New insight into the pathogenesis of atopic dermatitis from analysis of the mutual association between permeability barrier dysfunction and allergic inflammation

Yutaka Hatano

Department of Dermatology, Faculty of Medicine, Oita University, Yufu-shi, Oita, Japan

ARTICLE INFO

Article history:
Received: Feb 17, 2015
Accepted: Mar 19, 2015

Keywords:
allergic inflammation
atopic dermatitis
permeability barrier pH
PPAR α
stratum corneum

ABSTRACT

The mutual association between permeability barrier dysfunction and allergic inflammation is one of the most important issues in the pathogenesis of atopic dermatitis (AD). Permeability barrier abrogation not only induces cutaneous inflammation, but is also involved in the induction of T helper 2 (Th2)-type immunological reactions. Conversely, Th2 or other cytokines abrogate permeability barrier homeostasis. Some molecules and/or pathogenic factors have been found to be simultaneously involved in both aspects of AD. Decreases in filaggrin or peroxisome proliferator-activated receptor α, which are observed in AD lesions, not only disturb the permeability barrier function but could also directly augment cutaneous inflammation via the upregulation of proinflammatory cytokines. Elevation of the stratum corneum (SC) pH, which is also observed in AD lesions, could initiate and/or drive many of the pathogenic features including both the permeability barrier disturbance and induction of Th2-type inflammation via protease-activated receptor-2-dependent and -independent mechanisms, leading to the emergence and/or exacerbation of AD. Disturbance of the SC pH recovery function is observed in flaky tail mice and might be involved in the susceptibility to AD-like dermatitis of mice with genetic abnormalities associated with permeability barrier function. Disturbed SC acidity maintenance could be regarded as a missing link that connects genetic abnormalities associated with permeability barrier dysfunction and environmental factors in the pathogenesis of AD.

Introduction

The mutual association between permeability barrier dysfunction and allergic inflammation is one of the most important issues in the pathogenesis of atopic dermatitis (AD). This review first describes the cross-talk between these two aspects of AD. Next, some pathogenic molecules or factors that could be simultaneously involved in both aspects are described. Finally, this review proposes a possible mechanism by which genetic abnormalities associated with impaired permeability barrier function collaborate with environmental factors, resulting in the emergence and/or exacerbation of AD.

Mutual association between permeability barrier abnormality and allergic inflammation

Permeability barrier abrogation induces the production and secretion of a variety of proinflammatory cytokines, such as interleukin (IL)-1α, tumor necrosis factor (TNF) α, granulocyte macrophage colony-stimulating factor (GM-CSF), and IL-6. Therefore, repetitive permeability barrier abrogation alone causes substantial cutaneous inflammation via the upregulation of proinflammatory cytokines. Elevation of the stratum corneum (SC) pH, which is observed in AD lesions, could initiate and/or drive many of the pathogenic features including both the permeability barrier disturbance and induction of Th2-type inflammation via protease-activated receptor-2-dependent and -independent mechanisms, leading to the emergence and/or exacerbation of AD. Disturbance of the SC pH recovery function is observed in flaky tail mice and might be involved in the susceptibility to AD-like dermatitis of mice with genetic abnormalities associated with permeability barrier function. Disturbed SC acidity maintenance could be regarded as a missing link that connects genetic abnormalities associated with permeability barrier dysfunction and environmental factors in the pathogenesis of AD.
As described above, the mutual association between permeability dysfunction and allergic inflammation has been elucidated. IL-4 inhibits the upregulation of ceramide synthesis by TNF-α and interferon (IFN) γ or by permeability barrier abrogation, thus resulting in disturbance of permeability barrier homeostasis. IL-4, IL-13, and IL-31 reduce the expression of epidermal differentiation-related molecules such as involucrin, loricrin, and filaggrin, which are important elements in permeability barrier homeostasis. In addition, Th2 cytokines upregulate the expression of kallikrein-related peptidase 7, which accounts for the degradation of corneodesmosomes. The combined data suggest that Th2 cytokines have negative effects on permeability barrier homeostasis and SC integrity/cohesion. A variety of cytokines other than Th2 cytokines are also known to disturb permeability barrier function. IL-17 and IL-22 reduce the expression of filaggrin, profilaggrin processing enzymes, cellular adhesion-related molecules, and tight junction (TJ)-related molecules. IFN-γ, TNF-α, and IL-25 also reduce the expression of filaggrin.

