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The microbiome in autoimmune diseases

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Summary

The microbiome is represented by microorganisms which live in a symbiotic way with the mammalian. Microorganisms have the ability to influence different physiological aspects such as the immune system, metabolism and behaviour. In recent years, several studies have highlighted the role of the microbiome in the pathogenesis of autoimmune diseases. Notably, in systemic lupus erythematosus an alteration of the intestinal flora (lower *Firmicutes/Bacteroidetes* ratio) has been described. Conversely, changes to the gut commensal and periodontal disease have been proposed as important factors in the pathogenesis of rheumatoid arthritis. At the same time, other autoimmune diseases (i.e. systemic sclerosis, Sjögren's syndrome and anti-phospholipid syndrome) also share modifications of the microbiome in the intestinal tract and oral flora. Herein, we describe the role of the microbiome in the maintenance homeostasis of the immune system and then the alterations of the microorganisms that occur in systemic autoimmune diseases. Finally, we will consider the use of probiotics and faecal transplantation as novel therapeutic targets.

Keywords: anti-phospholipid, autoimmune diseases, faecal transplantation, microbiome, probiotics, rheumatoid arthritis, syndrome systemic lupus erythematosus, systemic sclerosis, Sjögren's syndrome

Introduction

The human body is densely populated by commensal and symbiotic microbes, the majority of the constituent microorganisms being bacteria. These microbes occupy different habitats such as gut, skin, vagina and oral. Not only are the types and abundance of microbes different in different organs, but these may also differ in different individuals. The genome of these microorganisms and their ecosystems constitute a microbiome. Factors such as diet, environment, host genetics and mode of delivery may be the reason behind the wide microbial diversity [1]. The presence of the microbiome and microbial products regulate the development and function of the immune system in the host. Furthermore, other physiological aspects of the mammalian (metabolism, behaviour) are affected by commensal microorganisms [2]. Recently, many scientists have focused on the importance of the commensal bacteria in the pathogenesis of several diseases, including autoimmune diseases. The aim of this review is to describe the main alterations of the microbiome that occur in autoimmune diseases [1].

Alterations of the microbiome in pregnancy and childhood

During pregnancy, the microbiome undergoes profound changes, in particular in the vagina and gut. In a recent study, Koren *et al.* [2] found that there were differences between the microbiome in women in the first trimester of pregnancy with that of the third trimester: in the last months of pregnancy an abundance of *Proteobacteria* and *Actinobacteria* and a depletion of *Faecalibacterium* (bacterium butyrate-producer with anti-inflammatory effects) resulted. These alterations of microbiome, known as dysbiosis, can induce weight gain, insulin-resistant and metabolic inflammation if the microorganisms contained in the gut of the mice at the third trimester have been transferred into germ-free mice [2,3]. The fetal

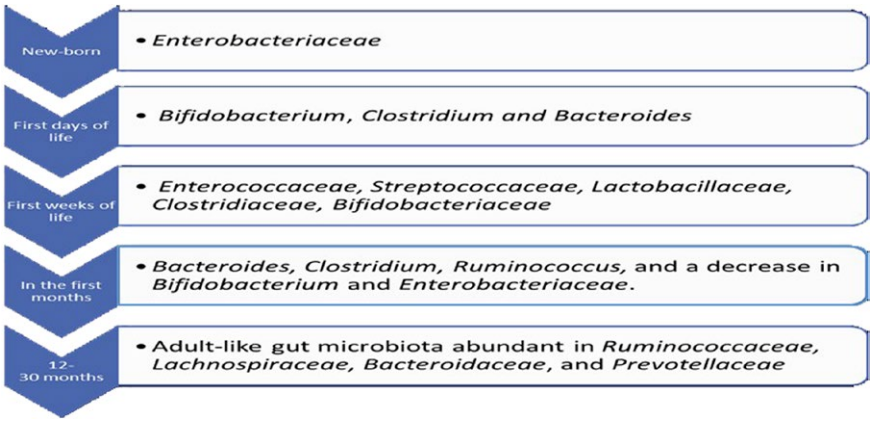

Fig. 1. The composition of the gut microbiota throughout life.

