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Metagenomic approach in study and treatment of various skin diseases: a brief review

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Abstract

Background: Skin is a complex ecosystem hosting a diverse microbial population as well as distinct environmental niches leading to hundreds of skin conditions that affect humans. There is an evident shift towards the metagenomic analysis from less efficient and strenuous culture-based techniques in biomedical research, thus creating a new dimension for dermatological study. A systematic and comprehensive study of skin microbiome appraises the dynamics between species, their interaction with the immune system, and composition in diseases.

Research: Metagenomics include research techniques like next-generation sequencing, sequencing of amplicon-based assays, shotgun metagenomics, gene prediction, metatranscriptomics, and statistical and comparative studies allowing us to access the functional and metabolic diversity of the skin microbiome and their role in host health. In disorders like acne, dandruff, seborrheic dermatitis, and bovine digital dermatitis, metagenomics provides information about the organisms present conferring the condition, inter-microbial interactions, and expression profiles of communities.

Conclusion: We have enriched our understanding of the uncultured world resulting in a better understanding of microbe interaction with each other and their host. Metagenomic analysis provides glimpses into topographical and interpersonal complexity that defines the skin microbiome. It has led to an advanced study of dermatological disorders like acne, dandruff, seborrheic dermatitis, atopic dermatitis, bovine digital dermatitis, and psoriasis, and this knowledge is a breakthrough in dermatology research for creating better therapeutic solutions and personalized treatments.

Keywords: Skin, Metagenomics, Microbiome, Dermatological disorders

Background

Skin is the first outermost layering representing a physical barrier to infections and potential assault by foreign organisms or toxic substances. This complex ecosystem is broadly composed of sebaceous areas (including the face and back); moist areas (including the toe/finger web space and arm pit); dry areas (including the forearm and buttock); sites containing varied densities of hair follicles, skin folds, and skin thicknesses; and characteristic host genetics (Wilantho et al. 2017). This confers to a suitable environment for harboring rich and diverse physiological populations of microorganisms. The microbiome includes bacteria, fungi, viruses, parasites, and microeukaryotes which play significant role in dermatological disorders (Mathieu et al. 2013).

Previously, studies were done using culture-cultivated methods but have proved to be less efficient as less than 1% of bacterial species can be cultivated with standard lab conditions leading to a vast majority of microorganisms gone unnoticed (Chen and Tsao 2013). Hence, for an unbiased identifying and characterizing of skin microbiota and their genetic content, metagenomics and next-generation sequencing techniques are used (Mende et al. 2012). The term metagenome allows for the contribution of all the genes and genetic elements of the microorganisms in and on the host. Metagenomics refers to the structural and functional study of complex microbial communities and their interaction with the host (Virgin and Todd 2011). The

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objective of this study in characterizing the skin microbiome is to define the microbial community and study their consequences for better understanding of the skin diseases. This approach includes amplification, sequencing, and analysis of the hypervariable region of the prokaryotic 16S rRNA gene as a proxy of the full-length gene and other phylogenetic marker genes (Rasheed et al. 2013). Oligonucleotide usage patterns can be utilized for identification of differences across complex microbial communities (Wan et al. 2017).

Metagenomic study permits collection, curation, and extraction of useful information from enormous datasets which is a significant computational challenge. Metagenomics include genomic DNA extraction, library construction, shotgun sequencing, taxonomic composition analysis, statistical analysis, etc (Fig. 1). This development has reframed our knowledge about the skin microbiome and its interactions with the host epithelial and immune system in various dermatological disorders (Kergourlay et al. 2015; Bzhalava et al. 2014; Martín et al. 2014), hence making way for the prevention and treatment of these diseases through diagnostic, prognostic, and therapeutic applications.

