Longitudinal Changes in Skin Microbiome Associated with Change in Skin Status in Patients with Psoriasis

Hailun WANG[1], W. M. Mandy CHAN[2], Henry H. CHAN[2] and Herbert PANG[1]
[1]School of Public Health, and [2]Division of Dermatology, Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

The aim of this study was to identify key microbes associated with change in skin status (lesional vs normal). Longitudinal changes in the skin microbiome between patients with psoriasis and healthy family controls living in the same household were studied using whole genome metagenomic shotgun sequencing at 4 time-points. There were significant changes in abundance of the pathogen *Campylobacter jejuni* and its higher taxonomic levels when the skin status of patients with psoriasis changed. There were significant longitudinal variations in alpha diveristy ($p < 0.001$) and beta diversity ($p < 0.05$) of the skin microbiome in patients with psoriasis, but not in the healthy control group, which indicated composition of skin microbiome in patients with psoriasis was different from healthy control and was dynamically less stable. This study will serve as the basis for future temporal studies of the skin microbiome and probiotic therapeutics.

Key words: skin microbiome; psoriasis; skin status; microbial diversity.

Accepted Sep 11, 2020; Epub ahead of print Sep 18, 2020

Acta Derm Venereol 2020; 100: adv00329.

Corr: Herbert Pang, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pok Fu Lam, Hong Kong, China. E-mail: herbpang@hku.hk

SIGNIFICANCE

Psoriasis is a multifaceted chronic skin disease that causes pain and discomfort. Skin microbiome is the community of microorganisms that reside on the skin. Understanding the involvement of the microbiome in the health of human skin will help enable the development of novel therapies. The association between the skin microbiome and the pathogenesis of psoriasis over time is not well understood. This study identified key microbes associated with the change in skin microbiome in patients with psoriasis over time, with healthy family controls as comparison. Significant change of relative abundance in *Campylobacter jejuni* was observed when the skin status of patients with psoriasis changed from lesional to normal (adjusted $p < 0.05$).

Skin, the largest organ of the human body, acts as a protective barrier against external pathogenic organisms and harmful substances (1). It also harbours trillions of bacteria, fungi, viruses, and archaea, which collectively constitute the skin microbiome (2). The skin microbiome interacts with human health and has the ability to fine-tune the immune system of the human host (3) by modulating the local inflammatory milieu (4) and controlling the expression level of factors related to the immune system, such as antimicrobial peptides (5).

Advances in next generation sequencing (NGS) techniques have stimulated research into the composition of the skin microbiome and its implications for skin health and disorders. A commonly used technique used to study the composition of the bacterial community in the skin microbiome is 16S rRNA gene sequencing. Another recent technique, whole genome metagenomic shotgun sequencing (WGS), enables the classification of various microbial communities in addition to bacteria, and the investigation of the full complement of genomics, including its functional potential (6). The use of fast and efficient NGS techniques has revealed associations between the skin microbiome and the host cutaneous condition in a variety of skin diseases, including acne vulgaris (7, 8), atopic dermatitis (9, 10), rosacea (11), and psoriasis (12–16).

Psoriasis is a common, chronic immune-mediated skin disease that affects approximately 2% of the population worldwide (17). It is a multifaceted disease, the development of which involves various genetic and environmental risk factors. The skin microbiome has also been shown to play a role in psoriasis. For example, alpha diversity, which measures the richness and evenness of the microbial community, is lower in psoriatic lesional skin compared with control skin (12, 13). An increased ratio of 2 bacterial phyla, *Firmicutes* to *Actinobacteria*, has been found in psoriatic lesional skin compared with normal skin (14). A toxic substance produced by some strains of *Staphylococcus aureus* has been shown to correlate with psoriasis severity (15). A longitudinal study has observed a larger pretreatment heterogeneity and an increased variation in the skin microbiota in psoriatic lesional skin compared with that of normal skin during treatment with ustekinumab (16). Despite these studies reporting differences in the skin microbiome between psoriatic lesional skin and control skin at a single time-point, or a temporal trend during treatment, it is unclear how the skin microbiome changes with skin status. Few studies have examined whether the skin microbiome is associated with the recovery and recurrence of skin lesions over time.

