DERMATOLOGICA SINICA 33 (2015) 64–69

Contents lists available at ScienceDirect

Dermatologica Sinica

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

REVIEW ARTICLE

Psoriasis as a barrier disease

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ARTICLE INFO

Article history:
Received: Feb 13, 2015
Revised: Mar 22, 2015
Accepted: Apr 23, 2015

Keywords:
epidermal barrier
mouse model
psoriasis
skin inflammation

ABSTRACT

Skin is equipped with a barrier function, in particular, to prevent invasion of pathogens. Skin barrier is composed of a mechanical barrier, a permeability barrier, and innate and adaptive immunity barriers. Psoriasis is an inflammatory skin disease, which develops through the interaction of epidermal keratinocytes and immune cells, although its pathoetiology has not been fully understood. Recent studies revealed that defects in epidermal barrier-related genes were associated with a risk of psoriasis. Indeed, psoriasis is characterized by compromised barrier function, similar to atopic dermatitis (AD), in which mutations of the filaggrin gene play a role. However, it remains to be determined whether epidermal barrier disruption leads to an altered inflammatory/immunological response in psoriasis. In this review, I demonstrate evidence, in human psoriasis as well as mouse models, showing that barrier insult contributes to psoriasis development through alteration of the innate and adaptive immunity.

Epidermal barrier function in stratum corneum

One of the major functions of the epidermis is as a permeability barrier to prevent the inward or outward passage of water and small molecules. The permeability barrier of the skin resides largely in the stratum corneum (SC), and it depends upon a two-compartment system, that is, corneocytes (cellular) and lipid-rich matrix (intercellular). SC lipids are derived from the content of lamellar bodies in granular cells and comprise a mixture of sphingolipids, cholesterol, and fatty acids, arranged as intercellular membrane bilayers that are required for the epidermal permeability barrier.[1] Sphingolipids, particularly ceramides, representing approximately 50% of SC lipid content by weight, play an essential role for the permeability barrier in the intercellular space and for the water retention of SC.[1] *De novo* synthesis of sphingolipids starts with condensation of serine and palmitoyl-CoA (Coenzyme A), and this reaction is catalyzed by serine palmitoyl transferase (SPT), the rate-limiting enzyme, which is ubiquitously found in various tissues, particularly in epidermal keratinocytes.[2] Previous studies have demonstrated that *de novo* synthesis of SC lipids was stimulated by barrier perturbations, including extraction of lipids from SC with organic solvents, removal of SC layer by tape stripping, and dietary restriction of an essential fatty acid.[3] Barrier disruption induces biosynthesis of epidermal ceramides, cholesterol, and fatty acids, through an increase in the activities of respective rate limiting enzymes, SPT, 3-hydroxy-3-methylglutaryl CoA reductase (HMG CoA reductase), acetyl-CoA carboxylase, and fatty acid synthase.[3–8] By contrast, the topical application of inhibitors of either HMG CoA reductase[9] or SPT[5] immediately after barrier disruption resulted in reduction of cholesterol or sphingolipid synthesis, respectively, thereby demonstrating delayed barrier repair. Thus, epidermal lipid synthesis is tightly regulated by the barrier condition to maintain epidermal integrity.

Inflammatory skin diseases and barrier disruption

Inflammatory skin diseases are often associated with barrier defects, although the cause and effect relationship is complex. The discovery of loss-of-function mutations in the *filaggrin* (*FLG*) gene in patients with atopic dermatitis (AD) revealed that disruption of the skin barrier is the primary cause of the disease.[10] Skin barrier dysfunction in AD contributes to an increase of allergic risk due to increased sensitization to environmental antigens.

Psoriasis is also a common inflammatory skin disease that develops through genetic and epigenetic factors. Until 30 years ago, psoriasis was considered to be a keratinocyte disease, but the intervention by use of cyclosporine A with a successful efficacy has

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.

