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REVIEW

Human Microbiome: Composition and Role in Inflammatory Skin Diseases

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Abstract
This review focuses on recent evidences about human microbiome composition and functions, exploring the potential implication of its impairment in some diffuse and invalidating inflammatory skin diseases, such as atopic dermatitis, psoriasis, hidradenitis suppurativa and acne. We analysed current scientific literature, focusing on the current evidences about gut and skin microbiome composition and the complex dialogue between microbes and the host. Finally, we examined the consequences of this dialogue for health and skin diseases. This review highlights how human microbes interact with different anatomic niches modifying the state of immune activation, skin barrier status, microbe–host and microbe–microbe interactions. It also shows as most of the factors affecting gut and skin microorganisms' activity have demonstrated to be effective also in modulating chronic inflammatory skin diseases. More and more evidences demonstrate that human microbiome plays a key role in human health and diseases. It is to be expected that these new insights will translate into diagnostic, therapeutic and preventive measures in the context of personalized/precision medicine.

Keywords Skin · Microbiome · Bacteria · Inflammatory skin diseases

Introduction

In the past years, advances in sequencing technologies along with new bioinformatic developments have allowed the scientific community to investigate microbes that inhabit our oceans, soils, the human body and elsewhere (Gilbert and Dupont 2011). The Human Microbiome is the collection of all the microorganisms living in association with the human body. Different microbial communities are found in different anatomical sites like nasal passages, oral cavity, skin, gastrointestinal tract and urogenital tract. These communities consist of a variety of microorganisms including eukaryotes, archaea, bacteria, viruses and skin mites. Bacteria of the Human Microbiome are numerically superior compared to the human cell and their genetic heritage is clearly superior to the human genome (Human Microbiome Project Consortium 2012). The recent research on the Human Microbiome has provided data which suggest that these microbes are generally not harmful to us, they are essential for maintaining health, being sensitive to genetic and environmental influences. An ever-growing number of studies have demonstrated that changes in the composition of our microbiome correlate with numerous disease states, raising the possibility that the manipulation of these communities could be used to treat illnesses (Lynch and Pedersen 2016). So the aim nowadays is to produce databanks of skin/gut microbiome samples each specific for a pathology to detect new challenging therapeutic strategies (Human Microbiome Jumpstart Reference Strains Consortium 2010). The NIH Common Fund Human Microbiome Project (HMP) was established in 2008, with the aim of characterizing the human microbiome and analysing its role in human health and disease. The HMP has developed metagenomic protocols for creating, processing and interpreting distinct types of high-throughput metagenomic data available to the scientific community (Human Microbiome Project Consortium 2012). Traditional microbiology has focused on the study of individual species as isolated units. However, the vast majority

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of microbial species have never been successfully isolated as viable specimens for analysis, presumably because their growth is dependent upon a specific microenvironment that has not been, or cannot be, reproduced experimentally (Bik et al. 2006; Verhelst et al. 2004). This aspect has caused an underestimation of biodiversity. For this reason, a new sequencing approach has been developed to overcome the limits of the 16s rRNA method, by sequencing genomic libraries made from DNA extracted from microbial communities sampled from natural environments. This approach is called "metagenomics" (Gilbert and Dupont 2011; Handelsman 2004; Tyson et al. 2004).

The Gut Microbiome: Composition and Functions

According to the hologenome concept, evolution in human can be linked to its symbiotic associated microbiota, whose influence reaches the entire host organism (Partida-Rodríguez et al. 2017; Requena et al. 2013). The imbalance in the composition and function of these intestinal microbes is called "dysbiosis" and is associated with different diseases (Lynch and Pedersen 2016). The healthy intestinal microbiota is an ecological community of trillions of microorganisms, containing viruses, bacteria, protozoa and fungi. The composition of the gut microbiota is influenced by stage of life, nutrition, lifestyle, gender, diurnal changes and despite the large number of distinct bacterial taxa, they belong to a small number of phyla. *Bacteroidetes* and *Firmicutes* are the most abundant taxa in the intestinal microbiota of healthy adult (Abdallah Ismail et al. 2011; Kundu et al. 2017). Thanks to next-generation sequencing of the small subunit ribosomal RNA (16s rRNA), it is now known that approximately 500–1000 bacterial species inhabit the human adult intestine, the predominant genera being *Bacteroides, Bifidobacterium, Eubacterium, Clostridium, Peptococcus, Peptostreptococcus, Lactobacillus* and *Ruminococcus* (Ley et al. 2008). The in utero environment has, until recently, been considered sterile. However, DNA sequencing-based microbial studies have detected bacterial species in the placentas of healthy mothers, in amniotic fluid of preterm infants, in the umbilical cord blood (Jiménez et al. 2005). Also the transient microbial community in the meconium supports a possible in utero route of colonisation (Table 1) (Aagaard et al. 2014; Di Giulio et al. 2008; Gosalbes et al. 2013). The way a baby is delivered influences postnatal microbial exposure: babies born by vaginal delivery are exposed to vaginal microbes (*Lactobacillus* and *Prevotella* spp.); otherwise, the microbiome of babies born via C-section is dominated by *Staphylococcus, Corynebacterium* and *Propionibacterium* spp., that resemble microbial communities of skin (Dominguez-Bello et al. 2010; Penders et al. 2006). During the first years of life, due to the introduction of solid foods, the composition of the intestinal microbiome becomes more complex, with a reduction of *Bifidobacteria* (Cheng et al. 2016). During puberty, major changes are driven by hormones, expressing genes related to development and growth, while the adult microbiome is more associated with inflammation and obesity (Agans et al. 2011; Hollister et al. 2015). During the adulthood, the composition of the gut microbiome reaches a certain stability, increasing microbial richness and complexity, with the predominance of anaerobes (Yatsunenko et al. 2012). Aging is accompanied by significant

Table 1 The Gut Microbiome during life (modified from Kundu et al. 2017)

In utero	Neonatal period	Childhood (first 2–3 years)	Puberty	Adulthood	Old age
~~Sterility hipotesis~~ Bacteria in: -placentas -amniotic fluid -umbilical cord blood -meconium ↓ in utero colonization = Low diversity ↑proteobacteria	Vaginal delivery: ↑Lactobacillus ↑Prevotella C-section delivery: ↑Staphylococcus, ↑Corynebacterium ↑Propionibacterium Breast milk: ↑Lactobacillus ↑Bifidobacterium ↑Staphylococcus ↑Enterococcus Formula milk: Alteration of early colonizers?	Solid foods: ↓Bifidobacteria ↑Microbiome richness	Influences by sex hormones: -↑genes of development / growth - acquisition of antibiotic resistance genes	↑Microbiome richness ↑Microbiome stability ↑↑anaerobes Antibiotic resistance genes ↓ Bacteroides, Bifidobacterium, Eubacterium, Clostridium, Peptococcus, Peptostreptococcus, Lactobacillus, Ruminococcus.	Changes in lifestyle: ↓Bacteriodetes ↑Firmicutes

