

## Microbiome in Sjögren's syndrome: here we are

Manasson *et al*<sup>1</sup> wrote an interesting review on what is known with regard to the application of microbiome research for diagnostic and research purposes within autoimmunity and rheumatology. The authors focused this review on the connection between the microbiome and rheumatoid arthritis (RA) as for long it has been presumed that microbiota are contributors to the development and progression of RA. Besides RA, the review also discussed microbiome studies in systemic lupus erythematosus (SLE) and systemic sclerosis. Remarkably, no attention was paid by Manasson *et al* to the potential involvement of the microbiome in Sjögren's syndrome (SS). SS is the second most prevalent systemic rheumatic autoimmune disease after RA and the potential involvement of the microbiome in SS-patients is yet also extensively reported. The current knowledge on the relationship between the human microbiome and SS reveals possible pathogenic mechanisms and forms a basis for future treatment options through influencing the microbiome. Thus, the current knowledge on the SS–microbiome connection is an important addition to the review of Manasson *et al*.<sup>1</sup>

Thus far, all studies that compared the gut microbiome of SS patients with healthy or population controls have shown that the composition of the gut microbiome in SS patients differs from controls.<sup>2–7</sup> Mandl *et al*<sup>3</sup> found that severe intestinal dysbiosis (measured with a 16S rRNA-based dysbiosis test) was more prevalent in primary SS (pSS) patients (21%) than in healthy controls (3%). Importantly, SS patients with severe intestinal dysbiosis had higher disease activity score, higher faecal calprotectin and lower C4 concentrations in blood samples, suggesting a connection between dysbiosis in the gut microbiome, gut inflammation, systemic inflammation and disease severity. Other studies also reported correlations between gut microbiome parameters and SS disease severity, especially related to dry eye symptoms.<sup>2,5</sup>

A relatively frequent finding in the gut microbiome of SS patients is a higher relative abundance of phylum Bacteroides, expressed as a lower Firmicutes:Bacteroides ratio, compared with controls.<sup>4,5,7</sup> We have previously shown that the relative abundance of three Bacteroides species (ie, *B. vulgatus*, *B. uniformis* and *B. ovatus*) was significantly higher in pSS patients (n=39) than in population controls (n=965).<sup>4</sup> Similar to patients with SS, SLE patients also showed a lower Firmicutes:Bacteroides ratio in the gut microbiome.<sup>4,8</sup> The three aforementioned Bacteroides species were also higher in SLE patients than in population controls.<sup>4</sup> Another Bacteroides species, *Bacteroides thetaiotaomicron* (*B. theta*), was higher in pSS and SLE patients compared with controls, but only significant for SLE.<sup>4</sup> The species *B. theta* is of major interest, because Greiling *et al*<sup>9</sup> identified this species as a potential gut pathobiont (ie, a potential pathogenic micro-organism, which, under normal circumstances, is harmless). Its pathogenic role could be ascribed to the finding that lysates of *B. theta* can bind to serum from anti-Ro60-positive SLE patients. Furthermore, B-cell and T-cell responses to the Ro60-protein occurred after monoclonisation of mice with *B. theta*, subsequently leading to enhanced lupus-like disease in mice.<sup>9</sup> Because anti-Ro60 autoantibodies are observed in up to 70% of pSS patients, the findings of Greiling *et al*<sup>9</sup> may suggest a potential role for this species in the pathogenesis both for SLE and also for pSS. However, there is no evidence for an association between the presence of anti-Ro60 auto-antibodies in serum and *B. theta* relative abundance in faecal samples of both type of patients.<sup>4,9</sup> Therefore, future studies should both measure

relative abundance and also perform quantitative microbiome profiling.<sup>10</sup>

The Firmicutes:Bacteroides ratio as well as the overall gut microbiota composition of pSS patients and SLE patients are very similar and differ from that of population controls.<sup>4</sup> Dysbiosis may also be present in other systemic autoimmune diseases. Bellocchi *et al*<sup>6</sup> observed that the gut microbiome of patients with systemic autoimmune diseases (SS, SLE, primary antiphospholipid syndrome and undifferentiated connective tissue disease) differed from that of healthy controls, but not between the of the various systemic autoimmune diseases. Possibly, a dysbiosis in the gut microbiome may predispose to systemic inflammatory diseases.

De Paiva *et al*<sup>2</sup> showed in a mouse model for SS that gut dysbiosis worsens the response to desiccating stress and increased production of T-cell related cytokines in conjunctival epithelium. Zaheer *et al*<sup>11</sup> showed in another mouse model for spontaneous SS (CD25 knock-out mice) that germ-free CD25KO mice developed sooner and more severe dacryoadenitis than conventional housed mice. Furthermore, Zaheer *et al*<sup>11</sup> and Wang *et al*<sup>12</sup> showed in the same mouse model, that a faecal microbiome transplant from conventional mice to mice with SS-like lacrimal keratoconjunctivitis reversed the dry eye phenotype.

Multiple studies have confirmed that the oral microbiome in SS patients significantly differs from that of healthy individuals.<sup>2,13–21</sup> Although we cannot exclude the possibility that certain species of bacteria may be involved in the development of SS and that disease-specific factors of SS influence the oral microbiome, the consensus is that reduced salivary secretion is the most important factor in shaping the oral microbiome in SS.<sup>15,16,18,20</sup> For example, the relative abundance of specific microbiota (ie, genera Lactobacillus, Haemophilus and Neisseria) significantly correlated with salivary secretion rate.<sup>15,16</sup>

Manasson *et al*<sup>1</sup> provide a useful overview of the dos and don'ts for microbiome research in rheumatic diseases. Based on the studies discussed above, we suggest three additional 'do or don'ts'. First, studies should include more than one rheumatic disease in order to assess whether there is an underlying shared mechanism by which microbiota play a role in the pathogenesis of rheumatic autoimmune diseases. Second, studies should be extended from human case–control studies to intervention studies and other experimental approaches (eg, ex-vivo studies) in order to obtain essential additional knowledge to explain the results. Finally, human microbiome studies should not be restricted to faecal samples alone.

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