Cutaneous inflammation disturbs the TJ barrier, resulting in disturbance of the SC barrier. An increase in SC pH might be involved in SC barrier dysfunction due to abrogation of the TJ barrier.

Possible mechanisms for simultaneous involvement in both permeability barrier dysfunction and allergic inflammation

As described above, the mutual association between permeability barrier dysfunction and allergic inflammation, which results in a vicious cycle of both aspects, is an important issue in the pathogenesis of AD, and management of both aspects is essential for the treatment of patients with AD. In this context, it is rational to seek therapeutic strategies that take both aspects into account. Indeed, treatment of patients with AD both by restoring the permeability barrier function and by stopping allergic inflammation is required. Finally, we recently demonstrated that expression of TARC and RANTES was upregulated, and expression of transglutaminase 1 and loricrin was downregulated, in cultured human keratinocytes by transfection with small interfering RNA for PPARz. The combined data indicate that depressed PPARz expression might be involved in the pathogenesis of AD via simultaneous involvement in both allergic inflammation and permeability dysfunction and could be a rational therapeutic target that accounts for both aspects.

SC pH

Elevation of SC pH, a universal accompaniment to barrier defects, as well as to inflammation and environmental factors such as the use of alkaline soaps, are features of AD, and are likely to be “drivers” of several pathogenic features of AD, including both the permeability barrier disturbance and induction of Th2-type inflammation. The pathological consequences of an elevation in SC pH are thought to include two divergent pathways—PAR-2-dependent and -independent mechanisms. PAR2-independent, downstream effects include reduced activities of two key lipid processing enzymes, i.e., β-glucocerebrosidase (β-GC) and acidic sphingomyelase, which exhibit an acidic pH optimum, resulting in delayed maturation of lipid bilayers. An increase in SC pH also activates the kallikrein family of serine proteases in the outer epidermis, which accelerate the destruction of barrier-related components such as lipid processing enzymes and corneodesmosomes, while generating the active forms of IL-1α and IL-1β. By contrast, the receptor-dependent activation of PAR2 triggers Th2-type inflammation via the production of a variety of proinflammatory cytokines and TSLP in epidermal keratinocytes, and induction of mast cell degranulation. Accordingly, the maintenance of an acidic pH largely prevents the appearance of AD and the emergence of atopic march-like phenomena in repeatedly hapten-challenged mice. In addition, a PAR2 antagonist, NPS1577, attenuated the emergence of allergen-induced AD-like dermatitis in flaky tail mice, suggesting inflammation as described above) in AD. Therefore, strategies aimed at augmentation of filaggrin expression could not only restore barrier function but could also reduce susceptibility to allergic inflammation, thereby preventing the emergence of the vicious cycle in AD. Indeed, it has been reported that augmentation of filaggrin prevented the emergence of AD-like dermatitis in a murine model.

Peroxisome proliferator-activated receptor α

Peroxisome proliferator-activated receptors (PPARs) belong to the nuclear hormone receptors class II, and have three subtypes—PPARα, PPARβ/δ, and PPARγ. They are called liposensors because their ligands are lipids or lipid derivatives. Generally, PPAR signaling has positive effects on barrier homeostasis, but it can also have anti-inflammatory effects, although there are several differences between the PPAR subtypes. The activation of PPARs stimulates lipid synthesis and epidermal differentiation and accelerates recovery from permeability barrier dysfunction. Moreover, the development of the epidermal barrier is delayed in PPARz-deficient mice. Activators of PPARz suppress both allergic and irritant cutaneous inflammation in vivo. Interestingly, it has been reported that PPARz expression in the skin is reduced in patients with AD and that PPARz-deficient mice develop hapten-induced AD-like dermatitis more easily than wild-type mice. In addition, the expression of PPARα in the epidermis is reduced in similar hapten-induced murine AD models, and topical treatment with some PPARα activators exhibits a substantial therapeutic effect on murine AD both by restoring the permeability barrier function and by stopping allergic inflammation. Finally, we recently demonstrated that expression of TARC and RANTES was upregulated, and expression of transglutaminase 1 and loricrin was downregulated, in cultured human keratinocytes by transfection with small interfering RNA for PPARz. The combined data indicate that depressed PPARz expression might be involved in the pathogenesis of AD via simultaneous involvement in both allergic inflammation and permeability dysfunction and could be a rational therapeutic target that accounts for both aspects.