changes in lifestyle, such as decreased locomotion, nutritional changes, chronic consumption of medication, with a general expansion of *Bacteroidetes* and reduction of *Firmicutes* phyla. Microbiome-associated metabolites (vitamins B7 and B12, creatine) and their biosynthetic pathways are reduced in aging, contributing to muscle atrophy and frailty (Kundu et al. 2017; O'Toole et al. 2015). The gut microbiota in semi-supercentenarians (105–109 years old) is characterized by increased abundance of "health-associated" taxa like *Bifidobacterium, Christensenellaceae* and *Akkermansia* (Biagi et al. 2016). The intestinal microbiota participates in numerous biological functions, having a central role in the maintenance of human body's homeostasis. It plays a critical role in the maturation and education of the host immune response. The low complexity and competitiveness of the developing early postnatal microbiota cause vulnerability toward exogenous influences, so alterations of the host response during the postnatal period influence resistance to infection (Fulde and Hornef 2014; Joyce and Gahan 2014). It affects host-cell proliferation, especially the gut microbiota is required for heme-induced epithelial hyperproliferation and hyperplasia because of the capacity to reduce mucus barrier function, and also vascularisation (Ijssennagger et al. 2015; Parker et al. 2018). The gut microbiota regulates intestinal endocrine functions (Cani et al. 2013) and neurologic signalling (Sherman et al. 2015). Metabolic functions are involved in energy harvest through breaking down indigestible compounds and regulating storage of energy, synthesizing essential vitamins and assisting in absorption of micronutrients, in biotransformation of xenobiotics (Requena et al. 2013). Several studies put in evidence the central role of the intestinal microbiome in different metabolic diseases like obesity, diabetes, hyperinsulinemia, etc. Scientists have documented that diet-induced obese mice show an increase in the proportion of gut microbiota members of *Firmicutes* and a decrease in *Bacteroidetes* when compared with their lean relatives (Turnbaugh et al. 2006) and that transplantation of gut microbiota from obese to germ-free mice conferred an obese phenotype, demonstrating the transmissibility of metabolic phenotypes (Rosenbaum et al. 2015). Jung et al. (2016) underlined that changes in the composition of intestinal microbiota induced by changes in the activity of the conserved serine/threonine kinase mammalian target of rapamycin, a molecular marker of tissue inflammation, correlate with obese and diabetic phenotypes.

The Skin Microbiome: Composition and Functions

The skin is our most exposed organ, responsible for providing a barrier to the external environment that can resist a wide range of challenges and respond appropriately to penetrating dangers. However, despite a potent cutaneous immune system, an abundant and diverse collection of bacteria, fungi and viruses inhabit the human skin. It is estimated that the human skin is inhabited by approximately one million bacteria/cm^2 (Byrd et al. 2018; Grice et al. 2008). These microorganisms have been reported to vary between individuals and between different sites on the skin. The skin provides many niches in which large populations of microbes are subjected to variable ecological pressures including humidity, temperature, pH and the composition of antimicrobial peptides and lipids. In addition, skin structures such as hair follicles, sebaceous, eccrine and apocrine glands constitute discrete niches that harbour unique microbiota. Historically, detection and characterisation of the skin microbes depended on their cultivation from swabs of the skin surface (Evans and Stevens 1976). With the advent of DNA-based technologies for the detection and identification of microbial genes, it is now clear that the culturable microbes represent only a small fraction of the total organisms that interact at the surface. DNA sequencing techniques have sought to describe the diversity of microbes residing on and within our bodies, and as a shorthand for describing the ecology of the human body as a "biome", the microbial communities inhabiting us have collectively been called the "human microbiome". At least 19 phyla are known to be part of the bacterial skin microbiome. Major examples are *Actinobacteria* (51.8%), *Firmicutes* (24.4%), *Proteobacteria* (16.5%) and *Bacteroidetes* (6.3%). The majority of the identified genera are *Corynebacterium, Propionibacterium* and *Staphylococus* (Grice et al. 2009). Most microbiome studies concentrate on understanding bacterial composition, but the microbes present in human skin habitats are not limited to bacteria. Viruses, fungi and mites are also important parts of the skin microbiota. Based on shotgun sequencing, fungi were found to comprise less than 1% of the microbiota in most body sites, except for the region around the ears and forehead, which had relatively higher abundances (Oh et al. 2014). In all of these skin regions, the main fungi observed throughout the human body were *Malassezia* spp., and most commonly *M. restricta, M. globosa* and *M. sympodialis* (Findley et al. 2013). *Malassezia* species are lipophilic microbes that are frequently associated with sebum-rich areas of the skin (Xu et al. 2007). The genus *Malassezia* comprised more than 90% of the relative abundances of fungi found in the human skin. One of the few exceptions was observed in the feet, which are colonized with much lower proportions of the genus *Malassezia*, and much more diverse fungal communities. Other eukaryotes that colonize the human skin belong to the phylum *Arthropoda*. Like *Malassezia* species, *Demodex* mites favour lipids of the sebum (Lacey et al. 2011). To date, two of the 0.2–0.4 mm long mite species are known to inhabit human skin. *D. folliculorum* is found in hair follicles in clusters with other mites of the same species. The smaller mite *D. brevis* resides alone in sebaceous glands or in meibomial glands which

are located at the rim of the eyelids (Lacey et al. 2009). Genomic studies based on shotgun sequencing have further been able to identify a vast viral population in the skin: the skin virome (Foulongne et al. 2012; Hannigan et al. 2015). Most of the skin virome was composed of bacteriophages, which are DNA viruses targeting bacteria. Of these, *Propionibacterium* and *Staphylococcus* bacteriophages were predominant in most skin sites. A few other viruses such as papillomavirus, polyomavirus and poxvirus were identified despite the fact the individuals had no clinical lesions. Even with development and improvement of these genomic studies, a large abundance of viral DNA found with shotgun sequencing could not be annotated, because viruses do not have conserved regions in their genome, as observed with rRNA genes in bacteria and fungi, and viral databases are largely incomplete (Delwart 2013).

About the functions of skin microbioma, several lines of evidence have indicated that commensal bacteria from the skin produce molecules with antimicrobial properties that can function in vivo to restrict the growth of cutaneous pathogens. Indirectly, the presence of commensal microbes on the skin results in competition for nutrients and space, thus greatly impacting the potential for growth when pathogens are introduced on the skin surface (Gallo and Nakatsuji 2011). Cutaneous microbes can influence the structure and function of the skin without penetrating the epidermis. Of the *Firmicutes, S. epidermidis* comprises more than 90% of all aerobic resident microbiota and has many mutualistic anti-inflammatory actions which promote barrier function and inhibit colonisation with potentially pathogenic strains of *S. aureus* and potential pathogens. This includes production of antibacterial peptides (bacteriocins), immunomodulatory properties (inhibition of inflammatory cytokine production) and enhanced expression of tight junction proteins. Many of these actions are mediated through activation of the innate immune receptors on keratinocytes and other local immune cells (via Toll-like receptors: TLRs). For example, activation of TLR2 has been shown to increase the tight junction barrier in cultured keratinocytes, illustrating another role for commensal microbes in maintaining barrier homeostasis, a crucial aspect of host defense (Prescott et al. 2017; Yuki et al. 2011). In the context of this complex environment, skin microbiome may differentially modulate skin immunity. Naik et al. (2012), studying the role of skin microbiome in shaping skin immunity, found that in mice, the skin microbiota has an autonomous role in controlling the local inflammatory milieu and tuning resident T lymphocyte function. Skin commensals tuned the function of local T cells in a manner dependent on signalling downstream of the interleukin (IL)-1 receptor. Therefore, resident commensals are required for optimal IL-1 signalling in the skin, for promoting local effector responses. These results support the idea that defects in T-cell function at steady state or during inflammation result from an impaired dialogue with skin commensals. Thus, via their capacity to promote IL-1 signalling and consequently effector T-cell function, skin commensals are likely important drivers and amplifiers of skin pathologies (Naik et al. 2012). Commensal-specific T-cell responses result from the coordinated action of skin-resident dendritic cell subsets, revealing that tissue-resident cells are poised to sense and respond to alterations in microbial communities. This interaction may represent an evolutionary means by which the skin immune system uses fluctuating commensal signals to calibrate barrier immunity and provide heterologous protection against invasive pathogens (Naik et al. 2015). Viruses also influence the bacterial community structure and function by several mechanisms, including killing their host and mediating genetic exchanges. Several phages are known in *Staphylococcus, Pseudomonas* and *Propionibacterium* species (Ceyssens and Lavigne 2010). So far it is not clear to what extent bacteriophages have an impact on the skin microbiome. Phages have been shown to reduce microbial colonisation and pathology in a host-independent way.