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http://dx.doi.org/10.1016/j.dsi.2015.04.010

disclosed that an immune-mediated mechanism contributes to the development of psoriasis. Genetic studies and further evidence from animal models, in which xenotransplant of skins from psoriasis patients converted to psoriatic lesions by the injection of peripheral blood T cells taken from the patients.[11] also supported the immune-mediated mechanism for psoriasis. However, the pendulum has begun to swing back lately.[12] Previous studies have demonstrated skin barrier abnormality in psoriasis,[13] and recently, some epidermal genes have been documented as susceptibility genes for psoriasis.[14–16] To date, approximately 40 genes have been considered to be psoriasis susceptibility genes. GWAS (genome-wide association study) of psoriasis were summarized in detail by Zhang.[17] Representative genes and their potential functions are listed in Table 1. Candidate genes specific for epidermal cells, not for immune cells, involve β-defensin cluster genes, late cornified envelope (LCE) 3B and 3C genes, and corneodesmosin genes. The functions of these genes are antimicrobial protection, innate immunity of the epidermis, barrier function, and keratinocyte differentiation, respectively. A very recent study demonstrated that barrier discovery was compromised in uninvolved skin of psoriasis patients, supporting that barrier abnormality is the underlying pathogenesis of psoriasis.[18] Given that AD and psoriasis share many features regarding epidermal gene abnormalities, barrier defect, and involvement of immune cells, there is a difference in the balance of immune cell subsets that could cause the phenotypes that distinguish these diseases.[19] Previous studies revealed that epidermal barrier function directly regulates the cutaneous and/or systemic immune system[20,21] (Figure 1).

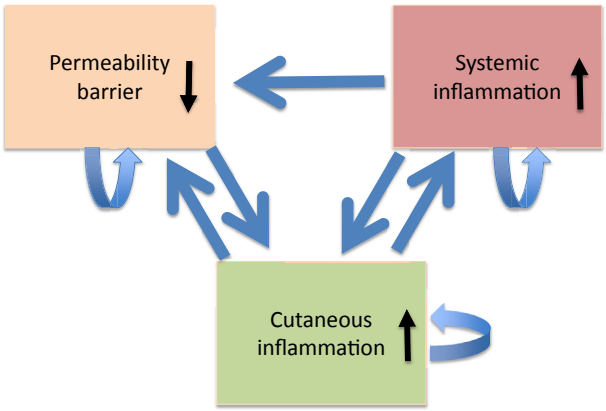

Figure 1 Crosstalk between permeability barrier abnormality, cutaneous, and systemic inflammation for development of inflammatory skin diseases. Arrows indicate soluble mediators including growth factors, cytokines, and chemokines.

Psoriasis and permeability barrier

SPT-KO (knockout) mice as a model of psoriasis

It has been known that psoriatic epidermis showed decreased ceramide levels compared to normal epidermis by immunostaining (Figure 2A). Correspondingly, the water holding capacity and barrier function of the epidermis were impaired in psoriatic lesions compared to the uninvolved skin of psoriatic patients and control healthy skin (Figure 2B). Since a previous study demonstrated that SPT is decreased in psoriatic lesions,[22] the decrease in ceramides may be, at least in part, due to an SPT insufficiency in the epidermis.

To explore the role for SPT in the epidermis, we generated keratinocyte-specific SPT-deficient mice (SPT-cKO mice) using the Cre/Lox system under the keratin 5 promoter.[23] They were born in accordance with the Mendelian law, but their skin was heavily xerotic, with a marked decrease of water holding capacity in the cornified layer (Figure 3). Immunostaining and image mass spectrometric analyses revealed a deficiency of epidermal ceramides in SPT-cKO mice. Although a barrier defect was not observed in newborn SPT-cKO mice, barrier recovery following tape stripping was heavily delayed compared with wild-type mice, indicating that recovery of acute barrier defects depended on the *de novo* ceramide synthesis, which requires SPT enzymatic activity. As they reached 2 weeks of age, they developed a barrier defect and psoriasis-like skin inflammation in the clinical appearance and pathology at the same time (Figure 4). Their skin inflammation involved activation of the interleukin-23 (IL-23)/IL-17 pathway, and exhibited an increased number of γδ-T cells that produced IL-17, so called γδ-17 cells, in the lesional skins and draining lymph nodes. Diseased epidermis exhibited psoriasis-like changes, acanthosis, hyperkeratosis, parakeratosis, neutrophilic microabscesses, and upregulation of various molecules, including keratin 6, S100A8/9, and β-defensins, The skin lesions were attenuated by systemic administration of anti-IL-23p40 antibody. Collectively, SPT deficiency resulted in barrier disruption, leading to the generation of psoriasis-like lesions, which recapitulated human psoriasis regarding clinical appearance and histopathology, as well as expressions of psoriasis-associated molecules.

