PROBIOTICS - A PROBABLE THERAPEUTIC AGENT FOR SPONDYLOARTHRPATHY

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ABSTRACT: Spondyloarthopathy (SpA) or spondyloarthrosis refers to any joint disease of the vertebral column. Among the entities of SpA, ankylosing spondylitis has drawn the attention of some researchers, because of its specific mechanism of disease progression. It has been studied earlier that its progression is due to the presence of HLA (human leukocyte antigen) - B27. It shows molecular similarity and immunological cross-reactivity with some of the gut microbiome. Since SpA could be treated or its symptoms could be lessen by medications, but medications itself show many side effects and other complications. Probiotic- being the natural product has been found to be effective against many SpA entities, including Ankylosing Spondylitis. It alters gut microflora somehow in such a way that it helps in reducing the predisposition of any factor to SpA. Here we consider the complex relationship between SpA pathogenesis and gut microbes; with discussion that how use of probiotics as an alternative drug therapy may treat or reduce the progression of SpA, which could be a better future target to treat SpA entities.

KEYWORDS: Ankylosing Spondylitis, HLA B27, Probiotics, Spondyloarthropathy.

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INTRODUCTION

Spondyloarthropathy (SpA) or Spondyloarthrosis are a divergent group of inflammatory arthritis that shares some of the genetic predisposing factors and clinical features (Gladman, 1998). Their most characteristic feature is inflammatory back pain (Linden and Heijde, 1998). We can explain the term spondyloarthropathy in a way that include joint involvement of vertebral column in case of any type of joint disease, including rheumatoid arthritis and osteoarthritis, but this term is specifically used for a group of disorders which share certain common features, and the group is often being termed as seronegative spondylarthropathies. Spondyloarthritis is closely associated with histocompatibility antigen HLA (human leukocyte antigen)-B27 (Brewerton et al., 1973).

Glimpse on Seronegative spondyloarthropathy (SNSA)

Seronegative spondyloarthropathy (or seronegative spondyloarthritis) is a group of diseases that involve the axial skeleton (Howe et al., 2007) along with negative serostatus. Moll et al. (1974) was the first who described the ‘seronegative spondyloarthopathies’, with negative rheumatoid factor, sharing common clinical, radiological and genetic features. “Seronegative” indicates that diseases are negative for rheumatoid factor, with a different pathophysiological mechanism of disease than those seen in rheumatoid arthritis very commonly.

Circumstances

i. Ankylosing spondylitis (AS)

ii. Reactive arthritis (earlier known as Reiter’s syndrome) (ReA)

iii. Enteropathic spondylitis or spondylitis allied with inflammatory bowel disease (Crohn’s disease and ulcerative colitis)

iv. Psoriatic arthritis (PsA)

v. Isolated acute anterior uveitis

vi. Juvenile idiopathic arthritis

vii. Undifferentiated spondyloarthropathy (USpA)
CLASSIFICATION

Classification standard deliver definition for the disease groups to acquire clinical and epidemiological studies (Johnson et al., 2007; Akgul and Ozgocmen, 2011). These combinations of classification criteria bring together different information like symptoms, signs, laboratory findings, imaging, genetic factors and etiological agents. Most of the criteria groups in rheumatology developed as classification criteria for clinical research but they are unfortunately widely used as diagnostic tools for daily practice. For example, this was the case with formerly the American Rheumatism Association criteria (for the classification of rheumatoid arthritis) and the European Spondylarthropathy Study Group (ESSG) preliminary criteria for the classification of spondyloarthropathies (Dougados and Gossec, 2007).

When the ESSG classification pattern for SpA was amply studied it got certified for the population studies (Boyer et al., 1993; Collantes et al., 2000; Cury et al., 1997; Erturk et al., 1997; Zochling et al., 2005) and has a good sensitivity of 75% and a specificity of 87%. A substitute classification plan by Amor et al (Table-1) (1990) is more complicated but gives improved sensitivity (85%) and specificity (90%), because of the inclusion of common extra-articular manifestations of disease, including enthesopathy, dactylitis, eye disease and HLA-B27 positivity. Amor’s criteria are a list of signs based on a scoring system of laboratory, radiologic and clinical features and do not require an entry criterion (Amor et al., 1990).

