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Review

The Role of the Microbiome in the Development of an Autoimmune Reaction in Rheumatoid Arthritis

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Abstract

Patients with rheumatoid arthritis (RA), a chronic inflammatory illness, have joint inflammation, increasing tissue damage, and severe disability, all of which negatively impact quality of life. While the precise mechanisms behind RA remain unknown, there is growing evidence that both the onset and development of the illness are closely linked to an imbalance in the intestinal microbiota. Variations in the microbial content of RA patients and healthy people suggest that the gut microbiota plays a part in regulating immunological responses and fostering inflammation. Thus, therapies aimed at restoring the microbiome to its original state have demonstrated encouraging results in terms of increasing therapeutic efficacy, improving patient outcomes, and delaying the progression of disease. However, more research is needed to clarify the intricate interactions between the intestinal microbiota and autoimmunity mechanisms in RA.

Keywords: autoimmune disease; rheumatoid arthritis; gut microbiota; dysbiosis; microbiome

1. Introduction

Progressive inflammation of the synovial joints is a hallmark of rheumatoid arthritis (RA). This inflammatory disease can cause significant disability and impair various organ systems, including the cardiovascular, respiratory, and neurological systems [1]. About 1% of adults globally are diagnosed with RA, the majority of whom are women. The etiology of RA is complicated and unclear, making RA more difficult to diagnose and treat. The autoimmune response is thought to be caused by a combination of genetic and environmental factors [2]. Indeed, genetic predisposition plays an important role, as individuals possessing certain genes have been shown to exhibit a greatly increased risk of RA onset; meanwhile, RA is more common in first-degree relatives of persons with RA than in the general population [3]. Notably, smoking is an extremely significant environmental risk contributor to RA. Moreover, women have a 3-fold higher risk of developing RA than men, which indicates that female hormones may also play a role in the onset of the disease [4].

Current treatments for RA include nonsteroidal anti-inflammatory drugs (NSAIDs), immunosuppressants (glucocorticoids), and disease-modifying antirheumatic drugs (DMARDs). However, the ineffectiveness and severe adverse reactions of current RA therapies have necessitated an attempt at developing novel, safe, and cost-effective strategies. There is a need to consider new mediators and participants in the pathogenesis of RA, which may serve as an impetus for the creation of improved therapeutic agents. In this sense, the microbiota—the group of bacteria that live in the intestine—is an appropriate subject for research since 97% of the human microbiota is found in the gastrointestinal system, with the large intestine serving as the primary habitat of the microbiota [5]. It is not unexpected that intestinal microbiota dysbiosis has been linked to the emergence of numerous systemic autoimmune diseases, including RA. This is because the ability of the gut microbiota has been shown to regulate a broad spectrum of physiological processes, aiding in maintaining immunological barriers. It should be noted that any disruption in the composition of the gut microbiota can lead to disease [6]. Therefore, this review investigates the role of the microbiome in the onset of an immunological reaction in RA.

2. Cells Involved in the Pathogenesis of RA

RA is an inflammatory disease caused by multicellular communication and cytokine interactions, resulting in various pathological responses. The induction and progression of RA require the involvement of osteoclasts, synovial fibroblasts, T cells, B cells, and natural killer (NK) cells, among other cells. To release inflammatory cytokines, such as IL-1, IL-6, IL-17, tumor necrosis factor (TNF)-α, and others, these lymphocytes can be stimulated by nuclear factor kappa B (NF-κB), mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase-protein kinase B (PI3K–Akt), and Janus kinase-signal transducer and activator of transcription (JAK–STAT) signaling routes [7].

2.1 Synovial Fibroblasts

Synovial fibroblasts play an active role in the pathogenesis of RA by undergoing various biological processes such as signal transduction, gene regulation, and metabolism. Healthy synovial tissue is usually free of inflammatory cells; however, in the diseased state, the influx of inflammatory cells and the subsequent release of inflammatory factors lead to the pathological activation of synovial fibroblasts. Stimulated by TNF-α and IL-1, synovial fibroblasts secrete Receptor Activator of Nuclear factor Kappa-B Ligand (RANKL) and induce macrophages to transform into osteoclasts [8]; meanwhile, fibroblasts produce and release matrix metalloproteinases (MMPs). Together with these signals, Th1 cell-derived macrophage microvesicles (MMVs) also trigger the PI3K/Akt signaling pathway, which dramatically increases the levels of TNF, IL-1β, and MMPs. MMP production in synovial fibroblasts is induced by NF-κB signaling [9]. MMP-3 breaks down a variety of extracellular matrices, whereas MMP-1 selectively breaks down fibrous collagen. Vascular endothelial growth factor (VEGF) directly impacts the vascular endothelium in synovial tissues, promotes the growth of endothelial cells, raises microvascular permeability, causes vascular membrane creation, and damages cellular material in the inflammatory joint. Furthermore, following NF-κB activation, transforming growth factor β (TGF-β) in joints causes synovial fibroblasts to produce VEGF and IL-6, creating a feedback mechanism in the synovial tissue that persistently encourages the creation of pannus [10].

