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Connecting the Dots: From Skin Barrier Dysfunction to Allergic Sensitization, and the Role of Moisturizers in Repairing the Skin Barrier

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ABSTRACT

The skin is one of the largest immunologic organs in the body and a continuous target for allergic and immunologic responses. Impairment of the skin barrier increases the likelihood of external antigens and pathogens entering and creating inflammation, which can potentially lead to skin infections, allergies, and chronic inflammatory diseases such as atopic and contact dermatitis. Functionally, the skin barrier can be divided into four different levels. From outermost to innermost, these highly interdependent levels are the microbiome, chemical, physical, and immune levels. The objective of this review is to provide an update on current knowledge about the relationship between skin barrier function and how dysfunction at each level of the skin barrier can lead to allergic sensitization, contact dermatitis, and the atopic march, and examine how to best repair and maintain this barrier through the use of moisturizers.

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INTRODUCTION

The skin is one of the largest immunologic organs in the body and a continuous target for allergic and immunologic responses. Rising incidences of allergies have been reported worldwide. While the cause of this rise is not totally clear, it has been attributed to factors such as poor nutrition, stress, use of antibiotics, and growing up in clean urban homes while exposed externally to high air pollution.[1-5] The skin barrier is the first interface between the environment and our immune system. This interface is constantly exposed to endogenous and exogenous factors including ultraviolet radiation, pollution, and damaging skincare products. Impairment of the skin barrier increases the likelihood of external antigens, irritants, and pathogens passing into the skin and driving inflammation, potentially leading to skin infections, allergies, and chronic inflammatory skin diseases such as atopic dermatitis (AD) and contact dermatitis (CD).[6] This phenomenon has been referred to as "transcutaneous sensitization", and is highly dependent on skin barrier dysfunction.[7]

Skin Barrier Anatomy

Anatomically, the skin barrier can be divided into the epidermis and the dermis. The epidermis primarily consists of keratinocytes arranged in several layers, with the stratum corneum (SC) at the top, a layer of cornified keratinocytes that physically prevents invaders from entering. The dermis contains collagen and elastin fibers, fibroblasts, proteoglycans, and nerve endings.

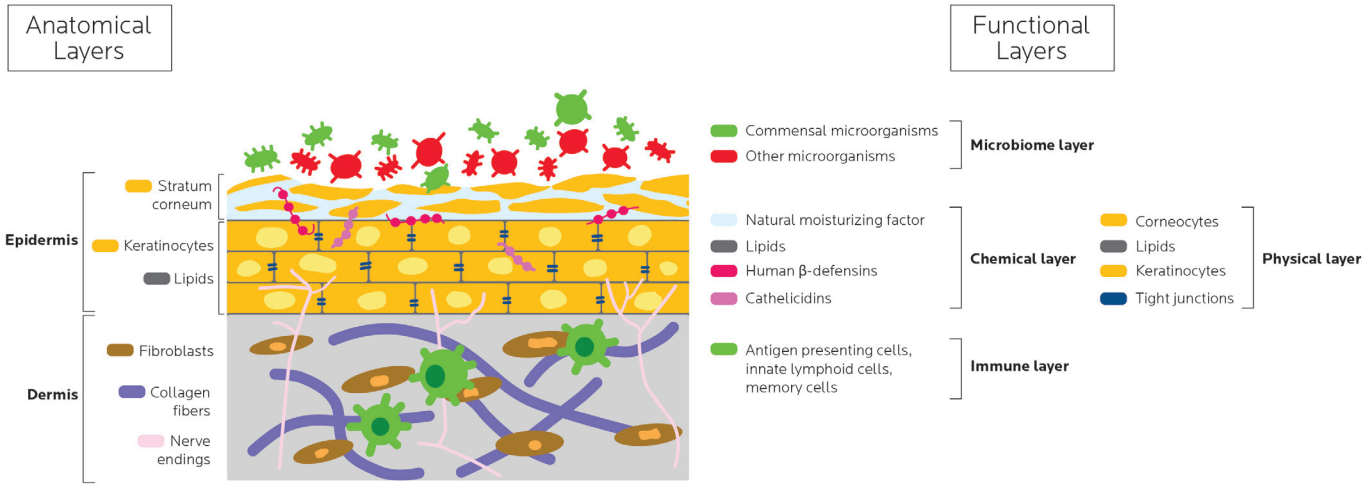
Functionally, the skin barrier can be divided into four strata: the microbiome, chemical, physical, and immune layers (Figure 1). The microbiome layer consists of living microbial communities. The chemical layer includes natural moisturizing factors (NMF), human β-defensins, and the acid mantle, which maintains an acidic surface pH.[8] Tight junctions and the SC constitute important parts of the physical layer, which also produces some of the compounds of the chemical layer. Sensing danger signals through pathogen- and damage-associated molecular patterns, resident immune cells of the immune layer work to clear invasions, repair the barrier, and maintain homeostasis. While each layer has unique functions, it also works interdependently in upholding overall integrity of the skin barrier.[9]

