We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter 5

The Gut Microbiota and Inflammation in Rheumatoid Arthritis

Reem Hamdy A. Mohammed and
Hesham Ibrahim I. Elmakhzangy

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/67368

Abstract

"Mutualism" is a well-defined relationship that describes a form of cooperation between two living organisms of different species that ends up with a beneficial outcome for each one. Any disruption to such a relationship by an external trigger or a potential intruder puts at risk the well-being of both. In humans, oral and gut microbiota provide a noteworthy model of beneficial mutualism. Multiple recent evidences point to the possible pathologic consequences of a disruption to this ecosystem (altered microbiota profile or dysbiosis) on human well-being. The gut-joint axis found its clear way "Proof of Principle" in the pathogenesis of autoimmune rheumatic diseases including rheumatoid arthritis (RA), seronegative spondyloarthropathies, and Behcet's disease in a number of studies. Current therapeutic trends are directed towards the diverse biologic and immune-pathogenic factors involved in the disease process. Addressing dysbiosis in RA features an attractive future therapeutic target. In this chapter, authors aim to explore the recent evidences regarding the pathogenic role of "gut dysbiosis" in rheumatoid arthritis (RA), highlighting the spectrum of immune-pathogenic events that might contribute to disease evolution and inspecting future directives of research.

Keywords: Mutualism, microbiota, dysbiosis, pathogenesis, autoimmune rheumatic diseases, rheumatoid arthritis

1. Rheumatoid Arthritis and The Microbiome Theory "The Revival of an Old Hypothesis"

Rheumatoid arthritis (RA) is a systemic immune-mediated chronic inflammatory disease that predominantly targets diarthrodial joints contributing to synovial inflammation, joint destruction, and deformity. The disease has been initially recognized as a complex genetically based

inflammatory joint disease, a concept that was redefined toward a multifactorial immune-mediated etiology. The etiopathogenesis of rheumatoid arthritis is typically a challenge incorporating complex network of genetic factors (HLA genes), environmental and biological factors (infections, a dominant pro-inflammatory profile, dysbiosis), as well as individual habits (smoking) interacting to shape up disease phenotype [1, 2].

An infectious etiology of RA has been proposed for decades, Banntyne and Wohlmann in 1896 were the first to suggest a mycobacterial etiology behind the development of rheumatoid arthritis, a theory that awaited solid scientific evidence. The hypothesis of "molecular mimicry" and cross-reactivity between epitopes of microbial origin with a self-protein was among the proposed mechanisms to explain the role of infectious agents in the breakdown of immune tolerance in RA. Certain viral infections like Epstein-Barr virus (EBV), cytomegalovirus (CMV), and Parvovirus B19 have been additionally claimed as potential etiopathogenic agents in RA [3–9].

1.1. The oral sepsis hypothesis

In the 1900s, the oral sepsis hypothesis and its relation to arthritis led to the use of teeth extraction as a prevalent treatment of disease for several decades. The impact of polymicrobial phylotypes and the pro-inflammatory burden in periodontitis proved its contribution to the pro-inflammatory drive in RA. The *Porphyromonas gingivalis*, a Gram-negative anaerobe bacterium and part of periodontopathic microbiome, contributes to protein citrullination, which leads to anticitrullinated autoantibody (ACPA) formation and joint inflammation in RA [6–13].

The infectious profile further extended to include other pathogenic bacterial species as wells as cell membrane proteins of mycoplasma in RA like *Proteus mirabilis* (*sharing sequence similarities to peptide sequences at amino acid position 67–74 of the HLA-shared epitope in RA and bacterial-specific antibodies detected in sera of RA patients*) [14, 15]. The presence of specific *Escherichia coli*, *Mycoplasma fermentans*, and *Klebsiella pneumonia* in the gut has been associated with RF positivity and has been linked to inflammatory arthritis in many ethnic populations [16].

1.2. The infectious hypothesis and therapeutic evidences

The relationship between infections and arthritis was indirectly reinforced by the time antimicrobials showed an observable beneficial effect in the amelioration of arthritis. In the 1940s, sulfasalazine was the first rationally designed drug in the field of rheumatology, where RA was thought to be caused by Streptococci found in milk. Sulfasalazine was designed as a deliberate attempt to combine a sulfonamide antibiotic with a salicylate anti-inflammatory agent through an azo bond. Such "combination therapy" brought up good initial responses in RA as well as enteropathies. The triple DMARD therapy (a combination of methotrexate, sulfasalazine and hydroxychloroquine) currently stands among the first few recommendations in RA patients with poor prognostic features and moderate to high levels of disease activity [17–21].

http://dx.doi.org/10.5772/67368

Certain antibiotics like tetracycline have proven efficacy in the treatment of early seropositive RA which led to the approval of minocycline, as a DMARD [22, 23]. Clarithromycin is another example that gave observable beneficial effects in some refractory cases [24]. Treatment with probiotics, particularly *Bifidobacterium*, *Lactobacillus*, and *Faecalibacterium prausnitzii*, showed protective effects in NSAID-treated animal models of arthritis. Theories regarding supplementations of microbiome-derived molecules with immune-modulating properties (e.g., Polysaccharide A, short-chain fatty acids) provide promising novel immune regulatory effects by possibly downregulating pro-inflammatory cytokines with upregulation of the anti-inflammatory profile [25–27].

2. The human gut ecosystem

Mutualism is a well-defined relationship between living organisms. The term describes a form of cooperation between two living organisms of different species that ends up with a beneficial outcome for each one. Partners in a mutualistic relationship make headway together with each forming a part of the other's environment and maintaining its homeostasis in a typically harmless yet useful way. A disruption to such a relationship by an external trigger or a potential intruder puts at risk the well-being of both. In humans, oral and gut microbiota provide a noteworthy model of beneficial mutualism. Multiple recent evidences point to the possible pathologic consequences of a disruption to this ecosystem (altered microbiota profile or dysbiosis) on human well-being. The gut-joint axis found its clear way "Proof of Principle" in the pathogenesis of autoimmune rheumatic diseases including RA, seronegative spondyloarthropathies, and Behcet's disease in a number of studies.

