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Letter to the Editor

Gram-positive anaerobe cocci are underrepresented in the microbiome of filaggrin-deficient human skin

To the Editor:

Next-generation sequencing technologies and powerful bioinformatics tools have revealed that diversity and composition of the skin microbiota of healthy volunteers strongly depends on the topographical location on the body and has a high degree of interpersonal variation. Nevertheless, the dominant types of bacteria remain relatively stable over time, and specific bacteria are associated with dry, moist, and/or sebaceous microenvironments. Microbial communities, genetic host factors, and the environmental factors at a particular moment constitute a complex relationship that is essential for skin barrier homeostasis. More recent studies have also focused on the microbiota of diseased and injured skin as alterations to microbial communities have been associated with cutaneous disorders. In the present study, we selected ichthyosis vulgaris (IV) as a model disease to investigate whether genetic polymorphisms resulting in altered stratum corneum (SC) composition and structure affect the microbiota composition of human skin and the cutaneous host response. Genetic deficiency or haploinsufficiency of the histidine-rich epidermal protein filaggrin (FLG) is associated with IV and atopic dermatitis (AD).

Here, we report 2 novel findings with respect to FLG deficiency and cutaneous microbiota. First, we show that FLG deficiency is associated with a low relative abundance of proteolytic Gram-positive anaerobic bacteria.

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FIG 2. Keratinocyte responses differ between bacterial stimulations. FLG$^{+/+}$ keratinocyte cultures (n = 10) were stimulated for 10 hours with bacteria. Expression of 6 host defense genes was measured by quantitative PCR. For each gene, the unstimulated cell culture was set to 1. Data are represented as mean ± SEM. For statistics (repeated-measures ANOVA with Bonferroni post hoc test), see Table E5.
coci (GPAC), and a general underrepresentation of bacterial taxa that are capable of using histidine. Second, we report that exposure of cultured epidermal keratinocytes to *Finegoldia magna* induces the expression of antimicrobial proteins and proinflammatory cytokines, and that this response is distinct from other skin commensals such as *Propionibacterium acnes, Corynebacterium aurimucosum*, and *Staphylococcus capitis*, and the skin pathogen *Staphylococcus aureus*.

All experimental procedures were performed as described in this article’s Online Repository at www.jacionline.org. We analyzed the skin microbiota of the lower leg, which is typically a location where the ichthyotic skin alterations (dry and scaly skin) are most prominent. Patients and healthy controls were genotyped for FLG mutations (see Table E1 and Fig E1 in this article’s Online Repository at www.jacionline.org). None of the patients with IV in our study had eczematous lesions present at the lower leg, thereby excluding (lesional) AD-associated microbiome alterations as a confounding factor. Biophysical measurements showed increased transepidermal water loss and decreased SC hydration in FLG−/− subjects compared with FLG+/− subjects (see Fig E2 in this article’s Online Repository at www.jacionline.org). Rarefaction curves show that the phylogenetic diversity between the FLG-deficient and FLG-proficient state, or candidate-discriminating genera supported a significant difference in the microbiota composition (see Figs E3 and E4 in this article’s Online Repository at www.jacionline.org). Microbiome samples were subsequently analyzed by barcoded 16S marker gene sequencing (see Tables E2 and E3 in this article’s Online Repository at www.jacionline.org). Rarefaction curves show that the phylogenetic diversity does not differ between FLG+/+, FLG−/+ and FLG−/− samples (see Figs E3 and E4 in this article’s Online Repository at www.jacionline.org). Redundancy analysis revealed a significant effect of FLG deficiency on microbiota composition (see Fig E5 in this article’s Online Repository at www.jacionline.org). A lower relative abundance of GPAC (average 1.7% of the total genera) was found in FLG−/− skin compared with FLG+/+ skin (average 9.3% of the total genera) (see Fig E6 and Excel file E1 in this article’s Online Repository at www.jacionline.org). These genera included *Finegoldia, Anaerococcus, and Pseudomonas*.
REFERENCES