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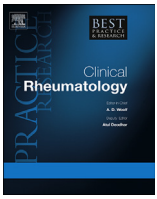

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Microbes, helminths, and rheumatic diseases

Francisco Airton Castro Rocha [a, *], Ana Margarida Duarte-Monteiro [b], Licia Maria Henrique da Mota [c], Ana Carolina Matias Dinelly Pinto [a], João Eurico Fonseca [b]

[a] Departamento de Medicina Clínica, Liga de Reumatologia e Doenças Autoimunes, Faculdade de Medicina, Universidade Federal do Ceará, Fortaleza, CE, Brazil
[b] Serviço de Reumatologia e Doenças Ósseas Metabólicas, Hospital de Santa Maria, CHULN and Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Centro Académico de Medicina de Lisboa, Lisboa, Portugal
[c] Hospital Universitário de Brasília, Programa de Pós-graduação em Ciências Médicas, Faculdade de Medicina, Universidade de Brasília, Brazil

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A B S T R A C T

There has been a progressive interest on modifications of the human defense system following insults occurring in the interface between our body and the external environment, as they may provoke or worsen disease states. Studies suggest that billions of germs, which compose the gut microbiota influence one's innate and adaptive immune responses at the intestinal level, but these microorganisms may also impact rheumatic diseases. The microbiota of the skin, respiratory, and urinary tracts may also be relevant in rheumatology. Evidence indicates that changes in the gut microbiome alter the pathogenesis of immune-mediated diseases such as rheumatoid arthritis and ankylosing spondylitis but also of other disorders like atherosclerosis and osteoarthritis. Therapeutic strategies to modify the microbiota, including probiotics and fecal microbiota transplantation, have been received with skepticism, which, in turn, has drawn attention back to previously developed interventions such as antibiotics. Helminths adapted to humans over the evolution process, but their role in disease modulation, particularly immune-mediated diseases, remains to be understood.

* Corresponding author. Instituto de Biomedicina, Laboratório de Investigação em Osteoartropatias, Rua Cel. Nunes de Melo, 1315 1º, Andar, Rodolfo Teófilo, 60430-270, Fortaleza, CE, Brazil.
E-mail address: arocha@ufc.br (F.A. Castro Rocha).

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The present review focuses on data concerning modifications of the immune system induced by interactions with microbes and pluricellular organisms, namely helminths, and their impact on rheumatic diseases. Practical aspects, including specific microbiota-targeted therapies, are also discussed.

A new model for rheumatic diseases: host-parasite interaction

The coevolution between germs and humans has been marked by mankind development-related modifications. Migratory flows and industrialization have affected farming, food intake, housing, and clothing, causing a profound impact on the environment [1].

The most compelling evidence of genetics' relevance to the pathophysiology of rheumatic diseases is the association of the human histocompatibility antigen HLA-B27 with inflammatory spondyloarthropathies (SpA). HLA-B27 prevalence varies across populations and some HLA-B27 variants have been associated with a decreased prevalence of ankylosing spondylitis, highlighting the complexity of this association [2]. Of interest, concordance rates for identical twins in rheumatoid arthritis (RA) vary from 15% to 30%, which is similar to the 30%–40% concordance rate in type I diabetes, a disease considered to have a clear and strong genetic influence [3]. As most prevalent rheumatic diseases are not directly associated with specific genes, it is likely that various genes, together with environmental agents, influence the natural course of such disorders.

The possibility that germs (microbes) present in the human body modulate the immune response is a classical concept. However, direct causality relying on Koch's postulates has been difficult to prove, thereby limiting the association of a specific germ with a disease. Fastidious germs and asymptomatic carrier states represent challenges when attempting to implicate a specific insulting agent as the cause of a disease. Germs populating "open" body areas such as the skin, oral cavity, respiratory, and gastrointestinal systems, as well as "extracellular" and secretory components are collectively called the microbiome, a term that does not encompass multicellular agents that may also be relevant in this context like worms and fungi. Modern biotechnology is based on complex DNA sequencing rather than culture and staining procedures. Although this has greatly improved the identification of germs, it has also added to the complexity of when attempting to understand parasite-host interactions [4,5]. Microbiome issues have attracted the interest of various researchers who have produced excellent articles and reviews on the subject of germs and human interactions. Nonetheless, not much attention has been granted to helminths, which might potentially have a role in this scenario.

A decrease in the prevalence of infections and infestations was previously associated with an increased prevalence of allergic and autoimmune diseases among populations living in Western developed countries. Moreover, water purification, massive vaccination, and other sanitary measures provided health benefits to people living in industrialized countries [6]. Still, these apparently healthful "cleaning" strategies could also reduce human microbiota diversity, which could in some way negatively impact one's health. Likewise, improvement in health care practices can also render adverse events. Recent outbreaks, such as the arboviruses epidemics in Brazil in the last 10 years [7] and the ongoing coronavirus pandemic, lead to the immediate incorporation of individual practices aiming at the protection against contamination. Attitudes like avoiding contact with other people and the use of handrails in public transportation, or wearing gloves and masks are deliberately taken in an attempt to prevent infection [8]. While this course of action is understandable during a pandemic, excessive handwashing or showers, avoidance of child contact with unprotected soil, grass, and animals, may compromise the stimulation of the human immune system, thereby jeopardizing the body's response to infections [6,9]. Although it is still debatable, reduced breastfeeding and increase in cesarean delivery as well as massive vaccination were also shown to have a negative impact on immune development, being associated with increased prevalence of allergic and autoimmune diseases [10].