gastrointestinal tract is believed to be sterile, and microorganisms colonize the intestine of the fetus during delivery through the birth canal (Fig. 1) [4,5]. During childhood, the gut microbiome can be influenced by several environmental factors, such as geographic area, breast feeding, solid food and ways of delivery. Vaginally delivered infants acquire bacterial communities resembling their own mother's vaginal microbiota (*Lactobacillus*, *Prevotella*, *Sneathia* spp.). Conversely, Caesarean-section infants harbour bacterial communities similar to those found on the skin surface (*Staphylococcus*, *Corynebacterium* and *Propionibacterium*) [4,6]. The ability of the gastrointestinal mucosa of the newborn to adapt to the colonization of microorganisms is not entirely understood. Realistically, the colostrum and breast milk are rich in immunoglobulin (Ig)A, which are important to neutralize pathogens and to avoid translocation through the intestinal epithelia, therefore ensuring the homeostasis between symbiotic gut bacteria and the mucosa epithelium. Maternal milk contains several metabolites, such as gangliosides, lactoferrin (Lf) and human milk oligosaccharides (HMOs) that provide protection against anti-infective agents [1,7]. Furthermore, HMOs exhibit some prebiotic effects contributing to the colonization of specific bacteria, i.e. *Bifidobacterium longum*, thus preserving the integrity of the intestinal barrier. Moreover, existing dendritic cells in breast milk might contribute to neonatal immunological imprinting by influencing the nature of the immune response to the commensal antigens [8–11]. The immaturity of the immune system of the newborn and tolerogenic environment factors could explain how the microbiome has been accepted by the neonate gut. Therefore, the dialogue between commensals and host plays a crucial role in the development and homeostasis of the immune system [1,12,13]. This is possible through pattern recognition (PRR) receptors, that include Toll-like receptor (TLR) families, nucleotide-binding oligomerization domains (NOD) as receptors (NLR), type C lectin receptors (CLR), cytosolic DNA receptors (CDR) and retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) [14]. In part, TLRs are present mainly on the membrane of immune and epithelial cells and are able to recognize conserved molecular motifs, such as molecular models associated with microbes (MAMPS) expressed by the resident microbiota or molecular models associated with pathogens (PAMPS) produced by microbial invaders [15,16]. The microorganism commensals are also implicated in the development both of the lymphoid structure in the intestinal tract (i.e. Payer's patch, isolated lymphoid follicles) and for the promotion of epithelial cell maturation and angiogenesis of gastrointestinal mucosa [1,17,18]. Furthermore, the symbiotic bacteria (*Bacteroides fragilis*), through the production of sphingolipids, can influence activation of the invariant natural killer T (iNK T) and then conditioning the immune system into adulthood [19,20]. It is now clear that the microbiome induces regulatory responses and consequently the immunological tolerance through manifold pathways. In this regard, the regulatory T cell (T_{reg}) forkhead box protein 3 (FoxP3$^+$), which manifests itself both in the thymus and in the extrathymus through (i) production of regulatory cytokines [transforming growth factor (TGF)-β, interleukin (IL)-10 and IL-35], (ii) modulations of the antigen-presenting cell (APC) function [lymphocyte-activation gene 3 (LAG-3), cytotoxic T lymphocyte antigen (CTLA)-4, granzyme/perforin] and (iii) alteration of the cellular metabolism [CD25, CD39/CD73, indoleamine 2,3-dioxygenase (IDO) induction in dendritic cells (DC)], have all been associated with the function of T_{reg} cells in distinct inflammatory contexts [21,22]. In the intestinal tract, the commensal microorganisms could modulate the T_{reg} function through the production of IL-10 and TGF-β. *B. fragilis* produces polysaccharide A (PSA) capable of inducing IL-10 production by the intestinal T cells, and limit T helper type 17 (Th17) responses during intestinal

inflammation [23]. At the same time, other bacterial metabolites, such as short-chain fatty acids (SCFAs), and in particular butyrate, increase the function of T_{reg} cells and macrophages by inhibiting the expression of the histone deacetylases gene (HDAC) [23,24]. However, alterations in the microbiome (dysbiosis) can result from the exposure to various environmental factors, including diet, toxins, drugs and pathogens. Of these, enteric pathogens have the greatest potential to cause microbial dysbiosis and can trigger both local and systemic inflammation. The alteration of the composition of the microbiome and the barrier function can allow the development of autoimmune and chronic inflammatory diseases, metabolic dysfunction and cancer [1,5].

Microbiome and autoimmune diseases

Autoimmune diseases (AIDs) result from an individual's immune system attacking self-tissues, with an estimated incidence of approximately 3–5% worldwide. The pathogenesis is not understood completely, but environmental factors (life-style, diet, drugs, infections) and certain genetic backgrounds have been proposed [25,26]. The human microbiome might be a major player in autoimmunity, as the loss of immune tolerance can be caused by microbial composition changes [1,5]. Microorganisms can elicit the immune response against the host if the mechanisms of tolerance fail for several reasons (Fig. 2) [27–31]. Recently, Rinaldi *et al.* [32] found that autoantibodies directed against the cell wall mannan of the yeast *Saccharomyce cerevisiae* (phosphopeptidomannan), a ubiquitous commensal microorganism, were detected in several autoimmune diseases with different sensibilities (i.e. rheumatoid arthritis, systemic lupus erythematosus, anti-phospholipid syndrome). More specifically, anti-*S. cerevisiae* antibodies (ASCAs) are a specific serological marker of Crohn's disease (CD) by appearing before CD onset in 32% of cases. In addition, *S. cerevisiae* is used as an adjuvant in vaccines, and this has led scientists to think of a hypothetical risk of developing abnormal immune activation that may be associated with an autoimmune/inflammatory syndrome induced by adjuvants (ASIA) [32,33]. Inflammatory bowel diseases (IBD) such as CD and ulcerative colitis (UC) represent an example of how the alteration of gut microbiome could induce disease. Notably, numerous studies have shown that both CD and UC are associated with a reduced complexity of the commensal microbiota and consistent shifts to a dysbiotic state. In a similar manner to that observed during acute mucosal infections, both CD and UC are characterized by the outgrowth of the phyla proteobacteria, in particular the Enterobacteriaceae family and *Fusobacteriaceae* [34–36].