The Skin Microbiota and Dysbiosis

Like the gut microbiota, the healthy skin microbiota is fairly stable.[10,11] It is populated by commensal organisms including bacteria, viruses, fungi, and mites, with the *Staphylococcus*, *Cutibacterium*, and *Corynebacterium* genus dominating. It is thought that commensal bacteria regulate potentially pathogenic species. As the outermost layer, microbial communities are first responders to changes in the environment and transmit signals to the immune system.[9,12]

Dysbiosis, or disruption of balance in the microbiome layer, has been extensively studied in the context of AD, the first

FIGURE 1. Anatomical and functional layers of the skin barrier.



step of the atopic march.[13] In AD skin, *Staphylococcus aureus* is more abundant than normal, with reduced populations of other species. While exact mechanisms of dysbiosis contributing to barrier disruption have not been fully elucidated, several factors likely contribute, including the production of exotoxins by *Staphylococcus aureus*.[14] The distribution of bacterial communities on the cutaneous surface depends on factors such as moisture content, temperature, environment, and sebaceous gland abundance.[15] Regulating skin microbiota could be one way to control AD, restore the skin barrier, and potentially prevent subsequent development of IgE sensitization and atopic march.[16-18]

The Chemical Skin Barrier

The chemical layer includes antimicrobial compounds such as human β-defensins, NMF, and lipids. NMF includes hygroscopic compounds, amino acids, and their derivatives. Many of these are products of filaggrin breakdown, some of which may have antimicrobial properties.[9] Human β-defensins, or host peptides in the skin known for their direct antimicrobial activity, have been shown to attract immune effector cells and induce cytokine and chemokine production in keratinocytes. They also regulate tight junction and epidermal barrier function.[19,20] Cathelicidins are another group of antimicrobial peptides that play a similar role.[21] Commensal skin bacteria also produce antimicrobial peptides that can protect against *Staphylococcus aureus*.[18]

In healthy individuals, the skin pH is generally maintained between 4-6, and deviation can result in abnormal permeability.[9] Removal of natural antimicrobial peptides and elevation of skin pH from the use of alkaline products create an unfavorable environment for the healthy skin microbiota, further demonstrating the interdependence of the levels.[22] Additionally, following experimental skin barrier disruption and provocation of irritant contact dermatitis (ICD), changes in skin lipid composition were reported.[23] The sulfur-rich part of the SC may act as a redox barrier, buffering chemicals coming into contact with the skin.[24]

The Physical Skin Barrier

Disruption of the physical layer of the skin barrier enhances entry of foreign substances. Corneocytes, which are flattened and denucleated mature keratinocytes, constitute the "bricks" of the SC, while lipid-rich "mortar" fills the gaps between.[25] Below the SC is the stratum granulosum, made of keratinocytes that have granules containing proteins such as filaggrin. Keratinocytes also produce lipids such as triglycerides and cholesterols functioning as part of the chemical level. Tight junction proteins connect adjacent keratinocytes within the stratum granulosum to form a barrier against water and solutes.[9]

