 doi:10.20944/preprints201809.0215.v1

Title: Elucidating role of bacteria in psoriatic disease: from skin and gut perspectives.

Bakytgul Yermekbayeva[1]*, Togzhan Algazina[2], Madina Razbekova [1]*, Albert Pinhasov[3], Gulnar Batpenova[2], Almagul Kushugulova[4]

Affiliations:

[1]Corporate Fund "University Medical Center", Astana, Kazakhstan

[2] Astana Medical University, Astana, Kazakhstan

[3]Ariel University, Ariel, Israel

4"National Laboratory Astana" Nazarbayev University, Astana, Kazakhstan

*These authors contributed equally.

Corresponding author: Yermekbayeva Bakytgul. Address: Corporate Fund "University Medical Center", 5/1, Kerei Zhanibek khandar street, Astana, Kazakhstan, 010000. E-mail: bakytgul@yahoo.com. Telephone: +7 7172 69 24 71

Abstract.

Psoriasis is a chronic inflammatory disease characterized by skin lesions. Psoriasis development has been associated both with genetic and environmental factors. Though skin and gut microbiota has been implicated in number of pathologies including atopic dermatitis, inflammatory bowel disease, Crohn's disease, allergy, obesity, its role has been poorly studied in psoriatic disease, which incorporates both psoriasis and psoriatic arthritis. This literature review summarizes the most recent and major findings on microbiota features in psoriatic disease as well as gives immune system role in the given condition. Despite conflicting findings, psoriasis patients were frequently found to have distinct microbial composition in both skin and guts especially in the major bacterial phyla, *Firmicutes*, *Bacteroidetes*, and *Akkermansia*. Furthermore, bacterial DNA has been found in psoriatic patients both locally and systemically, and altogether suggesting role of bacteria in the chronic disease and future studies in this field.

Keywords: gut microbiota; skin microbiota; inflammation; psoriasis; psoriatic arthritis; dysbiosis

Introduction.

Psoriasis is a chronic immune-mediated inflammatory disease that occurs in 2-4% of people worldwide affecting skin and in 30% of cases joints (psoriatic arthritis) [1]. It is characterized by recurrent skin plaques, epidermal keratinocytes hyperproliferation, and thickening of the skin [2,3]. Psoriasis is also noted with the increased abundance of immune cells and inflammatory biomarkers both on local and systemic levels. Along with the symptoms, psoriasis increases susceptibility to cardiovascular diseases, autoimmune diseases including diabetes, which further diminishes quality of life and elevates burden of disease [4]. Psoriasis occurs in both sexes predominantly before age of 40 (peak is between 16 and 22 years) in 70% of cases [5].

A growing body of literature suggest the role of microbiome, especially in guts, in chronic inflammatory pathologies including inflammatory bowel disease, atopic dermatitis, and psoriasis [6-10]. Indeed, the human microbiota provides the organism with the nutrients and modulates the immune system. Interestingly, approximately 90% of all gut germs are similar in healthy people and compose a 'core' microbiome [11]. Diet, infections, drug use, and traumas are major factors influencing human microbiome and may play a role in psoriatic exacerbations. [12-14]

Gut microbiota can regulate the immune system not only locally, but it also possibly influences the immune mechanisms occurring outside the intestines. Additionally, dysbiosis, an imbalance of beneficial and pathogenic microbes in intestines, might take place in patients with psoriasis and psoriatic arthritis, and thus having potential of affecting systems beyond the human guts. For example, Bacterial DNA were detected in blood of

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 September 2018 doi:10.20944/preprints201809.0215.v1

psoriasis patients [15]. Furthermore, bacterial metabolites were found in joints of psoriatic arthritis patients, which could occur there through blood or lymph system [16]. Hence, imbalance of gut microflora can have an impact not only on skin but also on joint health. Nevertheless, there is lack of studies and reviews with an emphasis of the human bacterial microbiota peculiarities in psoriasis and psoriatic arthritis. For this reason, the review article will summarize the recent studies on skin and gut microbiota changes as well as immunologic background in psoriatic patients.

Immune mechanisms involved in psoriatic disease.

Psoriasis and psoriatic arthritis have been associated with the impaired immune pathways. Number of immune system cells including dendritic cells and T-cells have been found in psoriatic lesions of psoriasis patients and in synovial fluid of joints of psoriatic arthritis patients [17]. The former cells produce tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-20 (IL-20), interleukin-23 (IL-23), while the latter ones secrete interleukin-17 (IL-17), interleukin-21 (IL-21), interleukin-22 (IL-22), and interferon- γ (IFN-γ) [18, 19]. Keratinocytes were also detected to take part in the skin inflammation in psoriasis, namely by producing antimicrobial peptides, interleukin—8 (IL-8), interleukin-20 (IL-20), chemokine (C-C motif) ligand 20 (CCL-20) as well as recruiting T-cells, neutrophils, macrophages [18-21]. In turn, T helper 1 (Th1) and T helper 17 (Th17) cells trigger proliferation of keratinocytes and make them produce inflammatory mediators, and thus contributing to complex circuit of immune pathology of psoriasis [19].