2.2 Osteoclasts and Osteoblasts

In RA, another cellular contribution comes from the imbalance between osteoclasts and osteoblasts, which forms the main driver of bone destruction. Bone remodeling depends on the balance between bone formation and destruction, which maintains bone homeostasis [11]. Meanwhile, osteoclasts can influence the mechanism involved in bone resorption [11]. Moreover, bone-resorbing osteoclasts are frequently formed in the synovium of arthritic joints when RANKL activates synovial fibroblasts and B lymphocytes. Following the activation of NF-κB and MAPK from their monocyte progenitors, IL-6 and IL-17 drive osteoclast development by inducing RANKL expression. TNF-α can stimulate osteoclast development and maturation and enhance the quantity of osteoclast precursor cells in bone marrow [12]. Moreover, mature osteoclasts attach to bone tissue by identifying vitronectin, hydroxyapatite, and its receptor. To aid in the decomposition of collagen and bone, osteoclasts also lower the pH of the interaction region and release a variety of matrix-degrading enzymes, including MMPs and tartrate-resistant acid phosphatases. Meanwhile, the action of osteoclasts is controlled by endocytosing products of decomposition, which promotes ongoing bone deterioration and facilitates bone mineralization and matrix deposition [13].

Mesenchymal stem cells in bone marrow undergo differentiation into osteoblast precursors when cytokines are present, such as TGF-β and insulin-like growth factor 1 (IGF-1). According to studies, osteoblasts from RA patients exhibited higher levels of Wnt/β-catenin signaling pathway stimulation, which reduced bone formation and promoted osteoblast death, primarily caused by TNF-α and IL-1 [14].

2.3 T Cells

Autoreactive T lymphocytes form the third reason for cartilage damage and inflammation in joints. The development and course of RA are significantly influenced by several $CD4^+$ T cell subtypes, particularly Th1/Th2 and Th17/regulatory T cell (Treg) imbalance. Th1 and Th17 cells secrete large concentrations of inflammatory cytokines such as interferon-gamma (IFN-γ) and IL-17A, which can lead to monocyte activation, osteoclast formation, synovial cell proliferation, and vessel formation. It has been shown that IFN-γ secreted by Th1 can block Th17 development. Thus, T cell plasticity may lead to a shift between different Th cell subsets in autoinflammatory diseases. Indeed, Th17 cells represent a “unique” subset of cells that can divide into various kinds of effectors [15]. In contrast to traditional Th17 or Th1 cells, Th1 cells produced from Th17 cells are more pathologically dangerous, as evidenced by a higher proliferative potential and proinflammatory cytokine output [16]. While Th1 cells are primarily responsible for increasing or extending tissue inflammation at a later stage, inappropriately stimulated Th17 cells are rapidly created and contribute to the early stages of inflammation. Therefore, Th1 cells might have a connecting role in the etiology of RA. Alternatively, Tregs and Th2 cells inhibit the immune system throughout the course of the illness [16].

2.4 B Cells

In addition to T cells, autoreactive B cells are also found in the joints of patients with RA. Recent studies have identified an emerging subset of B cells, known as double negative 2 (DN2) B cells, which are induced by naïve B cells and are positively associated with disease activity. DN2 B cell-derived TNF-α accelerates IFN-β secretion and RASF activation via the TNF-α-mediated Extracellular signal-regulated kinases ½ (ERK1/2) and JAK–STAT1 pathways [17]. DN2 B cells are the major precursors of pathogenic antibody-secreting cells (ASCs) in the RA synovium. Moreover, the antigen of DN2 B cells is presented to induce Th17 polarization and bone destruction [18]. Meanwhile, ASCs secrete autodestructive factors such as rheumatoid factor (RF) and anti-citrullinated protein/peptide antibodies (ACPAs), which are involved in the pathogenesis of RA. These antibodies can destroy synovial tissue, synovitis, and bone by forming immune complexes, stimulating the secretion of proinflammatory cytokines, and participating in the complement cascade or directly binding to osteoclasts [19].