Skin Microbiome and Chronic Inflammatory Skin Diseases

Human microbiome interacts with human host by secretion of metabolites from microbes that are scanned by immune system for information about metabolic state and colonisation. This continuous crosstalk is important for the establishment and maintenance of host homeostasis. Alteration in microbiome composition could lead to a shift in immune system reactivity and subsequently to inflammatory disease development (Tlaskalova-Hogenova et al. 2011). For this reason, in the past few years the possibility to translate findings in microbiome research into developing new integrated model of the pathogenesis of inflammatory disease has aroused a lot of interest. The attention has been focused also to unveil novel potential therapeutic targets. An emerging evidence supports the existence of communication axes between gut and skin (Arck et al. 2010; Bowe et al. 2014), suggesting that not only skin microbiome influences the pathogenesis of many skin inflammatory disorders, such as atopic dermatitis (AD), psoriasis, acne and hidradenitis suppurativa (Honda and Littman 2016). Although there are convincing findings to suggest that dysbiosis causes or promotes disease, the underlying mechanisms are not fully understood. It has been established that microbiotal dysbiosis can be caused by genetic predisposition, infections and changes in diet and nutritional status, as well as by the use of antibiotics (Honda and Littman 2016). Dysbiosis lead to an aberrant activation of immune cells, compromising barrier function of the epithelium. Disruption of the epithelial barrier might,

therefore, lead to dysregulated immune responses to commensal microbes, stabilisation of a pro-inflammatory community of microbes and, ultimately, to the chronic inflammation (Honda and Littman 2016). Future studies should focus on how skin and gut dysbiosis contribute as well as can play a protective role against chronic inflammatory skin diseases. In Table 2 we summarize significant changes in skin and gut microbiome associated with chronic inflammatory skin diseases.

Atopic Dermatitis

AD is a chronic inflammatory skin disease affecting ~ 10 to 20% of the general population (Williams 2005). AD is a complex multifactorial disease, associating with both genetic risk factors and environmental stimuli (Bin and Leung 2016; Sandilands et al. 2007). Among environmental factors, it has been demonstrated that perinatal exposure to indoor and outdoor allergens and pollutants as well as nutrition and microbiome play a crucial role to influence severity and clinical course of the disease (Byrd et al. 2017; Kong et al. 2012; Williams and Gallo 2015). Dysbiosis has been hypothesized as one of the key hallmark, driving disease severity and tendency to relapse (Williams and Gallo 2015). It includes a decreased Gram-negative bacteria and an abnormal skin colonisation by *S. aureus* (Kong et al. 2012). Indeed, many studies have reported that *S. aureus* was abundant on lesional AD skin compared with non lesional as well as healthy skin (Bourrain et al. 2013; Gonzalez et al. 2016; Kong et al. 2012; Oh et al. 2013; Seite et al. 2014; Shi et al. 2016). Interestingly, it has been shown that with respect to xerotic areas, inflamed ones and during a flare, the abundance of *S. aureus* increased dramatically in untreated patients (Kong et al. 2012). However, in lesional AD skin other species were also incresead, such as *S. epidermidis* and *S. haemolyticus* (Kong et al. 2012; Oh et al. 2013; Seite et al. 2014). Since these species produce antibacterial compounds, such as antimicrobial peptides and bacteriocins, a relative decrease in

Table 2 Significant changes in skin and gut microbiome associated with chronic inflammatory skin diseases

Disease	Significant changes in skin microbiome	Significant changes in gut microbiome
AD	↑ *Staphylococcus aureus* (1–6) ↑ *Staphylococcus epidermidis* (1, 3, 6) ↑ *Staphylococcus haemolyticus* (1, 3, 6) ↓ Propiniumbacterium (1, 5) ↓ Corynebctarium (1, 5) ↓ Streptococcus (1, 5)	↑ *Staphylococcus aureus* (7) ↑ *Faecalibacterium prausnitzii* (8) ↓ *Escherichia coli* (9)
Pso	↑ Streptococcus (10, 11) ↑ Propiniumbacterium (10, 11) ↑ Corynebctarium (10, 11) ↑ *Staphylococcus aureus* (10, 11) ↓ Firmicutes (10, 11) ↓ Actinobacteria (10, 11)	↑ *Escherichia coli* (12, 13) ↓ *Faecalibacterium prausnitzii* (12, 13)
HS	↑ *S. aureus* (14, 15, 16, 17) ↓ *S. aureus* (18) ↑ Coagulasi-negative staphylococci (14, 18) ↑Corynebacterium (14, 19) ↑ *Porphyromonas* and *Peptoniphilus* (19) ↑ Milleri group streptococci (*S. anginosus, S. constellatus, S. intermedius)* (20) ↑ Actinomycetes (20) ↑ Prevotella, Porphyromonas (20)	= *Escherichia coli* (21) = *Faecalibacterium prausnitzii* (21)
Acne	↑ Propionibacterium Acnes (22, 23, 24) ↑ *Staphylococcus epidermidis* (25, 26, 27, 28) ↑ Proteobacteria and Firmicutes (28) ↓ Actinobacteria (28) ↑ Streptococcus (29) ↑ Malassezia species (30, 31)	↑ *Escherichia coli* (32) ↑ Bacteroides (33)

(1) Kong et al. (2012); (2) Shi et al. (2016); (3) Oh et al. (2013); (4) Bourrain et al. (2013); (5) Gonzalez et al. (2016); (6) Seite et al. (2014); (7) Nowrouzian et al. (2017); (8) Orivuori et al. (2015); (9) Song et al. (2016); (10) Alekseyenko et al. (2013); (11) Gao et al. (2008); (12) Ivanov et al. (2009); (13) Stepankova et al. (2007); (14) Ring and Emtestam (2016); (15) Jemec et al. (1996); (16) Lapins et al. (1999); (17) Kurzen et al. (2008); (18) Sartorius et al. (2012); (19) Ring et al. (2017b); (20) Guet-Revillet et al. (2017); (21) Eppinga et al. (2016); (22) Fitz-Gibbon et al. (2013); (23) Ladizinski et al. (2014); (24) NIH HMP Working Group et al. (2009); (25) Christensen et al. (2016); (26) Wang et al. (2014); (27) Wang et al. (2014); (28) Dreno et al. (2017); (29) Coughlin et al. (2017); (30) Findley et al. (2013); (31) Grice (2014); (32) Juhlin and Michaëlsson (1983); (33) Loveman et al. (1955)

