Pfizer. Dr Reeder and Ms Mahan state no conflict of interest.

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Abnormal Epidermal Barrier Recovery in Uninvolved Skin Supports the Notion of an Epidermal Pathogenesis of Psoriasis

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TO THE EDITOR

Psoriasis is generally considered to be an immunologically initiated disorder, which shares certain common susceptibility loci with autoimmune diseases (Zhang, 2012). Yet, both clinical experience (Gottlieb *et al.*,1990; Griffiths *et al.*, 1995; Volden *et al.*, 2001) and recent molecular studies (Mischke *et al.*, 1996; Kim *et al.*, 2011; Vermeij *et al.*, 2011; Bergboer *et al.*, 2012) support an emerging concept that psoriasis could be ''driven'' by a primary defect in epidermal permeability barrier function. Clinicians know well that psoriasis predictably flares during winter months (Park and Youn, 1998; Kwon *et al.*, 2012) when the barrier is under additional stress owing to low stratum corneum (SC) hydration, which accelerates transepidermal water loss (TEWL) rates (Lin, 2009; Muizzuddin *et al.*, 2013). They also appreciate that sites vulnerable to epidermal trauma, such as the extensors of the extremities and the scalp, are preferentially involved in psoriasis. The Koebner phenomenon offers an additional, eloquent example of how psoriasis can be provoked by external perturbations. Finally, improvement of epidermal permeability barrier function by occlusion alone often alleviates psoriasis (e.g., Friedman, 1987).

Among psoriasis susceptibility genes, PSORS4 is located on chromosome 1q21, within the epidermal differentiation complex, which encodes numerous proteins required for epidermal differentiation and formation of the cornified envelope (Mischke *et al.*, 1996), a structure that is critical for the permeability barrier (Vermeij *et al.*, 2011). In addition, deletion of differentiation-related proteins, such as keratin1, whose levels are reduced in psoriasis (Thewes *et al.*, 1991; Bata-Csörgö and Szell, 2012), not only compromises the permeability barrier but also leads to upregulation of inflammatory genes and altered cytokine production in a pattern that resembles psoriasis (Roth *et al.*, 2012). Finally, in experimental models, disruption of the epidermal permeability barrier in otherwise normal skin stimulates epidermal hyperproliferation (Proksch *et al.*, 1991; Man *et al.*, 2008), cytokine production (Denda *et al.*, 1996; Wood *et al.*, 1996), downstream inflammatory cell infiltration (Proksch *et al.*, 1996; Lin *et al.*, 2013), and epidermal vascular endothelial growth factor production, leading to dermal capillary proliferation (Elias *et al.*, 2008), all of which are prominent features of psoriasis.

Although prior studies have demonstrated phenotype-dependent abnormalities in basal permeability barrier function in psoriatic lesions (Ghadially *et al.*, 1996), the uninvolved skin in psoriasis reportedly displays normal TEWL levels (Takahashi *et al.*, 2014). Yet, expression levels of filaggrin, a protein of known importance for the barrier (Scharschmidt *et al.*, 2009; Irvine *et al.*, 2011), and loricrin are reportedly lower than normal in uninvolved skin sites of psoriasis (Kim *et al.*, 2011). Because alterations in the epidermal differentiation should predict an abnormality in barrier function, we hypothesized that if abnormal epidermal function has a role in the pathogenesis of psoriasis then epidermal function should be abnormal in uninvolved psoriatic skin. Hence, we assessed changes in epidermal function in the uninvolved and involved skin of a large cohort of Chinese patients, with either stable or progressive psoriasis.

In all, 44 patients with psoriasis vulgaris and 68 normal controls were enrolled in the study (Table 1). All participants were provided written informed consent. This study was carried out according to the Helsinki Declaration Principles and the protocol approved by the Human Research Subcommittee, Dalian Skin Disease Hospital. Stable psoriasis was defined as no recent development of new lesions, as well as no recent expansion of pre-existing lesions, whereas progressive psoriasis was defined as recent or ongoing development of new lesions and prominent inflammation, often accompanied by

Abbreviations: SC, stratum corneum; TEWL, transepidermal water loss

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Table 1. Characteristics of subjects

Stage	Gender	*n*	Mean age ± SEM (years)
Psoriasis			
Stable	Male	15	33.07 ± 2.63
	Female	10	38.60 ± 2.72
Progressive	Male	10	36.20 ± 2.80
	Female	9	36.33 ± 2.44
Control			
Normal	Male	34	39.15 ± 0.96
	Female	34	38.47 ± 1.36
Total		112	

pruritus. None of the psoriatic patients had other skin or systemic disorders, and controls had no history of psoriasis, other skin disorders, or systemic conditions that could affect SC biophysical properties. No topical medications were used by patients for ⩾1 week prior to study; no skin care products were applied to measured sites for ⩾24 hours prior to measurements; and measured sites were not washed with either soaps or surfactants for ⩾2 hours prior to study.