Following this line of thought, researchers have previously compared the immune system with the central nervous system based on the idea that establishing connections and plasticity are probably vital to the functioning of both systems. Based on this assumption, avoiding contact with germs may result in more vulnerability [11].

One possible mechanism for the breastfeeding benefit is the presence of oligosaccharides in human milk, which could modulate the intestinal microbiota. It was recently shown that mice exposed to these oligosaccharides did not develop a type 1 experimental diabetes. That effect was linked to modifications of the intestinal microbiota, leading to an increase in short-chain fatty acid content in the gut. Xiao et al. (2018) used their results to justify benefits of exclusive breastfeeding in humans. We should consider that oligosaccharides isolated from human milk rather than mouse milk were offered to animals. Applying that premise to mammalian milk it might well be that cow's milk could be beneficial to humans, provided that both contain the same type and amount of oligosaccharides [12].

Examples of a possible link between robust sanitary measures and increased incidence of immune-mediated diseases include the augmented prevalence of asthma in developed countries [13], at the same time that autoimmune diseases appear less frequent or less severe in Nigeria, where proper sanitation is still to be implemented [14]. Inflammatory bowel diseases, *e.g.,* Crohn's disease, are considered perfect models of the association between changes in dietary habits and less exposure to germs with increased incidence of diseases considered to be immune-mediated. Crohn's disease is currently more prevalent in wealthy populations living in the Northern Hemisphere, but numbers appear to be increasing in developing countries, possibly due to dietary modification and sanitary improvements [15]. Other immune-mediated diseases including type 1 diabetes, systemic lupus erythematosus (SLE), RA, and multiple sclerosis have also been reported to be less prevalent in developing countries [6].

“Everything is autoimmune until proven otherwise” was once said, claiming for a ubiquitous role of autoimmunity in any disease state. Thus, splitting diseases into immune or nonimmune-mediated would merely serve didactic purposes [16]. Innate immune mechanisms operate in close association with adaptive immune responses, modulating the body's defense against tissue damage caused by a germ, trauma, or cancer. This also applies to housekeeping processes such as digestion, breathing, and senescence, which generate by-products that may cause harm to the host. For instance, uric acid released in the event of cell death alerts the immune system, unleashing apoptosis to avoid systemic and potentially harmful inflammation [17]. Atherosclerosis and cardiovascular damage have been associated with changes in the intestinal microbiota. Of interest, studies have linked the processing of phosphatidylcholine in the intestine to increased atherogenesis by producing trimethylamine-N-oxide (TMAO) [18]. Accordingly, the modification of the intestinal microbiota by dietary changes, repopulation of the gut flora, or administration of probiotics could lead to a marked reduction in plasma and urine TMAO levels, which was associated with a decreased risk of major cardiovascular events [19,20]. Although we may not consider atherosclerosis a *bona fide* immune-mediated disease, above-described results indicate that microbiota changes could alter disease course. Limitations of these studies include the assessment of TMAO levels systemically as well as the evaluation of the microbiota only at the intestinal level. In fact, antibiotics might have altered the microbiota in other sites such as the skin, oral cavity, and respiratory tract, which were not directly evaluated. Although causality is hard to prove, data reinforces the need to pursue the concept of an association between atherosclerosis and microbiota.

It is beyond our scope to fully discuss all aspects of the microbiome. We will focus on bacteria and their products, and helminths as triggers or modulators of disease processes in rheumatic diseases.

Tissue homeostasis as barriers to germs

The microbiota has gained more and more relevance as a driver in the pathogenesis of various rheumatic diseases including RA, SLE, and, more recently, osteoarthritis [6,21]. The gastrointestinal tract appears as a natural target, partially because it harbors a great and diverse number of bacteria. Nutritional habits, antibiotic use, constipation as well as gastrointestinal infections are some factors that may alter the bowel's microbiome. Considering the huge number of cells linked to immune mediation in the gut, *e.g.,* cell population in Peyer's patches, modifications of the gut flora definitely

impact one's immune response [5]. Animal studies showed that the modification of the intestinal bacterial flora influenced the severity of antigen-induced arthritis (AIA) [22] and experimental allergic encephalomyelitis – i.e., the most commonly used animal model for human multiple sclerosis [23]. Changes in the cytokine profile of those animals, with predominance of type 2 T helper (Th) cell responses and increase in the number of T regulatory (Treg) cells, were associated with improvement following the restoration of a "normal" flora in germ-free animals that received fecal transplantation [5].