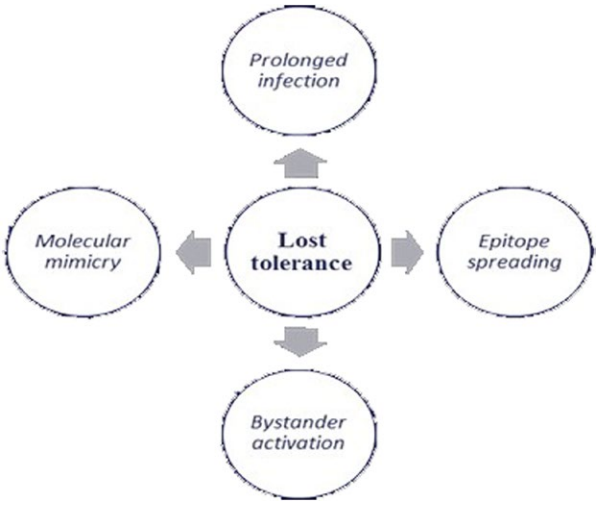

Fig. 2. The loss of tolerance.

Moreover, adherent-invasive *E. coli*, *Yersinia* and *Clostridium difficile* are much more common in patients affected by Crohn's disease than healthy individuals and, in some mouse models, these bacteria have been shown to be key contributors to IBD [37–39]. Evidence from neuroscience research suggests that the microbiome is essential for development and maturation of the central nervous system, as well for behavioural and cognitive functions. Communication between the central nervous system and gut is bidirectional, and is referred to as the 'gut microbiota–brain axis'. The gut can interact with the brain through several pathways and through commensal metabolism, such as short-chain fatty acid (SCAFs), 5-hydroxytryptamine (5-HT) and gamma-aminobutyric acid (GABA) [40,41]. Multiple sclerosis (MS) is an autoimmune disease characterized by the invasion of the central nervous system by immune cells (i.e. CD4 and CD8 T cells, B cells and activated monocytes), resulting in the demyelination of neurones and subsequent pathology [42]. Patients affected by MS exhibit a decrease in the percentage of several *Bacteroides* (i.e. *B. stercoris*, *B. coprocola*, *B. coprophilus)*, *Faecalibacterium* and SCAFs producing bacteria and increase of *Methanobrevibacter, Enterobacteriaceae* and *Akkermansia* [43]. Conversely, treatment with disease-modifying drugs induces an increase of *Prevotella* compared with untreated patients [44]. Furthermore, intestinal colonization by the *C. perfringens* type B is associated with relapse in MS. Toxins produced by *C. perfringens* can induce microvascular complications leading to neuronal and oligodendrocyte damage [43–45]. According to many researchers, dysbiosis also seems to be involved in the pathogenesis of type 1 diabetes mellitus (T1DM). In an interesting Chinese study, the faecal samples of children with T1DM were lower in abundance

of bacteria than healthy controls, in particular *Intestinimonas*, a newly isolated Gram-positive and anaerobic bacteria producing butyrate. Comparatively, an increase of *Blautia* was found in these patients [46].

Rheumatoid arthritis (RA)