other species, including *Propionibacterium, Corynebacterium* and *Streptococcus*, occurs during flares in involved AD skin. This is responsible for a low bacterial diversity on AD skin respect to control skin (Gonzalez et al. 2016; Kong et al. 2012). Significant differences between young children and adults-teenagers have been identified: in AD non-lesional skin, the microbiome diversity was significantly higher in young children than in adults-teenagers (Shi et al. 2016). The potential therapeutic benefit of microbiome modulation is still little known in AD. Recently, it has been reported that treatment with culturable Gram-negative bacteria from healthy controls was associated with enhanced barrier function, innate immunity activation and control of *S. aureus* in a mouse model of AD. These findings highlight that a livebiotherapeutic approach may hold promise for treatment of AD patients (Myles et al. 2016). Regarding the fungal microbiome in AD skin it is characterized by high *non-Malassezia* fungal diversity respect to healthy skin, including *Aspergillus, C. Albicans* and *C. diffluens* (Oh et al. 2013; Zhang et al. 2011). The 50% of *S. aureus* that colonized skin AD is toxin producing. These toxins, such as superantingens, α-δ-toxin and proteases, contribute to inflammation and skin barrier dysfunction activating the host inflammasome (Geoghegan et al. 2018; Park et al. 2016). Moreover, *S. aureus* was able to directly activate immune response, penetrating into epidermidis and increasing the expression of several interleukins, such as IL-4, IL-13 and IL-22, as well as to directly impair skin barrier by stimulating keratinocytes to produce serine protease (Nakatsuji et al. 2016; Williams et al. 2017). Although multiple studies, reported above, have shown increased *S. aureus* colonisation in children and adult AD patients, a question remains still unclear: does *S. aureus* precede the onset of the disease? Recently, Kennedy et al. (2017) concluded that *S. aureus* colonizes skin after onset of AD. However, another recent larger longitudinal study detected *S. aureus* colonisation before clinical onset of AD (Meylan et al. 2017). This evidence is very interesting, suggesting that *S. aureus* may cause AD. More than skin dysbiosis, it has been established that disturbances in gut microbiome could also represent a risk factor for AD development. The use of antiobiotics intrapartum increased the risk for AD by 1.99 (Wohl et al. 2015). *S. aureus* was isolated from rectal swabs from infants aged 0–2 months (Nowrouzian et al. 2017). There is an inverse correlation with intestinal *E. coli* colonisation and disease severity (Orivuori et al. 2015) Moreover, a recent study has observed an enrichment of *F. prausnitzii* F6 in AD patients with respect to controls, most distinct in youngest patients (Song et al. 2016).

Psoriasis

Psoriasis (Pso) is a chronic inflammatory disease affecting approximately 2–4% of the world's population (Parisi et al. 2013). Upon a genetic predisposition, several environmental factors, including bacterial infection, antibiotic treatment or profound changes in diet, can play the role of "triggers" (Bhatia et al. 2014; Debbaneh et al. 2014; Di Meglio et al. 2014). These evidences suggest a potential important involvement of microbiome in the disease, even if how host–microbe interaction contributes to Pso pathogenesis is still largely unknown (Fry et al. 2013). Certanly, this interaction is able to activate innate immune response involving TLRs, that are known to be up-regulated in Pso (Zeng et al. 2017). This triggers several signaling transduction pathways (e.g. JNK and IKKβ/NF-κB), leading to inflammatory cytokine and chemokine production, such as tumor necrosis factor α, the most important inflammatory mediator of Pso pathogenesis. Many microbes have been reported to be able to regulate the balance of Th1/Th2 immune response, such as *B. fragilis* (Zeng et al. 2017) via producing polysaccharide A as well as *B. infantis* (Groeger et al. 2013). Fry et al. (2013, 2015) proposed another very interesting link between microbiome and Pso: they suggested that Pso may reflect an abnormal innate immune response to the skin microbiome, mainly driven by IL-23 and IL-17, rather than being an autoimmune disease. Using a mouse model of Pso it has been demonstrated that antibiotics targeting Gram-negative and Gram-positive bacteria could ameliorate psoriasiform dermatitis inhibiting the production of IL-17 and IL-22 (Zanvit et al. 2015). IL-22-producing T cells seem to play a crucial role in the aggravation of skin inflammation (Zanvit et al. 2015). It is well known that *Streptococci* are trigger factors for Pso (Norrlind 1950; Robinson 1953; Valdimarsson et al. 1995), especially, for the guttate subtype. However, a recent evidence has shown how streptococcal throat infections are also associated with exacerbations of chronic plaque Pso (Thorleifsdottir et al. 2016). Presence of bacteria, including *S. pyogenes*, has been demonstrated in the peripheral blood of patients with guttate and chronic plaque Pso (Munz et al. 2010). Moreover, the potential therapeutic role of tonsillectomy in Pso has been discussed in the past few years (Rachakonda et al. 2015). Microbial infections are not only well-known risk or aggravating factor, but also a tool of natural selection for a pro-inflammatory genotype that predisposes to Pso development (McFadden et al. 2009; Naldi et al. 2001). Microbiome associated with psoriatic skin lesion is significantly different from that associated with healthy skin. It has been reported that there was a trend towards decreased bacterial diversity in Pso. *Propionibacterium, Corynebacterium, Streptococcus* and *Staphylococcus* were significantly increased in lesional skin compared with non lesional as well as healthy skin (Alekseyenko et al. 2013; Gao et al. 2008). On the other hand, *Firmicutes* and *Actinobacteria* were significantly reduced in psoriatic skin (Alekseyenko et al. 2013; Gao et al. 2008). An interesting recent study showed significant alterations of skin microbiome after treatment

with ultraviolet B (UVB) in psoriatic patients (Assarsson et al. 2018). The authors reported lower abundance of the genera *Staphylococcus, Finegoldia, Anaerococcus, Peptoniphilus, Gardnerella, Prevotella* and *Clostridium* in lesional psoriatic skin after UVB. Moreover, *Pseudomonas* significantly decreased in lesional and non-lesional skin. Although these results are very fascinating further studies are needed to confirm them.

However, the link between microbiome and Pso may be not limited only to skin microbiome, since it has been demonstrated that gut microbiome also profoundly influenced the immune system development and reactivity (Eppinga et al. 2016; Ivanov et al. 2009; Stepankova et al. 2007). A recent study analysed the link among microbiome, T cells and the formation of psoriatic lesions in the imiquimod-induced murine model of Pso (Zákostelskáet al. 2016). Interestingly, it has been shown that antibiotics changed gut microbiome composition and prevented severe forms of skin inflammation. Moreover, the results demonstrated how microbiome was able to drive skin inflammation by inducing stronger Th17 activation (Zákostelská et al. 2016), supporting the fascinating hypothesis of Pso as a disease promoted by an abnormal innate immune response. Another important aspect regards how genetic polymorphisms in the genes associated with Pso could contribute in changes of microbiome and whether this changes are present before clinical manifestation onset. Future studies are needed to properly answer to this question.