Among these cytokines, IL-22, TNF-α, and IFN-γ are regarded as the major players in psoriatic inflammation. Furthermore, they are the key molecules in the most commonly reported immune mechanism associated with psoriasis, namely IL-23/IL-17 axis [20,21]. IL-17, which is produced by Th17 cells, was numerously found to be upregulated in both psoriatic lesions and bloodstream of patients with psoriasis and psoriatic arthritis [22-29]. Interestingly, IL-17 seems to influence not only skin regions with lesions but also overexpression of downstream proteins in keratinocytes in the distant non-lesion skin of psoriatic patients comparing to non-psoriatic controls [30]. Meanwhile, the key role of IL-23 in both psoriasis and psoriatic arthritis is supported by a study, in which IL-23 was injected to mice and triggered formation of psoriasis-like lesion in them [31]. The researchers detected this impact via overexpressed levels of IL-22, TNF-α, IL-17A and IL-17F. IL-23 is also believed to participate in activation Th 17 cells, and subsequently IL-17 and IL-22 production [32]. Moreover, IL-23 was found in significantly higher levels in psoriatic plaques than in the uninvolved skin [28], and thus suggesting an important role of IL-23 in psoriasis.

Role of skin and gut microbiota.

Skin and gut are the organs that comprise many functions are crucial for survival and proper homeostasis. Indeed, both of them are intensely vascularized and heavily connected with the rest of the organism via nervous, lymphatic, and blood systems. They are also densely colonized with the microbes because of their constant contact with the external environment. These features provide skin and gut their role in barrier and protection from external stimuli through immune modulation and certain microbial composition. Significant deviations in “healthy” microbiota composition are associated with number of diseases including inflammatory bowel disease, Crohn’s disease and ulcerative colitis [33-37]. Overview of studies and their major findings in skin and gut microbiota is given in Table 1.

Skin microbiota in psoriatic disease.

Normal skin microbiota is comprised of *Actinobacteria*, *Firmicutes*, *Proteobacteria*, *Bacteroidetes* phyla [38]. However, reports on diversity of skin microbiota is conflicting with majority of them reporting decreased Shannon index [39-41]. Psoriasis involved skin as well as skin biopsy samples in psoriasis patients had the highest relative abundance of *Firmicutes* relative to healthy participants and the lowest proportion of *Actinobacteria* comparing with the uninvolved psoriatic and healthy skin [39,41]. In contrast, one psoriatic subject from Drago et al., 2016 [42] revealed decreased abundance of *Firmicutes*, and samples taken from skin biopsies of psoriasis and control patients showed lower proportion of

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 September 2018 doi:10.20944/preprints201809.0215.v1

Actinobacteria though without statistical significance probably due to small sample size. Meanwhile, skin biopsies as well as skin swabs had greater proportions of *Proteobacteria* in psoriatic patients rather than in controls [41, 42]. However, skin biopsies were taken only from psoriatic plaques and healthy controls, and thus leaving bacterial composition in non-lesion sites underrepresented. Nevertheless, skin biopsies can give more in-depth information on microbiota in deeper levels of the skin than solely skin swabs.

Streptococcus genera, which was earlier implicated in contribution to psoriasis development from tonsils infections, was also found in greater proportions in psoriatic plaques than in uninvolved skin [39]. In contrast, Drago et al., 2016 [42] showed decreased frequency of *S.aureus* in psoriatic patient than in atopic dermatitis and control in lesions but bacterial frequency was almost the same in non-lesion skin among three patients. Since study was performed on three patients only, and thus limiting generalizability of the results. Along with this genera, *Staphylococcus* and *Corynebacterium* were also found in greater relative abundance in psoriatic plaques in contrast to uninvolved and control skin samples in several studies [39, 40, 42], though Drago et al., 2016 compared psoriatic plaques with healthy skin and atopic dermatitis skin. In addition, *Propionibacteria* were also reported to have increased proportion in psoriatic skin comparing with control from both skin swabs and skin [40,41]. In contrast, abundance of *Cupriavidus*, *Flavisolibacter*, *Methylobacterium*, and *Schlegelella* genera was significantly lower in psoriasis patients than in controls probably due to increased proportions of the previous genera leading to dysbiosis [41]. Moreover, Drago et al., 2016 found that *Rhodobacteraceae* and *Corynebacteraceae* families were more abundant in psoriatic lesions than in atopic lesions and healthy controls. However, non-lesion skin in all of three types of skin (atopic dermatitis, psoriasis and healthy) did not differ in relative proportions of bacterial families. Similarly, frequency of *Paracoccus* was higher approximately by 50% in psoriasis patients than in atopic dermatitis and controls but did not differ in uninvolved skin between three types of patients. These findings on bacterial diversity and composition in skin of psoriasis may suggest role of bacteria in the inflammation and disease progression.

Gut microbiota in psoriatic disease.

