The evidence for microbiome manipulation in inflammatory arthritis

Hannah Jethwa\textsuperscript{1} and Sonya Abraham\textsuperscript{2}

Abstract

The human body consists of millions of commensal bacteria (the microbiome), with the intestinal tract being the most prevalent site of colonization. This colonization process begins at birth, and despite numerous factors such as ageing, diet and drug use affecting the microbiome make-up, by adulthood the composition of the gut bacteria is relatively consistent across local populations. The recent advent of new scientific techniques has enabled us to explore how the microbiome affects health and, in particular, has shed light on the involvement of the microbiome in the pathogenesis of inflammatory disease. In this review we highlight the current evidence for microbiome manipulation in inflammatory arthritis in animal and human models and discuss potential therapeutics targeting the microbiome as treatment for these diseases.

Key words: microbiome, bacteria, inflammatory arthritis, spondyloarthritis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, dysbiosis

Introduction

The skin, oral cavity, upper respiratory tract, female genital tract and gut are all colonized by commensal and symbiotic microorganisms—this is known as the microbiome. Of these, the gut contains by far the most densely populated ecosystem, consisting of bacteria, Archaea and eukaryotic microorganisms. The intestine of a healthy adult has been shown to contain $\sim 10^{14}$ non-eukaryotic cells, of which bacteria are the most prevalent \cite{1}. Within these bacterial populations are a relatively sparse number of dominating phyla, including Bacteroidetes (most abundant), Actinobacteria, Proteobacteria, Firmicutes, Verrucomicrobia and Fusobacteria.

Microbial colonization of the gut begins at birth when the baby has exposure to bacteria in the maternal vaginal canal. During early life the composition of the gut microbiome is determined by multiple factors, such as maternal weight, delivery method, milk composition, the make-up of the maternal microbiome and possibly genetic factors \cite{2}.

The gastrointestinal tract functions as a barrier against antigens from a variety of microorganisms. The composition of the adult human gut microbiome can be classed into three discrete and constant enterotypes, each defined by the high abundance of Bacteroides, Prevotella or Ruminococcus \cite{3}. Diet appears to be an important factor for the gut microbiome composition, and studies across distinct geographical locations highlight the strong association between the staple diet on the gut bacterial composition \cite{4}.

Various protective mechanisms have been adapted to protect the intestinal lamina propria and systematic circulation against gut microbiota, including: a physiological barrier (mucus layer, proteins with antimicrobial properties and IgA antibodies), tight junctions between intestinal epithelial cells (providing a physiological barrier as well as antibacterial properties) and the lamina propria innate immune system (e.g. macrophages and dendritic cells), leading to stimulation of the adaptive immune response \cite{5}.
Due to its juxtaposition to the host’s intestinal immune system and its aptitude for manipulating immune responses, the gut microbiome has a significant influence on local homeostasis.

The microbiome and autoimmune disease
Recent insights from genetic analysis of gut microbial populations suggest that the microbiome characterizes an important environmental factor in the development of local tissue disruption and clinical disease; this is due to an alteration in commensal species resulting in the initiation of an inflammatory cascade via the innate and adaptive immune system [5].

The innate immune response is composed of a vital component known as the inflammasome pathway, which stimulates proinflammatory IL-1 and IL-18 production [5]. Elinav et al. [6] studied knockout mice that lacked various inflammasome-related genes and subsequently demonstrated colitis exacerbations, suggesting that this pathway is important for maintaining health.

Relation to inflammatory arthritis
The concept of bacterial involvement in the pathogenesis of rheumatoid arthritis dates back to the 19th century, when Bannatyne and Wohlmann [7] suggested the disease may be caused by a mycobacterium.

Later research into the gut–joint–axis hypothesis (Fig. 1) was prompted by knowledge that up to 20% of patients with chronic IBD have recurrent episodes of peripheral arthritis. Furthermore, reactive arthritis is known to develop following exposure to various gut bacteria, such as Shigella, Salmonella, Yersinia and Campylobacter species, further suggesting an overlap between bacteria and arthritis [8].