2.5 NK Cells

NK cells, as part of the innate immune system, can interact directly or indirectly with other immune cells and participate in the progression of RA. High numbers of $CD38^+$ NK cells and low numbers of $CD38^+$ NK-like T cells from the synovial fluid of RA patients suppress the differentiation of Treg cells. Additionally, when IL-2 and IL-15 are activated, NK cells located in the synovial fluid in patients with erosive deformable RA release larger levels of TNF-α and IFN-γ than those in non-deformable RA. Consequently, the released TNF-α and IFN-γ further encourage dendritic cell (DC) maturation to improve the proliferation of T cells and any subsequent differentiation [20].

2.6 Microbiome-Mediated Regulation of Immune Cells

One piece of evidence supporting the involvement of the microbiome in the pathogenesis of RA is the effect of different microbial communities on cells involved in this process. Thus, the microbiome can influence inflammatory reactions and joint restoration. Bacterial lipopolysaccharides (LPS) from *E. coli* and peptidoglycans from *Lactobacillus casei* activate toll-like receptors (TLRs) 2/4 on synovial fibroblasts, inducing IL-6, TNF-α, and MMP production via MyD88-dependent signaling [21]. Scher *et al.* [22] demonstrated that metabolites of *Prevotella copri* (acetate and succinate) directly stimulate synovial fibroblasts to produce VEGF. Short-chain fatty acids (SCFAs), particularly butyrate, which is produced by some bacterial strains, inhibit osteoclastogenesis by activating G-protein coupled receptor 43 (GPR43) receptors and suppressing RANKL expression [23]. Lucas *et al.* [24] showed that butyrate promoted a 60% reduction in NF-κB activity in osteoclasts. Indole-3-propionic acid, produced by Clostridium sporogenes, promotes regulatory Treg differentiation by activating the aryl hydrocarbon receptor (AhR) [25].

3. The Role of the Microbiome in the Pathophysiology of RA

The function of the gut microbiota in the pathophysiology of RA has been investigated and demonstrated by an increasing number of research and treatment trials in recent years [26–28]. Therefore, the gut microbiota is now thought to be a component of the environmental elements that significantly influences the onset and course of RA [29].

3.1 Molecular Mimicry

The immunopathogenesis of RA is a complex molecular process. In genetically predisposed, disease-susceptible individuals, environmental factors trigger the loss of immunological tolerance to self-antigens, the production of autoantibodies, and the activation of autoreactive T cells. Citrullinated epitopes in various autoantigens, particularly antigens originating from host microorganisms, are recognized by RA-specific ACPAs. Consequently, immunological intolerance may result from dysbiosis [30]. The intestinal microbiota influences the host immune system and metabolic balance, while the commensal microbiome modulates the responses of T cell subsets to infections. Pathogen-associated molecular patterns (PAMPs) are recognized by a complex of pattern recognition receptors (PRRs), such as nucleotide oligomerization domain-like receptors (NLRs) and TLRs, which enable the innate immune response to defend the host against invasion. Commensal bacteria have different abilities to interact with PRRs, resulting in proinflammatory or anti-inflammatory responses. Furthermore, Gram-positive and Gram-negative bacteria induce different signaling pathways in both innate and adaptive immune cascades [29]. PAMPs from dysbiotic bacteria activate dendritic cells through PRRs. LPS from Gram-negative bacteria (elevated in RA microbiomes) triggers TLR4 signaling, leading to NF-κB activation and proinflammatory cytokine production [31].

Molecular mimicry has been suggested as a possible pathogenetic mechanism in many autoimmune conditions, including RA [32]. Gut microbial proteins can trigger a T cell-mediated autoimmune reaction by imitating autoantigens, leading to the production of autoantibodies and circulating cytokines. Two peptides that indicate prevalent gut bacterial species in RA patients were examined in one study [33]. Filamin A (FLNA) and N-acetyl-glucosamine-6-sulfatase (GNS), both of which were substantially produced in cartilage fluid and synovial cells. When contrasted with healthy controls, FLNA and GNS were found to be autoantigens that can cause T cell autoreactivity in over 50% of RA patients. FLNA possesses homologous epitopes with antigens of *Prevotella sp.* and *Butyricimonas sp.*, another gut commensal, whereas the GNS protein shares sequence similarities with epitopes from antigens of *Prevotella sp.* and *Parabacteroides sp.* Therefore, one way *Prevotella* can trigger RA is through mimicking the molecular structure of GNS and FLNA [33].

3.2 Microbial Metabolites

Gut flora-derived metabolites represent another potential mechanism that putatively links the gut microbiota to the pathogenesis of RA. These small molecules are generated when bacteria degrade food items, when the gut flora alters metabolites from the host, or when gut bacteria manufacture their own byproducts.

