atopic dermatitis, *J. Clin. Invest.* 113 (5) (2004) 651–657.
- [13] J.K. Gittler, A. Shemer, M. Suarez-Farinas, J. Fuentes-Duculan, K.J. Gulewicz, C. Q. Wang, H. Mitsui, I. Cardinale, C. de Guzman Strong, J.G. Krueger, E. Guttman-Yassky, Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis, *J. Allergy Clin. Immunol.* 130 (6) (2012) 1344–1354.
- [14] L. Chen, H. Deng, H. Cui, J. Fang, Z. Zuo, J. Deng, Y. Li, X. Wang, L. Zhao, Inflammatory responses and inflammation-associated diseases in organs, *Oncotarget* 9 (6) (2018) 7204–7218.
- [15] W.H. Boehncke, Systemic inflammation and cardiovascular comorbidity in psoriasis patients: causes and consequences, *Front. Immunol.* 9 (2018) 579.
- [16] J. Kim, B.E. Kim, D.Y.M. Leung, Pathophysiology of atopic dermatitis: clinical implications, *Allergy Asthma Proc.* 40 (2) (2019) 84–92.
- [17] H. Husein-ElAhmed, M. Steinhoff, Effectiveness of ustekinumab in patients with atopic dermatitis: analysis of real-world evidence, *J. Dermatol. Treat.* 33 (4) (2022) 1838–1843.
- [18] Z. Qiu, Z. Zhu, X. Liu, B. Chen, H. Yin, C. Gu, X. Fang, R. Zhu, T. Yu, W. Mi, H. Zhou, Y. Zhou, X. Yao, W. Li, A dysregulated sebum-microbial metabolite-IL-33 axis initiates skin inflammation in atopic dermatitis, *J. Exp. Med.* 219 (10) (2022).
- [19] H. Vaher, K. Kingo, P. Kolberg, M. Pook, L. Raam, A. Laanesoo, A. Remm, T. Tenson, K. Alasoo, U. Mrowietz, S. Weidinger, K. Kingo, A. Rebane, Skin colonization with *S. aureus* can lead to increased NLRP1 inflammasome activation in patients with atopic dermatitis, *J. Invest. Dermatol.* (2023).
- [20] G. Pappa, D. Sgouros, K. Theodoropoulos, A. Kanelleas, E. Bozi, S. Gregoriou, K. Krasagakis, A.C. Katoulis, The IL-4/-13 Axis and Its Blocking in the Treatment of Atopic Dermatitis, *J. Clin. Med.* 11 (19) (2022).
- [21] K. Kim, H. Kim, G.Y. Sung, An interleukin-4 and interleukin-13 induced Atopic Dermatitis human skin equivalent model by a skin-on-a-chip, *Int. J. Mol. Sci.* 23 (4) (2022).

- [22] B. Yang, H. Wilkie, M. Das, M. Timilshina, W. Bainter, B. Woods, M. Daya, M. P. Boorgula, R.A. Mathias, P. Lai, C.R. Petty, E. Weller, H. Harb, T.A. Chatila, D.Y. M. Leung, L.A. Beck, E.L. Simpson, T.R. Hata, K.C. Barnes, W. Phipatanakul, J. M. Leyva-Castillo, R.S. Geha, The IL-4R α Q576R polymorphism is associated with increased severity of atopic dermatitis and exaggerates allergic skin inflammation in mice, *J. Allergy Clin. Immunol.* (2023).
- [23] J.K. Choi, J.Y. Park, S. Lee, Y.A. Choi, S. Kwon, M.J. Shin, H.S. Yun, Y.H. Jang, J. Kang, N. Kim, D. Khang, S.H. Kim, Greater Plasma Protein Adsorption on Mesoporous Silica Nanoparticles Aggravates Atopic Dermatitis, *Int. J. Nanomed.* 17 (2022) 4599–4617.
- [24] A. Mesjasz, M. Zawadzka, M. Chalubinski, M. Trzeciak, Is Atopic Dermatitis Only a Skin Disease? *Int. J. Mol. Sci.* 24 (1) (2023).
- [25] P.D. Arkwright, J.J. Koplin, Impact of a Decade of Research Into Atopic Dermatitis, *J. Allergy Clin. Immunol. Pr.* 11 (1) (2023) 63–71.
- [26] B. Homey, M. Steinhoff, T. Ruzicka, D.Y. Leung, Cytokines and chemokines orchestrate atopic skin inflammation, *J. Allergy Clin. Immunol.* 118 (1) (2006) 178–189.
- [27] P.M. Elias, M. Steinhoff, "Outside-to-inside" (and now back to "outside") pathogenic mechanisms in atopic dermatitis, *J. Invest. Dermatol.* 128 (5) (2008) 1067–1070.
- [28] K.A.M. Al-Afif, M.A. Buraik, J. Buddenkotte, M. Mounir, R. Gerber, H.M. Ahmed, A.M. Tallman, M. Steinhoff, Understanding the Burden of Atopic Dermatitis in Africa and the Middle East, *Dermatol. Ther. (Heide)* 9 (2) (2019) 223–241.