The existence of epitopes on bacteria that induce immune responses cross-reactive with cartilage episodes have been described [9], and studies have shown a considerable degree of cross-reactivity between Escherichia coli, Klebsiella pneumonia, Yersinia enterocolitica and Bacteroides fragilis (all thought to be associated with IBD, AS and reactive arthritis) [10].

One theory suggests an increased permeability of the gut wall lumen results in exposure of the immune system to commensal microorganisms that otherwise would not result in disease. A confounding factor to studies of this hypothesis are the use of NSAIDs, which are known to increase intestinal permeability [2]. Mielants et al. [11], however, demonstrated increased intestinal permeability in patients with RA, spondyloarthritis and IBD and,
interestingly, this finding was also noted in patients who had not been treated with NSAIDs.

**RA**

RA is a chronic inflammatory disease that can result in joint inflammation and associated systemic extra-articular features. RA development is associated with the dysregulation of normal immune function, involving an amplified production of autoantibodies as well as pro-inflammatory T lymphocytes [12].

Although the exact mechanism resulting in RA pathogenesis remains to be elucidated, early theories suggested specific genes that had the potential to induce joint inflammation and disease. Genome-wide association studies have recognized multiple susceptibility alleles, including those that influence T cell differentiation, alteration of peptide affinity or antigen selection [13]. Genetic factors, however, do not appear to be sufficient for disease development, as studies in monozygotic twins reveal genetic heritability to be \(\frac{24}{60}\%\) [14]. An environmental trigger, therefore, is likely to be required to trigger disease in individuals with a genetic predisposition [12].

A potential trigger factor may be microbiome variations.

**Oral bacteria**

Multiple clinical studies have suggested a significant link between RA and periodontopathic bacteria (Table 1); for example, patients with longstanding active RA have a considerably increased frequency of periodontal disease, and patients with periodontal disease have an increased prevalence of RA compared with those without [15].

Furthermore, research looking at serum and synovial fluid specimens from patients with RA detected the presence of high levels of antibodies against anaerobic bacteria and bacterial DNAs implicated in periodontal disease (e.g., *Porphyromonas gingivalis*, *Tannerella forsythensis* and *Prevotella intermedia*), and antibiotics targeting these bacteria (such as Ornidazole, Levofloxacin and Clarithromycin) appear to be effective against RA, independent of disease stage or severity [15].

Chukkapalli *et al.* [16] employed an established murine model of periodontitis induced by chronic polymicrobial infection with three notable human periodontal bacterial pathogens (*P. gingivalis*, *T. denticola* and *T. forsythia*) to determine whether periodontitis induction enhanced arthritis in a collagen-induced arthritis mouse model. Their study revealed exacerbated clinical signs of arthritis, systemic spread of periodontal bacteria and marked levels of MMP3 compared with mice without oral bacteria administration. Joint histopathology of these mice revealed elevated levels of inflammatory cell infiltration, articular cartilage destruction, pannus formation and bone distortion compared with the collagen control mice, demonstrating a causal association between these oral pathogens and an increased severity in induced arthritis.

Various links to RA pathogenesis have been demonstrated, for example, periodontopathic bacteria are potent stimulators of TNF\(\alpha\) and other proinflammatory cytokines in humans, anti-CCP targets epitopes created by deamination of arginine residues in autoantigenic proteins, and Th17 cells (and IL-17) play an important role in the pathogenesis of RA, and these cells appear at the sites of chronic inflammation in human periodontal disease. Furthermore, oral pathogens have been shown to promote RF production, both directly (antibacterial) and indirectly (Toll-like receptor ligation), both locally (in gingival tissue) and systemically (in serum) [15]. In keeping with this, peptidylarginine deiminase expression has been demonstrated in *P. gingivalis*, and *P. gingivalis* proteinase is responsible for the epitope development in the Fc region of RF. Furthermore, patients with untreated periodontitis have been shown to have higher anti-CCP levels than healthy controls, and treatment of their underlying *P. gingivalis* infection leads to lower serum anti-CCP levels.

