

Flaky Tail Mouse as a Novel Animal Model of Atopic Dermatitis: Possible Roles of Filaggrin in the Development of Atopic Dermatitis

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1. Introduction

Understanding of human diseases has been enormously expanded by the use of animal models, because they allow for in-depth investigation of pathogenesis and provide invaluable tools for diagnostic and pharmaceutical purposes. Atopic dermatitis (AD) is a chronic, relapsing form of skin inflammation, a disturbance of epidermal-barrier function that culminates in dry skin, pruritus, and IgE-mediated sensitization to food and environmental allergens (Bieber, 2008, Mori, et al., 2010, Tokura, 2010). AD is a common disease with no satisfactory form of therapy; therefore, understanding the mechanism of AD through animal models is an urgent issue to be solved (Jin, et al., 2009, Matsuda, et al., 1997, Shiohara, et al., 2004). The complexity and variability of AD and multiple genetic and environmental factors underlying AD make creating a reproducible, accessible, and relevant animal model of AD particularly challenging (Scharschmidt & Segre, 2008).

Thus far, a number of mouse models have been developed. These models can be categorized into three groups: (1) models induced by epicutaneous application of sensitizers; (2) transgenic mice that either overexpress or lack selective molecules; and (3) mice that spontaneously develop AD-like skin lesions. These models display many features of human AD, and their studies have resulted in a better understanding of the pathogenesis of AD. They allow for an in-depth dissection of the mediators and cells that are critical for the development of allergic responses (Jin, et al., 2009).

Located at the interface between the body and the environment, the epidermis is an elaborate structure that shares few properties with other biological barriers. Key functions include providing physical and biochemical protection (O'Regan & Irvine, 2010), and playing important roles in host defense, inflammation, and regulation of immune responses (Schleimer, et al., 2007). Patients with AD exhibit impaired skin barrier functions and abnormal structure and chemistry of the stratum corneum (SC) (Leung & Bieber, 2003). Alteration of the skin barrier in AD is evidenced by reduction in the water content of the SC and by increased transepidermal water loss (TEWL) (Aioi, et al., 2001). Skin barrier dysfunction has emerged as a critical driving force in the initiation and exacerbation of AD and as "driver" of disease activity (Cork, et al., 2009, Elias, et al., 2008), although it has once been noted as a disease of immunological etiology (Leung & Bieber, 2003).

Elias et al. proposed the outside-to-inside pathogenic mechanisms in AD for the following reasons: (1) the extent of the permeability barrier abnormality parallels the severity of the

disease phenotype in AD; (2) both the clinically uninvolved skin sites and the skin cleared of inflammation continue to display significant barrier abnormalities; (3) emollient therapy comprises effective ancillary therapy; and (4) specific replacement therapy which targets the prominent lipid abnormalities that account for barrier abnormality in AD, not only corrects the permeability-barrier abnormality but also comprises an effective anti-inflammatory therapy for AD (Elias, et al., 2008).

The evidence for a primary structural abnormality of the SC in AD is derived from a recently discovered link between the incidence of AD and loss-of-function mutations in the gene encoding filaggrin (*FLG*). Genetic studies have shown a strong association between AD and this mutation (Jin, et al., 2009). Moreover, there is a dose-response relationship between *FLG* deficiency and disease severity, such that patients with double-allele or compound heterozygote mutation in *FLG* display more severe and earlier-onset AD and an increased propensity for AD to persist into adulthood (Brown, et al., 2008, Irvine & McLean, 2006). This rapidly growing body of work has led to a paradigm shift in conception of AD pathogenesis, with increasing weight being placed on the role of a primary barrier abnormality that then precipitates downstream causing immunologic abnormalities as proposed (Elias, et al., 2008).

Based on these findings, it is assumed that mice that have a genetic defect in barrier function will provide a model of AD closer to the human disease than models provided by epidermal sensitization with allergens or haptens or by transgenic overexpression of cytokines in the skin or disruption of immune genes, and that these mice will have an advantage over NC/Nga mice in which the genetic defect is not known. Application of the knowledge gained from existing mouse models of AD to mice with genetic defects in skin barrier function should provide us with AD models that closely mimic human disease (Jin, et al., 2009).

2. Filaggrin and atopic dermatitis

2.1 Filaggrin mutation and atopic dermatitis

Filaggrin protein is localized in the granular layers of the epidermis. Profilaggrin, a 400-kDa polyprotein, is the main component of keratohyalin granules (Candi, et al., 2005, Listwan & Rothnagel, 2004). In the differentiation of keratinocytes, profilaggrin is dephosphorylated and cleaved into 10-12 essentially identical 27-kDa filaggrin molecules, which aggregates in the keratin cytoskeleton system to form a dense protein-lipid matrix in humans (Candi, et al., 2005). This structure is thought to prevent epidermal water loss and impede the entry of external stimuli, such as allergens, toxic chemicals, and infectious organisms. Therefore, filaggrin is a key protein in the terminal differentiation of the epidermis and in skin-barrier function (Gan, et al., 1990).

The genetic contribution of *FLG* loss-of-function mutations to AD is now well established. *FLG* mutation was first identified in ichthyosis vulgaris (IV), a common keratinizing disorder (Irvine & McLean, 2006). In 2006, Palmer et al. first identified two such mutations within the *FLG* gene, which strongly predispose to AD as well as IV (Palmer, et al., 2006). Since then, several additional studies have confirmed this association and discovered other mutations within this gene that predispose to AD. To date, approximately 40 loss-of-function *FLG* mutations have been identified in IV and/or AD in European and Asian populations. (Brown, et al., 2008, Marenholz, et al., 2006, Nomura, et al., 2007, Rodriguez, et al., 2009, Sandilands, et al., 2006, Sandilands, et al., 2007). Major differences exist in the spectra of *FLG* mutations observed between different ancestral groups, and each population is likely to have a unique set of *FLG* mutations (Osawa, et al., 2011).