- [29] J. Meng, Y. Li, M.J.M. Fischer, M. Steinhoff, W. Chen, J. Wang, Th2 Modulation of Transient Receptor Potential Channels: An Unmet Therapeutic Intervention for Atopic Dermatitis, *Front Immunol.* 12 (2021), 696784.
- [30] S.G. Bak, H.J. Lim, Y.S. Won, S. Lee, S.H. Cheong, S.J. Lee, E.Y. Bae, S.W. Lee, S. J. Lee, M.C. Rho, Regulatory Effects of Lycium barbarum Extract and Isolated Scopoletin on Atopic Dermatitis-Like Skin Inflammation, *Biomed. Res Int* 2022 (2022) 2475699.
- [31] Q.W.S. Lai, Q. Fan, B.Z. Zheng, Y. Chen, T.T. Dong, K.W.K. Tsim, Edible bird's nest, an Asian health food supplement, possesses anti-inflammatory responses in restoring the symptoms of atopic dermatitis: An analysis of signaling cascades, *Front Pharm.* 13 (2022), 941413.
- [32] H.P. Lee, W. Choi, K.W. Kwon, L. You, L. Rahmawati, V.D. Luong, W. Kim, B. H. Lee, S. Lee, J.H. Kim, J.Y. Cho, Inhibitory Effects of *Grewia tomentosa* Juss. on IgE-Mediated Allergic Reaction and DNCB-Induced Atopic Dermatitis, *Plants (Basel)* 11 (19) (2022).
- [33] W. Liu, W. Song, Y. Luo, H. Dan, L. Li, Z. Zhang, D. Zhou, P. You, Angelica Yinzi alleviates 1-chloro-2,4-dinitrobenzene-induced atopic dermatitis by inhibiting activation of NLRP3 inflammasome and down-regulating the MAPKs/NF- κ B signaling pathway, *Saudi Pharm. J.* 30 (10) (2022) 1426–1434.
- [34] S.S. Ahn, H. Yeo, E. Jung, S. Ou, Y.H. Lee, Y. Lim, S.Y. Shin, β -Caryophyllene Ameliorates 2,4-Dinitrochlorobenzene-Induced Atopic Dermatitis through the Downregulation of Mitogen-Activated Protein Kinase/EGFR1/TLSP Signaling Axis, *Int. J. Mol. Sci.* 23 (23) (2022).
- [35] Y. Wang, P. Zhang, J. Zhang, T. Hong, Inhibitory Effect of Bisdemethoxycurcumin on DNCB-Induced Atopic Dermatitis in Mice, *Molecules* 28 (1) (2022).
- [36] J.H. Lee, J.Y. Lim, Y.D. Jeon, D.H. Yun, Y.M. Lee, D.K. Kim, Extract of Wheatgrass and Aronia Mixture Ameliorates Atopic Dermatitis-Related Symptoms by Suppressing Inflammatory Response and Oxidative Stress In Vitro and In Vivo, *Antioxid. (Basel)* 12 (1) (2022).
- [37] G.E. Woo, H.J. Hwang, A.Y. Park, J.Y. Sim, S.Y. Woo, M.J. Kim, S.M. Jeong, N. Y. Sung, D.S. Kim, D.H. Ahn, Anti-atopic activities of sargassum horneri hot water extracts in 2,4-dinitrochlorobenzene-induced mouse models, *J. Microbiol. Biotechnol.* 33 (3) (2023) 1–8.
- [38] S.G. Bak, H.J. Lim, E.J. Park, Y.S. Won, S.W. Lee, S. Lee, S.I. Park, S.J. Lee, M. C. Rho, Effects of *Vigna angularis* extract and its active compound hemiphloin against atopic dermatitis-like skin inflammation, *Heliyon* 9 (2) (2023), e12994.
- [39] J. Luo, Y. Li, Y. Zhai, Y. Liu, J. Zeng, D. Wang, L. Li, Z. Zhu, B. Chang, F. Deng, J. Zhang, J. Zhou, L. Sun, D-Mannose ameliorates DNCB-induced atopic dermatitis in mice and TNF- α -induced inflammation in human keratinocytes via mTOR/NF- κ B pathway, *Int Immunopharmacol.* 113 (Pt A) (2022), 109378.
- [40] Q. Liu, M. Li, N. Wang, C. He, X. Jiang, J. Li, Calcium-based antimicrobial peptide compounds attenuate DNFB-induced Atopic Dermatitis-like skin lesions via Th-cells in BALB/c mice, *Int. J. Mol. Sci.* 23 (19) (2022).
- [41] N. Yang, H. Shao, J. Deng, Y. Liu, Network pharmacology-based analysis to explore the therapeutic mechanism of Cortex Dictamnii on atopic dermatitis, *J. Ethnopharmacol.* 304 (2023), 116023.
- [42] Y.J. Lee, D.S. Im, Inhibitory effect of oroxylin A in a mouse model of Atopic Dermatitis, *Inflammation* (2022).
- [43] J.I. Silverberg, L.E. French, R.B. Warren, B. Strober, K. Kjoller, M.O.A. Sommer, P. Andres, J. Felding, A. Weiss, D. Tutkunkardas, T. Skak-Nielsen, E. Guttman, Pharmacology of orismilast, a potent and selective PDE4 inhibitor, *J. Eur. Acad. Dermatol. Venereol.* (2022).
