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Review

Gut microbiota and inflammatory joint diseases

Maxime Breban [a,b,c,*]

[a] Service de Rhumatologie, Hôpital Ambroise-Paré (AP–HP), 9, avenue Charles-de-Gaulle, 92100 Boulogne-Billancourt, France
[b] Laboratoire d'Excellence, Université Paris Diderot, Sorbonne Paris Cité, 75013 Paris, France
[c] INSERM U1173, UFR des Sciences de la santé Simone-Veil, Université de Versailles-Saint Quentin, 2, avenue de la source de la Bièvre, 78180 Montigny-le-Bretonneux, France

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ABSTRACT

In most chronic inflammatory diseases, the cause remains unknown. Chronic infection is, however, among the current hypotheses. Recent technological advances have allowed in-depth studies of the gut microflora, or microbiota, which contains a vast array of organisms, most of which cannot be cultured. Inflammatory bowel disease has been associated with distinctive changes in the gut microbiota, which persist between disease flares and may play a pathogenic role. Links have been demonstrated between the gut microbiota and joint inflammation in murine models of arthritis but have received little attention in human patients. Recent work has nevertheless demonstrated substantial alterations in the gut microbiota in patients with rheumatoid arthritis, psoriatic arthritis, or spondyloarthritis, with differences across diagnoses and studies. Interestingly, some of these alterations resemble those now firmly established in inflammatory bowel disease; examples include decreased microbial diversity and lower frequencies of bacterial groups belonging to the Firmicutes phylum known to have immunoregulatory properties. These new findings open up important new horizons both for understanding disease and for developing novel biomarkers and treatment strategies.

1. Introduction

Most of the chronic inflammatory diseases remain unexplained. Genetic factors have been an active field of research in recent years that has identified many susceptibility factors. Each of these factors, however, generally plays only a small role, and genetics only partially explain the development of chronic inflammatory diseases [1].

The role for the environment has received less research attention. Environmental factors include microorganisms, in particular those found in vast amounts in the gut. The microorganisms that colonize the gut, designated collectively by the term microbiota or microbiome, are more numerous than the cells in the human body (up to 10^{14} per individual). Most commensal gut microorganisms are strictly anaerobic bacteria that cannot be cultured. This vast territory long remained uncharted, since it was not readily accessible to investigation. Nevertheless, growing evidence suggests that imbalances in the microbiota (or dysbioses) may contribute to the pathogenesis of chronic inflammatory disease that remain unexplained to date. Interestingly, the gut microbiota is transferred in part from mother to child, and its composition may be influenced in part by genetic factors [2,3].

New tools developed in recent years, such as high-throughput sequencing, have provided a clear picture of the gut microbiota [4]. These tools involve either sequencing bacterial DNA fragments that encode species-specific 16S ribosomal RNAs or sequencing all bacterial DNAs then assigning them to genes, which can then be grouped into species by comparison with a reference gene catalogue. The catalogue for the human gut now contains about ten million bacterial genes ascribed to a few thousand species. Overall, these species seem to exert beneficial effects, such as protection of the gut mucosa against invasion by pathogenic organisms, transformation of food constituents into useful nutrients, and maintenance of immune system homeostasis [5]. The species found in the microbiota vary widely across individuals, in large part due to environmental factors, particularly the diet. Thus, each individual carries a few hundred bacterial species in a distinctive distribution that remains relatively unchanged throughout adulthood [5]. However, although the predominant species differ across individuals, they belong to the same phylogenetic branches found in all humans. The three main phyla in humans thus account for 98% of the gut microbiota. They are Firmicutes, which include the genera *Eubacterium*, *Clostridium*, *Ruminococcus*, and *Butyrivibrio*;

* Correspondence. Service de Rhumatologie, Hôpital Ambroise-Paré, 9, avenue Charles-de-Gaulle, 92100 Boulogne, France.
E-mail address: maxime.breban@aphp.fr

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Table 1
Taxonomy of the main bacterial species found in the human gut microbiota.

Relative abundance	Phylum	Genus	Group	Anaerobe metabolism	Gram stain
Dominant flora					
30–52%	Firmicutes	*Eubacterium*	*rectale* (cluster XIVa)	Obligate	+
		Clostridium	*coccoides* (cluster XIVa)	Obligate	+
		Clostridium	*leptum* (cluster IV)	Obligate	+
		Ruminococcus	(clusters IV and XIVa)	Obligate	+
		Butyrivibrio	(cluster XIVa)	Obligate	+
9–42%	Bacteroidetes	*Bacteroides*		Obligate	–
		Prevotella		Obligate	–
		Porphyromonas		Obligate	–
1–13%	Actinobacteria	*Bifidobacterium*		Obligate	+
		Colinsella-Atopobium		Obligate	+
Subdominant flora					
2%	Lactobacillae	*Lactobacillus*		Obligate	+
2%	Streptococci	*Streptococcus*		Facultative	+
0.4–1%	Enterobacteria	*Escherichia*		Facultative	–