Issues regarding innate immune mechanisms are receiving more attention, given their importance to the physiology of the gastrointestinal tract. Integrity of the mucosa with a protective layer of mucus, acid pH in the stomach, biliary fluid, maintenance of junctions between epithelial cells as well as the presence of antimicrobial secreted peptides, *e.g.,* defensins and cathelicidins, and immunoglobulin A constitutively present in the lumen represent first-line defenses against invaders. Distinguishing "normal flora" from invading organisms can be made by pattern recognition receptors (PRR) exposed in intestinal epithelial cells, which include toll-like receptors and nucleotide-binding oligomerization domain (NOD)-like receptors. Sensing of pathogens or endogenous stimuli released from dying or damaged cells by PRR leads to the downstream activation of intracellular signal transduction inflammatory pathways [4,5]. A concerted effort between both innate and adaptive immune responses is then constructed to face damage. It has been proposed that the cost to the immune system progressively increases in a stepwise process resulting from the engagement or disruption of successive protective barriers [24]. Simple as it may seem, normal peristalsis contributes to dispatch pathogenic material. During constipation, delayed bowel emptying favors the proliferation of germs, and the disturbance of vesical bladder clearance leads to recurrent urinary tract infections, particularly in women [25,26]. In developing countries with poor sanitation, recurrent episodes of diarrhea compromise maintenance of a normal flora due to the disruption of the gut epithelia, as well as to altered restoration of the normal flora secondary to speedy bowel movements [27]. On the other hand, seniors are more susceptible to constipation. This may further compromise gut flora and favor the development of diverticula, which are potential sites of inflammation [28]. Tissue-resident lymphocytes, eosinophils, macrophages, and Treg cells are present in the intestinal barrier acting to contain the inflammatory insult. Breaches in the gastrointestinal barrier expose immunocompetent cells located in the lamina propria and increase the systemic migration of germs or their constituents (antigens) allowing their encounter with professional dendritic antigen-presenting cells in mesenteric lymph nodes, amplifying an inflammatory response that should have been kept locally. In the appropriate unlucky host, bearing a susceptible genotype, the triggering of a complex immune response spreads systemically [4,5,24]. Although unproven, one may speculate that the highly irrigated synovial tissue with fenestrated capillaries and easily accessible immune competent cells, such as type A synoviocytes, are a preferable harbor to those germs or their parts (antigens), where they can foster a sustained immune response.

Medications used to treat rheumatic diseases also modify our microbiome. Sulphasalazine, which has antibiotic properties, is still an option to treat inflammatory bowel disease (IBD) and chronic inflammatory arthropathies [29,30]. Minocycline, marketed primarily as an antibiotic, was until recently used as a disease-modifier drug in RA [31]. Methotrexate, a cornerstone in the treatment of RA, as well as leflunomide may have part of their therapeutic benefit linked to changes in the host microbiome [32]. More recently, fexofenadine, a compound to treat chronic allergic diseases, was shown to inhibit tumor necrosis factor (TNF) activity, revealing an immunomodulatory role to fexofenadine not hitherto described [33]. Chloroquine also has antiviral activity and has just been shown to inhibit *in vitro* coronavirus replication in concentrations that could be achieved in clinical practice [34]. Of interest, the recent worldwide arbovirus Chikungunya outbreak has been associated with joint manifestations, which could derive from a direct viral activity or the triggering of existing subclinical inflammation in joints [35]. In addition, other viruses like Epstein-Barr and parvovirus B19 have long been associated with the pathogenesis of immune-mediated diseases. Hence, the recent proposed antiviral chloroquine activity could well be an additional mechanism to explain its effective response to treat various rheumatic diseases, including the ability to ameliorate musculoskeletal manifestations following Chikungunya infection [36].

Vulnerability to infections particularly in the immunocompromised host occurs in "open systems" such as the skin, respiratory, urogenital, and gastrointestinal tracts. Periodontitis has been shown to

have a major role in the pathogenesis of RA. However, recent epidemiological data may question periodontitis relevance in RA pathogenesis. Using modelling to extrapolate collected data, both the prevalence and burden of RA were reported to be higher in high-income populations where oral hygiene is presumably better [37]. Edentulation is highly prevalent among low-income Brazilians, and chronic periodontitis is the major cause of tooth loss during adulthood [38]. Yet, RA burden was shown to be milder in Brazil and other low-income areas of the globe, as compared to wealthy regions. Also, we have reported very low Childhood Health Assessment Questionnaire (CHAQ) scoring, meaning a favorable outcome, among low-income juvenile idiopathic arthritis (JIA) patients living in one of the less developed areas in Brazil. Indeed, it is surprising that the CHAQ scores were lower than those collected among JIA patients evaluated in the Pediatric Rheumatology International Trials Organization (PRINTO) and Childhood Arthritis and Rheumatology Research Alliance (CARRA) registries that gather data from high-income populations, with presumably better sanitation and oral hygiene. Although it may just be coincidental, there is a high prevalence of helminthiasis in our low-income population leading us to speculate whether helminths or their products downmodulate inflammation in autoimmune diseases, thus decreasing severity [39] (Fig. 1).