Typically atopic manifestations follow a certain sequence, called the atopic march, beginning with AD in early infancy, followed by food allergy, asthma and the development of allergic rhinitis (Illi, et al., 2004). The association of *FLG* mutation with atopic march has been reported in cases involving pediatric asthma (Muller, et al., 2009), peanut allergy (Brown, et al., 2011), atopic asthma (Poninska, et al., 2011), allergic rhinitis (Poninska, et al., 2011) and nickel allergy (Novak, et al., 2008).

In addition, epidemiological studies have identified extremely significant statistical association between *FLG* mutation and AD. Intriguingly, these mutations are highly associated with several characteristics in AD patients, such as reduced level of natural moisturizing factor (NMF) in the SC (Kezic, et al., 2008), increased incidence of dry and sensitive skin (Sergeant, et al., 2009), clinical severity and barrier impairment (Nemoto-Hasebe, et al., 2009), allergen sensitization and subsequent development of asthma associated with eczema (Weidinger, et al., 2008), and serum levels of IgE (Wang, et al., 2011). On the other hand, several studies failed to identify an effect of *FLG* mutations on AD, such as skin conditions assessed by clinical scoring of AD and measurement of TEWL in a French population (Hubiche, et al., 2007). A similar lack of association was reported in contact allergy (Carlsen, et al., 2011) and pediatric eczema (O'Regan, et al., 2010).

As the conceptual framework underlying AD moves from solely immunological to epidermal barrier defects, the role of filaggrin and its putative mechanisms in priming AD have come under closer scrutiny. *FLG* mutations are postulated to have wide-ranging downstream biological effects, which include altered pH of SC, cutaneous microflora and aberrant innate and adaptive immune responses (O'Regan & Irvine, 2010).

2.2 Filaggrin and altered skin barrier function

AD is characterized by eczematous skin lesion, dry skin, pruritus, increased TEWL, and enhanced percutaneous penetration of both lipophilic and hydrophilic compounds (Jakasa, et al., 2011, Wollenberg & Bieber, 2000). The skin barrier defect is one of the primary events that initiate disease pathogenesis, allowing the entrance of numerous antigens into the epidermis in patients with AD (Onoue, et al., 2009, Osawa, et al., 2011). The *FLG* mutation carriers have demonstrated elevated TEWL (Jungersted, et al., 2010, Kezic, et al., 2008), basal erythema, skin hydration, increased skin pH (Jungersted, et al., 2010, Nemoto-Hasebe, et al., 2009), SC thickness (Nemoto-Hasebe, et al., 2009), impaired SC integrity upon repeated tape stripping (Angelova-Fischer, et al., 2011), and increased diffusivity of PEG 370 (Jakasa, et al., 2011) compared to healthy donors. Nevertheless, these alterations found in *FLG* mutation carriers are not consistently correlated with AD since AD patients without *FLG* mutation might also share some similar features. (Hubiche, et al., 2007, Jakasa, et al., 2011, Jungersted, et al., 2010, Kezic, et al., 2008). It is, therefore, suggested that other factors besides *FLG* loss-of-function mutations modulate skin barrier integrity, especially in AD.

Since the skin barrier is related to intercellular lipid bilayers of the SC, it might be interesting to examine the composition and the organization of intercellular lipids of the SC in AD patients in relation to *FLG* genotype and disease severity (Jakasa, et al., 2011). Carriers of *FLG* mutations showed significantly reduced levels of NMF in the SC (Kezic, et al., 2008). Similar lipid composition of *FLG* mutation carriers and individuals with normal filaggrin was observed (Angelova-Fischer, et al., 2011, Jungersted, et al., 2010), but a lower ceramide/cholesterol ratio was detected in the former group (Angelova-Fischer, et al., 2011). Filaggrins proteolytically degraded into a pool of free amino acids including histidine and glutamine which are further converted to, respectively, urocanic acid (UCA) and 2-

pyrrolidone-5-carboxylic acid (PCA). The concentrations of UCA and PCA in SC in the carriers of *FLG* mutations were significantly lower than those in healthy donors (Kezic, et al., 2009). Therefore, filaggrin deficiency is sufficient to impair epidermal barrier formation.

An *in vitro* experiment using filaggrin knocked down human organotypic skin cultures showed enhanced penetration of hydrophilic dye Lucifer yellow, smaller lamellar bodies, and deficiency of their typical lamellae without altered lipid composition (Mildner, et al., 2010). In addition, UCA, one of the filaggrin-derived free amino acids and as an important UV absorbent within SC, was decreased following filaggrin knocked down, leading to increased sensitivity to UVB-induced keratinocyte (KC) damage (Mildner, et al., 2010).

2.3 Filaggrin and altered immunobiology

The SC serves as a biosensor of the external environment and a link between innate and adaptive immune systems (Vroiling, et al., 2008). The critical association between the abnormal barrier in AD and Th2 polarization may in part be explained by the production of the cytokine, thymic stromal lymphopoietin (TSLP) (Ebner, et al., 2007). TSLP is expressed by epithelial cells, with the highest levels seen in lung-derived and skin-derived epithelial cells (Soumelis, et al., 2002, Ziegler, 2010), and is highly detected in the lesional skin of AD (Soumelis, et al., 2002). Inducible TSLP transgene specifically in the skin leads to the development of a spontaneous Th2-type skin inflammatory disease with the hallmark features of AD (Yoo, et al., 2005).