Filaggrin, an important protein of the epithelial barrier, aggregates and organizes keratin filaments.[26] Mutations in the gene for filaggrin are a major risk factor for developing AD.[27] Defects in skin barrier result from a combination of factors including filaggrin defects and deficiency of other skin barrier proteins, enhancing allergen sensitization via the skin.[28] Importantly, even for individuals with normal filaggrin genes, in the presence of inflammatory mediators, Th2 signaling increases susceptibility to AD.[29] Specifically, keratinocytes differentiated in the presence of Th2 cytokines IL-4 and IL-13 demonstrate decreased filaggrin expression.[30] This may be why individuals with AD are more likely to acquire CD.[23,31] Mutations in the same gene have been linked to increased risk of developing food allergies.[32]

Chronic skin diseases including AD, ichthyosis, and psoriasis often present with a disturbed SC. Patients with these diseases are advised to avoid contact with irritants or allergens that can lead to CD.[23]

The Immune Skin Barrier

The immune layer includes resident antigen presenting cells, innate lymphoid cells, adaptive memory cells, and others, all working together. Because cells of the immune level are distributed throughout the skin, this level is highly intertwined with the others. It responds to various signals and directs subsequent behavior of the epithelium.[9] For example, cells in the skin express toll-like receptors, a type of pattern recognition receptor that responds to pathogen-associated molecular patterns.[33,34] When these receptors are engaged, cells secrete substances such as cytokines and human β-defensins.[15] Following impairment of physical barrier, allergens and irritants can come into contact with cells of the immune barrier, particularly Langerhans cells, which process these exogenous haptens and initiate T-cell responses.[23] Previous research has shown that disruption of the physical barrier subsequently leads to an increase in Langerhans cells even in the basal layers and upper epidermis where these cells are not usually found. Increased numbers of epidermal Langerhans cells have also been found in allergic contact dermatitis (ACD) and ICD.[35]

Skin Barrier Dysfunction Can Lead to Allergic Sensitization and Atopic March

Disruptions to the skin barrier increase the likelihood of irritants, pathogens, and allergens provoking inflammatory responses. Because skin barrier compromise can consequentially lead to other allergic reactions such as to food and potentially progress to diseases such as CD, it seems especially important to address disruptions early. Skin barrier disruption has been shown to cause AD early in life, which can subsequently lead to allergic rhinitis and asthma, a phenomenon known as the atopic march.[36] AD is a skin disease that causes chronic pruritus often beginning in the first years of life and resolving by adulthood in only about 60% of the population. Numerous studies have pointed to AD as the first step in the progression of the atopic march.[37]

Furthermore, allergies can develop by sensitization through skin.[26] Food sensitization is six times more likely to develop in children with AD than in those without.[38] A study of adult workers at a mouse research facility found that physician-diagnosed eczema was a risk factor for mouse sensitization as determined through skin-prick testing and suggests that skin barrier dysfunction may increase risks of aeroallergen sensitization not only in childhood but throughout life.[39]

However, allergies can develop as a consequence of skin barrier defects even in the absence of the development of AD and the atopic march. In fact, neonatal skin barrier dysfunction at birth predicts food allergies at 2 years of age, even without AD.[40] Similarly, even in the absence of AD, children with skin barrier defects are more likely to develop asthma.[26]