The symptoms in the above criteria contributing 1 point, 2 points or 3 points; a score of 6 or more classifies a patient as having SpA or not. The key concepts veiled each classification set are however the same.

Inflammatory back pain (IBP)

Inflammatory back pain is one of the noted symptom of the SpA and moreover inflammation of sacroiliac joints, spine and spinal entheses. Though its value for the diagnosis,

<table>
<thead>
<tr>
<th>TABLE 1. Amor criteria for the classification of spondyloarthropathy (Amor et al., 1990). NSAID- Nonsteroidal anti-inflammatory drug; HLA- Human leukocyte antigen</th>
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<tbody>
<tr>
<td>Amor criteria</td>
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<tr>
<td>Clinical symptoms or past history of scoring:</td>
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<tr>
<td>Points</td>
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<tr>
<td>Lumbar or dorsal pain at night, or lumbar or dorsal morning Stiffness</td>
</tr>
<tr>
<td>Asymmetrical oligoarthritis</td>
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<tr>
<td>Buttock pain</td>
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<tr>
<td>Alternating buttock pain</td>
</tr>
<tr>
<td>Sausage-like finger or toe</td>
</tr>
<tr>
<td>Heel pain</td>
</tr>
<tr>
<td>Iritis</td>
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<tr>
<td>Non-gonococcal urethritis or cervicitis accompanying, or within 1 month before, the onset of arthritis</td>
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<tr>
<td>Acute diarrhoea accompanying, or within 1 month before, the onset of arthritis</td>
</tr>
<tr>
<td>Presence of history of psoriasis and/or balanitis and/or of inflammatory bowel disease (ulcerative colitis, Crohn’s disease)</td>
</tr>
<tr>
<td>Radiological findings</td>
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<tr>
<td>Sacroilitis (grade &gt;2 if bilateral, grade &gt;3 if unilateral)</td>
</tr>
<tr>
<td>Genetic background</td>
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<tr>
<td>Presence of HLA-B27 and/or family history of ankylosing spondylitis, reactive arthritis, uveitis, psoriasis or chronic inflammatory bowel disease</td>
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<tr>
<td>Response to therapy</td>
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<td>Definite improvement of musculoskeletal complaints with non-steroidal anti-inflammatory drugs (NSAIDs) in less than 48 h or relapse of the pain in less than 48 h if NSAIDs discontinued</td>
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<td>A patient is considered as having a spondylo-arthropathy if the sum of the scores is 6 or more</td>
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classification and screening in primary care settings is not well identified. Clinical history has been proposed as a screening test to distinguish patients with SpA among those who have chronic back pain (Rudwaleit et al., 2006). We can say that, criteria for IBP were derived from studies comparing patients with AS and patients with back pain of other etiologies and from studies based on expert opinion. Though IBP is considered as the headmost clinical symptom for axial SpA, yet its sensitivity and specificity with respect to diagnosis of axial SpA does not exceed 80% (Sieper et al, 2009).

Calin et al (1977) examined 42 patients with AS and 24 patients with other origin of back pain for 5 features of back pain: (1) insidious onset; (2) age at onset < 40 years; (3) duration of back pain ≥3 months; (4) associated with morning stiffness; and (5) improvement with exercise. IBP was considered if 4 of 5 features were present, and these were the first criteria for IBP. Calin's criteria have 95% specificity and 76% sensitivity but the successive studies showed low sensitivity and specificity (Gran, 1985; Linden and Fahrer, 1988). Adding a single criterion “getting out of the bed at night” improved the sensitivity of these criteria (Gran, 1985). Modified New York Criteria (mNY) for AS integrated features of the Calin's criteria made the definition of back pain in patients with AS: low back pain and stiffness for more than 3 months, along with the improvement on exercising but is not relieved by rest (Table-2) (Linden et al., 1984).