K5.signal transducer and activator of transcription 3 C transgenic mouse and barrier function

Signal transducer and activator of transcription 3 (Stat3) is a cytoplasmic protein, and Stat3 dimer translocates in the nucleus upon activation through phosphorylation at a tyrosine residue, so that it activates gene expression of downstream molecules, including cyclin D1, c-myc, bcl-x families of antiapoptosis, vascular endothelial growth factor, and many others. Thus, Stat3 plays critical roles in cell proliferation, cell survival, and angiogenesis of a variety of cells as well as including cancer cells.[24] Since psoriatic epidermis showed Stat3 activation, we generated keratinocyte-specific Stat3C transgenic mice, termed K5.Stat3C mice, in which the epidermis exhibited activation-prone Stat3.[25] K5.Stat3C mice spontaneously developed psoriasis-like skin lesions in the tails and limbs, where mechanical stress was frequently given. Stat3C mice also developed psoriasis-like lesions following wounding stimuli, tape stripping or topical treatment with phorbol ester, TPA (12-Otetradecanoylphorbol-13-acetate). The skin lesions well mimicked human psoriasis not only in clinical appearance and histopathology,

Table 1 Representative psoriasis susceptibility genes and their functions.

Susceptibility genes	Expected roles
HLA-Cw6 (*MHC region*; *PSORS1*)*ERAP1*	Antigen presenting cells, CD8 cells, NK cells
IL12B, *IL23R*, *IL23A*	Th1,Th17 pathway
TNFAIP3, *TNIP1*	NF-κB signals
LCE3C, *LCE3B(LCE gene cluster)*, *CDN*	Epidermal barrier function
DEFB4	Antimicrobial defence

