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Water Mobility in the Stratum Corneum

Mobility of Water Molecules in the Stratum Corneum: Effects of Age and Chronic Exposure to the Environment

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TO THE EDITOR
It is well established that water in the stratum corneum (SC) has a critical role in skin physiology (Rawlings and Matts, 2005). Depending on their mobility, determined by the strength of hydrogen bonds and space limitations, SC water molecules can be grouped into three categories (Bulgin and Vinson, 1967; Walkley, 1972; Takenouchi et al., 1986; Walling and Dabney, 1989; Gilard et al., 1998; Gniadecka et al., 1998; Kasting et al., 2003; Pieper et al., 2003; Visscher et al., 2003; Yadav et al., 2007; Nakagawa et al., 2011; Vyumvuhore et al., 2013): (a) “bound”

hBD-2 in the sebocytes from T-zone enhanced antimicrobial activity against P. acnes and inhibited the expression of proinflammatory cytokines, such as IL-8 and tumor necrosis factor-α.

Our data showed that the T-zone had a low incidence of inflammatory acne lesions compared with U-zone. These data support the previous findings that hBD-2 levels indicate the presence of antiinflammatory lipids, which inhibit inflammation, therefore, only a few clinically inflammatory lesions occur (Georgel et al., 2005; Zouboulis et al., 2010). Previous studies demonstrated that FFAs enhance the innate antibacterial defenses of the skin by inducing the expression of AMP (Lee et al., 2008; Nakatsuji et al., 2010). Our findings also showed that considerable FFAs in the high-sebum-secreting area (T-zone) induce more abundant hBD-2 expression, and enhanced antimicrobial activity against P. acnes and inhibited the expression of proinflammatory cytokines. However, it needs to further evaluation for the expression of other AMP in each area, because other AMP may also have a role in regional difference of inflammatory acne lesions (Lee et al., 2008, 2009). There was a previous study that hBD-2 strikingly killed P. acnes at concentrations higher than 10 mM (Nakatsuji et al., 2010). Although we showed which amount of hBD-2 in sebocytes from T-zones able to influence the growth of P. acnes in vitro, it needs further in vivo study especially in acne lesions. In conclusion, we suggest that increased hBD-2 in the T-zone prevents the progress of comedones to papulopustular lesions via either an upregulation of antiinflammatory sebaceous lipid synthesis and/or an inhibitory activity of P. acnes proliferation. These data suggest a functional link between topographical variation of inflammatory acne lesions and innate immunity in acne pathogenesis. Further studies of the relationship between hBD-2 expression and P. acnes in acne lesion are warranted to gain the confirmation of the effects of hBD-2 on regional difference of inflammatory acne lesions.

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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Abbreviations: NMF, natural moisturization factor; SC, stratum corneum
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Walkley, 1972; Takenouchi et al., 1986; Walling and Dabney, 1989; Gilard et al., 1998; Gniadecka et al., 1998; Kasting et al., 2003; Pieper et al., 2003; Visscher et al., 2003; Yadav et al., 2007; Nakagawa et al., 2011; Vyumvuhore et al., 2013): (a) “bound”
The mobility of water in the SC.

Means of providing some perspective to a continuum of bound states. However, weakly defined, and in reality there are water molecules. These “states” are hydrogen bonds with their surrounding molecules that can diffuse more freely, the binding site; and (c) most mobile, order, forming a “loose cloud” around can be secondary, tertiary, or higher with “bound” water molecules and molecules that form hydrogen bonds directly hydrogen-bonded to SC structural molecules; (b) intermediately mobile, molecules that can form hydrogen bonds with “bound” water molecules and can be secondary, tertiary, or higher order, forming a “loose cloud” around the binding site; and (c) most mobile, molecules that can diffuse more freely, continuously forming and breaking hydrogen bonds with their surrounding water molecules. These “states” are weakly defined, and in reality there is a continuum of bound states. However, it can be useful to use this analysis as means of providing some perspective to the mobility of water in the SC.

Confocal Raman microspectroscopy is the only in vivo method to date that can generate concentration profiles of SC components as a function of distance from the skin surface (Caspers et al., 2001). Water concentration profiles (% mg water/mg protein) can be constructed following a calibration procedure, using the spectral bands 3,350–3,550 cm⁻¹ (OH stretching) and 2,910–2,965 cm⁻¹ (CH stretching). Water content is low at the skin surface, and it gradually increases to a plateau at the junction between the SC and the stratum granulosum. However, the range 3,350–3,550 cm⁻¹ is limited to the spectral contributions of the more mobile water molecules (Vyumvuhore et al., 2013). These authors have defined the band ranges (subbands of the OH stretching mode) that correspond to the three mobility states described above.

The objective of the current study was to examine whether age and chronic environmental exposure affect the relative distribution profiles of these three states in the SC. The production of natural moisturization factors (NMFs) that may influence these distribution profiles and their dependence on age and exposure to the environment are also examined.

