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GRADO EN MEDICINA

TRABAJO FIN DE GRADO

Interacciones entre la microbiota intestinal y el sistema inmune
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Implicaciones en la artritis reumatoide
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Una revisión bibliográfica

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-
Implications in rheumatoid arthritis
-
A literature review

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Santander, Junio de 2025

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INTERACTIONS BETWEEN GUT MICROBIOTA AND THE IMMUNE SYSTEM - IMPLICATIONS IN RHEUMATOID ARTHRITIS
-
A LITERATURE REVIEW

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Palabras clave: Microbiota intestinal, artritis reumatoide, disbiosis, autoinmunidad, homeostasis inmunitaria, permeabilidad intestinal, mimetismo molecular.

Keywords: Gut microbiota, rheumatoid arthritis, microbial dysbiosis, autoimmunity, immune homeostasis, intestinal permeability, molecular mimicry.

RESUMEN:

La artritis reumatoide es una enfermedad autoinmune crónica caracterizada por una inflamación sistémica y destrucción articular. Su etiopatogenia multifactorial implica tanto factores genéticos como ambientales. Asimismo, estudios recientes destacan el papel fundamental de la microbiota en la modulación de la respuesta inmune y el desarrollo de la AR. Esta revisión bibliográfica explora las interacciones bidireccionales entre la microbiota intestinal y el sistema inmune, enfatizando sus implicaciones en la patogénesis y progresión de la enfermedad. La disbiosis, definida como un desequilibrio en la composición y función de la microbiota, se ha asociado con desregulación inmunitaria, pérdida de tolerancia, aumento de la permeabilidad intestinal y activación de células T y B autoreactivas. Ciertos taxones bacterianos, como *Prevotella copri* y *Collinsella aerofaciens*, han sido implicados en vías proinflamatorias, mientras que comensales beneficiosos, como *Faecalibacterium prausnitzii*, parecen ejercer efectos protectores. Asimismo, los metabolitos microbianos, en particular los ácidos grasos de cadena corta, desempeñan un papel primordial en el mantenimiento de la homeostasis inmunitaria. Esta revisión aborda también nuevas estrategias terapéuticas dirigidas a la microbiota, como son los probióticos, las intervenciones dietéticas y el trasplante de microbiota fecal. Se destaca su potencial en la modulación de la actividad de la enfermedad y la mejoría del pronóstico clínico. La comprensión de la compleja interacción entre la microbiota intestinal y el sistema inmune resulta prometedora, pudiendo brindar nuevos abordajes diagnósticos y terapéuticos a la AR.

ABSTRACT:

Rheumatoid arthritis is a chronic autoimmune disorder characterized by systemic inflammation and joint destruction. Its multifactorial etiopathogenesis involves both genetic and environmental factors. Furthermore, emerging evidence highlights the pivotal role of the gut microbiota in modulating immune responses and contributing to RA development. This literature review explores the bidirectional interactions between the gut microbiota and the immune system, emphasizing their implications in RA pathogenesis and progression. Dysbiosis, defined as an imbalance in the composition and function of the gut microbiota, has been associated with immune dysregulation, loss of tolerance, increased intestinal permeability, and the induction of autoreactive T and B cell responses. Specific microbial taxa, such as *Prevotella copri* and *Collinsella aerofaciens*, have been implicated in pro-inflammatory pathways, while certain beneficial commensals like *Faecalibacterium prausnitzii* appear to confer protective effects. Moreover, microbial metabolites, particularly short-chain fatty acids, play an essential role in maintaining immune homeostasis. This review also discusses current and emerging microbiota-targeted therapeutic strategies, including probiotics, dietary interventions, and fecal microbiota transplantation, highlighting their potential for modulating disease activity and improving patient outcomes. Understanding the complex interplay between the gut microbiota and the immune system may pave the way for novel diagnostic and therapeutic approaches in RA.

GLOSSARY:

Rheumatoid Arthritis (RA): Chronic systemic autoimmune disease characterized by persistent synovial inflammation, joint destruction and presence of autoantibodies such as rheumatoid factor and anti-citrullinated protein antibodies, leading to progressive disability and systemic complications.

Gut Microbiota: The complex and dynamic community of microorganisms, primarily bacteria, that reside in the gastrointestinal tract, playing essential roles in host metabolism, immune modulation, and protection against pathogens.

Dysbiosis: Disruptions in gut microbial composition, diversity or function, associated with increased intestinal permeability, immune dysregulation, and susceptibility to inflammatory and autoimmune diseases.

Short-Chain Fatty Acids (SCFAs): E.g. Acetate, propionate, butyrate. Microbial fermentation products derived from dietary fiber, with immunomodulatory effects and significant importance in the maintenance of gut barrier integrity.

Anti-Citrullinated Protein Antibodies (ACPAs): Autoantibodies directed against citrullinated peptides, commonly present in individuals with RA, implicated in disease pathogenesis and utilized as early diagnostic markers.

Gut-Associated Lymphoid Tissue (GALT): A critical component of the mucosal immune system that includes Peyer's patches, isolated lymphoid follicles, and the vermiform appendix. It serves as primary site for antigen sampling and the induction of adaptive immune responses to luminal microbes.

Toll-Like Receptors (TLRs): Subtype of pattern recognition receptors (PRRs) expressed in immune and non-immune cells, that recognize conserved microbial structures (MAMPs) and initiate innate immune responses.

NOD-Like Receptors (NLRs): Cytosolic PRRs that detect intracellular microbial components or cellular stress signals, leading to the activation of inflammatory responses.

Th17 Cells: Subset of $CD4^+$ T cells characterized by the secretion of interleukin-17, involved in host defense against extracellular pathogens and implicated in the pathogenesis of autoimmune and inflammatory diseases.