**Table 1** Bacterial species found to be relevant in the pathogenesis of RA

<table>
<thead>
<tr>
<th>Species</th>
<th>Cavity</th>
<th>Species population size compared with normal (if commensal)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Porphyromonas gingivalis</em> [15]</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td><em>Tannerella forsythensis</em> [15]</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td><em>Prevotella intermedia</em> [15]</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td><em>Tannerella denticola</em> [16]*</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td><em>Tannerella forsythia</em> [16]*</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>Streptococcal A, B, C [21]*</td>
<td>Gut</td>
<td></td>
</tr>
<tr>
<td><em>Lactobacillus casei</em> [21]</td>
<td>Gut</td>
<td></td>
</tr>
<tr>
<td><em>Yersinia enterocolitica</em> [23]*</td>
<td>Gut</td>
<td></td>
</tr>
<tr>
<td><em>Lactobacillus salivarius</em> [25]</td>
<td>Gut, Oral</td>
<td>Increased</td>
</tr>
<tr>
<td><em>Prevotella</em> spp. (esp. <em>P. copri</em>) [26]</td>
<td>Gut</td>
<td>Increased</td>
</tr>
<tr>
<td>Bacteroides [26]</td>
<td>Gut</td>
<td>Decreased</td>
</tr>
<tr>
<td>Actinobacteria [26]</td>
<td>Gut</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

*Studies on murine/rat models.*
levels, suggesting the presence of *P. gingivalis* may induce autoimmunity in susceptible individuals [16].

Th17 cells (and IL-17) impact on the pathogenesis of RA, and these cells appear in the sites of chronic inflammation in human periodontal disease; for example, *P. gingivalis* antigen has been shown to preferentially stimulate T cells to express IL-17 [15].

**Gut bacteria**

Advances in metagenomics analysis of gut microbiota have revealed microbiome dysbiosis in IBD; more recently, this has also been noted in patients with RA [18] (Table 1). Data suggests that the presence of segmented filamentous bacteria alone can alter CD4+ T cell regulation, resulting in upregulation of IL-17+ Th17 cells [19] and the subsequent risk of inflammatory disease, and this has recently been implicated in the pathogenesis of autoimmune arthritis [19].

Multiple studies using arthritis-prone animals have revealed that bacterial colonization is necessary for disease onset. The initial depiction of the potential involvement of gut organisms in arthritis pathogenesis was in the 1970s when rats raised under germ-free conditions developed severe joint inflammation with 100% penetrance in an adjuvant-induced arthritis model, compared with only mild disease (with low incidence) in the control group with normal gut microbiota [20]. This suggests that although microorganisms are not essential for arthritis development, they could have a potential suppressive effect through immune response modulation.

To further investigate the role of gut bacteria, Koga et al. [21] established induction of acute joint inflammatory lesions in multiple mouse strains following the systemic injection of group A streptococcus and *Lactobacillus casei* cell walls or their peptidoglycan subunits; this was earlier demonstrated in rats with streptococcal groups A, B or C [22].

*Yersinia enterocolitica* also appears to induce arthritis; in 1993, Gripenberg-Lerche et al. [23] showed that i.v. injections of this bacteria caused arthritis in susceptible rats, without causing joint infection.

Lichtman et al. [8] demonstrated reactivation of arthritis induced by small bowel bacterial overgrowth in a rat model. The initial monoarticular arthritis was induced by a group A streptococci intra-articular injection. When joint swelling was settling, jejunal self-filling blind loops were surgically created to induce experimental small bowel bacterial overgrowth, which in turn led to reactivation of arthritis; of note, the creation of self-emptying blind loops (resulting in insignificant bacterial growth) or sham operation did not affect arthritis activity, suggesting that the surgical procedure alone was not sufficient to explain the results. This reactivation of arthritis was averted by use of anti-TNFα anti-serum and an IL-1R antagonist, implicating these cytokines in the facilitation of joint disease following an intestinal insult. Furthermore, treatment with metronidazole and recombinant bacterial/permeability-increasing protein (which act against anaerobic bacteria and endotoxin, respectively) also inhibited arthritis reactivation, suggesting a primary role for luminal bacterial overgrowth.