Numerous studies have examined the immunoregulatory function of SCFAs. Moreover, an anti-inflammatory action of SCFAs was proposed following the discovery of reduced SCFA levels in RA patients and animal studies [34]. These studies examined the possible immune-regulating function of pentanoate [34]. The anti-inflammatory capabilities of pentanoate are demonstrated by raised IL-10 expression and lowered IL-17 expression in $CD4^+$ effector T lymphocytes. The fermentation of certain food ingredients affects the amount of valeric acid present [34]. Additionally, *Prevotella* has been shown to primarily produce acetate with insignificant amounts of pentanoate, which is consistent with the potential involvement of *Pre-*

votella in autoimmune conditions [35]. Propionic acid, an additional SCFA, can inhibit Th2 effector activity by activating the GPR41 receptor that is found in dendritic cells. Moreover, propionic acid exhibits immunoregulatory actions by encouraging Treg development and increasing IL-10 levels. Butyric acid modulates Treg polarization and reduces the generation of proinflammatory cytokines. Butyrate has been proposed to potentially prevent the spread of RA by inhibiting the generation of autoantibodies [36]. Some beneficial bacteria, such as Clostridium clusters IV and XIVa, promote Treg expansion through SCFA production, particularly butyrate, which enhances Foxp3 expression via histone deacetylase inhibition [37]. In RA patients, a 3-fold reduction in butyrate-producing bacteria was observed alongside a corresponding 60% decrease in fecal butyrate levels, correlating with reduced Treg frequencies (8.2% vs 12.1% in healthy controls; $p < 0.001$) [38].

In preclinical RA, amino acids have been identified as molecules generated from the gut flora. Branched-chain amino acids can facilitate the control of RA as sources for SCFA production. Indeed, researchers have evaluated the connection between RA, gut metabolites, and gut microbiota [36]. The feces of two equal groups, 26 patients and healthy people, were examined. While Fusicatenibacter, Megamonas, and Enterococcus were more common in healthy controls, the study found that RA patients had higher abundances of Klebsiella, Escherichia, and Flavobacterium [39]. Metabolomic studies have revealed that patients with RA had decreased levels of fecal intermediates such as kynurenic acid, traumatic acid, N-alpha-acetyl-L-lysine, 5-hydroxyindole-3-acetic acid, and 3-hydroxyanthranilic acid [36]. Type 3 innate lymphoid cells (ILC3s) are particularly responsive to microbial signals, producing IL-17 and IL-22 in response to bacterial metabolites such as tryptophan derivatives [40]. Sonnenberg *et al*. [41] demonstrated that depleting the microbiota reduces the number of ILC3s in gut-associated lymphoid tissues by 70%.

3.3 Intestinal Permeability and Cell Signaling

Proposed causes of systemic immune responses in RA patients include weakened barrier function and increased intestinal permeability [42]. Dysbiosis compromises intestinal barrier function through multiple mechanisms. Pathogenic bacteria produce enzymes that degrade tight junction proteins (claudin-1, occludin, ZO-1), while beneficial bacteria normally strengthen barrier function through SCFA-mediated enhancement of mucin production [43]. Zonulin, a biomarker of intestinal permeability, is elevated 2.5-fold in RA patients compared to controls [44]. Thus, increased permeability allows bacterial antigens and metabolites to translocate systemically, triggering immune responses in distant tissues, including synovial joints, through molecular mimicry mechanisms [45].

Collinsella aerofaciens is another species that has also been linked to the onset of RA. The potential for the downregulation of tight junction protein expression by *Collinsella spp*. has been demonstrated to increase intestinal permeability in mouse models of RA. Notably, the integrity of the epithelial barrier is known to become compromised following *Collinsella aerofaciens* growth. External antigens pass through the intestinal wall, enter host tissues, and enter the bloodstream, causing immunological reactions in the joints. Additionally, RA patients have exhibited elevated levels of zonulin, a prehaptoglobin that induces intestinal permeability and leaky gut syndrome. Similar findings have also been observed in animals with collagen-induced arthritis, which is a model of RA. Moreover, enhanced intestinal permeability and higher zonulin contents in this controlled environment preceded the onset of arthritis [46]. Treatment with a zonulin antagonist improved disease symptoms, possibly suggesting that leaky gut syndrome may be an initiating event in the RA cascade [43]. Impaired intestinal mucosal barrier function has also been implicated in the pathogenesis of juvenile idiopathic arthritis (JIA) and ankylosing spondylitis (AS).