### TABLE 2. Modified New York Criteria for AS (Linden et al., 1984)

<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>Radiological criterion</th>
</tr>
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<tr>
<td>Low back pain and stiffness for more than 3 months, which improves with exercise, but is not relieved by rest</td>
<td>Sacroiliitis grade ≥ 2 bilaterally or grade 3–4 unilaterally</td>
</tr>
<tr>
<td>Limitation of motion of the lumbar spine in both the sagittal and frontal planes</td>
<td>Definite AS is present if the radiological criterion is associated with at least one clinical criterion</td>
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<tr>
<td>Limitation of chest expansion relative to normal values correlated for age and sex</td>
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**Imaging**

Diagnosis, classification and monitoring for patients with SpA are done through imaging of the sacroiliac joints and the spine.

**HLA B-27**

Positivity of HLA B-27 is remarkably relevant to the early diagnosis of SpA. 5% to 10% population are HLA B-27 and positivity of HLA B-27 in patients with AS and SpA changes to 70% to 95% and nearly 70%, respectively (Rostom et al., 2010).

**SPECTRUM**

**Ankylosing spondylitis**

Ankylosing spondylitis is the most common and most typical form of SpA. This disease is two to three times more common in men than women. Ankylosing spondylitis generally begins with back pain and stiffness at a young age but various presentations, such as peripheral arthritis and enthesopathy may antedate back symptoms in some patients. Late aggression of AS after the age of 45 is uncommon however in some patients it may reasonably be diagnosed late. One of the presenting features is Inflammatory low back pain but not exclusively specific to AS. Uveitis history, positive family history for AS, impaired spinal mobility or chest expansion supports the diagnosis (Khan, 2002). One of the characteristics of the disease is the axial involvement and 90% of patients have radiographic sacroiliitis during the development of the disease. A patient can be classified as having definite AS if at least one clinical criterion (IBP, limitation of lumbar spine or limitation of chest expansion) plus radiologic criterion (bilaterally grade 2 or unilateral grade 3–4 sacroiliitis) are fulfilled. Spinal mobility restriction rest and radiological sacroiliitis may reflect structural damage and spinal/thoracic pain may reflect active inflammation and structural damage as well.

**Axial spondyloarthritis**

It takes years for Sacroiliitis on plain radiographs from the onset IBP and in patients the symptoms of IBP alone are not diagnostic. To assist physicians for early diagnosis of SpA Berlin criteria were developed. In this criterion set, the clinical, laboratory (HLA B-27) and imaging (MRI of sacroiliac joints) features were included. The diagnosis of recent-onset axial SpA (pre-radiographic SpA) can be established in patients who have clinical features without radiographic changes but sacroiliitis on MRI. The role of MRI as a diagnostic tool is analyzed by this study (Rudwaleit, 2004).

**Peripheral spondyloarthritis**

Patients with peripheral manifestations including peripheral arthritis, dactylitis and enthesitis and without back pain were included.

**Psoriatic arthritis**

Psoriatic arthritis (PsA) is an inflammatory arthritis combined with cutaneous psoriasis. Patients with this may have peripheral arthritis (oligoarthritis or polyarthritis), enthesitis,
dactylitis or sacroiliitis/spondylitis (Cantini et al., 2010). In the beginning of the century it was thought that PsA occur coincidentally with rheumatoid arthritis (RA) and psoriasis. As a distinct disease it was adopted for the first time in 1964. On the basis of clinical and radiological features, the distinction was made between RA and PsA (Rudwaleit and Taylor, 2010). PsA patients tend to have inflammatory axial involvement similar to AS. There are several differences from the classical AS (Helliwell, 2005) (1) asymmetrical sacroiliitis; (2) non-marginal syndesmophytes; (3) asymmetrical syndesmophytes; and (4) more frequent involvement of the cervical spine.

