

The gut microbiome dysbiosis and its potential role in psoriatic arthritis

In past decades, gut microbiome perturbations appeared to play a role in the development of several autoimmune diseases. Microbiome dysbiosis together with genetic, lifestyle and/or diet factors may composedly affect the etiology of autoimmune diseases. Studies about the role of the gut microbiome in psoriatic arthritis (PsA), a chronic autoimmune disease of the joint, are limited. We propose that intestinal dysbiosis-associated microbiota or gut microbiota-derived products might reach the joint by translocation to the circulation leading to T-cell activation and inflammation that underline PsA. Future studies on the intestinal microbiome associated with psoriatic arthritis can provide new targets for diagnostic and treatment strategies. Recognizing the PsA 'early warning phases' could offer new windows of opportunities regarding prevention.

Keywords: gut microbiome • microbiota • mycobiome • psoriasis • psoriatic arthritis • spondylarthritis • Th17

Psoriatic arthritis (PsA) is a chronic inflammatory joint disease strongly related to psoriasis presenting with pain and stiffness in the joints [1]. The incidence of PsA is increasing over the past decades [2]. The high incidence may be related to factors as western lifestyle or increased awareness of the diagnosis by physicians. The geographic variation shows a higher prevalence in the European population and a significantly lower prevalence in the Japanese population [3]. This may be due to genetic factors or to environmental factors as lifestyle and diet. The extent of knowledge on the etiology of PsA and other autoimmune diseases in general is still limited. Nonetheless, the complex etiology of autoimmune diseases is highly intriguing and is the main focus of several basic and clinical research studies outlined below.

PsA can be seen as a systemic disease with the primary disease site at the joint with extra-articular (systemic) manifestations. This concept is supported by the findings that PsA as an inflammatory arthropathy is associated with skin and/or nail psoriasis [4,5] and other

possible systemic features [6–8]. Besides manifestation in the skin, gut inflammation has been demonstrated in the spondyloarthritis group, a familial group which includes PsA [6,9–12]. The best example of a GI tract disease associated with gut inflammation and a disturbance of the gut microbiome is inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis [13]. The disease phenotype and genotype seem to be associated with an aberrant composition of the gut microbiota [14]. IBD is associated with both PsA and psoriasis [15]. Comorbidities in PsA and psoriasis overlap and involve metabolic syndrome, cardiovascular comorbidities, hypertension and depression [16].

We will shortly describe several hypotheses regarding the etiology of PsA that have passed during the past decades. First of all, a strong hereditary component is present in PsA. Family studies have described that the concordance in monozygotic twins is higher than among dizygotic twins [17]. A higher incidence among first-degree relatives [3] and

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a strong association of PsA with certain HLA alleles [18] has also been demonstrated. The genetic association of PsA might be due to arthritis or due to psoriasis, but PsA is not a separate entity of psoriasis. Traumatic injury may also play a causal role in the development of psoriasis and PsA, the so called 'Koebner phenomenon or effect' [19]. PsA might be caused by a single pathogenic infection inside the joint or have its origin at distant sites including the GI tract. Western lifestyle and diet might also play a role due to a strong association of PsA with obesity, directly linked to lifestyle and diet, which has been described in literature [20,21]. A more general assumption is that autoimmune diseases develop in patients exposed to (unknown) environmental factors with an underlying genetic susceptibility.

If PsA is caused by different internal and external factors, we wonder if there is a more general hypothesis available to connect all these separate factors? The gut microbiome might be the missing link in the pathogenesis of PsA and other autoimmune diseases in patients with a particular genetic background.

The human body is home to an array of microbial species whose primary function in the various human ecosystems remains unclear [22]. The human intestine on its own harbors a complex microbial community that is estimated to contain approximately 100 trillion cells, belonging to over 1000 species [23]. Similar to the gut, the skin represents another important interface between the host and the environment. Microbial profiling has revealed the presence of highly diverse commensal communities along distinct topographical skin sites [24,25]. Both the skin and the gut microbiome influence immune tissue development and function, as well as in promoting systemic inflammation in the context of autoimmunity [26]. Despite our growing understanding of the consequences of this host-microbe alliance for the local immune function, the degree to which the gut and the skin microbiota contributes to autoimmunity remains elusive. Although the skin microbiome might play a role in PsA [27], here we will focus on the profound role of the gut microbiome in autoimmune diseases.