The aim of the current study was therefore to investigate the key skin microbes connected with change in skin status in psoriasis. A WGS technique was used to deter-

mine the temporal skin microbiome profile of patients and healthy family controls living in the same household. In addition, differences in longitudinal changes in the skin microbiome between patients with psoriasis and family controls were characterized.

MATERIALS AND METHODS

Study design

The study was designed to investigate the association between longitudinal changes in skin microbiome and skin status of patients with psoriasis. A household-based sampling design was used. Skin samples were collected at 4 time-points from patients and healthy family controls living in the same household: baseline, and 3 follow-up time-points (duration between 2 consecutive time-points, median (interquartile range; IQR) 5.8 months (3.6–8.3 months). The sampling time-points were related to the status of the skin lesions. In particular, the focus was on samples that related to changes in skin status, in order to determine the changes in the skin microbiome with flare-up or clearing of the lesions.

This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (project UW-085). Written informed consent was obtained from all study participants before the study began. Eligible participants with psoriasis were recruited from the Family Cohort (18) and the Hong Kong Psoriasis Patients Association with baseline skin samples (19), with subsequent skin status changes at follow-up time-points.

Subjects

A total of 12 subjects were recruited from 6 different households. Subjects (patients and family controls) from 5 households underwent collection of skin samples at 4 time-points, and subjects from 1 household at 3 time-points. Subjects' ages ranged from 33 to 75 years at the time of recruitment. Eligible family controls were subjects with healthy skin condition who lived in the same household as a patient. Subjects who had used antibiotic treatment (systemic or topical) within one month prior to sample collection at baseline were excluded. Five of the 6 patients had taken topical steroids within 30 days before samples were obtained during at least one of their visits. Only one of the 6 patients had received biologic therapy within 30 days before samples were obtained during at least one of their visits. None of the patients reported having ultraviolet (UV) phototherapy.

All study subjects provided written informed consent prior to participation in the study.

Skin sample collection

All subjects agreed to provide skin swab specimens. Eligible cases were psoriasis patients with a lesion and a contralateral non-lesion in at least one of the following locations: elbow, forearm, knee, or scalp at baseline, and a change in skin status in at least one of these locations at follow-up. Samples from the left side and right side of different body locations of eligible cases were also collected. Samples from one side of the matched body locations of family controls were collected. ESwab (Copan Diagnostics, Murrieta, CA, USA) was used to collect skin swab specimens from all subjects. Each skin swab sample was taken from a circle with a radius of approximately 2 cm by swabbing back and forth 25 times.

DNA extraction and whole genome sequencing sequencing

Genomic DNA from each skin sample was extracted using a QIAamp DNA Mini Kit (QIAGEN, Germantown, MD, USA), following the manufacturer's instructions for swab specimens. The DNA library was prepared using the KAPA HyperPrep Kit (Kapa Biosystems, Wilmington, MA, USA). Shotgun sequencing was performed using a HiSeq 1500 platform (Illumina, San Diego, CA, USA, 2 ×100 bp paired-end sequencing) for baseline samples and NovaSeq 6000 system (Illumina, San Diego, CA, USA, 2 ×150 bp paired-end sequencing) for the follow-up samples.

Microbial operational taxonomic units annotation

Raw sequence reads aligned to adapters and human contaminant were removed for the quality control. Remaining reads were assembled into contigs (long continuous sequences) by IDBA-UD (20). Classification, clustering and annotation of the microbial operational taxonomic units (OTUs) were performed using DIAMOND (21) and MEGAN (22). MEGAN long read (23) mode was used for the binning of OTUs, as contigs were the input data. Relative abundance (%) of normalized read count of annotated OTUs from different taxonomic ranks by MEGAN was used as the estimation of microbial abundance.