RA is a chronic autoimmune disease characterized by inflammation and pain of the joints with varying degrees of systemic involvement in the presence of rheumatoid factor (RF) and anti-citrullinate peptide antibodies (ACPA). Although the genetic background plays an important role, other environmental risk factors, such as tobacco use and infection, have shown strong evidence for the pathogenesis of the disease. Recently, alteration of microbiota has attracted the attention of many researchers [47]. Several studies have found an association between periodontitis and RA. The chronic oral inflammation caused by oral bacteria and leucocyte infiltration with progressive destruction of the alveolar bone seems to share the same pathogenetic mechanisms with RA: (i) accumulation of leucocyte infiltration; (ii) release of inflammatory cytokines and mediators such as prostaglandin E_2 (PGE_2), tumour necrosis factor (TNF)-α, interleukin (IL)-1b, IL-6, IL-12, IL-17, IL-18, IL-33, granulocyte–macrophage colony-stimulating factor (GM-CSF), monocyte (CSF (M-CSF), receptor activator of nuclear factor kappa-B ligand (RANKL), matrix metalloproteinases (MMPs) and nitric oxide (NO) [48]. Furthermore, *Porphyromonas gingivalis*, a bacterium linked to the pathogenesis of the periodontitis, has the unique ability to convert the amino acid arginine to the amino acid citrulline: a process called citrullination, through the production of peptidylarginine deiminase. The protein, which contains the amino acid citrulline, is recognized by the autoantibodies ACPA that are highly specific for RA [49]. Recently, Brusca *et al.* [50] found that there were more organisms than simply *P. gingivalis* which cause periodontal disease (i.e. *Anaerglobus geminatus* and *Prevotella/Leptotrichia*) and were related to the presence of anti-citrullination antibodies. It was found that there is a positive correlation between antibodies to *P. gingivalis* and the presence of anti- cyclic citrullinated peptide (CCP) in patients with juvenile idiopathic arthritis. In the oral flora, bacteria such as *P. intermedia*/*Tannerella forsythia* were found and high titres of antibodies against these microorganisms have been detected in the serum and synovial fluids of patients with RA [51]. Otherwise, other scientists [52] found that IgG antibodies to *P. intermedia* and *C. ochracea* were associated with a lower prevalence of RF [52–54]. However, there is evidence that the treatment of periodontal disease may improve RA symptoms [55]. Unlike these studies, analysis of a cohort of 292 patients with RA did not demonstrate any correlation between periodontal disease and RA [56]. The oral cavity is not only the place in the human body that was colonized by bacteria. The majority of microorganisms present in our body are harboured in the human gut, thus affecting the balance between pro- and anti-inflammatory immune responses [57]. As mentioned above, the butyrate produced by intestinal bacteria could explain anti-inflammatory properties through the differentiation of T_{reg} lymphocytes. Also, polysaccharide A produced by *B. fragilis* binds TLR-2 on the surface of lymphocytes and DCs. It thus promotes the maturation of $CD4^+$ lymphocytes into T_{reg} lymphocytes and the production of anti-inflammatory cytokines such as IL-10 [54–58]. Rogier *et al.* [59] reported a decrease of *Bacteroidaceae* and an increase of *Firmicutes* and *Proteobacteria* (i.e. *Ruminococcaceae*, *Lachnospiraceae*) and *Desulfovibrinocaceae* during the immune-priming phase of arthritis in the collagen-induced arthritis (CIA) mice model. The authors suggested particularly that an alteration of the intestinal microbiome during the immune-priming phase could induce an inflammatory response in the joints. Conversely, administration of antibiotics decreased the severity of arthritis in mice models. This result is due to a decrease in the abundance of segmented filamentous bacteria, a commensal that influences the adaptive immunity and the innate immune system through an increase of IgA secretion and a development of Th17 lymphocytes, respectively [59,60]. Recently, other studies have demonstrated that the gut microbiome of a new-onset RA was characterized by an increase of *P. copri* and lower numbers of *Bifidobacteria*, the *Bacteroides–Porphyromonas* group, the *B. fragilis* subgroup and *Eubacterium rectal–Clostridium coccoides* [52,53,61]. Interestingly, Moreno *et al.* [62] suggested that *P. copri* might play a key role in the pathogenesis of RA in patients with a lower level of genetic susceptibility, where environmental factors are critical for the development of the disease. In accordance with Scher [63], *P. copri* was inversely proportional to the presence of shared-epitope risk alleles and abundance of *Bacteroides*. Chen *et al.* [64] obtained different results on the basis of stool evaluations from 40 patients with RA and a control group. No relationship between the occurrence of *P. copri* with early RA was determined. In contrast, *Eggerthella*, *Faecalibacterium* and *Colinsella* were found in faecal samples of patients affected by RA. Larger counts of *L. salivarius*, *L. iners* and *L. ruminis* were found in patients in the control group and *L. mucosae* was found solely in patients with RA. Also, an increase of *Clostridium* bacteria was detected in the faecal samples of mice models of RA with the RA-susceptible DRB1*0401 gene [65,66]. Other authors have hypothesized that the microbiome diversity could

influence the response to therapy with methotrexate (MTX) in patients affected by RA. A microbiome rich in *Prevotella* has been shown to decrease tetrahydrofolate (THF) biosynthesis through a decrease of purine metabolic pathway. According to the author, this may have therapeutic implications, because methotrexate (MTX), a folate analogue, and a dihydrofolate (DHF) reductase inhibitor exhibits a pharmacological effect on the same metabolic pathway [63]. Nevertheless, many other scientists have shown that the pharmacological activity of MTX occurs mainly through an increase of cyclic AMP concentration [67]. Alterations of commensal bacteria have also been discovered in the low respiratory tract and in the urinary system. Notably, an association between erosive RA and *Pseudonocardia* colonization in the lung was suggested [68], and the number of *Proteobacteriacea* was increased in patients affected by RA [69]. Despite previous speculations, other studies report a decrease in an abundance of *Actinomyces*, *Prevotella* and *Porphyromona*s in the bronchoalveolar lavage (BAL) of RA patients [68]. Conversely, several studies found a strong correlation between urinary infections supported by *Proteus mirabilis* and rheumatic disease [70], given that patients affected by RA exhibit antibodies against *P. mirabilis* in the serum. Thus, the authors suggested that chronic infection triggers activation of the immune system and the development of RA in certain genetic backgrounds and in the presence of unknown environmental factors [71,72].