**Predisposition of HLA-B27 to Ankylosing Spondylitis (entity of Spondyloarthropathy) by altering microbiome**

Approximately four decades have passed since two groups first reported the noteworthy relationship between HLA B27 and ankylosing spondylitis (Brewerton et al., 1973, Schlostein et al., 1973; Rosenbaum and Davey, 2011). This is arguably the strongest association between a genetically determined factor and a genetically complex, immune-mediated disease. Many features of ankylosing spondylitis are same as that of inflammatory bowel disease. Patients having inflammatory bowel disease may develop sacroiliitis, peripheral arthritis, uveitis, or aphthous stomatitis, all potential manifestations of ankylosing spondylitis or its first cousin, another HLA B27-related disease, reactive arthritis. In contrary, patients with ankylosing spondylitis or reactive arthritis frequently have inflammatory bowel disease, although it may be clinically mysterious (Mielants et al., 1985). Now there is general agreement that bowel flora plays a causative role in inflammatory bowel disease (Friswell et al., 2010, Tannock, 2010, Kang et al., 2010; Zhernakova et al., 2008). And several of the genetic factors identified as predisposing to inflammatory bowel disease including Nucleotide-binding oligomerization domain-containing protein 2 (NOD2) and Caspase recruitment domain-containing protein 9 (CARD9) (Zhernakova et al., 2008 and Waterman et al., 2011) participate in the recognition or response to microbial products.

Many other immune-mediated diseases, including all the diseases in the spondyloarthropathy family, are considered to have a bacterial pathogenesis. Many researchers have noted a relationship between spondyloarthropathy and bacterial flora. The most accepted connection is the ability of *Chlamydia* and certain strains of *Salmonella*, *Shigella*, *Yersinia*, or *Campylobacter* to trigger reactive arthritis. Some have observed colonization with *Klebsiella* in bowel flora of patients with ankylosing spondylitis (Rashid and Ebringer, 2006) and this colonization might erupt anterior uveitis (Ebringer, 1988). Others have reported a cross reactivity between antisera to a specific isolate of *Klebsiella* and HLA B27 itself (Geczy et al., 1980). HLA B27 does have a noteworthy degree of sequence identity with proteins derived from Gram-negative bacteria (Scofield et al., 1993; Scofield et al., 1995). Monoclonal antibodies to HLA B27 may cross react with specific Gram negative bacteria (Bohemen et al., 1984). When endotoxin from Gram negative bacterial cell walls were injected into the footpad of a rat, it induces an acute anterior uveitis with some similarity to what is characteristic of the HLA B27-related spectrum of disease (Rosenbaum et al., 1980).

Since all these observations are sometimes decades old, their failure to gain widespread acceptance might relate in some cases to the inability to replicate the findings as well as the inability to link the pathogenesis of ankylosing spondylitis to any of the above conclusions. That linkage is becoming more apparent. It is hypothesized that HLA B27 influences the composition of the body’s endogenous flora and that this “B27-shaped flora” causes ankylosing spondylitis.

HLA B27 itself affects the immune response to HIV (Loffredo et al., 2009) and hepatitis C (Neumann-Haefelin et al., 2006), and virus derived products stimulate the innate immune system. When HLA B27 was transfected into a monocyte-derived cell line, it reduces the proliferative response to endotoxin (Penttinen et al., 2002), an effect that could relate indirectly to HLA B27 altering bacterial flora. The replication of *Salmonella* is increased in a monocyte cell line if it expresses HLA B27 (Penttinen et al., 2004). HLA B27 also forces humoral immunity for several Gram-negative bacteria (Sahly et al., 1998; Mäki-Ikola et al., 1998). Increased antibody titers to bacterial cell wall have been found in spondyloarthritits patients (Park et al., 1984). Adjuvant arthritis in rats is induced by cell walls from *Mycobacteria* that bear many similarities to spondyloarthropathy including spinal disease, periosteal new bone formation, uveitis, and nongonococcal urethritis (Rosenbaum, 1981). Rats expressing HLA B27 show increased susceptibility to adjuvant arthritis (Duivenvoorde et al., 2012). Ankylosing spondylitis is predominantly a male disease and general so has a powerful influence on bacterial colonization (McKenna et al., 2008). These types of observations provide circumstantial support for the hypothesis that HLA B27 predisposes to ankylosing spondylitis by virtue of the gene’s effect on the body’s endogenous flora.