- [44] X. Han, T. Ma, Q. Wang, C. Jin, Y. Han, G. Liu, H. Li, The mechanism of oxymatrine on atopic dermatitis in mice based on SOCS1/JAK-STAT3 pathway, *Front Pharm.* 13 (2022) 1091090.
- [45] Y. Liu, J. Zienkiewicz, H. Qiao, K.N. Gibson-Corley, K.L. Boyd, R.A. Veach, J. Hawiger, Genomic control of inflammation in experimental atopic dermatitis, *Sci. Rep.* 12 (1) (2022) 18891.
- [46] S. Lavazais, M. Jargosch, S. Dupont, F. Labéguère, C. Menet, C. Jagerschmidt, F. Ohm, L. Kupcsik, I. Parent, C. Cottareaux, F. Marsais, L. Oste, A. Van de Water, T. Christophe, S. De Vos, P. Fallon, F. Lauffer, P. Clément-Lacroix, K. Eyerich, R. Brys, IRAK4 inhibition dampens pathogenic processes driving inflammatory skin diseases, *Sci. Transl. Med* 15 (683) (2023) eabj3289.
- [47] J.W. Seo, H.J. Lee, Y.M. Youk, G.H. Nam, Y.M. Kim, *Torilis japonica* extract suppresses the induction of Atopic Inflammation, *Int. J. Mol. Sci.* 24 (3) (2023).
- [48] S. Cadau, M. Gault, N. Berthelemy, C.Y. Hsu, L. Danoux, N. Pelletier, D. Goudouneche, C. Pons, C. Lepreux, V. André-Frei, M. Simon, S. Pain, An inflamed and infected reconstructed human epidermis to study Atopic Dermatitis and skin care ingredients, *Int. J. Mol. Sci.* 23 (21) (2022).
- [49] X. Ni, Y. Xu, W. Wang, B. Kong, J. Ouyang, J. Chen, M. Yan, Y. Wu, Q. Chen, X. Wang, H. Li, X. Gao, H. Guo, L. Cui, Z. Chen, Y. Shi, R. Zhu, W. Li, T. Shi, L. F. Wang, J. Huang, C. Dong, Y. Lai, IL-17D-induced inhibition of DDX5 expression in keratinocytes amplifies IL-36R-mediated skin inflammation, *Nat. Immunol.* 23 (11) (2022) 1577–1587.
- [50] S. Nunomura, D. Uta, I. Kitajima, Y. Nanri, K. Matsuda, N. Ejiri, M. Kitajima, H. Ikemitsu, M. Koga, S. Yamamoto, Y. Honda, H. Takedomi, T. Andoh, S. J. Conway, K. Izuhara, Periostin activates distinct modules of inflammation and itching downstream of the type 2 inflammation pathway, *Cell Rep.* 42 (1) (2023), 111933.
- [51] D. Bayarsaihan, Epigenetic mechanisms in inflammation, *J. Dent. Res* 90 (1) (2011) 9–17.
- [52] M. Berdasco, M. Esteller, Clinical epigenetics: seizing opportunities for translation, *Nat. Rev. Genet.* 20 (2) (2019) 109–127.
- [53] A. Ahmad, Cancer epigenetics: clinical perspectives, *Curr. Cancer Drug Targets* 19 (7) (2019) 513–514.
- [54] A. Ahmad, Epigenetics in personalized management of lung cancer, *Adv. Exp. Med Biol.* 890 (2016) 111–122.
- [55] A. Ahmad, S. Azim, H. Zubair, M.A. Khan, S. Singh, J.E. Carter, R.P. Rocconi, A. P. Singh, Epigenetic basis of cancer health disparities: looking beyond genetic differences, *Biochim Biophys. Acta Rev. Cancer* 1868 (1) (2017) 16–28.
- [56] J.E. Kim, J.S. Kim, D.H. Cho, H.J. Park, Molecular mechanisms of cutaneous inflammatory disorder: Atopic Dermatitis, *Int. J. Mol. Sci.* 17 (8) (2016).
- [57] Y. Lian, L. Meng, P. Ding, M. Sang, Epigenetic regulation of MAGE family in human cancer progression-DNA methylation, histone modification, and non-coding RNAs, *Clin. Epigenetics* 10 (1) (2018) 115.
- [58] I. Gareev, Y. Gileva, A. Dzidzaria, O. Beylerli, V. Pavlov, M. Agaverdiev, B. Mazarov, I. Biganyakov, A. Vardikyan, M. Jin, A. Ahmad, Long non-coding RNAs in oncology, *Noncoding RNA Res* 6 (3) (2021) 139–145.
- [59] M. Farhan, M.F. Ullah, M. Faisal, A.A. Farooqi, U.Y. Sabitaliyevich, B. Biersack, A. Ahmad, Differential methylation and acetylation as the epigenetic basis of resveratrol's anticancer activity, *Med. (Basel)* 6 (1) (2019).