Filaggrin

Filaggrin is an important epidermal differentiation-related molecule and plays critical roles in permeability barrier homeostasis. Interestingly, it has been recently shown that keratinocytes transfected with small interfering RNA against the profilaggrin gene can produce greater quantities (vs. control) of TSLP, which is an essential cytokine for the induction of the Th2-type immunological reaction. It has also been reported that the keratinocytes of flaky tail mice, in which filaggrin is deficient owing to a loss-of-function mutation of profilaggrin, produce more of the proinflammatory cytokine, IL-1β, compared with those of wild-type mice. These results illustrate that an abnormality in a barrier-related molecule could, simultaneously, modulate the functions relevant to allergic inflammation in keratinocytes. Expression of filaggrin is known to be downregulated genetically or secondarily (i.e., via allergic reaction). In addition to augmentation of proinflammatory cytokine production, PAR2 activation following permeability barrier abrogation stimulates the production of thymic stromal lymphopoietin (TSLP) in keratinocytes. The induction of a Th2-type immunological reaction by sensitization through permeability barrier-abrogated skin is now thought to be involved in the emergence of allergic disorders in multiple organs, such as asthma, rhinitis, and food allergy.
Figure 1 Possible hypothesis on the pathogenesis of atopic dermatitis. Based on the contents in the present review, a possible story could be made on the pathogenesis of atopic dermatitis (AD). Genetic abnormalities associated with impaired permeability barrier not only cause permeability barrier dysfunction but also could be directly involved in susceptibility to cutaneous inflammation, leading to the subclinical state. At the subclinical state, it may get difficult to maintain stratum corneum (SC) acidity following the elevation of SC pH by the environmental factors equivalent to SC neutralization stimuli. In concert with the environmental factors, substantial cutaneous inflammation emerges and a vicious cycle is operated, resulting in AD. Der. = dermis; Epi. = epidermis; Ker. = keratinocyte; SC = stratum corneum.

the importance of PAR-2 signaling in the pathogenesis of AD. The combined data suggest that abrogation of SC acidity and/or PAR2 signaling could be therapeutic targets for simultaneous mediation of both allergic inflammation and permeability barrier dysfunction.

Possible mechanisms for collaboration of genetic abnormalities associated with impaired epidermal barrier and environmental factors

Collaboration of the genetic background associated with impaired epidermal barrier with environmental factors is essential in the emergence of AD. However, the mechanism by which people with genetic abnormalities related to the skin barrier show susceptibility to allergic inflammation when suffering from environmental factors, remains obscure. Of note, environmental factors such as scratching, the use of alkali soap, and low humidity are generally involved in permeability barrier abrogation, leading to an elevation of SC pH. As mentioned above, elevation of SC pH could trigger or drive many pathways leading to the emergence and/or exacerbation of AD. Therefore, disturbance of the maintenance of SC acidity might be the missing link that connects genetic abnormalities associated with an impaired epidermal barrier and environmental factors. Interestingly, it has been recently revealed that SC recovery function following elevation of SC pH is disturbed in flaky tail mice, which have two genetic abnormalities associated with the permeability barrier (i.e., filaggrin and Tmem79/Matt). Thus, disturbance of the maintenance of SC acidity might be involved in the susceptibility of flaky tail mice to AD-like dermatitis. Indeed, in these mice, a compensatory mechanism for the maintenance of SC acidity, i.e., elevation of sodium/proton pump N+/H+ antiporter 1 (NHE1) activity, was already fully exploited at the steady state, presumably because of subclinical permeability barrier abrogation and/or inflammation caused by the genetic abnormalities, with the result that it could not compensate for exogenous SC-neutralization stimuli.

Conclusion

It is essential to investigate the mutual association between permeability barrier dysfunction and allergic inflammation to clarify the pathogenesis of AD. Such investigations could not only elucidate the complicated pathogenesis in which genetic abnormalities and environmental factors collaborate in a sophisticated manner, but also sow the seeds of new scientific and therapeutic strategies in AD (Figure 1).

References