For instance, earlier it was believed that diseases like acne and dandruff were caused mainly due to the presence of *Propionibacterium acnes* and Malassezia fungi respectively. But several comprehensive metagenomic study findings have showed that the diseases are rather constituted by involvement of complex microbial communities and are detected by further taxonomic analysis (Barnard et al. 2016; Chng et al. 2016). Dermatological disorders which have been studied and analyzed through metagenomic approaches are acne vulgaris, dandruff, seborrheic dermatitis, atopic dermatitis, bovine digital dermatitis, psoriasis, vitiligo, melanoma, lupus erythematosus, basal cell carcinoma, erythema, and hidradenitis suppurativa (Table 1) (Actis & Rosina 2013; Horton et al. 2015; Fyhrquist et al. 2016; Guet-Revillet et al. 2017; Kocarnik et al. 2015). This review covers our current knowledge on some of these dermatological disorders and potential aspect of metagenomics in dermatological research.

Skin microbiome

Skin represents a physical barrier to infection as a result of epidermis cohesion, protecting our bodies from potential assault by foreign organisms or toxic substances. There is a delicate balance between host and the skin microbiota including symbiotic bacteria, fungi, parasites, and viruses (Mathieu et al. 2013). Disruptions in the balance on either side can result in skin disorders. These diseases can be studied by characterizing the skin microbiota and analyzing how it interacts with the host (Hannigan and Grice 2013). The surface of the skin is cooler than the core body temperature and is slightly acidic, and squames are continuously shed from the skin surface as a result of terminal differentiation (Fuchs and Raghavan 2002). It mainly consists of sebaceous areas, moist areas, dry areas, and sites containing varied densities of hair follicles, skin folds, and skin thicknesses. Sebaceous glands being relatively anoxic support the growth of facultative anaerobes such as acne causing *Propionibacterium acnes*, which contain lipase-encoding genes that degrade skin lipids of sebum as revealed by full genome sequencing (Liu et al. 2015). Other dominant bacterial genera present in the skin are Staphylococcus and Corynebacterium. The major fungus found on the surface is the Malassezia (formerly known as Pityrosporum) genus which plays role in causing the common skin disease, dandruff, studied and confirmed by 18S

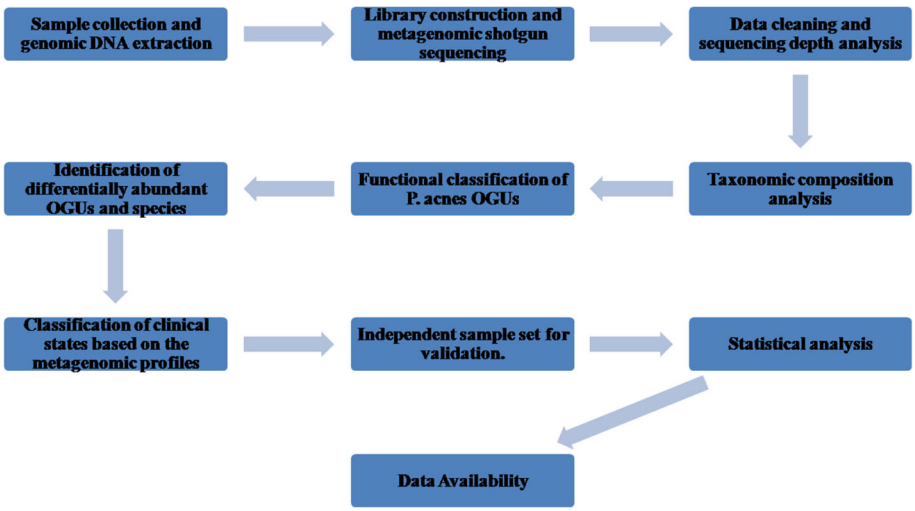

Fig. 1 Basic steps involved in a metagenomic study

Table 1 List of diseases which have been studied using metagenomics

Dermatological diseases in which metagenomic studies have been done successfully	Some common dermatological diseases with potential metagenomic studies
Acne vulgaris	Contact dermatitis
Seborrheic dermatitis	Skin rash
Atopic dermatitis	Wart
Bovine digital dermatitis	Keratosis
Psoriasis	Lichen planus
Vitiligo	Rosacea
Melanoma	Bullous pemphigoid
Lupus erythematosus	Melanocytic nevus
Basal cell carcinoma	Pemphigus
Erythema	Hyperpigmentation
Hidradenitis suppurativa	Ichthyosis

rRNA gene and ITS region sequencing (Tanaka et al. 2016). Whole-genome shotgun metagenomics has made it possible to study the skin viruses, most common being the human papillomavirus (HPV), human polyomaviruses (HPyVs), and circoviruses (Arroyo Mühr et al. 2015; Ma et al. 2014; Tse et al. 2012).