Indeed, studies in murine models of arthritis demonstrated a direct effect of *Collinsella aerofaciens* on intestinal barrier integrity. Chen *et al*. [47] showed that the monocolonization of mice with *C. aerofaciens* led to a significant reduction in the expression of tight junction proteins (claudin-1, occludin, ZO-1) in the small intestine compared to control mice. Moreover, Alpizar-Rodriguez *et al*. [48] demonstrated in a dextran sulfate sodium-induced colitis model that administration of *C. aerofaciens* exacerbated intestinal barrier damage through activation of the NF-κB signaling pathway. Additional mechanistic studies by Chen *et al*. [47] revealed that *C. aerofaciens* produces specific enzymes (β-glucosidases and α-rhamnosidases) that are capable of degrading the intestinal mucin layer, thereby disrupting the first line of epithelial barrier defense. Based on these results, increased intestinal permeability by the intestinal microbiota is hypothesized to represent another possible way that dysbiosis contributes to the onset of RA [49].

The mechanisms of microbiome influence on the development of RA are summarized in Table 1.

4. Microbiome-Targeted Therapeutic Strategies for RA

4.1 Using Probiotics and Prebiotics to Treat RA

Probiotics assist the host in maintaining a healthy microbiome and help restore the balance of intestinal microflora after dysbiosis. Furthermore, probiotics can create bioactive compounds that affect the immune system of the host and cause desired outcomes [50]. In addition, probiotics have been reported to have a beneficial effect on intestinal permeability. Several studies have shown the potential beneficial effects of probiotics in preventing and treating RA. The most studied are the effects of Lactobacillus and Bifidobacterium, which are known to produce anti-inflammatory compounds such as SCFAs [51]. *Lactobacillus casei* has been demonstrated to raise anti-inflammatory

Table 1. The mechanisms through which the microbiome influences the development of RA.

Mechanism	Description	Key microbial species	Molecular/functional insights
Molecular mimicry	Gut microbial proteins share sequence homology with host autoantigens, triggering autoreactive T cell responses and ACPA production.	*Prevotella sp.*, *Parabacteroides sp.*, *Butyricimonas sp.*	GNS and FLNA mimic human proteins; both are overexpressed in the synovium of RA patients and can elicit T cell activation.
Microbial metabolites	Bacterial metabolites modulate immune responses, especially SCFAs that regulate cytokine balance and Treg/Th17 polarization.	*Prevotella sp.*, *Klebsiella*, *Escherichia*, *Flavobacterium* (in RA); *Megamonas*, *Fusicatenibacter*, *Enterococcus* (in controls)	Decreased butyrate, pentanoate, and other SCFAs reduce anti-inflammatory signaling. Increased pathogenic taxa correlate with altered fecal metabolites.
Increased intestinal permeability	Dysbiosis leads to the breakdown of the gut barrier, allowing translocation of microbial antigens and triggering systemic autoimmunity.	*Collinsella aerofaciens*	Downregulation of tight junction proteins and elevated zonulin levels lead to leaky gut, preceding arthritis onset.
Cell signaling via PRRs	Microbial PAMPs interact with host pattern recognition receptors (e.g., TLRs, NLRs), modulating inflammation.	Gram-positive and Gram-negative commensals	Differential PRR activation promotes pro- or anti-inflammatory cytokine production, contributing to immune dysregulation.

ACPAs, anti-citrullinated protein/peptide antibodies; GNS, N-acetyl-glucosamine-6-sulfatase; FLNA, filamin A; SCFAs, short-chain fatty acids; Treg, regulatory T cell; RA, rheumatoid arthritis; PRRs, pattern recognition receptors; PAMPs, pathogen-associated molecular patterns; TLRs, toll-like receptors; NLRs, nucleotide oligomerization domain-like receptors.

IL-10 and decrease proinflammatory cytokines TNF-α and IL-12 in RA patients. Additionally, the cohort of individuals using this probiotic showed a reduction in RA symptoms. The treatment of five strains of *Bifidobacterium adolescentis* was reported to correct dysbiosis in the gut microbiota, restore a proper balance between pro- and anti-inflammatory signals, and ameliorate the clinical manifestations. In a mouse model, additional research showed that *B. longum* RAPO treatment alleviated RA symptoms, such as decreased RA prevalence, arthritis index, inflammatory conditions, and bone and cartilage degradation. *B. longum* RAPO may also help reduce RA by preventing the release of IL-17 and other inflammatory cytokines, which suggests that this bacterium could potentially reduce RA [52]. Alipour *et al.* [53] in a randomized controlled trial (RCT) of 60 RA patients showed that introducing *L. casei* for 8 weeks significantly reduced the levels of DAS28 (3.8 ± 0.6 vs. 4.7 ± 0.5; $p < 0.001$) and TNF-α. Ouwehand *et al.* [54] conducted a study of 200 patients and demonstrated that *L. rhamnosus* GG reduced morning stiffness by 40%. Moreover, Mohammed *et al.* [55] performed a meta-analysis of five RCTs (n = 387) and found that probiotics promoted a moderate effect in reducing inflammatory markers (standardized mean difference = –0.4, 95% confidence interval (CI): –0.7, –0.1).

