stronger effects will be exerted in formulations containing a combination of NAG with other depigmenting agents. Those well-tolerated combinations, which also provide some hydration and anti-wrinkling effects, have an advantage for their wide potential of applicability.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jdermsci.2011.06.002.

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Letter to the Editor

Staphylococcus aureus in relation to physical, physiological and subjective conditions of apparently normal human skin

To the Editor,

Staphylococci are facultative anaerobic, Gram-positive bacteria that cause infections in humans and various animal species [1]. *Staphylococcus aureus* is an opportunistic pathogen responsible for a broad range of infections in human such as food poisoning and pneumonia [2]. It is frequently found on human skin and known as a commensal organism [3]. It secretes several toxins and enzymes which are associated with a variety of cutaneous and systemic diseases such as atopic dermatitis (AD), impetigo, furuncle, subcutaneous abscess, staphylococcal scalded skin syndrome and toxic shock syndrome [4]. It can colonize the tissues when protective systems are breached, such as in AD patients having low immunity and an impaired skin barrier. Under such conditions, a vicious circle may ensue: *S. aureus* colonize the lesions [5] and secret toxins and/or enzymes that induce itching and disrupt the skin barrier. Attempts have been made for controlling the balance of skin microflora to improve AD [5]. Considering *S. aureus* influences AD lesions, we assume that *S. aureus* can also influence normal skin. However, unlike diverse reports on the pathogenic effects of *S. aureus* in skin diseases, there are no reports on its impact on normal healthy skin. In this study, we investigated correlations between *S. aureus* presence on apparently normal skin and cutaneous conditions.

The facial (cheeks and forehead) contents of *S. aureus* were pre-screened in 121 healthy volunteers aged between 24 and 50 years (age 34.2 ± 5.2, 102 males and 19 females) using a modified contact agar method [6] employing square (3.3 cm × 3.3 cm) Easystamp® *Staph* agar plate (Hanil Komed, Seoul, Korea). These plates were contacted directly with the test regions (cheeks and forehead) and incubated at 32 °C for 48 h. After detection of suspected colonies, confirmation for *S. aureus* was made by Vitek identification system (BioMerieux, Marcy l'Etoile, France).

Based on the pre-screening results (the number of colonies as well as whether *S. aureus* is detected or not), the age distribution, and willingness of volunteers for further evaluation of physical conditions of skin and considering the number of volunteers in each group, we selected 33 subjects, aged between 26 and 50 years, and divided into group-S (*S. aureus*–positive, 15 subjects aged 36.7 ± 5.2, 12 males) and group-C (*S. aureus*–negative, 18 subjects aged 34.7 ± 5.6, 16 males) for evaluations of total facial aerobes and detailed skin conditions. The total facial aerobes for the panel were tested using same methodology as discussed earlier and

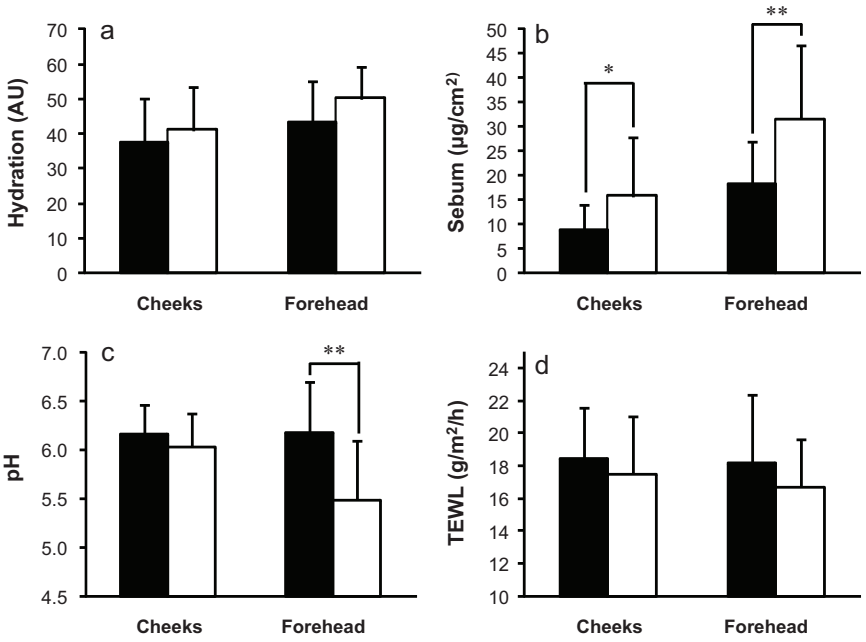

Fig. 1. Instrumental measurements for skin characteristics of group-S (■) and group-C (□). Hydration (a), sebum secretion (b), skin pH (c) and trans-epidermal water loss or TEWL (d) in 33 subjects were measured. Rods and error bars indicate means and standard deviations, respectively. Statistical analysis was conducted using SPSS® 10 for windows computer software (SPSS Science, Chicago, IL, USA). The Student's *t*-test for unpaired data was used to assess differences between values referring to 2 groups. *($p < 0.05$) and **($p < 0.01$) were considered statistically significant. AU: arbitrary units.