Hidradenitis Suppurativa

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease defined by recurrent nodules, abscesses, fistulae and scarring involving the intertriginous regions. Although the clinical presentation of HS is strongly reminiscent of bacterial infection, the role of bacteria remains controversial. Indeed, the efficacy of antibiotics may support a microbial role in disease pathogenesis, whereas the most often isolated bacterial specimens are commensal bacteria (Ring and Emtestam 2016). The polymicrobial flora and in particular the dominating occurrence of commensal bacteria in HS lesions may raise speculations on the pathogenetic significance of this recurring bacteriological finding (Ring et al. 2015). *S. aureus* is frequently found in HS and has often been proposed as having a potential role in the disease (Jemec et al. 1996; Lapins et al. 1999). It is well known that a predominant part of patients with HS are smokers and *S. aureus* has also been linked to this habit (Kromann et al. 2014). Interestingly, Matusiak et al. (2014) found that among the recruited population, subjects with *S. aureus* were heavy smokers. Moreover, it has been speculated that an association between *S. aureus* and nicotine may influence the disease development as nicotine may promote the growth of this pathogen (Kurzen et al. 2008). Jemec et al. (1996) proposed that *S. aureus* may be involved only in the initial process of disease, facilitating anatomical alterations in the hair follicles by inflammation and necrosis. Other several microbes have been detected in HS: Sartorius et al. (2012) found *Coagulase-negative staphylococci* (CNS) in the deep layers of ten patients undergoing carbone dioxide laser. Nine of the patients carried *Corynebacterium* spp. and *two alpha-haemolytic streptococci* at various levels. Among the anaerobic microorganisms, Gram-positive cocci were the most common bacteria. Contrary to what they expected, *S. aureus* was not found in any cultures from acute inflammatory nodules of HS exacerbations (Sartorius et al. 2012). Recently it has been reported a case–control study in patients with HS and healthy controls. The following five microbiome types were identified: *Corynebacterium* species (type I), *Acinetobacter* and *Moraxella* species (type II), *S. epidermidis* (type III), *Porphyromonas* and *Peptoniphilus* species (type IV), and *P. acnes* (type V). In lesional skin, microbiome types consisted predominantly of type I or type IV. Microbiome type IV was not detected in healthy controls (Ring et al. 2017b). It has been hypothesized that clinically unaffected HS skin would also have an increased presence of biofilm compared with that of healthy controls. Nevertheless, a case–control study, investigating the morphology of the axillary skin microbiota, showed fewer bacteria and less biofilm in patients with HS compared with healthy controls (Ring et al. 2017a). Mixed anaerobic microbiota are associated with HS lesions. Guet-Revillet et al. (2017) detected anaerobes in 83% of lesions versus 53% of control samples, combined with milleri group streptococci (*S. anginosus, S. constellatus, S. intermedius*) and *actinomycetes* in 33% and 26% of cases, respectively. The authors have identified 43 taxa associated with HS lesions. Two Gram-negative anaerobic taxa, *Prevotella* and *Porphyromonas*, predominated, contrasting with a reduced abundance of aerobic commensals. Two main additional taxa, *Fusobacterium* and *Parvimonas*, correlated with the clinical severity of HS (Guet-Revillet et al. 2017). Very few data are available among gut microbiota and HS. It is known that HS co-occurs more often with inflammatory bowel disease (IBD) than expected. IBD patients harbour an altered intestinal microbiome characterized by a depletion of *Faecalibacterium prausnitzii* and increase of *Escherichia coli*. Eppinga et al. (2016) found no significant difference in *F. prausnitzii or E. coli* abundance in HS patients. Moreover, since the prevalence of obesity among HS patients is very high, we should consider this aspect: particularly it has been recently described how the gut microbiota may change depending on the age among obese subjects (Del Chierico et al. 2018).

Acne

Acne is a common inflammatory skin disease affecting 70–80% of adolescents with a considerable psychological and social impact (Fabbrocini et al. 2014). *P. acnes* is known to be one of the main factors involved in the development of acne (Bellew et al. 2011; Bhambri et al. 2009). Even though the association between *P. acnes* and acne vulgaris is well established, very few studies have investigated the skin microbiota of patients with acne. Cutaneous bacterial communities have been shown to be involved in inflammatory responses as well as immune homoeostasis and both are known for triggering acne (Belkaid and Segre 2014; Byrd et al. 2018). During adolescence, androgen hormones lead to an increase production of sebum and a high colonisation of *P. acnes* inside the sebaceous gland (Findley and Grice 2014). Sorel Fitz-Gibbon et al. (2013) compared skin microbiome at strain level as well as genome levels of *P. acnes* between acne and healthy individuals. They identified potential genetic determinants of various *P. acnes* strains associated with acne or healthy subjects. *P. acnes* plays a physiological role in inhibiting the invasion of pathogenic bacteria while allowing other commensal *Staphylococci* strains such as *S. epidermis* to grow (Ladizinski et al. 2014; NIH HMP Working Group et al. 2009). Indeed, *S. epidermidis* and *P. acnes* have been shown to interact. In details, Christensen et al. (2016) screened 77 *P. acnes* strains isolated from healthy and acne-affected skin, representing all known phylogenetic clades (I, II, and III), for their antimicrobial activities against 12 *S. epidermidis* isolates. One particular phylogroup (I-2) exhibited a higher antimicrobial activity respect to other *P. acnes* phylogroups whereas the majority of *S. epidermidis* strains were able to inhibit *P. acnes* (Christensen et al. 2016). Other authors have also analyzed this interaction suggesting that *S. epidermidis* owns an arsenal of different mechanisms to inhibit proliferation of *P. acnes* participating in the equilibrium of the microbiota (Wang et al. 2014). Moreover, it has been shown that *S. epidermidis* inhibits *P. acnes*-induced inflammation in skin (Xia et al. 2016). Skin microbiota in acne is obviously influenced by topical treatment, since most of them are represented by antibiotics and/or antiseptics. Dreno et al. (2017) investigated characteristics of skin microbiota in subjects with acne before and after the application of erythromycin 4% or a dermocosmetic. Before starting therapy, microbiota samples showed an overabundance of *Proteobacteria* and *Firmicutes* and an under-representation of *Actinobacteria. Propionibacteria* represented less than 2% of the bacteria on the skin surface. *Staphylococcus* remained the predominant genus of the superficial skin microbiota. Both topical treatments are able to modify skin microbiota: erythromycin reduced the number of *Actinobacteria* while the dermocosmetic reduced both the number of *Actinobacteria* and *Staphylococcus* spp. (Dreno et al. 2017). In addition, several factors, such as hygiene and environment, may involve changes in the microbiota composition among healthy and acneic skin (Bouslimani et al. 2015). It has to be taken into account that there are different types of acne depending also by the age; in fact, acne tends to be more comedonal in preadolescents. Given this, it has been hypothesized that the microbiome of preadolescents might be different. Coughlin et al. (2017) found that preadolescents with acne were colonized with a greater diversity of cutaneous bacteria than controls and the most commonly identified bacterium was *Streptococcus*. Regarding fungi, microbiota in sebaceous areas tends to be less diverse than bacterial communities, dominated by *Malassezia* species, specifically *M. restricta* and *M. globosa* (Findley et al. 2013; Grice 2014). Even though, Numata et al. (2014) found that acne patients and controls did not show significant differences in *Propionibacterium* and *Staphylococcus* spp. populations. Only a few researchers have investigated the gut microbiome in acne patients. Stokes and Pillsbury (1930) found that a high percentage of acne patients had hypochlorhydria: hypochlorhydria has been shown to be a significant risk factor for small intestinal bacterial overgrowth, which can cause increased intestinal permeability, leading to systemic inflammation (Lombardo et al. 2010; Reddymasu et al. 2010). Several studies suggested that intestinal permeability might be augmented in acne vulgaris (Clark et al. 2017). Strickler et al. (1916) demonstrated an enhanced reactivity to stool-isolated coliforms in 66% of the acne patients respect to controls. Juhlin and Michaëlsson (1983) found the presence of lipopolysaccharide endotoxins from *E. coli* in the serum of acne patients. These results suggest that gut microbes may enhance the presence of circulating endotoxins in the blood of acne vulgaris patients compared to healthy controls. Indeed, acne appears to have a potential gut-skin connection that may be caused by gut microbiota modifications. Loveman et al. (1955) found that *Bacteroides* species were more commonly isolated from acne patients. Russian investigators observed that 54% of acne patients have differences in their intestinal flora compared to healthy control (Volkova et al. 2001).