The term "microbiota" is defined as the ecological community of symbiotic, commensal, and pathogenic microorganisms that literally inhabit the human body and effectively contribute to human health and might contribute to disease. According to their contributions to human health, they can be classified to symbiomes and pathobiomes. The symbiome microbiota are groups of microorganisms predominantly bacterial as well as fungal (previously recognized as normal flora) that get acquired at birth and inhabit every part of the human body from the skin to mucosa (mouth, eyes, gut, and genital tracts). The alimentary tract represents an established microbial habitat for almost 29–30% of the overall commensal/symbiome population in the human body. They involve over 500 bacterial species encoding around three million different genes constituting a complex challenging ecosystem, difficult to differentially analyze or understand [28, 29].

2.1. The development of the human microbiota profile

The general composition of gut microbiota is much similar in most healthy individuals; however, the individuals' microbiota profile retains a highly personalized pattern (fingerprint). This pattern helps to keep in situ homeostasis in healthy individuals; therefore triggers of dysbiosis are expected to offer a threat to the humans' well-being in a variety of forms.

At birth: The initial shape up of the different microbial colonies of the gut begins as early as childbirth by the time the newborn gets exposed to microorganisms that inhabit the maternal genital tract during normal vaginal delivery (first encounter), maternal fecal bacteria, or the skin in the case of caesarian section. The fetal fingerprint of microbiota gets additionally shaped up by the skin as well as breast milk microbiota that add their signature to this microbial network [30].

Adulthood: The typical adult microbiota profile emerges by the end of the first year with more than 1000 different species from a dozen different divisions colonizing the gastrointestinal tract (4×10^{13} colonizing bacteria). The profile becomes increasingly stable with age. The acquired bacterial species pass through a series of modifications with colonies competing for survival, alternating their dominance aiming to establish phylogenetic richness and species diversity at the same time. Serial microbial evolutions are proven to be largely dependent on a multiplicity of host as well as environmental factors (the host genetics, the maternal microbiota, and mode of delivery as major determinants). Breast milk composition is another proven shaping factor of individuals' microbiota profile (*Bifidobacterium* is among the dominant gut microbiota in breast-fed infants compared to artificially fed ones and is deficient in patients with RA). Aging; lifestyle patterns including diet, smoking, and obesity; and infections also contribute [31–34].

2.2. The identification and characterization of gut microbiota

The human microbiome project served as a major contributor toward better understanding of the human microbiome. For a sufficient period of time, the conventional culture-based methods were the only methods available and routinely used for identification of gut microbiota, with over 500 bacterial species successfully isolated, cultured, and characterized from the human GI tract [35].

The majority of gut microbiota (over 80%) could not be technically cultivated ranking the culture-based methods as an investigative technique of limited value in determining the actual microbial diversity. The revolutionary era of the human microbiome project announced in 2007 and the utilization of novel culture-independent molecular techniques have successfully contributed to the in-depth understanding of such complex human microbiome network. Such culture-independent techniques target the highly conserved 16S ribosomal RNA (rRNA) gene sequence (a component the 30S subunit of prokaryotic ribosomes) of bacterial and archaeal microorganisms. Universal PCR primers targeting these conserved regions can be used for gene amplification to provide the complete nucleotide sequence of the 16S rRNA without prior knowledge of which bacterial species are present. Concomitantly, the 16S rRNA gene also contains hypervariable regions that provide species-specific signature sequences and enable unbiased bacterial identification utilizing next-generation sequencing platforms. Examples of these molecular techniques include quantitative polymerase chain reaction (qPCR), temperature or denaturing gradient gel electrophoresis (TGGE or DGGE), terminal-restriction fragment length polymorphism (T-RFLP), and fluorescent in situ hybridization (FISH). The next-generation sequencing and phylogenetic microarrays promote the in-depth analysis of the complete phylogenetic diversity of the intestinal microbiota, whereas the whole-genome shotgun sequencing is a technique currently applied for identification of the metabolic and enzymatic pathways present in these microbial communities. Such techniques were able to identify a portion of predominant species in the human gut [36–38].

http://dx.doi.org/10.5772/67368

Genomic culture-independent techniques disclosed that the human intestine is dominated by two divisions of bacteria, Bacteroidetes and Firmicutes, and both contribute to more than two-thirds of the total gut microbiota including anaerobes such as *Bacteroides*, *Porphyromonas*, *Bifidobacterium*, *Lactobacillus*, and *Clostridium* [13, 34, 39, 40].

2.3. The human-microbiota interdependence

Microbiota are involved in a number of structural, biological, protective, and metabolic processes including angiogenesis, postnatal intestinal maturation, and xenobiotic metabolism. They are additionally involved in the synthesis of vitamins, the digestion, and uptake of nutrients. Microbiota are capable of metabolically simplifying nutritional components through the process of fermentation; an important example is the indigestible carbohydrates (complex starch and dietary fibers) as well as short-chain fatty acids (SCFA, e.g., acetate, butyrate, and propionate) which constitute a critical prerequisite in a number of host physiological functions [41].

2.3.1. Microbiota and immunity

A unique harmonious and complex interplay exists between gut microbiota and the local as well as the systemic immune response in humans. Colonizing microbiota and their products have a profound effect on the development and maintenance of the immune system integrity [42–45].