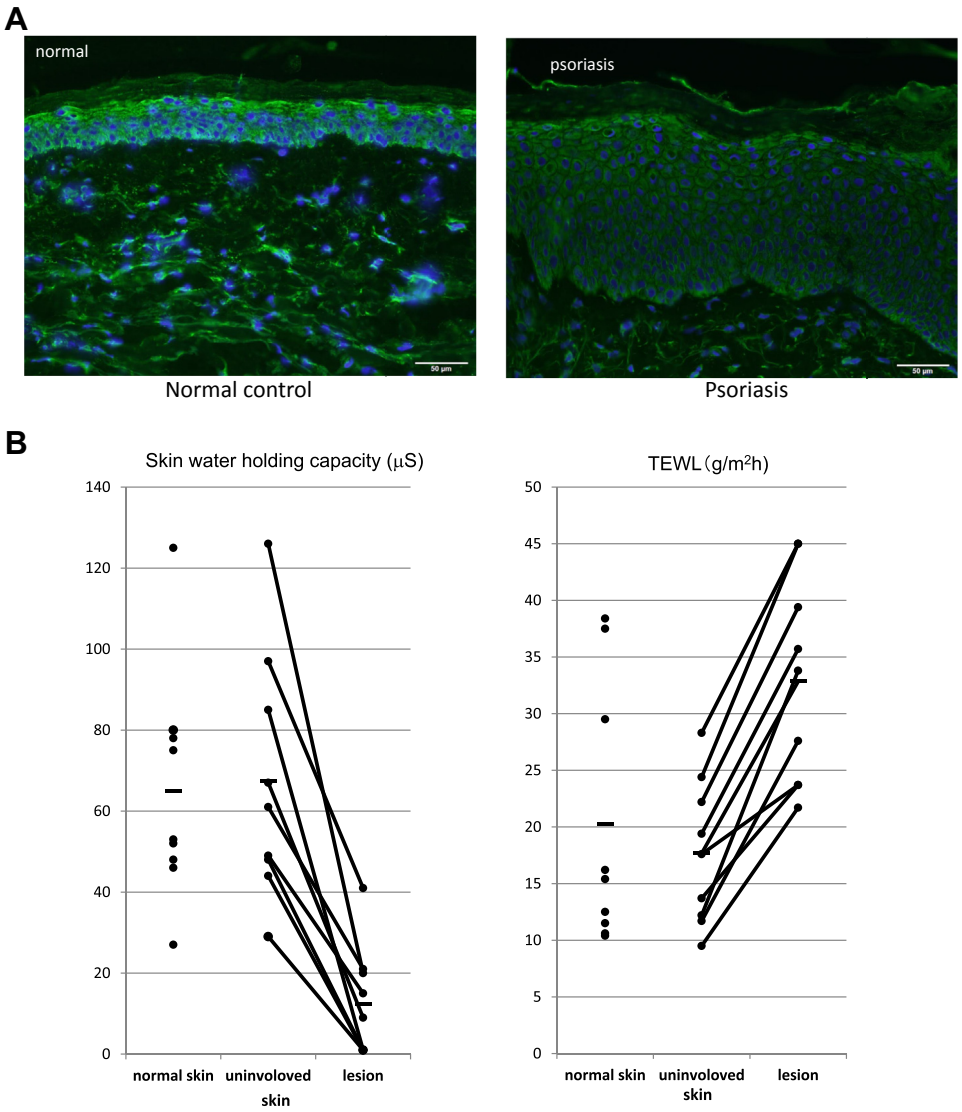

Figure 2 (A) Deficiency of epidermal ceramides in psoriasis. Staining of normal healthy control skin and psoriatic lesions with anticeramide antibody. (B) Abnormalities of water holding capacity and barrier function in psoriatic lesions. Comparison of skin water holding capacity (μS) and transepidermal water loss (TEWL, g/m^{2}h) between normal healthy skin, uninvolved, and lesional skin from psoriasis patients. *Note*. From "Contrasting pathogenesis of atopic dermatitis and psoriasis—part I: clinical and pathologic concepts," by K. Nakajima, M. Terao, M. Takaishi, S. Kataoka, N. Goto-Inoue, M. Setou, K. Horie, F. Sakamoto, M. Ito, H. Azukizawa, S. Kitaba, H. Murota, S. Itami, I. Katayama, J. Takeda, S. Sano, 2013, *J Invest Dermatol*, 133, p. 2555–65. Copyright 2013. *Society of Investigative Dermatology*. Adapted with permission

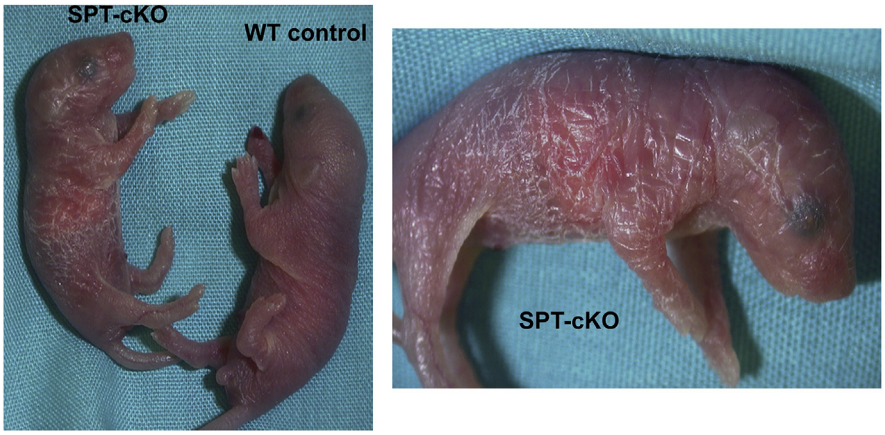

Figure 3 Gross appearance of newborn serine palmitoyl transferase (SPT)-cKO mouse. *Note*. From "Contrasting pathogenesis of atopic dermatitis and psoriasis—part I: clinical and pathologic concepts," by K. Nakajima, M. Terao, M. Takaishi, S. Kataoka, N. Goto-Inoue, M. Setou, K. Horie, F. Sakamoto, M. Ito, H. Azukizawa, S. Kitaba, H. Murota, S. Itami, I. Katayama, J. Takeda, S. Sano, 2013, *J Invest Dermatol*, 133, p. 2555–65. Copyright 2013. *Society of Investigative Dermatology*. Adapted with permission.

