Microbiota in Rheumatoid Arthritis

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Rheumatoid arthritis is a chronic systemic immune-mediated disease caused by genetic and environmental factors. It is often characterized by the generation of autoantibodies that lead to synovial inflammation and eventual multi-joint destruction. A growing number of studies have shown significant differences in the gut microbiota composition of rheumatoid arthritis (RA) patients compared to healthy controls.

arthritis microbiome dysbiosis

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease found in roughly 1% of the population worldwide and that affects women more than men. It is characterized by polyarticular joint swelling, tenderness, and systemic inflammation due to the production of self-antigens (anti-rheumatoid factor or anti-citrullinated protein antibodies) in joint spaces. Substantial insights into RA pathophysiology suggest that various inflammatory pathways lead to an altered immune system and disease onset. The inflammatory pathway in RA is characterized by an imbalance in the anti-inflammatory—pro-inflammatory cytokine ratio, induced by alterations in the Th1 cell profile. There is release of IL-1, IL-6, and TNF-α from inflammatory cells in affected joint spaces, with concurrent decreases in IL-11, IL-13, and IL-10 [1]. Previously having high mortality and morbidity, the prognosis of RA has improved significantly in recent decades due to the development of more effective treatment options, including conventional disease-modifying anti-rheumatic drugs (DMARDs) and biologics that allow affected patients to achieve low disease activity or even clinical remission.

While the exact etiopathogenesis of RA is not well understood, it is currently thought that clinical presentation of RA results from genetically susceptible individuals coming into contact with environmental factors that induce targeted activation of the immune system, leading to disease. This theory is backed by monozygotic twin population studies showing low concordance rates between twins but high heritability rates [2][3][4]. Smoking is the environmental factor most consistently associated with RA development, but other factors include infections, diet, and perturbations in the oral and gut microbiota [5]. While significant research has focused on genetic factors, there is a growing realization that the host microbiota, especially the gut microbiota, play a crucial role in the development and progression of RA. In concert with the gut-associated lymphoid tissue, the gut microbiome is involved in maintaining immune homeostasis and acts as an indicator of the host's health status. Perturbation of this interaction can affect mucosal and systemic immunity, and promote various inflammatory and autoimmune diseases [6][7][8].

2. What Is the Gut Microbiome?

The microbiome is a term first coined by Whipps et al. in their work on rhizosphere micro-organisms, where they defined it as a “characteristic microbial community in a reasonably well-defined habitat that has distinct physiochemical properties as their theater of activity” [9]. Joshua Lederberg evolved this understanding and defined the microbiome as constituting the ecological communities of commensal, symbiotic, and pathogenic micro-organisms that share our body space. This interpretation allowed bacteria, fungi, protista, archaea, phages, viruses, and plasmids to all be members of a microbiome. Additionally, it is essential to distinguish between the terms microbiome and microbiota. While the microbiota is the collection of micro-organisms in a specified environment, the microbiome is the summation of all genetic material of the microbiota and their metabolic byproducts.

2.1. Development of the Gut Microbiome

The development of the microbiome starts at birth. The current consensus is that prior to birth, humans are sterile. While some studies contest this idea, noting the physiologic placenta and amniotic fluid colonization [10][11], more research must be done to validate the claim. In the immediate neonatal period, the infant’s intestine comes into contact with the maternal and external environment and is colonized. Depending on the mode of delivery, the microbiome’s composition will differ. Infants that are vaginally delivered are colonized with maternal vaginal *Lactobacillus*, *Prevotella,* and *Sneathia* on their skin and oral mucosa [12], and Enterobacteriaceae and breast milk Bifidobacteria colonize their intestine. Those delivered by C-section are colonized by more common skin microbes such as *Staphylococcus* [11]. Interestingly, a pilot study has shown that infants born via C-section and exposed to vaginal fluids at birth had microbiome compositions similar to those delivered vaginally, showcasing the importance of environmental exposure in the initial development of the microbiome.

The microbiome continues to change with time as the host ages. Development of the gastrointestinal system and the transition to an adult diet allows it to fully mature, becoming populated with the phyla *Firmicutes*, *Actinobacteria*, *Fusobacteria*, *Proteobacteria,* and *Bacteroidetes*, with the *Firmicutes* and *Bacteroidetes* representing over 90% of the population [13]. **Table 1** further notes the common bacterial populations found in the gut microbiome. It is important to note that, even in healthy individuals, taxonomical variations exist due to differences in diet, geography, and lifetime medication and antibiotic use [14]. Despite these differences, the composition of the adult gut microbiome can be classified into three clusters, or enterotypes, based on species composition [13].

Table 1. Taxonomic data of most common gut microbial populations [15].