Regulatory T cells (Treg Cells): Subset of $CD4^+$ T cells essential for immune tolerance and homeostasis, primarily through the secretion of anti-inflammatory cytokines such as IL-10 and TGF-β.

Microbe-Associated Molecular Patterns (MAMPs): Conserved molecular structures derived from microorganisms, recognized by host pattern recognition receptors. They trigger innate immune responses essential for pathogen detection and immune activation.

Germ-free (GF): Experimental condition or organism entirely devoid of living microorganisms. Used in research to study host-microbiota interactions and the role of microbiota in health and disease.

INDEX:

1. INTRODUCTION

The human microbiota comprises a diverse collection of microorganisms – including bacteria, viruses, fungi and archaea - that inhabit various anatomical sites throughout the body. Collectively, their gene content surpasses that of the human genome by approximately 100-fold. The gastrointestinal tract represents the main reservoir, being predominantly colonized by bacteria belonging to the *Firmicutes* and *Bacteroidetes* phyla in healthy adults, whereas bacteria from the *Proteobacteria, Actinobacteria, Fusobacteria* and *Verrucomicrobia* phyla are found in lower proportions. The microbiome's composition is influenced by intrinsic factors (mode of delivery, local environmental conditions such as pH, intestinal permeability, …), as well as extrinsic determinants (diet, antibiotic exposure, pharmaceutical interventions, …), thereby exhibiting great variability among individuals. (1)

This ''second genome'' functions symbiotically under homeostatic conditions, playing a pivotal role in metabolic processes, immune homeostasis, and disease susceptibility. Conversely, disruptions in its composition and function, a state known as dysbiosis, have been implicated in the pathogenesis of various chronic and immune-mediated diseases, including type 1 diabetes, cardiovascular disorders, inflammatory bowel disease (IBD), and rheumatoid arthritis (RA). Microbial dysbiosis contributes to these conditions through mechanisms such as increased intestinal permeability, immune dysregulation, and altered production of microbial metabolites. (2)

Autoimmune diseases arise from immune dysregulation leading to chronic inflammation, mediated by both cellular and humoral responses against self-proteins. The strongest genetic associations in autoimmune diseases are located within the major histocompatibility complex (MHC), which encodes the human leukocyte antigen (HLA) class II alleles, particularly DR and DQ. Notably, the autoimmune disease–associated HLA loci predominantly involve the DR2, DR3, and DR4 alleles. Although these alleles potentiate immune responses against pathogens, they may also predispose to autoimmunity via molecular mimicry and altered antigen presentation. (3) While genetic predisposition plays a significant role, the low concordance rates in twins and variability in disease manifestations among genetically identical individuals, underscore their multifactorial nature, with multiple environmental factors playing a critical role. (4)

In conditions such as RA, preclinical autoreactivity may precede symptomatic onset by years. RA is a chronic systemic autoimmune disorder characterized by joint inflammation, autoantibody production, progressive disability, and multiple comorbidities, including cardiovascular and pulmonary diseases. (1) RA development is driven by a combination of genetic and environmental factors, with the HLA-DRB1 allele, bearing the shared epitope (SE), being the most significant genetic risk factor. (1) Immune dysregulation in RA includes alterations in T and B cell function, Th17/Treg imbalance, elevated pro-inflammatory cytokines, and the presence of anti-citrullinated protein antibodies (ACPAs), which serve as early biomarkers and indicators of disease severity. Environmental influences, such as smoking, diet and microbial infections, further contribute to disease onset. (4)

Recent advancements in high-throughput sequencing methodologies, including 16S rRNA gene amplicon sequencing and whole-genome metagenomics, have facilitated microbiome characterization, renewing interest in its role in autoimmune diseases such as RA. The mucosal surfaces of the oral cavity, lungs, and gut are constantly exposed to a high load of microbial antigens, which may compromise immune tolerance and precipitate RA development in genetically predisposed individuals. Dysbiosis has been consistently observed in RA patients. Specific microorganisms, including *Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans*, and other pathogens, have been implicated in triggering autoimmunity by promoting citrullination and pro-inflammatory immune responses. (1,4)

While the exact mechanisms by which microbiota influence RA pathogenesis are still being elucidated, accumulating evidence supports a causal relationship between microbial dysbiosis and systemic autoimmunity. This review integrates current clinical and molecular evidence on interactions between host microbiota and the immune system, emphasizing their implications in RA development and evaluating their potential as diagnostic and prognostic biomarkers. Additionally, therapeutic strategies targeting microbiota modulation, including dietary modifications, probiotics, and fecal microbiota transplantation, are discussed as emerging approaches in RA management.

2. SEARCH METHODOLOGY

For this literature review, a non-systematic search was conducted in the PubMed database. MeSh terms were applied to cover all controlled vocabulary related to each search concept. The following keywords were employed as search terms: ‘’rheumatoid arthritis’’, ‘’gut microbiota’’, ‘’microbiome’’, ‘’immune system’’ “microbiota host interaction”, “immunomodulation”, “diet”, “probiotics” and “fecal microbiota transplant”. To enhance the accuracy of the search and limit the literature retrieval, Boolean operators AND and OR were used for term combinations.

The results obtained were filtered to include publications from the past 15 years, prioritizing comprehensive review articles and clinical trials published in high-impact journals that were most relevant to the topic under investigation. Additionally, the reference lists of certain articles were reviewed for the identification of papers of interest, ensuring a more extensive and thorough examination of the subject.

