Editorial

**Prevotella copri** and the microbial pathogenesis of rheumatoid arthritis

**Prevotella copri** y la patogenia microbiana de la artritis reumatoide

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To be able to decide what is relevant in science was never as difficult as today. The proliferation of journals and the Internet are a source of all kinds of new descriptions and interpretations, many of them right, but many others wrong or misleading. Such is the case for rheumatoid arthritis (RA) that, despite all the knowledge and new therapies, still remains an enormous challenge for its understanding. Although RA therapy has reached high levels of reasonability and many new drugs, especially biologicals, are now directed at mediators of inflammation and tissue damage known to participate in RA, most of its pathogenesis remains poorly understood. The recent finding that a high percentage of RA patients and mice with inflammatory RA-like arthritis are carriers of particular strains of bacteria in their microbiota could be a major advance in our understanding of the disease. But, without a critical approach, it might lead to additional confusion instead of the much needed clarification.

**Historical perspective**

Although several hints of familial occurrence of RA had long indicated that the disease affected only genetically susceptible individuals, the major steps in our understanding of RA started with the discovery of rheumatoid factor in 1948. This was the first indicator of the autoimmune origin of RA that led to a great deal of research. Although RA therapy has reached high levels of reasonability and many new drugs, especially biologicals, are now directed at mediators of inflammation and tissue damage known to participate in RA, most of its pathogenesis remains poorly understood. The recent finding that a high percentage of RA patients and mice with inflammatory RA-like arthritis are carriers of particular strains of bacteria in their microbiota could be a major advance in our understanding of the disease. But, without a critical approach, it might lead to additional confusion instead of the much needed clarification.

The microbiome

More recently, as in other pathologic states, the role of normal or abnormal microbiome (but not specific pathogens) has attracted a great deal of (probably too much) attention. Undoubtedly, the great loads of bacteria in our bodies, mainly the gut, are...
of major importance in shaping our physiology,\textsuperscript{24} but we are still far from understanding many aspects of host-commensal interactions in normal and pathological states. For instance, males and females have qualitative and quantitative differences in immune competence and susceptibility to autoimmune disease.\textsuperscript{25} In mice, these appear to be explained by the effects of male androgens on the gut microbiota, which leads to a lower immunoreactivity and decreased susceptibility to autoimmune diabetes. RA is more frequent in females, which could be related to the microbiota.\textsuperscript{26}

Recent studies yielded evidence of two possible links between particular Gram-negative anaerobic bacilli and RA development in humans. The first one is periodontal disease caused by \textit{Porphyromonas gingivalis}\textsuperscript{27,28} and the second is the prevalence, in the gut microbiota, of \textit{Prevotella copri}.\textsuperscript{3}

But wait! As interesting and potentially relevant as these findings appear, one must be careful. Let us not forget that through the years, the etiology of RA has been attributed to conditions ranging from infections such as tuberculosis,\textsuperscript{14} amebiasis,\textsuperscript{21} Epstein Barr virus,\textsuperscript{17} Proteus\textsuperscript{20}; endocrine imbalance,\textsuperscript{30} to surgical procedures,\textsuperscript{14} to mention just a few. In some cases it led, mostly by serendipity, to useful therapies (i.e. gold), but in others to harmful failures (insulin causing hypoglycemia). Although some of these considerations have been completely wrong, others are of importance because they are clues to identifying some of the predisposing and triggering factors for RA. Indeed it was the notion that RA was caused by hypoadrenalism and not its inflammatory nature that led Hench to the use of cortisone for RA.\textsuperscript{32}