- [60] A.E.A. Surace, C.M. Hedrich, The role of epigenetics in autoimmune/inflammatory disease, *Front Immunol.* 10 (2019) 1525.
- [61] G. Herberth, M. Bauer, M. Gasch, D. Hinz, S. Röder, S. Olek, T. Kohajda, U. Rolle-Kampczyk, M. von Bergen, U. Sack, M. Borte, I. Lehmann, Maternal and cord blood miR-223 expression associates with prenatal tobacco smoke exposure and low regulatory T-cell numbers, *J. Allergy Clin. Immunol.* 133 (2) (2014) 543–550.
- [62] D. Hinz, M. Bauer, S. Röder, S. Olek, J. Huehn, U. Sack, M. Borte, J.C. Simon, I. Lehmann, G. Herberth, Cord blood Tregs with stable FOXP3 expression are influenced by prenatal environment and associated with atopic dermatitis at the age of one year, *Allergy* 67 (3) (2012) 380–389.
- [63] G.A. Dhar, S. Saha, P. Mitra, R. Nag Chaudhuri, DNA methylation and regulation of gene expression: Guardian of our health, *Nucl. (Calcutta)* 64 (3) (2021) 259–270.
- [64] A. Ahmad, Special issue: epigenetic regulation of cancer progression: promises and progress, *Semin Cancer Biol.* 83 (2022) 1–3.
- [65] O.Y. Olisova, N.G. Kochergin, L.N. Kayumova, T.M. Zavarykina, A.A. Dmitriev, A. Y. Asanov, Skin DNA methylation profile in atopic dermatitis patients: A case-control study, *Exp. Dermatol.* 29 (2) (2020) 184–189.
- [66] Y. Liang, P. Wang, M. Zhao, G. Liang, H. Yin, G. Zhang, H. Wen, Q. Lu, Demethylation of the FCER1G promoter leads to Fc ϵ RI overexpression on monocytes of patients with atopic dermatitis, *Allergy* 67 (3) (2012) 424–430.
- [67] J.G. Holm, T. Agner, M.L. Clausen, S.F. Thomsen, Determinants of disease severity among patients with atopic dermatitis: association with components of the atopic march, *Arch. Dermatol. Res* 311 (3) (2019) 173–182.
- [68] Y. Liang, B. Yu, J. Chen, H. Wu, Y. Xu, B. Yang, Q. Lu, Thymic stromal lymphopoietin epigenetically upregulates Fc receptor γ subunit-related receptors on antigen-presenting cells and induces T(H)2/T(H)17 polarization through dectin-2, *J. Allergy Clin. Immunol.* 144 (4) (2019) 1025–1035, e7.
- [69] E. Rodríguez, H. Baurecht, A.F. Wahn, A. Kretschmer, M. Hotze, S. Zeilinger, N. Klopp, T. Illig, K. Schramm, H. Prokisch, B. Kühnel, C. Gieger, J. Harder, L. Cifuentes, N. Novak, S. Weidinger, An integrated epigenetic and transcriptomic analysis reveals distinct tissue-specific patterns of DNA methylation associated with atopic dermatitis, *J. Invest. Dermatol.* 134 (7) (2014) 1873–1883.
- [70] Y. Yoshida, K. Hayakawa, M. Fujishiro, K. Ikeda, H. Tsushima, T. Hirai, M. Kawasaki, M. Tominaga, Y. Suga, K. Takamori, Y. Watanabe, I. Sekigawa, S. Morimoto, Social defeat stress exacerbates atopic dermatitis through downregulation of DNA methyltransferase 1 and upregulation of C-C motif chemokine receptor 7 in skin dendritic cells, *Biochem Biophys. Res Commun.* 529 (4) (2020) 1073–1079.
- [71] B.E. Kim, D.Y.M. Leung, Significance of skin barrier dysfunction in Atopic Dermatitis, *Allergy Asthma Immunol. Res* 10 (3) (2018) 207–215.
- [72] Y. Mitamura, I. Ogulur, Y. Pat, A.O. Rinaldi, O. Ardicli, L. Cevhertas, M. C. Brüggem, C. Traidl-Hoffmann, M. Akdis, C.A. Akdis, Dysregulation of the epithelial barrier by environmental and other exogenous factors, *Contact Dermat.* 85 (6) (2021) 615–626.
- [73] P. Chioesilapatham, H. Ogawa, F. Niyonsaba, Current insights into the role of human β -defensins in atopic dermatitis, *Clin. Exp. Immunol.* 190 (2) (2017) 155–166.

- [74] Y.H. Noh, J. Lee, S.J. Seo, S.C. Myung, Promoter DNA methylation contributes to human β -defensin-1 deficiency in atopic dermatitis, *Anim. Cells Syst. (Seoul.)* 22 (3) (2018) 172–177.
- [75] R. Osawa, M. Akiyama, H. Shimizu, Filaggrin gene defects and the risk of developing allergic disorders, *Allergol. Int.* 60 (1) (2011) 1–9.
- [76] A. Sandilands, C. Sutherland, A.D. Irvine, W.H. McLean, Filaggrin in the frontline: role in skin barrier function and disease, *J. Cell Sci.* 122 (Pt 9) (2009) 1285–1294.