3. INTESTINAL MICROBIOTA AND IMMUNE RESPONSE

The gut microbiota, a diverse collection of bacteria, archaea, fungi, protozoa, and viruses, establishes a predominantly mutualistic relationship with its host, contributing to metabolic, neuroendocrine, and immunological functions (e.g. carbohydrate fermentation, vitamin synthesis, and epithelial defense) (1). Notably, its interactions with the immune system are complex and bidirectional, playing a critical role in immune system development, modulation, and homeostasis. (5)

THE GASTROINTESTINAL TRACT AS AN IMMUNOLOGICAL HUB

The intestinal epithelium comprises absorptive epithelial cells, including enterocytes and colonocytes, as well as specialized cellular subpopulations such as Goblet cells, M cells, Paneth cells, and enteroendocrine cells, supported by the gut-associated lymphoid tissue (GALT). The GALT represents a complex network of immune structures including Peyer's patches, lymphoid follicles, and a variety of immune cells, such as intraepithelial lymphocytes (IELs), macrophages, dendritic cells, natural killer cells, and innate lymphoid cells (ILCs). These components coordinate immune responses against pathogens while preserving tolerance to commensals and dietary antigens, a process maintained through central and peripheral tolerance mechanisms. (5)

The gastrointestinal tract serves as a major immunological organ, housing a diverse microbial community which coexists with the host. (1) Selective permeability must be maintained to enable the absorption of nutrients and microbial metabolites while preventing the translocation of pathogens and excessive immune activation. (5) This barrier is assembled by a single layer of intestinal epithelial cells and a dense mucus cover, primarily composed of the hyperglycosylated mucin MUC2, which modulates antigen immunogenicity through dendritic cell imprinting toward anti-inflammatory phenotypes. Tight junctions further regulate epithelial permeability, with microbial-derived signals, such as indole, enhancing barrier integrity via upregulation of tight junction proteins and cytoskeletal components. Antimicrobial peptides (AMPs) and secretory immunoglobulin A (IgA) constitute additional defensive elements, restricting microbial invasion and translocation. (6)

IMPACT OF EARLY-LIFE MICROBIAL COLONIZATION

The establishment of the gut microbiota begins at birth and is highly dynamic during early life. Factors such as the mode of delivery and breastfeeding have profound effects on the initial microbial colonization, which, in turn, influences the maturation of the immune system. During infancy, microbiota composition exhibits high intra- and inter-variability, before stabilizing around the age of three years. This early dynamic period is crucial. Disruptions during this window, whether due to environmental, dietary or pharmacological factors, can have lasting impacts on immune development and may predispose individuals to immune-mediated diseases later in life. (5)

The "hygiene hypothesis'' posits that reduced microbial exposure in early life, may impair the normal maturation of the immune system, leading to deficiencies in lymphoid tissue development and function. (5) This is demonstrated in germ-free (GF) mice, which exhibit significant reductions in Peyer's patches, Th17 cells, IgA production, and αβ and γδ intra-epithelial lymphocytes, which can be rapidly restored upon microbial colonization. (6) This impaired immune education is considered as a potential trigger of the increasing prevalence of autoimmune and inflammatory conditions observed in developed countries. (7)

GUT MICROBIOTA AND THE INNATE IMMUNE RESPONSE

The gut microbiota plays a pivotal role in shaping both innate and adaptive immune responses through direct and indirect mechanisms. (5,7) The innate immune system, which provides rapid responses to microbial challenges, primarily interacts with the microbiota via pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) and NOD-like receptors (NLRs). These receptors recognize microbe-associated molecular patterns (MAMPs) and pathogen-associated molecular patterns (PAMPs), such as bacterial cell wall components (lipid A, peptidoglycan, flagella, lipopolysaccharide) and nucleic acids. (7) These interactions regulate microbial composition and tissue integrity, and trigger interferon (IFN)-mediated immune memory, not only limiting pathogen spread but also priming the tissue for adaptive immune responses (6). Furthermore, microbiota influence myeloid and lymphoid cell differentiation through PRRs, as well as white blood cell proliferation and cytokine profiles through transcriptional and epigenetic modifications, underscoring their systemic role in immune homeostasis. (7)

Paneth cells contribute to innate immunity by secreting AMPs. These peptides are essential for maintaining a balanced microbial community, as they selectively eliminate pathogenic bacteria while sparing beneficial commensals. (6)

Microbiota-derived metabolites, such as bile acids and short-chain fatty acids (SCFAs), products of dietary fiber fermentation, are capable of inducing epigenetic modifications that influence cytokine production and immune cell differentiation via G-protein-coupled receptors. (1) SCFAs can modulate the balance between tolerogenic and inflammatory responses, thereby influencing the development of immune memory. (1,6) For instance, in germ-free mice, the absence of SCFA-producing commensals impairs the differentiation of colonic Treg cells and the development of memory CD8+ T cells, highlighting the essential role of the microbiota in establishing long-term immune competence. (6)

The microbiota plays a critical role in regulating ILCs, which reciprocally influence the composition and function of the microbial community. (7) ILCs contribute to mucosal tissue repair and host immune defense through the secretion of cytokines in response to microbial-derived signals. (6) Among the ILC subsets, ILC1s are primarily involved in antiviral immunity, whereas ILC2s mediate type 2 immune responses against parasitic infections. (7) Of particular interest, the commensal bacterium *Ruminococcus gnavus*, which has been associated with an increased risk of allergic disease in children, has been shown to activate IL2s, leading to eosinophil and mast cell infiltration in the colon and lungs of murine models, highlighting their potential role in modulating immune tolerance (6).

