

Human microbiome: What's new in scalp diseases

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Introduction

The human body is colonized by 100 trillion of microorganisms, including bacteria, archaea, viruses and very tiny eukaryotes [1]. In particular, the total number of bacteria in a reference man is reported to be around $3.8 \cdot 10^{13}$. The total number of fungal cells, the so-called 'mycobiome' is orders of magnitude smaller than that of bacterial cells [2]. Together with other less abundant (<0.1%) microorganisms, fungi are component of the rare biosphere [3,4] which significantly impact human health protection from pathogens [5].

The definition of the human microbiome is accompanied by terminology confusion since the term "microbiota" and "microbiome" are often used interchangeably. According to a correct definition, the term "microbiota" has to be referred to the microbial community associated with humans and the term "microbiome" both to microbes and the genes they share with humans.

Early study on human microbiome started in the 1680s by Antonie van Leeuwenhoek [6,7] highlighting for the first time the profound differences in the microbial community at different body sites.

Once these difference became obvious several large-scale microbiome projects have been launched all around the world [8-10] in order to explain the reasons behind microbial diversity and factor affecting it by mean of both culture-dependent and independent methods.

Advances in molecular and genetic techniques as well growing interest within the field resulted in an increase of the number of scientific publications on the topic, especially after the so-called "Microbiome Boom" between 2012 and 2013s (Figure 1).

Eubiotic microbiome for the human health

Different species of bacteria, fungi, and virus may inhabit the human body. Bacterial members belong mainly to Actinobacteria, Firmicutes, Proteobacteria, and Bacteroidetes phyla [11-14]. Each individual posses unique microbial communities residing in different anatomic site and each of this site harbor a peculiar microbial community, performing a specific function [7,15-18].

More similarity has been found between microbial communities at the same body site than between different body sites in the same individual [7]. At the same time, a large degree of intrapersonal variation has been found even in the absence of disease [7,19].

Microbiome biodiversity evolves fast from birth till the first year of life [20,21] continuously increasing its complexity with age [22-25].

Since human microbiome is characterized by a great variability the identification of a group of microorganisms related to health status is

not simple [26,27]. For the first time, in 2014, Shafqat and co-authors [28] changed the perspective by linking the health status to a core of metabolic and biological functions elicited by the microbiome in each body sited, independently from the microorganisms that would provide these functions. This is strictly related to higher consistency of the metabolic pathways across people compared to microbiome diversity [26]. Therefore in several recent studies high microbial diversity has been correlated to health [29] and temporal stability [30]. A healthy microbiome corresponds with a status of balance beneficial for the host. This state is also known as eubiosis. When extrinsic or intrinsic factors alter this balance microbiome switches to dysbiosis, losing in most cases, its biodiversity.

Many different factors can influence microbiome biodiversity either positively and negatively. Among these i) age [20,21,31]; ii) environmental factors [32]; iii) diet [33-36]; iv) inheritance [37]; v) antibiotics consumption [38,39]. To maintain is state of healthiness, the microbiome has to possess two main property: "resistance" and "resilience", that 's to say the ability to return to the previous healthy state [26,40].

There is an increasing evidence that lower degree of resistance and especially resilience may lead to several human disease predisposition as to the prevalence of various human disorders [41] as a consequence of microbiome dysbiosis.

Disease such as dental caries, bacterial vaginosis, obesity, autoimmune disease, diabetes, gastrointestinal and dermatological diseases have been linked to changing in microbial eubiotic balance [41]. More and more evidence is also accumulating as regards intercorrelation between microbiome, especially the intestinal one, and central nervous system and behavior [42,43]. More interesting, recently, the presence of a larger axis, the gut-brain-skin axis has been validated [44,45] paving the way to new therapeutic approaches.