no significant differences were observed in total aerobic bacterial counts. Physical conditions of skin, such as hydration, sebum secretion, pH and trans-epidermal water loss (TEWL) were measured using corneometer (CM 820, Courage+Khazaka, Koln, Germany), sebumeter (SM 815, Courage+Khazaka, Koln, Germany), skin pH meter (PH 900, Courage+Khazaka, Koln, Germany) and vapormeter (SWL-2, Delfin, Kuopio, Finland), respectively. The abnormal skin conditions such as scaling and pimples were scored by dermatologist with visual assessments. Before measurements of the physical conditions and visual assessments of skin, subjects were rested for 15 min in an environmentally controlled room (temperature 25 °C, relative humidity 40%) after washing their faces with soap and drying gently with paper towels. Subjective skin conditions of skin type, scaling, roughness and sensitivity were surveyed by questionnaires.

Sebum secretion of group-S was significantly lower than group-C at cheeks ($p < 0.05$) and forehead ($p < 0.01$). Skin pH was significantly ($p < 0.01$) higher in group-S at forehead as compared to group-C. Hydration was lower and TEWL was higher in group-S. The skin conditions of group-S were regarded as relatively dry, damaged and more alkaline than group-C with remarkable differences on foreheads (Fig. 1). The visual assessments demonstrated more scaling and pimples in group-S. Particularly, the prevalence of scaling in group-S was almost double to that of group-C, i.e. 40.0% vs. 22.2% (Fig. 2a). More subjects in group-S revealed that their skins were more dry (40.0% vs. 33.3%), scaling (73.3% vs. 50.0%), rough (53.3% vs. 33.3%) and sensitive (66.7% vs. 44.4%) but less oily (33.3% vs. 61.1%) as compared to group-C (Fig. 2b).

Results of instrumental, visual and subjective assessments showed that the skin conditions of group-S were inferior to that of group-C (Figs. 1 and 2). The skin pH is higher in AD patients [5] and this high skin pH related to various skin disorders including seborrheic dermatitis and psoriasis through, at least in part, the disrupted skin barrier [7]. Therefore, in addition to the higher TEWL, the higher skin pH of group-S implies higher possibility of barrier dysfunction. Our results suggest that *S. aureus* colonization correlates with deterioration of apparently normal healthy skin and damaged skin conditions. However, it remains unclear whether *S. aureus* colonization is the cause or the result of skin deterioration. The significance of staphylococcal protease as an environmental factor that contributes to the primary sensitization

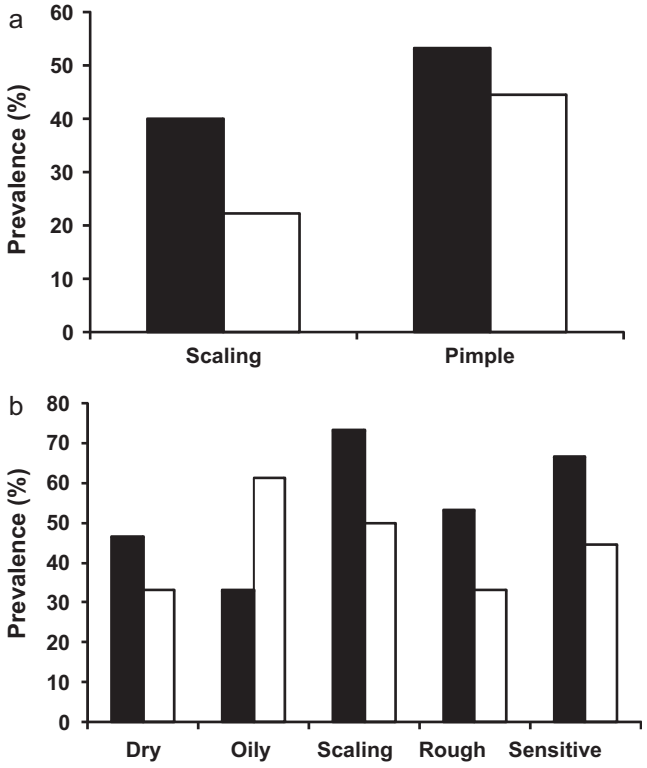

Fig. 2. Visual and subjective evaluations for skin characteristics of group-S (■) and group-C (□). (a) Visual assessments: the prevalence for scaling and pimple of 33 subjects were scored by a clinical scientist. (b) Subjective evaluation by questionnaire: 33 subjects answered questions about their skin type, scaling, roughness, and sensitivity.