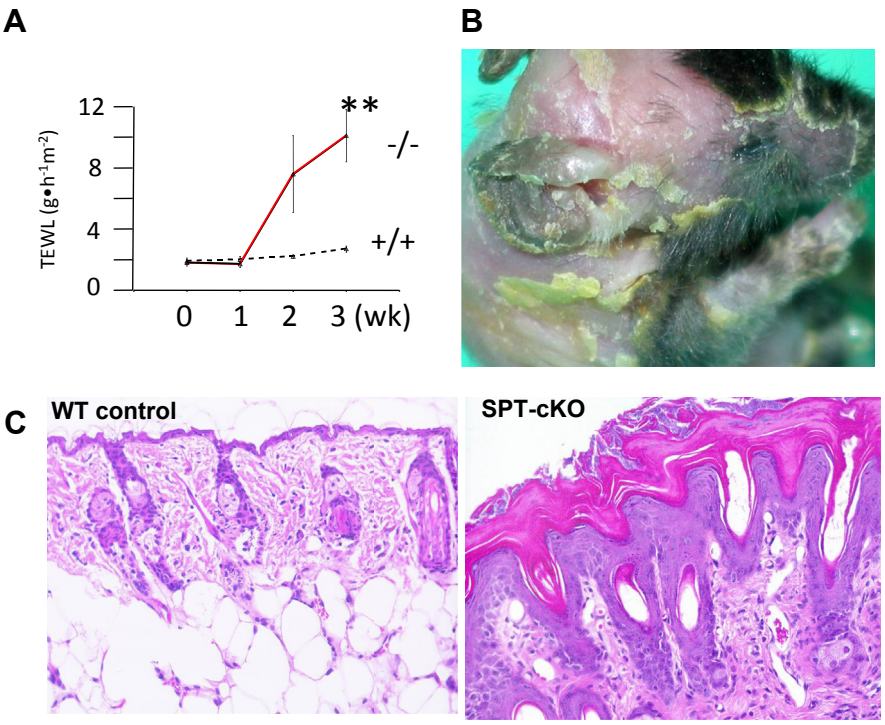

Figure 4 Barrier defect and simultaneous skin disease in serine palmitoyl transferase (SPT)-cKO mice. (A) Transepidermal water loss (TEWL) over time. (B) Scaly erythematous lesion over entire body in SPT-cKO at 21 days of age. (C) Hematoxylin and eosin staining. *Note*. From "Contrasting pathogenesis of atopic dermatitis and psoriasis—part I: clinical and pathologic concepts," by K. Nakajima, M. Terao, M. Takaishi, S. Kataoka, N. Goto-Inoue, M. Setou, K. Horie, F. Sakamoto, M. Ito, H. Azukizawa, S. Kitaba, H. Murota, S. Itami, I. Katayama, J. Takeda, S. Sano, 2013, *J Invest Dermatol*, 133, p. 2555–65. Copyright 2013. *Society of Investigative Dermatology*. Adapted with permission.

but also in gene profiles[26] and sensitivity to biologic agents used in psoriasis patients, such as anti-IL-17, anti-IL-12/IL-23p40, and anti-IL-23p19 antibodies.[27]

Knowing that psoriasis patients tend to have new lesions after wounding or mechanical stress, so called Koebner phenomenon, K5.Stat3C mice harbored a similar epidermal condition, where the barrier perturbation led to psoriasiform inflammation. We observed that, like SPT-cKO mice, K5.Stat3C showed delayed barrier recovery after tape stripping compared with wild-type mice (Figure 5). Meanwhile, they developed a psoriasis-like phenotype, whereas no such change occurred in nontransgenic control mice