Though role of microbiota, especially skin flora, has been reported to differ in patients with psoriasis and psoriatic arthritis, impact of gut microbiota on disease progression is still poorly studied. One of the studies speculating role of gut microbes in psoriasis used antibiotics to target gut bacteria and imiquimod to develop psoriasis-like disease, which included changes in the outer and inner layers of the skin (extensive reddening, thickening and reddening of the skin, increased proliferation of keratinocytes, and impaired epidermal differentiation [43]. Overall, antibiotics-treated adult mice had decreased abundance of gut bacteria (*Bacteroidetes, Actinobacteria*, and *Cyanobacteria*) in gut and skin, less rigorous skin lesions and had decreased production of IL-22 and IL-17 producing T-cells in skin compared with control mice treated with imiquimod only. In lamina propria of guts of adult antibiotics group, Th17 cell levels were lower than in controls. Additionally, expression of chemocine receptor 6 (CCR6) molecule on T-cell surface, which takes part in migration of Th17 cells from intestines to skin was also lower compared with the non-antibiotics group. Moreover, the groups based on the antibiotics treatment time, either during neonatal or adult period, had different psoriasis-like disease development. The authors suggested that disrupted gut microbiota from early stages of life can have an impact on psoriasis development. Though mice treated with antibiotics in neonatal period had more severe symptoms and elevated levels of inflammatory cells (IL-22 and IL-17 T-cells) in skin of psoriasis-like disease than non-antibiotics group, there were no reported comparisons with adult-treated antibiotics mice from symptoms and inflammation perspectives, and thus leaving differences between antibiotics-treated groups for further investigations. Nevertheless, *Bacteroidetes* phylum, *S24-7*, *Lachnospiraceae* and *Ruminacoccaceae* families were decreased in guts of adult-treated antibiotics mice, while abundance of *Tenericutes* phylum, *Lactobacillaceae* (both gut and skin) and *Alcaligenacea* families were in greater proportions than in neonatally-treated

 doi:10.20944/preprints201809.0215.v1

antibiotics mice. These findings suggested that gut bacteria can modulate microbiota composition, inflammation mechanisms and disease progression in psoriasis.

Possible role of gut-skin axis in psoriasis was studied in imiquimod-induced psoriasis-like skin inflammation in germ-free, antibiotics-treated and standard-treated mice [44]. Overall, both germ-free and antibiotics-treated groups were more resistant to the disease development than conventional mice. This study revealed that these groups developed less severe skin lesions, scaling, thickening of skin, smaller extent of hyperkeratosis and acanthosis. Though they did not find imiquimod's effect on gut microbiota changes, they showed that antibiotics could result in decreased composition of *Lactobacillales* order (*Firmicutes* phylum) but increased abundance of bacteria from the same phylum, namely *Clostridiales* and *Erysipelotrichiales* orders. Additionally, *Actionobacteria* (*Coriobacteriales* and *Campylobacteriales* orders) were also decreased in the antibiotics group. These findings imply that gut dysbiosis can alter predisposition to psoriasis-like skin inflammation, and altered bacterial composition does not necessarily guarantee psoriasis symptoms development. Conventionally-reared mice also had larger spleens and decreased production of T cells both locally (spleen) and systemically (lymph nodes) than germ-free and antibiotics-groups Imiquimod was not found to change microbiota in gut of mice, and thus the imiquimod-induced model might not completely show the psoriasis development, similar in humans.

The most recent study on the gut microbiome composition in psoriasis patients obtained the distinguishing psoriasis microbiome [45]. The authors found bacterial DNA in blood samples of psoriatic patients, especially in those with the predominance of *Prevotella* genus (*Bacteroidetes* phylum, enterotype 2) and who also had greater inflammation indicators. Regarding bacterial composition, the psoriatic patients had lower abundance of *Bacteroides* and greater proportions of *Akkermansia* species and *Faecalibacterium* compared to the healthy subjects. In contrast to most of the studies on skin microbiota, bacterial diversity (the Shannon index) was higher in psoriatic patients than in healthy group, but the authors explain this difference due to high PASI index in participants of this study, which could influence the gut microbiota, and sequencing methods. However, in psoriasis patients with bacterial translocation, this diversity was lower than in those without bacterial DNA in their blood, though no particular type of bacteria was peculiar for the former group. Moreover, PASI score did not differ in both groups, but bacterial translocation was previously reported to be associated with increased inflammation status in psoriasis [15]. The latter patients (without bacterial translocation) were found to differ in abundance of *Parabacteroides*, *Collinsella*, *Blautia*, and *Ruminococcus* genera with the rest of the patients. Though the authors used data of healthy patients from the Human Microbiome Project Database, there is little known about whether they were appropriately matched with the psoriasis patients to avoid additional confounders apart from age and sex, which could influence the differences between groups. Nevertheless, this study provided new evidence on gut microbiome features in psoriasis and future prospective for studies in bacterial translocation and psoriasis.