Data analysis and statistics

R statistical software (24) was used for all statistical analyses and data visualization. Orders of the abundance of OTUs were ranked based on the median of the mean relative abundance of the skin samples from the same subject and body location over time. Low abundant OTUs (relative abundance $<0.1\%$) were filtered out. Alpha and beta diversities were determined as described previously (19). In order to determine the key taxa associated with the change in skin status, a reference distribution of the change in the relative abundance between 2 time-points was calculated from control skin samples. Four types of change in skin status: lesion to normal; normal to lesion; lesion to lesion; and normal to normal were defined for patients' skin samples. Distributions of the change in relative abundance in an investigated microbe were compared between patients and controls among 4 different types of change in skin status using a permutation test. Longitudinal patterns of microbial relative abundance levels over different time-points were quantified by the first principal component (PCA1) of principal component analysis (PCA). A linear mixed effects model using lme4 (25) was applied to compare differences in longitudinal changes in microbial abundance, microbiome diversities, and to provide estimates of the longitudinal pattern between patients and controls, adjusting for within-subjects effect and sex. False-positive rate (FDR) was used to adjust for the multiple comparisons. R packages ggplot2 (26) and ggtree (27) were used to visualize the results.

RESULTS

Summary of study subjects and samples obtained

A total of 141 skin samples were collected from 12 subjects at 4 time-points: 24 samples from patients and 12 from family controls at baseline, first and second follow-ups; and 22 samples from patients and 11 from family controls at third follow-up (one household was lost to follow-up).

Composition of the skin microbiota

Fig. S1[1] summarizes the composition of the top 10 most abundant taxa at different taxonomic levels in patients' lesional skin, patients' normal skin, and controls' normal

skin over different time-points. At the phylum level (Fig. S1a[1]), *Proteobacteria* (median (IQR) 52.5% (39.6–64.0%)), *Actinobacteria* (31.2% (20.7–46.1%)), *Bacteroidetes* (8.5% (2.9–15.4%)), and *Firmicutes* (1.4% (0.6–3.1%)) were identified. These 4 major phyla have also been reported in other skin microbiome-related studies (1, 28, 29). The median relative abundances of other phyla were less than 1%. At the family level (Fig. S1b[1]), the 3 most abundant families were *Pseudomonadaceae* (18.4% (1.2–31.2%)), *Propionibacteriaceae* (11.4% (3.9–21.3%)) and *Moraxellaceae* (6.2% (2.7–12.4%)). *Pseudomonadaceae* and *Moraxellaceae* are both in the phylum *Proteobacteria*. At the genus level, *Pseudomonas* was the most dominant genus (22.2 (1.5–37.2%)), and the dominance of *Pseudomonas* was documented previously (30). *Acinetobacter*, *Moraxella* and *Propionibacterium* were other abundant genera that had a median relative abundance >2%. At the species level, a total of 1,364 different species were annotated. The top 10 most abundant species accounted for 12.8% of the total bacterial community, according to the median of the mean relative abundance over time.

Key taxa and change in skin status

To invesitgate whether a microbe was associated with the change of skin status in patients vs controls, permutational test with 999 permutations was used to compare the change in relative abundance in a microbe among 4 different types of change in skin status between patients and controls. 4 microbial taxa had one or more types of change with significant differences. Fig. S2[1] shows box-plot comparison of the extent of changes in relative abundance in different types of change in skin status and the reference for these taxa. The significantly different comparisons were indicated by an asterisk. In particular, the species *Campylobacter jejuni* and its higher taxonomic levels, the *Campylobacter* genus, and the *Campylobacteraceae* family, all showed significant differences between the transition from lesion to normal status and the reference normal with respect to the distribution of change in relative abundance (Fig. S2a–c[1]). Compared with the reference distribution, all *Campylobacter jejuni*-related taxa underwent a significantly more negative change in relative abundance when the skin status changed from lesion to normal. Conversely, for the transition from normal to lesion, these taxa consistently underwent a more positive change in relative abundance compared with the reference, and a significance change was observed in the *Campylobacteraceae* family. The Gordoniaceae family showed a more positive change in its relative abundance for the transition from lesion to normal for patients vs controls. And conversely, a significantly more negative change of relative abundance in Gordoniaceae for the transition from normal to lesion was observed. (Fig. S2d[1]).