Therapeutic Manipulation of Microbiome

The realisation that commensal microorganisms are not only simple "passengers" onto our bodies, but instead have key roles in our physiology, including adaptive-immune responses and metabolism, as well as in disease, is one of the most exciting scientific advances in recent years (Blaser et al. 2013). Corresponding to the increased understanding of the role of human microbiome in influencing host health and disease, there has been an intense investigation of potential means to manipulate human microbiome

and improve health (Young 2016). Moreover, the acquired knowledge that changes in human microbiome promote cutaneous inflammation has raised the question whether it could be manipulated for therapeutic intent as well as its resilience could have implications on treatments effectiveness of chronic inflammatory skin diseases. Indeed, microbiome, especially on the skin, is an easily accessible target for therapeutic intervention; thus cutaneous as well as intestinal microbiology have been attractive areas of research for decades, providing important insights into bacterial, fungal, and viral populations living on the skin and in the gut (Human Microbiome Project Consortium 2012). However, while investigations into human-associated microbial communities were once limited by culture-based techniques, the advent of next-generation sequencing technologies has completely revolutionized the methods to characterize human microbiome, introducing the concept of "precision microbiome manipulation" (Grice 2014). For example, it is well known that bacteriophages can be induced to replicate and lyse their host upon UV exposure, so an intriguing hypothesis has been that UV exposure might change bacterial communities composition via predator–prey dynamics between bacteriophages and their hosts (Grice 2015). As we have already reported, in a recent investigative report, Assarsson et al. (2018) demonstrated that narrow-band Ultra Violet B (nbUVB) therapy significantly alters the skin microbiome of subjects with moderate-to-severe Pso. In particular, after nbUVB treatment, responder patients had a significantly lower relative abundance of the phylum *Firmicutes* as well as *Pseudomonas* in both lesional and non-lesional skin and a significantly lower relative abundance of the phylum *Bacteroidetes* in non-lesional skin, compared with non-responders (Assarsson et al. 2018). Other studies have confirmed that UV radiations lead to various changes in the landscape of microbial communities of the skin (Dotterud et al. 2008; Hon et al. 2016; Thyssen et al. 2015). Moreover, UV exposure also induces the production of antimicrobial peptides, which participate in innate immune responses and activate and mediate adaptive immune responses (Niyonsaba et al. 2007; Patra et al. 2016). In AD patients has been shown that UVB treatment significantly reduced skin-surface bacteria, mainly the *S. aureus* count, and decreased the production of super-antigens, which are known to be potential triggers of immune responses (Dotterud et al. 2008; Thyssen et al. 2015). Beyond this, an alternative approach to positively manipulate microbiome has been developed, based on the recognised idea that functional integrity as well as microbial residents of the intestinal tract are able to indirectly modulate host inflammatory pathways (Ohland and Jobin 2015). Therefore, modifications aimed at achieving, restoring and maintaining the activity of gastrointestinal microorganisms have been proven to be useful for the improvement of host health conditions (Markowiak and Śliżewska 2017). Among them, the most common manipulation strategy occurs through the diet. Indeed, gut microbiome is positively modified by the ingestion of live organisms, as probiotics, as well as by the use of prebiotics, which promote the growth of commensal organisms in the gut, and/or of antibiotics, which remove or suppress undesirable microbial components (Markowiak and Śliżewska 2017). Additionally, faecal transplantation is currently used to treat recurrent *Clostridium difficile* infection (CDI), a gastrointestinal disease responsible of the gut microbiome perturbations (Rao and Young 2015). Moreover, given the strong correlation existing between gut and skin microbiome, most of the factors affecting the gastrointestinal microorganisms' activity, have demonstrated to be effective also in modulating chronic inflammatory skin diseases (O'Neill et al. 2016).

Probiotics and Prebiotics in Chronic Inflammatory Skin Diseases

Probiotics are food ingredients defined as "living microorganisms which, when administered in adequate amounts, confer a health effect to the host" (Food and Agriculture Organization and World Health Organization Expert Consultation 2001). Upon ingestion, these agents, resistant to gastric acid digestion and bile salts, barricade the epithelium and mucosal surfaces in the intestine, thus preventing pathogens adherence and invasion (Servin and Coconnier 2003). Currently, the most common types of microorganisms used as probiotics are LBA, such as *Lactobacilli*, and *Bifidobacteria*, but products incorporating other organisms as Gram-positive cocci, bacilli, yeasts, and *E. coli* have been applied (Borriello et al. 2003). In particular, they may be naturally occurring microbes (as is the case for all used in food), or microbes that have been genetically altered for a specific effect (Sanders et al. 2010). Otherwise, prebiotics are "non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limiting number of bacterial species already resident in the colon" (Gibson and Roberfroid 1995). Therefore, any food ingredient that enters the large intestine is a candidate, but only those resistant to fermentation can be classified as prebiotics (Gibson 1998). Moreover, although probiotics and prebiotics have been widely used in the past for the treatment/prevention of gastrointestinal disorders, a growing number of evidences has suggested that they, modulating the composition of microbial community, induce both innate and adaptive immune responses which extend beyond the gut and may even affect also the skin (Ouwehand et al. 2002). To date, probiotics exert their health effects on the skin directly, through cutaneous formulations (skin microbiome) or indirectly, through dietary supplementary formulations and intestinal microflora improvement (gut microbiome) (Roudsari et al. 2015). Nevertheless, not many studies

