Permeability and immune barrier differences of healthy human skin

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INTRODUCTION

The skin exhibits several essential functions, including its role in formation and maintenance of the barrier. The skin has two major barrier elements, i.e., the stratum corneum and the tight junction layer. Besides these, it is also equipped with a complex network of cells and soluble mediators as part of the skin immune system (SIS). The anatomical and histological skin structure is characterized by major differences on distinct regions, due to variable numbers of sebaceous, eccrine, and apocrine glands at different body sites, resulting diverse chemical milieu on the skin surface. The skin microbiota has also been shown to exhibit remarkable differences on topographically distinct skin areas; indeed, specific commensal flora have been associated with moist, dry (sebaceous gland poor-SGP), or sebaceous (sebaceous gland rich-SGR) microenvironments. On the other hand, the immunological and permeability barrier of the healthy skin is considered to be unified on the whole body surface - albeit recent indirect findings have challenged this dogma. In fact, the microbiota was shown to exert remarkable influence on the barrier's immune and barrier function.

HYPOTHESIS

The immunological and permeability barrier of the healthy skin is considered to be unified on the whole body surface - however, recent findings have challenged this dogma since microbial and chemical milieu exhibit remarkable differences on topographically distinct skin areas, moreover we also provided evidence (by comparative transcriptomic and subsequent pathway enrichment analyses validated by qPCR and IHC) that these regions exhibit a characteristic innate and adaptive immune milieu (increased chemokine expression and homeostatic IL-17 dominance in SGR skin)^{1,2}. As an extended continuation of our previous works, we aimed to investigate at the molecular level whether permeability barriers of SGR and SGP regions are also different. For this, we investigated selected molecules of the permeability barrier at the gene and protein levels.

METHODS

In order to explore the in-depth differences of permeability barriers between SGR and SGP skin (8 SGR and 8 SGP skin biopsies), genes were selected for RT-PCR analysis based on literature data. Five groups were formed: the most important antimicrobial peptides (AMPs), important barrier structure molecules, desmosome and tight junction components and enzymes related to barrier formation. Finally, to verify the differential expressions in the two skin regions also at the protein level, certain molecules were subjected to IHC and image analyses.

CONCLUSIONS

Similarly to the prominently different immune tuning of SGP and SGR region^{1,2} we could also detect barrier differences between the distinct skin regions which together may explain the characteristic localization of certain immune mediated skin disorders and distinct skin sites may require distinct barrier repair therapies. We propose that the notable differences in skin immune milieu and the differences in barrier parameters between SGR and SGP regions are connected to the distinctions in the composition of microbiota and skin surface micromilieu between the two regions. Our data call the attention to the proper selection of healthy skin controls in research and also to the development of new barrier restoring strategies that take into consideration the region-specific characteristics of the skin barrier and SIS.

Figure 3. Healthy SGR skin is characterized by a non-inflammatory T helper 17 (Th17/IL-17) milieu. The non-inflammatory Th17/IL-17 milieu of SGR skin is combined with significantly altered expression of chemokines, AMPs and differences in permeability barrier molecules (a,b). From the above molecules CCL2, CCL20, S100A7, A8, A9, hBD-2, lipocalin, KRT17 and LOR have been proven to be IL-17-related (c). By contrast, the inflammatory IL-17 effects and the production of pro-inflammatory cytokines are not characteristic to this region, suggesting that IL-17 has a distinct, homeostatic role in healthy SGR skin.

RESULTS

Figure 2. Protein expressions of barrier structure molecules, desmosome and tight junction components, enzymes related to barrier formation and antimicrobial peptides in SGP and SGR skin regions.

Figure 2. Representative images for immunostaining and quantification of epidermal levels of FLG, LOR, KRT1, KRT6, KRT17, CDSN, DSG1, TGM5, S100A8, and LCN2 in SGP and SGR skin sections. The graphs show the mean $\pm$ SEM of measured protein levels (* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$, as determined by Mann-Whitney U-test).

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