Mononuclear phagocytes (MNPs) within the lamina propria, including dendritic cells and macrophages, play a key role in sampling microbial antigens from the gut lumen and presenting them to T cells, thereby activating adaptive immunity. Specific subsets, such as $CD103^+$ and $CD11^+$ dendritic cells, migrate to mesenteric lymph nodes where they imprint gut-homing characteristics on T cells, ensuring that immune surveillance remains focused in regions where microbial interactions are most intense. In contrast, $CX3CR1^+$ MNPs are specialized for trans-epithelial antigen sampling, though they exhibit limited capacity to prime T cells under homeostatic conditions. However, disruptions such as antibiotic-induced dysbiosis can result in aberrant $CX3CR1^+$-mediated translocation of non-invasive bacteria to mesenteric lymph nodes, eliciting maladaptive immune responses and contributing to systemic disease. (7)

GUT MICROBIOTA AND THE ADAPTIVE IMMUNE RESPONSE

Adaptive immunity is characterized by antigen-specific responses mediated by T and B cells. (5) B cells contribute significantly to mucosal defense through the production of secretory IgA. (6) IgA traps microbes within the mucus layer, preventing epithelial invasion, and modulates bacterial properties, such as oxidative stress resistance. The production of intestinal IgA is driven by B cells via T cell-dependent (TD) and T cell-independent pathways (TI), specifically targeting commensal bacterial antigens. Homeostatic IgA is predominantly produced in a TI way, rapidly generating low affinity polyreactive IgA against a broad range of microbial antigens. In contrast, TD responses involve repeated somatic hypermutation and affinity maturation in germinal centers, targeting protein antigens. (7)

CD4+ T cell subsets play a crucial role in regulating immune homeostasis within the gut. They are activated in response to microbial colonization, with healthy individuals exhibiting a pool of microbiota-reactive memory $CD4^+$ T cells that contribute to immune surveillance and readiness. (6) These cells secrete IFN-γ, IL-17A, and TNF, promoting the activation of epithelial and intestinal stromal cells, thereby preserving mucosal integrity under homeostatic conditions. However, during inflammatory states, the circulating levels of these microbiota-reactive memory $CD4^+$ T cells are reduced, which might reflect their selective recruitment to the inflamed gut. (8)

Regulatory T cells (Treg) and Th17 cells exemplify the dual nature of CD4+ T cell responses. Tregs maintain immune tolerance by suppressing excessive inflammatory responses through effector cell apoptosis and the production of anti-inflammatory cytokines. (7) Conversely, Th17 cells mediate protective immunity against extracellular pathogens. The differentiation of Th17 cells is regulated by specific bacterial species. Certain commensals such as *Segmented filamentous bacteria* (*SFB*) promote non-inflammatory Th17 differentiation, whereas pathobionts like *Citrobacter spp.* trigger pro-inflammatory Th17 responses, potentially contributing to autoimmune conditions. Although microbiota-derived signals drive Th17 differentiation in the gut and skin, oral Th17 cell development appears to be independent of microbial colonization. (6)

A key effector molecule produced by Th17 cells, as well as type 3 ILCs, is IL-22. Its synthesis is stimulated by microbial peptides, notably indole-3-aldehyde, derived from dietary tryptophan metabolism by commensal bacteria. This cytokine plays an essential role in maintaining epithelial barrier function, promoting mucosal tissue repair and AMPs production. Therefore, it bridges innate and adaptive immunity and is critical for mucosal defense while limiting inflammation. (9)

T follicular helper (Tfh) cells constitute another pivotal component of the adaptive immune system. These cells are essential for germinal center formation and the production of high-affinity antibodies and memory B cells. Furthermore, they are implicated in the maintenance of gut microbiota homeostasis. Disruptions in their function can lead to changes in microbial composition. Conversely, the presence of a healthy microbiota is necessary for an adequate Tfh cell development, as shown in GF mice, where Tfh cell differentiation is impaired, but can be restored through microbial signals. (6)

Additionally, invariant natural killer T cells (iNKTs), a subset of innate-like T cells, also display a microbiota-dependent development. GF mice exhibit immature iNKTs with defective antigen responsiveness, whereas monocolonization with *Bacteroides fragilis* or exposure to its sphingolipids restores iNKT function and protects against oxazolone-induced colitis. These examples highlight the role of microbiota in immune homeostasis. (6)

BIDIRECTIONAL CROSSTALK

The gut microbiota and immune system engage in a dynamic, bidirectional interaction. (1) Microbial signals are essential for immune system maturation, as demonstrated by the underdeveloped immunity observed in germ-free mice. (7) On the contrary, immune alterations can alter microbial composition, as evidenced by gut dysbiosis in MyD88-deficient mice. MyD88 is a key adapter protein in PRR signaling, and therefore in innate immunity, implicated in microbiota homeostasis by limiting inflammatory Th17 expansion. (6) This interdependence raises the question in autoimmune conditions such as RA, whether dysbiosis may be a cause or consequence of immune dysregulation. (1)

The preservation of gut microbiota homeostasis is essential for optimal intestinal and systemic immune function. (1) Disruptions in host–microbiota interactions, whether due to antibiotic exposure, diet, or microbial dysbiosis, can impair intestinal barrier integrity, promote pathogen susceptibility, and aberrant immune responses. (5,6) Such disturbances have been implicated in the development of multiple immunologically-driven diseases, including IBD, celiac disease, RA, and neurodegenerative disorders. (5,6) Given the bidirectional host-microbiota interactions, therapeutic strategies aimed at restoring microbial balance represent a promising strategy for immune function modulation and reducing inflammation. (7)

4. DYSREGULATION OF THE MICROBIOME-IMMUNITY INTERACTION IN AUTOIMMUNE DISEASES

Immune-mediated disorders emerge in genetically predisposed individuals when mechanisms of immune tolerance fail, resulting in immune-driven tissue injury, notably autoimmunity, alloimmunity, allergy, and autoinflammation. Genetic, epigenetic, and environmental factors can provoke aberrant immune responses directly against the microbiota, causing dysbiosis. In addition, this dysregulation can compromise immune tolerance, thereby initiating or exacerbating inflammatory and autoimmune responses through several interconnected pathways: (5)