4.2 Fecal Microbiota Transplant

Fecal microbiota transplant (FMT) is one of the most efficient methods for rapidly reversing gut microbiota dysbiosis. FMT involves injecting a fecal culture from a healthy donor into the digestive system of patients to restore the equilibrium of the intestinal microbiota [56]. Nonetheless, the therapeutic impact of the FMT may be attributed to the underlying possible causes. However, following the use of a donor fecal suspension, the variation in intestinal microbiota and composition is restored, intestinal barrier function is improved, mucosal inflammation is decreased, and intestinal microbiota-derived substances, such as SCFAs, are increased, thereby improving regional and systemic immunological homeostasis [57]. FMT was included in the accepted treatment guidelines for *Clostridium difficile* infections after the efficacy of the bacterium was initially investigated for treating enteric diseases. FMT has previously undergone limited success in clinical studies in patients with ulcerative colitis and type 1 diabetes, among other autoimmune conditions. The effectiveness of FMT has also been shown in an animal model of Systemic Lupus Erythematosus (SLE) [58]. After testing a patient with complicated SLE who had been contaminated with the parasite *Blastocystis hominis*, the procedure led to a substantial improvement in the general state of the patient and a decrease in all manifestations, including glomerulonephritis,

nutritional deficiency, indigestion, and serious loss of appetite. The safety and effectiveness of the FMT technique were successfully verified in a pilot clinical trial that included an additional 20 patients with acute SLE [59]. Zeng *et al*. [60] reported the first RCT of FMT in RA (n = 30): 73% of the patients experienced a reduction in DAS28 levels of $>$1.2 after 12 weeks without serious adverse events.

4.3 Diet and Lifestyle

Strong evidence exists that a healthy diet and lifestyle can restore gut microbiota dysbiosis, thereby lowering inflammation and easing the manifestations of RA. Meanwhile, restoring immunological tolerance and preserving the integrity of the intestinal barrier are two potential methods to achieve the therapeutic impact. The Mediterranean diet, characterized by a high intake of dietary fiber from fruits, vegetables, and legumes, supports this healing impact. After 28 days of a diet modification, a focused study found that high-fiber food additives improved the Th1/Th17 ratio, decreased bone erosion indicators, and enhanced the amount of systemic Tregs in RA patients [38]. Additionally, dietary fiber enhances intestinal barrier integrity by promoting the growth of beneficial bacteria that increase SCFA synthesis. Other essential components of the Mediterranean diet that also boost the production of tight junction proteins are vitamin D and polyphenols. Although the exact process has yet to be identified, the amino acids tryptophan and glutamine have been shown to decrease inflammation in the gut and affect the transfer of bacteria [61]. According to certain reports, zinc also plays a significant role in avoiding intestinal barrier disruption. Moreover, vitamin C has shown therapeutic promise as a regulator of the gut flora [62]. In this study, mice received 100 mg/kg of vitamin C every day for six weeks. Notably, vitamin C supplementation successfully corrected the imbalance in the gut microbiota, lowering the amount of proinflammatory mediators, such as TNF-α and IL-6, which suppress inflammation and effectively reduce the manifestations of arthritis [62]. Vadell *et al*. [63] conducted a 6-month RCT (n = 51) that demonstrated a Mediterranean diet rich in fiber reduced C-reactive protein levels by 45% and improved microbial diversity.

4.4 Safety Assessment of Microbiome-Targeted Therapies

Potential safety concerns may limit the availability of the above-described therapies for treating RA. The following adverse effects (AEs) reported for probiotics should be highlighted: sepsis in immunocompromised patients, with eight cases of *Lactobacillus bacteremia* per 10,000 treatment courses [64]; D-lactic acidosis associated with high doses of *L. acidophilus* [65]. Potential difficulties may also be connected with the interactions of probiotics with immunosuppressive therapy (methotrexate, biologics). The risks associated with FMT can include the transmission of pathogenic microorganisms, such as Extended-Spectrum Beta-Lactamase (ESBL)-producing *E. coli* [66] and autoimmune reactions, with new allergic reactions occurring in 2–5% of patients [67]. Dietary interventions have the potential to increase the risk of nutrient deficiencies due to strict elimination diets and social and psychological limitations. Thus, safety recommendations may include donor screening for FMT in accordance with international protocols, monitoring immune status during probiotic therapy, and gradual dietary adjustments under dietitian supervision [68].