The reactivation of arthritis in this rat model was suggested to be due to several mechanisms: systemic absorption of intestinal bacterial polymers (such as lipopolysaccharide) and direct deposition in the injured joint or liver, resulting in excess production of inflammatory cytokines, systemic release of cytokines from intestinal inflammation into the circulation and induction of arthrogenic T cell populations by the intestinal mucosa, mesenteric lymph nodes, or the joint itself [8].

In 2010 Wu et al. [24] showed that K/BxN mice (inflammatory arthritis model) maintained in germ-free conditions demonstrated lower antibodies titres to glucose-6-phosphate isomerase, Th17 cells and inflammatory joint disease in comparison with those with specific pathogen-free gut microbiota, indicating that the presence of commensal microbes is a necessity for autoimmunity [24]. When these mice were relocated from a germ-free to a pathogen-free environment, they soon developed arthritic features and, of note, colonization with segmented filamentous bacteria alone was sufficient to activate arthritis via intestine-driven induction of a Th17 response; an early phase of arthritis induction in these mice was suggested to likely be due to the stimulation of antigen-presenting cells within the intestinal lamina propria.

This group further proposed that the undeveloped state of the immune system in germ-free conditions and in neonates asserts that the presence of commensal microbes drive normal immune maturation. For example, humans (including neonates) maintained in germ-free conditions can demonstrate lower IgG and IgA antibody compliments and, in murine models, gut-resistant bacteria have been shown to powerfully influence the development and/or maintenance of certain CD4+ T cell subsets [24].

Zhang et al. [25] performed metagenomic shotgun sequencing (a process that allows the sequencing of thousands of organisms in parallel, thus allowing detection of organisms that are present in small quantities) and a metagenome-wide association study of the faecal, dental and salivary microbiome from a cohort of patients with RA compared with non-RA controls. They revealed dysbiosis in the microbiomes of patients with RA compared with controls at all three sites; in particular, *Haemophilus* spp. were depleted in patients with RA and negatively correlated with serum autoantibody levels, whereas *Lactobacillus salivarius* was overrepresented in RA and was seen in amplified numbers in cases of very active RA. Interestingly, they also demonstrated that these disparities can be partially redressed by DMARDs.

Other groups have also demonstrated dysbiosis in patients with RA via 16S rRNA sequencing, demonstrating an overrepresentation of *Prevotella* species (especially *P. copri*) in the faeces of patients with new-onset RA, along with a reduction in Bacteroides species [3]. Furthermore, a number of metagenomics linkage groups (MLGs) that were enhanced in control samples correlated negatively with inflammatory markers (CRP) and autoantibodies.
specific to RA (RF and anti-CCP). Interestingly, some MLGs enhanced in patients with RA demonstrated positive correlations with these autoantibodies as well as IgG and IgA levels; this relative distribution of MLGs is informative with regards to the molecular mimicry hypothesis, in which the microbial production of cross-reactive epitopes leads to an immune response against self, and proposes the possible advantage for MLGs as markers for RA pathophysiology [12].

Disparities in oral and gut organisms accompanied by alterations in the relative wealth of genes encoding specific functional traits have been demonstrated; for example, modules accountable for lipopolysaccharide biosynthesis and transport and types II, III and IV secretion systems were enriched in faecal samples from controls, in keeping with the relative depletion of Gram-negative bacteria in those with RA [25]. This provides potential insight into drivers of dysbiosis. Lactobacillus salivarus, for example, can withstand the high reactive oxygen species concentrations found at sites of inflammation, and the relatively high abundance of this species in those with RA may be reflective of a heightened immune response at the sample sites. Moreover, the enrichment of zinc transport systems genes in RA oral samples could potentially influence zinc-dependent matrix metalloproteinase activity, providing possible clues about the bacterial contribution to disease pathogenesis [12].