Scher et al., 2016 [46] also studied gut microbiota composition in psoriasis and psoriatic arthritis group. The sample size, study design (bacterial DNA regions for analysis), participants (psoriatic arthritis and psoriasis), sociodemographic characteristics as well as season of samples extraction might be the reasons for the observed differences in bacterial diversity between studies. Scher et al., 2016 [42] found *Ruminococcus*, *Akkermansia*, *Pseudobutyrivibrio*, and *Clostridia* were less present in gut of psoriatic arthritis patients, and *Parabacteroides* and *Coprobacillus* had smaller abundance in psoriasis participants than in healthy group. Notably, the gut microbiota differed among psoriasis arthritis and psoriasis only patients with the *Akkermansia*, *Ruminococcus* being less frequently found and *Bacteroidetes* and *Coprobacillus* having higher abundance in the former group. Apart from gut bacterial composition, Scher et al., 2016 [46] also looked at inflammatory status of psoriatic arthritis patients only. Notably, secretory Immunoglobulin A levels (sIgA) were increased and fecal Receptor activator of nuclear factor kappa-B ligand (RANKL) was decreased in

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 September 2018 doi:10.20944/preprints201809.0215.v1

psoriatic arthritis group compared to psoriasis and healthy participants. Meanwhile, psoriasis patients had elevated serum psoriasin/S100 (commonly overexpressed in psoriasis) as well as fecal osteoprotegerin (OPG), which is inhibitor of RANKL [47]. Moreover, the study revealed that medium-chain fatty acids (MCFAs, hexanoate and heptanoate), which previously showed antibacterial effects, were decreased in both psoriasis groups [48]. Though short chain fatty acids (SCFAs) were implicated to possess anti-inflammatory effects on skin and produced by *Bacteroidetes*, which are commonly decreased in psoriasis, in this research, SCFAs (acetate, butyrate, propionate) levels were similar between groups. Finally, *Akkermansia* and *Ruminococcus* had positive correlation with MCFAs (hexanoate, heptanoate), Akkermansia alone was negatively corelated with fecal sIgA and short chain fatty acids (acetate, butyrate) and *Coprobacillus* had inverse correlation with S100. Fecal RANKL was positively corelated with *Lachnosiparaceae*, which were both low in psoriatic arthritis. However, sole correlation analysis can omit important confounders, which may influence observed associations.

Masallat et al., 2016 [49] analyzed psoriasis and gut microbiome from different perspectives, bacterial ratio and their association with PASI index. They found out that psoriasis group had significantly higher ratio of *Firmicutes/Bacteroidetes* than healthy patients though bacterial count of *Firmicutes*, *Bacteroidetes* did not exert differences between groups. Nevertheless, *Actinobacteria* count was higher in healthy group, which is opposite to later study of Codoner et al., 2018 and in concordance with Scher et al., 2016 *Firmicutes/Bacteroidetes* ratio had statistically significant positive correlation with PASI index in contrast to *Actinobacteria* phyla. However, the participants were recruited during one year, and hence gut bacteria composition can change with the seasons and contribute to observed differences in intestinal flora. Additionally, none of the discussed studies took into account anti-psoriatic therapies and diet (vegetarian, vegan, gluten-free, lactose-free), which could possibly influence immune status and microbiota composition.

The beneficial inhabitant of the human intestine, *F.prausnitzii* (*Firmucutes* phylum), produces butyrate (short chain fatty acid) that provides energy for colonocytes, takes part in protection from oxidative stress, possesses anti-inflammatory features and plays role in regulation of T effector cells and regulatory T cells (Tregs)[50-52]. Moreover, *F.prausnitzii* also produces mitochondria-associated membrane (MAM) protein, which has been implicated to inhibit nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway in intestines and possibly have an effect outside intestines, especially in the skin immune status [53-54]. For example, Eppinga et al., 2016 [55] looked at abundance *Faecalibacterium prausnitzii* and *E.coli* (*Proteobacteria* phylum) in intestines of patients with psoriasis, inflammatory bowel disease and hidradenitis suppurativa. They found that psoriasis group (for all type and plaque-type psoriasis only) had significantly decreased proportion of *F.prausnitizii* than healthy controls. There was no correlation between PASI index and *F.prausnitzii* abundance, but no adjustments were made for potential confounders. Nonetheless, there were no significant differences in age, sex, smoking, BMI, race between healthy and psoriasis groups. Though the total bacterial DNA was similar between psoriasis and healthy participants, but low *F.prausnitzii* abundance in both groups, these findings suggest that there could be overabundance of other bacteria such as *E.coli,* which was increased in psoriasis group. The researchers also took data on any therapy used during the study, which was absent in most of the participants, and diet that can possibly affect gut microbiota composition.

Probiotics in psoriatic disease.

Provision of beneficial microbes and their effect on patients with psoriasis has also been studied. For example, *Bifidobacteria infantis* (*B.infantis*), which was previously reported to induce regulatory T cells in peripheral blood of healthy participants, was also shown to substantially decrease TNF-α, C-reactive protein levels and in a small extent IL-6 in 75% of psoriasis patients after 6-8 week of daily probiotic intake[15, 56]. Notably, all these pro-inflammatory biomarkers were increased in psoriasis patients compared with the healthy controls.