- [77] J.P. Thyssen, S. Kezic, Causes of epidermal filaggrin reduction and their role in the pathogenesis of atopic dermatitis, *J. Allergy Clin. Immunol.* 134 (4) (2014) 792–799.
- [78] J. Lee, A. Jang, S.J. Seo, S.C. Myung, Epigenetic regulation of filaggrin gene expression in human epidermal keratinocytes, *Ann. Dermatol.* 32 (2) (2020) 122–129.
- [79] K.D. Chen, Y.H. Huang, M.M. Guo, L.S. Chang, C.H. Chu, L.F. Bu, C.L. Chu, C. H. Lee, S.F. Liu, H.C. Kuo, DNA Methylation Array Identifies Golli-MBP as a biomarker for disease severity in childhood Atopic Dermatitis, *J. Invest. Dermatol.* 142 (1) (2022) 104–113.
- [80] M. Schedel, S.M. Leach, M.J. Strand, T. Danhorn, M. MacBeth, A.V. Faino, A. M. Lynch, V.D. Winn, L.L. Munoz, S.M. Forsberg, D.A. Schwartz, E.W. Gelfand, P. J. Hauk, Molecular networks in atopic mothers impact the risk of infant atopy, *Allergy* 78 (1) (2023) 244–257.
- [81] W.C. Liew, G.M. Sundaram, S. Quah, G.G. Lum, J.S.L. Tan, R. Ramalingam, J.E. A. Common, M.B.Y. Tang, E.B. Lane, S.T.G. Thng, P. Sampath, Belinostat resolves skin barrier defects in atopic dermatitis by targeting the dysregulated miR-335: SOX6 axis, *J. Allergy Clin. Immunol.* 146 (3) (2020) 606–620, e12.
- [82] M.T. Buckley, J. Yoon, H. Yee, L. Chiriboga, L. Liebes, G. Ara, X. Qian, D. F. Bajorin, T.T. Sun, X.R. Wu, I. Osman, The histone deacetylase inhibitor belinostat (PXD101) suppresses bladder cancer cell growth in vitro and in vivo, *J. Transl. Med.* 5 (2007) 49.
- [83] E. Dissanayake, Y. Inoue, MicroRNAs in Allergic Disease, *Curr. Allergy Asthma Rep.* 16 (9) (2016) 67.
- [84] L. Ma, H.B. Xue, F. Wang, C.M. Shu, J.H. Zhang, MicroRNA-155 may be involved in the pathogenesis of atopic dermatitis by modulating the differentiation and function of T helper type 17 (Th17) cells, *Clin. Exp. Immunol.* 181 (1) (2015) 142–149.
- [85] Y. Liang, C. Chang, Q. Lu, The genetics and epigenetics of atopic dermatitis-filaggrin and other polymorphisms, *Clin. Rev. Allergy Immunol.* 51 (3) (2016) 315–328.
- [86] J.S. Mervis, J.S. McGee, DNA methylation and inflammatory skin diseases, *Arch. Dermatol. Res.* 312 (7) (2020) 461–466.
- [87] L. Bin, D.Y. Leung, Genetic and epigenetic studies of atopic dermatitis, *Allergy Asthma Clin. Immunol.* 12 (2016) 52.
- [88] A.D. Schmidt, C. de Guzman, Strong, current understanding of epigenetics in atopic dermatitis, *Exp. Dermatol.* 30 (8) (2021) 1150–1155.
- [89] L. Möbus, S. Weidinger, H. Emmert, Epigenetic factors involved in the pathophysiology of inflammatory skin diseases, *J. Allergy Clin. Immunol.* 145 (4) (2020) 1049–1060.
- [90] Z. Mu, J. Zhang, The role of genetics, the environment, and epigenetics in Atopic Dermatitis, *Adv. Exp. Med. Biol.* 1253 (2020) 107–140.
- [91] B. Nedoszytko, E. Reszka, D. Gutowska-Owsiak, M. Trzeciak, M. Lange, J. Jarczak, M. Niedoszytko, E. Jablonska, J. Romantowski, D. Strapagiel, J. Skokowski, A. Siekierzyska, R.J. Nowicki, I.T. Dobrucki, A. Zaryczanska, L. Kalinowski, Genetic and epigenetic aspects of Atopic Dermatitis, *Int. J. Mol. Sci.* 21 (18) (2020).
- [92] F. Gibson, A. Hanly, N. Grbic, N. Grunberg, M. Wu, M. Collard, R.M. Alani, Epigenetic dysregulation in autoimmune and inflammatory skin diseases, *Clin. Rev. Allergy Immunol.* 63 (3) (2022) 447–471.
- [93] C.H. Baloh, R.A. Mathias, Recent progress in the genetic and epigenetic underpinnings of atopy, *J. Allergy Clin. Immunol.* 151 (1) (2023) 60–69.
- [94] A.A. Eapen, S. Parameswaran, C. Forney, L.E. Edsall, D. Miller, O. Donmez, K. Dunn, X. Lu, M. Granitto, H. Rowden, A.Z. Magier, M. Pujato, X. Chen, K. Kaufman, D.I. Bernstein, A.L. Devonshire, M.E. Rothenberg, M.T. Weirauch, L. C. Kottyan, Epigenetic and transcriptional dysregulation in CD4⁺ T cells in patients with atopic dermatitis, *PLoS Genet.* 18 (5) (2022), e1009973.