Epidermal functions were evaluated in psoriatic lesions on the extensor forearms and contralateral, uninvolved skin sites, and comparable sites in normal controls. TEWL and SC hydration were assessed using probes (TM300 for TEWL and CM825 for hydration, respectively) connected to a MPA5 (C&K, Cologne, Germany). A pH900 pH meter with a flat surface electrode (C&K) was used to measure skin surface pH. For assessment of barrier recovery kinetics, TEWL was measured both immediately (0 hours) and at 3 hours after six sequential D-Squame applications, and percent barrier recovery was then calculated. All subjects rested at 20–24 °C, at a relative humidity of 50–55%, for at least 30 minutes before measurements were taken. As psoriasis often flares during late autumn and winter through early spring, all studies were performed during February and March 2012 and during October 2013, representing early spring and autumn seasons in northern China.

Consistent with prior findings (Ghadially *et al.*, 1996), our results showed that both stable and progressive psoriatic lesions displayed significantly higher basal levels of TEWL than the uninvolved skin and the skin sites of normal control subjects (Figure 1a). Barrier recovery was also delayed in the involved skin of both progressive and stable psoriasis (Figure 1b). Although basal TEWL readings in uninvolved sites of both stable and progressive disease were comparable to those in normal skin, barrier recovery kinetics were significantly delayed in the uninvolved skin sites of patients with progressive psoriasis (Figure 1b).

Previous studies have demonstrated that elevations in SC pH influence permeability barrier homeostasis (Mauro *et al.*, 1998; Hachem *et al.*, 2005), and, conversely, that barrier disruption increases SC pH (Man *et al.*, 2009). Hence, we next measured changes in surface pH in normal and psoriatic patients. As seen in Figure 1c, the surface pH of both involved and uninvolved skin sites in progressive psoriasis patients was significantly higher than that in normal controls ($P<0.001$); an apparent elevation in SC pH was also observed in stable psoriatic lesions, although the results did not achieve statistical significance. In contrast, the uninvolved skin of stable psoriasis displayed normal surface pH (Figure 1c).

Because SC hydration is a critical regulator of epidermal proliferation and cutaneous inflammation (Denda *et al.*, 1998; Denda, 2000), we next assessed SC hydration in involved and uninvolved psoriatic skin sites. SC hydration markedly declined in involved skin of both progressive and stable psoriasis, but hydration levels were normal in uninvolved skin sites of both psoriatic cohorts (Figure 1d).

Recently, the central role of epidermal permeability barrier abnormalities in the pathogenesis of inflammatory dermatoses has attracted increased attention. Previous studies have shown that a sustained defect in permeability barrier function predisposes skin to the development of epidermal hyperplasia and inflammation, resulting in part from the stimulation of a cytokine cascade that recruits a downstream inflammatory cell infiltration (Proksch *et al.*, 1996; Elias *et al.*, 1999; Elias and Wakefield, 2011). Because not only the involved but also the uninvolved skin sites of patients with progressive disease display altered epidermal function, the results presented here are consistent with an emerging concept that an underlying abnormality in epidermal function initiates, triggers, or exacerbates psoriasis, together supporting an ''outside-to-inside'' concept of psoriasis pathogenesis (Elias *et al.*, 1999). The fact that stable uninvolved psoriatic skin sites do not display a demonstrable defect in epidermal function can be explained by the reestablishment of a steady state, in which epidermal function has largely been normalized, coupled with reduced exposure to external stressors that otherwise place additional stress on the barrier. Nonetheless, it should be noted that the uninvolved skin of psoriasis could still display subtle abnormalities that are not detectable by the biophysical technique utilized here. For example, we have shown accelerated movement of the water-soluble, electron-dense tracer, lanthanum nitrate, in some situations where TEWL levels otherwise appeared normal (e.g., Scharschmidt *et al.*, 2009).

A defective permeability barrier not only stimulates epidermal proliferation (Proksch *et al.*, 1991) but also increases pro-inflammatory cytokine expression, as well as increasing Langerhans cell and mast cell infiltration (Nickoloff and Naidu 1994; Proksch *et al.*, 1996; Wood *et al.*, 1992, 1996; Lin *et al.*, 2013). Moreover, the abnormalities in surface pH in the uninvolved skin of progressive psoriasis could further predispose to disease expression in psoriasis as follows (Supplementary Figure S1