Skin Barrier Dysfunction Can Lead to Contact Dermatitis

CD can be irritant (80%) or allergic (20%) and, unlike AD, can develop later in life. ICD is a non-immunologic, inflammatory reaction to irritating agents including solvents, detergents, alcohol, and other chemicals which result in dose-dependent direct tissue damage. Excessive wetness, due to prolonged contact with water, perspiration, or bodily fluids can also lead to ICD. ICD lesions are typically erythematous, dry, possibly edematous and fissuring, with symptoms of burning, tingling or soreness within minutes to hours of contact with the irritant. ACD is an immunologic, delayed-type hypersensitivity reaction to an allergen, which is usually a small molecular weight molecule or hapten that conjugates with skin proteins and induces activated epidermal keratinocytes to release inflammatory cytokines. This immunologic response eventually leads to sensitization to an allergen upon initial contact, and upon subsequent exposure, an elicitation phase occurs. The main symptoms of ACD are pruritus and the appearance of an erythematous eruption, typically scaly, edematous, or vesicular in the acute stage and lichenified in the chronic stage. The cutaneous eruption due to ACD is usually delayed by a few days.[31]

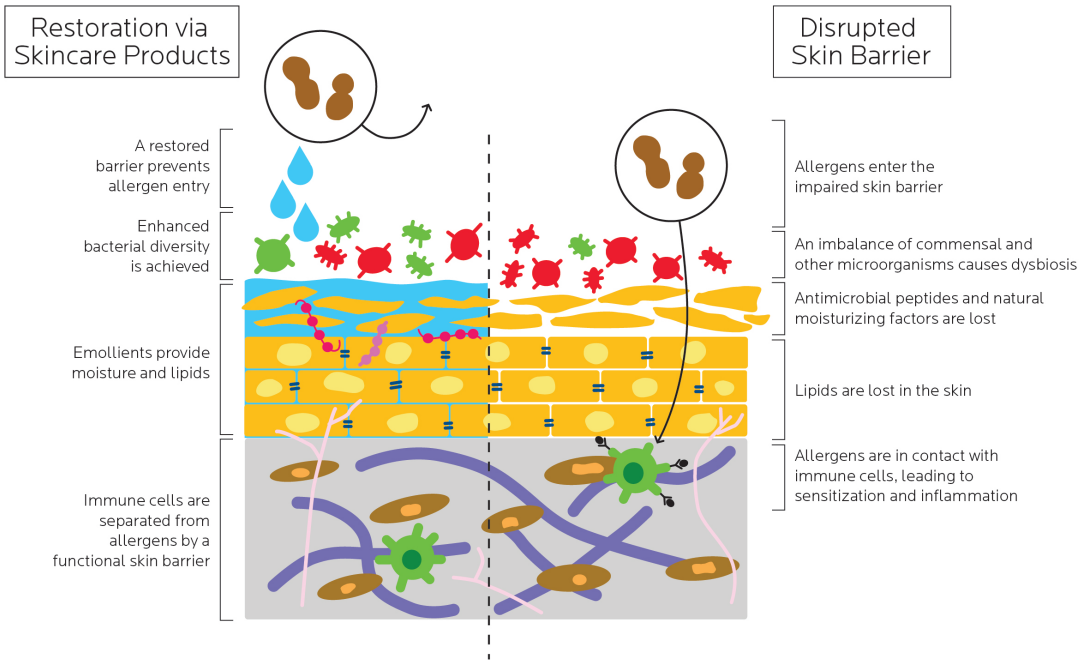
Irritants and allergens were once strictly distinguished. However, the distinction is now blurring, as in many cases, CD cannot be definitively attributed to irritant or allergic mechanisms by clinical observation. ICD and ACD commonly overlap as many allergens at high enough concentrations can also act as irritants. For example, strong allergens such as poison ivy are also irritants.[23] Dysfunctional skin barriers increase the chance of allergen entry into the epidermis and understanding how to minimize penetration of chemicals is important in preventing CD.

Repair of the Skin Barrier May Be a Therapeutic Strategy in the Prevention of Allergic Sensitization, Atopic March, and Contact Dermatitis

Dysfunction at any functional level of the skin barrier can lead to atopic march, allergies, and CD; therefore, repair of the barrier before these conditions progress is essential. Most research on early intervention in skin barrier repair pertains to AD, however, similar logic can be presumed for prevention of ACD, as ACD shares molecular mechanisms with AD, including increased cellular infiltrates and cytokine activation.[41] Additionally, patients with AD are more likely to develop CD.