5. The Importance of Microbiome Alterations to Diagnose a RA-Associated Microbiome

5.1 Prevotella Copri

Early diagnosis is essential to treat RA quickly and prevent further joint deterioration. The literature contains a large number of contradictory findings that relate RA to gut dysbiotic conditions. The genus *Prevotella*, and specifically *P. copri*, is more prevalent among individuals with early RA than in healthy controls, according to a general finding across investigations [69,70]. In established, treated patients, no excess of *P. copri* was found [67]. Additionally, large-scale metagenomic sequencing has shown that the gut microbiome of RA patients contains higher levels of other *Prevotella* species besides *P. copri*. Interestingly, *P. copri* is thought to have contributed to the pathophysiology of RA by activating inflammatory reactions and molecular mimicry, which connect host and microbial epitopes [71]. *P. copri* metabolites activate the NLRP3 inflammasome in intestinal macrophages, leading to IL-1β and IL-18 release [72]. These cytokines, along with bacterial-induced TNF-α, create a proinflammatory milieu that promotes Th17 differentiation and suppresses Treg function. Honda and Littman [73] showed that specific bacterial strains can induce IL-6 production in gut epithelial cells through MyD88-dependent pathways. Segmented filamentous bacteria (SFB) and *P. copri* have both been shown to induce Th17 differentiation by stimulating dendritic cells to produce IL-6, IL-23, and TGF-β [74].

Several additional studies have demonstrated the influence of *Prevotella copri* on the development of RA. Scher *et al*. [22] showed that *P. copri* abundance is significantly elevated in new-onset untreated RA patients compared to healthy controls (relative abundance: 0.237 vs. 0.072; $p < 0.001$). Pianta *et al*. [30] further exhibited that *P. copri*-derived antigens trigger cross-reactive T cell responses against human proteins, particularly FLNA and GNS. Metagenomic analysis by Kishikawa *et al*. [69] identified specific *P. copri* strains (clade A) that correlate with disease activity scores (DAS28) in Japanese RA patients.

5.2 Collinsella

Human RA has also been linked to several other bacterial taxa, such as Actinomyces, Collinsella, Lactobacillus, and Eggerthella [75]. This demonstrates how the pathophysiology of arthritis with inflammation may involve intri-

cate interactions among several species, as well as genetic and other environmental influences. In mice models of RA, the species *Collinsella aerofaciens*, in particular, has been shown to increase intestinal permeability by decreasing the levels of tight junction proteins. *Collinsella aerofaciens* increased the incidence and severity of arthritis, as well as several inflammatory chemokines, including NF-κB1, C-X-C motif chemokine ligand 1 (CXCL1), CXCL5, and IL-17A. Chen *et al*. [47] found *C. aerofaciens* to be enriched in the gut microbiota of RA patients (7.5-fold increase; $p < 0.01$). Mechanistically, Chen J *et al*. [47] demonstrated that *C. aerofaciens* produces enzymes that degrade mucin glycoproteins, compromising intestinal barrier integrity. In collagen-induced arthritis models, *C. aerofaciens* colonization increased arthritis severity by 40% compared to controls [76]. These findings suggest that gut dysbiosis may cause RA by increasing intestinal permeability [71].

5.3 Lactobacilli

It has been observed that patients with both early and chronic RA exhibit an overrepresentation of Lactobacillus species. Research on mice supports the association between Lactobacillus and RA. In IL-1ra -/- mice, *L. bifidus* monocolonization was sufficient to cause arthritis, and Collagen-Induced Arthritis (CIA) mice showed an overrepresentation of Lactobacillus species before arthritis developed [77]. Lactobacillus species, including *Prevotella*, have been proposed to have a role in RA pathogenesis by activating Th1 cell reactions and increasing Th17 cells and Th17-related cytokines. Nonetheless, numerous human and mouse studies have demonstrated that oral treatment with Lactobacillus species improved arthritis and lowered inflammation [48].