Longitudinal changes in major taxa and microbial diversity

Fig. S3a[1] shows the phylogenetic relationship between taxa identified as showing significant longitudinal changes (adjusted $p<0.05$, linear mixed effects model) at different taxonomic levels and in different groups of skin samples. Most of the taxa with significant longitudinal changes were in the phylum *Proteobacteria* and from skin samples from patients. The genus *Acinetobacter* and its lower level species, *Acinetobacter junii* and *Acinetobacter baumannii*; family *Sphingomonadaceae* and its lower level genera, *Sphingomonas* and *Sphingobium*; and family *Caulobacteraceae* changed over time in skin samples from patients. Phylum *Chloroflexi* changed over time in skin samples from family controls. The family *Comamonadaceae* changed over time in skin samples from both patients and controls.

Microbial alpha and beta diversities were calculated from the abundance profile at the species level to evaluate longitudinal changes in skin microbiota in patients and family controls. The alpha diversity measured using the Shannon diversity index revealed a significant change over time in patients with psoriasis ($p<0.001$, linear mixed effects model), while there were no significant changes over time in the control group ($p=0.4$) (Fig. S3b[1]). In addition, levels of alpha diversity in patient skin were lower than in control skin at each time-point. Beta diversity, estimated using PCoA1, changed significantly over time in skin samples from patients ($p<0.05$), but not in skin samples from family controls ($p=0.1$) (Fig. S3b[1]).

Longitudinal pattern in relative abundance of taxa between patients and controls

Although no significance was found with the adjustment for multiple comparisons, 4 taxa, *Corynebacterium* and *Mucilaginibacter* genera, *Tsukamurella tyrosinosolvens* and *Janibacter indicus* species, had raw p-values <0.05. The mean relative abundances and the standard error of the mean over different time-points for these 4 taxa in skin samples from patients and controls are shown in Fig. S4[1]. Four taxa were not significantly differential in the longitudinal pattern between patients and controls after the adjustment. However, at 2 or more time-points, the range of relative abundances of these taxa between patients and controls, measured as the mean and standard error of the mean, were visually separated.

DISCUSSION

The skin microbiome can modulate the host immune system and is associated with the pathogenesis of a number of skin disorders. Advances in sequencing techniques of-

[1]https://doi.org/10.2340/00015555-3638

fer more reliable, faster and more affordable approaches to analysing the composition of the skin microbiome. Recent research into the skin microbiome in diseased and healthy hosts has investigated its temporal stability (31, 32) and temporal variations (16, 28, 33) after receiving skin therapy. Psoriasis is a chronic skin disorder, in which the patient's skin status can switch between lesion and normal over time. However, there is little published research regarding the microbes correlated with this change in skin status. The current study investigated longitudinal changes in the skin microbiome in patients with psoriasis and in healthy family controls over a period of one year. The most important finding of this study was the identification of key microbial taxa associated with the change in skin status in people with psoriasis. The relative abundance of *Campylobacter jejuni* species and its higher taxonomic levels, *Campylobacter* genus, and *Campylobacteraceae* family, were found to be significantly reduced when the skin status changed from lesional to normal, but increased when the skin status changed from normal to lesional. *Campylobacter jejuni* and its related microbial taxa were not statistically significant in the longitudinal analyses. This implies that the change in relative abundance of these microbes pooled across pairwise time-points were associated with the change in skin status, but were not present when longitudinal dynamics and patterns were considered. *Campylobacter jejuni*, is a leading pathogen causing bacterial gastroenteritis, including a potentially fatal paralytic autoimmune disorder as secondary sequelae (34). In addition, *Campylobacter jejuni* is associated with erysipelas-like skin lesions in patients with hypogammaglobulinaemia (35). A strong association between anti-*Campylobacter fetus* antibodies and psoriatic arthritis has been observed (36). Skin infection with *Campylobacter bacteremia* is a frequent manifestation in immunocompromised patients (37). Furthermore, *Campylobacter* infections are associated with a variety of autoimmune disorders, such as reactive arthritis, systemic lupus erythematosus and vasculitis (38). Our finding of an increase in *Campylobacter jejuni* during the change from normal to lesional skin in psoriasis, and a reduction in *Campylobacter jejuni* during the change from lesional to normal skin suggest a link between *Campylobacter jejuni* and the pathogenesis of psoriatic lesion. In addition, in the current study the *Gordoniaceae* family was significantly decreased when the skin status changed from normal to lesional, and increased when the skin status changed from lesional to normal. *Gordoniaceae* is in the phylum *Actinobacteria*. Although few studies have reported on the *Gordoniaceae* family, it has been observed previously that the reduction in phylum level *Actinobacteria* in psoriatic lesional skin is greater than that in the normal skin of both patients and controls (14). Our findings provide a detailed picture of the disease, by narrowing down the *Actinobacteria* phylum to its lower level family *Gordoniaceae*, which may be negatively associated with psoriatic skin lesions.