As dysfunction can occur in various levels of the cutaneous barrier, repair should, therefore, target multiple levels. Recently, a study on infants evaluating the colonization of pathogens on skin demonstrated that increased commensal staphylococci early in life lowered the risk of developing AD by 12 months. The most prevalent species associated with protection from AD development were *Staphylococcus epidermidis* and *Staphylococcus cohnii*.[42] Furthermore, exposure to antibiotics in the first

FIGURE 2. Restoration of the disrupted skin barrier via skincare products.



year of life increases the risk of childhood AD.[43] Collectively, these findings confirm an important role of skin microbiota in the development of cutaneous tolerance and maintaining the skin barrier against allergens.

AD has also been linked to sensitization to food allergens, leading to food allergies. Randomized trials have been conducted to determine the efficacy of applying emollients to newborn babies to prevent AD development in infancy and in childhood.[44-47] Daily use of one emollient reduced cumulative incidence of AD at six months.[44] Fewer newborns given moisturizers developed AD and those with AD had significantly higher sensitization rates against egg whites.[45] Use of a slightly acidic ceramide-rich emollient on newborns showed a trend toward reduced risk of both AD and food sensitization.[46] Thus, in the context of preventing allergic sensitization, and atopic march, targeting AD through skin barrier repair via emollient usage in infancy is especially important and research indicates there may be an optimal window of time for doing so.[37,48] However, in other skin diseases such as CD that can develop at any age, targeting skin barrier repair via emollient usage later in life may be justified for similar reasons.

The Role of Moisturizers in Skin Barrier Repair

Epicutaneous antigens are sensitizers that lead to allergy development, especially in the setting of a dysfunctional skin barrier. It is important to counsel patients that skincare is as much about what is excluded as it is about what is included in a product. Avoidance of common allergens such as fragrance, unnecessary botanicals, or certain preservatives should be advised, especially for atopic patients.

Emollients can help repair the skin barrier (Figure 2).[44-46] Emollients improve the barrier function of the SC by providing water and lipids, and slightly acidic emollients can potentially enhance ceramide synthesis.[49] Sufficient lipid replacement therapy reduces inflammation and restores epidermal function. Conventional barrier ointments form protective films over the skin barrier which are impermeable to environmental allergens and irritants but can also trap heat in the area, prevent perspiration, and cause discomfort. They may also be perceived as cosmetically unacceptable, which can directly affect adherence.[50] Newer products focus on cosmetically elegant formulations with minimalist ingredient lists, that also seek to promote the delivery of pharmacological substances through the SC.[51]

Recently, the focus of skincare products that enhance the cutaneous barrier has been on targeting the restoration of the microbiome layer.[13,52,53] These newer formulas not only protect the skin but also help manage inflammation and neuromediator activation to preserve both the skin barrier and diversity in microbiota. Incorporation of prebiotics, or components that selectively modulate desired bacterial growth, may be helpful.[15] Prebiotics include ingredients like thermal spring waters, such as from La Roche-Posay, France, which have unique mineral components and trace elements.[54] Additionally, usage of an emollient containing thermal spring waters, shea butter, and

niacinamide has not only been shown to increase bacterial diversity but also to improve AD symptoms.[55]

CONCLUSION

The various functional levels (microbiome, chemical, physical, immune) of the skin barrier are all necessary to maintain skin integrity and are highly interdependent. Dysfunction can occur at solitary or multiple points and may have a domino effect on other levels. It is increasingly clear that barrier dysfunction leads to allergic sensitization, the atopic march, and CD. Thus, maintenance and restoration of the skin barrier are paramount to preventing these conditions. This may be achieved to greater and lesser degrees through the use of various moisturizers.

In an ideal product, each aspect of the skin barrier would be considered. Attributes such as avoiding preservatives that can damage the microbiota while perhaps even having pre- or probiotics to support the microbiota, using pH-neutral and gentle ingredients to support the chemical layer, combining occlusives, humectants, and emollients for the physical barrier, and avoiding fragrance and common allergens and irritants to minimize the chance for immune activation are all desirable and should be considered when evaluating a potential moisturizer.

