DERMATOLOGICA SINICA 33 (2015) 74–77

Contents lists available at ScienceDirect

Dermatologica Sinica

journal homepage: http://www.derm-sinica.com

REVIEW ARTICLE

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.

Copyright © 2015, Taiwanese Dermatological Association.
Published by Elsevier Taiwan LLC. All rights reserved.

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).[1] 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 excess production of proinflammatory cytokines.[2] It has been shown that barrier abrogation-induced inflammation is accompanied by a T helper 2 (Th2)-type reaction with eosinophilic infiltration and expression of the chemokines thymus and activation-regulated chemokine (TARC) and regulated on activation normal T cell expressed and secreted (RANTES).[3] Permeability barrier abrogation also increases stratum corneum (SC) pH, thereby initiating a variety of cascades that induce or augment inflammation, including induction of Th2 type inflammation, in a protease-activated receptor (PAR) 2 activation dependent or independent

Conflicts of interest: The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in this article.

* Department of Dermatology, Faculty of Medicine, Oita University, 1-1 Idaigaoka, Hasama-machi, Yufu-shi, Oita 879-5593, Japan.
E-mail address: HATANO@oita-u.ac.jp.

http://dx.doi.org/10.1016/j.dsi.2015.03.007
1027-8117/Copyright © 2015, Taiwanese Dermatological Association. Published by Elsevier Taiwan LLC. All rights reserved.

manner.[1] In addition to augmentation of proinflammatory cytokine production, PAR2 activation following permeability barrier abrogation stimulates the production of thymic stromal lymphopoietin (TSLP) in keratinocytes.[4,5] 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.[6–8]

Conversely, it has been recognized that allergic inflammation disturbs the permeability barrier function. First, involvement of Th2 cytokines in permeability barrier dysfunction has been elucidated. IL-4 inhibits the upregulation of ceramide synthesis by TNFα and interferon (IFN) γ or by permeability barrier abrogation, thus resulting in disturbance of permeability barrier homeostasis.[9,10] IL4, 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.[11–13] In addition, Th2 cytokines upregulate the expression of kallikrein-related peptidase 7,which accounts for the degradation of corneodesmosomes,[14] and downregulates expression of desmoglein 1, which is one of the most important components of corneodesmosomes.[15] 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.[16,17] IFNγ, TNFα, and IL-25 also reduce the expression of filaggrin.[18–20]

Cutaneous inflammation disturbs the TJ barrier,[21] resulting in disturbance of the SC barrier.[21,22] An increase in SC pH might be involved in SC barrier dysfunction due to abrogation of the TJ barrier.[22]

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, recent advances related to this issue have implicated some molecules or pathogenic factors that account for both aspects simultaneously and, which, therefore, could serve as promising targets for the development of new therapeutic strategies.

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.[23] 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.[24] 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 inflammation as described above) in AD.[1,11] 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.[25]

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.[26] 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.[26] Moreover, the development of the epidermal barrier is delayed in PPARα-deficient mice.[27] Activators of PPARα suppress both allergic and irritant cutaneous inflammation *in vivo*.[28] Interestingly, it has been reported that PPARα expression in the skin is reduced in patients with AD and that PPARα-deficient mice develop hapten-induced AD-like dermatitis more easily than wild-type mice.[29] 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.[30,31] 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 PPARα.[32] The combined data indicate that depressed PPARα 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.[1] 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-GlcCer'ase) and acidic sphingomyelinase, which exhibit an acidic pH optimum, resulting in delayed maturation of lipid bilayers.[1] 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.[1] 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.[1,33] Accordingly, the maintenance of an acidic pH largely prevented the appearance of AD and the emergence of atopic march-like phenomena in repeatedly hapten-challenged mice.[34,35] In addition, a PAR2 antagonist, NPS1577, attenuated the emergence of allergen-induced AD-like dermatitis in flaky tail mice, suggesting

Download English Version:

https://daneshyari.com/en/article/3196437

Download Persian Version:

https://daneshyari.com/article/3196437

Daneshyari.com