Filaggrin

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Filaggrin (FLG) is a large (37-kD), histidine rich protein named after its ability to aggregates keratin intermediate filaments (Filament aggregating Protein). FLG is an important epidermal structural protein, crucial to the structure and function of the stratum corneum (SC) and is largely involved in the maintenance of skin barrier function. FLG deficiency or dysfunction can lead to various skin disorders such as xerosis, ichthyosis vulgaris and atopic dermatitis (AD). It has been proposed that the level of FLG and its degradation products are influenced not only by the FLG loss-of-function mutations but also by endogenous or exogenous factors.

Keywords: atopic dermatitis ; skin barrier ; filaggrin ; biologicals ; small molecule therapies

1. Introduction

Filaggrin (FLG), which is processed from profilaggrin, is a key protein that facilitates terminal differentiation of the epidermis and formation of the protective skin barrier. FLG and its degradation products contribute to skin hydration, pH balance, epidermal barrier integrity and microbial defense. An increased skin permeability has been proposed as the most plausible mechanism linking FLG deficiency and AD. Proteomic analysis on skin equivalent models revealed that molecular consequences resulting directly from FLG deficiency are complex and include the dysregulation of proteins relevant to inflammatory, proteolytic and cytoskeletal functions [1]. In murine models of AD, FLG deficiency alters both the intracellular and extracellular architecture of keratinocytes, interferes with lipid secretion, reduces inflammatory thresholds to irritants and haptens, permits increased allergen penetration and enhances skin inflammation [1][2][3][4][5][6]. Mutations in the FLG gene can lead to impaired skin barrier function nad represents the strongest genetic risk factor for developing AD. However, FLG mutations are only found in 10–50% of AD cases and the majority of children with AD and FLG mutations outgrow their disease [7][8]. These observations suggest that there are also aquaried mechanisms at play that downregulate the expression of FLG.

Despite its high prevalence and effect on the quality of life, safe and effective systemic therapies approved for long-term management of AD are limited. One of the goals of the current research efforts is the development of new therapeutic approaches that target specific pathophysiological pathways. Based on the aforementioned insights into the role of the FLG in the pathogenesis of AD, restoring skin barrier function through upregulation of FLG expression could be a potential therapy for all patients with AD regardless of mutation status. The purpose of this review is to highlight fundamental regulatory mechanisms of skin barrier-related molecules, such as FLG, and to discuss innovations in the therapy of AD, including biologics, small molecules therapies and other drugs targeting FLG upregulation (Table 1).

2. Genetic Causes of FLG Deficiency

The FLG gene is large repetitive gene located in the epidermal differnetiation complex (EDC), a claster of more than 70 genes located on chromosome 1q21. The EDC region includes genes encoding many barrier-related proteins that are essential for epidermal maturation and differentiation [9][10]. The FLG mutations are located in the third exon of the gene and as the loss-of-function mutations they cause a reduction or complete absence of the expressed protein depending on the number of mutations the individual carries [11][12]. Although it was previously reported that FLG mutations are less common in African populations, recent whole-exome sequencing studies have revealed rare FLG variants in this ethnic group [13][14]. Additionally, the spectrum of the most frequent mutations varies between Asian populations, African populations and white populations [15][13][16]. Nevertheless, several genome-wide association studies (GWASs) that include meta-analyses were able to replicate the association of FLG with AD in different populations [47]. Thus, FLG loss-of-function mutations remain the strongest identified and widely replicated genetic risk factor for AD.

Therefore, the development of a therapy aimed to treat the most significant genetic defect in AD is warranted. One of the theoretical gene-based approaches to FLG replacement might include the use of “read-through” drugs which focusing on mutant allele and might be achieved by skipping of the nonsense FLG mutations during RNA splicing or incorporating of

amino acids at the mutation site. These drugs are currently being tested for other genetic diseases with promising results [17][18]. Despite being potentially applicable, therapies directly targeting the reduced production of FLG protein due to genetic variation are not currently available.

3. Indirect FLG Replacement Therapy

It was demonstrated that the SC levels of PCA, UCA and histidine are influenced by both FLG genotype and the severity of AD [19]. FLG is a histidine-rich protein and histidine is a substrate for histidase which generates UCA in upper SC Those findings point to the possibility of using oral L-histidine supplementation in the therapy of AD. Those studies indicate that oral L-histidine supplementation is a safe, nonsteroidal approach suitable for long-term use in skin conditions associated with FLG deficits, such as AD.

4. Acquired FLG Deficiency–Regulation of FLG Expression

Accumulated data have shown that FLG expression is not stable and is amenable to modulation by external and internal stimulants [20][6][21][22][23]. The downregulation of FLG is confirmed to be systemic and secondary to dysregulated expression of Th2-associated (IL-4, IL-13) and Th22-associated (On the other hand, recent studies reported that activation of aryl hydrocarbon receptor (AHR), a ligand-activated transcription factor, plays an essential role in upregulating the expression of FLG [21][22][23]. There are also findings available about environmental factors and exposomal influences that have a significant effect on FLG expression [20][6].