Maintaining skin integrity is probably as relevant as avoiding gut damage for adequate immune homeostasis. Ultraviolet radiation, trauma, and tick bites are common causes of lesions inflicted to the skin, paving a way to stimulate immune competent cells located in the dermis. Stratification of skin layers and the presence of continuous capillaries and fat tissue keep inflammatory stimuli away from direct contact to “hidden” professional antigen-presenting cells of the skin, such as the dendritic Langerhans cells. In addition, innate immune mechanisms, including tight junctions between cells, pigmentation, hair follicles, sweat, and sebaceous material prevent access to cells located in the dermis. As an analogy to gut barriers, it seems that every effort is made to avoid access of germs, or their parts (antigens), to satellite lymph nodes, where antigen presentation and systemic widespread inflammation ensues.

It was suggested that a homeostatic response of intestinal cells to commensals is under tight regulation, including the production of antibodies to those germs. That tolerance could be broken during infections, triggering the proliferation of $CD4^+$ T cells both to the invading pathogen as well as to commensals, developing memory cells to the new infecting agent. In a specific host that equilibrium could be lost leading to unresolving inflammation like that occurring in Crohn's disease [40]. Similar mechanisms could be the reason for the occurrence of gastrointestinal manifestations in SpA. A recent report has shown that skin-resident T lymphocytes constitutively expressing interleukin (IL)-17A coexist with commensals, contributing to tissue integrity. Harmful stimuli represented by trauma,

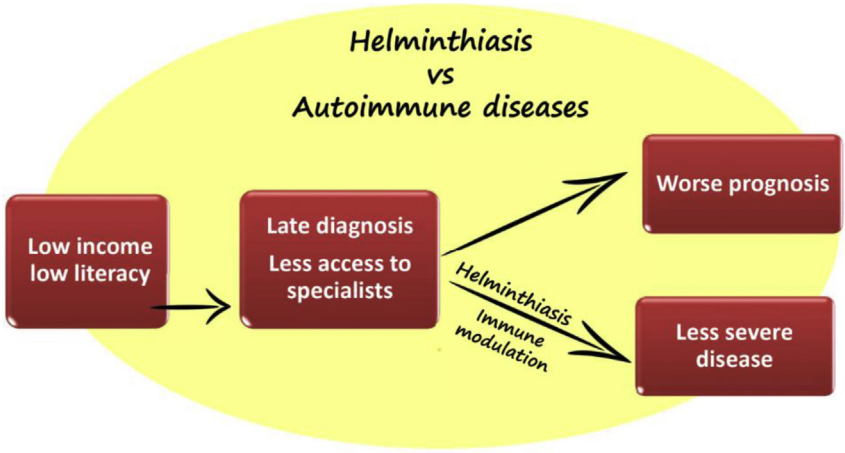

Fig. 1. In developing regions, despite low income and low literacy that negatively impact disease outcome, helminths' infestations may downmodulate inflammation, resulting in less damage.

infection, or insect bite brake barriers, promoting cell plasticity so that the cytokine repertoire is now enriched with IL-5 and IL-13, leading to prolonged inflammation. Therefore, skin barriers help maintain homeostasis by avoiding contact of stimuli to professional cells of the immune system [41]. Once a certain stimulus, in a susceptible host, surpasses that initial defense, systemic inflammation is unleashed, provoking non-resolving autoinflammatory or autoimmune diseases, whether affecting mainly innate or adaptive immune responses, respectively.

Helminths as modulators of the inflammatory response

As mentioned above, worldwide epidemiological data show that the burden of RA varies across the globe, with numbers appearing to be higher in developed countries [37]. Previous estimates of RA have suggested a 0.5%–1.0% prevalence in wealthy regions, with lower prevalence in underdeveloped countries, varying from 0.1% to 0.5% [42]. However, we have to bear in mind that more accurate data were collected in developing regions. Thus, despite some discussion, research suggests RA is less prevalent and/or less severe among low-income populations. Paradoxically, delay in diagnosis, less access to specialists, failure to comply with treatment and unavailability of disease-modifying compounds presumably carry a negative impact to the treatment of chronic inflammatory arthropathies [43].