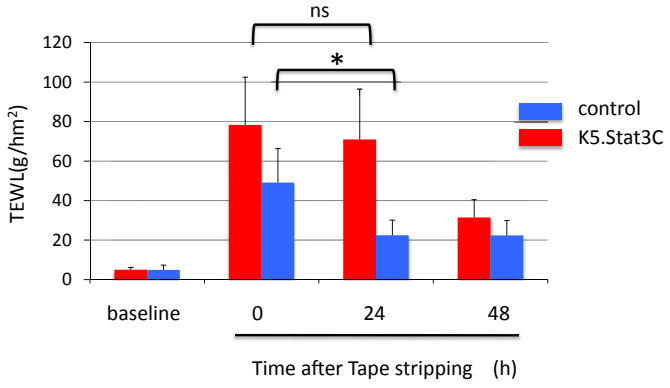

Figure 5 Delayed barrier recovery following tape stripping in K5.Stat3C mice. Blue and red bars indicate control wild-type and K5.Stat3C mice, respectively. *Note*. From "Contrasting pathogenesis of atopic dermatitis and psoriasis—part I: clinical and pathologic concepts," by K. Nakajima, M. Terao, M. Takaishi, S. Kataoka, N. Goto-Inoue, M. Setou, K. Horie, F. Sakamoto, M. Ito, H. Azukizawa, S. Kitaba, H. Murota, S. Itami, I. Katayama, J. Takeda, S. Sano, 2013, *J Invest Dermatol*, 133, p. 2555–65. Copyright 2013. *Society of Investigative Dermatology*. Adapted with permission

(Figure 6). This strongly suggests that keratinocyte Stat3 activation provides susceptibility to barrier defects, which results in psoriasis-like changes, including epidermal hyperplasia, neutrophilic accumulation in the epidermis, and dermal cell infiltrates. It is intriguing that the *Stat3* gene was recently found to be one of the psoriasis susceptibility genes.[28]

Conclusion

The skin is positioned at the interface of internal milieu and the external environment, and is equipped with physical, chemical, and immunological barriers against pathogen invasion. Perturbation in SC intercellular lipids following UV irradiation or physical injury to the skin promptly initiates the *de novo* synthesis of them, and DNA synthesis of epidermal keratinocytes, to restore the breached skin barrier and reestablish homeostasis as soon as possible.[3–8] Antimicrobial peptides (AMPs) are also barrier components of the innate immunity defense during infection and injury. AMPs can recruit leukocytes to skin and stimulate them to release cytokines and chemokines. Psoriatic lesions are abundant in AMPs, including LL37, hBD-2, hBD-3, and S100A7/8/9.[29] By contrast, AMPs are all downregulated in AD, being susceptible to infection.[30] Although these two diseases share some features of epidermal abnormality, such as barrier defects, the difference of immunological polarity may stem from the innate immunity associated with AMPs in the epidermis. In conclusion, we hypothesize that psoriasis develops through the excessive response to a barrier defect that finally leads to Th17-skewed adaptive immunity (Figure 7). This involves: (1) barrier insults by trauma, infection, and others; (2) abnormal response of barrier recovery, which may be due to intercellular lipids deficiency, LCE gene defects, or abnormality in the intracellular signaling such as Stat3 activation; (3) resulting excessive AMPs, and abnormalities of epidermal differentiation and