Therefore, therapeutic strategies that involve blocking the cytokine-mediated FLG downregulation or enhancing FLG expression may be beneficial in treating AD. A primary target is downstream of the IL-4/IL-13 axis and the AHR axis, while the other minor targets, although promising, are not fully understood.

Both oxidative (dioxins and bezno[α]pyrene) and antioxidative (coal tar, soybean tar, phytochemicals) AHR ligands induce upregulation of FLG and other differentiation-related molecules. AHR activation promotes FLG expression directly via AHR/ARNT binding to the one or two xenobiotic responsive elements in the promoter region of the FLG gene [24][25][26]. In parallel, AHR signaling regulates oxidative stress in keratinocytes. Therefore, antioxidative AHR agonists are expected to be promising candidates for AD treatment in which skin barrier disruption, Th2 inflammation and oxidative stress upregulation are observed.

The topical application of coal tar is the oldest known dermatological treatment and is efficacious in reducing inflammation and itch in AD. first demonstrated that coal tar activates AHR, upregulates FLG expression to wild-type levels, and restores the IL-4/IL-13-STAT6-mediated downregulation of FLG [27]. Glyteer is a delipidated soybean tar that has been widely used for the treatment of various inflammatory skin diseases in Japan since 1924 as an alternative to a coal tar remedy. Glyteer exhibits biological properties similar to those of coal tar [28].

Tapinarof activates both AHR and NRF2, resulting in increased skin barrier protein expression, including FLG, reduced oxidative stress, decreased proinflammatory Th2 cytokine expression and re-established skin homeostasis [29][30]. Two early clinical trials demonstrated that topical tapinarof at 0.5% and 1.0% is efficacious for the treatment in patients with mild-moderate and severe AD. In phase 2, double-blind, vehicle-controlled trial in patients with AD aged 12 to 65 years, tapinafor achieved a 75% or greater improvement in EASI score (EASI-75) at week 12 in more than 50% of patients treated once daily. More recently, another phase 2b trial demonstrated that 1% tapinarof cream led to statistically significant and clinically meaningful improvements in efficacy analyses, including the proportion of patients achieving EASI-75 and EASI-90 (90% or greater improvement in EASI score) and the overall improvements in EASI scores and BSA (body surface area) affected.

Historically, it has been demonstrated that interleukin IL-4 and IL-13 play a key role in AD pathogenesis [31][32][33][34]. The gene expression of Th2-derived cytokines, IL-4 and IL-13, is significantly higher in the lesional skin of AD patients compared with the normal skin or unaffected AD skin [34][35][36]. The Th2 predominance is likely to progress from non-lesional to lesional skin and from acute and chronic lesions in AD [37]. The importance of Th2 deviations in AD is supported by the fact that AD-like phenotype can be induced in murine models overexpressing

Dupilumab is the first biologic approved as a first-line treatment for moderate-to-severe atopic dermatitis in patients aged 6 years and older in the USA and in patients aged 12 years and older in the EU (approval for children aged 6–12 years is pending). Translational studies demonstrated that dupilumab reduces the expression of Th2-associated cytokines and

chemokines as well as Th17 Additionally, after 4 weeks of dupilumab treatment, a significant reduction in the expression of the epidermal hyperplasia-related gene, T cells and dendritic cells were observed [38][39]. Concurrent with these changes, dupilumab increases the expression of terminal differentiation genes such as FLG [39].

The efficacy of dupilumab has been studied in several phase 3 trials that demonstrated efficacy and a favorable safety profile in patients with moderate-to-severe AD inadequately controlled with topical medications. Additionally, significantly more patients in dupilumab groups had improvement in Dermatology Life Quality Index (DLQI) score [40]. A recent review of real-life data from 22 studies, presented dupilumab as a successful and well-tolerated therapy for AD that demonstrated a significant reduction in EASI score as well as clinical improvement along with the quality of life improvement [41]. Many trials with dupilumab in the pediatric population are ongoing, including evaluation of the efficacy in patients aged 6 months to 17 years, and characterizing long-term safety and efficacy with long-term use [42] (Table 3).

Dupilumab consistently demonstrates an acceptable, placebo-like safety profile, with conjunctivitis, nasopharyngitis and injection-site reactions as the most common adverse events. Data from three randomized phase 3 trials supported the use of dupilumab as a systemic treatment for the long-term management of moderate-to-severe AD without routine laboratory monitoring in clinical practice [40][43][44]. In a follow-up study in adults given 300 mg dupilumab weekly up to 76 weeks, Deluren et al. showed sustained efficacy in 92.9% of patients with no additional safety signals [45]. However, further study should focus on long-term and uncommon side-effects that are insufficiently assessed in trials to date.