2.3.1.1. The microbiota and T-cell differentiation, proliferation, and functions

Evidences support the existence of immune cross talks between the microbiota-derived products and the gut epithelium that involves molecular exchange of bacterial signals recognized by host receptors to mediate beneficial outcomes for both the microbiome and human beings [42–47]. The gut microbiota have the potential to effectively stimulate and direct the host innate and adaptive immune responses in humans by triggering instructional signals to the immune cells, particularly regulatory T (Treg)-cell and T-helper (Th) cell differentiation.

2.3.1.2. Short-chain fatty acids and Treg cells

SCFAs are actively produced by anaerobic microbiota in the colon as fermentation products of digestion-resistant dietary fibers [46, 47]. SCFAs produced locally in the colon are either absorbed and metabolized within the colonocytes or transported into the circulation to reach other organs, such as the liver and muscles. SCFAs exert direct and indirect regulatory effects on epithelial cells, antigen-presenting cells, and T cells via multiple mechanisms including metabolic regulation, histone deacetylase inhibition (HDAC inhibition), and G-protein–coupled receptor (GPCR) activation.

SCFAs can be converted to Acetyl-CoA and integrated into the citric acid cycle (Krebs cycle). Acetyl-CoA is a central molecule that stores energy and is eventually oxidized to CO_2 for energy production (the cellular energy [ATP/ADP] level increases). This boosts a homeostatic T-cell sensor mammalian target of rapamycin (mTOR) to be activated in T cells which skews T-cell differentiation into effector T cells such as Th1 and Th17 cells at the expense of $FoxP3^+$ T cells. mTOR activation also promotes the generation of $IL\text{-}10^+$ cells. Thus, the SCFA regulation

of cell metabolism and mTOR accounts for the increased generation of Th1 cells, Th17 cells, and IL-10^+ cells.

The activation of SCFA-binding G-protein–coupled receptors (GPCRs) such as GPR41, GPR43, GPR109A, and Olfr78 initiates T-cell differentiation.

All major SCFAs such as C2, C3, C4, and C5 have HDAC inhibitor activity. Class I/II HDACs are major targets of SCFA inhibition in a concentration-dependent pattern. Treg generation was increased as a result of HDAC inhibition by SCFAs and histone H3 acetylation in key regulatory regions of the Foxp3 locus.

SCFAs can indirectly affect T cells through their effects on DCs. They suppress the development of bone marrow progenitors into myeloid DCs and inhibit functional maturation of DCs in vitro. For example, C4 suppressed the maturation of bone marrow-derived DCs and production of IL-12 but increased the expression of IL-23p19. Valproic acid, a branched short-chain fatty acid and potent HDAC inhibitor that suppressed the maturation of human DCs in vitro, inhibits the upregulation of T-cell–activating molecules such as MHC II, CD80, CD86, and IL-12.

These effects are combined to create the overall tolerogenic gut environment with a strong barrier function.

2.3.1.3. Microbiota and cytokine production

Microbiota produce stimulatory signals to gut macrophages to produce interleukin-1 (IL-1). IL-1 acts on type 3 innate lymphoid cells in the intestine, producing colony-stimulating factor 2 (CSF-2). CSF-2 induces myeloid cells (including dendritic cells and macrophages) to produce immune regulatory cytokines (retinoic acid and IL-10) which support the conversion and expansion of regulatory T cells (Treg) critical for maintaining immune tolerance in the gut.

Microbiota have the capacity to produce a certain set of microbial products—gut microbiota–derived butyrate and polysaccharide A PSA (e.g., *Bacteroides fragilis*) that mediates the conversion of CD4+ T cells into Interleukin (IL)-10 producing Foxp3+ Treg cells offering immune protection. Such microbiome-derived molecule further promotes immunologic tolerance via TLR2 signaling pathway directly on Foxp3(+) Treg cells [47, 48].

The "segmented filamentous bacterium (SFB)" is another symbiotic gut commensal that is capable of inducing the appearance and activation of Th17 cells in the lamina propria, which secrete the pro-inflammatory cytokine (IL-17) and thereby enhance mucosal immune responses of the host [49].

2.3.1.4. Experimental evidences illustrated the impact of dysbiosis on the immune system and T-cell function

Multiple experimental evidences revealed that a germ-free environment is associated with a decline in neutrophil count and function [42–45]. Recognition of peptidoglycans from gut

http://dx.doi.org/10.5772/67368

microbiota by the cytosolic recognition receptor nucleotide oligomerization domain 1 (NOD1) is capable of enhancing the killing activity of marrow-derived neutrophils contributing to immune integrity. A germ-free environment was associated with impaired neutrophil phagocytic function, superoxide function, and nitric oxide generation, which could not be restored upon pathogen exposure. Germ-free rats lack the microbe-derived ATP capable of stimulating dendritic cells (CD70 and CX3CR1) involved in the subsequent differentiation of Th17 cells. Additionally, in germ-free rats, systemic, not gut macrophages, were reduced, and gut macrophages lack macrophage-activation markers, such as MHC class II.

Early-life microbial exposures alter sex hormone levels and modify the progression to autoimmunity in the nonobese diabetic (NOD) mouse model of type 1 diabetes (T1D). Colonization by commensal microbes elevated serum testosterone and protected NOD males from T1D. Furthermore, transfer of gut microbiota from adult males to immature females altered the recipient's microbiota, resulting in elevated testosterone and metabolomic changes, reduced islet inflammation and autoantibody production, and T1D protection [45].

3. The gut-microbiome checkpoints

Under normal conditions the human body has established a number of locally protective mechanisms and checkpoints to maintain immune integrity. These checkpoints include:

3.1. Mucosal buffer zone: "first-line defense"

Mucosal buffer zone represents an effective physicochemical barrier which is composed of the thick mucus layer, a number of antimicrobial proteins, and secretory IgA antibodies. The components of this barrier coalesce to minimize the contact and dilute any possible pathological microbial trigger between the commensal microbes in the gut lumen and intestinal epithelial cells that line the gut wall [50, 51].