TSLP has been shown to activate dendritic cells to drive Th2 polarization, through upregulation of the co-stimulatory molecules CD40, CD80, and OX40L, triggering the differentiation of allergen-specific naïve CD4⁺ T cells to Th2 cells that produce IL-4, IL-5, and IL-13 (Ebner, et al., 2007, Soumelis, et al., 2002).

Patients with Netherton syndrome (NS), a severe ichthyosis in which affected individuals experience a significant predisposition for AD, have elevated levels of TSLP in their skin. Upregulated kallikrein (KLK) 5 in the skin of NS patients directly activates proteinase-activated receptor 2 (PAR-2) and induces nuclear factor kappaB-mediated overexpression of TSLP, intercellular adhesion molecule 1, TNF- α , and IL-8. This phenomenon occurs independently of the environment, adaptive immune system and underlying epithelial barrier defect (Briot, et al., 2009, Briot, et al., 2010). *In vitro* study using human keratinocyte cell line HaCaT cells and reconstituted human epidermal layers transfected with filaggrin siRNA showed increased production of TSLP via toll-like receptor (TLR) 3 stimulation (Lee, et al., 2011). These findings suggest that reduced filaggrin levels may influence innate immune response via TLR stimuli and elevate TSLP, leading to AD-like skin lesions.

AD is one of the emerging diseases in which epidermal dysfunction increases allergen and microbial penetration in the skin, with the consequent development of adaptive Th2 immune responses (Kondo, et al., 1998) within regional lymphoid tissue. The resultant Th2 cells may then home back to the skin or lungs, where they recognize allergen in the skin (McPherson, et al., 2010), which leads to local Th2 inflammation, reduced antimicrobial peptide expression (Nomura, et al., 2003), and filaggrin downregulation (Howell, et al., 2007). Indeed, the induction of circulating allergen-specific CD4⁺ T cells may be an important prerequisite underlying the pathogenesis of the atopic march (O'Regan, et al., 2009). Among moderate-to-severe AD patients, the *FLG* mutation carriers showed a greater number of house dust mite Der p1-specific IL-4 producing CD4⁺ T cells, suggesting that filaggrin mutations predispose to the development of allergen-specific CD4⁺ Th2 cells. The

same result could be seen among HLA-DRB1*1501 (a HLA class II complex which is immunodominant in individuals with AD (Ardern-Jones, et al., 2007)) positive adult individuals with moderate-to-severe AD and *FLG* mutations (McPherson, et al., 2010).

3. Flaky tail mouse as a novel animal model of atopic dermatitis

3.1 Origin of flaky tail mice

The above findings indicate the involvement of filaggrin in the development of AD. Therefore, the impact of filaggrin deficiency on cutaneous biological functions *in vivo* should be analyzed in detail. To address this issue, animal models are of great value.

Flaky tail mice (*Flg^{ft}*), first introduced in 1958, are spontaneously mutated mice with smaller ears, tail constrictions, and a flaking tail skin appearance (Lane, 1972). *Flg^{ft}* mice were outcrossed onto B6 mice at Jackson Laboratory (Bar Harbor, ME, USA) (Lane, 1972, Presland, et al., 2000) (Note: Although this strain was crossed with B6, it is not a B6 congenic strain but rather a hybrid stock that is probably semi-inbred). Homozygous *Flg^{ft}* mice have dry, flaky skin which expresses reduced amounts of profilaggrin mRNA and abnormal profilaggrin protein that is not processed to filaggrin monomers (Fallon, et al., 2009, Presland, et al., 2000).

Recently, it has been revealed that the gene responsible for the characteristic phenotype of *Flg^{ft}* mice is a single nucleotide deletion at position 5303 in exon 3 (5303delA) of the profilaggrin gene, resulting in a frameshift mutation and premature truncation of the predicted protein product. The copy number of the filaggrin repeat contained within this gene varies depending on the background strain. This mutant occurs in an allele with 16 copies of the filaggrin repeat (Fallon, et al., 2009).

Flg^{ft} mouse carries double gene mutation, *Flg* and matted (*ma*) in which the locations of the mutated genes are within close linkage to one another (Lane, 1972). The *ma* gene characteristic reported by Searle & Spearman (1957) causes the body-hair of affected mice to be brittle and inflexible, which results in longitudinal splitting and breaking due to friction against the cage and other objects. This mutation is a fully penetrant recessive house-mouse mutant which belongs to the "naked" category (i.e., a house-mouse with baldness resulting from the breaking of hairs or from hereditary hairlessness). This mutation can be identified morphologically by (1) erection of hairs, (2) matting of hair in clumps, (3) a tendency towards baldness, (4) a change from black- to brown-colored melanin in old hairs. The age at which this mutant is first identified based on external appearance varies from between two to four weeks (Jarret A, 1957, Searle A.G., 1957).

Recognition of the features of this mouse is more evident between 5 and 14 days of age when constricted, flaking tail skin and thickened short pinna of the ears are observed. In addition, *Flg^{ft}* mice are often smaller than their normal siblings at this age. Routine histological sections stained with hematoxylin and eosin showed that the stratum granulosum in *Flg^{ft}* mice at 1, 2, 4, and 8 days of age does not contain as many granular layers as that of non-*Flg^{ft}* mice (Lane, 1972). Mice of the *Flg^{ft}* genotype express an abnormal profilaggrin polypeptide that does not form normal keratohyalin F-granules and is not proteolytically processed to filaggrin. Therefore, filaggrin is absent from the cornified layers in the epidermis of the *Flg^{ft}* mouse (Fallon, et al., 2009, Presland, et al., 2000, Scharschmidt, et al., 2009). Consistently, we and others have described that *Flg^{ft}* mice express a truncated and smaller profilaggrin protein that is not processed to filaggrin (Fallon, et al., 2009, Moniaga, et al., 2010, Presland, et al., 2000) (Fig.1).

