



Published in final edited form as:

J Invest Dermatol. 2014 November ; 134(11): 2843–2846. doi:10.1038/jid.2014.205.

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

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Keywords

Psoriasis; Stratum Corneum; Permeability Barrier; Hydration; pH; Transepidermal Water Loss

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 (Bergboer et al., 2012; Kim et al., 2011; Mischke et al., 1996; Vermeij et al., 2011) 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 due to low stratum corneum 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 the formation of the cornified envelope (Mischke et al., 1996), a structure that is critical for the permeability barrier (Vermeij et al., 2011). Additionally, 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

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All authors declare no conflicts of interest

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 (Man et al., 2008; Prokch et al., 1991), cytokine production (Denda et al., 1996; Wood et al., 1996), downstream inflammatory cell infiltration (Lin et al., 2013; Proksch et al., 1996), 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 reportedly are 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 plays 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.

44 patients with psoriasis vulgaris and 64 normal controls were enrolled (Table 1). All participants were given written informed consent. This study was carried out according to the Helsinki Declaration Principles and to 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, while progressive psoriasis was defined as recent or ongoing development of new lesions and prominent inflammation, often accompanied by 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 stratum corneum (SC) biophysical properties. No topical medications were used by patients for one week prior to study; no skin care products were applied to measured sites for 24 hour 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. Transepidermal water loss (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, Cologne, Germany) was used to measure skin surface pH. For assessment of barrier recovery kinetics, TEWL was measured both immediately after (0 hours) and 3 hours after 6 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 min before measurements were taken. Since 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 skin sites of normal control subjects (Fig. 1a). Barrier recovery was also delayed in the involved skin of both progressive and stable psoriasis (Fig. 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 (Fig. 1b).

Previous studies have demonstrated that elevations in SC pH influence permeability barrier homeostasis (Hachem et al., 2005; Mauro et al., 1998); 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 was significantly higher than in normal controls ($p < 0.001$), and an apparent elevation in SC pH was also observed in stable psoriatic lesions, though the results did not achieve statistical significance. In contrast, the uninvolved skin of stable psoriasis displayed a 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 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 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 does not display demonstrable defect in epidermal function, can be explained by the reestablishment of a steady-state, where 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., Scharshmidt et al., 2009).

A defective permeability barrier not only stimulates epidermal proliferation (Proksch et al., 1991), but it 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 (Supplemental Figure 1): An elevation in pH inevitably activates serine proteases (kallikreins) in the outer epidermis, which 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 E and Egelrud T, 1997), initiating the cytokine cascade. Finally, reduced SC hydration, which often parallels abnormalities in barrier function, alone places further stress on the barrier, 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 due to primary abnormalities in epidermal structural proteins, analogous to atopic dermatitis, and further aggravated by exogenous stress to barrier (Supplemental Figure 1). Our findings further suggest that approaches that normalize barrier function could prove valuable for the prevention and/or treatment of psoriasis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported in part by National Institutes of Health grants AR 19098 and the Medical Research Service, Department of Veterans Affairs Medical Center.

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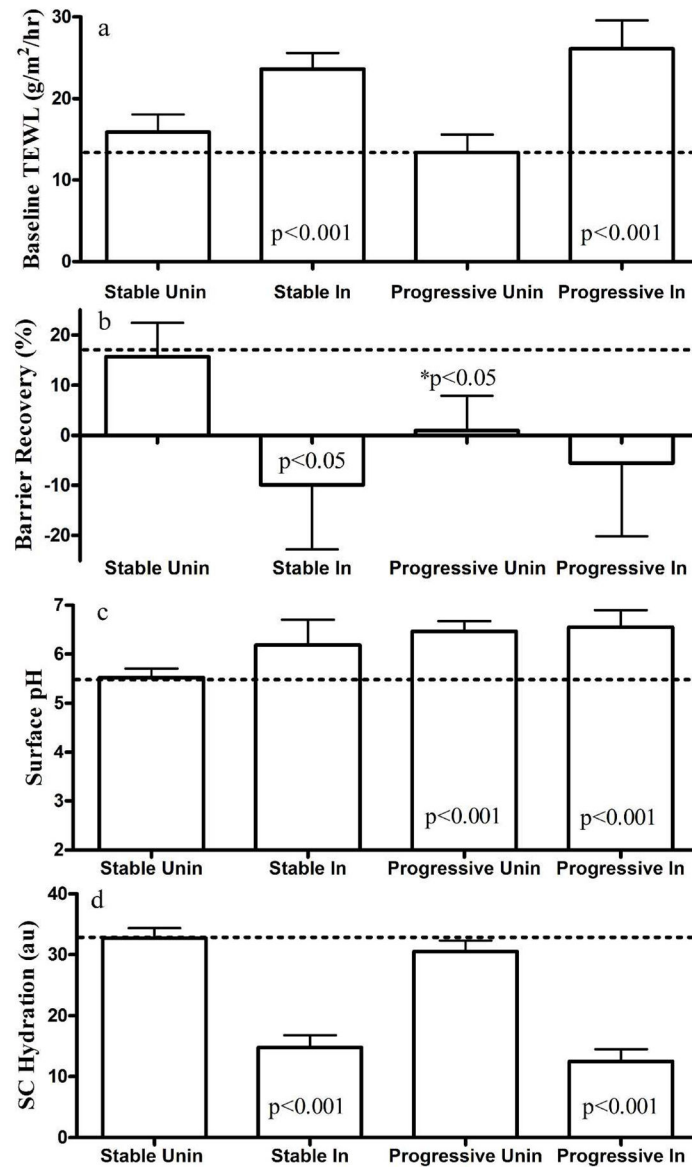


Figure 1. Comparison of SC Biophysical Properties among Normal, Involved and Uninvolved Psoriatic Skin Sites

a & b depicts basal TEWL and barrier recovery rates, respectively. c & d presents skin surface pH and SC hydration, respectively. Results are expressed as mean \pm SEM in comparison with normal skin, as shown by the horizontal dotted lines. GraphPad Prism 4 software (GraphPad Software, Inc., La Jolla, CA, USA) 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 where the differences between normal and progressive uninvolved skin were determined with unpaired T test. $P < 0.05$ was considered to a statistically significant difference. Significant differences are shown in the figures and numbers of subjects are detailed in Table 1.

Table 1

Characteristics of Subjects

Stage	Gender	N	Mean Age \pm SEM (year)
<u>Psoriasis</u>			
Stable	Male	15	33.07 \pm 2.63
	Female	10	38.60 \pm 2.72
Progressive	Male	10	36.20 \pm 2.80
	Female	9	36.33 \pm 2.44
<u>Control</u>			
Normal	Male	34	39.15 \pm 0.96
	Female	34	38.47 \pm 1.36
<u>Total</u>		112	

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