3.2. Intestinal epithelial cells: "second-line defense"

Microbiota that escape the initial "buffer zone" encounter a second defense strategy represented by the tight junctions formed between the intestinal epithelial cells featuring a physical barrier.

Epithelial cells produce a variety of antimicrobial/bactericidal proteins, such as defensins, cathelicidins, and C-type lectins and express Toll-like receptors (TLRs) in their cell membrane. Toll-like receptors (TLRs) present on the surface of cells of innate immunity recognize pathogen-associated molecular patterns (PAMPs) with activation of the signaling adaptor molecule MyD88 (myeloid differentiation primary-response protein 88) provoking a downstream inflammatory responses. Lipopolysaccharides (LPS) are important components of the outer membrane of all Gram-negative bacteria. TLR4 is a natural ligand for LPS and upon binding to LPS leads to activation of cell and secretion of inflammatory cytokines. Cytokines in turn activate cells of the adaptive immune system that generates antigen-specific response [52].

3.3. The Innate and Adaptive Immune responses of the Lamina Propria "Third-Line Defense"

The composition and function of the gut microbiota play a critical role in regulating the Th17/Treg cell balance in the lamina propria. The innate cells in lamina propria constitute an important local line of immune defense that constantly surveys the gut lumen tracing undesirable antigens. The first is the intestinal macrophage system that phagocytoses microorganisms bypassing the first- and second-line barriers. The second is the lamina propria dendritic cells (DCs, antigen-presenting cells) that present foreign peptides complexed with MHC class II molecules for priming of antigen-specific B- or T-cell receptors to initiate an adaptive immune response.

T helper cells feature another key player when primed via a complex network of receptors, cytokines, and transcription factors enabling their differentiation into several pro-inflammatory or anti-inflammatory subsets. The type 1 T helper (Th1) response develops in response to intracellular pathogens, while type 2 T helper (Th2) and type 17 T helper (Th17) cells are predominantly stimulated after identification of extracellular organisms [53, 54].

4. Dysbiosis and autoimmune inflammatory arthritis

Multiple animal models of human autoimmune diseases (AD) suggest the direct involvement of commensal microbiota in disease development. A change to a single bacterial species and/or the entire community leads to an imbalance between the pathobiome and the symbiome immune responses with breakdown of self-immune tolerance provoking a number of ADs [47]. Mono-colonization with *Lactobacillus bifidus* in IL-1 receptor antagonist knockout mice resulted in rapid onset of arthritis which was dependent on Toll-like receptor activation by *L. bifidus*. The arthritis onset was preventable by promoting a germ-free environment [52]. Mono-colonization of germ-free mouse with single gut-microbiome "segmented filamentous bacterium (SFB)" is sufficient to induce fully functional TH17 cells that produce pro-inflammatory cytokines IL-17 and drive the onset of arthritis. The SFB upregulates the production of acute-phase isoforms of serum amyloid A (SAA) in the ileum, which can act on dendritic cells (DCs) from the small intestinal lamina propria to induce Th17 differentiation [49, 55]. Also, colonization of the mice gut with *Prevotella copri* (*P. copri*) can enhance experimental dextran sulfate sodium-induced colitis which is capable of initiating a pro-inflammatory drive in human arthritis. The *P. copri* genome encodes phosphoadenosine phosphosulfate reductase, an oxidoreductase that participates in the production of thioredoxin. Thioredoxin (TRX) is a cellular reducing catalyst induced by oxidative stress and is involved in the redox regulation of transcription factors such as NF-kappa B. TRX has been widely implicated in the pathogenesis of RA with significantly increased concentrations observed in both RA serum and synovial fluid [56–58].

Finally, commensal bacteria can produce and secrete large amounts of adenosine 51-triphosphate (ATP) that can activate a unique subset of lamina propria cells, CD70highCD11clow cells. The CD70highCD11clow subset cells could express Th17-inducing molecules, such as IL-6, IL-23p19, and transforming-growth-factor-_-activating integrin AV, and induce Th17 differentiation [59].

http://dx.doi.org/10.5772/67368

The metabolome theory: The analysis of bacterial metabolites and their association with specific taxa unveiled significant scientific data on potential mechanistic link in RA. The abundance of the *Collinsella* genus correlated strongly with high levels of three metabolites (beta-alanine, alpha-aminoadipic acid, and asparagine) in RA. The immune-stimulatory role of the *Collinsella* in RA was confirmed using a human epithelial cell line and a humanized mouse model of collagen-induced arthritis (CIA). *Collinsella* increased gut permeability by reducing the expression of tight junction protein in the human intestinal epithelial cell line CACO-2, induced production of the pro-inflammatory cytokine interleukin IL-17A. In humanized CIA, *Collinsella* enhanced disease severity. All together, these data suggest that it seems to have an essential role in altering gut permeability and disease severity as confirmed in experimental arthritis [60].

5. Altered Gut Microbiota and Inflammation in Rheumatoid Arthritis.

The Th17 pathway is one of the main inflammatory pathways. Th17 cells and its signature cytokine IL-17 have been involved in mediating pannus growth, osteoclastogenesis, and synovial neo-angiogenesis. Circulating Th17 cells as well as the IL-17 are significantly elevated in patients with RA. IL-17 induces RANKL expression in human synovial fibroblasts, leading to the loss of the RANKL/OPG balance with subsequent enhancement of osteoclastogenesis and bone erosion. IL-17 also increases the production of vascular endothelial growth factor (VEGF) in rheumatoid fibroblast-like synoviocytes (FLS), contributing to the angiogenesis in rheumatoid synovium. Finally, IL-17 stimulates the expression of various pro-inflammatory cytokines (e.g., IL-1β, TNF-α, and IL-6) and matrix-degrading enzymes (e.g., matrix metalloproteinase (MMP)-1, matrix metalloproteinase-2, matrix metalloproteinase-9, and matrix metalloproteinase-13) in whole synovial tissue, synovial fibroblasts, and cartilage, thus promoting inflammation, extracellular matrix breakdown, and cartilage destruction during RA development [61–65].