Human gut dysbiosis in other autoimmune diseases such as CD

Autoimmune disease-associated studies revealed correlations between bacterial taxonomic abundance and some clinical phenotypes especially in a disease such as CD [28,29]. Three theories of microbial etiopathogenesis have been proposed for CD: a dysbiosis (an imbalance between potentially 'beneficial' and potentially 'harmful' bacteria); the presence of an unidentified pathogen; and excessive bacterial translocation [30,31].

The application of high throughput sequencing techniques and other approaches has demonstrated that no specific pathogen is associated with 100% of CD [26,32-34] suggesting that future studies need to be focused on the level of bacterial translocation and the dysbiosis in CD patients. Thus far, a limited number of studies examined the bacterial translocation relevant to CD. The available data suggest that bacterial DNA is present in the mesenteric lymph nodes of CD patients [35], and also within host tissues, such as the liver, the adipose tissue and the blood [36-38]. In contrast to the translocation, the dysbiosis hypothesis is supported in many studies that ascribe the disturbance in the balance of the pathogenic and beneficial bacteria in the gut [39]. Furthermore, the dysbiosis found in autoimmune disease can either be a result of decreased levels of *Firmicutes* and *Faecalibacterium prausnitzii*, and an increase in *Bacteroidetes* and *Enterobacteriaceae*, particularly in patients who have ileal involvement. An important recent finding on the GI tract bacterial community dysbiosis is that individuals with a low GI tract bacterial richness are characterized by an inflammatory phenotype when compared with high bacterial richness individuals. Furthermore, only a few bacterial species have been sufficient to distinguish between individuals with high and low bacterial richness and the inflammatory phenotype [40]. Among these species is *Faecalibacterium* (formerly *Fusobacterium*) *prausnitzii*, which belongs to the *Clostridium leptum* subgroup (cluster IV) of the phylum *Firmicutes* and is one of the most abundant bacteria in the human gut ecosystem. A decrease in the abundance of *F. prausnitzii* and a decreased microbial diversity are common to the intestinal microbiome of different CD populations (Europe, Japan and the USA) [41]. Therefore, analyses of specific dysbiosis-associated bacteria like *F. prausnitzii* and/or the level of bacterial DNA in the blood introduces new opportunities to identify targets and predictive biomarkers as well as to define new strategies for pharmacological, immunomodulatory vaccines and nutritional applications relevant to patients with autoimmune diseases.

Recent evidences for the link between the microbiome & inflammatory joint diseases

Although scarce evidence from research is available about the relationship between the microbiome and PsA [42], several clinically tractable (GI) microbiome signatures do exist for another chronic inflammatory joint disease, rheumatoid arthritis (RA) [43,44]. In several animal models of arthritis, mice are persistently healthy when raised in germ-free conditions. However, the introduction of specific gut bacterial species is sufficient to induce joint inflammation [45-47].

Antibiotic treatment both prevents and abrogates a RA-like phenotype in several mouse models. Although, until recently, no specific microorganism has been shown to be associated with the disease. Based on the discovery that bacteria-induced Th17 cells directly contribute to the onset of arthritis in gnotobiotic mice [47], a recent study has analyzed the fecal microbiota in patients with RA [44]. With the use of 16S ribosomal RNA gene sequencing of the microbiota in patients with new-onset (untreated) RA, chronic (treated) RA, PsA and age- and ethnicity-matched healthy controls have been analyzed. Importantly, a marked association of the intestinal anaerobic bacterium, *Prevotella copri*, with new-onset RA patients and not with other patient groups have been found. Colonization of mice with *P. copri* has demonstrated a proinflammatory potential of this organism and suggested that new-onset RA-associated *P. copri* may contribute to the pathogenesis of human arthritis [44]. Although important, these findings have been derived from relatively small study groups and the analyses have been only focused on the bacterial community in the intestine excluding the vast majority of other microorganisms colonizing the human gut.

Together with bacteria in the gut, recent studies highlighted a neglected colonic fungal and yeast microbial community (mycobiome) [48,49]. Studies on the mycobiome in relation to PsA have not been performed, but are timely due to the notorious host inflammatory reactions to fungi. Of a special importance for PsA is the generation of IL-17-producing immune cells (Th17) as part of the anti-fungal adaptive responses [50]. Because IL-17RA signaling plays a critical role in the development of inflammation of the joint [51], the host immune responses to *Candida* and other members of the intestinal and skin mycobiome could have a serious implication for PsA pathogenesis. Therefore, it is essential to map the intestinal mycobiome along with the bacteria associated PsA to further explore them in diagnostic and treatment strategies.