Culture-independent techniques and personalized treatment approaches

Earlier, the information and knowledge regarding the skin-associated microbes were primarily derived by culturing the microorganism and defining its phylogeny and taxonomy through phenotypic, microscopic, and biochemical relationships. But majority of microorganisms are retractile to cultivation or are unable to grow under the specified conditions, and thus, this approach significantly underestimates the complexity of the sample (Hugenholz et al. 1998). Hence, access to metagenomics has extensively fueled the growing segment of research in study and treatment of various dermatological disorders. Metagenomic analysis involves isolating DNA from an environmental sample or component under study, cloning the DNA into a suitable vector, transforming the clones into a host bacterium, and screening the resulting transformants for phylogenetic markers or "anchors," such as 16S rRNA and recA, for expression of certain traits like enzyme activity or antibiotic production, or for finding other conserved genes (Ferretti et al. 2017; Lau et al. 2017; Hannigan et al. 2015; Lane et al. 1985).

Metagenomic study generally includes preparation and sequencing of amplicon-based assays, shotgun metagenomics, primary computational analysis, and statistical and comparative studies (Kim et al. 2017). The shotgun metagenomic method comprises of collection and analysis of total DNA from the community without relying upon marker genes and sequencing directly (Eisen, 2007). Another approach can be of consequent sequencing of amplified targeted microbial regions usually contained in the 16S Rrna called ribosomal community profiling (Zinicola et al. 2015; Pace et al. 1985). Marker genes used in these techniques enclose both conserved regions, which allow for PCR primer binding and phylogenetic analysis, along with variable regions, whose sequences allow to be used for inferring the taxonomic composition of the community (Grice 2015).

Metatranscriptomics is a useful way to study species present in abundance as instead of DNA, RNA is obtained from a skin sample and then sequenced using next-generation sequencing (Baldrian et al. 2012; Poinar et al. 2006; Schuster, 2007). The transcriptome data provides this information better with the previously amplified RNA. Metatranscriptomic study detects majorly the live microorganisms due to unstable RNA sample as compared to DNA (Urich et al. 2008).

High-throughput sequencing technique does not require cloning of the DNA before sequencing, making the process less strenuous and time-consuming. Accuracy of assemblies obtained can be improved by correcting misassemblies using the paired-end tags by various assembly programs like Phrap assembler or velvet assembler (Chen and Pachter 2005). BLAST is used for rapid search of phylogenetic markers in existing databases used in MEGAN (Wooley et al. 2010). Sequences are binned, a process of association of a particular sequence with an organism, in order to perform comparative analysis of diversity using tools like PhymmBL, AMPHORA, and SLIMM which use individual reference genome to get reliable relative abundance by minimizing the false-positive hits (Kunin et al. 2008). There is an advent of faster and efficient tools like CLARK which can perform taxonomic annotation at extremely high speed than BLAST-based approaches like MG-RAST or MEGAN (Nicola et al. 2012). Comparison of obtained

sequences against reference databases like KEGG can give functional comparisons between metagenomes (Mitra et al. 2011). Metagenomic study permits collection, curation, and extraction of useful information from enormous datasets which is a considerable computational challenge, hence leading to the analysis of functional potential of the skin microbiome, improvement of metabolic pathways, about genes encoding virulence and pathogenicity factors, and hence can be used for creating new therapeutic solutions to treat such diseases.

