Loss of Skin Microbial Diversity and Alteration of Bacterial Metabolic Function in Hidradenitis Suppurativa

TO THE EDITOR

Hidradenitis suppurativa (HS) is a chronic scarring inflammatory skin disease affecting the pilosebaceous units of the axilla, inframammary folds, groin, and buttocks. Several previous microbiome studies consistently have

Abbreviations: HS, hidradenitis suppurativa; HSL, hidradenitis suppurativa lesional; HSN, hidradenitis suppurativa nonlesional

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Figure 1. Bacterial β-diversity is significantly decreased in HS compared with normal skin. (a) Experimental design showing the sampling locations and relative sampling depth of the glue and swab methods (red and blue bars). Follicular biopsy isolates the microbiota within the hair follicle and swabs sample microbiota from the skin’s surface and the upper portions of the hair follicle. (b) α-diversity for normal (n = 34 samples from 10 individuals), HSN (n = 36 samples from 11 individuals), and HSL (n = 36 samples from 11 individuals) skin samples. Wilcoxon rank sum test, P < 0.05 considered significant. (c) BCDI for
shown that bacterial dysbiosis exists in HS compared with normal skin (Guet-Revellet et al., 2017; Nikolakis et al., 2017; Ring et al., 2017b; Ring et al., 2017a). The HS microbiome has been studied by invasive and noninvasive sampling of nonlesional and lesional skin using culture and next generation sequencing analyses. The functional consequences of dysbiotic communities in HS skin remain unexplored.

In this study, we investigated whether microbial dysbiosis in HS was specific to a particular body site or skin niche and then applied a computational approach to analyze the functional impacts of the dysbiotic communities uncovered. We also applied our computational approach to a previously published study of 30 patients with HS and 24 normal individuals (Ring et al., 2017b). In our study, a small cohort of 10 normal subjects and 11 HS subjects were enrolled after providing written informed consent, including males and females, ages 19–61 years. Demographics, clinical metrics, and lifestyle factors were documented for all subjects (Supplementary Table S1). Cyanoacrylate follicular biopsy (glue) and swab samples were collected from the axilla vault and inguinal crease (groin) for each individual, and both nonlesional (HSN) and lesional (HSL) skin was sampled in patients with HS (Figure 1a). HSN skin appeared clinically normal and was ~5 cm from an active lesion; lesional skin was an intact inflammatory nodule. The lesion was ~2-fold more abundant in HS skin. Like previous studies, Cutibacterium was more abundant in normal skin (18.8% vs. 1%, P < 0.05), and Peptostreptococci and Porphyromonas were more abundant in HS skin (Figure 1e). Staphylococcus and Corynebacterium comprised ~35% of the bacteria, and Corynebacterium was ~2-fold more abundant in HS skin. Like previous studies, Cutibacterium was more abundant in normal skin (18.8% vs. 1%, P < 0.05), and Peptostreptococci and Porphyromonas were more abundant in HS skin (Figure 1e; Supplementary Tables S4 and S5). The top 10 most abundant genera in normal and HS (HSL and HSN averaged) skin are shown in Figure 1e. Staphylococcus and Corynebacterium comprised ~35% of the bacteria, and Corynebacterium was ~2-fold more abundant in HS skin. Like previous studies, Cutibacterium was more abundant in normal skin (18.8% vs. 1%, P < 0.05), and Peptostreptococci and Porphyromonas were more abundant in HS skin (Figure 1e; Supplementary Tables S4 and S5). Overall, in HS skin, the relative abundance of skin commensals decreased, and opportunistic anaerobic pathogens increased.

Within HS skin, no difference in α- or β-diversity was observed when comparing axilla versus groin or skin surface versus follicle (loss of heterogeneity), but in healthy skin, α-diversity was significantly different between body site and skin niche (Figure 1f; Supplementary Figures S1 and S2). Correlations between bacterial diversity and subject demographics were also investigated (Supplementary Tables S1 and S6; Supplementary Figure S3). In patients with HS, a trend in altered β-diversity (P = 0.063) emerged between smoking and nonsmoking (Figure 1g) and between alcohol users and nonusers (P = 0.078) (Figure 1h), suggesting that lifestyle factors may impact skin microbiome diversity.

