

Commensal Gut Bacteria and the Etiopathogenesis of Rheumatoid Arthritis



Although the exact sequence of steps required to induce rheumatoid arthritis (RA) is unclear, both genetic and environmental factors appear to be important. In recent years the genetics of RA have been extensively studied, with a number of important gene associations described. These studies have confirmed the importance of major histocompatibility complex (MHC) genes and identified other loci that are currently being explored. However, estimates of heritability suggest that genetic factors are only responsible for around 50% of the risk of developing RA¹. This means that environmental factors and gene-environment interactions must also play a significant role. Despite this understanding, much less attention has been focused on determining the important environmental exposures involved. It has been hard to define with certainty important environmental factors although some success has come from the description of a strong link between smoking and RA².

Infectious organisms are attractive as potential environmental triggers for the development of RA. They are ubiquitous, can alter immune functioning, and a number of infectious organisms have been strongly associated with seronegative spondyloarthropathies. We are all surrounded by an environment saturated with microorganisms that also live as commensal flora on and in our bodies. This results in our continuous exposure to a multitude of different bacteria and viruses. A number of these have previously been associated with RA, including *Mycobacterium tuberculosis*, *Proteus mirabilis*, *Escherichia coli*, Epstein-Barr virus, retroviruses, and parvovirus B19³. However, no one specific organism has emerged as a key environmental factor responsible for the development of disease.

Lack of success in defining a dominant microbial stimulus may be for a number of reasons. With the realization that the disease process in RA begins many years before clinical disease expression, the possibility is raised that we have been looking too late. The RA-associated autoantibodies rheumatoid factor (RF) and anti-citrullinated peptide may be

present 10 years before onset of clinical disease⁴. Perhaps the important events in the development of RA occur decades before disease becomes overt, possibly even during infancy or childhood. Thus, studies that have largely concentrated on the time around disease onset would miss environmental factors that act early in life. Another attractive possibility is that one specific organism is less important than the total burden of infectious exposure over a period of time. This “burden” is a challenge to measure. One approach is to look at evidence of exposure to a panel of common infections. For example, the cumulative exposure of an individual to a wide range of infectious organisms (cytomegalovirus, hepatitis A, herpes simplex type I and II, *Chlamydia pneumoniae* and *Helicobacter pylori*) affects the level of immune activation as measured by interleukin 6 (IL-6) and highly sensitive C-reactive protein (hs-CRP) levels⁵. Perhaps a particular pattern or volume of infectious exposure might alter immune function and be important in RA etiopathogenesis.

Further evidence for the role of broad infectious exposure to development of RA comes from animal models. In rodent adjuvant and collagen-induced arthritis the incidence and severity of arthritis are increased when animals are reared in a germ-free environment^{6,7}. Similar findings have come from the study of allergies where increased exposure to infectious organisms appears to decrease the incidence and severity of disease. An important message from this work is that infectious exposure important to RA development may result from unrecognized occult exposures to microorganisms without clinical evidence of infection.

Other clues to the importance of bacteria in RA come from studies of therapy. Both sulfasalazine and minocycline have been shown to be effective treatments in RA. Monocycline appears to inhibit matrix metalloproteinases, but both agents may act through antibacterial effects⁸. In addition, bacterial DNA and peptidoglycans have also been found in the synovium of individuals with RA^{9,10}.

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There is no site of greater interaction between microorganisms and the human body than the digestive tract. Commensal gut bacteria interact with specialized gut mucosa-associated lymphoid tissue (MALT), and there are specific immunoglobulins active on mucosal surfaces (sIgA). The gut is a special site for the immune system as exposure to antigens through this route can produce tolerance. The number of bacteria present in the adult gut is 1–2 kg, of which more than half have never been cultured¹¹. Despite the numbers in healthy individuals, these organisms appear to be beneficial, maintaining normal immune system function, denying space for pathogenic bacteria, and helping with digestion of food. However, despite this mainly symbiotic relationship even commensal gut bacteria can induce arthritis in animal models^{12–14}. It also appears that the genetic background of an individual, including their MHC genes, influences the composition of the intestinal flora¹⁵.

In this edition of *The Journal* Jussi Vaahtovuori and colleagues describe the presence of a different composition of fecal bacteria in individuals with RA when compared to controls¹⁶. They included individuals with recent onset RA (≤ 6 mo) and controls with fibromyalgia. Patients who had previously taken disease modifying antirheumatic drugs (DMARD) or prednisolone, who were currently taking antibiotics, or who had recently had gastroenteritis were excluded. The authors used flow cytometry, 16S rRNA hybridization, and DNA-staining. This molecular biological approach allowed analysis of the quantity of intestinal microbes and the bacterial genera present. The results showed less *Bifidobacteria*, *Bacteriodes-Porphyromonas-Prevotella*, *Bacteroides fragilis* subgroup, and *Eubacterium rectale-Clostridium coccoides* group in the guts of RA patients when compared to controls. The authors considered other causes of changed gut flora and excluded individuals with extreme dietary habits. The patients included were all from a similar geographical area, none had received DMARD, and smoking habits were similar in the RA and control groups.

A role for commensal gut bacteria in allergy and inflammatory bowel disease has been demonstrated with similar evidence. Infants with eczema appear to have significantly lower counts of *Bifidobacterium* and *Clostridium* but higher counts of total lactic acid-producing bacteria in their guts when measured in stool samples¹⁷. Adults with Crohn's disease have less *Bacteriodes-Porphyromonas-Prevotella* in the gut versus healthy controls^{18,19}.

Questions remain. Is this a case of cause or effect? Do individuals with RA have a smaller total number of bacteria in the gut or smaller numbers of particular bacterial groups but with a broader spectrum of different bacteria (perhaps some being arthritogenic)? What effect does treatment have on the composition of gut microbes? Does the composition of gut microbes change following successful versus unsuccessful treatment? How might changes in gut flora produce

changes in immune function that may lead to inflammatory joint disease? Does this explain the reported improvement in symptoms and signs seen in individuals with RA who start a vegetarian/vegan diet^{20,21}?

The important environmental drivers of RA are still being sought. However, it is conceivable that different compositions of gut flora may alter the normal physiological interactions within the intestine and expose the immune system to bacterial antigens with arthritogenic potential. Perhaps when looking for microbial triggers for RA in the environment we need to spend time looking at our most common exposure to bacteria in the form of the abundant commensal bacteria teeming on and in us every day.

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