In the current study, the longitudinal changes in the composition of the skin microbiome in patients with psoriasis and their healthy family controls was also delineated. The results regarding the 4 major phyla, *Proteobacteria*, *Actinobacteria*, *Bacteroidetes* and *Firmicutes*, in the skin microbiome, both in patients with psoriasis and in controls, were consistent with previous observations (1, 28 29). The dominance of the genus *Pseudomonas* in the skin microbiome in the current study has also been reported previously (30). Moreover, we found significant longitudinal variations in alpha diversity, beta diversity and several microbial taxa in patients with psoriasis, but not in the healthy skin of family controls. The stability of the skin microbiome in healthy skin over time has been reported previously (32, 39). In addition, we found the alpha diversity at each time-point was lower in patients' skin than in controls, which was consistent with the findings of previous cross-sectional studies (12, 13). The results of the current study imply a less stable composition of the skin microbiome in patients with psoriasis compared with healthy controls. These results also reveal the important role of a stable skin microbiome in the maintenance of healthy skin homeostasis.

In summary, using a novel household-based design, this study investigated the longitudinal dynamics of the composition of the skin microbiome in patients with psoriasis and healthy family controls at 4 time-points. Using healthy family controls as a reference, key microbial taxa associated with the change in skin status in patients with psoriasis were identified. Although numerous therapies have been licensed for psoriasis, the natural history of psoriasis remains unclear, and accessing appropriate therapy remains a challenge (40). With advances in understanding of the role of the skin microbiome in maintaining healthy skin, recent studies have examined the use of probiotic therapy to modulate the condition of the skin (41, 42). The results of the current study, in particular the identification of 2 key microbial taxa associated with changes in skin status, could indicate potential targets for probiotic therapy. Further research into the skin microbiome is needed to better understand the longitudinal dynamics of skin status in psoriasis and its implication for future therapeutics.

ACKNOWLEDGEMENTS

The authors would like to thank the study participants. Special thanks are extended to the Hong Kong Psoriasis Patients Association, Xiaoxin I. Yao (HKU), Eva S. Leung (HKU), Kang K. Yan (HKU), Yinpeng Wang (HKU), Jun Tao (HKU) and Japio W. Fung (HKU). Part of the computations were performed using high-performance research computing facilities offered by the Information Technology Services, of the University of Hong Kong.

This study was partially supported by Research Grants Council – General Research Fund, Hong Kong, No. 17157416.

The authors have no conflicts of interest to declare.