Phylum	Class	Order
Firmicutes	Clostridia	Clostridiales
	Bacilli	Lactobacillales

Phylum	Class	Order
	Erysipheoltrichia	Erisophelotrichales
	Negativicutes	Selenomonadales
		Veillonellales
Bacteroidetes	Bacteroidia	Bacteroidales
Actinobacteria	Coriobacteria	Coriobacteriales
		Eggerthellales
	Actinobacteria	Bifidobacteriales
Fusobacteria	Fusobacteria	Fusobacteriales
Proteobacteria	Gammaproteobacteria	Enterobacteriales
		Aeromonadales

2.2. Gut Microbiome Function

The gut microbiota carries out a variety of physiological functions that help maintain health homeostasis, most of which revolve around the production of metabolites. With the consumption of food products, the microbial populations work to break down and derive energy from complex molecules, such as polysaccharides, lipids, and proteins. For example, Akkermansia is a bacterium commonly found in the human gut [16] that turns mucin into short-chain fatty acids (SCFAs), including acetate. Other beneficial bacteria such as Firmicutes use acetate to produce butyrate, a vital energy source for cells lining the gut. A recent study by Sun et al. reported a higher prevalence of the mucin-degrading Akkermansia in healthy subjects than in RA patients in the Chinese population [17]. Akkermansia is also inversely associated with obesity, diabetes, inflammation, and metabolic disorders. Response to fecal microbiota transplantation in treating irritable bowel syndrome also correlated with an increased relative abundance of Akkermansia. Reduction in the *Ruminococcus*, *Lachnospira*, and *Blautia genera*, as well as in the *Akkermansia muciniphila* species, is also reported in psoriasis [18][19][20], psoriatic arthritis, and spondyloarthritis [21], and negatively correlated with the serum levels of C3 in SLE patients [22].

A significant flow of carbon from dietary fibers to the host is through the transformation of non-digestible carbohydrates (e.g., cellulose and resistant starch), and through the fermentation process by the co-operative activity of commensal bacteria, into short chain fatty acids (SCFA) [23][24][25][26]. The major SCFA products are formate, acetate, propionate, and butyrate. Fermentation of protein-derived branched-chain amino acids also contributes to acetate and propionate production. Locally, SCFAs affect the intestine function via activation of Treg cells and can exert systemic effects following transport to other organs. A deficiency in SCFA production has been related to immune insufficiency and dysregulation in RA [27]. SCFA has a variety of functions. They activate signaling pathways via G-protein coupled receptors (GPCR), with three important ones being GPR41, GPR43, and GPR109A. Activation of GPR109A found on intestinal macrophages promotes anti-inflammatory properties, including the production of IL-10, and allows them to induce differentiation of T-regulatory cells [28]. The binding of

acetate to GPR43 on intestinal epithelial cells (IEC) can cause hyperpolarization through potassium efflux, leading to the activation of the NLRP3 inflammasome complex [29]. The function of GPR41 was studied in GPR41/GPR43 KO mice, showing that exposure to oral infection, gut barrier disruption induced by ethanol, or TNBS-induced colitis led to increased expression of pro-inflammatory genes [30].

SCFA are also integral in aiding local cell proliferation. Germ-free (GF) or specific pathogen-free (SPF) mice showed a lower IEC proliferation ability than healthy controls. However, the proliferation rate improved when treated with SCFA and commensal bacterial populations. Conversely, SCFAs have been shown to suppress cancer cell proliferation and induce autophagy instead of apoptosis in colon cancer lines, to protect the local environment [31]. SCFA also functions in the stabilization of the gut epithelial barrier. Butyrate induces genes in the encoding of tight-junction proteins and stabilization of hypoxia-inducible factor-1 (HIF-1), which is important in maintaining barrier stability [32].

The gut microbiota also plays an essential role in nutritional homeostasis by producing essential vitamins, amino acids, and bile acids. For example, Bifidobacteria and Lactobacillus have been shown to be associated with increased intestinal barrier protection, and *Faecalibacterium prausnitzii*, *Roseburia*, *Bacteroides vulgatus*, and *Akkermansia muciniphila* are butyrate-producing bacteria. Vitamin K and the B group vitamins biotin, folate, niacin, pantothenate, pyridoxine, riboflavin, thiamine, and cobalamin are known to be produced by the microbiota. Vitamin K is essential for the normal function of the clotting cascade. GF mice grown without external vitamin supplementation were shown to have low PT levels and increased rates of hemorrhage events [33]. Many of the B vitamins are important in the stimulation of the immune system. Folate (B9) promotes the survival of T-regulatory cells through the downregulation of NK cell activity [34], while pyridoxine (B6) promotes the growth of *Bacteroides*, a key fighter of Salmonella typhimurium infections [35]. In addition, the production of vitamins such as menadione and coenzymes Q1-Q3 and 1,4-naphthoquinone helps inhibit pathogen growth and reduce exotoxin production by infecting Gram-positive bacteria [34]. While most of the amino acids in the intestines are derived from dietary sources, a small percentage are synthesized de novo by the gut microbiome; from 1 to 20% of circulating lysine originates from the gut microbiota [36]. Additionally, the production of D-amino acids is important in forming bacterial cell walls and inhibiting biofilm formation. D-serine can accumulate intracellularly during EHEC infections and suppress their type III secretion system, restricting colonization [37].