Regarding SLE, it was shown that low-income patients living in the Northeast of Brazil had similar long-term damage evaluated by the Systemic Lupus Collaborating Clinics' (SLICC) criteria, compared to patients from developed countries [44]. Helminthiasis are still highly prevalent in the Northeast of Brazil and, according to recommendations of the World Health Organization, it is current practice to prescribe prophylactic anti-helminthics to decrease the burden of parasite infections and helminths' infestations (https://extranet.who.int/rhl/topics/preconception-pregnancy-childbirth-and-postpartum-care/antenatal-care/who-recommendation-preventive-anthelminthic-treatment; downloaded on Feb 15, 2020). Helminths have for a long time been considered relevant modulators of the immune response [45]. There are reports on the benefit of the administration of *Trichuris suis* eggs to treat patients with Crohn's disease [46]. Our group has shown that animals subjected to collagen-induced arthritis and treated with a crude *Ascaris suum* extract have decreased inflammation with the reduction of cytokine release into inflamed joints [47]. We then identified the gene sequence of a peptide from the *A. suum* extract present in the celomic fluid of that worm, which shows anti-inflammatory activity in mice subjected to AIA. Intramuscular administration of a plasmid with the correspondent gene sequence decreased inflammation in AIA mice, apparently through a shift of the macrophage population into an M2 phenotype (unpublished data). It is worth mentioning that oral administration of *A. suum* extract, rather than viable worms as with *T. suis* experiments, was effective, providing a proof-of-concept to support the idea that helminthic products released into the bowel modulate the inflammatory response [47]. It has also been previously shown that an excretory-secretory product of *Acanthocheilonema vitae* has an immunomodulatory role, being able to decrease osteoclast-mediated bone resorption through the modification of the gut microbiota [48]. Helminths or their products might have beneficial and harmful effects to the host. Difficulties in establishing a net result should not prevent efforts to dissect those mechanisms, both to understand the pathophysiology of immune-mediated diseases as well as to develop therapeutic alternatives (Fig. 2) [49,50].

PADS, citrullination, and HLA-B27 – are microbes and rheumatic diseases related?

In 2006, Inman wrote “Perhaps a word of caution is needed for the critics and a word of encouragement for those hunting microbes in the joints,” when referring to the possible role of infection in the development of rheumatic diseases, specifically SpA [51]. He compared this concept to the relationship between *Helicobacter pylori* infection and gastritis, which was at first met with skepticism, but is nowadays accepted as a fact [51,52].

When talking about “microbes in the joints,” one can discuss the topic from the perspective of infection and how it can contribute to the development of certain rheumatic diseases, but also in a broader sense, considering the human microbiome (more specifically, the gut microbiome) and how it

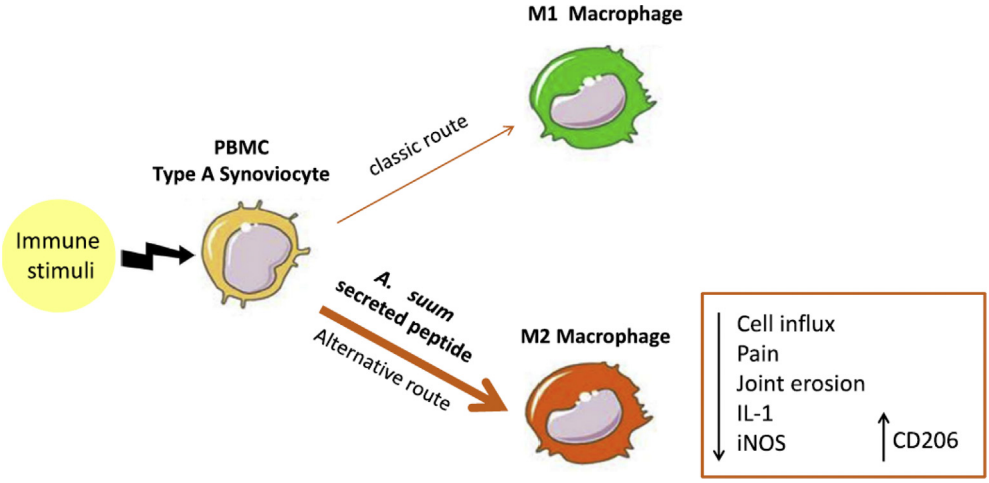

Fig. 2. Possible mechanism where secretory products from *A. suum* drive macrophage differentiation into an M2 phenotype, leading to the decreased release of inflammatory mediators.

can be related to these disorders, specifically inflammatory arthropathies [51,53]. The understanding of the depth of this relationship could, in the future, yield new forms of treatment [54].

SpA, as a group, are characterized by findings of asymmetric oligoarthritis, axial involvement, particularly of the sacroiliac joints, and inflammatory back pain, enthesitis, and characteristic extra-articular features, including acute anterior uveitis, and psoriasis [51,55]. Ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), and IBD-related arthritis [55] all share an association with HLA-B27 [51]. The HLA-B2705 subtype is the one that's most commonly associated with SpA [56]. In fact, the presence of this allele is the greatest risk factor for the development of SpA [57]. Parallel to the genetic predisposition, there has been mounting evidence for the role of infection in the pathogenesis of SpA [58,59].

The clearest example of this association is illustrated by ReA [51]. For a long time, there has been evidence that *Chlamydia trachomatis* (an obligate intracellular parasite of eukaryotic cells [60]) plays a role in the development of inflammatory arthropathies [61]. The pathogenesis of *Chlamydia*-related arthritis can be considered distinct from that associated with enteric bacteria because it involves metabolically active organisms residing long-term within monocytic cells in synovial tissues, after the resolution of primary genital infection and migration of cells to the joint, a process that is known as persistence [56,61–63]. There is also evidence that differences in the expression of heat shock protein-60 genes may contribute to organism persistence [64].

