Editorial paper

Reumatologia 2020; 58, 4: 189–190
DOI: https://doi.org/10.5114/reum.2020.98427

How the gut microbiota contributes to changes of autoimmune phenotype – from molecular studies to clinical utility

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Analyzing the current state of knowledge about the microbiota and the microbiome, nobody would expect that microorganisms living in the human body would have such a huge impact on our health state and the pathogenesis of many entities. The idea that gut microorganisms could affect the development of inflammatory bowel diseases seems to be quite rational, but a connection with depression seems rather tenuous. Surprisingly, a link between the gut-brain axis and microbiota also exists [1].

Nevertheless, long before the investigation of the microbiome became technically possible, it was suggested that gut microbes are involved in autoimmunity, leading to clinical inflammatory arthritis. The occurrence of inflammatory and autoimmune diseases, including rheumatic diseases, has been growing worldwide, but at the same time, we can also observe increased physician knowledge and earlier diagnosis. Moreover, research on the microbiome results mostly from the development of new, high-throughput technologies.

To date, the cause of rheumatic diseases is not fully understood, but it is believed that a combination of genetic and environmental factors is involved in their pathogenesis. Despite the constant evolution of the knowledge about its epidemiology, genetic susceptibility and pathophysiological mechanisms, rheumatic diseases remain disorders with a very variable course and significant inter-individual variability. They have an unpredictable prognosis, depending mainly on the severity of disease activity, organ damage, and response to the treatment. Recently, disturbed microbial composition and function, defined as "dysbiosis", has been proposed as one of the potential mechanisms that may be important for the autoimmune rheumatic disease phenotype [2, 3]. However, the links between rheumatic diseases and the microbiome remain largely unknown.

Unicellular organisms were pioneers in the evolution of the Earth's ecosystem. The co-evolution of bacteria and other symbiotic microbes such as archaea, viruses, fungi, and protozoa with their multicellular hosts has gradually built a unique micro-ecosystem, termed the "microbiota", whereas microbes with their genomic elements are defined as the microbiome [4].

Microorganisms can implant on open surfaces such as the skin, digestive tract, respiratory system and urogenital tract and develop into local microflora with distinctive features. Overall, the microflora shares a survival niche with its hosts, exhibiting traits such as adaptation to the environment and interdependence with the hosts, and plays a unique and key role in human physiological and pathological processes. The gut microbiota is the main source of microbes that can exert beneficial or pathogenic effects on the host's health [5].

The first association between rheumatoid arthritis (RA) development and infectious organisms dates to the back 1990s [6] when the correlation between the level of antibodies against *Bacteroides gingivalis* and *Eubacterium saburreum* and periodontosis in RA patients was described. Further research revealed that *Porphyromonas gingivalis*, the major aetiological agent of periodontosis, expresses peptidylarginine deiminase, which is a crucial enzyme in the citrullination process. Interestingly, anti-cyclic citrullinated peptide autoantibody and citrullinated peptide are involved in the breaking of self-tolerance and development of autoimmunity in RA [7].

According to the recent findings, in the case of lupus nephritis, the internal gut environment may play a more critical role than genetic factors in renal flares [8].

The microbiome modulates many aspects of the normal functions of the immune system and gut such as provisions of nutrients, absorption, as well as metabo-

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Submitted: 5.08.2020; **Accepted:** 6.08.2020

lism. Abundant evidence suggests that Treg/Th17 balance is regulated by the microbiome [9].

The commensal *Bacteroides fragilis* controls the balance between Th1 and Th2 cells as well as managing regulatory T (Treg) cell development. Moreover, *Clostridia* spp. and bacteria-derived SCFAs are powerful mediators of the effect of the microbiota on Treg cell induction. The segmented filamentous bacteria promote the function of Th17 cells through IL-23, IL-22 and serum amyloid A. The "crosstalk" between the gut microflora and the immune system plays an important role in inducing tolerance to self-antigens and commensal bacteria, not only in the intestinal mucosa, but also at the systemic level, without compromising their ability to respond to invading pathogens. Another aspect is the interaction between microbial ligand and Toll-like receptors (TLRs) which are crucial components of innate immunity. It seems that TLR pathways in intestinal epithelial cells depend on cell polarization (apical and basolateral cell sides) [10].

Sometimes, a product of commensal bacteria may serve as a potential diagnostic tool. An example can be found in the case of lipid 654 and multiple sclerosis. Lipid 654 is a lipodipeptide produced by gastrointestinal and oral bacteria and is found to be a human and mouse Toll-like receptor 2 ligand. Multiple sclerosis patients in comparison to healthy subjects or patients with Alzheimer's disease are characterized by a very low serum level of abovementioned lipid.

Nevertheless, translation of knowledge about the impact of the microbiome/microbiota to autoimmune disease pathogenesis and medical intervention may be difficult because of its huge complexity. Promising results of fecal microbiota transplantation have already been obtained. However, characteristics of a healthy microbiome and a validated medical procedure have to be determined.

The microbiome is one of the paradigms for personalized medicine, because biologic differences in patient microbiomes persist and they will likely persist. Therefore, a more accurate understanding of the molecular pathways leading to dysbiosis-related pathologies can enable the development of individualized interventions that could help us control the development, progression, and variable symptoms of autoimmune diseases. Consequently, microbiome characterization and manipulation may be a potential therapeutic strategy for improving and potentially fully re-establishing the normal functioning of the immune system.

The authors declare no conflict of interest.

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