Significant functional differences between the microbiota of normal, HSN, and HSL skin were identified using a computational approach (Figure 2a; Supplementary Materials and Methods) with several significantly enriched Kyoto Encyclopedia of Genes and Genomes orthologs, level 1 (n = 3/6), level 2 (n = 15/51), and level 3 (n = 52/301) (Supplementary Table S7). Because our sample size was small, the same computational analyses were performed on publicly available data from 30 patients with HS and 24 normal individuals (Ring et al., 2017b). Enriched Kyoto Encyclopedia of Genes and Genomes orthologs between these two data sets are highly correlated (Spearman correlation, ρ = 0.76; P < 0.01). Metabolic pathways were impacted particularly in HS relative to normal skin in both data sets, indicating that metabolic dysfunction is likely present in HS skin (Figure 2b). The genera that contributed to specific metabolic pathways differed between HS and normal skin. Cutibacterium contributed significantly to both propanoate metabolism and retinol metabolism in normal skin, whereas Corynebacterium was the dominant contributor to propanoate metabolism in HS skin but played little role in retinol metabolism (Figure 2c and d; Supplementary Tables S8 and S9). Several amino acid and vitamin metabolism pathways were altered in HS skin that contribute to sour body odor as well as an acidic skin pH (Alavi et al., 2018; Chng et al., 2016; Lam et al., 2018). In vitro and in vivo studies to confirm these findings are warranted.

Decreased Cutibacterium abundance in HS likely is due to destruction of the pilosebaceous units during disease progression (Kamp et al., 2011) and may indicate that disruption of pilosebaceous unit architecture precedes development of clinically detectable lesions. Alternatively, a microenvironment inhospitable to Cutibacterium...
Figure 2. KEGG Ontology indicates functional differences between microbiota of HS and normal skin. (a) PCA plot of the overall functional differences of Level 3 KEGG between normal (n = 34), HSN (n = 36), and HSL (n = 36) skin samples. Multiple group statistical analysis was performed (Kruskal-Wallis H-test, Bonferroni correction). (b) Selected Level 2 (bold, subgroups of metabolism) and Level 3 (nonbold, individual pathway maps, subgroups of bolded level 2 heading above) KEGG Ortholog pathways enriched in HS (HSN + HSL) and normal skin in both this data set (Schneider et al., 2019) and the data set from Ring et al. (JAMA Dermatology 2017 accession number PRJEB15266). FWER significant < 0.05. (c, d) Top 10 genera contributing to metabolic pathways with each
colonization may exist in early stages of HS because of antimicrobial peptides and inflammatory mediators initiated by follicular keratinocytes (Hotz et al., 2016). Because Cutibacterium produces propionic acid with antimicrobial activity against opportunistic pathogens (Shu et al., 2013), loss of Cutibacterium may allow overgrowth of opportunistic pathogens (Figure 2e). Stabilizing Cutibacterium to maintain homeostasis and keep pathogenic communities at bay may improve HS symptoms.

Restoring a normal metabolome using probiotics, prebiotics, or microbiome transplants may be helpful in HS symptom resolution. Vitamin B12 supplementation in acne patients has been shown to impact C. acnes B12 metabolic pathways, suggesting positive association between host interventions and the bacterial metabolome (Kang et al., 2015), and similar strategies may be applied for normalizing the bacterial metabolome through supplementation in HS (Figure 2b; Supplementary Table S7).

In conclusion, bacterial dysbiosis is present at the skin’s surface, in the follicle, and at distinct body sites in HS compared with normal skin. Computational analyses suggest that bacterial dysbiosis extends to overall functional dysbiosis. Determining the exact contribution of bacteria to HS pathology may identify new therapeutic options.

Data availability statement
Data sets related to this article can be found at https://www.ncbi.nlm.nih.gov/bioproject/PRJNA549733, hosted at Sequence Read Archive under the identifier PRJNA549733.

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SUPPLEMENTARY MATERIAL
Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2019.06.151.

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CONFLICT OF INTEREST
JSK has served as a consultant with Incyte and ChemOncTryx as a speaker for AbbVie and has conducted clinical trials with AbbVie, Incyte, InflaraRx, and UCB. The remaining authors state no conflict of interest.

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column representing the mean bacterial OTU abundance from all samples collected from one individual. Icons in the top right indicate significantly different genera, P < 0.05 (Supplementary Table S9). (c) Propanoate metabolism, (d) retinol metabolism, (e) Proposed model of bacterial dysbiosis in HS skin. FWER, family-wise error rate; HS, hidradenitis suppurativa; HSL, hidradenitis suppurativa lesional; HSN, hidradenitis suppurativa nonlesional; KEGG, Kyoto Encyclopedia of Genes and Genomes; OTU, operational taxonomic unit; PC1, principal component 1; PC2, principal component 2; PCA, principal component analysis.