\textbf{Porphyromonas gingivalis and periodontal disease}

The possible link of particular periodontal pathogens to connective tissue damage, including RA, in the modern era was first proposed by Engel et al. (1978) in studies of human fibroblasts exposed to \textit{Actinomyces viscosus} extracts,\textsuperscript{2} whereas the relation of rapidly progressing periodontitis to HLA-DR4 was described by Katz et al.\textsuperscript{34} Over the following years, studies from different groups established a link between \textit{Porphyromonas gingivalis} and RA, leading some to believe that this bacterium was critical for the development of RA, or even the etiological agent, based on: (1) the high prevalence of \textit{P. gingivalis} positive periodontal disease (PD) among RA patients and vice-versa;\textsuperscript{35} (2) the presence of high titers of anti-\textit{P. gingivalis} antibodies in RA;\textsuperscript{28} (3) \textit{P. gingivalis} expresses an endogenous peptidyl-arginyl deiminase (PAD) capable of citrullinating human protein substrates;\textsuperscript{36} (4) periodontal treatment leads to amelioration of RA activity.\textsuperscript{37} However, not all RA patients have PD and/or \textit{P. gingivalis}.\textsuperscript{2,35} Moreover, anti-\textit{P. gingivalis} antibodies do not predict rheumatoid arthritis.\textsuperscript{38} Finally, native bacterial PAD, which is truncated, lacks enzymatic activity,\textsuperscript{39} as opposed to previous studies that used recombinant (non truncated) bacterial PAD.\textsuperscript{36}

Does it mean that \textit{P. gingivalis} has no role in the pathogenesis of RA? Probably not, but it is not a specific pathogen, but an inciden- ficial agent non-specifically triggering autoimmune. Thus, \textit{P. gingivalis} is not the etiologic agent of RA.

\textbf{The gut microbiota}

Recent studies have brought a new partner that might help the understanding of the relationship between microbes, RA and other autoimmune diseases. Dan Littman and coworkers studied the gut microbiota in patients with new onset RA (NORA), compared to established (chronic) RA, psoriatic arthritis (PsA) and healthy individuals.\textsuperscript{3} A high proportion of NORA patients had significantly increased ratio of \textit{Prevotella} over Bacteroides organisms. The \textit{Prevotella} species in NORA patients was \textit{Prevotella copri} with statistical significances of \textit{P. copri} prevalence in NORA vs. healthy individuals, chronic RA or PsA $p=0.00002612, 0.00001031$ and 0.01698, respectively, very significant indeed. However, not all NORA patients had increased \textit{P. copri}, indicating that it is a very important, but not unique, contributing factor for the development of RA.

Studies in mice have shown that the presence of segmented filamentous bacteria (SFB) in the microbiota contributes significantly to the development of autoimmune disease in genetically susceptible hosts.\textsuperscript{4} It has been shown that the composition of the gut microbiota contributes to shape the immune system into a proinflammatory state through differentiation of CD4+ $+$ lymphocytes to the Th17 subset.\textsuperscript{40} Gut SFB, but not Bacteroides drive Th17 development and enhance arthritis in mice.\textsuperscript{41} Littman and coworkers colonized mice intestines with \textit{P. copri} to find that it favors Th17 development and experimental dextran sulfate sodium-induced colitis.\textsuperscript{3} This suggests that the role of \textit{P. copri} in human RA could be similar, as Th17 lymphocytes are the major inducers of tissue damage in RA.\textsuperscript{42} On the other hand, \textit{Porphyromonas gingivalis} also drives Th17 cell differentiation.\textsuperscript{33,34} Thus, Th17 induction represents an important link among at least two of the bacteria associated to RA and suggests that additional microbes will be identified in the future as associated to RA.

One final observation of potential importance was that the increased prevalence of \textit{P. copri} in NORA patients was inversely related to positivity for the shared epitope. The authors interpret this finding as an indication that the role of \textit{P. copri} in RA could be more important in patients with a lower load of genetic susceptibility loci, where exogenous triggers of the disease are critical.\textsuperscript{3}

Whatever the mechanism, it deserves further investigation as it is relevant for the understanding of RA and could have therapeutic implications.

In conclusion, RA is a complex genetically determined inflammatory condition of autoimmune origin, where external agents, mainly microbes, contribute in a variable manner to its onset and to its flares. Analysis of the available information must always be careful and one must not create artificial links to explain apparent contradictions. It usually leads to confusion, and waste of time and money that could be used for rational research. As Casaubon points in Umberto Eco’s novel Focault’s Pendulum “I believe that you can reach the point where there is no longer any difference between developing the habit of pretending to believe and developing the habit of believing.” Let us keep science free of this.

\textbf{References}