One major application of metagenomics in diseases are personalized medicine, defined as a medical procedure involving molecular profiling, medical imaging, and lifestyle data that separates patients into different groups—with medical decisions, practices, interventions and/or products being tailored to the individual patient based on their predicted response or risk of disease (Afshinnekoo et al. 2017). Thus, we have now the ability to affordably and rapidly generate large datasets which are used to interpret data obtained from microbial community via analytical tools and databases (Wylie et al. 2014). Such advanced study lead to the use of effective and safe probiotics (live microorganisms or their components that confer health benefits) for the use in skin diseases that may be influenced by the gut microbiota along with prebiotics consisting of substrates that promote the growth and/or metabolic activity of beneficial indigenous microbiota for treating skin diseases due to microbial cause (Grice 2015).

Metagenomics in skin disorders

Acne

Acne vulgaris (commonly called acne) is the most common skin disorder characterized by abnormalities of sebum production by the pilosebaceous unit (commonly known as the hair follicle), bacterial proliferation, and inflammation and affects 80–85% of the population (Barnard et al. 2016). This disease is most prevalent in adolescents (85%) and rarely occurs in adults (11%) (White 1998). *Propionibacterium acnes* is said to be an important pathogenic factor accounting for nearly 90% of the microbiota demonstrated by 16SrRNA metagenomic study along with other microbes *Staphylococcus epidermidis*, *Propionibacterium humerusii*, and *Propionibacterium granulosum* (Fitz-Gibbon et al. 2013).

After examining various healthy and acne patients, it was found that such human diseases are often caused by certain strains of a species, rather than the entire species being pathogenic. *P. acnes* contribute to skin health also by preventing the colonization of opportunistic pathogens as it maintains an acidic pH by converting sebum to free fatty acids (Liu et al. 2015). Thus, only some strains are related to acne and not all. The metagenomic approach in determining disease associations provides significant result as it is more commanding and less biased than traditional methods.

There was no statistically significant difference in the relative abundance of *P. acnes* found when comparison of acne patients and normal individuals was performed (Wilantho et al. 2017). The examination of differences at the strain level of *P. acnes* by defining each unique 16S rDNA sequence as a 16S rDNA allele type, called a ribotype (RT), was done and hence allowed us to compare the *P. acnes* strain populations in individuals (Barnard et al. 2016). The balance between acne and metagenomic elements determines the virulence and health properties of the skin microbiota in disease and health (Kwon and Suh 2016).

This study provides novel insights into the microbial environment and mechanism of acne pathogenesis and hence can lead to designing of probiotic and phage therapies as potential acne treatments for maintaining a healthy skin.

Dandruff and seborrheic dermatitis (SD)

Dandruff is a prevalent mild chronic inflammatory condition of the scalp characterized by itching and scaling of the skin on the scalp (Soares et al. 2016). Seborrheic dermatitis being considered the more severe form of dandruff affects areas other than the scalp with sebaceous glands like the face and chest. Generally, this includes events like dysbiosis and disruption of skin barrier and epidermal cellular proliferation and differentiation (Soares et al. 2016). This common disease affects approximately half the population of adults worldwide, mainly caused by the Malassezia fungi. But recent research has suggested that the microbial communities present are more complex (Byrd et al. 2017).

Several comprehensive analyses like next-generation sequencing (NGS), performed on healthy and dandruff-suffering scalps, have revealed that Propionibacterium, Staphylococcus, and Corynebacterium are the three most abundant genera in both healthy and dandruff subjects but with the Malassezia sp. being the vast majority of fungi. The most abundant, *M. restricta* along with *M. globosa*, *M. sympodialis*, *M. dermatis*, *M. japonica*, *M. obtusa*, *M. pachydermatis*, *M. sloofiae*, and *M. furfur*, were detected by further taxonomic analysis (Byrd et al. 2017). Metagenomic and molecular studies have shown that *Propionibacterium acnes* is found to be greater in healthy scalps while *Staphylococcus epidermidis* in dandruff scalp along with bacterial genera Pseudomonas, Leptotrichia, Micrococcus, Selenomonas, Erwinia, Enhydrobacter, and Bartonellaceae and fungal genera Candida, Aspergillus, and Filobasidium, and more Malassezia by 26S r RNA molecular analysis (Wan et al. 2017) (Fig. 2). Further studies on scalp and forehead by high-throughput 16S rDNA and ITS1 sequencing, pyrosequencing, and