**Proves substantiating immunological, microbiological, and molecular link between microbes and self antigens in inducing Spondyloarthropathy**

In the early twentieth century, the first evidence of the epidemiological link between microbes and SpAs was disclosed, where a triad of urethritis, conjunctivitis, and arthritis, had been termed as Reiter’s syndrome, which had been found to follow a dysenteric or venereal infection (Calin, 1998). Later Reiter’s syndrome was identified as a form of ReA and since then each of the triggering bacterial agents including *Yersinia*, *Campylobacter*, *Shigella*, and *Salmonella* enterogenic bacteria as well as *Chlamydia* urogenital pathogens has been found to have an approximately equal role in the progression of this disease (Leirisalo-Repo, 2005; Townes, 2010). Although epidemiological proof for the involvement of microbial agents in other disease entities of SpAs are lacking, a considerable degree of molecular, immunological, as well as microbiological data are available to support the role of *Klebsiella pneumoniae* in
the etiopathogenesis of both AS (Ebringer et al., 2011) and CD (Crohn’s disease) (Rashid et al., 2009). Apart from some evidence for the role of Mycobacteria (Rambukkana et al., 1993), show ever, no other microbes have been implicated in the causation of psoriasis.

It has been found that microbes completely influence the immune response. For example, animals that are nurtured in a germ free environment fail to develop a normal immune system or normal lymphoid architecture (Hill and Artis, 2010). Multiple cell lineages (B cells, T helper 17 (Th17) development, regulatory T cells (Treg), Th1/Th2 balance and Cluster of differentiation 8 (CD8) T cells) are atypical in germ free animals (Hill and Artis, 2010). Correspondingly an HLA B27 positive rat that normally develops colitis, skin lesions, and arthropathy remains usually healthy in a germ free environment (Taubrog, 1994) and several murine models of colitis has been cured by a germ free environment (Schwerbrock et al., 2004).

Evidence for molecular mimicry

_Klebsiella_ microbes possess various antigens that show molecular similarity and immunological cross-reactivity with HLA-B27 or other self-antigens and these have been demonstrated in several independent studies. A molecular homology has been found between a hexameric amino acid sequence, “QTDRED” present in both HLA-B*2705 molecules (residues 72-77) and _Klebsiella pneumoniae_ nitrogenase reductase enzymes (residues 188-193) (Schwinnbeck, 1987). A structural similarity has been found between the “DRDE” amino acid sequences (residues 596-599) present in the Pul-D secretion protein from _Klebsiella_ pullulanase enzyme, and the “DRED” amino acid motif (residues 74-77) present in the HLA-B27 molecules (Fielder et al., 1995). Another molecular similarity composed of repeated triplet amino acid sequences “G-x-P” has been discovered between Pul-A secretion protein from _Klebsiella_ pullulanase enzyme and collagen types I, III, and IV (Fielder et al., 1995) mainly contained in the ligaments and cartilaginous structures of spinal vertebral large joints and uvea.

Evidence for immunological cross-reactivity

Antibodies obtained from a rabbit immunized with HLA-B27-positive lymphocytes showed positive reactions with the antigenic extracts of five gut-inhabiting bacterial agents including _Klebsiella, Enterobacter, Salmonella, Shigella_, and _Yersinia_ microbes indicating the presence of shared cross-reactive antigens (Welsh et al., 1980). Allogeneic anti- HLA-B27 antibodies obtained from human tissue typing sera were found to bind to _Klebsiella_ antigens more than other tissue typing sera (Avakian et al., 1980). Anti-HLA-B27 monoclonal antibodies were found to bind more specifically to 60 and 80 Kd components of _Klebsiella_, whereas no such reactivity was demonstrated by five other monoclonal antibodies (Ogasawara et al., 1986).