REFERENCES

1. Grice EA, Segre JA. The skin microbiome. Nat Rev Microbiol 2011; 9: 244–253.
2. Kong HH, Segre JA. Skin microbiome: looking back to move forward. J Invest Dermatol 2012; 132: 933–939.
3. Belkaid Y, Segre JA. Dialogue between skin microbiota and immunity. Science 2014; 346: 954–959.
4. Naik S, Bouladoux N, Wilhelm C, Molloy MJ, Salcedo R, Kastenmuller W, et al. Compartmentalized control of skin immunity by resident commensals. Science 2012; 337: 1115–1119.
5. Gallo RL, Hooper LV. Epithelial antimicrobial defence of the skin and intestine. Nat Rev Immunol 2012; 12: 503–516.
6. Kong HH. Details matter: designing skin microbiome studies. J Invest Dermatol 2016; 136: 900–902.
7. Dreno B, Martin R, Moyal D, Henley JB, Khammari A, Seite S. Skin microbiome and acne vulgaris: Staphylococcus, a new actor in acne. Exp Derm 2017; 26: 798–803.
8. Li CX, You ZX, Lin YX, Liu HY, Su J. Skin microbiome differences relate to the grade of acne vulgaris. J Dermatol 2019; 46: 787–790.
9. Chng KR, Tay AS, Li C, Ng AH, Wang J, Suri BK, et al. Whole metagenome profiling reveals skin microbiome-dependent susceptibility to atopic dermatitis flare. Nat Microbiol 2016; 1: 16106.
10. Kennedy EA, Connolly J, Hourihane JO, Fallon PG, McLean WHI, Murray D, et al. Skin microbiome before development of atopic dermatitis: early colonization with commensal staphylococci at 2 months is associated with a lower risk of atopic dermatitis at 1 year. J Allergy Clin Immunol 2017; 139: 166e72.
11. Picardo M, Ottaviani M. Skin microbiome and skin disease: the example of rosacea. J Clin Gastroenterol 2014; 48: S85–S86.
12. Alekseyenko AV, Perez-Perez GI, De Souza A, Strober B, Gao Z, Bihan M, et al. Community differentiation of the cutaneous microbiota in psoriasis. Microbiome 2013; 1: 31.
13. Fahle´n A, Engstrand L, Baker BS, Powles A, Fry L. Comparison of bacterial microbiota in skin biopsies from normal and psoriatic skin. Arch Dermatol Res 2012; 304: 15e22.
14. Gao Z, Tseng CH, Strober BE, Pei Z, Blaser MJ. Substantial alterations of the cutaneous bacterial biota in psoriatic lesions. PLoS ONE 2009; 3: e2719.
15. Tomi NS, Kra¨nke B, Aberer E. Staphylococcal toxins in patients with psoriasis, atopic dermatitis, and erythroderma, and in healthy control subjects. J Am Acad Dermatol 2005; 53: 67e72.
16. Loesche MA, Farahi K, Capone K, Fakharzadeh S, Blauvelt A, Duffin KC, et al. Longitudinal study of the psoriasis-associated skin microbiome during therapy with ustekinumab in a randomized phase 3b clinical trial. J Invest Dermatol 2018; 138: 1973e81.
17. Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med 2009; 361: 496–509.
18. Leung GM, Ni MY, Wong PT, Lee PH, Chan BH, Stewart SM, et al. Cohort profile: FAMILY cohort. Int J Epidemiol 2017; 46: e1.
19. Wang H, Chan HH, Ni MY, Lam WW, Chan WMM, Pang H. Bacteriophage of the skin microbiome in patients with psoriasis and healthy family controls. J Invest Dermatol 2020; 140: 182–190.e5.
20. Peng Y, Leung HC, Yiu SM, Chin FY. IDBA-UD: A de novo assembler for single-cell and metagenomic sequencing data with highly uneven depth. Bioinformatics 2012; 28: 1420e8.
21. Buchfink B, Xie C, Huson DH. Fast and sensitive protein alignment using DIAMOND. Nat Methods 2015; 12: 59e60.
22. Huson DH, Beier S, Flade I, Go´rska A, El-Hadidi M, Mitra S, et al. MEGAN community edition – interactive exploration and analysis of large-scale microbiome sequencing data. PLOS Comput Biol 2016; 12: e1004957.