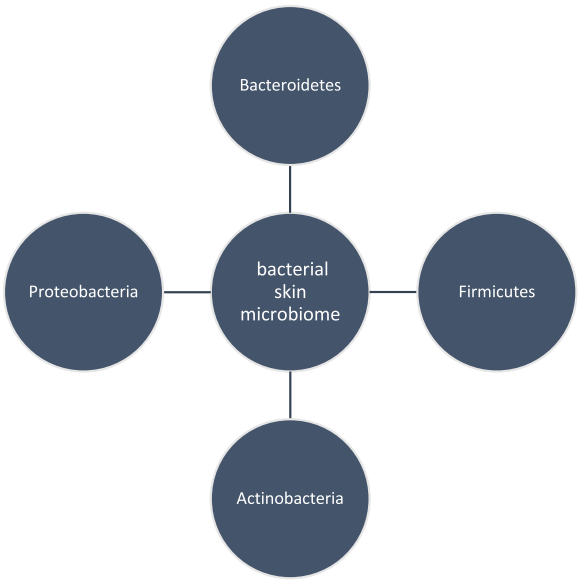

Fig. 2 Common bacteria present on the skin

qPCR (Fig. 3) have shown that both lesional and non-lesional skin sites contain Acinetobacter, Corynebacterium, Staphylococcus, Streptococcus, and Propionibacterium with Propionibacterium being more abundant in non-lesional sites (Wan et al. 2017).

These technological advancements have increased our knowledge of the disease etiology and the role of the microbiome in the symptom development significantly in recent years which could be helpful for redefining the therapeutic approaches.

Atopic dermatitis

Atopic dermatitis (AD) is another frequently studied disease using metagenomics. AD is a chronic, noninfectious, recurring inflammatory disease characterized by itching and xerosis that affects majorly children (approximately 15% children were affected in the USA). Effective treatments of this disease include antibiotics, corticosteroids, and dilute bleach baths (Huang et al. 2009). AD patients have an altered microbial community, and the pathogenesis is mainly associated with skin colonization by *Staphylococcus aureus* and immune hypersensitivity (Song et al. 2016; Weidinger et al. 2006). Filaggrin deficiency also plays role in AD as seen in mouse model with mutation in St14 that regulates filaggrin processing leading to increased Corynebacterium and Streptococcus and decreased Pseudomonas species (Scharschmidt et al. 2009). A 16S-rRNA-based metagenomic study of this disease has shown that both *S. aureus* and *S. epidermidis* increased in AD flares along with changes in abundance of some non-staphylococcal species leading to decreased bacterial diversity (Kong et al. 2012). There is domination of Staphylococcus, Pseudomonas, and Streptococcus in AD with Alcaligenaceae, Sediminibacterium, and Lactococcus being the characteristic of healthy skin, studied by high-throughput pyrosequencing on a Roche 454 GS-FLX