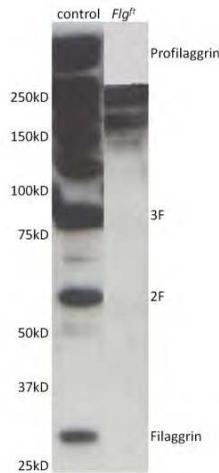


Fig. 1. *Flg^{fl}* mouse has a truncated and smaller profilaggrin and a lack of filaggrin protein.

3.2 Flaky tail mouse and ichthyosis vulgaris

Ichthyosis vulgaris (IV) is a heterogeneous autosomal skin disease characterized by dry and scaly skin, mild hyperkeratosis, and a decreased or absent granular layer that either lacks, or contains morphologically abnormal, keratohyalin granules (Manabe, et al., 1991). Several lines of evidences point to a genetic defect in a gene encoding *FLG* in IV. Immunoblotting studies showed that filaggrin protein was absent or markedly reduced in the epidermis of individuals with IV (Fleckman, et al., 1987, Sybert, et al., 1985). In line with this, it was proposed that *Flg^{fl}* mice could provide insight into the molecular basis of the filaggrin-deficient human skin disorder IV. The epithelia of *Flg^{fl}* mice showed defects in tissue organization especially in the tail, an attenuated granular layer, reduced profilaggrin and a lacked of filaggrin granules in SC. In addition, keratinocytes culture from *Flg^{fl}* mice synthesized reduced amounts of profilaggrin mRNA and protein (Presland, et al., 2000).

3.3 Flaky tail mouse in a steady state

An early report demonstrated that *Flg^{fl}* mice without the *ma* mutation showed flaky skin as early as postnatal day 2, but became normal in appearance by 3 to 4 weeks of age without spontaneous dermatitis except for their slightly smaller ears (Lane, 1972). Later, the lack of filaggrin in the epidermis was proposed in the commercially available strain of *Flg^{fl}* mice, which has both *Flg* and *ma* mutations, as a model of IV, and therefore there was no discussion about the cutaneous inflammatory conditions from the perspective of AD (Presland, et al., 2000).

There have been four recent papers of *Flg^{fl}* mice as a model of filaggrin deficiency: the first paper used *Flg^{fl}* mice from which the *ma* mutation had been eliminated with four additional backcrosses to B6 mice (Fallon, et al., 2009), and the others used the commercially available *Flg^{fl}* mice (Moniaga, et al., 2010, Oyoshi, et al., 2009, Scharschmidt, et al., 2009). The first report showed only histological abnormality without clinical manifestation (Fallon, et al., 2009), and the second demonstrated spontaneous eczematous skin lesions after 28 weeks of

age (Oyoshi, et al., 2009), and the third contained no notice of any spontaneous dermatitis in *Flg^{fl}* mice (Scharschmidt, et al., 2009).

The fourth paper by Moniaga et al. have demonstrated that *Flg^{fl}* mice showed spontaneous dermatitis with skin lesions mimicking human AD as early as 5 weeks of age with mild erythema and fine scales and the cutaneous manifestations advanced with age in a steady state under SPF conditions (Moniaga, et al., 2010) (Fig. 2). The first manifestations to appear when mice were young were erythema and fine scaling; pruritic activity, erosion, and edema followed later (Fig. 3). In contrast, no cutaneous manifestation was observed in either C57BL/6 mice, studied as a control, or heterozygous mice intercrossed with *Flg^{fl}* and B6 mice kept under SPF conditions. There was no apparent difference in terms of clinical manifestations based on the gender of *Flg^{fl}* mice throughout the period (Moniaga, et al., 2010).

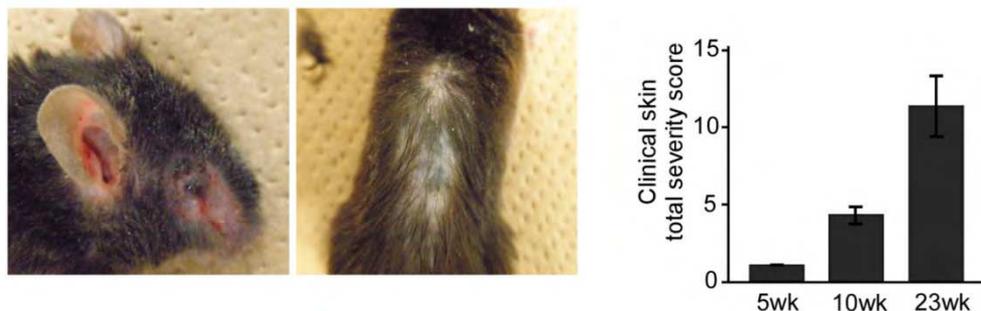


Fig. 2. Clinical photographs of 20-week-old *Flg^{fl}* mice (left panel) and total clinical severity scores (right panel)