Chen et al., 2017 [57] induced psoriasis-like disease with imiquimod treatment in mice

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 September 2018 doi:10.20944/preprints201809.0215.v1

and fed them with *Lactobacillus pentosus* (*L.pentosus*) GMNL-77 to look at symptoms development and immune status differences. Strains of *L.pentosus* has been implicated with suppression of inflammatory mechanisms in *C.albicans* infection in stomach, modulating production of immunoglobulins A and M, IL-6, IL-10, IFN-γ in intestines, reduction of microbial lipopolysaccharide in guts and blood, decrease of *Firmicutes/Bacteroidetes* ratio in intestines, and possession of antibiotic properties [58-63]. The findings of Chen et al., 2017 [57] revealed that mice given *L.pentosus* GMNL-77 had significantly less psoriasis-like skin lesions and decreased hyperproliferation of keratinocytes compared with the imiquimod only treated group. The probiotic-treated mice had reduced expression levels of inflammatory biomarkers such as TNF-α, IL-6, IL-23, IL-17A, IL-22 in skin. Meanwhile, T cells' (Th17 and Th22) number in spleen and the organ's size itself was reduced as well. Though this study looked at skin and spleen omitting gut microbiota composition and intestinal immune status, its findings suggest that probiotics can take role in alleviating symptoms and inflammation in psoriasis and provide new directions for usage of beneficial bacteria in treatment of the psoriatic disease.

Conclusion.

Recent evidence suggests that the gut microbiome can contribute to the development of psoriasis and psoriatic arthritis. On the other hand, the skin microbiome may be important in the development of psoriasis, but it is not clear whether it plays a role in the development of its systemic forms. Hence, since psoriasis is associated with altered skin and gut microbiome, it is tempting to suggest that skin and gut complement each other in the pathogenesis of psoriasis, and possibly of psoriatic arthritis. Further studies are needed to evaluate properly the interrelation between skin and gut microbiota and psoriatic disease.

Table 1. Summary of the recent skin and gut microbiome studies in psoriatic disease.

Scope of study	No.of patients	Groups	Major findings	Reference
Skin microbiota: skin swabs	39	Psoriasis and healthy patients	In psoriatic plaques: ↑ Shannon index ↑ *Firmicutes* ↑ *Streptococcus* ↑*Staphylococcus* ↑ *Corynebacterium* ↓ *Actinobacteria* ↓ *Proteobacteria*	Gao et al
Skin microbiota: skin swabs	199	Psoriasis and healthy patients	In psoriatic plaques: ↓ Shannon index ↑ *Corynebacterium* ↑ *Streptococcus* ↑ *Staphylococcus* ↑ Odds ratio for having lesions in *Schlegelella* and *Acidobacteria Gp4* positive groups	Alekseyenko et al.
Skin microbiota: skin biopsy	22	Psoriasis and healthy patients	In psoriasis: ≈ Shannon index ↑ *Proteobacteria* ↓ *Staphylococcus* ↓ *Propionibacteria*	Fahlen et al.
Gut microbiota: stool and blood samples	352	Psoriasis and healthy patients	In psoriatis: ↑ Shannon index ↓ *Bacteroides*	Codoner et al.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 September 2018 doi:10.20944/preprints201809.0215.v1

			↑ *Akkermansia* ↑ *Faecalibacterium* Positive for bacterial DNA in blood samples ↑ Bacterial translocation in *Prevotella*-dominant group	
Gut microbiota: stool samples	48	Psoriasis, psoriatic arthritis and healthy patients	In psoriasis and psoriatic arthritis: ↓ Shannon index ↓ MCFAs In psoriatic arthritis: ↓ *Akkermansia* ↓ *Ruminococcus* ↑ Fecal sIgA ↓ RANKL In psoriasis: ↓ *Parabacteroides* ↓ *Coprobacillus* ↓ *Bacteroidetes* ↓ *Coprobacillus* ↑ S100	Scher et al.
Gut microbiota: stool and blood samples	90	Psoriasis and healthy patients	In psoriasis: ↑ ratio of *Firmicutes/Bacteroidetes* ↓ *Actinobacteria* Positive correlation of *Firmicutes/Bacteroidetes* ratio with PASI index Negative correlation of *Actinobacteria*	Masallat et al
Gut microbiota: stool samples	62	Psoriasis and healthy patients	In psoriasis: ↓ *F. prausnitzii* ↑ *E.coli*	Eppinga et al.

Conflict of interest.

The authors state no conflicts of interest.

References.

[1] Pap, T., & Sunderkötter, C. (2017). Psoriasis versus Psoriasisarthritis. Zeitschrift für Rheumatologie, 76(6).

[2] Roberson EDO, Bowcock AM. Psoriasis genetics: Breaking the barrier. Trends Genet 2010;26:415–23. doi:10.1016/j.tig.2010.06.006.

[3] Mari NL, Simão ANC, Dichi I. N-3 Polyunsaturated Fatty Acids Supplementation in Psoriasis: a Review. Nutrire 2017;42:5. doi:10.1186/s41110-016-0029-3.

[4] Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 1. Overview of psoriasis and

guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol 2008;58:826–50. doi:10.1016/j.jaad.2008.02.039.

[5] Higgins E. Psoriasis. Med (United Kingdom) 2017;45:368–78. doi:10.1016/j.mpmed.2017.03.010.

[6] Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature 2010;464:59–65. doi:10.1038/nature08821.

[7] Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature 2010;464:59–65. doi:10.1038/nature08821.