23. Huson DH, Albrecht B, Bağcı C, Bessarab I, Górska A, Jolic D, et al. MEGAN-LR: new algorithms allow accurate binning and easy interactive exploration of metagenomic long reads and contigs. Biol Direct 2018; 13: 6.
24. R Core Team (2014). R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; Austria. Available from: http://www.R-project.org/
25. Bates D, Machler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. J Stat Softw 2015; 67: 1e48.
26. Wickham H. ggplot2: Elegant graphics for data analysis. New York: Springer-Verlag; 2016.
27. Yu G, Smith D, Zhu H, Guan Y, Lam TT. ggtree: an R package for visualization and annotation of phylogenetic trees with their covariates and other associated data. Meth Ecol Evol 2017; 8: 28–36.
28. Brandwein M, Fuks G, Israel A, Al-ashhab A, Nejman D, Straussman R, et al. Temporal stability of the healthy human skin microbiome following Dead Sea climatotherapy. Acta Derm Venereol 2018; 98: 256–261.
29. Gao Z, Tseng C-h, Pei Z, Blaser MJ. Molecular analysis of human forearm superficial skin bacterial biota. Proc Nat Acad Sci 2007; 104: 2927–2932.
30. Grice EA, Kong HH, Renaud G, Young AC; NISC Comparative Sequencing Program, Bouffard GG, et al. A diversity profile of the human skin microbiota. Genome Res 2008; 18: 1043–1050.
31. Flores GE, Caporaso JG, Henley JB, Rideout JR, Domogala D, Chase J, et al. Temporal variability is a personalized feature of the human microbiome. Genome Biol 2014; 15: 1.
32. Oh J, Byrd AL, Park M, Kong HH, Segre JA, Program NCS. Temporal stability of the human skin microbiome. Cell 2016; 165: 854–866.
33. Kwon S, Choi JY, Shin J,W, Huh CH, Park KC, Du MH, et al. Changes in lesional and non-lesional skin microbiome during treatment of atopic dermatitis. Acta Derm Venereol 2019; 99: 284–290.
34. Crofts AA, Poly FM, Ewing CP, Kuroiwa JM, Rimmer JE, Harro C, et al. Campylobacter jejuni transcriptional and genetic adaptation during human infection. Nat Microbiol 2018; 3: 494–502.
35. Kerstens PJ, Endtz HP, Meis JF, Oyen WJ, Koopman RJ, van den Broek PJ, et al. Erysipelas-like skin lesions associated with Campylobacter jejuni septicemia in patients with hypogammaglobulinemia. Eur J Clin Microbiol Infect Dis 1992; 11: 842–847.
36. Lapadula G, Iannone F, Covelli M, Numo R, Pipitone V. Anti-enterobacteria antibodies in psoriatic arthritis. Clin Exp Rheumatol 1992; 10: 461–466.
37. Pacanowski J, Lalande V, Lacombe K, Boudraa C, Lesprit P, Legrand P, et al. Campylobacter bacteremia: clinical features and factors associated with fatal outcome. Clin Infect Dis 2008; 47: 790–796.
38. Louwen R, Hays JP. Is there an unrecognised role for Campylobacter infections in (chronic) inflammatory diseases? World J Clin Infect Dis 2013; 3: 58–69.
39. Byrd AL, Belkaid Y, Segre JA. The human skin microbiome. Nat Rev Microbiol 2018; 16: 143–155.
40. Reid C, Griffiths CEM. Psoriasis and treatment: past, present and future aspects. Acta Derm Venereol 2020; 100: adv00032.
41. Nodake Y, Matsumoto S, Miura R, Honda H, Ishibashi G, Matsumoto S, et al. Pilot study on novel skin care method by augmentation with Staphylococcus epidermidis, an autologous skin microbe – a blinded randomized clinical trial. J Dermatol Sci 2015; 79: 119–126.
42. Paetzold B, Willis JR, Pereira de Lima J, Knödlseder N, Brüggemann H, Quist SR, et al. Skin microbiome modulation induced by probiotic solutions. Microbiome 2019; 7: 95.