AD has been always considered as a paradigmatic in which both IL-4 and IL-13 play pivotal roles, however, recent evidence confirmed that these cytokines are differentially expressed and have different functions in atopic inflammation [46][47][48]. Recent transcriptomic analyses have revealed that in AD, IL-13 is expressed at a high level in both subacute and chronic skin lesions, whereas IL-4 expression is low or nearly undetectable [49]. Additionally, expression levels of IL-13 in lesional skin have been strongly correlated with disease severity, as measured by the SCORing atopic dermatitis tool [50]. The overexpression of IL-13 causes skin barrier dysfunction by decreasing the FLG expression via down-regulation of the OVOL1-FLG axis and up-regulation of periostin-IL-24 axis [51].

In a proof-of-concept phase 2 study of adults with moderate-to-severe AD, lebrikizumab was investigated as an add-on therapy to TCs. The primary endpoint, a 50% reduction in EASI score (EASI-50) at week 12, was achieved in a significantly large number of patients with lebrikizumab than with placebo (82.4% in the treatment group vs. 62.3% in the placebo group) Lebrikizumab was well tolerated with most common adverse events such as upper respiratory tract infections, conjunctivitis and herpesvirus infections that were mild and occurred at a similar incidence in lebrikizumab groups compared to placebo [52]. Lebrikizumab is currently in phase 3 trials in adults and children with AD aged 12 years and more [42] (Table 3).

Tralokinumab studied in different doses in phase 2b study in adults with moderate-to-severe AD showed a significant improvement in EASI and IGA scores. The ECZTRA 3 study evaluated the efficacy and safety of tralokinumab in combination with TCs in AD, which is more reflective of the likely clinical use in daily practice [53]. The use of tralokinumab in pediatric AD is currently being studied in two phase 3 clinical trials [42]. Other biologic such as ASLAN004, a fully human monoclonal antibody that targets the IL-13Rα1 receptor, is currently in clinical trials for the treatment of AD [48] (Table 3).

The janus kinases (JAKs), a family of tyrosine kinases (TYKs), including JAK1, JAK2, JAK3, and TYK2, are the first signal transducers in a pathway from cell membrane to the nucleus. They are associated with the intracellular domain of the cytokine receptors, after the binding of ligands to receptors, they are phosphorylated and transfer the signal to STAT family transcription factors which subsequently translocate to the nucleus leading to the activation of targeted gene expression [54]. The JAK-STAT pathway is a master regulator of immune function and has been implicated in modulating multiple immune pathways involved in AD, including Th2, Th22, Th1, and Th17. Several studies have demonstrated significant overexpression of JAKs and activation of JAK-STAT signaling within lesional skin of AD patients [55][56]. Thus, inhibiting JAKs that regulate multiple steps in AD pathogenesis seems to be conceptually attractive as a treatment option [57][58][59].

Since IL-4 and IL-13 affect keratinocyte differentiation and inhibit the expression of FLG through JAK-STAT signaling, JAK inhibitors potently restore FLG expression following in vitro pretreatment with IL-4/IL-13 cytokine in human keratinocyte and improve skin barrier function [60][61]. Interestingly, in normal human keratinocytes and in the reconstructed human skin equivalent model JTE-052 promoted the production of terminal differentiation proteins, including FLG in the presence or absence of Th2 cytokines by inhibiting STAT3 activation [60]. Clarysse et al. have shown that tofacitinib (JAK1/3 inhibitor) pretreatment preserved epidermal morphology, reduced STAT3 and STAT6 phosphorylation and upregulated FLG gene expression in 3D skin models of AD [61]. These findings demonstrate the feasibility of JAK inhibitors as possible therapeutic agents for AD that work by improving skin barrier function.

In phase 3, double-blind, vehicle-controlled studies, delgocitinib 0.5% ointment demonstrated remarkable improvement of EASI over 4 weeks and this effect was sustained through the following 24-weeks extensional treatment period with mild adverse events [62]. In addition, the long-term safety and efficacy of delgocitinib ointment were reported in a 52-week open-label study of Japanese adult patients with AD. Delgocitinib ointment improved clinical signs and symptoms also in pediatric patients aged 2 to 15 years with AD and was well tolerated [63]. Tofacitinib, a potent JAK1/JAK 3 inhibitor, is also under development as a topical treatment agent for AD.

In addition, several JAK inhibitors are under development for AD treatment via oral administration. As two phase 3 clinical trials for baricitinib in AD are currently completed, it may be among the first JAK inhibitors to be approved for systemic AD treatment. Upadacitinib is a second-generation selective JAK1 inhibitor and it is a promising therapy not only for AD but also for additional inflammatory diseases, with 37 clinical trials currently underway evaluating its use in various disorders. Currently, a phase 3 study including younger patients with AD is underway.