Gomez et al. [26] demonstrate that HLA-DRB1*0401 mice (that are susceptible to arthritis representative of RA in humans) harbour an altered gut microbiome compared with those resistant to arthritis development (with HLA-DRB1*0402). In particular, members of Bacteroidetes and Actinobacteria were twice as prevalent as Firmicutes in the arthritis-resistant strain. These authors suggest the loss of sex and age-driven differences in the gut microbiome are attributed to these differences and that this dysbiosis, in addition to differential expression of Th17-regulating gene transcripts and altered gut lumen permeability, may contribute to disease susceptibility.

Spondyloarthritis

Members of the spondyloarthritis family include AS, reactive arthritis, undifferentiated spondyloarthritis, arthritis in IBD and the pauci-articular and axial forms of PsA. This group of conditions have strong genetic components and an association with the MHC class I gene HLA-B27 [2].

Hammer et al. [27] developed a strain of rats transgenic for human HLA-B27 that developed a form of arthritis similar to human spondyloarthritis, associated with intestinal inflammation. Interestingly, rats bred in germ-free conditions did not develop disease, but developed arthritis when exposed to specific pathogen-free enteric bacteria.

Taurog et al. [28] further implicated the role of the microbiome in an animal model of spondyloarthritis. They showed that HLA-B27 transgenic rats raised in a germ-free environment developed inflammatory skin and genital lesions, but not inflammatory intestinal or peripheral joint disease. This alludes to the concept that gut and joint inflammation are interconnected through the part played by the microbiome in immune homeostasis [29].

More recently, Ruutu et al. [30] studied a mouse strain designed to spontaneously develop chronic autoimmune arthritis with features similar to those in human RA. When raised in specific pathogen-free conditions, these mice remained well until exposed to curdlan (a β-1,3-glucan derived from yeast, fungal and bacterial cell walls); instead of developing disease reminiscent of RA, these mice developed a spondyloarthritic-like disease involving the ankles, feet and Achilles tendons, plantar fasciitis, spondylitis and ileitis. This provides further evidence for involvement of the bacteria in disease pathogenesis and, interestingly, although this strain was designed to represent RA (and even produces RF and anti-CCP antibodies), the CD4+ T cells have been shown to be initiated via an IL-23-dependent pathway, which triggers production of IL-1, IL-6 and TNFα, all of which are known to be fundamental in the pathogenesis of IBD and spondyloarthritis [2].

PsA

PsA is a chronic inflammatory joint disease associated with the presence of HLA-B27 that is distinct from other spondyloarthropathies, based on characteristic clinical features, immunogenetic associations, musculoskeletal imaging and histopathologic analyses [31]. It has a strong association with skin disease—up to 30% of patients with psoriasis develop PsA, suggesting the skin microbiome, which has previously been implicated in the pathogenesis of psoriasis, may also be involved in PsA development.

Eppinga et al. [1] hypothesize the presence of a ‘skin–joint–gut’ axis in PsA, that is induced or mediated by the microbiome; the Th17 pathway is thought to play a key role, as demonstrated in Fig. 2. In line with this, CD4+ and CD8+ T cell expansions have been demonstrated in the synovial membrane, synovial blood and peripheral blood of patients with PsA, highlighting the importance of T cells in PsA pathogenesis [1].

From studies in RA, it is now known that intestinal dysbiosis can determine the direction of differentiation of naïve CD4+ T cells into either effector T cells or Tregs; the balance between Tregs and the T cell effector subsets Th1, Th2 and Th17 is fundamental for immune homeostasis, with an imbalance resulting in chronic inflammatory disease [1]. In keeping with this, germ-free animals have been shown to demonstrate Th2-dominated immune responses; immune homeostasis was interestingly restored upon introduction of intestinal microbes [32].

In human studies on patients with psoriasis, the most significant disease response was noted in those in whom Th17 was blocked, compared with those in whom TNFα and IL-22 were blocked; this further suggests the importance of Th17 as an inducer of inflammation in psoriasis, and potentially also in PsA [33].

In a more recent study, Scher et al. (2015) used 16S rRNA sequencing methods in patients with psoriasis and...
PsA and identified that these patients had a lower relative abundance of multiple intestinal bacteria. Interestingly, the gut microbiota profile in patients with PsA was similar to that found in patients with IBD and was associated with changes in specific inflammatory proteins unique to this group but distinct from those in patients with psoriasis alone and healthy controls; this intriguingly suggests a distinct gut microbiome composition in this inflammatory arthritis group [34].