Another interesting aspect to consider is that only a minority of patients with *Chlamydia* genital infection develop ReA. This could be explained by findings of Gérard (2010) that showed only ocular serovar group Chlamydiae in synovial biopsies from arthritis patients, who were PCR-positive for *C. trachomatis* DNA in that tissue and not genital serovar. This could mean that the composition of the initial inoculum influences the probability of arthritis development [65]. These data, if confirmed, could be relevant when thinking about a way to monitor, which patients will go on to develop or have a greater risk of developing arthritis. Nevertheless, it is important to note that these findings were based on the evaluation of only four patients [65]. Similarly, *C. pneumoniae* has also been accepted as an etiological agent for inflammatory arthritis [66,67]. Earlier, it was believed that antibiotic treatment of patients with *Chlamydia*-induced arthritis was ineffective [59,61,63,68], but recent studies indicate antibiotic therapy might be beneficial [56,69]. However, this efficacy is not complete as the proposed treatment (6 months of oral antibiotic therapy with either doxycycline or azithromycin, both combined with rifampin) improves joint symptoms in 63% of patients and leads to remission in 22% [51], indicating that other mechanisms might be involved in the development of arthritis, which if better understood, could lead to the development of novel therapeutic targets [54,59].

Besides *Chlamydia*, enteric pathogens such as *Campylobacter jejuni, Clostridium difficile, Escherichia coli, Salmonella, Shigella*, and *Yersinia*, and respiratory pathogens like *Chlamydia pneumoniae* or *Mycoplasma pneumoniae* have also been shown to give rise to reactive joint processes. Evidence for the benefit of antibiotic therapy directed at those bacteria is sparse, because it does not appear to alter the course of arthritis [56].

The actual concept of ReA makes the history of infection a required criterion for its diagnosis, but, unlike in septic arthritis, inflammatory arthritis is not directly caused by the infection of joint tissue (positive culture), instead it follows an extra-articular infection [51,56]. As for other SpAs, which comprise the majority of diseases in this group, with ReA accounting for less than 2% of the overall disease burden [70], the role of infection (whether there is a role or what that role is) is not as well established. Nonetheless, there has also been some evidence regarding this matter [51,59,71,72] – various authors have discussed the role of *Chlamydia*, not only in ReA but also in undifferentiated SpA [71]. Rashid et al. (2016) reported a link between elevated levels of *Klebsiella* antibodies and AS in various geographical locations [73], and the development of this disease appears to be related to the presence of *K. pneumoniae* aerogenes in the gastrointestinal tract [58].

The role of HLA-B27 has been a focus of research when trying to understand SpA. In ReA, HLA-B27 is present in 50%–80% of patients [74]. There are several theories that attempt to define how exactly HLA-B27 predisposes to SpA and how it is implicated in its pathogenesis [56,75]. This is of particular relevance in the context of the arthritogenic peptide hypothesis, according to which microbial peptides mimic certain self-peptides. Specifically, HLA-B27 may have structural features that are shared with bacteria, causing reactivity of HLA-B27-specific, $CD8^{+}$ bearing cytotoxic T lymphocytes, leading to autoimmunity and tissue damage and inflammation [58,76]. Zhang et al. (2018) stated that AS seems to be related to *K. pneumoniae* infection in HLA-B27-positive patients, based on consistent findings of raised anti-*K. pneumoniae* antibodies and the presence of molecular mimicry between the HLA-B27 molecule and bacterial antigens [58].

Because some patients who are HLA-B27 negative also develop ReA, other investigations have focused on the role of specific microbial factors in the pathogenesis of the disease. For example, in patients with ReA and documented *S. typhimurium* infection, it has been suggested that *Salmonella* outer membrane protein is able to stimulate IL-17/IL-23 production in synovial immune cells, possibly contributing to arthropathy [77], considering the well-established role of this pathway in SpA [78,79,81].

There has also been some focus on the role played by microbes that inhabit the human body and do not represent a state of infection – in this case, the focus has been centered around the gastrointestinal microbiota (oral and gut microbiota) – and its possible implication in the pathogenesis of SpA [80–82]. Changes in the homeostasis and balance of the microbiota can lead to subtle but perhaps profound alterations in the balance with the host's immune system, leading to a state of inflammation that may contribute to disease.

The correlation between HLA-B27 and AS has been known since the 1970s [83,84]. This relationship is also true for the other SpA, as stated above. Studies indicate inflammatory bowel disease, or at least intestinal inflammation is more prevalent in SpA patients (AS or others) and some genes associated with AS are also associated with IBD [83,85], including genes related to gut physiology and immunology. Based on these associations, it has been postulated that imbalances and defects in gut microbiota can play a role in the pathogenesis of SpA [85,86], because there is a significant clinical, genetic, immunological, and microbiological overlap between IBD and SpA [55]. Not surprisingly, there has also been evidence that HLA-B27 affects the gut microbiome and its metabolites, and perhaps the handling of bacteria during infection [82,83].