The cutaneous and scalp microbiome

As the largest organ in human body [46,47] skin hosts an enormously diverse arrangement of the microorganism [48]. They belonging mainly to genus *Corynebacterium*, *Propionibacterium*, and *Staphylococcus* [11-14]. Microorganisms from this genus are differently predominant in each skin sites [14,49] and this depending on variability in terms of water content, of sebaceous glands, temperature, exposure to the environment [14]. For example drier sites showed Proteobacteria as the main phyla; on the contrary skin sites enriched in sebaceous

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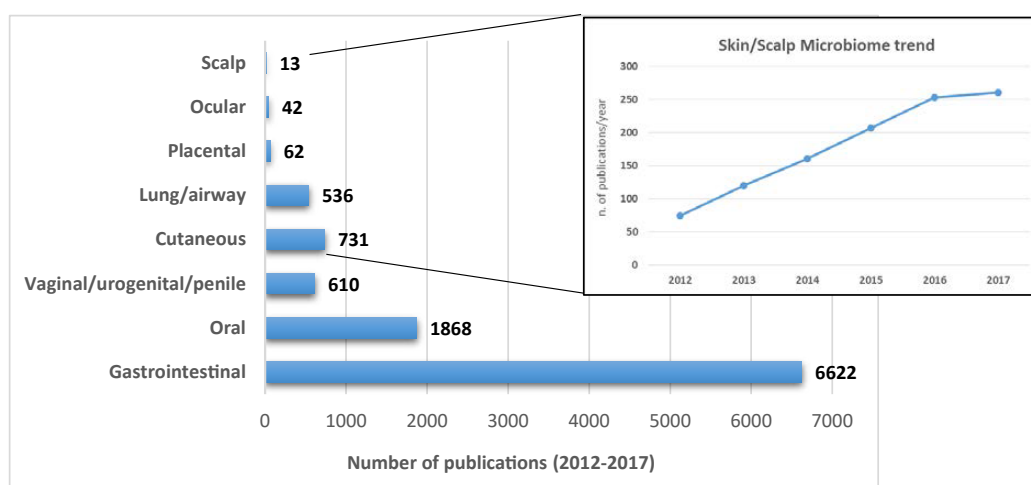


Figure 1. Microbiome research on different body sites. Number of results obtained by using the following keywords: “microbiome”, “microbiota”, “microflora”, “<body site>” on PubMed (retrieved 31 December 2017)

glands are populated mainly by species belonging to Actinobacteria such as suborders of Propionibacterineae and Corynebacterineae.

Study the role of skin microbiome for human health is acquiring importance day by day. First studies have been focused on pathogens affecting the skin but more recent works highlighted the crucial role of resident microbial communities in skin healthiness [50-52]. Microorganisms, establishing a symbiotic relationship with the skin, and this results, in the majority of the time, as beneficial both for microbial community and for the host [53-55]. Many skin conditions have been linked to an imbalance in this symbiotic mutualistic relationship [50,56-58]. For example, a diminishing in the abundance of *Propionibacterium* and *Actinobacteriaceae* has been linked to persistent skin infections [59]. Other studies reported the higher expression of Firmicutes and lower expression of Actinobacteria in psoriatic lesions [47,60]. A modification of the microbiome has also been shown to be implicated in another chronic inflammatory condition, atopic dermatitis [47]. The implication of *Propionibacterium acnes* in acne development is well established [61] but, more recently the involvement of other microorganisms has also been postulated [52]. Therefore, it has been shown that *Staphylococcus epidermidis* and *Staphylococcus aureus* inversely correlate each other and shifting of this correlation may increase the risk of skin diseases' onset [50].

Study of skin microbiome represent a novel diagnostic and therapeutic approach to many skin conditions, also including that strictly related to the scalp.

Although obviously sharing some characteristics with skin, scalp presents some distinctive tracts such as thickness, hair growth, more blood vessels and more sebaceous glands. These unique features expose scalp area to different peculiar diseases. As part of the skin organ, the scalp is in a symbiotic relationship with microbial communities that inhabits it and, since scalp unique features, this community is expected to be peculiar. As shown in Figure 1, The number of publications on the microbiome related to scalp area is very limited and published works are mainly related to the role of scalp microbiome in dandruff [62,63]. Thanks to advances in sequencing and metagenomic, new tools are currently available to study the role of the microbiome.

No studies are currently reported as regards microbiome involvement in scalp conditions related to hair growth, such as androgenetic alopecia, alopecia areata, and scarring alopecia. Considering the impact of such disease on human health and

their increasing incidence, the understanding on the impact of the microbiome and related changes could represent an improvement in clinical practice as well a tool for the development of advanced targeted therapeutic approaches.