To sum up, JAK inhibitors demonstrate considerable efficacy for the treatment of AD. However, more studies should be conducted to evaluate their long-term efficacy and safety profile in particular. Involvement of the JAK-STAT pathway in the signaling of multiple cytokines, mediating immune response and hematopoiesis suggests a potentially increased risk of infection, thromboembolic events and hematological events [54][64]. The overall incidence of serious adverse effects of using oral JAK inhibitors for AD treatment is low, however, a topical formulation of those drugs appears to have a more favorable safety profile.

In addition to Th2 deviation, IL-22 produced by Th22 cells is also linked to the chronicity and amplification of skin inflammation in AD [33][34][35]. IL-22 overexpression promotes epidermal proliferation and disrupts barrier function by inhibiting the terminal differentiation of keratinocyte. Thus, there is a strong rationale for anti-IL-22 therapy in AD patients. This treatment seems to be particularly promising amongst African American, Asian and pediatric patients with AD, who are characterized by dominant Th22.

Fezakinumab is an IL-22-blocking monoclonal antibody that, in phase 2a study in adult patients with AD, showed significant clinical improvement versus placebo. However, the result was observed only in patients with severe disease (SCORAD > 50), whereas there was no significance in reducing the SCORAD score in patients with milder disease [65] In another study of fezakinumab transcriptomic improvement and downregulations of multiple immune pathways, including Th1, Th2, Th17, and Th22, were restricted to the subgroup of patients with baseline IL-22-expression [66].

Novel topical and systemic targeted therapies of AD.

Although IL-17-producing Th17 cells have been proposed to play a potential role in AD, the pathogenic significance of IL-17A is not fully understood and conflicting results on this issue have been reported [33][67][68]. However, greater expression of Th17-related markers was observed in some phenotypes such as Asian, intrinsic, pediatric and elderly AD patients [69] [35][68]. Thus, it is hypothesized that IL-17 targeting may have some benefit in selected populations. IL-17A is reported to downregulate the expression of FLG via the C/CAAT-enhancer-binding proteins, particularly C/EBPB, which is another important transcription factor for IL-17A signaling [70][71].

Secukinumab, a selective anti-IL-17 inhibitor, was trialed in a 52-week phase 2 study in patients with moderate-to-severe AD. The results of this study, which integrated clinical assessments with extensive cellular and genomic biomarkers in skin, demonstrated that IL-17 is not a valid therapeutic target in patients with AD, including the subsets of patients with higher Th17 activation [72]. The results of another phase 2 trial investigating the efficacy of secukinumab in patients with moderate to severe AD (Secu_in_AD) are not available yet.

Although enhanced expression of IL-24 is observed in the epidermis of model mice and in AD skin lesions, its implication in AD pathogenesis remains elusive [73]. IL-24 is produced by Th2 lymphocytes and keratinocytes after stimulation with type 2 cytokines, such as IL-4, IL-13, and IL-31. IL-4/ Those observations suggested that combined treatment with AHR modulator and JAK inhibitors may be a promising strategy for more effective AD therapy [74].

Jin et al. found that adiponectin (Acrp30) treatment upregulated FLG expression in a dose-dependent and time-dependent manner through a SIRT1-mediated signal transduction pathway in human keratinocytes [75]. A recent study in mouse primary keratinocyte showed that treatment with the apolipoprotein B mRNA editing enzyme complex (APOBEC3) siRNA increases the expression levels of FLG and other keratinocyte differentiation markers [76]. Furthermore, widely used moisturizers, such as petrolatum, urea and glycerol, have been shown to alter the structure of the epidermis and increased the expression of key barrier differentiation proteins, including FLG, in patients with and without AD, in addition to reducing skin inflammation and inducing AMP expression [77][78][79].

Recently, the trend toward using medicines from nature as an alternative treatment for diseases, especially skin inflammation has been observed. An increasingly long line of evidence has indicated that certain herbal medicines can be helpful in skin disorders characterized by abnormalities in barrier function associated with reduced FLG levels. A more recent study in a mice model of AD revealed that both apigenin and other biologically active compounds present in celery, apigetrin and luteolin have ameliorative effects on AD signs and symptoms [80]. Several components of a clinically proven Chinese medicinal pentaherbs formula, such as apigenin, quercetin, luteolin, ursolic acid and rosmarinic acid have been reported as the key compounds acting on crucial biological processes involved in AD, including inflammatory response, apoptosis, response to hypoxia and nitric oxide biosynthesis.

Although the strategies presented above appear to be promising most of these candidate drugs still have not advanced beyond in vitro and in vivo models and their beneficial effect in human AD is yet to be determined.

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