Gut microbiome in rheumatic diseases

In a recent study, Deshayes *et al* used 16S ribosomal RNA gene sequencing to analyse the gut microbiome in patients with familial Mediterranean fever (FMF) complicated or not by AA amyloidosis and in patients with AA amyloidosis of another origin.¹ Compared with healthy controls, FMF was associated with decreased α -diversity (ie, microbial richness and evenness) and altered composition of the gut microbiome. Certain operational taxonomy units (OTUs) belonging to the *Clostridiales* were associated with FMF, whereas two OTUs were overrepresented in AA amyloidosis among FMF patients. The authors suggested that intestinal microorganisms may play a role in the clinical expression and pathogenesis of these diseases. In a similar study, decreased species richness diversity was shown in the microbiome of patients with systemic lupus erythematosus (SLE). Moreover, SLE was associated with intestinal outgrowth of *Ruminococcus gnavus* of the *Lachnospiraceae* family that was most pronounced in those with lupus nephritis and correlated with disease activity.²

These and previous studies in spondyloarthritis and rheumatoid arthritis reflect the growing interest of researchers to the role of the gut microbiome in shaping local and systemic immune responses and in pathogenesis of various rheumatic diseases.³ We agree with Deshayes *et al* that in the future microbiome engineering might be a useful approach to control FMF and other rheumatic diseases, for example, via correction of the altered signalling pathways, production of metabolites with drug-like activities or anti-inflammatory molecules.⁴ The utility of this strategy will probably depend on the specific role of the microbiome in the complex interplay of genetics, environment and immunity at different stages of a particular disease. Targeting each of these key components might be necessary to restore the equilibrium between them.³

However, the clinical significance of the currently available evidence should not be overestimated, and it is too early to make any far-reaching conclusions. Which came first: the chicken or the egg? This causality dilemma always arises during microbiome studies revealing associations with health or disease.⁵ The old adage that 'correlation does not imply causation' was recently reinforced by Duvallet *et al* who performed a cross-disease meta-analysis of 28 published case-control gut microbiome studies.⁶ Some diseases were characterised by the presence of potentially pathogenic bacteria, while others showed a depletion of health-associated microbes. Nevertheless, many bacteria, which related to certain diseases in individual studies, in fact, were non-specifically associated with multiple disorders, indicating a shared response to health and disease.

Gut microbiome composition differs across regions and ethnicities, changes over time, and can be influenced by multiple factors, including, among others, diet, lifestyle, hormonal cycles, disease, comorbidity, exposure to antimicrobial agents, and so on. Certain region-specific factors influencing gut microbiome composition could predominate over others, which may have a profound impact on the results of the screening studies. In the Dutch population, individuals belonging to a certain ethnic group and living in the same city tended to share gut microbiota characteristics. Hence, the ethnic origin of individuals may be an important factor to consider in microbiome research,⁷ particularly in patients with FMF, which shows a marked ethnic distribution.

Antibiotic and non-antibiotic drug use may be another confounding factor in gut microbiome studies. Maier *et al* found that 24% of more than 1000 drugs, including members of all therapeutic classes, inhibited the growth of at least one representative gut bacterial strain.⁸ Of note, side effects resembling those of antibiotics, for example, diarrhoea, which frequently occurs in colchicine users, were associated with anticommensal activity. Therefore, regular drug treatment may contribute to a decrease in the diversity of microbiomes.

Proof-of-concept studies using disease-associated bacteria are needed to establish the implication of putative candidate for the onset of disease or its beneficial effects.⁵ Such research will be a challenge for investigators since many gut bacteria are present in low numbers and cannot be cultivated in quantities sufficient for *in vivo* testing.⁹ Moreover, the choice of microbiota subpopulation, that is, faecal, luminal or mucosa-associated, might be important for a proper stratification of patients.⁵

In summary, it is well-known that pathogenic microorganisms contribute to the aetiology and/or clinical course of certain rheumatic diseases, that is, reactive arthritis (genitourinary or gastrointestinal infections), polyarteritis nodosa (hepatitis B virus (HBV)), cryoglobulinaemic vasculitis (hepatitis C virus (HCV)) or granulomatosis with polyangiitis (*Staphylococcus aureus*). Vaccination against HBV infection has already resulted in a significant decrease in the incidence of polyarteritis nodosa, whereas wider treatment coverage of patients with HCV infection may have a similar effect on the epidemiology of HCV-associated cryoglobulinaemic vasculitis.¹⁰ Pioneering research of human microbiome is likely to provide greater insights into the mechanisms of inflammatory disease and may even lead to new treatment or prevention solutions. However, disease associations from the individual case-control studies should be interpreted with caution since most of them may found to be non-specific and indicative of a shared response to disease.⁶ *Correlation isn't causation, but sure is a hint* (Edward Tufte, American Statistician).

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