3. Microbiota in Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic autoimmune disease caused by genetic and environmental factors. Genetic research into rheumatoid arthritis is substantial; over 300 single-nucleotide polymorphisms (SNP) or risk loci have been found across all chromosomes in genome-wide association studies (GWAS), with roughly 100 being replicated in further meta-analyses [38]. However, the findings from these studies only explain a fraction of disease variance in patients and are not considered sufficient to guarantee disease development. The investigation was expanded and began to look at environmental factors, particularly the gut microbiome, as a critical factor in the etiology of RA. Hypotheses connecting the microbiome and RA are not novel. Andrews and Hoke associated “albuminous putrefaction” in the intestinal tract with the development of symptoms, and Hunter proposed the “oral

sepsis hypothesis" that dental infections were correlated to RA [39]. Albuminous putrefaction (AP) is defined as the fermentation of water-soluble proteins present in food through the diversity of chemical reactions by bacteria in the intestine, thus leading to the formation of ptomaine ammonia compounds and hydrocarbons, which are known to alter the intestine integrity and gut microbiome.

Interestingly, Andrew and Hoke reported that the process of AP was present in rheumatoid patients and could be changed by correcting the type of food uptake. However, they were unclear whether the rheumatic condition occurred due to putrefaction or secondarily to the disease [40]. Regardless, a potential causal relationship is proposed in RA patients. With laboratory technological advances, research moved to animal models.

3.1. Experimental Animal Models

In one of the first studies done, Kohashi et al. found that in an adjuvant-induced arthritis model, GF rats developed severe arthritis, with a 100% incidence compared to SPF and conventional (CV) F344 rats. The study concluded that the presence of bacterial flora in the CV group modulated the development of the immune system, leading to a suppressed immune response with the induction of bacterial PG [41]. Other studies were done on the three main experimental animal models of arthritis: CIA, collagen-induced arthritis; K/BxN, mice expressing both the T cell receptor (TCR) transgene KRN and the MHC class II molecule A(g7); and SKG mice, which harbor a point mutation in the ZAP-70 gene, yielding reduced T-cell receptor (TCR) signaling.

3.2. CIA Model

Some studies utilized the CIA model, where injection of a type II collagen and Freund's adjuvant emulsion leads to an inflammatory arthritic condition. In the initial stages of disease in affected mice, there are critical changes in the gut microbial populations. There is a decrease in *Bacteroidetes* and an increase in *Firmicutes* and *Proteobacteria*, all of which cause perturbations in metabolite production [42]. It is thought that the reduction in Bacteroidetes phylum leads to a reduction of CD4+ differentiation into $T_{regulatory}$ cells, resulting in an overall pro-inflammatory state. Interestingly, CIA mice grown in a GF environment that subsequently have *Bacteroides* introduced to the intestine showed an increase in $T_{regulatory}$ (T-reg) cell population through stimulation of CD4+ cells by polysaccharide A, an immunomodulatory molecule released by *Bacteroides* [43]. A later study focused on the function of the intestinal barrier in this model. CIA mice exhibiting clinical disease had higher levels of zonulin, a protein essential in the modulation of tight junction permeability and previously shown to be more highly expressed in autoimmune conditions. Pre-treatment of mice with larazotide acetate, a zonulin antagonist, reduced arthritis onset [44].

3.3. SKG Model

In the SKG model, a point mutation in the Zap-70 gene leads to reduced T-cell signaling and altered thymic T-cell selection, causing spontaneous development of an inflammatory arthritic state [45]. When grown under GF conditions, the disease was not present. However, inoculation with *Prevotella* (discussed later) induced inflammatory arthritis [46].

3.4. K/BxN Model

Other studies utilized the K/BxN model, where mice expressed both the T-cell receptor (TCR) transgene KRN and MCH class II molecule A (g7). This led to the development of autoantibodies to glucose-6-phosphate and resultant severe inflammatory arthritis [47]. When grown in GF conditions, arthritis severity was significantly reduced, due to a decrease in autoantibody production and Th17 cells. The introduction of segmented filamentous bacteria (SFB) upregulates amyloid output in the ileum, inducing differentiation of Th17 cells and level reinstation, leading to arthritis [48]. SFB colonization generally induces a pro-inflammatory state. Small populations have been found in the human gut and are associated with increased IgA [49]. Flak et al. found increased gut permeability due to reduced numbers of tight junctions compared to healthy controls [50].

3.5. IL1rn -/- Model

Interleukin-1 receptor antagonist knock-out mice (il1rn -/-) spontaneously developed an autoimmune T-cell mediated arthritis, due to excessive IL-1 signaling. They did not develop the autoimmune disease when raised in a germ-free environment. Lack of IL-1RA reduces intestinal microbial diversity, specifically causing a decrease in *Ruminococcus* and *Prevotella* populations. This change causes an increase in Th17 cells, which are implicated in RA pathogenesis [51][52]. Interestingly, when the GF mice were colonized with *Lactobacillus bifidus*, they developed an arthritic state similar to the initially mentioned group, due to bacteria-induced activation of toll-like receptors (TLR) and a resultant imbalance in T-regulatory–Th17 homeostasis [53].

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