about the use of probiotics and prebiotics in dermatology have been conducted, with the exception of AD, and even in this context their clinical use is resulted controversial (Baquerizo Nole et al. 2014). In 2008, a first meta-analysis of ten randomized trials comprising 781 children found that probiotics were not effective in AD treatment (Boyle et al. 2008) as well as a second meta-analysis of others ten trials encompassing 1898 children demonstrated that they might be more efficacious in preventing AD than treating it (Lee et al. 2008). Subsequently, a double blind randomized placebo-controlled study investigated the effects of the use of the *Lactobacillus plantarum CJLP133* strain in AD prevention. This study, performed for a time period of 12 weeks among children who were 1 and 12 years old, showed an improvement in SCORAD, with a concomitant decrease in interferon γ, eosinophil,and IL-4 counts (Han et al. 2012). A more recent trial demonstrated that in a high-risk birth cohort, maternal supplementation from 35 weeks' gestation until 6 months if breastfeeding and infant supplementation until 2 years with *Lactobacillus rhamnosus HN001* was able to decrease the prevalence of AD in these children at 4 years, but without a significant SCORAD reduction (Wickens et al. 2013). Moreover, two prospective randomized and placebo-controlled trials using only prebiotic galacto-oligosaccharides or a mixture of prebiotics showed that they failed to reduce severity of AD in infants (Boženský et al. 2015; van der Aa et al. 2010), while another trial suggested their temporary preventive effect (Kukkonen et al. 2007). In addition, several investigations reported that the appropriate use of probiotics and prebiotics (synbiotics) could bring significantly better results as part of the treatment of AD in children (Chang et al. 2016). Regarding the role of probiotics and prebiotics in adult AD, there are even fewer data. Clinical trials showed that *lactobacilli* as well as *Lactobacillus paracasei K71* were useful in decreasing itch and burning scores in AD patients (Betsi et al. 2008; Moroi et al. 2011). Moreover, the oral application of *Lactobacillus salivarius LS01* and *Bifidobacterium breve BR03* for 12 weeks to adult patients with AD improved severity, quality of life and ratio of Th17/Treg cells diminishing immune activation and microbial translocation (Drago et al. 2012; Iemoli et al. 2012). Similarly, prebiotics administered simultaneously with black currant seed oil resulted effective in reducing the development of AD (Foolad and Armstrong 2014). The effects of probiotics and prebiotics in modulating AD inflammation could be related to several mechanisms including inhibition of Th2 and stimulation of Th1 response, upregulation of Treg cells, acceleration of skin and mucosa barrier function, increase of intestinal microflora diversity and inhibition of *S. aureus* attachment (Baquerizo Nole et al. 2014). Promising results in AD have been also obtained through the application of topical probiotic extracts, able to disrupt *S. aureus* biofilm, as already demonstrated in vitro by showing that topically applied *Lactobacillus rhamnosus GG* increased epidermal keratinocyte survival during bacterium exposure (Mohammedsaeed et al. 2014). On the other hand, there are very few studies investigating the use of probiotics and prebiotics in Pso. Vijayashankar and Raghunath (2012) described the case of a woman with generalized pustular Pso who improved after oral administration of *Lactobacillus* for 6 months. In 2013, a randomized, double-blind, placebo-controlled trial demonstrated that oral administration of *Bifidobacteria infantis 35624* for 6–8 weeks significantly reduced inflammatory biomarker as well as plasma cytokine levels in 26 psoriatic patients (Groeger et al. 2013). Conversely, numerous in vitro and in vivo data have supported the use of probiotics and prebiotics in acne treatment (Kober and Bowe 2015). Acne pathophysiology involves several processes including follicular hyperkeratinization, excess in sebum production, *P. acnes* colonisation and an inflammatory cascade activation (Al-Ghazzewi and Tester 2010). Probiotics, often supplied with prebiotics, have been shown to directly inhibit *P. acnes* through the production of antibacterial proteins. In vitro, *S. salivarius* demonstrated to inhibit the growth of *P. acnes* and group A streptococci through the production of a bacteriocin-like inhibitory substance (Bowe et al. 2006). Similarly, *Lactococcus sp. HY 449* strains inhibited the growth of *S. epidermidis, S. aureus, S. pyogenes* and *P. acnes* through the secretion of bacteriocins (Oh et al. 2006). Clinically, topical application of probiotics resulted in being able to modify the barrier function of the skin with a secondary increase in its antimicrobial properties. Specifically, *S. thermophiles*, applied as a cream for 7 days, increased ceramide production both in vitro and in vivo (Di Marzio et al. 2003, 2008). Kang et al. (2009) found that topical application of an *Enterococcus faecalis* probiotic lotion for 8 weeks reduced inflammatory lesions by over 50% versus placebo. A reduction in acne count, size and associated erythema was again noted during a clinical study of *Lactobacillus plantarum* extract (Muizzuddin et al. 2012). Moreover, other studies have demonstrated that orally consumed prebiotics and probiotics reduced systemic markers of inflammation and oxidative stress occurring in acne disease (Mikelsaar and Zilmer 2009; Schiffrin et al. 2007). In addition to better clinical outcomes among patients supplemented with probiotics, researchers reported better tolerance and compliance with antibiotics (Kober and Bowe 2015). Probiotics and prebiotics decrease the side effects imparted by systemic antibiotics while working synergistically with the latter in treating inflammatory acne. Thus, they may be considered a therapeutic option and/or adjunct for acne treatment by providing a synergistic anti-inflammatory effect with systemic antibiotics while also reducing potential adverse events secondary to chronic antibiotic use (Jung et al. 2013). On the other hand, to date, there are no evidences about the use of probiotics and prebiotics in HS.

Their effects in chronic inflammatory skin diseases are summarized in Table 3.

Antibiotics in Chronic Inflammatory Skin Diseases

Nowadays, antibiotics are used for systemic and topical inflammatory skin diseases treatment, taking advantage of their antiseptic, bacteriostatic as well as anti-inflammatory and immunomodulating properties (Owczarek et al. 2011). However, a major gap in our current understanding is how these therapies affect human microbiome (Langdon et al. 2016). Is has been proved that topical antibiotics significantly alter skin microbiome with critical implications for cutaneous host defense (SanMiguel et al. 2017). In the gut, antibiotics have been found to cause not only a transient loss in bacterial diversity but also a long-term loss of microbiome members beyond the direct antibiotic targets (Jakobsson et al. 2010; Robinson and Young 2010). This effect on off-target microbes probably is the result of indirect relationships between bacterial species forged through ecosystem-wide processes, such as metabolite exchange and product removal (Willing et al. 2011). Furthermore, after the cessation of antibiotic treatment and restoration of skin as well as gut bacterial density, the long-term changes in microbial community composition facilitate colonisation by pathogens, thus promoting the problem of antibiotic resistance (Chen and Tsao 2013). In AD, the most common treatments against *S. aureus* infections include both topical and oral antibiotics (Williams and Gallo 2015). Although many of them, including mupirocin, flucloxacillin, retapamulin and cephalexin, are able to kill *S. aureus* in the short term on AD patients, it has been proved that bacteria colonisation typically relapsed in these patients after 4–8 weeks of antibiotic treatment (Gilani et al. 2005). Moreover, the recent rise of MRSA strains as well as their ability to colonize AD skin is a clear demonstration of antibiotic altering effects on microbiome (King et al. 2006). Antibiotic therapy for AD patients may be also relatively non-specific: targeting mostly all Gram-positive bacteria, they could affect beneficial microbes such as *S. epidermidis* on the skin as well (Williams and Gallo 2015). Similarly, the use of topical antibiotics for the treatment of acne vulgaris has been shown to increase antibiotic-resistant *P. acnes* and *S. epidermidis*, and promote *S. aureus* nasal colonisation (Bowe and Leyden 2011; Eady et al. 2003; Levy et al. 2003) as well as oral antibiotics have been associated with antibiotic-resistant *P. acnes* and oropharyngeal *S. pyogenes* infections (Bowe and Leyden 2011; Eady et al. 2003). In particular, changes in microbial flora have been found in acne patients treated with oral isotretinoin (Coates et al. 2005). Although it causes a dramatic reduction in *P. acnes*, there are some antibiotic-resistant strains that remain viable and persist after completion of oral isotretinoin therapy (Basak et al. 2013; Coates et al. 2005). Moreover, even if there are limited data, some evidences suggest that oral isotretinoin increases fecal colonisation eSBL-producing *E. coli* (Basak et al. 2013). Regarding tetracyclines, currently the most frequently used oral antibiotics in dermatology, several findings have demonstrated that a prolonged antibiotic therapy, such as in acne and HS, may increase skin, nasal and/or oropharyngeal carriage of *S. aureus* thus encouraging the antibacterial resistance evolution (Ozuguz et al. 2014). Interestingly, although

Table 3 Effects of probiotics and prebiotics in chronic inflammatory skin diseases

Disease	Oral pre/probiotics	Cutaneous pre/probiotics
AD	No conclusive results (1) More efficacious in preventing rather than treating in children (2–6) More efficacious in children when used together (synbiotics) (7) Useful in itch and burning in adult patients (8–12)	Promising results (13) Able to disrupt *S. aureus* biofilm (13)
Pso	Very few studies (14, 15) Clinical improvement (14) Significantly reduction of inflammatory biomarkers and plasma cytokine levels (15)	[a]
HS	[a]	[a]
Acne	Clinical improvement (16) Inhibition of *P. acnes* (17) Reduction of systemic inflammatory and oxidative stress markers (18, 19) Induction of better tolerance and compliance to antibiotic therapy (16)	Reduction in acne count, size and associated erythema (20) Improvement of skin barrier function with increase of antimicrobial properties (20–22)