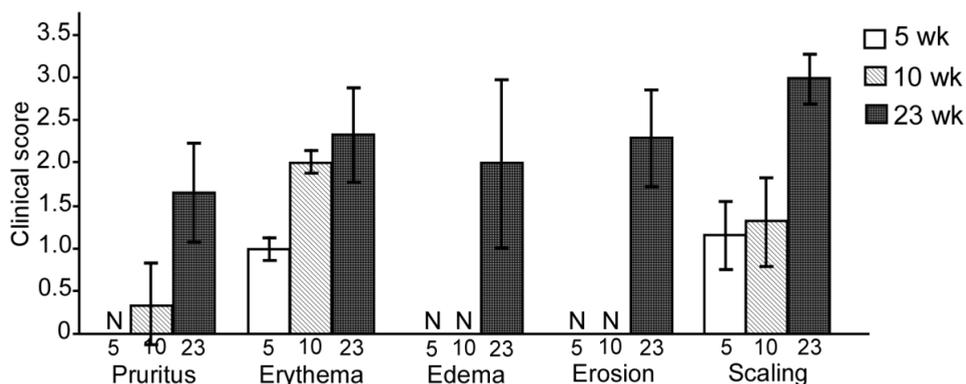


Fig. 3. Characteristics of the clinical skin lesions.

Histological examination of the skin of *Flg^{fl}* mice stained with H&E revealed epidermal acanthosis, increased lymphocyte and mast cell infiltration and dense fibrous bundles in the dermis, in both younger (8-week-old) and older (18-week-old) *Flg^{fl}* mice; none of these conditions were observed in B6 mice (Fig. 4) (Moniaga, et al., 2010). These features were also reported in other studies (Fallon, et al., 2009, Oyoshi, et al., 2009) with more total cells,

lymphocytes, eosinophils, and mononuclear cells in *Flg^{fl}* mice compared to control mice. These data support the diagnosis of AD-like dermatitis in *Flg^{fl}* mice in the steady state under SPF conditions.

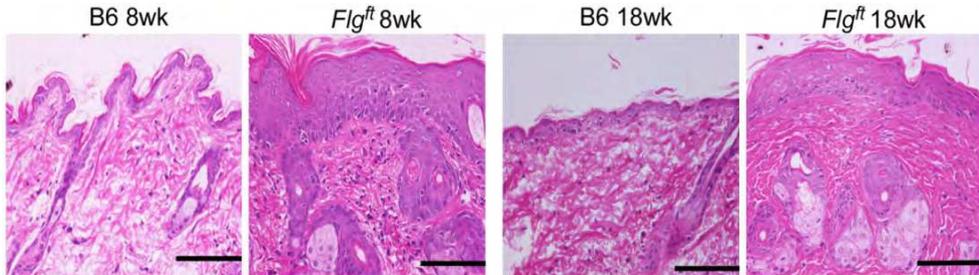


Fig. 4. Hematoxyllin and eosin (H&E)-stained sections in 8- and 18-week old mice. Scale bar, 100 μ m

Therefore, there exist discrepancies among the results of four recent papers on the cutaneous manifestation in the steady states. It seems to be related to the presence or absence of the *ma* mutation and/or variation in the genetic backgrounds of the different strains used, and to environmental factor. It has been reported that Japan carries a higher morbidity of AD than other countries (1998, Williams, et al., 1999), possibly due to environmental factors such as pollen. Because barrier dysfunction is a common characteristic of AD (Elias, et al., 2008, Nomura, et al., 2007, Palmer, et al., 2006), TEWL is commonly measured as an indicator of barrier function (Gupta, et al., 2008). TEWL was significantly higher in *Flg^{fl}* mice than in B6 mice from an early age (4 weeks) to an older age (16 weeks) (Fig. 5) (Moniaga, et al., 2010).

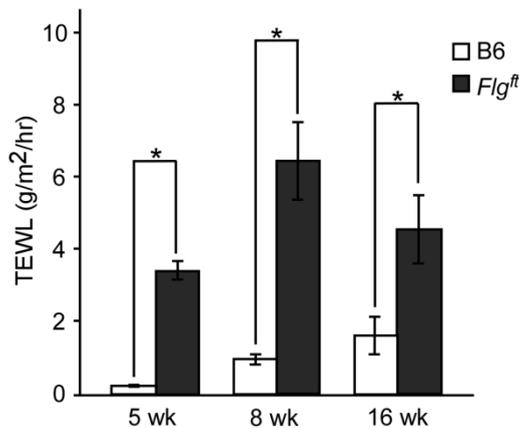


Fig. 5. TEWL through dorsal skin of 5-, 8-, and 16-week-old B6 and *Flg^{fl}* mice.

Flowcytometry analysis of cells isolated from ear skin confirmed that *Flg^{fl}* skin contained significantly increased percentages of CD4⁺ T cells and Gr-1⁺ neutrophils, but not CD11c⁺ dendritic cells, compared with ear skin from controls (Moniaga, et al., 2010, Oyoshi, et al., 2009).

The extent of severity of AD is known to be correlated with elevated serum IgE levels (Novak, 2009). Serum IgE and IgG1 levels in *Flg^{fl}* mice were significantly higher than those in control mice in the steady state under SPF conditions (Moniaga, et al., 2010, Oyoshi, et al., 2009). In addition, the numbers of CD4⁺ and CD8⁺ cells in the skin draining LNs in *Flg^{fl}* mice were significantly higher than those in control mice, but those of the spleen were similar for both groups. Thus, an enhanced cutaneous immune reaction seems to be induced in *Flg^{fl}* mice due to the condition of their skin induced by filaggrin and/or matted deficiency.