Systemic lupus erythematosus (SLE)

SLE is a heterogeneous autoimmune disease with a wide range of clinical and serological manifestations. The disease course is marked by remissions and relapses and may vary from mild to severe. The prevalence ranges from 20 to 200 cases per 100 000 people and women are affected more often than men. The pathogenesis of SLE is not understood completely; it is thought to involve hormonal factors, environmental factors (infection, drugs, ultraviolet A light) and genetic causes [73]. However, in previous years it has been suggested, as in other autoimmune diseases, that the gut microbiota could play an important role in the development of SLE (Table 1). In patients with SLE, a lower *Firmicutes*/*Bacteroidetes* ratio and the abundance of several genera have been reported: *Rhodococcus*, *Eggerthella*, *Klebsiella*, *Prevotella*, *Eubacterium* and *Flavonifractor* were enriched significantly, while *Dialister* and *Pseudobutyrivibrio* were decreased in SLE patients [74,75]. It is not known whether the alteration of commensal bacteria results as a consequence of the disease process or dysbiosis contributes to the lupus onset [76]. According to Johnson *et al.* [77], dysbiosis is associated with local inflammatory responses (specifically the Th17 response) and high circulating levels of antibodies against ds-DNA and histone. Moreover, immune responses generated by inflammatory commensals could be promoting the activation of the systemic lymphocyte and T_{reg}–Th17 transdifferentiation. However, in patients with SLE, lower levels of *Synergistetes* (a microorganism associated positively with the *Firmicutes* to *Bacteroidetes* ratio) were found [78]. Therefore, under physiological conditions, *Synergistetes* decrease serum levels of IL-6 (a proinflammatory cytokine) and may stimulate B1 cells to secrete natural protective IgM anti-phosphorylcholine. This can be achieved by down-regulating inflammation in several ways [clearance of apoptotic cells and cellular debris, removal of oxidized lipids, blockade of mitogen-activated protein kinase (MAPK) activation and other proinflammatory mediators] [79,80]. Reduction in the abundance of *Lactobacillaceae* and an increase of *Lachnospiraceae* were observed in patients with SLE [81,82]. Recently, it was demonstrated that *Lactobacillis* spp. and *L. reuteri* could have a positive effect on renal function in mice affected by lupus nephritis. In this study, treatment with *Lactobacillus* spp. improved the intestinal permeability (altered before the nephritis onset), decreased inflammatory cytokines (i.e. IL-6 and IL-18) and increased anti-inflammatory cytokines (i.e. IL-10, TGF-β) and T_{regs}. It also demonstrated an improvement of renal disease through the decrease in IgG2a (one of the major immune deposits) and of the IFN-γ level. However, such evidence was not present in male mice, suggesting that the influence of microbiome is sexually related, dependent and indicating a role for sex hormones in the regulatory function of the gut microbiota on lupus [83]. In accordance with other findings, Bankole *et al.* [84] highlighted an increase of *Protebacteria phyla* and family of *Lachnospiraceae* and a decrease *of Rikenellaceae*, *Odoribacteraceae*, *Christensenellaceae* and *Peptococcaceae* families in samples from 21 patients with SLE.

Anti-phospholipid syndrome (APS)

APS is an acquired autoimmune disorder that manifests clinically as recurrent venous or arterial thrombosis and/or fetal loss. Characteristic laboratory abnormalities in APS include persistently elevated levels of antibodies directed against membrane anionic phospholipids [i.e. anti-cardiolipin (aCL) antibody, anti-phosphatidylserine] or their associated plasma proteins, such as beta-2 glycoprotein I (β2GPI) or evidence of a circulating anticoagulant. The incidence of APS is approximately five cases per 100 000 people per year, with a prevalence of approximately 40–50 cases per 100 000 people [85,86].

Table 1. Main alterations of microbiome in autoimmune diseases.

Bacteria	SLE	RA	SS	APS	SSc
Acinetobacter johnsonii			↑[94]skin		
Akkermansia muciniphila					
Alistipes finegoldii			↓[97]gut		
Anaerglobus geminatus		↑[50] oral			
Bacteroidetes		↓[59] gut	↑[94]gut		
Bacteroides fragilis					↓[100] gut
Bifidobacterium		↓[53] gut	↓[97] gut		↑[100] gut
Campylobacter					
Capnocytophaga sputigena			↑[94]oral		
Capnocytophaga ochracea			↑[94] oral		
Christensenellaceae	↓[74-75] gut				
Clostridia-like bacterium (XIVa–IV)		↑[66] gut			↓[100]gut
Clostridium coccoides		↓[53] gut			
Corynebacteriium amycolatum			↑[94] skin		
Dialister	↓[74] gut				
Eggerthella	↑[74] gut	↑[64] gut			
Enterococcaceae					
Escherichia, Shigella, Enterobacter			↓[96] gut		
Eubacterium	↑[75]gut	↓[53] gut			
Eubacterium rectal		↓[61] gut			
Faecalibacterium prausnitzii[e]		↑[64] gut	↓[96] gut		↓[101]gut
Firmicutes[a]	↓[74]gut	↑[59] gut	↑[95] gut		
Flavonifractor					
Fusobacterium			↓[96] gut		↑[100]gut
Klebsiella	↑[74] gut				
Lachnospiraceae	↑[81] gut	↑[59] gut			
Lactobacillaceae[b]	↓[81,101]gut	↑[64] gut			↑[101]gut
Leptotrichia		↑[49] oral	↓[97] gut		
Methanobrevibacter,					
Odoribacteraceae	↓[74] gut				
Peptococcaceae					
Porphyromonas gingivalis[d]		↑[49] oral			
Prevotella disiens			↓[94] oral		
Prevotella Intermedia[c]		↑[51]oral			
Protebacteria		↑[69] lung			
Proteus mirabilis		↑[70] urinary t.			
Pseudobutyrivibrio					
Pseudocardia		↑[69] lung			
Rhodococcus	↑[74-44] gut				
Rhodotorula glutinis					↑[102]skin
Rikenellaceae	↓[94-94] gut				
Roseburia intestinalis				↑[89]gut	
Ruminococcaceae		↑[59] gut			
Spirochetes					
Streptococcus			↑[95] oral		
Synergistetes	↓[78] gut		↓[95] oral		
Tannerella forsythia		↑[51] oral			
Veillonella			↑[95]oral		

[a]A lower *Firmicutes/Bacteroidetes* ratio in systemic lupus erythematosus (SLE) patients. Conversely, *Firmicutes* are increased in rheumatoid arthritis (RA) and Sjögren's syndrome (SS) patients.