1. **T Helper Cell Skewing:** T cell differentiation towards inflammatory (Th1, Th17 cell responses) or pro-repair states is influenced by pathogenic and commensal gut microbes, respectively. Remarkably, the same commensal species can induce different immune responses during homeostasis versus inflammation. (10) An example is *Akkermansia muciniphila,* which induces murine T follicular helper cells in vivo under homeostasis and Th17 cells in the context of inflammation. (11)

2. **Bystander Activation:** Under inflammatory conditions and infections, autoreactive T and B lymphocytes can be activated in an antigen-independent manner, through the stimulation of innate immune receptors (TLRs and NOD-like receptors) by MAMPs from commensal bacteria, such as LPS or peptidoglycan. (12,13)

3. **Epitope Spreading:** Tissue disruption by infections or dysbiosis can expose hidden antigens, leading to immune responses against self-proteins. (12) Auto-antigen modifications, such as oral citrullination by *A. actinomycetemcomitans* in RA, may also promote the targeting of multiple self-epitopes. (14)

4. **Molecular Mimicry:** Structural similarities between microbial and self-antigens can lead to cross-reactivity, stimulating autoreactive T and B cells, and therefore triggering autoreactive immune responses, even affecting distant non-gut organs. (15,16)

5. **Dual T Cell Receptors (TCRs):** Some T cells express dual TCRs that recognize both microbial and self-antigens, contributing to autoimmune activation. This mechanism explains how *SFB* promote Th17 cells and autoimmunity in murine models genetically prone to arthritis. (17)

The influence of the microbiota extends beyond the gastrointestinal tract to include the oral cavity, where dysbiosis contributes to Th17-mediated periodontal inflammation and bone loss. Oral pathogens such as *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* have been implicated in systemic conditions like erosive RA, through autoantigen citrullination and teeth and joint destruction, respectively. (18) Moreover, oral commensals can migrate to the gut, potentially influencing autoimmune conditions such as ulcerative colitis, Crohn’s disease, and lupus. (16,19)

Finally, emerging evidence suggests that the impact of the microbiota is not confined to barrier surfaces. Microbial influences are increasingly recognized in non-barrier organs, including the liver, kidneys, joints, eyes, and brain. (20) Anatomically connected organs such as the pancreas and liver are particularly vulnerable to microbial translocation and can amplify systemic autoimmune diseases in non-gut organs. Thereby, conditions like type 1 diabetes and autoimmune pancreatitis may be exacerbated. (13,21,22) Although these correlations are well established, definitive causal relationships between microbiota alterations and systemic autoimmunity remain to be fully elucidated. (5)

5. GUT MICROBIOTA IMPLICATIONS IN THE ETIOPATHOGNESIS OF RHEUMATOID ARTRHITS

RA is a chronic autoimmune disease characterized by synovial inflammation and systemic immune dysregulation. (1) While its precise etiology remains incompletely understood, a multifactorial model involving genetic susceptibility and environmental factors is well established. Genetic determinants, such as HLA class II alleles encoding the shared epitope (SE), particularly HLA-DRB1∗0401 and DQ8 (3), interact with environmental influences - including diet, smoking, obesity and stress - leading to disease onset and progression. Notably, many of these factors influence the composition of the gut microbiota, suggesting a mechanistic link between microbial perturbations and immune dysregulation. (1)

Recent advances in high-throughput sequencing technologies have facilitated detailed characterization of the human microbiome, revealing consistent patterns of dysbiosis in individuals with RA, although a distinct RA-specific microbiome has not been definitively defined. (4) Accumulating evidence suggests that gut microbial imbalances represent a critical factor in RA pathogenesis. (1) In both early and established RA, patients consistently exhibit reduced microbial diversity and an enrichment of pro-inflammatory taxa, particularly *Prevotella copri*, *Collinsella aerofaciens*, and *Eggerthella lenta*. On the other hand, beneficial commensals associated with anti-inflammatory properties and the production of SCFAs, such as *Faecalibacterium prausnitzii* and *Coprococcus*, are frequently depleted. This shift toward a pro-inflammatory intestinal environment may promote immune activation and systemic inflammation. (3,23)

Experimental studies using GF murine models, which are devoid of microbiota, provide compelling support for a causal role of gut microbiota in RA.(3) GF mice do not develop arthritis unless colonized with specific microbial taxa. Colonization with *P. copri* or microbiota from RA patients in SKG and IL-1ra^{-}/$^{-}$ mice induces a Th17-dominant immune response, leading to systemic inflammation and joint pathology. (4) Similarly, reconstitution of GF K/BxN mice with *Segmented filamentous bacteria (SFB)* alone is sufficient to restore Th17 cell differentiation and precipitate autoimmune arthritis. (6,24) *SFB*, a gut-residing commensal, influences the host's immune system by promoting the differentiation and activity of Th17 cells in the GALT. Th17 cells secrete interleukin-17 (IL-17), a cytokine central to RA pathogenesis through its promotion of inflammation and germinal center formation, essential for the production of high-affinity autoantibodies. Neutralization of IL-17 in specific-pathogen-free (SPF) mice halts arthritis progression and reduces autoantibody titers, further confirming the pathogenic role of this T cell subset. These findings establish a mechanistic link between gut microbial composition, mucosal immune modulation, and systemic autoimmunity. (24)

Multiple mechanisms through which gut dysbiosis contributes to autoimmunity and the progression of RA have been suggested, including: (**Fig. 1**) (1)