AD is thought to be mediated by helper T cell subsets, such as Th1, Th2, and Th17 (Bieber, 2008, Hattori, et al., 2010, Koga, et al., 2008). In the steady state, the skin of *Flg^{fl}* mice showed no difference of Th1 cytokine IFN- γ and Th2 cytokines IL-4 and IL-13 compared to the control. In contrast, there is a significant increase in mRNA expression of the Th17 cytokine IL-17, IL-17 promoting cytokines IL-6 and IL-23 (p19), and IL-17 inducible neutrophil attractant chemokine CXCL2 in *Flg^{fl}* mice (Moniaga, et al., 2010, Oyoshi, et al., 2009).

3.4 Flaky tail mouse showed enhanced percutaneous allergen priming

Since the barrier dysfunction is a key element in the establishment of AD, it is necessary to evaluate outside-to-inside barrier function from the perspective of invasion of external stimuli. Scharschmidt et al. reported increased bidirectional paracellular permeability of water-soluble xenobiotics by ultrastructural visualization in *Flg^{fl}* mice suggesting a defect in the outside-to-inside barrier. The ultrastructural visualization of tracer perfusion was analyzed by water-soluble, low molecular weight, electron-dense tracer lanthanum nitrate or fluorophore calcium green with enhanced penetration in *Flg^{fl}* mice. The data demonstrated that filaggrin deficiency leads to alterations in basal barrier function through a defect in the SC extracellular matrix and greater permeability through the same paracellular pathway that is used by water itself when exiting the skin (Scharschmidt, et al., 2009).

A new method for evaluating outside-to-inside barrier function quantitatively by measuring the penetrance of fluorescein isothiocyanate isomer 1 (FITC) through the skin has been developed (Moniaga, et al., 2010). The epidermis of *Flg^{fl}* mice contained a higher amount of FITC than that of B6 mice did (Fig.6 left panel). Consistently, fluorescence intensities observation in the epidermis of both mice showed stronger fluorescence in *Flg^{fl}* mice (Fig.6 right panel). In addition, the *Flg^{fl}* embryo was entirely dye permeable to toluidine blue solution compared to its control littermate.

Another AD-like dermatitis model to test allergen priming of the skin in these mice was performed by application of ovalbumin (OVA) (Oyoshi, et al., 2009). Non tape-stripped skin of *Flg^{fl}* mice exposed to OVA exhibited significantly increased epidermal thickening, hyperkeratosis, spongiosis, acanthosis, and cellular infiltrates, as well as TEWL compared to control mice. mRNA levels for IL-17, IL-6, IL-23, IL-4, IFN- γ and CXCL2 but not IL-5 and IL-13 in the skin of *Flg^{fl}* mice after OVA exposure were significantly higher than those of control mice. The systemic immune response following cutaneous exposure revealed increased specific IgG and IgE to OVA, and splenocytes proliferated and produced OVA-specific Th1, Th2, Th17 and regulatory T cell cytokines (Fallon, et al., 2009, Oyoshi, et al., 2009). These findings demonstrate that *Flg^{fl}* mice tend to generate allergen-specific IgE and cytokine following cutaneous allergen challenge to the skin even without additional barrier disruption.

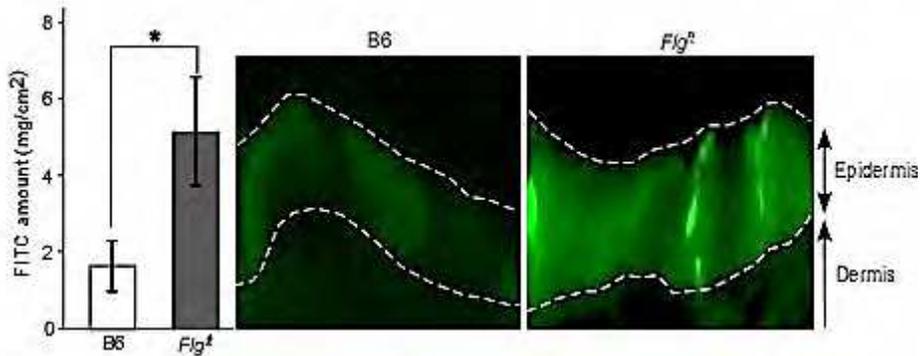


Fig. 6. Amount of FITC in the skin of B6 and *Flg^{fl}* mice (left panel) and fluorescence intensities of FITC of the skin (right panel) after topical application.

3.5 Altered immunobiology response in flaky tail mouse

The skin abnormality associated with AD is well known to be a predisposing factor to sensitive skin (Farage, et al., 2006, Willis, et al., 2001) and allergic contact dermatitis (Clayton, et al., 2006, Mailhol, et al., 2009). However, children with atopic dermatitis had lower PPD induration size compared to healthy donors, but this was not statistically significant (Gruber, et al., 2001, Yilmaz, et al., 2000). In humans, sensitive skin is defined as reduced tolerance to cutaneous stimulation, with symptoms ranging from visible signs of irritation to subjective neurosensory discomfort (Farage, et al., 2006, Willis, et al., 2001). The question of whether human AD patients are more prone to allergic contact dermatitis than nonatopic individuals is still controversial (Mailhol, et al., 2009).

Using phorbol myristate acetate (PMA) as an irritant, *Flg^{fl}* mice exhibited an enhanced ear swelling response compared to age-matched B6 mice throughout the experimental period (1 hr to 140 hrs). In addition, *Flg^{fl}* mice showed an increased skin-sensitized contact hypersensitivity (CHS) reaction to haptens, a form of classic Th1- and Tc1-mediated delayed-type hypersensitivity to haptens, emphasized by increased IFN- γ production, and terminated by regulatory T cells (Honda, et al., 2010, Mori, et al., 2008, Wang, et al., 2001). CHS is induced by epicutaneous sensitization and challenge. The ear thickness change was more prominent in *Flg^{fl}* mice than in B6 mice. In addition, the relative amount of IFN- γ in the ear of *Flg^{fl}* mice was higher than that of B6 mice.