[b]Reduction in the abundance of *Lactobacillaceae* and an increase of *Lachnospiraceae* are observed in patients with SLE. In SSc patients *Lactobacillaceae* are increased.

[c]High titres of antibodies against *Prevotella intermedia* have been detected in the serum and synovial fluids of patients with RA.

[d]*Porphyromonas gingivalis* converts the amino acid arginine to the amino acid citrulline. The protein which contains the amino acid citrulline is recognized by the anti-citrullinate peptide antibodies (ACPA).

[e]*Faecalibacterium prausnitzii* is increased in patients with RA and decreased in SS and SSc patients.

The pathogenesis is poorly understood: environmental factors and genetic background have been proposed and, in previous years, the role of the microbiome and infections have been suggested. Shoenfeld *et al.* [87] showed that mice immunized with proteins from *Haemophilus influenzae*, *Neisseria gonorrhoeae* or tetanus toxoid have developed antibodies that recognized cardiolipin, β2GPI and the amino acid sequences contained in the proteins. Conversely, naive mice infused with these antibodies developed significant thrombocytopenia, prolonged activated partial thromboplastin time and pregnancy loss similar to mice treated with pathogenic anti-β2GPI. These studies suggested that molecular mimicry could be a potential explanation for the induction of pathogenic aPLs [88]. Recently, it has been demonstrated that commensal, in particular segmented filamentous bacteria (SFB), influence T cell phenotypes and also both T-dependent and T-independent antibody production. If the microbiome homeostasis is disrupted (i.e. infections, drugs), proinflammatory interactions could occur with local and systemic effects on the immune system, including breaches of the mucosal barriers and generation of commensal-specific memory T cells and autoantibodies. Therefore, it is likely that commensal bacteria may promote breaks in tolerance and the induction of persistent aPLs in genetically predisposed individuals [89]. Notably, the authors suggested that *Roseburia intestinalis*, an anaerobic Gram-positive bacterium extremely common in the gut of patients affected by APS, has many homologous sequences to both the major B and T cell epitopes and thus it could stimulate lymphocytes [89].

Sjögren's syndrome (SS)

SS is a chronic autoimmune inflammatory disorder characterized by a reduction in the production of saliva, tears and pancreatic juice. Distinctive changes occur in the exocrine glands (salivary glands, tear glands, pancreas, glands of the alimentary and respiratory tracts). Also, lymphocytic ($CD4^+$) T cells, DCs and B cells can infiltrate polyclonal B cell hyperactivity and autoantibody production (anti-SSA/Ro60 antibodies). The incidence of SS is estimated at approximately seven per 100 000 people and the highest incidence rates are reported in studies from Europe and Asia [90]. The pathogenesis of SS includes multiple genetic and non-genetic interacting factors. There is an involvement of innate and adaptive immunity, as well as neuroendocrine and neuropathic processes. Biopsies of glandular and extra-glandular sites are characterized by lymphocytic infiltration, with immune-histological evidence for the involvement of numerous elements of innate and adaptive immune responses. Furthermore, cellular adhesive molecules, metalloproteinases and neural transmitters show alterations in the affected target organs [91]. Several studies report an intimate association between SS and Epstein–Barr virus (EBV)/Coxsackie virus infections [92,93]. Conversely, commensal bacteria could have an important role in the pathogenesis of SS. Peptides derived from oral, gut and skin commensal bacteria (Table 1) may induce an immune response by activation of Ro60-reactive T cells. Specifically, they are found in the oral flora (*P. disiens*, *Capnocytophaga sputigena* and *C. ochracea*) and in the gut flora (*B. finegoldii*, *B. intestinalis*, *B. fragilis* and *Alistipes finegoldii*) and two are found on the skin (*Corynebacteriium amycolatum* and *Acinetobacter johnsonii*) [94]. Therefore, in SS patients, oral dysbiosis has been found with an increase of Firmicutes, specifically *Streptococcus* and *Veillonella*, and decreased in *Synergistetes* and *Spirochaetes* [95]. Furthermore, de Paiva *et al.* [96] discovered that faecal samples from SS patients had an approximately 50% reduction in the genus *Faecalibacterium*, which includes *F. prausnitzii*, one of the predominant butyrate producers in the intestine. There was also a significant increase in the enteric pathogens, such as *Escherichia/Shigella* and *Enterobacter*. In addition, the researchers did not find any difference in the microbial composition between control and SS patients, except for an increase in *Streptococcus* and decrease in numbers of *Leptotrichia* and *Fusobacterium*. Moreover, patients with severe dysbiosis, meaning decreased levels of bacteria from the genera *Bifidobacterium* (38 *versus* 3%; $P < 0{\cdot}001$) and *Alistipes* (19 *versus* 3%; $P = 0{\cdot}017$) could have higher disease activity (evaluated by Sjögren's syndrome Disease Activity Index), lower levels of complement component and higher levels of faecal calprotectin [97].