Here we show our preliminary results on a panel of about 15 subjects for group affected by androgenetic alopecia (AGA), alopecia areata (AA), and lichen planopilaris (LPP), respectively. Each group has been compared to a panel of healthy subjects.

The main bacterial species (*P. acnes*, *S. epidermidis*, and *S. aureus*) inhabiting the scalp subject's were identified by quantitative PCR using species-specific primers.

All scalp conditions analyzed were correlated with a higher incidence of *P. acnes* compared to the population used as control ($p < 0,005$). Additionally, in subjects affected by AGA ratio between *S. epidermidis* and *S. aureus* diminished. This diminishing is more evident in subjects affected by AA where *S. aureus* becomes predominant on *S. epidermidis*. The role of *P. acnes* in the pathogenesis of hair casts and alopecia has previously been hypothesized [64] and our study represents the first clinical evidence correlating microbiome unbalancing to scalp hair disorders.

In subjects affected by LPP, a form of scarring alopecia, the predominance of *P. acnes* persists but is less evident than in the previous diseases analyzed (Figure 2). This could be linked to the loss of sebaceous glands commonly found in patients affected by LPP [65]. Our results showed also a higher *S. epidermidis*/*S. aureus*. It would be interesting, in future works, to analyze how this ratio would change according to a different stage of inflammation and in more lesional forms.

Conclusion

Nowadays, the study of human microbiome represents a novel diagnostic and therapeutic approach to treat many human conditions, also including that strictly related to skin and scalp.

The findings we included in the present work represent just an overview of a larger pioneer study on the involvement of changing of the microbiome in scalp diseases, especially that related to hair growth.

Even just preliminary, our results strongly highlighted, for the first time, the role exerted by unbalancing on the normal resident microbial community in hair growth-related conditions.

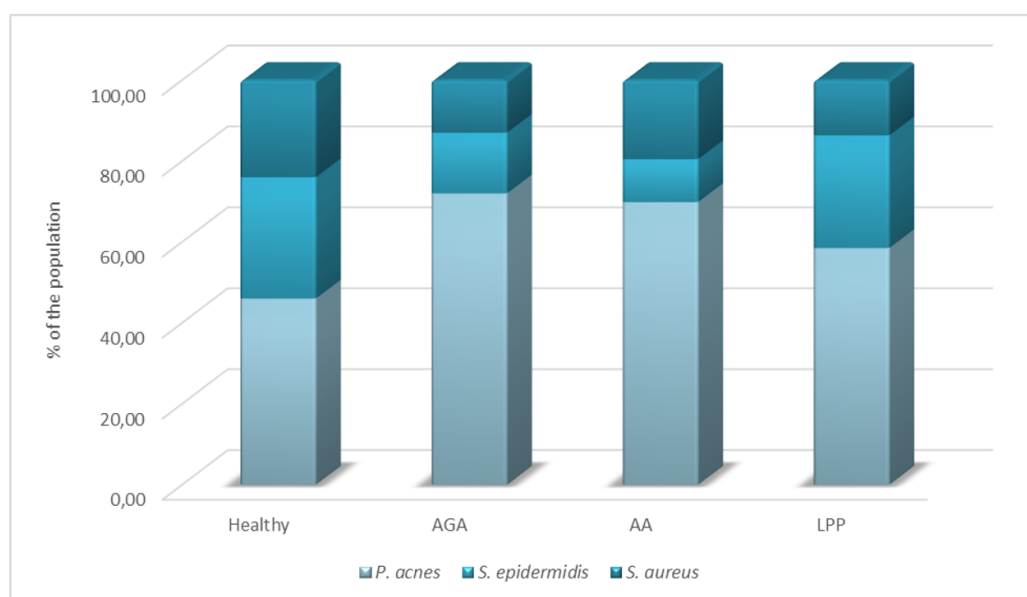


Figure 2. RT-qPCR quantification (% of the population) of main bacterial species (*P. acnes*, *S. epidermidis*, and *S. aureus*) inhabiting the scalp in the subject's affected by androgenetic alopecia (AGA), alopecia areata (AA), and lichen planopilaris (LPP), respectively. N=15

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