DISCLOSURES

S. Seité is employee of La Roche-Posay, France. M. Lin has served as a consultant for L'Oreal/La Roche-Posay. P. Lio has served as a consultant and speaker for L'Oreal/La Roche-Posay. He has also been a consultant/advisor for Micreos, Pierre-Fabre, Johnson & Johnson, Syncere Skin Systems, Altus Labs, AOBiome, Galderma, IntraDerm, Unilever, and is a board member of the National Eczema Association. T. Lazic Strugar has served as a consultant for L'Oreal/La Roche-Posay. P. Lio and T. Lazic Strugar received a writing grant from L'Oreal for this manuscript. A. Kuo has no conflicts.

REFERENCES

1. Kilpelainen M, Terho EO, Helenius H, Koskenvuo M. Body mass index and physical activity in relation to asthma and atopic diseases in young adults. *Respir Med.* 2006;100(9):1518-1525.
2. Bloomfield SF, Rook GAW, Scott EA, Shanahan F, Stanwell-Smith R, Turner P. Time to abandon the hygiene hypothesis: new perspectives on allergic disease, the human microbiome, infectious disease prevention and the role of targeted hygiene. *Perspect Public Heal.* 2016;136(4):213-224.
3. Sonnenburg ED, Smits SA, Tikhonov M, Higginbottom SK, Wingreen NS, Sonnenburg JL. Diet-induced extinctions in the gut microbiota compound over generations. *Nature.* 2016;529(7585):212-U208.
4. Okada H, Kuhn C, Feillet H, Bach JF. The 'hygiene hypothesis' for autoimmune and allergic diseases: an update. *Clin Exp Immunol.* 2010;160(1):1-9.
5. Kuo CH, Kuo HF, Huang CH, Yang SN, Lee MS, Hung CH. Early life exposure to antibiotics and the risk of childhood allergic diseases: an update from the perspective of the hygiene hypothesis. *J Microbiol Immunol Infect.* 2013;46(5):320-329.
6. Gilles S, Akdis C, Lauener R, et al. The role of environmental factors in allergy: A critical reappraisal. *Exp Dermatol.* 2018;27(11):1193-1200.
7. Jin H, He R, Oyoshi M, Geha RS. Animal models of atopic dermatitis. *J Invest Dermatol.* 2009;129(1):31-40.
8. Surber C, Humbert P, Abels C, Maibach H. The acid mantle: a myth or an essential part of skin health? *Curr Probl Dermatol.* 2018;54:1-10.
9. Eyerich S, Eyerich K, Traidl-Hoffmann C, Biedermann T. Cutaneous barriers and skin immunity: differentiating a connected network. *Trends Immunol.* 2018;39(4):315-327.
10. Faith JJ, Guruge JL, Charbonneau M, et al. The long-term stability of the human gut microbiota. *Science.* 2013;341(6141):1237439.
11. Oh J, Byrd AL, Park M, Program NCS, Kong HH, Segre JA. Temporal stability of the human skin microbiome. *Cell.* 2016;165(4):854-866.
12. Grice EA, Segre JA. The skin microbiome. *Nat Rev Microbiol.* 2011;9(4):244-253.
13. Seite S, Bieber T. Barrier function and microbiotic dysbiosis in atopic dermatitis. *Clin Cosmet Investig Dermatol.* 2015;8:479-483.
14. Nakamura Y, Oscherwitz J, Cease KB, et al. Staphylococcus delta-toxin induces allergic skin disease by activating mast cells. *Nature.* 2013;503(7476):397-401.
15. Baldwin HE, Bhatia ND, Friedman A, Eng RM, Seite S. The role of cutaneous microbiota harmony in maintaining a functional skin barrier. *J Drugs Dermatol.* 2017;16(1):12-18.
16. Bjerre RD, Bandier J, Skov L, Engstrand L, Johansen JD. The role of the skin microbiome in atopic dermatitis: a systematic review. *Br J Dermatol.* 2017;177(5):1272-1278.
17. Kobayashi T, Glatz M, Horiuchi K, et al. Dysbiosis and staphylococcus aureus colonization drives inflammation in atopic dermatitis. *Immunity.* 2015;42(4):756-766.
18. Brunner PM, Leung DYM, Guttman-Yassky E. Immunologic, microbial, and epithelial interactions in atopic dermatitis. *Ann Allergy Asthma Immunol.* 2018;120(1):34-41.