- Autoantigen modification
- Immune system activation and polarization toward proinflammatory phenotypes
- Molecular mimicry between microbial and host epitopes
- Increased intestinal permeability

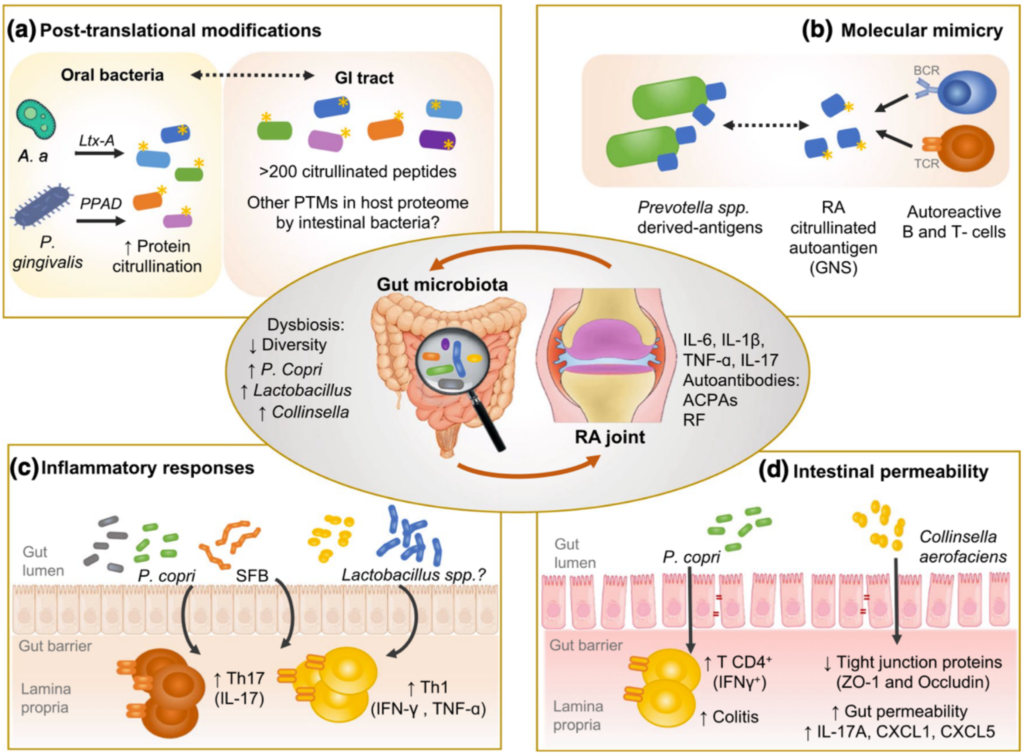

Fig. 1 – Molecular mechanisms by which altered-gut microbiota contributes to rheumatoid arthritis etiopathogenesis. (1)

Citrullination, a post-translational modification (PTM) mediated by peptidyl arginine deiminases (PADs), represents another key mechanism in RA pathogenesis. The generation of neoepitopes can trigger the production of ACPAs, hallmarks of RA. Environmental factors, including smoking and microbial infections, promote citrullination. (3) The periodontal pathogens *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* contribute via bacterial PADs and host PAD activation, respectively. Moreover, both pathogens are implicated in periodontal disease, which is associated with RA. The chronic inflammation in periodontitis may promote the systemic spread of citrullinated antigens, further enhancing autoimmunity. (25,26) Additionally, the gut microbiota may induce other PTMs, broadening the autoantibody repertoire associated with RA. This microbial citrullination may induce a cross-reactive immune response that breaches self-tolerance. (1)

Emerging evidence suggests that ACPAs originate in mucosal tissues during the preclinical phase of RA. Individuals at risk, characterized by seropositivity for ACPAs or RF without clinical symptoms, often exhibit elevated IgA-ACPAs and circulating plasmablasts. ACPAs contribute to RA pathogenesis through Fc receptor-mediated activation of innate cells, immune complex formation and induction of osteoclastogenesis, promoting joint inflammation and bone erosion. (1)

Prevotella copri has been increasingly implicated in the etiopathogenesis of RA. Studies have consistently shown a higher abundance of *P. copri* in individuals with treatment-naïve new-onset RA and in individuals at risk, suggesting a potential role in disease initiation. (6,1) The proposed mechanisms include the induction of proinflammatory immune responses and molecular mimicry. (4) In early RA patients, a *P. copri*-derived peptide bound to HLA-DR molecules has been found to induce Th1 inflammatory responses. Additionally, IgA and IgG antibodies against such peptide have been detected in both early and established RA, correlating with Th17 cytokine profiles (notably IL-17 and IL-23) and ACPAs levels. (27)

Molecular mimicry between microbial antigens and host proteins constitutes another potential mechanism underlying the development of RA. Certain *P. copri* epitopes exhibit structural similarity to N-acetylglucosamine-6-sulfatase, a citrullinated autoantigen capable of inducing T and B-cell responses in approximately half of RA patients. It is hypothesized that the recognition of *Prevotella*-derived epitopes in genetically susceptible individuals leads to T-cell activation and their subsequent migration to the joints. (28) Similarly, other RA-associated gut bacteria, including *Collinsella aerofaciens* and *Eggerthella lenta*, resemble host autoantigens, such as type II collagen, potentially triggering autoreactivity. (3)