The gut microbiota is acquired postpartum and its composition can be influenced by various factors during its development until around 3 years of age, when it seems to stabilize. During a person's lifetime, the gut microbiota can be affected by diet and nutrition and also antibiotic use – disturbances in its balance can be a factor for disease [53]. A study that analyzed biopsies from the terminal ileum of 9 AS patients showed the microbiome in AS patients was different from healthy subjects, with a greater abundance of *Bacteroidaceae, Lachnospiraceae, Porphyromonadaceae, Rikenellaceae*, and *Ruminococcaceae* and lower abundance of *Prevotellaceae* and *Veillonellaceae* [53].

Data has shown that HLA-B27 can determine an increase in the intestinal permeability, which results in continuous antigenic stimulation with the activation of effector T cells [53,82,87]. HLA-B27 can also induce an endoplasmic reticulum stress response and promote autophagy/unfolded protein responses (UPR), resulting in the release of TNF, IL-17, overexpression of IL-23 by Paneth Cells, and interferon-γ and increase in Th17 cells [83]. IL-23 can regulate the maturation of autoreactive Th17 cells and induce chronic inflammation by stimulating IL-17, IL-6, IL-8, and TNF production in neutrophils and macrophages [88].

There has also been evidence that HLA-B27 may interact directly with Gram-negative bacteria, either by provoking an immune response through antigen mimicry (as previously discussed) or by altering genes expressed by bacteria, thus affecting dendritic cell function and influencing the immune response [89].

Despite the relationship between SpA, HLA-B27, and the microbiome, the best example of the influence of gut dysbiosis in the pathogeneses of rheumatic diseases is still RA and its relationship with citrullinated proteins [90–92].

Proteins are ubiquitous in the human body, assuming different forms and specific functions. After syntheses in ribosomes, they are further altered and specialized through posttranslational modification, which includes various processes. One of such processes, involving the conversion of arginine amino acid into citrulline amino acid, is called citrullination and occurs physiologically during apoptosis. This “biological operation” is catalyzed by peptidylarginine deiminase enzymes (PADs) and produces an amino acid that is not encoded by the genome, being solely produced by this process [93]. There has been extensive research and data that demonstrate the role of PADs in the development of immune-mediated diseases [93], and in the field of rheumatology, this is particularly relevant with respect to RA.

In humans, there are five PAD isoenzymes (from 1 to 6) expressed in various tissues and organs that contribute to many of the body's physiological functions. They are actively expressed in the intestinal epithelium, making it a source of citrullinated peptides [90]. Changes in oral microbiota can also influence progression and outcomes in RA [53] and *Porphyromonas gingivalis* (PG) has been ascribed a major role. It is present in the oral cavity and proliferates in patients affected by periodontitis. The PAD expressed by PG can lead to citrullination and may explain the close association between RA and periodontitis, an inflammatory disease of the oral mucosa [92]. There are actually reports of a direct correlation between the serum level of antibodies and PG plus ACPAs in RA patients [94]. However, as we mentioned above, discrepancies concerning increased RA burden in regions with better oral hygiene may question the relevance of periodontitis in RA pathogenesis [37].

When considering the role of gastrointestinal microbiota and infection in rheumatic diseases, the best characterization was achieved in RA, through the understanding of the process of citrullination and its relationship with oral microbiome, mainly PG. In SpA, altered intestinal permeability and HLA-B27's role in the induction of that disruption may trigger antigenic stimulation with T cell activation [53].

It is also relevant to refer, in respect to citrullination, that it was thought that citrullinated proteins were specific to the synovium of RA patients, but recent reports revealed citrullinated proteins are also present in the synovium of non-RA inflammatory conditions [95], which may account for its probable role in other inflammatory arthropathies.

Therapeutic proposals

Antibiotic use may be considered a mixed blessing in the context of therapeutics. While it is undisputable that antibiotics are lifesaving in many cases, widespread and unnecessary use of such compounds, particularly those with a broad-spectrum profile, leads to the development of bacterial resistance as well as alterations to the microbiome. Modifications of the immune response occur secondarily to the eradication of commensal microorganisms, which are important stimuli to intestinal cells.

Probiotics are commonly regarded as a useful and harmless strategy to reconstitute the gastrointestinal flora following antibiotic use. Probiotics can be routinely prescribed by physicians and other health care professionals, and may also be found as over-the-counter products, on the premise of restoring homeostasis. However, there is a lack of adequate studies documenting those benefits, not to

mention that probiotics are marketed without complying with strict rules used for drugs' approval. By not being appropriately regulated, neither the safety nor the efficacy of probiotics have been specifically documented.

It was recently shown that the supplementation of probiotics to humans or mice that received broad-spectrum antibiotics led to a delayed restoration of the previous normal flora. On the other hand, autologous fecal microbiota transplantation (FMT) shortened the time for reconstitution of the gut flora [96]. Although Suez et al. (2018) have correctly discussed limitations and extrapolations from their single study in healthy volunteers, results justify a closer look into advertised benefits of probiotic use, regardless of indication, highlighting the need for data to adequately document harms and benefits.