To further assess the immune responses of *Flg^{fl}* mice, we elicited a delayed-type hypersensitivity (DTH) response through non-epicutaneous sensitization and challenge. Mice were immunized intraperitoneally with OVA, and challenged with a subcutaneous injection of OVA into the footpad. In contrast to the CHS response induced epicutaneously, the resulting footpad swelling in *Flg^{fl}* mice tended to be lower than that in wild-type mice. This finding is consistent with the observation on tuberculin tests in human. The levels of IFN- γ in the spleen were comparable between *Flg^{fl}* mice and wild-type mice. Thus, Th1/Tc1 immune responses were enhanced in *Flg^{fl}* mice only when the stimuli operated via the skin, suggesting that the enhanced immune responses seen in *Flg^{fl}* mice depend on skin barrier dysfunction and skin barrier function regulates cutaneous immune conditions, which hints at a possible mechanism involved in human AD.

A reduced threshold in *Flg^{fl}* mice for contact dermatitis was also reported. These mice showed enhanced propensity to irritant contact dermatitis via low-dose phorbol ester TPA

which provokes only marginal inflammation in wild-type mice, and displayed a reduced threshold for the development of hapten-induced acute allergic contact dermatitis by oxazolone (Ox). Repeated Ox challenges with lower doses of Ox revealed AD-like dermatitis in *Flg^{fl}* mice as shown by severe barrier abnormality (enhanced TEWL) and AD-like histological changes (Scharschmidt, et al., 2009).

3.6 Flaky tail mouse denotes human AD

Clinical studies have provided evidence that a house dust mite allergen plays a causative or exacerbating role in human AD (Kimura, et al., 1998), and that a strong correlation exists between *FLG* mutation patients and house dust mite-specific IgE (Henderson, et al., 2008). *Dermatophagoides pteronyssinus* (Dp) is a common mite aeroallergen, which is frequently involved in inducing human AD. Dp exhibits protease activities, and Der p1, Der p3, and Der p9, derived from Dp, are especially capable of activating the PAR-2 in human KC (Jeong, et al., 2008, Vasilopoulos, et al., 2007). A recent report has shown that activation of PAR-2 through Dp application significantly delays barrier recovery rate in barrier function-perturbed skin or otherwise compromised skin (Jeong, et al., 2008). Therefore, Dp may play a dual role in the onset of AD, both as an allergen and proteolytic signal and as a perturbation factor of the barrier function, leading to the persistence of eczematous skin lesions in AD (Jeong, et al., 2008, Roelandt, et al., 2008). It has also been reported that BALB/c and NC/Nga mice develop an allergic cutaneous immune response to mite antigens when they are applied to the skin after vigorous barrier disruption by means of tape-stripping or sodium dodecyl sulfate treatment (Kang, et al., 2006, Yamamoto, et al., 2007). Intriguingly, the application of Dp ointment to the skin without additional barrier disrupt induced dermatitis in *Flg^{fl}* mice, while this treatment did not induce any skin inflammation in control C57BL/6 mice (Fig.7). Petrolatum alone, used instead of Dp ointment as a control, induced no skin manifestation (Fig. 7).

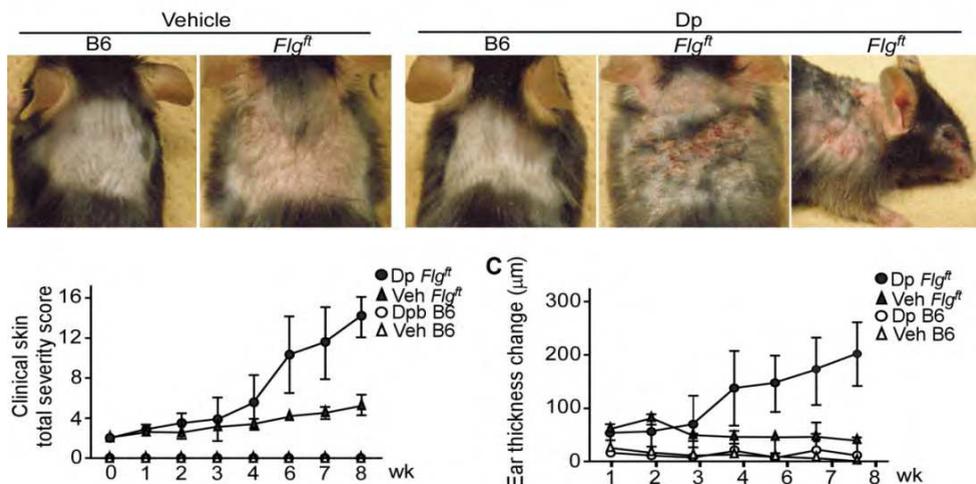


Fig. 7. The mite-induced dermatitis model showed severe eczematous skin lesion after being topically treated with Dp ointment in *Flg^{fl}* mice, as well as ear thickness change.

Histological examination of H&E-stained sections of involved *Flg^{fl}* skin after 16 applications showed acanthosis, elongation of rete ridges, and dense lymphocyte and neutrophil infiltration in the dermis, accompanied by an increased number of mast cells in the dermis. Consistently, scratching behavior, TEWL, and Dp-specific IgE levels were significantly higher in *Flg^{fl}* mice than in B6 mice (Fig.8) (Moniaga, et al., 2010). Thus the treatment of *Flg^{fl}* mice with Dp ointment, even without prior barrier disruption, remarkably enhanced both the clinical manifestations and the laboratory findings that correspond to indicators of human AD.