Furthermore, gut dysbiosis plays a critical role in comprising intestinal barrier integrity, thereby contributing to the pathogenesis of RA. Increased intestinal permeability, also referred to as “leaky gut syndrome”, facilitates the translocation of microbial antigens and metabolites into the systemic circulation, promoting both local and systemic immune activation. (28) Notably, *Collinsella aerofaciens* and *Eggerthella lenta* have been shown to directly impair epithelial integrity via disruption of tight junction (TJ) proteins, such as ZO-1 and occludin, and enhancing inflammatory mediators, including IL-17A, IL-23, CXCL1, CXCL5 and NF-κB1, further amplifying systemic inflammation. (29) Low fiber diets contribute to dysbiosis by heightening the overgrowth of *C. aerofaciens*, as well as other pro-inflammatory species, while simultaneously depleting beneficial butyrate-producing bacteria like *Eubacterium*, *Fusobacterium* and *Faecalibacterium*. Since butyrate is essential for epithelial cell proliferation, mucin production and gut barrier integrity, its depletion can exacerbate intestinal permeability and promote immune dysregulation. (23)

Converging evidence from human and animal studies highlights the pivotal role of gut microbiota dysbiosis in the pathogenesis of rheumatoid arthritis. Dysbiosis acts both as a mediator and modulator by altering mucosal immunity, compromising intestinal barrier integrity, and promoting systemic Th17 responses. These changes increase intestinal permeability and drive chronic systemic inflammation, contributing to the initiation and perpetuation of autoimmunity in genetically predisposed individuals. Consequently, targeting the gut microbiota to restore immune homeostasis may represent a promising therapeutic strategy in RA management.

6. CLINICAL RELEVANCE AND THERAPEUTIC IMPLICATIONS

GUT MICROBIOTA AS A DIAGNOSTIC AND THERAPEUTIC RESPONSE BIOMARKER

The gut microbiota has gained interest as a dynamic biomarker for RA diagnosis, prognosis, and therapeutic stratification. (4) Distinct microbial signatures have been associated with disease activity, clinical parameters, serological markers, and pro-inflammatory cytokine profiles (such as TNF-α and IL-17A). For instance, *Collinsella, Alloprevotella*, *Akkermansia*, and members of the *Euryarchaeota* taxa show positive correlations with disease severity (30,31), while *Bifidobacterium* and *Haemophilus* are inversely associated (32). These findings suggest a complex interplay between microbial communities and systemic inflammation.

Methotrexate (MTX), the first-line therapy for RA, significantly modulates gut microbiota composition and function. Conflicting evidence suggests that MTX-induced changes in *Prevotella spp*. abundance may have strain- or niche-specific effects. Some studies associate higher *Prevotella* abundance with poor response (33), while others report favorable outcomes (34). Microbial metabolic activity, including tetrahydrofolate and L-methionine biosynthesis, is enriched in MTX responders, indicating that gut microbial function contributes to therapeutic efficacy. (33)

Microbiome analyses reveal that MTX responders exhibit increased microbial diversity, and shifts in specific taxa over time, such as enrichment in *Bacteroides vulgatus* and *Prevotellaceae*, and reduction in *Bifidobacteriaceae* and *Oscillospiraceae.* (33,35) Moreover, the pre-treatment ex vivo microbial metabolism of MTX may predict clinical response, highlighting the potential of microbial enzymatic profiles as predictive tools. (33)

In addition to MTX, other conventional and biological DMARDs modulate gut microbiota, yet therapeutic outcomes remain variable. Microbiota-driven modulation of host immunity offers a promising avenue for precision medicine approaches, aimed at restoring immune homeostasis with reduced adverse effects. Given current limitations, larger longitudinal and metagenomic studies are needed to validate specific microbial taxa as robust biomarkers for early diagnosis, disease monitoring, and therapeutic response in RA.

POTENTIAL OF GUT MICROBIOTA MANIPULATION FOR RA TREATMENT

The gut microbiota is highly dynamic and can be modulated through various interventions such as dietary changes, probiotics, prebiotics, and fecal microbiota transplantation (FMT). In the recent years, these microbiota-targeted therapies have gained increasing interest in their potential in mitigating autoimmune conditions like RA.

USE OF PROBIOTICS

The impact of commensal and probiotic bacteria on RA is highly strain specific. While certain *Lactobacillus* strains, such as *L. salivarius, L. acidophilus*, and *L. casei* exhibit anti-inflammatory effects in both clinical and experimental models, others such as *L. rhamnosus* lead to no improvement in active RA patients. (36) Interestingly, *L. salivarius* is enriched in patients with active RA (37), despite its capacity in animal models to reduce synovial inflammation and increase Treg populations (36,38), reflecting the complexity of host-microbe interactions in RA.

Probiotic supplementation, particularly with L*. rhamnosus GR-1, L. reuteri RC-14*, and *L. casei 01 strains*, has shown variable outcomes in RA patients. While some studies report reductions in inflammatory biomarkers and improvements in metabolic parameters, others have observed no clinical benefit. Nonetheless, experimental models suggest that specific strains can restore gut microbial homeostasis and mitigate joint damage. (39,40)

Notably, *Lactobacillus kefiri*, a probiotic strain derived from kefir, has shown immunomodulatory effects with potential relevance to RA. Its administration in mice leads to increased IgA levels, reduced pro-inflammatory mediators, dendritic cell maturation suppression and mitigates synovitis and bone erosion (41–43). However, clinical validation is still needed.

A clear example of the importance of strain specificity is seen in the opposing roles of *Prevotella* species. *P. copri* has been implicated in the onset of RA, whereas *P. histicola*, a small intestinal commensal, displays immunomodulatory properties. Experimental evidence shows that *P. histicola* can alleviate disease severity, enhance gut barrier function, and promote regulatory T cell responses through the production of beneficial metabolites. (44)

These divergent outcomes highlight the necessity for strain-level characterization of probiotics.