[8] Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature 2010;464:59–65. doi:10.1038/nature08821.

[9] Scher JU, Littman DR, Abramson SB. Review: Microbiome in Inflammatory Arthritis and Human Rheumatic Diseases. Arthritis Rheumatol 2016;68:35–45. doi:10.1002/art.39259.

[10] Cho I, Blaser MJ. The human microbiome: At the interface of health and disease. Nat Rev Genet 2012;13:260–70. doi:10.1038/nrg3182.

[11] Clements SJ, R. Carding S. Diet, the intestinal microbiota, and immune health in aging. Crit Rev Food Sci Nutr 2018;58:651–61. doi:10.1080/10408398.2016.1211086.

[12] Schalkwijk J. A role for the microbiome in psoriasis? Br J Dermatol 2018;178:999–1000. doi:10.1111/bjd.16471.

[13] van der Meulen TA, Harmsen HJM, Bootsma H, Spijkervet FKL, Kroese FGM, Vissink A. The microbiome–systemic diseases connection. Oral Dis 2016;22:719–34. doi:10.1111/odi.12472.

[14] Fry L, Baker BS. Triggering psoriasis: the role of infections and medications. Clin Dermatol 2007;25:606–15. doi:10.1016/j.clindermatol.2007.08.015.

[15] Ramírez-Boscá A, Navarro-López V, Martínez-Andrés A, Such J, Francés R, Horga de la Parte J, et al. Identification of Bacterial DNA in the Peripheral Blood of Patients With Active Psoriasis. JAMA Dermatology 2015;151:670–1. doi:10.1001/jamadermatol.2014.5585.

[16] Chalovich JM, Eisenberg E. NIH Public Access. Magn Reson Imaging 2013;31:477–9. doi:10.1016/j.immuni.2010.12.017.Two-stage.

[17] Choy E. T cells in psoriatic arthritis. Curr Rheumatol Rep 2007;9:437–41. doi:10.1007/s11926-007-0071-5.

[18] Lowes MA, Kikuchi T, Fuentes-Duculan J, Cardinale I, Zaba LC, Haider AS, et al. Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. J Invest Dermatol 2008;128:1207–11. doi:10.1038/sj.jid.5701213.

[19] Chiricozzi A, Guttman-Yassky E, Suárez-Farĩas M, Nograles KE, Tian S, Cardinale I, et al. Integrative responses to IL-17 and TNF-α in human keratinocytes account for key inflammatory pathogenic circuits in psoriasis. J Invest Dermatol 2011;131:677–87. doi:10.1038/jid.2010.340.

[20] Lande R, Botti E, Jandus C, Dojcinovic D, Fanelli G, Conrad C, et al. The antimicrobial peptide LL37 is a T-cell autoantigen in psoriasis. Nat Commun 2014;5:1–15. doi:10.1038/ncomms6621.

[21] Novelli L, Chimenti MS, Chiricozzi A, Perricone R. The new era for the treatment of psoriasis and psoriatic arthritis: Perspectives and validated strategies. Autoimmun Rev 2014;13:64–9. doi:10.1016/j.autrev.2013.08.006.

[22] Caproni M, Antiga E, Melani L, Volpi W, Del Bianco E, Fabbri P. Serum levels of IL-17 and IL-22 are reduced by etanercept, but not by acitretin, in patients with psoriasis: A randomized-controlled trial. J Clin Immunol 2009;29:210–4. doi:10.1007/s10875-008-9233-0.

[23] Takahashi H, Tsuji H, Hashimoto Y, Ishida-Yamamoto A, Iizuka H. Serum cytokines and growth factor levels in Japanese patients with psoriasis. Clin Exp Dermatol 2010;35:645–9. doi:10.1111/j.1365-2230.2009.03704.x.

[24] Suárez-Fariñas M, Li K, Fuentes-Duculan J, Hayden K, Brodmerkel C, Krueger JG. Expanding the psoriasis disease profile: Interrogation of the skin and serum of patients with moderate-to-severe psoriasis. J Invest Dermatol 2012;132:2552–64. doi:10.1038/jid.2012.184.

[25] Wang CQF, Suárez-Fariñas M, Nograles KE, Mimoso CA, Shrom D, Dow ER, et al. IL-17 induces inflammation-Associated gene products in blood monocytes, and treatment with ixekizumab reduces their expression in psoriasis patient blood. J Invest Dermatol 2014;134:2990–3. doi:10.1038/jid.2014.268.

[26] Martin DA, Towne JE, Kricorian G, Klekotka P, Gudjonsson JE, Krueger JG, et al. The emerging role of IL-17 in the pathogenesis of psoriasis: Preclinical and clinical findings. J Invest Dermatol 2013;133:17–26. doi:10.1038/jid.2012.194.

[27] Kagami S, Rizzo HL, Kurtz SE, Miller LS, Blauvelt A. IL-23 and IL-17A, but Not IL-12 and IL-22, Are Required for Optimal Skin Host Defense against Candida albicans. J Immunol 2010;185:5453–62. doi:10.4049/jimmunol.1001153.