Potential therapeutics targeting the microbiome

Antibiotics

Antibiotics are known to alter the composition of the intestinal microbiome, potentially leading to adaptation of the immune system resulting in immunosuppression and thus a beneficial response in cases of inflammatory joint disease [1]. In a mouse model using C57BL/6, IL10−/− mice antibiotic treatment resulted in an altered composition of intestinal bacteria [35]; after treatment cessation the bacterial communities approached baseline profiles, disclosing the concept of microbial resilience [36].

Furthermore, studies of rats with adjuvant-induced arthritis treated with oral vancomycin show an increase in E. coli in the distal ileum, which correlates with improved disease; this benefit is eradicated by treatment with colistin and/or tobramycin (which reduce E. coli levels) [37].

Randomized control trials have supported this animal data. Tilley et al. [38] showed promising results in a cohort of 219 patients with RA treated with minocycline compared with placebo. O’Dell et al. [39] further showed that patients with early seropositive arthritis respond better to a combination of MTX and doxycycline compared with MTX alone.

It has been proposed that although antibiotic use appears to be a temporary measure, use in infancy and regular use may result in permanent consequences for the microbiome composition [1]. Risks to this approach, however, are that significant microbiome disturbances may result in a greater risk of invasion by other pathogens.

Probiotics

Probiotics are viable microorganisms (bacteria or yeasts) that, if administered in sufficient quantities, beneficially affect the host by improving the intestinal microbial balance. They show favourable effects on development and stability of microflora, inhibit colonization by pathogens, influence the mucosal barrier by their trophic effect on the

Exposure of the immune system to cutaneous microorganisms may lead to an immune response; the Th17 pathway is believed to predominate. In predisposed individuals, such as those who are HLA-B27 positive, this immune response may result in joint inflammation.

---

Fig. 2 Proposed mechanism for the Skin–Joint–Axis in inflammatory arthritis

---
intestinal epithelium and stimulate both specific and non-
specific components of the immune system [40].

Immunological studies reveal that probiotics have dose-
and duration-dependent immunomodulatory effects on B-
and T cell proliferation, reduce their response to lectin
nitrogens and affect proinflammatory and anti-inflammatory
cytokine regulation [41].

In addition to promising animal studies, research has
demonstrated their favourable effects on human antibi-
otic-associated bowel disease, IBD, pseudomembranous
colitis and rotavirus enteritis; interestingly, they also appear
to be advantageous in non-intestinal pathologies, such as
urethral tract infections, vaginosis, Helicobacter pylori–induced gastritis and childhood respiratory tract in-
fecions, when used in combination with antibiotic treat-
ment [41]. Furthermore, Colifant (probiotic bacteria *E. coli*
083) use in pre-term babies decreases the presence of
pathogens, the number of infections, the need for anti-
biotics, and the incidence of allergies and repeated infec-
tions in later life when administered orally after birth [40].

Rovensky *et al.* [40] studied efficacy of treatment of ad-
juvant-induced arthritis in rats with Colifant alone, with
Colifant in combination with MTX, and with MTX alone.
They found that treatment with MTX and combination
treatment drastically reduced both inflammation and de-
structive joint disease, and the combination treatment im-
proved both arthrogram score and hind paw swelling more
significantly than MTX treatment alone. Treatment with
Colifant alone appeared to have no impact on disease ac-
tivity in this study; however, results suggested that this
probiotic can enhance the effects of MTX treatment [40].
Furthermore, a study by Baharav *et al.* [41] evaluated
the effects of *Lactobacillus* GG (LGG) on disease activity
in rats with tropomyosin arthritis (resembling Behcet’s dis-
ease in humans) and adjuvant arthritis (resembling human
RA). Interestingly, they observed that rats fed LGG-
containing yoghurt had reduced inflammation on histologi-

cal examination, transcending the effects of LGG alone.