Antibiotics are also used as modulators of immune response. Sulphasalazine is indicated in SpA and RA as a disease-modifying compound due to its immunomodulatory activity [29,31]. Until recently, tetracyclines (minocycline) were used as disease-modifying antirheumatic drugs because of their anti-inflammatory effects involving the inhibition of proinflammatory cytokines and matrix metalloproteinase activity [30]. Gold salts had their efficacy at least partially linked to antimicrobial activity and were formerly in use for RA treatment. Regarding ReA and despite difficulties in pointing to a specific germ as the causative agent, prolonged antibiotic use has been associated with decreased symptoms and disease duration [58,71]. Other medications already in use may have unsuspected antibiotic activity as the recently described antiviral chloroquine response. However, the most common and effective treatment for chronic inflammatory arthropathies relies on downmodulating inflammatory response-related targets with immune suppressors, aiming for symptom relief, and halting structural tissue damage.

Following the boom in microbiome research, other microbiota directed therapeutic interventions appeared. For instance, changing dietary habits as a means to increase the supply of short-chain fatty acids by ingesting fiber is also an appealing strategy to improve immune function, because it is perceived as a nonharmful alternative in addition to the low-calorie profile benefit. A high-fiber diet favors the production of short-chain fatty acids, particularly propionate and butyrate, which have anti-inflammatory and immunomodulating activities, and were associated with bone-sparing effects in RA patients. Mice subjected to short-chain fatty acids' administration had decreased bone resorption partially mediated by the downregulation of TNF receptor associated factor-6 and nuclear factor of activated T-cells, cytoplasmic 1 (NFATc1) genes [97].

As a therapeutic alternative to treat chronic inflammation, FMT attracts both interest and skepticism. The successful use of FMT in patients affected by *C. difficile* infections refractory to antibiotic treatment came as a proof-of-concept promising study [98]. Despite its recognized benefits, the procedure has its risks. Harmful contaminants can be supplied together with the "good guys" that would restore the intestinal flora after FMT. Indeed, the U.S. Food and Drug Administration issued a safety alert on June 13, 2019 about the serious adverse reactions due to the transmission of multidrug resistant organisms following FMT (www.fda.gov/media/86440, downloaded on Feb 02, 2020). The logistics behind the necessary standardization of appropriate FMT "components" include storage, "quality" control regarding donors, recipients, expiration date, to mention a few issues.

Given the difficulty in translating FMT into clinical practice and the inconsistent data on probiotic use, microbial active pharmaceutical ingredients have also been developed as treatment strategies for rheumatic diseases. Biological therapies involving the delivery of live organisms are a major challenge and regulations are being developed, but it was not without great care that the industry introduced biologicals into the therapeutic armamentarium of immune-mediated diseases. A recent review addressed issues about the development of microbial therapeutics, which is still in its early stages. Uncontrolled proliferation of a living organism, toxicity, and hypersensitivity reactions as well as long-term stability are some of the challenges that need to be overcome. Pharmacokinetics, pharmacodynamics, and the supply chain are matters of concern, particularly if one considers worldwide distribution. Gut barriers, including acidic pH, bowel movement, mucus layer, bile salts, to name a few, also affect the bioavailability of oral vaccines or stability of microbe-derived orally active compounds [99]. Challenges represent opportunities for improvement. Considering the interest of big pharma companies on live biotherapeutics, the marketing approval of a specific microbial therapy will likely happen in the near future.

Summary

Changes to the microbiota, not solely to intestinal microbiota, but also the skin, respiratory and urogenital tracts are associated to the pathogenesis of rheumatic diseases. Inflammatory components of the innate and adaptive immune response are involved in these changes which are relevant to diseases not commonly regarded as being immune-mediated such as osteoarthritis.

A role for helminths as modulators of the gut microbiota, at least in people living in developing countries, demands further investigation.

Interventions to alter the microbiota as a therapeutic strategy in rheumatic diseases have not proven benefit. At this moment, avoiding excess fat, salt and consumption of processed food are the best alternatives to preserve health.

Research agenda

- Identify causal relationships between microbiome perturbations and human rheumatic disease
- Define roles, for skin, respiratory, and urogenital tract microbiota in the pathogenesis of rheumatic diseases
- Conduct high-quality clinical trials with pharmaceutical grade probiotics in rheumatic diseases
- Identify mechanisms by which antibiotics modulate rheumatic diseases
- For patients with rheumatic disease, determine "healthy" and "harmful" dietary components that are simple, affordable, and readily available.

Practice points

- Antibiotic use should be made within specific indications, thereby trying to limit changes to the microbiota
- Attention should be given to innate immune mechanisms as modifiers of disease states
- Proven dietary recommendations for the treatment of rheumatic diseases are not yet available
- General recommendations, such as avoiding excess salt and fat and consuming fresh vegetables, are current best practices
- Benefits of probiotic use, at least in rheumatic diseases, demand *bona fide* data

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Conflict of interest

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