19. Kiatsurayanon C, Niyonsaba F, Smithrithee R, et al. Host defense (Antimicrobial) peptide, human beta-defensin-3, improves the function of the epithelial tight-junction barrier in human keratinocytes. *J Invest Dermatol.* 2014;134(8):2163-2173.
20. Kiatsurayanon C, Ogawa H, Niyonsaba F. The role of host defense peptide human beta-defensins in the maintenance of skin barriers. *Curr Pharm Des.* 2018;24(10):1092-1099.
21. Niyonsaba F, Kiatsurayanon C, Ogawa H. The role of human beta-defensins in allergic diseases. *Clin Exp Allergy.* 2016;46(12):1522-1530.
22. Schmid-Wendtner MH, Korting HC. The pH of the skin surface and its impact on the barrier function. *Skin Pharmacol Phys.* 2006;19(6):296-302.
23. Proksch E, Brasch J. Abnormal epidermal barrier in the pathogenesis of contact dermatitis. *Clin Dermatol.* 2012;30(3):335-344.
24. Pickard C, Louafi F, McGuire C, et al. The cutaneous biochemical redox barrier: a component of the innate immune defenses against sensitization by highly reactive environmental xenobiotics. *J Immunol.* 2009;183(11):7576-7584.
25. Nishifuji K, Yoon JS. The stratum corneum: the rampart of the mammalian body. *Vet Dermatol.* 2013;24(1):60-72 e15-66.
26. Han H, Roan F, Ziegler SF. The atopic march: current insights into skin barrier dysfunction and epithelial cell-derived cytokines. *Immunol Rev.* 2017;278(1):116-130.
27. Howell MD, Kim BE, Gao P, et al. Cytokine modulation of atopic dermatitis filaggrin skin expression. *J Allergy Clin Immunol.* 2007;120(1):150-155.
28. van den Oord RA, Sheikh A. Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. *BMJ.* 2009;339:b2433.
29. Liang Y, Chang C, Lu Q. The genetics and epigenetics of atopic dermatitis-filaggrin and other polymorphisms. *Clin Rev Allergy Immunol.* 2016;51(3):315-328.
30. Pellerin L, Henry J, Hsu CY, et al. Defects of filaggrin-like proteins in both lesional and nonlesional atopic skin. *J Allergy Clin Immunol.* 2013;131(4):1094-1102.
31. Fonacier LS, Dreskin SC, Leung DY. Allergic skin diseases. *J Allergy Clin Immunol.* 2010;125(2 Suppl 2):S138-149.
32. Venkataraman D, Soto-Ramirez N, Kurukulaaratchy RJ, et al. Filaggrin loss-of-function mutations are associated with food allergy in childhood and adolescence. *J Allergy Clin Immunol.* 2014;134(4):876-882 e874.
33. Miller LS, Modlin RL. Toll-like receptors in the skin. *Semin Immunopathol.* 2007;29(1):15-26.
34. Volz T, Kaesler S, Biedermann T. Innate immune sensing 2.0 - from linear activation pathways to fine tuned and regulated innate immune networks. *Exp Dermatol.* 2012;21(1):61-69.
35. Proksch E, Brasch J, Sterry W. Integrity of the permeability barrier regulates epidermal Langerhans cell density. *Br J Dermatol.* 1996;134(4):630-638.
36. Weidinger S, Novak N. Atopic dermatitis. *Lancet.* 2016;387(10023):1109-1122.
37. Bantz SK, Zhu Z, Zheng T. The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. *J Clin Cell Immunol.* 2014;5(2).
38. Tsakok T, Marrs T, Mohsin M, et al. Does atopic dermatitis cause food allergy? A systematic review. *J Allergy Clin Immun.* 2016;137(4):1071-1078.
39. Grant T, Dantzer J, Keet C, et al. Physician-diagnosed eczema is an independent risk factor for incident mouse skin test sensitization in adults. *Allergy Asthma Proc.* 2018;39(4):311-315.
40. Kelleher MM, Dunn-Galvin A, Gray C, et al. Skin barrier impairment at birth predicts food allergy at 2 years of age. *J Allergy Clin Immunol.* 2016;137(4):1111-1116 e1118.