for allergen, *S. aureus* colonization, skin barrier dysfunction and AD deterioration is recently reported [8]. The virulence factors produced by *S. aureus* have various biological characteristics to destroy epithelial barrier, inhibit opsonization, interfere neutrophil chemotaxis, inactivate neutrophil cytolysis and antimicrobial peptide [4,9,10]. Although further studies are required to examine this hypothesis, current evidence is sufficient to conclude that *S. aureus* and possibly some other skin microflora are directly related to aggravation of healthy skin conditions. Similar to diseased skin, *S. aureus* and subtle dysfunction of skin barrier in healthy skin can also be caught in a vicious circle, resulting in further breakdown of skin barrier and progress to outright deterioration.

These findings are meaningful as a first study to demonstrate that *S. aureus* is involved in skin deterioration, even in apparently healthy skin.

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Letter to the Editor

LEDGF/DFS70 activates the MK2/IL6/STAT3 pathway in HaCaT

Lens epithelium-derived growth factor (LEDGF), also known as dense fine speckles 70 kDa protein (DFS70), was isolated as a transcription cofactor, a survival factor and a target of autoantibodies in atopic dermatitis [1–3]. LEDGF/DFS70 has been implicated as a key player in cancer [4]. Psoriasis is a common skin disorder that is characterized by abnormal differentiation of the epidermal keratinocytes (KCs), inflammatory cells recruitment and changes in the endothelial vascular system. It has been suggested that psoriatic KCs have abnormal expression of various cytokines and chemokines, and deregulation of several signaling pathways. For example, psoriatic KCs are characterized by activation of the signal transducer and activator of transcription 3 (STAT3) [5]. Activated TNF-α and MAPK-activated protein kinase 2 (MK2) have also been observed in lesional psoriatic epidermis [6].

We recently found that LEDGF/DFS70 localizes to the nuclei of spinous layers as well as the basal layer of psoriatic skin, although LEDGF/DFS70 is restricted to the cytoplasm in cells of normal spinous layers [7,8]. We also generated stable cell lines which constitutively express enhanced green fluorescent protein-tagged LEDGF (EGFP-LEDGF-HaCaT) or EGFP alone (EGFP-HaCaT) as a control, and we demonstrated that LEDGF/DFS70 regulated the IL-6 via p38 phosphorylation and deregulated S100A7, S100A9 and filaggrin. In light of this, it was suggested that LEDGF/DFS70 plays a pivotal role in activating psoriatic KCs. This study aims to clarify how LEDGF/DFS70 contributes to the formation of psoriatic skin lesions.

To determine whether minichromosome maintenance 2 (MCM2) phosphorylation is increased in EGFP-LEDGF-HaCaT, we performed Western blot analyses. As shown in Fig. 1a, MCM2 (Ser53) was more phosphorylated in EGFP-LEDGF-HaCaT than in EGFP-HaCaT, although the levels of total MCM2 and MCM2 phosphorylation (Ser40/41) were the same. LEDGF/DFS70 has been shown to interact with the Cdc7-activator of S-phase kinase (ASK), which is essential for initiation of DNA replication throughout the S-phase, and LEDGF/DFS70 has been demonstrated to stimulate its enzymatic activity, increasing phosphorylation of MCM2 (Ser53) *in vitro* [9]. Our results are compatible with the previous reports and suggest that LEDGF/DFS70 may function as an S-phase regulator in the nuclei of proliferating KCs. To determine whether the Cdc7 is involved in MCM2 phosphorylation (Ser53) in EGFP-LEDGF-HaCaT, small interfering RNA (siRNA) was used to reduce Cdc7 expression (siCdc7) in EGFP-LEDGF-HaCaT, and then the amount of phosphorylated MCM2 (Ser53) was measured. Fig. 1b shows that the phosphorylation level of MCM2 (Ser53) was reduced compared to the controls (siCD4) when the Cdc7 protein level was reduced by siRNA.

We previously reported that EGFP-LEDGF-HaCaT have higher IL-6 expression and higher phosphorylation of STAT3 than EGFP-HaCaT has [7]. The gp130 receptor constitutes an essential signal transducing component of the IL-6 receptor complex, and IL-6-