- [95] B.O. Fagundes, T.R. de Sousa, A. Nascimento, L.A. Fernandes, F.D.R. Sgnotto, R. L. Orfali, V. Aoki, A. Duarte, S.S. Sanabani, J.R. Victor, IgG from adult atopic dermatitis (AD) patients induces nonatopic neonatal thymic gamma-delta T cells ($\gamma\delta$ T) to acquire IL-22/IL-17 secretion profile with skin-homing properties and epigenetic implications mediated by miRNA, *Int. J. Mol. Sci.* 23 (12) (2022).
- [96] T.R. de Sousa, B.O. Fagundes, A. Nascimento, L.A. Fernandes, F.D.R. Sgnotto, R. L. Orfali, V. Aoki, A. Duarte, S.S. Sanabani, J.R. Victor, IgG from adult atopic dermatitis (AD) patients induces thymic IL-22 production and CLA expression on CD4⁺ T cells: possible epigenetic implications mediated by miRNA, *Int. J. Mol. Sci.* 23 (12) (2022).
- [97] H. Jo, K. Shim, D. Jeoung, The crosstalk between FcεpsilonRI and sphingosine signaling in allergic inflammation, *Int. J. Mol. Sci.* 23 (22) (2022).
- [98] Y. Chen, M. Song, Z. Li, L. Hou, H. Zhang, Z. Zhang, H. Hu, X. Jiang, J. Yang, X. Zou, J. Pang, T. Zhang, P. Yang, J. Wang, C. Wang, FcεpsilonRI deficiency alleviates silica-induced pulmonary inflammation and fibrosis, *Ecotoxicol. Environ. Saf.* 244 (2022), 114043.
- [99] G.K. Arthur, G. Cruse, Regulation of trafficking and signaling of the high affinity ige receptor by fcepsilonribeta and the potential impact of fcepsilonribeta splicing in allergic inflammation, *Int. J. Mol. Sci.* 23 (2) (2022).
- [100] P. Andreu, M. Johansson, N.I. Affara, F. Pucci, T. Tan, S. Junankar, L. Korets, J. Lam, D. Tawfik, D.G. DeNardo, L. Naldini, K.E. de Visser, M. De Palma, L. M. Coussens, Fcγgamma activation regulates inflammation-associated squamous carcinogenesis, *Cancer Cell* 17 (2) (2010) 121–134.
- [101] S. Ben Mkaddem, M. Benhamou, R.C. Monteiro, Understanding Fc receptor involvement in inflammatory diseases: from mechanisms to new therapeutic tools, *Front Immunol.* 10 (2019) 811.
- [102] A. Pothmann, T. Illing, C. Wiegand, A.A. Hartmann, P. Elsner, The microbiome and atopic dermatitis: a review, *Am. J. Clin. Dermatol.* 20 (6) (2019) 749–761.
- [103] M.R. Williams, R.L. Gallo, The role of the skin microbiome in atopic dermatitis, *Curr. Allergy Asthma Rep.* 15 (11) (2015) 65.
- [104] T. Al-Qirim, A. Ahmad, Perspectives on cancer-microbiome conundrum, *Micro Micro Res.* 4 (2022) 17–21.
- [105] G.A. Ogunrinola, J.O. Oyewale, O.O. Oshamika, G.I. Olasehinde, The human microbiome and its impacts on health, *Int. J. Microbiol.* 2020 (2020) 8045646.
- [106] Y. Fan, O. Pedersen, Gut microbiota in human metabolic health and disease, *Nat. Rev. Microbiol.* 19 (1) (2021) 55–71.
- [107] Z. Al Bander, M.D. Nitert, A. Mousa, N. Naderpoor, The gut microbiota and inflammation: an overview, *Int. J. Environ. Res. Public Health* 17 (20) (2020).
- [108] J.C. Clemente, J. Manasson, J.U. Scher, The role of the gut microbiome in systemic inflammatory disease, *BMJ* 360 (2018) j5145.
- [109] A.S. Paller, H.H. Kong, P. Seed, S. Naik, T.C. Scharschmidt, R.L. Gallo, T. Luger, A. D. Irvine, The microbiome in patients with atopic dermatitis, *J. Allergy Clin. Immunol.* 143 (1) (2019) 26–35.
- [110] U. Wollina, Microbiome in atopic dermatitis, *Clin. Cosmet. Invest. Dermatol.* 10 (2017) 51–56.
- [111] V. Woo, T. Alenghat, Epigenetic regulation by gut microbiota, *Gut Microbes* 14 (1) (2022), 2022407.
- [112] P. Chen, G. He, J. Qian, Y. Zhan, R. Xiao, Potential role of the skin microbiota in inflammatory skin diseases, *J. Cosmet. Dermatol.* 20 (2) (2021) 400–409.
- [113] D. Simon, L.R. Braathen, H.U. Simon, Eosinophils and atopic dermatitis, *Allergy* 59 (6) (2004) 561–570.