[28] Fitch E, Harper E, Skorcheva I, Kurtz SE, Blauvelt A. Pathophysiology of psoriasis: Recent advances on IL-23 and TH17 cytokines. Curr Rheumatol Rep 2007;9:461–7. doi:10.1007/s11926-007-0075-1.

[29] Kagami S, Rizzo HL, Lee JJ, Koguchi Y, Blauvelt A. Circulating Th17, Th22, and Th1 cells are increased in psoriasis. J Invest Dermatol 2010;130:1373–83. doi:10.1038/jid.2009.399.

[30] Chiricozzi A, Suárez-Fariñas M, Fuentes-Duculan J, Cueto I, Li K, Tian S, et al. Increased expression of interleukin-17 pathway genes in nonlesional skin of moderate-to-severe psoriasis vulgaris. Br J Dermatol 2016;174:136–45. doi:10.1111/bjd.14034.

[31] Chan JR, Blumenschein W, Murphy E, Diveu C, Wiekowski M, Abbondanzo S, et al. IL-23 stimulates epidermal hyperplasia via TNF and IL-20R2–dependent mechanisms with implications for psoriasis pathogenesis. J Exp Med 2006;203:2577–87. doi:10.1084/jem.20060244.

[32] Teng MWL, Bowman EP, McElwee JJ, Smyth MJ, Casanova JL, Cooper AM, et al. IL-12 and IL-23 cytokines: From discovery to targeted therapies for immune-mediated inflammatory diseases. Nat Med 2015;21:719–29. doi:10.1038/nm.3895.

[33] Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell 2014;157:121–41. doi:10.1016/j.cell.2014.03.011.

[34] Frank DN, Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proc Natl Acad Sci USA 2007;104:13780–5. doi:10.1073/pnas.0706625104.

[35] Berg AM, Kelly CP, Farraye FA. Clostridium difficile infection in the inflammatory bowel disease patient. Inflamm Bowel Dis 2013;19:194–204. doi:10.1002/ibd.22964.

[36] Trivedi B. The surface brigade. Nature 2012;492:6–7. doi:10.1038/492S60a.

[37] Grice EA. The skin microbiome: potential for novel diagnostic and therapeutic approaches to cutaneous disease. Semin Cutan Med Surg 2014;33:98–103. doi:10.12788/j.sder.0087.

[38] Grice EA, Kong HH, Conlan S, Deming CB, Davis J, Young AC, et al. Topographical and Temporal Diversity of the Human Skin Microbiome. Science 2009;324:1190–2. doi:10.1126/science.1171700.

[39] Gao Z, Tseng CH, Strober BE, Pei Z, Blaser MJ. Substantial alterations of the cutaneous bacterial biota in psoriatic lesions. PLoS One 2008;3. doi:10.1371/journal.pone.0002719.

[40] Alekseyenko A V, Perez-Perez GI, De Souza A, Strober B, Gao Z, Bihan M, et al. Community differentiation of the cutaneous microbiota in psoriasis. Microbiome 2013;1:31. doi:10.1186/2049-2618-1-31.

[41] Fahlén A, Engstrand L, Baker BS, Powles A, Fry L. Comparison of bacterial microbiota in skin biopsies from normal and psoriatic skin. Arch Dermatol Res 2012;304:15–22. doi:10.1007/s00403-011-1189-x.

[42] Drago L, De Grandi R, Altomare G, Pigatto P, Rossi O, Toscano M. Skin microbiota of first cousins affected by psoriasis and atopic dermatitis. Clin Mol Allergy 2016;14:1–11. doi:10.1186/s12948-016-0038-z.

[43] Zanvit P, Konkel JE, Jiao X, Kasagi S, Zhang D, Wu R, et al. Antibiotics in neonatal life increase murine susceptibility to experimental psoriasis. Nat Commun 2015;6:1–10. doi:10.1038/ncomms9424.

[44] Zákostelská Z, Málková J, Klimešová K, Rossmann P, Hornová M, Novosádová I, et al. Intestinal microbiota promotes psoriasis-like skin inflammation by enhancing Th17 response. PLoS One 2016;11:1–13. doi:10.1371/journal.pone.015953.

[45] Codoñer FM, Ramírez-Bosca A, Climent E, Carrión-Gutierrez M, Guerrero M, Pérez-Orquín JM, et al. Gut microbial composition in patients with psoriasis. Sci Rep 2018;8:1–7. doi:10.1038/s41598-018-22125-y.

[46] Scher JU, Ubeda C, Artacho A, Attur M, Brusca S, Patel T, et al. NIH Public Access 2016;67:128–39. doi:10.1002/art.38892.

[47] Wolf R, Howard ZOM, Dong H, Xu J, Voscopoulos C, Voeshans K, et al. Chemotactic activity of S100A7 (psoriasin) is mediated by RAGE and potentiates inflammation with highly homologous but functionally distinct S100A15 .NIH Public Access 2009;129:77–83. doi:10.1021/ja064902x.Brilliant.

[48] Liberato MV, Nascimento AS, Ayers SD, Lin JZ, Cvoro A, Silveira RL, et al. Medium chain fatty acids are selective peroxisome proliferator activated receptor (PPAR) γ activators and Pan-PPAR partial agonists. PLoS One 2012;7:1–10. doi:10.1371/journal.pone.0036297.