Intestinal microbes or their products are able to translocate into the blood stream [38], possible partly due to a leaky gut caused by, for example, the production of inflammatory cytokines in the intestinal mucosa. Bacteria or fungi might translocate from the gut into the circulation toward the joints, a location easily accessible for antigens. This may result in a rapid T-cell invasion and inflammation since these T cells might be previously activated in the gut. In genetic susceptible individuals inflammatory arthritis might transit into a chronic form of arthritis such as PsA, whereas in subjects without an underlying susceptibility the body might resolve the inflammation itself. It is therefore suggestive that the PsA initiation site is not the joint, but might be the gut and/or the skin derived inflammation (Figure 1).

Therapeutic approaches targeting the microbiome

Diet

What is the reason that autoimmune diseases were unknown a century ago? Why is the prevalence of these diseases higher in industrialized and western countries? A change of diet results in a change of the composition of the gut microbiome [52]. This change in composition may result in a modulation of the immune system and alleviate or aggravate symptoms of the disease, depending on the type of diet. A limitation of investigation of the role of diet in disease is the compliance and discipline required by the patients. Not unexpectedly, obesity can lead to dysbiosis in the intestine as well [53,54]. If a modulation of diet can change the disease course or delay its development this would suggest a primary role of the gut microbiome in such diseases. Such relatively patient friendly diet based strategies need to be examined in future studies.

Anti-inflammatory medication

Immunosuppressive medication such as methotrexate, ciclosporin, sulfasalazine and biologicals might not

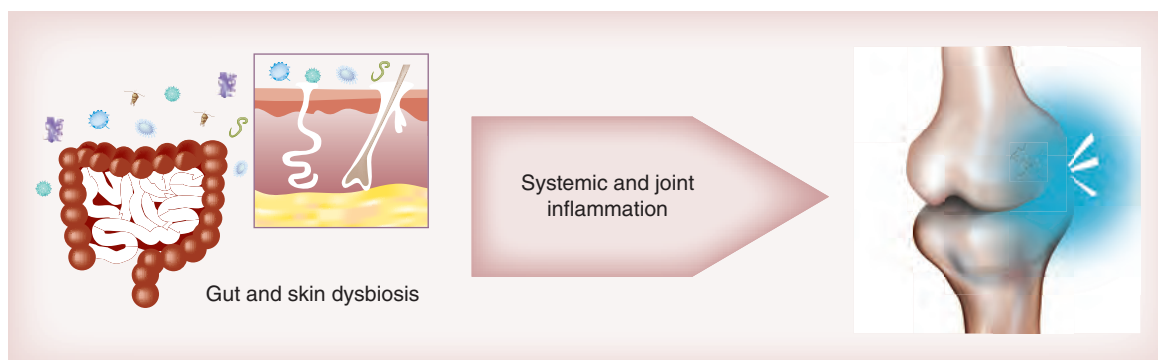


Figure 1. Gut and skin dysbiosis can underlie autoimmune reactions associated with joint inflammation in psoriatic arthritis.

only suppress the immune system but also might stimulate or deplete the abundance of particular bacteria in the gut microbiome. NSAIDs are highly effective in arthritis but NSAIDs might also be responsible for gut barrier dysfunction and disturbance of the gut microbiome. Endoscopically mucosal damage has been demonstrated in chronic NSAIDs users thereby increasing the gut permeability [55] and thereby creating an increased risk of translocation for bacteria or yeasts. Furthermore, NSAIDs are contraindicated in IBD and are a risk factor for flares. Interestingly, a recent study showed that the impact of 24-month treatment with etanercept or adalimumab showed a significant improvement of the metabolic syndrome features of PsA (waist circumference, triglycerides, high-density lipoprotein, cholesterol and glucose). For methotrexate, this benefit was not observed [56]. Another observation is that biologicals can improve the health-related quality of life of PsA patients [57]. Therefore, biologicals not only target specifically the joints and the skin but also the other features of this complex disease.

The paradox of anti-TNF therapy & antibiotics

Anti-TNF treatment is proven to be effective in psoriasis, IBD and PsA. Paradoxically, however, psoriasis can also be induced by anti-TNF-treatment. This has been demonstrated in several cases, of which the etiology remains to be investigated [58]. Therefore anti-TNF treatment can appear to be both cause and therapy of psoriasis warning on the careful use of the medication. Moreover, also other autoimmune diseases as cutaneous vasculitis, lupus-like syndrome, SLE and interstitial lung disease are described to be paradoxically induced by anti-TNF treatment [59]. The mechanism of this paradoxical reaction is unknown, the immune system is involved and modulation of the microbiome might be involved as well.