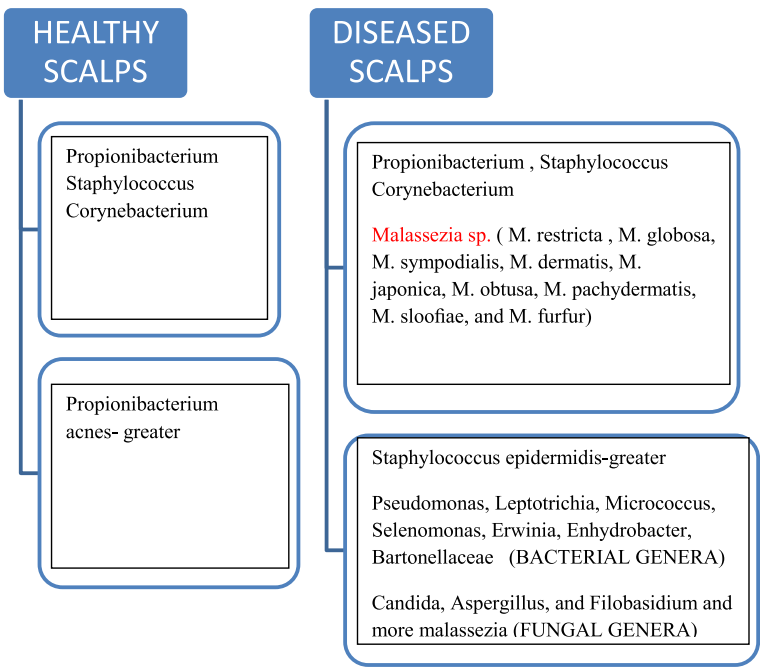

Fig. 3 Microbial genera present on healthy and dandruff subjects using next-generation sequencing (NGS), taxonomic analysis, high-throughput 16S rDNA and ITS 1 sequencing, pyrosequencing, and qPCR

platform (Kim et al. 2017). Hence, metagenomic analysis is important to study the action of these species and their association with the microbiome fluctuations and with one another. This will lead to designing of novel treatments like rebalancing of the skin microbiome.

Psoriasis

Psoriasis is a chronic inflammatory skin disease affecting about 2–3% of the world's population. Plaque psoriasis is the most common form of psoriasis affecting 85–90% of patients (Boehncke and Schon 2015). Although psoriasis is a skin disease, it can lead to development of psoriatic arthritis (PsA), metabolic syndromes, and cardiovascular diseases along with skin lesions (Grozdev et al. 2014). It has been known from the previously performed experiments that the immune system plays a key role in the disease pathogenesis. For PsA prevention in patients, the first step towards future development in therapeutics and early identification involves having the knowledge of the skin microbiome (Andersen et al. 2017; Castelino et al. 2014). Early culture-based studies identified Malassezia, group A and B beta-hemolytic streptococci, *S. aureus*, and *Enterococcus faecalis* being associated with the disease (Tett et al. 2017). 16S rRNA gene compositional analysis reveals that neonatal antibiotic treatment dysregulates skin microbiota and the imbalance is associated with development of experimental psoriasis. High-resolution shotgun metagenomics and finer strain-level analysis revealed decreased diversity and association of psoriasis with increase in Staphylococcus and its heterogeneity colonization and strain-level variability (Zanvit et al. 2015). Metagenomic study has been perceptive in understanding the taxonomic differences associated with psoriasis and hence offers the potential to overcome the limitations of culture-based studies.

Bovine digital dermatitis

It is a highly contagious infectious dermatitis with lesions near the interdigital spaces usually in cattle (Ganju et al. 2016). It causes discomfort and often severe lameness (LAMENESS, ANIMAL). Lesions can be either erosive or proliferative and wart-like with papillary growths and hypertrophied hairs. *Dichelobacter nodosus* and Treponema are the most commonly associated causative agents for this mixed bacterial infection disease (Drago et al. 2016; Krull et al. 2014) (year introduced, 2011).

Conclusions

Skin being the largest body organ leads to hundreds of skin conditions that have a significant impact on several aspects of human health and can lead to various skin disorders. It is vital to understand beneficial and harmful microorganisms and their mechanism. Advances in metagenomics and next-generation sequencing techniques have enhanced our ability to identify and characterize microbial communities colonizing the skin. It includes sensitive and rapid methods of sequencing to diagnose infection by comparing genetic material found in sample to a database of bacteria, viruses, and other pathogens. This field is promising in redefining therapeutic approaches for precision and personalized medicine and might transform management and treatment of dermatological disorders like acne vulgaris, seborrheic dermatitis, atopic dermatitis, psoriasis, and vitiligo by creating a broader view of disease etiology. However, for better diagnostic, prognostic, and therapeutic applications, further research is necessary to expand our understanding of healthy skin microbiota.

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Authors' contributions

YH conceived and designed the study. PN and YH wrote the manuscript. Both the authors approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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