Bacteroidetes, with the genera *Bacteroides*, *Prevotella*, and *Porphyromonas*; and the less abundant Actinobacteria, which include the genus Bifidobacterium. Bacteria found in smaller numbers include enterobacteria (e.g., *Escherichia coli*), Lactobacillus, and streptococci (Table 1). It is worth noting that the composition of the gut microbiota in the general population seems to fall into three main enterotypes, each characterized by the predominance of one bacterial group: *Ruminococcus*, *Bacteroides*, or *Prevotella* [6]. The predominant group seems influenced in part by the diet and may explain a number of dietary risk factors for diseases such as colon cancer, obesity, metabolic syndrome, and atherosclerosis. Thus, a diet high in animal fat and protein (the Western diet) is associated with predominance of the *Bacteroides* genus (which seems particularly abundant in patients with obesity and/or metabolic syndrome), whereas a diet with a higher carbohydrate content may promote the development of *Prevotella* [7,8].

Gut microbiota alterations with a potential role in disease development were first reported for chronic inflammatory bowel diseases (IBDs). Convincing evidence of gut dysbiosis has been obtained for both Crohn's disease and ulcerative colitis. Interestingly, gut microbiota changes have been demonstrated early in the course of IBD, before treatment initiation, as well as during disease remissions. These findings suggest that the gut dysbiosis may have a pathogenic role, as opposed to being a mere side effect of the chronic inflammation [9,10]. Crohn's disease is characterized by decreased diversity of the microbiota, particularly within the Firmicutes phylum, with diminished counts of bacteria belonging to the *Clostridium* clusters IV and XIVa (Table 1), such as the *Clostridium leptum* group (cluster IV, Table 1) and, more specifically, *Faecalibacterium prausnitzii*. On the other hand, patients with Crohn's disease harbor increased numbers of potentially proinflammatory facultative anaerobes such as adherent and invasive *E. coli* strains [10].

2. Influence of the microbiota on the immune response

Enormous research interest has been sparked by the possibility that commensal microorganisms, particularly those colonizing the gut, may influence immune responses. There is general agreement that some bacterial species may affect the immune system by directing it toward certain types of either effector or regulatory responses. The underlying mechanisms were recently unraveled in murine models.

Among gut commensal microorganisms, *Clostridium*, a genus of the Firmicutes phylum (clusters IV and XIVa, Table 1), exhibits the distinctive feature of preferentially colonizing the deepest folds of the gut mucosa, where the organisms come in direct contact with the epithelial cells, contributing to their good health by releasing butyrate, a key nutrient for colonocytes [11]. Butyrate is a short-chain fatty acid released (together with acetate and propionate) when polysaccharides in food are fermented by the gut microbiota. Butyrate also exerts direct antiinflammatory effects on gut cells, both by promoting chromatin hyperacetylation via histone deacetylase inhibition, thereby inhibiting gene transcription; and by inhibiting the activation of the transcription factor NF-κB, thus decreasing the production of proinflammatory cytokines. In addition, several *Clostridium* species belonging to clusters IV and XIVa contribute to the induction of CD4 + FoxP3+ regulatory T cells (Tregs) in the colonic mucosa and promote the production of anti-inflammatory mediators such as IL-10 by Tregs or of TGF-β and the enzyme indoleamine 2,3-dioxygenase (IDO) by colonic epithelial cells. In keeping with these effects, high levels of *Clostridium* clusters IV and XIVa confer resistance to allergy and gut inflammation in mouse models [11].

Bacteroides fragilis, another commensal bacterial species, specifically activates IL-10-producing CD4 + FoxP3+ Tregs via interaction of its capsular polysaccharide A with the TLR2 receptor expressed by these cells [12]. On the other hand, another clostridial species, *Candidatus arthromitus* or segmented filamentous bacteria (SFBs), which colonizes the mouse gut, is a powerful inducer of effector CD4+ T cells of the Th17 type [13]. This property was recently linked to the ability of SFBs to adhere to the gut epithelial cells and seems to be shared by other bacteria exhibiting the same properties, such as enterobacteria [14].

3. Role for the microbiota in animal models of arthritis

The potential influence of the microbiota on murine models of arthritis was evaluated long ago by raising mice in germ-free isolators then colonizing them selectively by microorganisms of interest.

Adjuvant arthritis induced in genetically susceptible rats by injecting bacterial peptidoglycan (Freund's adjuvant) is considered a model of both rheumatoid arthritis (RA) and reactive arthritis. Adjuvant arthritis is exacerbated in germ-free animals. Over 35 years ago, this finding prompted researchers to hypothesize the normal presence of a protective microbial flora acting via suppressor T cells [15]. Selective recolonization experiments demonstrated dominant protective effects of Gram-negative bacteria (*E. coli*, *Bacteroides*) contrasting with exacerbating effects of Gram-positive bacteria (*Bifidobacterium*, *Propionibacterium acnes*, *Lactobacillus*) [16]. Similarly, arthritis induced by immunizing rats against type II collagen, a specific constituent of the joint cartilage, was more severe in germ-free animals [17].

In contrast, germ-free conditions proved protective in other models of T-cell-dependent polyarthritis. Examples of such models