The gut mucosa represents a strategic landscape promoting a variety of interactions between the environment and the human host. They possess the potential to trigger autoimmunity in diverse ways. When genetic and/or environmental factors alter the balance in the microbiota composition, dysbiosis ensues. The metagenomics shotgun sequencing technique has revealed significant alterations in the microbiota profile in patients with RA. Evidences illustrated that changes in the symbiotic relationship between intestinal microflora and opportunistic bacteria as well as bacterial translocation from the gut to nasal mucosa or urinary tract may additionally enhance the risk of developing RA as well as disease-related comorbid conditions. Partial depletion of natural gut flora by antibiotic in experimental animals aggravates CIA [53].

Potentially harmful microorganisms/pathobiomes (such as SFB or *Lactobacillus*) dominate and create a local pro-inflammatory profile with local expansion of autoreactive Th1 and Th17-cell compartments, via secretion of stimulatory molecules as ATP adenosine-5′-triphosphate, SAA serum amyloid A, or CCL5 CC-chemokine ligand 5 signaling. The autoreactive T cells migrate to peripheral immune compartments and activate B cells to differentiate into autoantibody-producing plasma cells. These cells and antibodies then migrate to synovial tissue where the inflammatory cascade is amplified through the activation of effector components, includ-

ing macrophages, fibroblasts, osteoclasts, cytokines, and proteinases provoking arthritis and pannus formation. Dysbiosis in RA is associated with clinical indices of immune-mediated inflammation, such as the titers of immunoglobulin, autoantibodies, anti-cyclic citrullinated peptide (anti-CCP), and rheumatoid factor (RF) [17, 52, 55, 66].

5.1. Microbial colonies overpresented in RA

5.1.1. The Lactobacillus species

Lactobacillus fecal microbiome communities were found to be significantly increased in patients with early RA with those from healthy individuals [25] (**Table 1**). The abundance of *Lactobacillus salivarius* was associated with an increase in disease severity associating the increase in bacterial load.

Study	Patients vs. controls (number)	Sample	Technique	Microbiota profile Increased (++), decreased (--)
Vaahtovuo et al. [67]	Early RA (n= 51) vs. fibromyalgia (n= 50)	Stool	16S rRNA hybridization and DNA staining	Bifidobacteria --, *Bacteroides* --, Porphyromonas --, *Prevotella* --, *Bacteroides fragilis* --, *Clostridium coccoides* --
Gul'neva et al. [68]	Treatment-naïve RA (n= 94) vs. healthy (n= 97)	Stool, dental, saliva	Metagenomic shotgun sequencing	*Lactobacillus salivarius* ++, *Gordonibacter pamelaeae* ++, *Clostridium asparagiforme* ++, *Haemophilus* spp. --
Liu et al. [69]	Early RA (n= 15) vs. healthy (n= 15)	Stool	Quantitative real-time PCR	*Lactobacillus* ++
Scher et al. [57]	New-onset RA (n= 44) vs. healthy (n= 28)	Stool	16S rRNA gene and WGS sequencing	Prevotella copri ++, Bacteroidetes --
Zhang et al. [70]	RA (n= 30) vs. healthy (n= 30)	Stool	16S rRNA gene and WGS sequencing	Enterococci ++, Clostridia ++, Colibacteria ++, Lactobacteria --

Table 1. Microbiota profile in RA [57, 67–70].

5.1.2. The Prevotella copri species

A strong positive correlation was illustrated between the *Prevotella copri* (*P. copri*) and new-onset untreated RA (NORA). *Prevotella* was found to be overrepresented in NORA patients, and the relative abundance of *P. copri* in RA patients negatively correlates with the presence of HLA-DRB1-shared epitope. The relation between this specific microbiome and RA was further confirmed by the observation that the expansion of *P. copri* in RA patients could be suppressed to a similar state that was observed in healthy subjects after treatment with DMARDs that control of RA disease activity.

http://dx.doi.org/10.5772/67368

5.1.3. Other forms of gut microbiota

RA patients showed a dysbiotic gut microbiota characterized by a decrease in *Faecalibacterium* and an increase in *Collinsella* and *Eggerthella*. Large microbiota clusters including *Gordonibacter pamelaeae*, *Clostridium asparagiforme*, *Eggerthella lenta*, and Lachnospiraceae bacterium as well as small clusters of *Bifidobacterium dentium* and *Ruminococcus lactaris* were enriched in the gut of RA patients.

On the other hand, RA patients have significantly less bifidobacteria and microbiome of the *Bacteroides-Porphyromonas-Prevotella* group, *Bacteroides fragilis* subgroup, and *Eubacterium rectale-Clostridium coccoides* group and *Haemophilus* spp. in comparison to patients with non-inflammatory rheumatic diseases.

5.1.4. Protective microbiota species: Prevotella histicola "P. histicola"

Oral feeding of *P. histicola* in mouse models of RA led to decreased symptom frequency and severity and fewer signs of inflammation in diseased vs. controls. *P. histicola* administration is associated with an upregulation of the anti-inflammatory cytokine IL-10 and Treg cells in the lamina propria and spleen of mice with CIA with subsequent amelioration of immune inflammatory responses. *P. histicola* preserves gut epithelium integrity by lowering gut permeability and increased expression of tight junction proteins (zonulin and occludin) in treated mice compared to control. Treatment with *P. histicola* had fewer side effects (such as weight gain, villous atrophy, and increased gut permeability) that are linked with nonsteroidal anti-inflammatory drugs and other traditional medications used for treating RA. This microbiome is currently considered as potential future novel therapy in RA [71].