No significant difference was observed in the immunological reaction between HLA-B27 positive lymphocytes whether obtained from AS patients or healthy controls when treated against sera from rabbits immunized with _Klebsiella_ microbes in comparison to lymphocytes from HLA-B27 negative individuals, which indicates that there are no differences between antigenic specificities of HLA-B27 molecules whether taken from diseased or healthy individuals (Baines et al., 1990). IgA antibody levels against synthetic peptides carrying _Klebsiella_ or HLA-B27 cross-reactive antigens were found to be elevated in sera of Japanese AS patients compared to rheumatoid arthritis patients or healthy controls (Tani et al., 1997a), most probably due to the existing bacterial and self cross-reactive antigens in AS patients. Secretory IgA2 antibodies were found to be significantly increased against type I, III, and IV collagens in sera of Japanese patients with AS when compared to healthy individuals (Tani et al., 1997b).

Antibodies from sera of AS patients were found to be cytotoxic to HLA-B27-peptide-bearing cells as shown by increased percentage lysis for sheep red blood cells coated with HLA-B*2705 peptide when compared to patients with rheumatoid arthritis and healthy controls (Wilson et al., 2003), indicating that these auto-antibodies probably contribute to the immunological damages which take place at the pathological sites in patients with AS or CD (Rashid and Ebringer, 2011).

SPONDYLOARTHRITIS TREATMENT

Medication

All the spondyloarthropathies (ankylosing spondylitis, reactive arthritis, psoriatic arthritis, enteropathic arthritis, and undifferentiated spondyloarthropathy) have a common treatment systematic plan that involves medication, exercise and possibly physical therapy, good posture practices, and some other treatment options such as applying heat/cold to help relax muscles and reduce joint pain. Surgery could be an option in severe cases of ankylosing spondylitis.

Some variation in treatment depends on the type of spondyloarthritis. For example, in psoriatic arthritis, both the skin component and joint component must be treated. In enteropathic arthritis (spondylitis/arthritis associated with inflammatory bowel disease such as Crohn’s or ulcerative colitis), medications may need to be adjusted so the gastrointestinal component of the disease is not exacerbated.

The very first stage of medication in treating the pain and stiffness associated with spondylitis is NSAIDs (nonsteroidal anti-inflammatory drugs), which are also the foundation of treatment. However, NSAIDs can cause significant side effects, in particular, damage to the gastrointestinal tract. When NSAIDs are not enough to treat spondylitis, then the next stage of medications, (also known as second line medications), sometimes also called disease modifying anti-rheumatic drugs (DMARDS). This group of medications include: Sulfasalazine, Methotrexate and Corticosteroids.

Biologics or TNF Blockers are the most recent and one of the
most promising medications for the treatment of ankylosing spondylitis. These drugs have been shown to be highly effective in treating not only the arthritis of the joints, but also the spinal arthritis. These group medications include Enbrel, Remicade, Humira and Simponi.

**PROBIOTICS- Immunomodulator to potentially treat Spondyloarthropathies**

Probiotics are “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host” (Hill et al., 2014). The word Probiotic comes from the Greek word “pro” meaning “promoting” and “biotic” meaning “life”. “Probiotics” term discovered in the early 20th century, when Elie Metchnikoff, known as the “Father of Probiotics” had observed that rural dwellers in Bulgaria lived to very old ages despite extreme poverty and harsh climate. He theorized that health could be enhanced and senility delayed by manipulating the intestinal micro-biome with host-friendly bacteria found in sour milk. Generally bacteria are Probiotics, but there is a type of yeast also that can function as a probiotic. Probiotic foods include yogurt, kefir, sauerkraut, tempeh, kimchi and others. Dozens of different probiotic bacteria are there that have been shown to have health benefits. *Lactobacillus* and *Bifidobacterium* are the most common groups. Then there are many different species within each group, and each species has many strains.