DIETARY INTERVENTIONS

The relationship between specific dietary components and the development of RA remains inconsistent and is better captured through dietary pattern analyses. The Mediterranean diet—characterized by high consumption of fruits, vegetables, whole grains, legumes, fish, olive oil, and low red meat intake (45) —has been associated with reduced RA risk, potentially through the immunomodulatory effects of dietary fiber and the anti-inflammatory properties of omega-3 fatty acids. (46)

In contrast, Western dietary patterns, marked by high saturated fat intake, have been linked to increased intestinal permeability and systemic inflammation. (4) Furthermore, the frequently associated obesity exacerbates this inflammatory state via the release of adipokines and pro-inflammatory cytokines, contributing to RA pathogenesis and the associated cardiovascular comorbidities. (47)

Diet provides numerous compounds with anti-inflammatory and antioxidant properties, such as curcumin, which acts via NF-κB, cyclooxygenase-2 (COX-2), and iNOS inhibition, or capsaicin, through its binding to TRPV1 receptors in T lymphocytes, regulating their activation. 1,25-dihydroxyvitamin D also modulates immune responses by reducing pro-inflammatory cytokines secretion, suppressing B cell proliferation and autoantibody formation. (1)

Additionally, dietary fiber enhances SCFAs production by gut microbiota, particularly butyrate, which supports mucosal integrity and modulates immune responses. A recent study with high-fiber supplementation in RA patients showed improved immunological and bone erosion markers. (48)

Despite the limited data on specific diets or nutrient supplementation, clinical trials suggest potential therapeutic benefits. Dietary interventions may complement RA treatment by modulating gut microbiota, improving metabolic health, and reducing cardiovascular risk.

FAECAL MICROBIOTA TRANSPLANTATION

Faecal microbiota transplantation (FMT) is a procedure that modifies gut microbiota by transferring fecal material from a healthy donor to a recipient.(1) It is highly effective against *Clostridium difficile* infections and is being explored for various chronic and extra-intestinal conditions. Although no clinical data exist for its use in RA, ongoing trials aim to evaluate its efficacy and safety. (49) Given the gut's role in immune regulation, FMT may offer therapeutic and preventive potential for inflammatory diseases.

Given their low invasiveness and limited side effects, the use of probiotics, dietary modifications and fecal microbiota transplantation represent promising alternatives and complements for therapeutic intervention. Nonetheless, further investigation is necessary to establish their clinical effectiveness and safety.

7. CONCLUSIONS AND FUTURE PROSPECTS

As highlighted in this review, the intricate relationship between the gut microbiota and the immune system plays a central role in maintaining immune homeostasis. There is a growing body of evidence supporting the idea that disruptions in the microbial ecosystem, or dysbiosis, can alter this equilibrium and promote autoimmunity. This loss of beneficial commensals and enrichment of pro-inflammatory taxa acts both as a mediator and modulator of autoimmune diseases, contributing significantly to the development of rheumatoid arthritis. Understanding the dynamic interplay between host genetics, environmental exposures, and microbial composition is critical for elucidating the pathogenesis of RA. This might render the gut microbiota a modifiable factor in disease progression and treatment, allowing the generation of personalized therapeutic strategies for the prevention and management of RA.

Experimental studies using germ-free and genetically susceptible murine models, have helped unveil certain mechanisms through which specific gut bacteria can drive autoimmune responses. *Prevotella copri, Collinsella aerofaciens*, and other pro-inflammatory species have been identified as potential drivers of immune dysregulation. These microbes promote RA through multiple mechanisms, such as molecular mimicry, increased intestinal permeability, epitope spreading and Th17 cell-mediated inflammation. On the other hand, beneficial microorganisms, such as *Faecalibacterium prausnitzii* and other butyrate-producing bacteria, promote regulatory immune pathways, the synthesis of anti-inflammatory metabolites, and the maintenance of epithelial barrier integrity.

Recent metagenomic studies have confirmed consistent gut microbiota alterations both in early and established stages of RA. However, further studies are needed to validate their utility as biomarkers and therapeutic targets. Furthermore, the identification of microbial signatures preceding seroconversion and symptom onset could enable early risk stratification and preventive interventions. Although emerging evidence is advancing our understanding of how gut microbes influence immune regulation in RA, key areas like inter-individual variability, host-microbiome genetic interactions, and the role of other commensal microorganisms, such as viruses, remain largely unexplored.

From a clinical perspective, gut microbiota modulation through probiotic supplementation, dietary modulation and fecal microbiota transplantation, holds the potential to improve RA outcomes by restoring microbial balance and reducing inflammation. These personalized microbiome-targeted interventions are promising, though challenges remain in defining a ''healthy'' microbiome and the clinical translation of these findings. Large-scale, rigorous human trials will be required to determine their efficacy, safety, and long-term outcomes. Ultimately, a deeper understanding of the gut-immune axis will not only improve RA management but also shed light on other immune-mediated and inflammatory diseases.

8. ACKNOWLEDGEMENTS

Al llegar al final de esta etapa quisiera agradecer sinceramente a todos aquellos que me han acompañado en el camino.

Gracias a mis tutores, por su paciencia y por ayudarme a dar forma a este trabajo con criterio y claridad.

A mi familia, María y Mamá, por vuestro apoyo incondicional y constante. En especial a mi padre, por demostrarnos que la vocación y el amor por esta profesión se construyen cada día. Tu ejemplo siempre guiará nuestro camino.

A mis amigos, porque su compañía ha hecho este recorrido más llevadero, lleno de risas y grandes recuerdos.

Y por último a todos aquellos médicos que durante mis prácticas clínicas se han esmerado en mi formación, gracias por compartir vuestro tiempo, experiencia y forma de entender esta profesión.

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