6. Future perspectives

Multiple lines of evidence support the potential pathogenic role of gut dysbiosis in RA which makes gut microbiota a possibly promising new territory for drug targeting [72]. Restoring balance of gut microbiota might contribute to the improvement of disease symptoms in RA. Experimental models demonstrated the ability of certain microbial colonies to drive inflammation such as *P. copri* and SFB.

Thus, it is plausible to hypothesize that targeting the postulated pathobiomes might contribute to clinical improvement in RA. Despite the successful use of antimicrobials in RA, they lack microbial specificity in most studies.

"Mapping of the individual's microbiota profile and tracking their metabolic signatures might serve in the future design of a predictive profile of the potential to develop inflammatory arthritis, anticipate disease course, severity and specify more therapeutic strategies."

"Restoring balance in dysbiosis represents an advent toward novel treat to target therapeutic strategies in RA, a promising step toward an effective personalized medical approach."

Author details

Reem Hamdy A. Mohammed[1,*] and Hesham Ibrahim I. Elmakhzangy[2]

*Address all correspondence to: rmhamdy@yahoo.com

1 Department of Rheumatology/Clinical Immunology and Rehabilitation, School of Medicine, Cairo University-FRCP, Egypt

2 Department of Gastroenterology/Hepatology and Tropical Medicine, School of Medicine, Cairo University, Egypt

References

[1] Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. Arthritis Rheum. 1987;30:1205–13.

[2] Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. 2007;447:661–78.

[3] Taneja V. Arthritis susceptibility and the Gut Microbiome. FEBS Lett. 2014;588(22): 4244-4249.

[4] Alauzet C, Mory F, Carlier JP, Marchandin H, Jumas-Bilak E, Lozniewski A. *Prevotella nanceiensis* sp. nov., isolated from human clinical samples. Int. J. Syst. Evolut. Microbiol. 2007;57:2216–2220.

[5] de Pablo P, Dietrich T, McAlindon TE. Association of periodontal disease and tooth loss with rheumatoid arthritis in the US population. J. Rheumatol. 2008;35:70–76.

[6] Bannatyne G, Wohlmann A. Rheumatoid arthritis: its clinical history, etiology, and pathology. Lancet. 1896; 147 (3791):1120–5.

[7] Human Microbiome Project Consortium, Huttenhower C, Gevers D, Knight R, Abubucker S, Badger JH, et al. Structure, function and diversity of the healthy human microbiome. Nature. 2012; 486 (7402):207–14.

[8] Pineda MLA, Thompson SF, Summers K, de Leon F, Pope J, Reid G. A randomized, double-blinded, placebo-controlled pilot study of probiotics in active rheumatoid arthritis. Med. Sci. Monitor. 2011;17(6):CR347–5.

[9] Moen K, Brun JG, Valen M, Skartveit L, Eribe EK, Olsen I, et al. Synovial inflammation in active rheumatoid arthritis and psoriatic arthritis facilitates trapping of a variety of oral bacterial DNAs. Clin. Exp. Rheumatol. 2006; 24:656–63.

[10] Hunter W. Oral sepsis as a cause of disease. Br. Med. J. 1900; 2: 215–216.

[11] Mikuls TR, et al. Antibody responses to *Porphyromonas gingivalis* (P. gingivalis) in subjects with rheumatoid arthritis and periodontitis. Int. Immunopharmacol. 2009; 9: 38–42.

[12] Hitchon CA, et al. Antibodies to *Porphyromonas gingivalis* are associated with anticitrullinated protein antibodies in patients with rheumatoid arthritis and their relatives. J. Rheumatol. 2010; 37: 1105–1112.

[13] Loyola-Rodriguez JP, Martinez-Martinez RE, Abud-Mendoza C, Patino-Marin N, Seymour GJ. Rheumatoid arthritis and the role of oral bacteria. J. Oral Microbiol. 2010; http://dx.doi.org/10.3402/jom.v2i0.5784.

[14] Rashid T, Jayakumar KS, Binder A, Ellis S, Cunningham P, Ebringer A. Rheumatoid arthritis patients have elevated antibodies to cross-reactive and non cross-reactive antigens from Proteus microbes. Clin. Exp. Rheumatol. 2007;25:259–267.

[15] Ebringer A, Rashid T, Wilson C. Rheumatoid arthritis, Proteus, anti-CCP antibodies and Karl Popper. Autoimmun. Rev. 2010; 9: 216–223.

[16] Newkirk MM, Zbar A, Baron M, Manges AR. Distinct bacterial colonization patterns of *Escherichia coli* subtypes associate with rheumatoid factor status in early inflammatory arthritis. Rheumatology (Oxford) 2010; 49:1311–1316.

[17] Scher JU, Abramson SB. The microbiome and rheumatoid arthritis. Nat. Rev. Rheumatol. 2011; 7: 569–578.

[18] Svartz, N. The primary cause of rheumatoid arthritis is an infection—the infectious agent exists in milk. Acta Med. Scand. 1972; 192, 231–239.

[19] Hannonen P, Mottonen T, Hakola M, Oka M. Sulfasalazine in early rheumatoid arthritis. A 48-week double-blind, prospective, placebo-controlled study. Arthritis Rheum. 1993; 36, 1501–1509.

[20] O'Dell JR, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. N. Engl. J. Med. 1996; 334, 1287–1291.

[21] Saag KG, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum. 2008; 59, 762–784.

[22] Tilley BC, et al. Minocycline in rheumatoid arthritis. A 48-week, double-blind, placebo-controlled trial. MIRA Trial Group. Ann. Intern. Med. 1995; 122, 81–89.