The contradictory effects of the Lactobacillus species in RA can be explained by several factors, including strain specificity, host immune background, and microbial context. For example, *L. casei* Shirota induces high levels of IL-10 and exerts anti-inflammatory effects [78], whereas *L. bifidus* promotes Th17 responses through IL-6 production [77]. Legrand *et al*. [79] showed that different *L. rhamnosus* strains exert opposite effects on TNF-α production. In patients carrying HLA-DRB1*04 alleles, Lactobacillus may trigger molecular mimicry through the presentation of peptides homologous to human type II collagen [80], whereas in patients without these alleles, the same bacteria exert protective effects. Lactobacillus enhances Th17 responses in the presence of *Prevotella copri*, but promotes Treg differentiation when combined with *Bifidobacterium* [81].

5.4 Microbiome as a Diagnostic and Prognostic Biomarker

Numerous studies have demonstrated associations among certain bacteria and RA symptoms, suggesting that the microbiome could be a possible indicator of diagnosis [71]. Indeed, a positive correlation has been observed between alloprevotella and RF, Erythrocyte Sedimentation Rate (ESR), and C-reactive protein (CRP) [49]. Meanwhile, in another studies , the genera *Collinsella* and *Akkermansia* showed a positive correlation with disease activity [82,83]. In contrast, the markers of inflammation TNF-α and IL-17A showed a negative correlation with *Bifidobacterium* and a positive correlation with the phyla *Gammaproteobacteria*, *Enterobacteriaceae*, and *Klebsiella*. Additionally, there was a significant correlation between disease activity and the phylum *Euryarchaeota*. Multivariate analysis revealed that the phylum *Euryarchaeota* is an independent risk factor [84]. Serum antibody levels were found to be negatively connected with *Haemophilus* species. Current research on this topic is limited; however, larger longitudinal and metagenomic association studies may play a central role in identifying microbial biomarkers that will enable early diagnosis and therapeutic interventions [85].

6. Discussion

Even though RA treatment has advanced significantly in the past few years, some patients still do not respond to professionally prescribed medications, putting them at risk of life-threatening consequences or even mortality. In addition, some treatments cause side effects and are very expensive. Thus, there is a need to develop alternative treatments that are inexpensive, safe, and effective. Numerous data indicate that the gut microbiota influences virtually all biological processes in the host, and microbiota dysbiosis is associated with impaired immune tolerance and the development of RA. The relationship between microbiota imbalance and RA disease progression can be explained by several processes, including bacterial translocation due to increased intestinal permeability, molecular mimicry, and the generation of bacterial compounds that may cause citrullination or have immunomodulatory effects by inducing inflammation. However, gut dysbiosis-related clinical disorders might be curable. Probiotics and prebiotics, a specific diet, and FMT are the major strategies suggested for correcting intestinal dysbacteriosis in RA patients [86].

Addressing the gut microbiota holds significant promise for successful RA treatment, particularly because the microbiota involves mobilizing the inherent resources of the body rather than relying on costly medications or equipment. In both human and animal models of arthritis, probiotics and prebiotics have shown promise in modifying intestinal microbial composition, lowering inflammation, and easing signs and symptoms. Although many obstacles remain in probiotic studies, such as determining targets, routes, and processes, the numerous advantages probiotics provide to the organism keep researchers motivated to conduct further studies. One of the most significant environmental elements that triggers RA is diet, as intestinal homeostasis can be enhanced by influencing the gut flora. FMT performed in one patient showed preliminary efficacy and safety, but additional data from clinical trials with a larger number of patients are needed [87].

7. Conclusions

This review highlights the potentially important role of gut microbiota in the development and progression of RA. The accumulated evidence supports that dysbiosis, including overrepresentation of *Prevotella copri*, *Collinsella aerofaciens*, and certain Lactobacillus species, contributes to immune dysregulation through multiple mechanisms such as molecular mimicry, increased intestinal permeability, and altered microbial metabolite profiles. These microbiota-driven processes lead to enhanced production of proinflammatory cytokines, expansion of autoreactive T and B cells, and the breakdown of immune tolerance. Importantly, beneficial microbial metabolites, such as SCFAs, and interventions including probiotics, prebiotics, and FMT show promise in restoring microbial balance and mitigating inflammation. Dietary factors that support SCFA-producing bacteria and barrier integrity further underline the potential of non-pharmacological strategies in RA management. Together, these findings point to the microbiome not only as a contributing factor in RA pathogenesis but also as a valuable target for future diagnostics and therapy. Understanding how specific microbial shifts correlate with immune responses offers a promising direction for developing personalized microbiota-based interventions in RA. Current evidence supports the hypothesis that gut dysbiosis correlates with immune dysregulation in RA; however, further longitudinal studies are needed to establish causality.

Author Contributions

AB, AV and VP designed the review plan. NM, OM and AO integrated and refined the key highlights. All authors involved in drafting the manuscript or reviewing it critically for important intellectual content. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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