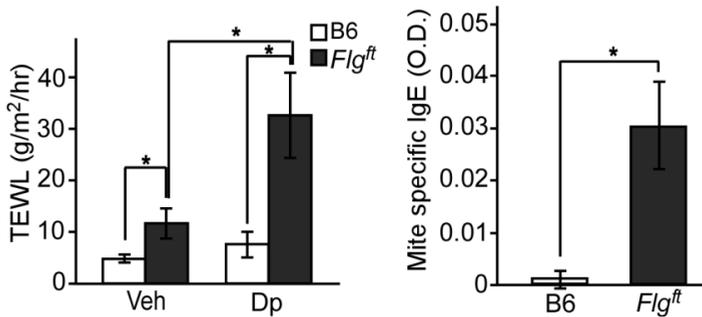


Fig. 8. TEWL and mite-specific serum IgE levels of *Flg^{fl}* mice and control mice after the last application.

4. Summary and future direction

We have summarized the findings on *Flg^{fl}* mice revealed by four different groups (Table 1). While most of these findings were consistent with each other, there still remain several issues to be solved, for example, the influence of the genetic background and other gene mutations in these mice.

	Fallon et al. (Fallon, et al., 2009)	Oyoshi et al. (Oyoshi, et al., 2009)	Scharschmidt et al. (Scharschmidt, et al., 2009)	Moniaga et al. (Moniaga, et al., 2010)
Spontaneous AD	-	+	n.r.	+
Increased TEWL in steady state	slightly	n.r.	+ (old age)	+
Histopathology AD like skin lesion in steady state	+	+	n.r.	+
Increase total IgE in steady state	n.r.	+	+	+
Enhanced cutaneous antigen ingress	+ (OVA)	+ (OVA)	+ (low dose oxaxolone)	+ (mite, D.p.)
Enhanced non cutaneous antigen (OVA-i.p) response	-	-	n.r.	-

Table 1. Summary of the phenotypes of flaky tail mice

Since *Flg^{ft}* mice are not a homogenous C57BL/6 background, two papers with spontaneous eczematous skin lesion on *Flg^{ft}* mice compared their outcomes with other mouse strains, such as C57BL/6 and BALB/c mice as controls (Oyoshi, et al., 2009); these two strains lie on opposite ends of the spectrum of T helper responses. Nevertheless, the skin inflammation and susceptibility to EC sensitization of non-tape stripped skin observed in *Flg^{ft}* mice were not observed in other strains. In the second paper, they observed immune responses in mice of other genotypes, such as BALB/c and C3H, as controls, but both of these lines exhibited much less severe CHS responses compared to *Flg^{ft}* mice (Moniaga, et al., 2010). These data suggested that the enhanced responses seen in *Flg^{ft}* mice were not solely due to their genetic background. In addition, other studies used the *Flg^{ft}* mice which were backcrossed four generations to a B6 strain (a background coding sequence showed 99.3% identity between B6 and *Flg^{ft}*), and similar enhanced responses to OVA-induced AD models were observed (Fallon, et al., 2009).

Furthermore, unlike human AD patients, most of whom are heterozygous for the *FLG* mutation, the heterozygous mice intercrossed with *Flg^{ft}* mice and B6 mice did not develop spontaneous dermatitis (Moniaga, et al., 2010). Similar results were obtained with the OVA-induced AD model, where homozygous, but not heterozygous (crossed with B6 mice) *Flg^{ft}* mice, showed enhanced susceptibility to cutaneous exposure to OVA (Fallon, et al., 2009). Not only human studies but also additional mouse studies will be required to clarify these relationships.

Since *Flg^{ft}* mice express a hair phenotype (matted), one cannot eliminate the possibility that some of the observations could have been influenced by the concurrent *ma* mutation (Scharschmidt, et al., 2009). Nevertheless, one study indeed removed the matted hair allele (*ma*) early in the course of backcrossing with B6 mice, and showed enhanced antigen (OVA) ingress in mice with the same *Flg* mutation, but no *ma* mutation in their background (Fallon, et al., 2009). The effect of the *ma* mutation in relation to the *Flg* mutation in commercially available *Flg^{ft}* mice in the development of AD-like skin lesions needs to be clarified in future studies.

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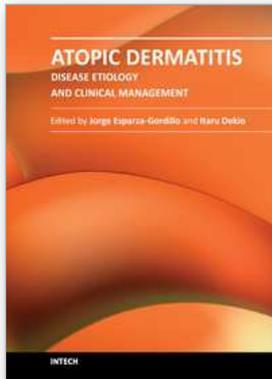
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Atopic Dermatitis is a common disease characterized by inflamed, itching and dry skin. This relapsing allergic disorder has complex etiology and shows a remarkably high clinical heterogeneity which complicates the diagnosis and clinical management. This book is divided into 4 sections. The first section (Disease Etiology) describes some of the physiological mechanisms underlying Atopic Dermatitis, including alterations in the immune system and the skin-barrier function. The important role of host-microorganism interactions on the pathophysiology of Atopic Dermatitis is discussed in the second section (Microorganisms in Atopic Dermatitis). An overview of the clinical diagnostic criteria and the disease management protocols commonly used is given in the third section (Diagnosis and Clinical Management). The last section (New Treatments) describes new therapeutic approaches that are not widely used but are currently being studied due to preliminary evidence showing a clinical benefit for Atopic Dermatitis.

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