In recent years the utilization of gnotobiotic mice (germ-
free mice colonized with specific microbiota at various life
stages) has improved our understanding of the role of the
microbiome in systemic disease [9]. For example, IL-1 re-
ceptor antagonist-knockout mice raised in a germ-free
environment did not develop autoimmune T cell–mediated
arthritis; mono-colonization of these mice with commensal
*Lactobacillus bifidus*, however, led to precipitous disease
onset, analogous in arthritis severity and incidence to
mice in a non-germ-free environment [42]. The onset of
disease in this model is driven by T regulatory/Th17 cell
homeostasis imbalance.

Mikov *et al.* [43] showed that coadministration of pro-
biotics with SSZ in rats led to increased levels of SSZ me-
tabolites in the colon, suggesting a possible synergistic
effect. Lee *et al.* [44], however, failed to reproduce this
result in humans. Furthermore, in a human study of probiotic
use in spondyloarthritis no benefit was found in comparison
with the control group [45], and in a study of patients with RA
with adjunctive probiotic therapy, an improvement was seen
in disability scores (HAQ) but not in ACR20 responses [46].

**Faecal microbiota transplantation**

Faecal microbiota transplantation is another potential
therapeutic approach for intestinal microbiota modulation,
and beneficial effects of this approach have been shown in
*Clostridium difficile* infection, in IBD and for increasing
insulin sensitivity in individuals with metabolic syndrome
[1]; potential benefits of this treatment have also been
suggested in inflammatory arthritis [1]. Limitations to this
approach, however, include expense of donor screening,
difficulties transporting donations, and infection control
risk [47].

An alternative to this is ‘synthetic stool’ therapy; how-
ever, this approach remains experimental [2].

**Discussion**

With this data, it is possible to surmise that patients with
inflammatory arthritis bear a distinctive enterotype that
may activate autoimmunity in those with genetic predis-
position. Additionally, certain enterotypes may be protective
in predisposed individuals [3].

The evidence grade for potential therapeutic modalities
such as antibiotic/probiotic use or the use of faecal micro-
bioa transplants remains too low to draw any strong con-
clusions regarding the efficacy of these treatments for
inflammatory arthritis, but current data does suggest po-
tential benefits for further research in these fields.
Potential adverse reactions to these treatment options,
however, needs to be considered; for example, a specu-
lative concern about probiotic use is that organisms may
be able to spread from the gastrointestinal tract into the
systemic circulation; although rare, cases of probiotic-
related bacteraemia and fungaemia have been reported
[48]. Furthermore, research is needed to identify whether
the possibility exists of transfer of antibiotic resistance
from biotic strains to pathogenic bacteria [48, 49].

The possibility of artificially engineering a site-specific
microbiome or of using synthetic biology to integrate in-
ducible beneficial effects in the microbiome is an exciting
therapeutic prospect. Indeed, the importance of micro-
bioe dysbiosis in inflammatory arthritis has been sug-
gested to be relevant in other conditions such as
metabolic syndrome, type 2 diabetes, atherosclerosis
and IBD [14].

Furthermore, data from animal models needs further
validation in humans owing to several dissimilarities be-
tween the two, such as microbiome variations [50].

Additional work is needed to further elucidate the mech-
anism by which microbes and their metabolites may
affect the immunopathogenesis of inflammatory arthritis;
this may also lead to the discovery of novel drug targets.

**Funding:** No specific funding was received from any
bodies in the public, commercial or not-for-profit sectors
to carry out the work described in this manuscript.

**Disclosure statement:** The authors have declared no
conflicts of interest.
References


10 Pease PE, Chahal H, Talack JE, Lane MR, Allan RN. Cross-reactivity studies on bacteria believed to be associated with inflammatory bowel disease (IBD), ankylosing spondylitis (AS) and reactive arthritis (ReA). Br J Rheumatol 1988;27:32–3.


13 The Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007;447:661–78.


33 Krueger JG. Hiding under the skin: a welcome surprise in intestinal Inflammation in ankylosing spondylitis (AS) and reactive arthritis (ReA). Br J Rheumatol 1988;31:1077–9.