Systemic sclerosis (SSc)

SSc is a complex and heterogeneous disease, with clinical forms ranging from limited skin involvement (limited cutaneous systemic sclerosis) to forms with diffused skin sclerosis and severe and often progressive internal organ involvement (diffuse cutaneous systemic sclerosis). Moreover, immunological disturbances, such as positive anti-nuclear antibody (ANA), anti-topoisomerase I (anti-Scl-70) antibody, anti-centromere antibody (ACA) and anti-RNA polymerase III antibody (anti-RNAPIII) were found [98,99]. It is well known that SSc patients have decreased commensal bacteria (Table 1), such as *Faecalibacterium* and *Clostridium*, and increased bacteria, such as *Fusobacterium* and γ-Proteobacteria, compared with healthy controls. However, SSc patients also had increased *Bifidobacterium* and *Lactobacillus*, which are typically decreased during the inflammation state.

Moreover, patients with moderate/severe gastrointestinal symptoms had decreased *B. fragilis* and increased *Fusobacterium* compared with SSc patients with no/mild symptoms [100]. According to Andréasson *et al.* [101], dysbiosis (lower abundance of *F. prausnitzii* and *Clostridiaceae* and, at the same time, relatively high levels of *Lactobacillus*) was more pronounced among patients with pulmonary fibrosis, oesophageal dysfunction and malnutrition (Table 1). In another study, the researchers used ribosomal RNA sequencing of forearm skin biopsies taken from patients with early (< 6 months) diffused and limited SSc and healthy controls. They discovered increased expression of *Rhodotorula glutinis* sequences in the patient samples; it has been supposed that *R. glutinis* might activate the immune system and in this way induce skin fibrosis [102].

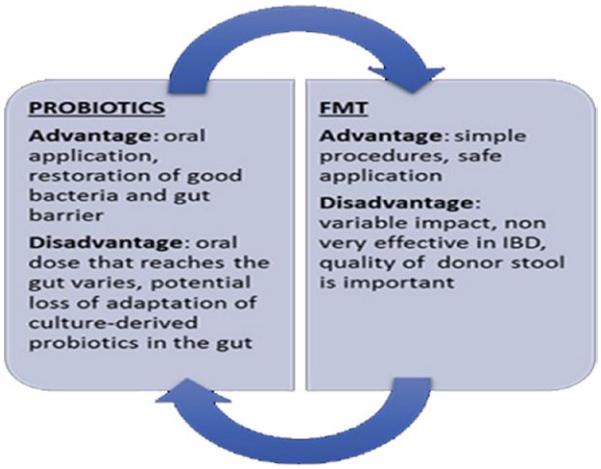

Fig. 3. Advantages and disadvantages between probiotics and faecal transplantation (FMT).

Discussion

The association between bacteria and autoimmune disease is well understood; alteration of microbiome 'dysbiosis' can induce autoimmune disease in people with certain genetic backgrounds and environmental factors. Dysbiosis can be categorized into three different types: (1) loss of beneficial organisms, (2) excessive growth of potentially harmful organisms and (3) loss of overall microbial diversity. Moreover, these three types are not mutually exclusive and can occur simultaneously [103]. Besides, different commensal can increase or decrease in amount according to disease, i.e. in MS *Prevotella* decreases, while in RA it increases [44,64]. Recently, studies have focused upon reversing the negative effects mediated by the microbiota during the disease state. It is possible to restore the healthy flora through administration of (i) probiotics, Gram-positive bacteria (i.e. *Bifidobacteriaum* spp., *Lactobacillus* spp., *Lactococcus* spp., *Pediococcus* spp. and other non-pathogenic strains of *E. coli*) [104]; and (ii) faecal microbiota transplantation (FMT), which consists of engrafting a healthy microbiota into patient recipients to reintroduce or re-establish a stable environment that influences both the endogenous microbes and the host [105] (Fig. 3). The scientific literature is rich with studies concerning probiotic treatments in autoimmune disorder. Recently, it has been demonstrated that in non-obese diabetic (NOD) mice the oral administration of a *Lactobacillaceae* protects mice from T1D by suppressing IL-1b and promoting the differentiation of $CD103^+$ tolerogenic DCs in the gut [106]. Moreover, in a multi-centre prospective cohort study, early probiotics supplementation has been shown to decrease the risk of islet autoimmunity in children with higher genetic risk of TDM1. [107]. In 45 RA patients the administration of *Bacillus coagulans* has ameliorated pain and has improved disability, antagonizing microbes that may be contributing to an inflammatory response and producing short-chain fatty acids such as butyric acid with anti-inflammatory activities [108]. In addition, the administration of *L. casei* reduces proinflammatory molecules (IL-1β, IL-2, IL-6, IL-12, IL-17, IFN-γ, TNF-α and Cox-2) in experimental arthritis [109]. Similarly, *Lactobacillus* spp. improves lupus symptoms, diminishes inflammation and restores the intestinal barrier, thereby increasing the expression of adhesion molecules in the gut [83,110]. Despite pharmacological drugs and the use of antibiotics that produce a negative impact on gut microbiota, there is a great deal of evidence that autoimmune diseases can be treated with antibiotics. Mu *et al.* [111] showed that the administration of oral antibiotics in lupus-prone MRL/lpr mice improve the disease by decreasing inflammatory cytokines (i.e. IL-17) and increasing IL-10, a cytokine with anti-inflammatory activity. Moreover, the authors demonstrated that the administration of vancomycin reduced the levels of anti-dsDNA IgG and proteinuria and improved intestinal permeability. In a recent review, Rosman *et al.* [112] described the usefulness of antibiotic therapy in autoimmune disorders through their anti-inflammatory and immunomodulatory properties (Fig. 4). In conclusion, further studies will be required to investigate the relationship between mammalian and commensals in order to develop novel therapeutic targets. The intestine at birth is an aerobic environment and only facultative anaerobes, such as members of the *Enterobacteriaceae* family, can grow. After few days, the intestinal lumen turns anaerobic, allowing only anaerobes such as *Bifidobacterium*, *Clostridium* and *Bacteroides* to colonize [4]. During the first few weeks, the microbiome of the infant gut is similar to the maternal skin and vaginal