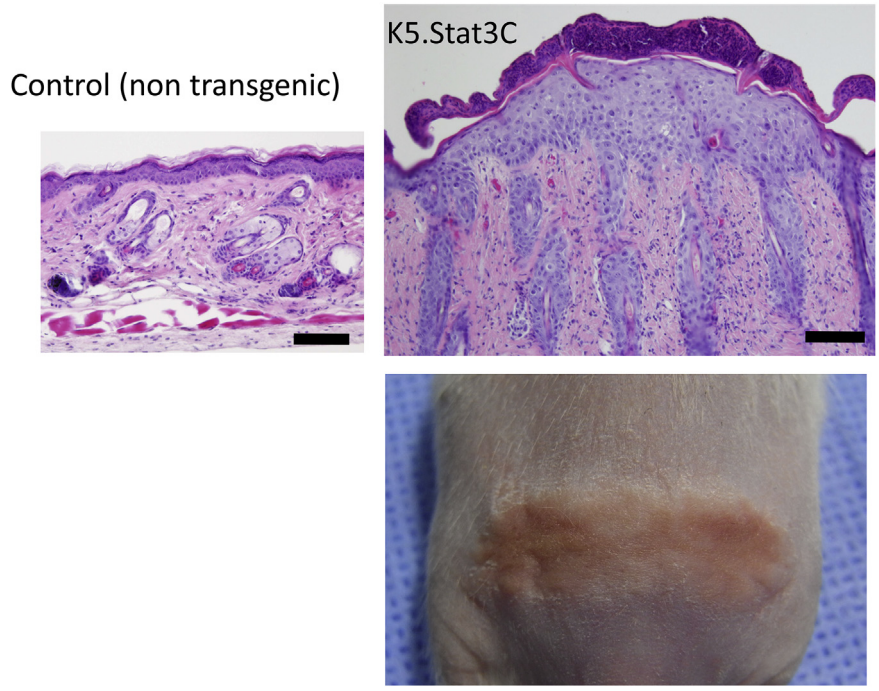

Figure 6 Development of psoriasis-like lesions in K5.Stat3C mice. Three days after tape stripping. Upper panels, hematoxylin and eosin H&E staining. Scale bars = 100 μm. Bottom panel, elevated erythematous lesion in the back of K5.Stat3C mouse. *Note*. From "Contrasting pathogenesis of atopic dermatitis and psoriasis–part I: clinical and pathologic concepts," by E. Guttman-Yassky, K.E. Nograles, J.G. Krueger, 2011, *J Allergy Clin Immunol*, *127*, p. 1110–8. Copyright 2011. *American Academy of Allergy, Asthma & Immunology*. Adapted with permission.

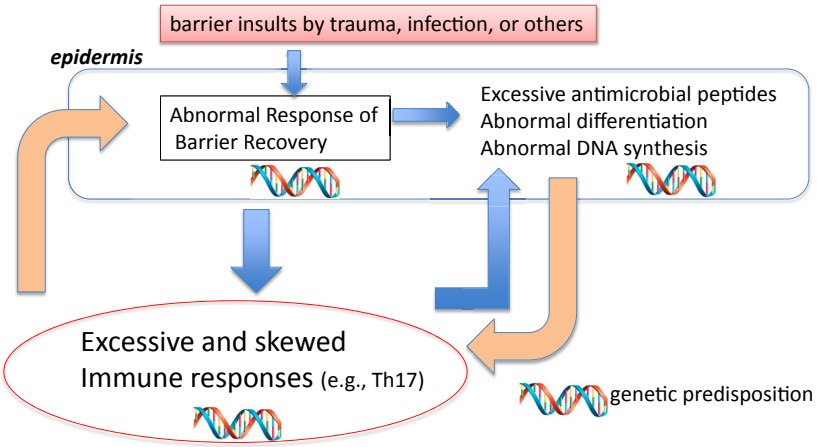

Figure 7 Summary illustrating the vicious cycle of barrier defect, innate immunity, and adaptive immunity for psoriasis development.

proliferation; and (4) all of which may lead to excessive, uncontrolled immune deviation toward Th17, for example. Thus, psoriasis pathogenesis represents a complicated vicious cycle composed of a barrier defect, innate immune activation, and skewed adaptive immunity, each step of which may be associated with genetic predisposition.

Acknowledgments

This work was in part supported by Grants-in-Aids for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (21591436, 21591467, 21591656), by a fund subsidy of "Research on Measures for Intractable Diseases" from Ministry of Health, Labour, and Welfare of Japan (H23-028), and by grants from Center of Biomembrane Functions Controlling Biological Systems of the Kochi University Research Center Project.

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