41. Gittler JK, Krueger JG, Guttman-Yassky E. Atopic dermatitis results in intrinsic barrier and immune abnormalities: implications for contact dermatitis. *J Allergy Clin Immunol.* 2013;131(2):300-313.
42. Kennedy EA, Connolly J, Hourihane JO, et al. Skin microbiome before development of atopic dermatitis: Early colonization with commensal staphylococci at 2 months is associated with a lower risk of atopic dermatitis at 1 year. *J Allergy Clin Immun.* 2017;139(1):166-172.
43. Tsakok T, McKeever TM, Yeo L, Flohr C. Does early life exposure to antibiotics increase the risk of eczema? A systematic review. *Brit J Dermatol.* 2013;169(5):983-991.
44. Simpson EL, Chalmers JR, Hanifin JM, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol.* 2014;134(4):818-823.
45. Horimukai K, Morita K, Narita M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol.* 2014;134(4):824-830 e826.
46. Lowe AJ, Su JC, Allen KJ, et al. A randomized trial of a barrier lipid replacement strategy for the prevention of atopic dermatitis and allergic sensitization: the PEBBLES pilot study. *Br J Dermatol.* 2018;178(1):e19-e21.
47. Chalmers JR, Haines RH, Mitchell EJ, et al. Effectiveness and cost-effectiveness of daily all-over-body application of emollient during the first year of life for preventing atopic eczema in high-risk children (The BEEP trial): protocol for a randomised controlled trial. *Trials.* 2017;18(1):343.
48. Natsume O, Ohya Y. Recent advancement to prevent the development of allergy and allergic diseases and therapeutic strategy in the perspective of barrier dysfunction. *Allergol Int.* 2018;67(1):24-31.
49. Hachem JP, Crumrine D, Fluhr J, Brown BE, Feingold KR, Elias PM. pH directly regulates epidermal permeability barrier homeostasis, and stratum corneum integrity/cohesion. *J Invest Dermatol.* 2003;121(2):345-353.
50. Del Rosso JQ. Factors influencing optimal skin care and product selection In: Draelos ZD, Thaman LA, eds. *Cosmetic Formulation of Skin Care Products* New York, NY: Taylor & Francis; 2006:115-121.
51. Hon KL, Leung AK, Barankin B. Barrier repair therapy in atopic dermatitis: an overview. *Am J Clin Dermatol.* 2013;14(5):389-399.
52. Lane ME, Hadgraft J, Oliveira G, Vieira R, Mohammed D, Hirata K. Rational formulation design. *Int J Cosmetic Sci.* 2012;34(6):496-501.
53. Al-Ghazzewi FH, Tester RF. Impact of prebiotics and probiotics on skin health. *Benef Microbes.* 2014;5(2):99-107.
54. Seite S. Thermal waters as cosmeceuticals: La Roche-Posay thermal spring water example. *Clin Cosmet Investig Dermatol.* 2013;6:23-28.
55. Seite S, Flores GE, Henley JB, et al. Microbiome of affected and unaffected skin of patients with atopic dermatitis before and after emollient treatment. *J Drugs Dermatol.* 2014;13(11):1365-1372.

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