[49] Masallat D, Moemen D, F. State A. Gut bacterial microbiota in psoriasis: A case control study. African J Microbiol Res 2016;10:1337–43. doi:10.5897/AJMR2016.8046.

[50] Lopez-Siles M, Khan TM, Duncan SH, Harmsen HJM, Garcia-Gil LJ, Flint HJ. Cultured representatives of two major phylogroups of human colonic Faecalibacterium prausnitzii can utilize pectin, uronic acids, and host-derived substrates for growth. Appl Environ Microbiol 2012;78:420–8. doi:10.1128/AEM.06858-11.

[51] Atarashi K, Tanoue T, Shima T, Imaoka A, Kuwahara T, Momose Y, et al. Induction of Colonic Regulatory T Cells. Science (80-) 2011;331:337–42. doi:10.1126/science.1198469.

[52] Qiu X, Zhang M, Yang X, Hong N, Yu C. Faecalibacterium prausnitzii upregulates regulatory T cells and anti-inflammatory cytokines in treating TNBS-induced colitis. J Crohn's Colitis 2013;7:e558–68. doi:10.1016/j.crohns.2013.04.002.

[53] Quévrain E, Maubert MA, Michon C, Chain F, Marquant R, Tailhades J, et al. Identification of an anti-inflammatory protein from Faecalibacterium prausnitzii, a commensal bacterium deficient in Crohn's disease. Gut 2016;65:415–25. doi:10.1136/gutjnl-2014-307649.

[54] Khan MT, Van Dijl JM, Harmsen HJM. Antioxidants keep the potentially probiotic but highly oxygen-sensitive human gut bacterium Faecalibacterium prausnitzii alive at ambient air. PLoS One 2014;9. doi:10.1371/journal.pone.0096097.

[55] Eppinga H, Sperna Weiland CJ, Thio HB, van der Woude CJ, Nijsten TEC, Peppelenbosch MP, et al. Similar depletion of protective Faecalibacterium prausnitzii in psoriasis and inflammatory bowel disease, but not in hidradenitis suppurativa. J Crohn's Colitis 2016;10:1067–75. doi:10.1093/ecco-jcc/jjw070.

[56] Groeger D, O'Mahony L, Murphy EF, Bourke JF, Dinan TG, Kiely B, et al. Bifidobacterium infantis 35624 modulates host inflammatory processes beyond the gut. Gut Microbes 2013;4:325–39. doi:10.4161/gmic.25487.

[57] Chen YH, Wu CS, Chao YH, Lin CC, Tsai HY, Li YR, et al. Lactobacillus pentosus GMNL-77 inhibits skin lesions in imiquimod-induced psoriasis-like mice. J Food Drug Anal 2017;25:559–66. doi:10.1016/j.jfda.2016.06.003.

[58] Maekawa T, Ishijima AS, Ida M, Izumo T, Ono Y, Shibata H, et al. Prophylactic Effect of <I>Lactobacillus pentosus</I> strain S-PT84 on <I>Candida</I> Infection and Gastric Inflammation in a Murine Gastrointestinal Candidiasis Model [Errata]. Med Mycol J 2016;57:E81–92. doi:10.3314/mmj.16-00012E.

[59] Kotani Y, Kunisawa J, Suzuki Y, Sato I, Saito T, Toba M, et al. Role of Lactobacillus pentosus strain b240 and the toll-like receptor 2 axis in Peyer's patch dendritic cell-mediated immunoglobulin A enhancement. PLoS One 2014;9:1–9. doi:10.1371/journal.pone.0091857.

[60] Lee JS, Cheng H, Damte D, Lee SJ, Kim JC, Rhee MH, et al. Effects of dietary supplementation of Lactobacillus pentosus PL11 on the growth performance, immune and antioxidant systems of Japanese eel Anguilla japonica challenged with Edwardsiella tarda. Fish Shellfish Immunol 2013;34:756–61. doi:10.1016/j.fsi.2012.11.028.

[61] Jeong JJ, Kim KA, Jang SE, Woo JY, Han MJ, Kim DH. Orally administrated Lactobacillus pentosus var. plantarum C29 ameliorates age-dependent colitis by inhibiting the nuclear factor-kappa B signaling pathway via the regulation of lipopolysaccharide production by gut microbiota. PLoS One 2015;10:1–16. doi:10.1371/journal.pone.0116533.

[62] Birhanu BT, Lee JS, Lee SJ, Choi SH, Hossain MA, Park JY, et al. Immunomodulation of Lactobacillus pentosus PL11 against Edwardsiella tarda infection in the head kidney cells of the Japanese eel (Anguilla japonica). Fish Shellfish Immunol 2016;54:466–72. doi:10.1016/j.fsi.2016.04.023.

[63] Xu Y, Zong X, Han B, Li Y, Tang L. *Lactobacillus pentosus* expressing porcine lactoferrin elevates antibacterial activity and improves the efficacy of vaccination against Aujeszky's disease. Acta Vet Hung 2016;64:289–300. doi:10.1556/004.2016.028.