(1) Baquerizo Nole et al. (2014); (2) Boyle et al. (2008); (3) Lee et al. (2008); (4) Han et al. (2012); (5) Wickens et al. (2013); (6) Kukkonen et al. (2007); (7) Chang et al. (2016); (8) Betsi et al. (2008); (9) Moroi et al. (2011); (10) Drago et al. (2012); (11) Iemoli et al. (2012); (12) Foolad and Armstrong (2014); (13) Mohammedsaeed et al. (2014); (14) Vijayashankar and Raghunath (2012); (15) Groeger et al. (2013); (16) Kober and Bowe (2015); (17) Oh et al. (2006); (18) Schiffrin et al. (2007); (19) Mikelsaar and Zilmer (2009); (20) Muizzuddin et al. (2012); (20) Di Marzio et al., (2003) (21) Di Marzio et al. (2008); (22) Kang et al. (2009)

AD: atopic dermatitis; HS: hidradenitis suppurativa; *P. acnes: Propionibacterium acnes*; Pso: psoriasis; *S. aureus: Staphylococcus aureus*

[a]Data not found

the role of streptococcal infection in the initiation of guttate Pso is well recognized, the use of antibiotics, such as oral erythromycin and phenoxymethylpenicillin, was not effective in the management of established disease or in preventing its development following streptococcal sore throat (Dogan et al. 2008).

Fecal Microbiota Transplant

Other methods have been described to manipulate the intestinal microbiota for therapeutic purposes. Fecal microbiota transplantation (FMT) involves administration of fecal material containing distal gut microbiota from a healthy person (donor) to patients with a disease or condition related to dysbiosis or an alteration in their normal gut microbiota. The goal of FMT is to treat disease by restoring phylogenetic diversity and microbiota more typical of a healthy person (Kelly et al. 2015).

Numerous case reports, retrospective case series and a single randomized controlled trial have shown benefit of FMT in patients with severe or recurrent CDI, with a mean cure rate of 87–90% for hundreds cases reported in the world literature to date. Improvement in symptoms after FMT has been associated with changes in microbial community structure, such as a decrease in *Proteobacteria* as well as restoration of microbial diversity, increase in secondary bile acid production and niche exclusion by other bacteria (Bakken 2015; Cammarota et al. 2014; Kassam et al. 2013; Van Nood et al. 2013). The safety of FMT is acceptable. Minor symptoms immediately after FMT are common and include abdominal discomfort, bloating, flatulence, diarrhoea, constipation, borborygmus, vomiting and transient fever (Kelly et al. 2015). More serious adverse events related to the procedure used to administer FMT, although rare, may occur. These include complications of endoscopy, such as perforation and bleeding and adverse effects related to sedation, such as aspiration. Transmission of enteric pathogens via FMT is also an important concern but appears to be rare with current screening (Kelly et al. 2014). There is now considerable interest in FMT in people not only with chronic gastrointestinal disorders, but also with autoimmune, cardiometabolic and other extraintestinal conditions. Preliminary case reports of FMT enemas in patients with IBD were promising, reporting that patients achieved clinical remission and maintained remission over long-term follow-up in many cases (Bennet and Brinkman 1989; Borody et al. 1989). Different metabolic conditions can affect the intestinal microbiota. Obese subjects show marked differences in the gut microbiome. Nevertheless, FMTs are not 100% effective, and there is even anecdotal evidence of unintended changes, such as sudden excessive weight gain post-FMT (Bashan et al. 2016; Vázquez-Baeza et al. 2018). A recent double-blind, randomized, controlled study that investigated the effects of gut microbiota transfer from lean subjects to obese subjects found improved insulin sensitivity and increased gut microbial diversity with increased butyrate producers after transplant (Vrieze et al. 2012). Regarding the vaginal microbe transplants from healthy individuals, it may overcome bacterial vaginosis (see https://clinicaltrials.gov/ identifier NCT02236429). Very few studies highlighted the role of FMT for skin diseases. Craig (2016) hypothesized the efficacy of FMT for AD among humans and dogs. Additional research is required to prove the efficacy and safety of this therapy when applied to skin diseases.

Models Used to Study Microbiome and Its Functions

Different animals have been extensively used as models to study microbiome and its activity on immune response and even on enteric and central nervous systems (ENS/CNS). For example, it has been demonstrated that the colonisation of gnotobiotic (Gn) piglets with *Lactobacillus rhamnosus GG* (LGG) and *Bifidobacterium lactis* (Bb12) can regulate the development of gut immunity and the severity of viral gut infections, strengthening the tight junctions of the ileum epithelium and resulting in less viral shedding and less severe diarrhoea after *Rotavirus* infection in comparison to un-colonized piglets (Kandasamy et al. 2014; Wang et al. 2016). Selected Gram-negative probiotics (e.g., *E. Coli Nissle*) appeared to be more effective than Gram-positive probiotics (e.g., *Lactobacillus* spp.) in enhancing protective immunity against *Rotavirus* infection/disease in the Gn piglet model (Zhang et al. 2014). Pretreatment of Gn piglets with combinations of probiotics (different *Bifidobacterium* strains) also reduced pathogen load after challenge with *Salmonella typhimurium* and improved recovery (Kandasamy et al. 2017). Moreover, Probiotics (*Lactobacillus, Bifidobacterium* and *Lactobacillus* spp.) have a positive immunomodulatory effect on vaccines in animal models (Valdez et al. 2014). In a study on healthy macaques, the animals responded with an increase in the frequency of IgA expressing B cells in colon and lymph nodes after treatment with different bacteria identified as probiotics. It remained unclear whether this effect was due to bacteria themselves or some of their products (Manuzak et al. 2016). Microbiota depleted animal models have also been used to determine whether transferring the gut microbiota of a person suffering from ENS/CNS disease to animals via fecal transplant can transfer disease symptomologie. Incredibly, adoption or potentiation of ENS/CNS disease endpoints after human-to-animal fecal transplant has been observed for slow transit constipation (Ge et al. 2017), depression (Kelly et al. 2016; Zheng and Zeng 2016), anxiety (De Palma et al. 2017) and Parkinson's disease (Sampson et al. 2016).

Conclusions

Recent skin microbiome investigations have provided insights into the different bacterial microbiota of distinct skin regions, furthering our knowledge about the composition of microbial communities that inhabit the human body. The microbiome composition is crucial in the instruction and support of the skin's immune system (Honda and Littman 2016). It is clear that microbiome interacts with human host by secretion of different metabolites generating a continuous crosstalk, important for the establishment and maintenance of host homeostasis. Alteration in microbiome composition could lead to a shift in immune system reactivity and subsequently to inflammatory diseases' development (Nakatsuji et al. 2016; Tlaskalova-Hogenova et al. 2011; Williams et al. 2017). This mechanism seems to be shared by some different skin diseases (Pso, HS, AD and acne) in which inflammation is the common thread (Belkaid and Segre 2014; Bhatia et al. 2014; McFadden et al. 2009; Naldi et al. 2001). With this descriptive information readily at hand, researchers are now poised to translate these findings into a deeper understanding of the complex relationships existing between commensals and their host. While several interesting discoveries have already been achieved, a number of important questions still remain to be answered. A joint effort in the fields of genomics, bioinformatics, infectious diseases, clinical microbiology, microbial ecology and dermatology will be necessary to best clarify the role of microbiome in human health. In particular, much more investigation and additional studies incorporating longitudinal design, consistent sampling methods, well-selected controls, and relevant clinical phenotyping and metadata are needed to examine the genomic of human microbiome and its possible role in different skin diseases' pathogenesis. These scientific approach will provide valuable information for the development of novel therapeutic strategies.

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