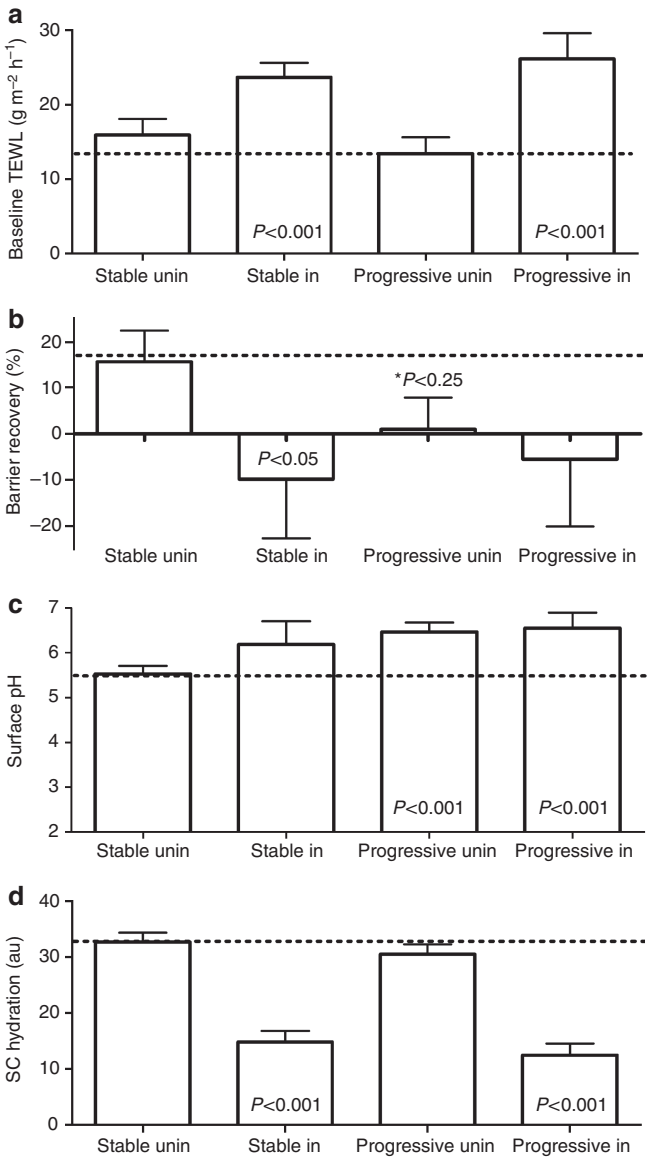

Figure 1. Comparison of stratum corneum (SC) biophysical properties among normal, involved, and uninvolved psoriatic skin sites. (**a**, **b**) Depict basal TEWL and barrier recovery rates, respectively. (**c**, **d**) Present skin surface pH and SC hydration, respectively. Results are expressed as mean ± SEM in comparison with normal skin, as shown by the horizontal dotted lines. GraphPad Prism 4 software (GraphPad Software, La Jolla, CA) was used for all statistical analysis. Dunnett's multiple-comparison test was used to determine the difference between normal and psoriasis-involved and -uninvolved skin, except in Figure 1b in which the differences between normal and progressive uninvolved skin were determined with the unpaired *t*-test. $P<0.05$ was considered to be a statistically significant difference. Significant differences are shown in the figures, and the numbers of subjects are detailed in Table 1. Progressive in, progressive involved; Progressive unin, progressive uninvolved; Stable in, stable involved; Stable unin, stable uninvolved; TEWL, transepidermal water loss.

online): an elevation in pH inevitably activates serine proteases (kallikreins) in the outer epidermis that in turn degrade lipid processing enzymes, leading to abnormal permeability barrier homeostasis (Hachem *et al.*, 2005), and catalyze pro-IL-1 beta to active IL-1 beta (Nylander-Lundqvist and Egelrud, 1997), initiating the cytokine cascade. Finally, reduced SC hydration, which often parallels abnormalities in barrier function, alone places further stress on the barrier as evidenced by the development of epidermal proliferation and the initiation of cutaneous inflammation in experimental animals exposed to low ambient humidity (Denda, 2000; Ashida *et al.*, 2001; Ashida and Denda, 2003). Coupling the present with prior findings, we hypothesize that psoriasis is characterized by a failure to complete barrier repair owing to primary abnormalities in epidermal structural proteins, analogous to atopic dermatitis, and is further aggravated by exogenous stress to barrier (Supplementary Figure S1 online). Our findings further suggest that approaches that normalize barrier function could prove valuable for the prevention and/or treatment of psoriasis.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/jid

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miR-330-5p Targets Tyrosinase and Induces Depigmentation

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TO THE EDITOR

There is increasing evidence that microRNAs (miRNAs), small noncoding RNAs, are involved in regulating melanogenesis. Various proteins, including TYR, DCT, MELANA, and TYRP1, whose mRNAs are potentially targeted by miRNAs orchestrate this process. miRNAs regulate gene expression: in general, they inhibit protein synthesis either by repressing translation or by destabilizing/degrading mRNAs by imperfect base pairing to the ''seed match'' region in the 5′UTR, CDS, or 3′UTR of the mRNA

Abbreviations: MITF, microphthalmia-associated transcription factor; mRNA, microRNA; NHEM, normal human epidermal melanocyte

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