Another interesting paradox is the use of antibiotics and the microbiome. Pathogenic infections might be risk factors playing a role in the disturbance of the microbiome underlying PsA. Although antibiotics can be an effective treatment for PsA [60,61] a depleted gut microbiota by antibiotics (enrofloxacin) administration showed an aggravation of collagen induced experimental arthritis due to an increased production of IL-17A [62]. Another study, however, showed a beneficial effect of antibiotics at collagen induced arthritis with inhibition of proinflammatory cytokines such as TNF- α [63]. The frequent use of antibiotics at a young age might strongly disturb the composition of microbiome, supporting the 'hygiene hypothesis' that is relevant for autoimmune diseases [64]. These contradicting observations may be in part due to the facts that depletion of the microbiome by antibiotics may favor

the growth of patient-specific yeast and fungi in the GI tract or the skin. Therefore the use of antimycotica might become a future PsA therapeutic approach. The influence of medication at the microbiome remains to be investigated.

From therapy to prevention

Immunosuppressive therapy is a cornerstone in the treatment of autoimmune diseases. We have to take in consideration, however, that an increased use of medication in our society might be related to a disturbance of the gut microbiome and thereby related to an increase in development of inflammatory diseases and their comorbidities. Currently in medicine, more effort is put into the development of therapeutics than into prevention. However, more focus at prevention and at the cause of the disease might lead to less requirement of therapy.

The development of an autoimmune disease might be an ongoing gradual process of development during several years. If, hypothetical, the microbiome plays a key role in the development of PsA, a change in lifestyle might lead to a change in the abundance of particular bacteria or to a more general shift in the diversity of the microbiome. When these early changes could be captured, they might be logically more easily to reverse than later in time. If possible to find, such early warning signals could indicate the preterm development of a disease before the disease has actual (and permanent) manifested. Particular bacteria or fungi in the gut microbiome could function as a biomarker for prediction of development of inflammatory diseases or as a prognostic predictor. Clearly established differences in the composition of the patients' microbiome may guide different therapeutic and personal medicine-based approaches.

Conclusion

Given the diversity and the heterogeneity in PsA it is likely that different factors contribute to the etiology of the disease. It is becoming apparent that gut dysbiosis is associated with different autoimmune diseases including PsA. Studies on the specific PsA-associated microbiota traits will be hampered by the inter- and intra-individual diversity, time and space, variations present within the microbiome. A careful patients' selection for microbiome studies is expected to reveal the gut-joint-skin axis in diseases such as PsA. The exact cause-effect relationship of the microbiome and disease can be further explored in epidemiological, mechanistic and clinical studies. It would be ideal to develop an early warning test based on the microbiota profiles allowing the identification of patients in an early stage of development of PsA and thereby

precluding it into development to a chronic phase. Preventing the development of PsA might be more feasible than to cure it. Therefore the robust definition of specific PsA pathobionts might become an important guiding factor for early diagnosis, in clinical decision or for monitoring the course of the disease.

Future perspective

The quantity and quality of research in the field of the human microbiome has grown tremendously in the past several years. With the exponential growth of the data available it is expected that more mysteries will be unraveled regarding autoimmune diseases including PsA. It is expected that large-scale microbiome-based epidemiological studies combined with mechanistic insights will pin-point to specific bacteria or fungi acting either as friend or enemy during autoimmune

diseases. The translocation of gut bacteria to the circulation will be also a focus of research in respect to the inflammation-drive human pathologies. Hopefully prevention, early diagnostic and patient stratification based on the microbiome will take an important place in the future healthy aging and personal medicine efforts.

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Executive summary

- The gut microbiome is hypothesized to play an important role in a wide range of autoimmune diseases as inflammatory bowel disease, psoriasis, rheumatoid arthritis and psoriatic arthritis.
- The gut microbiome might be a potential target in prevention, diagnostics and therapy.
- The development of psoriatic arthritis might be a gradual process associated with human gut microbiota 'early warning signals'.
- The paradoxical effect of drugs used in psoriatic arthritis should not be underestimated as they might play a causal role in development of inflammatory diseases.

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