[23] O'Dell JR, et al. Treatment of early seropositive rheumatoid arthritis: doxycycline plus methotrexate versus methotrexate alone. Arthritis Rheum. 2006; 54, 621–627.

[24] Saviola G, Abdi Ali L, Rossini P, Campostrini L, Coppini A, Gori M, Ianaro A, Bucci M, de Nucci G, Cirino G. Clarithromycin in rheumatoid arthritis patients not responsive to disease-modifying antirheumatic drugs: an open, uncontrolled pilot study. Clin. Exp. Rheumatol. 2002; 20: 373–378.

[25] Syer SD, Blackler RW, Martin R, de Palma G, Rossi L, Verdu E, Bercik P, Surette MG, Aucouturier A, Langella P, et al. NSAID enteropathy and bacteria: a complicated relationship. J. Gastroenterol. 2015; 50: 387–393.

[26] So JS, Kwon HK, Lee CG, Yi HJ, Park JA, Lim SY, Hwang KC, Jeon YH, Im SH. *Lactobacillus casei* suppresses experimental arthritis by down-regulating T helper 1 effector functions. Mol. Immunol. 2008; 45: 2690–2699.

[27] Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly-Y M, Glickman JN, Garrett WS. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science 2013; 341: 569–573.

[28] Simon GL, Gorbach SL. Intestinal flora in health and disease. Gastroenterology. 1984;86(1):174–93.

[29] Savage DC. Microbial ecology of the gastrointestinal tract. Annu. Rev. Microbiol. 1977; 31:107–33.

[30] Yeoh N, Burton J P, Suppiah P, Reid G, Stebbings S. The role of the microbiome in rheumatic diseases. Curr. Rheumatol. Rep. 2013; 15:314.

[31] Isolauri E. Development of healthy gut microbiota early in life. J. Paediatr. Child Health. 2012; 48(3):1–6.

[32] Urbaniak C, Burton JP, Reid G. Breast, milk and microbes: a complex relationship that does not end with lactation. Women's Health (Lond Engl). 2012; 8(4):385–98.

[33] Qin J, et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature. 2010;464:59–65.

[34] Eckburg PB, et al. Diversity of the human intestinal microbial flora. Science. 2005; 308:1635–1638.

[35] Rajilić-Stojanović M, Smidt H, De Vos WM. Diversity of the human gastrointestinal tract microbiota revisited. Environ. Microbiol. 2007; 9(9):2125–2136.

[36] Van den Bogert B, De Vos WM, Zoetendal EG, Kleerebezem M. Microarray analysis and barcoded pyrosequencing provide consistent microbial profiles depending on the source of human intestinal samples. Appl. Environ. Microbiol. 2011;77(6):2071–2080.

[37] Zoetendal EG, Akkermans AD, De Vos WM. Temperature gradient gel electrophoresis analysis of 16S rRNA from human fecal samples reveals stable and host-specific communities of active bacteria. Appl. Environ. Microbiol. 1998; 64(10):3854–3859.

[38] Human Microbiome Jumpstart Reference Strains Consortium, Nelson KE, Weinstock GM, Highlander SK, Worley KC, Creasy HH, Wortman JR, Rusch DB, et al. A catalog of reference genomes from the human microbiome. Science. 2010; 328:994–999.

[39] Quigley EMM. Therapies aimed at the gut microbiota and inflammation: antibiotics, prebiotics, probiotics, synbiotics, anti-inflammatory therapies. Gastroenterol. Clin. North Am. 2011;40 (1):207–22.

[40] Dimmitt RA, Staley EM, Chuang G, Tanner SM, Soltau TD, Lorenz RG. Role of postnatal acquisition of the intestinal microbiome in the early development of immune function. J. Pediatr. Gastroenterol. Nutr. 2010; 51(3):262–73.

[41] Lerner A, Aminov R, Matthias T. Dysbiosis may trigger autoimmune diseases via inappropriate post-translational modification of host proteins. Front. Microbiol. 2016;7:84.

[42] Mortha A, Chudnovskiy A, Hashimoto D, Bogunovic M, Spencer SP, Belkaid Y, Merad M. Microbiota-dependent crosstalk between macrophages and ILC3 promotes intestinal homeostasis. Science 2014; 343: 1249-288.

[43] Aychek T and Jung S. The axis of tolerance. Science 2014; 343: 1439–1440.

[44] Furusawa Y, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, Nakanishi Y, Uetake C, Kato K, Kato T, et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. Nature 2013; 504: 446–450.

[45] Markle JG, Frank DN, Mortin-Toth S, Robertson CE, Feazel LM, Rolle-Kampczyk U, von Bergen M, McCoy KD, Macpherson AJ, Danska JS. Sex differences in the gut microbiome drive hormone-dependent regulation of autoimmunity. Science 2013, 339: 1084–1088.

[46] Wu HJ, Wu E.. The role of gut microbiota in immune homeostasis and autoimmunity. Gut Microbes 2012; 3: 4–14.

[47] Kim CH, Park J, Kim M. Gut microbiota-derived short-chain fatty acids, T cells, and inflammation. Immune Network. 2014;14(6):277-288.

[48] Round JL, Lee SM, Li J, Tran G, Jabri B, Chatila TA, Mazmanian SK. The Toll-like receptor 2 pathway establishes colonization by a commensal of the human microbiota. Science 2011; 332: 974–977.

[49] Ivanov II, Atarashi K, Manel N, Brodie EL, Shima T, Karaoz U, Wei D, Goldfarb KC, Santee CA, Lynch SV, et al. Induction of intestinal Th17 cells by segmented filamentous bacteria. Cell 2009; 139: 485–498.

[50] Pullar T, Hunter JA, Capell HA. Which component of sulphasalazine is active in rheumatoid arthritis? Br. Med. J. 1985; 290: 1535–1538.