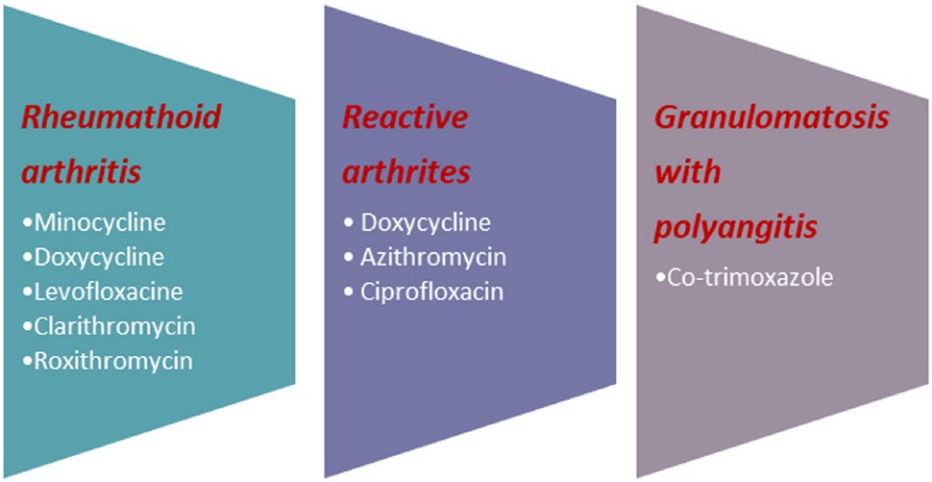

Fig. 4. Utility of antibiotic in autoimmune diseases.

microbiome, with *Enterococcaceae*, *Streptococcaceae*, *Lactobacillaceae*, *Clostridiaceae* and *Bifidobacteriaceae* the predominant bacterial taxa. During the first months the diet is almost exclusively milk, favouring milk oligosaccharide fermenters such as *Bifidobacterium*. With the weaning and introduction of solids foods, another rapid and important shift in gut microbiota occurs. The introduction of a variety of nutrients, many of which are polysaccharides not digested by host enzymes, trigger an increase in the abundance of *Bacteroides*, *Clostridium* and *Ruminococcus* and a decrease in *Bifidobacterium* and *Enterobacteriaceae*. In the subsequent 12–30 months, the infant gut microbiome progresses into an adult-like gut microbiota abundant in *Ruminococcaceae*, *Lachnospiraceae*, *Bacteroidaceae* and *Prevotellaceae*.

Microorganisms can elicit the immune response against the host if the mechanisms of tolerance fail in several ways: (i) epitope spreading consists of the development of autoimmune responses to endogenous epitopes following the release of self-antigens during an inflammatory response, which is caused by a change in protein structure, i.e. changing of amino acid residue from arginine to citrulline. This may result in an immune reaction not only against the original protein or in its citrullinated form, but also against other citrullinated proteins [27]; (ii) molecular mimicry is a mechanism by which infections can induce autoimmunity and occurs when foreign antigens share sequence or structural similarities with self-antigens. The immune responses can be directed against peptides with similar charge distribution and overall shape [28]. (iii) Bystander activation occurs when microbial infection stimulates Toll-like receptors (TLRs) and other pattern recognition receptors on antigen-presenting cells (APCs) with the production of proinflammatory mediators which, in turn, may lead to tissue damage [29]; and (iv) prolonged infection with a virus, such as EBV or HCV, can induce constant activation and proliferation of T cells, resulting in the production of monoclonal and polyclonal antibodies as well as immune complexes, leading to loss of tolerance [30,31].

Disclosure

The authors declare that they have no competing interests.

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