- [114] K.M. Leiferman, Eosinophils in atopic dermatitis, *J. Allergy Clin. Immunol.* 94 (6 Pt 2) (1994) 1310–1317.
- [115] M. Nagata, K. Nakagome, T. Soma, Mechanisms of eosinophilic inflammation, *Asia Pac. Allergy* 10 (2) (2020), e14.
- [116] C. Lombardi, A. Berti, M. Cottini, The emerging roles of eosinophils: implications for the targeted treatment of eosinophilic-associated inflammatory conditions, *Curr. Res. Immunol.* 3 (2022) 42–53.
- [117] A.D. Doyle, M.Y. Masuda, G.C. Pyon, H. Luo, A. Putikova, W.E. LeSuer, S. Flashner, M.A. Rank, H. Nakagawa, H. Kita, B.L. Wright, Detergent exposure induces epithelial barrier dysfunction and eosinophilic inflammation in the esophagus, *Allergy* 78 (1) (2023) 192–201.
- [118] É. Bélanger, A.M. Madore, A.M. Boucher-Lafleur, M.M. Simon, T. Kwan, T. Pastinen, C. Laprise, Eosinophil microRNAs play a regulatory role in allergic diseases induced in the atopic march, *Int. J. Mol. Sci.* 21 (23) (2020).
- [119] L. Yang, J. Fu, X. Han, C. Zhang, L. Xia, R. Zhu, S. Huang, W. Xiao, H. Yu, Y. Gao, Q. Liang, W. Li, Y. Zhou, Hsa_circ_0004287 inhibits macrophage-mediated inflammation in an N(6)-methyladenosine-dependent manner in atopic dermatitis and psoriasis, *J. Allergy Clin. Immunol.* 149 (6) (2022) 2021–2033.
- [120] A. Ahmad, Epigenetic regulation of immunosuppressive tumor-associated macrophages through dysregulated microRNAs, *Semin Cell Dev. Biol.* 124 (2022) 26–33.
- [121] S. Ahmad, S. Manzoor, S. Siddiqui, N. Mariappan, I. Zafar, A. Ahmad, A. Ahmad, Epigenetic underpinnings of inflammation: connecting the dots between pulmonary diseases, lung cancer and COVID-19, *Semin Cancer Biol.* 83 (2022) 384–398.
- [122] T. Tanaka, M. Narazaki, T. Kishimoto, IL-6 in inflammation, immunity, and disease, *Cold Spring Harb. Perspect. Biol.* 6 (10) (2014) a016295.
- [123] S. Biswas, A.A. Thomas, S. Chen, E. Aref-Eshghi, B. Feng, J. Gonder, B. Sadikovic, S. Chakrabarti, MALAT1: an epigenetic regulator of inflammation in diabetic retinopathy, *Sci. Rep.* 8 (1) (2018) 6526.
- [124] H.H. Yu, W. Zhao, B.X. Zhang, Y. Wang, J. Li, Y.F. Fang, Morinda officinalis extract exhibits protective effects against atopic dermatitis by regulating the MALAT1/miR-590-5p/CCR7 axis, *J. Cosmet. Dermatol.* (2023).
- [125] M. Massimini, E. Dalle Vedove, B. Bachetti, F. Di Piero, C. Ribecco, C. D'Addario, M. Pucci, Polyphenols and cannabidiol modulate transcriptional regulation of Th1/Th2 inflammatory genes related to canine atopic dermatitis, *Front Vet. Sci.* 8 (2021), 606197.
- [126] W.Ft Carson, S.E. Salter-Green, M.M. Scola, A. Joshi, K.A. Gallagher, S.L. Kunkel, Enhancement of macrophage inflammatory responses by CCL2 is correlated with increased miR-9 expression and downregulation of the ERK1/2 phosphatase Dusp6, *Cell Immunol.* 314 (2017) 63–72.
- [127] K.M. Lee, A. Jarnicki, A. Achuthan, A.J. Fleetwood, G.P. Anderson, C. Ellison, M. Feeney, L.K. Modis, J.E. Smith, J.A. Hamilton, A. Cook, CCL17 in inflammation and pain, *J. Immunol.* 205 (1) (2020) 213–222.
- [128] H. Kabata, A.L. Flamar, T. Mahlaköiv, S. Moriyama, H.R. Rodewald, S.F. Ziegler, D. Artis, Targeted deletion of the TSLP receptor reveals cellular mechanisms that promote type 2 airway inflammation, *Mucosal Immunol.* 13 (4) (2020) 626–636.
- [129] A. Datsi, M. Steinhoff, F. Ahmad, M. Alam, J. Buddenkotte, Interleukin-31: the "itchy" cytokine in inflammation and therapy, *Allergy* 76 (10) (2021) 2982–2997.
- [130] L.M. Roesner, T. Werfel, A. Heratizadeh, The adaptive immune system in atopic dermatitis and implications on therapy, *Expert Rev. Clin. Immunol.* 12 (7) (2016) 787–796.
- [131] E.B. Brandt, U. Sivaprasad, Th2 cytokines and atopic dermatitis, *J. Clin. Cell Immunol.* 2 (3) (2011).