The study was conducted according to the principles of the Declaration of Helsinki. Healthy female volunteers participated in the study following written informed consent, and they were divided into two age groups of 10 volunteers each: 20–30 and 50+ years of age. Raman data (Skin Analyzer 3510, River Diagnostics, Rotterdam, The Netherlands) were acquired on three skin sites: face (cheek), relatively exposed arm site (dorsal forearm), and relatively protected arm site (upper inner arm), following 15 min acclimatization in an environmentally controlled room (20°C, 40% relative humidity). The concentration profiles of water and total NMF, as well as the areas under the curve for the spectral bands defined by Vyumvuhore et al. (2013) (Figure 1a), were calculated from the Raman spectra using the Skin Tools software (River Diagnostics). To account for interpersonal differences in the SC thickness, the distance from the SC surface was normalized to the SC thickness measured from the Raman data (Bielfeldt et al., 2009). Data are presented as mean ± 1 SD. For group comparisons, a Student’s t-test was performed following confirmation of normality (Anderson-Darling test), and statistical significance was accepted at the level of α = 0.05.

The water concentration profiles for the three water states show a qualitatively similar pattern with that of total water: a low value close to the skin surface that monotonically increases to a plateau at the base of the SC (Figure 1b). There are minor differences between the two age groups, but distinct differences between body sites: the SC of the face has higher total water content compared with the arm sites.

By normalizing the profiles of the three water states to the total water, we obtain a different pattern that appears to be highly conserved between the two age groups and the three body sites.
tested (Figure 2a–c). Although the normalized profiles of the bound and most mobile water molecules decrease toward the skin surface, that of the intermediate group increases. The changes are subtle (<6% difference) but statistically significant and with low interpersonal variability (<7%). Interestingly, in the viable epidermis, the relative percentage of the three groups appears to be constant, independent of age or body site. The molecular ratios of bound: intermediate: most mobile water are 17:49:34.

Throughout the SC, corneocytes migrate and mature toward the surface (Harding et al., 2003), whereas proteins of the S100 family, including filaggrin, filaggrin-2, and hornerin, are broken down to give rise to an assembly of amino acids and other products, known as NMF (Rawlings, 2010). The sum of the profiles of these molecules is used to calculate the total NMF concentration profile (Figure 2d). The gradual increase of the total NMF concentration toward the SC surface is indicative of the proteolytic processes along the SC-exposing pockets of bound water molecules, increasing their mobility. This may explain the decrease in the relative amount of bound water and the concurrent increase in the amount of intermediately mobile water toward the SC surface. Another possible explanation is that part of the bound water is linked to lipid head-groups (Yadav et al., 2007), and the relative amount of this state is decreased as the lipid content in the outer SC is depleted. SC equilibrated to ambient conditions of 20–40% relative humidity is expected to have lower water content as we move toward the skin surface, and this water is expected to be more tightly bound pointing to the humectant role of the NMF. This could explain the shift from the most mobile water molecules toward the intermediately bound water molecules.

These observations provide important baseline information for the mobility state of water in the SC in healthy skin. This can be of interest in the study of water diffusion through the SC and trans-cutaneous drug delivery. The surprising consistency of the profiles between age groups and body sites implies that there is a tightly controlled mechanism that defines them. Such mechanisms are expected to be affected by the environmental temperature and humidity conditions (Vyumvuhore et al., 2013). Further studies will shed light on whether these patterns are conserved or differ in the case of pathological skin conditions, including barrier-related disorders, such as psoriasis, atopic dermatitis, ichthyosis, senile xerosis, diabetic-related dry skin, and so on.

In conclusion, chronological aging and chronic exposure to environmental factors do not affect the normalized concentration profiles of the three mobility states of water in the SC.
Although the profiles are flat in the viable epidermis, they demonstrate slight changes toward the SC surface. These changes are consistent between the age groups and body sites tested, and they can be explained by the enzymatic proteolysis of filaggrin and similar molecules.

CONFLICT OF INTEREST
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Replication of Associations between GWAS SNPs and Melanoma Risk in the Population Architecture Using Genomics and Epidemiology (PAGE) Study

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TO THE EDITOR

Melanoma is a considerable public health burden, with an estimated 76,690 new diagnoses and 9,480 deaths from melanoma in the United States in 2013 alone (Howlader et al., 2013). Multiplex families have pointed to important genetic factors for melanoma, including high-penetrance risk loci such as CDKN2A or CDK4 (Gruber and Armstrong, 2006). In sporadic disease, genome-wide association studies (GWAS) have also successfully identified at least eight single nucleotide polymorphisms (SNPs) associated with melanoma (Gerstenblith et al., 2010). Our study aimed to replicate these existing GWAS findings within the large Population Architecture using Genomics and Epidemiology (PAGE) study in order to further evaluate their association with melanoma.

In addition to genetic factors, other risk factors for melanoma include exposure to natural and artificial UVR, larger numbers of nevi, pigmentation traits (light versus dark hair, eye, and skin color), race/ethnicity (European versus non-European ancestry), skin response to UV exposure (burn versus tan), older age, and male sex (Gruber and Armstrong, 2006). Anatomic location of melanoma also tends to vary by sex, arising most commonly on the back, abdomen, and chest in males, and on the lower leg, hip, and thigh in females (Gruber and Armstrong, 2006). Females also appear to have lower risk of metastases and longer melanoma-specific survival than males (Joosse et al., 2011).

Abbreviations: EAGLE-BioVU, Epidemiologic Architecture of Genes Linked to Environment, accessing BioVU, the Biorepository of Vanderbilt University; GWAS, genome-wide association study; HGPS, Health Professionals Follow-up Study; MEC, Multiethnic Cohort Study; NHS, Nurses’ Health Study; PAGE, Population Architecture Using Genomics and Epidemiology; SNP, single nucleotide polymorphism; WHI, Women’s Health Initiative

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