[51] Ogrendik M. Effects of clarithromycin in patients with active rheumatoid arthritis. Curr. Med. Res. Opin.2007; 23: 515–522.

[52] Abdollahi-Roodsaz S, Joosten LA, Koenders MI, Devesa I, Roelofs MF, Radstake TR, Heuvelmans-Jacobs M, Akira S, Nicklin MJ, Ribeiro-Dias F, et al. Stimulation of TLR2 and TLR4 differentially skews the balance of T cells in a mouse model of arthritis. J. Clin. Investig. 2008, 118: 205–216.

[53] Dorożyńska I, Majewska-Szczepanik M, Marcińska K, Szczepanik M. Partial depletion of natural gut flora by antibiotic aggravates collagen induced arthritis (CIA) in mice. Pharmacol. Rep. 2014; 66: 250–255.

[54] Xu J, Lian F, Zhao L, Zhao Y, Chen X, Zhang X, Guo Y, Zhang C, Zhou Q, Xue Z, et al. Structural modulation of gut microbiota during alleviation of type 2 diabetes with a Chinese herbal formula. ISME J. 2015; 9: 552–562.

[55] Wu HJ, Ivanov II, Darce J, Hattori K, Shima T, Umesaki Y, Littman DR, Benoist C, Mathis D. Gut-residing segmented filamentous bacteria drive autoimmune arthritis via T helper 17 cells. Immunity 2010; 32: 815–827.

[56] Yoshida S, Katoh T, Tetsuka T, Uno K, Matsui N, Okamoto T. Involvement of thioredoxin in rheumatoid arthritis: its costimulatory roles in the TNF-alpha-induced production of IL-6 and IL-8 from cultured synovial fibroblasts. J Immunol. 1999; 163(1):351-8

[57] Scher JU, Sczesnak A, Longman RS, Segata N, Ubeda C, Bielski C, Rostron T, Cerundolo V, Pamer EG, Abramson SB, et al. Expansion of intestinal Prevotella copri correlates with enhanced susceptibility to arthritis. Elife 2013; 2: e01202.

[58] Maurice, MM, Nakamura H, Gringhuis S, Okamoto T, Yoshida S, Kullmann F, Lechner S, van der Voort EA, Leow A, Versendaal J, et al. Expression of the thioredoxin-thioredoxin reductase system in the inflamed joints of patients with rheumatoid arthritis. Arthritis Rheum. 1999; 42: 2430–2439.

[59] Atarashi K, Nishimura J, Shima T, Umesaki Y, Yamamoto M, Onoue M, Yagita H, Ishii N, Evans R, Honda K, et al. ATP drives lamina propria T(H)17 cell differentiation. Nature 2008; 455: 808–812.

[60] Taneja V, Krco CJ, Behrens MD, Luthra HS, Griffiths MM, David CS. B cells are important as antigen presenting cells for induction of MHC-restricted arthritis in transgenic mice. Mol. Immunol. 2007; 44: 2988–2996.

[61] Lubberts E, van den Bersselaar L, Oppers-Walgreen B., Schwarzenberger P, Coenen-de Roo, CJ, Kolls JK, Joosten LA, van den Berg WB. IL-17 promotes bone erosion in murine collagen-induced arthritis through loss of the receptor activator of NF-_B ligand/osteoprotegerin balance. J. Immunol. 2003, 17, 2655–2662.

[62] Kim KW, Kim HR, Park JY, Park JS, Oh HJ, Woo YJ, Park MK, Cho ML, Lee SH. Interleukin-22 promotes osteoclastogenesis in rheumatoid arthritis through induction of RANKL in human synovial fibroblasts. Arthritis Rheum. 2012; 64: 1015–1023.

[63] Ryu S, Lee JH, Kim SI. IL-17 increased the production of vascular endothelial growth factor in rheumatoid arthritis synoviocytes. Clin. Rheumatol. 2006; 25: 16–20.

[64] Moran EM, Mullan R, McCormick J, Connolly M, Sullivan O, Fitzgerald O, Bresnihan B, Veale DJ, Fearon U. Human rheumatoid arthritis tissue production of IL-17A drives matrix and cartilage degradation: synergy with tumour necrosis factor-_Oncostatin M and response to biologic therapies. Arthritis Res. Ther. 2009; 11: R113.

[65] Jovanovic DV, Di Battista JA, Martel-Pelletier J, Jolicoeur FC, He Y, Zhang M, Mineau F, Pelletier JP. IL-17 stimulates the production and expression of proinflammatory cytokines, IL-_ and TNF-_, by human macrophages. J. Immunol. 1998; 160: 3513–3521.

[66] Catrina AI, Joshua V, Klareskog L, Malmström V. Mechanisms involved in triggering rheumatoid arthritis. Immunol. Rev. 2016; 269: 162–174.

[67] Vaahtovuo J, Munukka E, Korkeamäki M, Luukkainen R, Toivanen P. Fecal microbiota in early rheumatoid arthritis. J. Rheumatol. 2008, 35, 1500–1505.

[68] Gul'neva MIU, Noskov SM. Colonic microbial biocenosis in rheumatoid arthritis. Klin. Med. 2011; 89: 45–48.

[69] Liu X, Zou Q, Zeng B, Fang Y, Wei H. Analysis of fecal Lactobacillus community structure in patients with early rheumatoid arthritis. Curr. Microbiol. 2013; 67: 170–176.

[70] Zhang X, Zhang D, Jia H, Feng Q, Wang D, Liang D. The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. Nat. Med. 2015; 21: 895–905.

[71] Jia W, Li H, Zhao L, Nicholson JK. Gut microbiota: a potential new territory for drug targeting. Nat. Rev. Drug Discov. 2008; 7: 123–129.

[72] Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly-Y M, Glickman JN, Garrett WS. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science 2013; 341: 569–573.

IntechOpen