- [132] F.D.R. Sgnotto, M.G. de Oliveira, A.A.L. Lira, A.H.S. Inoue, T.O. Titz, R.L. Orfali, L. Bento-de-Souza, M.N. Sato, V. Aoki, A.J.S. Duarte, J.R. Victor, IgG from atopic

- dermatitis patients induces IL-17 and IL-10 production in infant intrathymic TCD4 and TCD8 cells, *Int J. Dermatol.* 57 (4) (2018) 434–440.
- [133] L.S. Santos, F.D.R. Sgnotto, T.R. Sousa, R.L. Orfali, V. Aoki, A. Duarte, J.R. Victor, IgG from atopic dermatitis patients induces non-atopic infant thymic invariant natural killer T (iNKT) cells to produce IL-4, IL-17, and IL-10, *Int J. Dermatol.* 59 (3) (2020) 359–364.
- [134] P.M. Brunner, A.B. Pavel, S. Khattri, A. Leonard, K. Malik, S. Rose, S. Jim, On, A. S. Vekaria, C. Traidl-Hoffmann, G.K. Singer, D. Baum, P. Gilleaudeau, M. Sullivan-Whalen, J. Fuentes-Duculan, X. Li, X. Zheng, Y. Estrada, S. Garcet, H. C. Wen, J. Gonzalez, I. Coats, I. Cueto, A.U. Neumann, M.G. Lebwohl, J. G. Krueger, E. Guttman-Yassky, Baseline IL-22 expression in patients with atopic dermatitis stratifies tissue responses to fezakinumab, *J. Allergy Clin. Immunol.* 143 (1) (2019) 142–154.
- [135] M. Jin, J. Yoon, From bench to clinic: the potential of therapeutic targeting of the IL-22 signaling pathway in atopic dermatitis, *Immune Netw.* 18 (6) (2018), e42.
- [136] K.E. Nogales, L.C. Zaba, A. Shemer, J. Fuentes-Duculan, I. Cardinale, T. Kikuchi, M. Ramon, R. Bergman, J.G. Krueger, E. Guttman-Yassky, IL-22-producing "T22" T cells account for upregulated IL-22 in atopic dermatitis despite reduced IL-17-producing TH17 T cells, *J. Allergy Clin. Immunol.* 123 (6) (2009), 1244-52.e2.
- [137] T. Arshad, F. Mansur, R. Palek, S. Manzoor, V. Liska, A. Double, Edged sword role of interleukin-22 in wound healing and tissue regeneration, *Front Immunol.* 11 (2020) 2148.
- [138] H. Zhao, Y. Guo, Y. Sun, N. Zhang, X. Wang, miR-181a/b-5p ameliorates inflammatory response in monocrotaline-induced pulmonary arterial hypertension by targeting endocan, *J. Cell Physiol.* 235 (5) (2020) 4422–4433.
- [139] S.D. Gurien, M. Aziz, H. Jin, H. Wang, M. He, Y. Al-Abed, J.M. Nicastro, G. F. Coppa, P. Wang, Extracellular microRNA 130b-3p inhibits eCIRP-induced inflammation, *EMBO Rep.* 21 (1) (2020), e48075.
- [140] H. Gupta, M. Rubio, A. Siteo, R. Varo, P. Cisteró, L. Madrid, I. Cuamba, A. Jimenez, X. Martiáñez-Vendrell, D. Barrios, L. Pantano, A. Brimacombe, M. Bustamante, Q. Bassat, A. Mayor, Plasma MicroRNA profiling of plasmodium falciparum biomass and association with severity of malaria disease, *Emerg. Infect. Dis.* 27 (2) (2021) 430–442.
- [141] J.Z. Yi, J.S. McGee, Epigenetic-modifying therapies: an emerging avenue for the treatment of inflammatory skin diseases, *Exp. Dermatol.* 30 (8) (2021) 1167–1176.
- [142] S. Quah, G. Subramanian, P. Sampath, Repurposing belinostat for alleviation of atopic dermatitis, *Dermatol. Ther. (Heide)* 11 (3) (2021) 655–660.
- [143] R. Darlenski, A.L. Kozyskyj, J.W. Fluhr, L. Caraballo, Association between barrier impairment and skin microbiota in atopic dermatitis from a global perspective: unmet needs and open questions, *J. Allergy Clin. Immunol.* 148 (6) (2021) 1387–1393.
- [144] K. Szalus, M. Trzeciak, R.J. Nowicki, JAK-STAT inhibitors in atopic dermatitis from pathogenesis to clinical trials results, *Microorganisms* 8 (11) (2020).
- [145] L. Bao, H. Zhang, L.S. Chan, The involvement of the JAK-STAT signaling pathway in chronic inflammatory skin disease atopic dermatitis, *Jakstat* 2 (3) (2013), e24137.
- [146] A. Tsiogka, M. Kyriazopoulou, G. Kontochristopoulos, E. Nicolaidou, A. Stratigos, D. Rigopoulos, S. Gregoriou, The JAK/STAT pathway and its selective inhibition in the treatment of atopic dermatitis: a systematic review, *J. Clin. Med* 11 (15) (2022).