**Spondyloarthropathy and bowel disease**

On the basis of predominant symptoms, SpA can be classified as axial SpA, including both AS and nonradiographical axial SpA (nr-axSpA), or as peripheral SpA. The symbolic clinical features include inflammatory back pain, sacroiliitis, oligoarticular asymmetric synovitis, enthesitis, and frequent extra-articular symptoms such as anterior uveitis, psoriasis, and gut inflammation. IBD including ulcerative colitis and Crohn’s colitis is arguably the disease category in which dysbiosis of the microbiome is most strongly implicated in disease causation. Notably, there is significant overlap between IBD and SpA. Mielants et al. performed colonoscopies in 1980s on SpA patients without bowel symptoms, and they observed that up to half of these patients showed microscopic signs of bowel inflammation. Based on morphological characteristics two types were distinguished: an acute type resembling infectious enterocolitis and chronic inflammation in which normal mucosal architecture is disturbed. This type of inflammation was in fact indistinguishable from early Crohn’s disease (CD). These initiative findings have since then been confirmed by others, and include an association between CD-like inflammation and AS, ReA, or PsA. A similar presence of microscopic gut inflammation was also seen in the GIANT (Ghent Inflammatory Arthritis and spondylitis) cohort, a prospective follow-up study including newly diagnosed patients fulfilling the Assessment of SpondyloArthritis International Society (ASAS) criteria for axial and/or peripheral SpA (Praet et al., 2012).

A predictive model developed for axial SpA showed that a younger age, progressive disease, male sex, high disease activity as measured by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and restricted spinal mobility as measured by the Bath Ankylosing Spondylitis Metrology Index (BASMI) were all independently associated with microscopic gut inflammation (Praet et al., 2012).

**Bacteria and Spondyloarthropathy**

Multiple sets of observations implicate bacteria as being causally related to SpA pathogenesis, apart from the links between IBD and SpA.

**Bacteria**

Perhaps the clearest indication of the relationship between gut and joint in SpA is the triggering of ReA by antecedent gastrointestinal infections that include *Salmonella*, *Shigella*, *Yersinia*, and *Campylobacter*. Additionally, within 10–20 years up to 20% of patients with ReA develop AS (Leirisalo-Repo, 1998). Among the SpA family of diseases ReA is a classical member. It shares an association of AS with HLA B27 and involvement of the spine, peripheral joints, entheses, and the uretal tract. Urethral infections are also a trigger for ReA.

**Bacteria are convincingly implicated in animal models that replicate aspects of Spondyloarthropathy**

Several lines of rats that express HLA B27 and human beta-2 microglobulin have been generated by Taurog (2009). These rodents develop spondylitis, peripheral arthritis that includes dactylitis, colitis, and psoriasiform skin lesions, though the phenotype differs somewhat in the alternative derivations. If the rats are raised in a germ-free environment they markedly reduce colitis, arthritis, and skin disease. Certain bacterial strains can be fed to the germ-free rats such that remission is maintained, while other bacterial strains cause the diarrheal illness to return (Dieleman, 2003).

**Therapeutic Immunomodulation of the gut microbiota with Probiotics**

Probiotics, provide beneficial effects to the body, as it helps in the breakdown of food, synthesizing vitamins and many other substances in the intestinal tract, helpful in preventing colonization by pathogenic organisms, maintaining urinary and gut pH, and also reduce the production of pro-inflammatory substances. In rats many studies has been seen of the probiotic *Lactobacillus casei* to lower arthritis scores and levels of pro-inflammatory cytokines, even having a greater effect than indomethacin (Bedaiwi and Inman, 2014). It has been shown in many studies that even a single bacterial species in the gut can bias the homeostatic balance of the immune system in either direction. A common culturable commensal microorganism, *Bacteroides fragilis* ports anti-inflammatory responses by activating IL-10- producing Tregs through its polysaccharide A component, which subsequently damps Th17 responses (Round and Mazmanian, 2010). Intestinal
Probiotics and Spondyloarthritis

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