Can sexual dimorphism in rheumatoid arthritis be attributed to the different abundance of *Gardnerella*?

Rheumatoid arthritis (RA) is a common chronic inflammatory joint disease that can cause recurrent attacks of joint pain and swelling. Progression of RA eventually causes joint destruction, ankylosis and deformity, which are associated with significant increases in socioeconomic costs and burdens.^{1,2} Epidemiological studies conducted worldwide have shown that women are more likely than men of the same age to develop RA, and that the prevalence increases with age. More importantly, relevant literature indicates that the prevalence of RA continues to increase among women.^{3,4} In addition, female patients experience more severe joint dysfunction compared with male patients.⁴ Emerging data clearly demonstrate that women with RA have a significantly worse functional status as measured by instruments such as the 28-joint Disease Activity Score (DAS28), Health Assessment Questionnaire and visual analogue scale.^{4,5} Consequently, an understanding of the causes of this sexual dimorphism may provide new insights and guidance for the development of interventions intended to reduce the incidence of RA.

Previously, this sexual dimorphism of RA has been explained in terms of genes located on the X and Y chromosomes, sex hormones and specific physiological and psychosocial conditions.⁴ However, the above perspectives were accompanied by corresponding limitations. Notably, most of the relevant literature tended to elaborate from the perspective of sex hormones. Those studies focused on the effects of sex hormones on the immune system and enabled a detailed understanding of the target immune cells and immune-related genes regulated by sex hormones. Similarly, the causes of this sexual dimorphism remain equivocal.

Recent work by Kishikawa *et al* is expected to elucidate this phenomenon of RA. The researchers performed a genome-wide association study (GWAS) to analyse the role of the gut microbiome in Japanese patients with RA.⁶ In this study, faecal samples were subjected to whole-genome shotgun sequencing. Through case-control phylogenetic association tests conducted using a generalised linear regression model, nine strains present at significantly higher levels of abundance in patients with RA were finally identified, namely *Prevotella denticola*, *Gardnerella*, *Gardnerella vaginalis*, *Porphyromonas somerae*, *Prevotella marshii*, *Prevotella disiens*, *Bacteroides sartorii*, *Prevotella corporis* and *Prevotella amnii*.⁶ Moreover, the authors clearly demonstrated correlations of multiple *Prevotella* spp beyond *P. copri* with the aetiology of RA. Furthermore, a gene related to oxidative stress (R6FCZ7) was more abundantly expressed in patients with RA than in healthy subjects. Moreover, by comparing the results of a RA microbial GWAS with those of a RA GWAS, the authors determined a population-specific biological pathway linking the metagenome and host genome. These results newly revealed a relationship between the gut microbiome, host genome and RA pathology, and thus represent a new reference that better clarifies the aetiology of RA.⁶ Certainly, this study is expected to explain the sexual dimorphism of RA because of the nine strains mentioned by Kishikawa *et al*, *Gardnerella*, or *G. vaginalis*, is a clinical indicator of vaginitis in female patients. This gram-negative bacillus is isolated from female vaginal secretions and is the most frequent causative organism of vaginitis.^{7,8} Consequently, might we also

interpret the differential treatment of RA according to sex from the perspective of the microbiome?

We propose the following scientific hypothesis or conjecture: *Gardnerella* or *G. vaginalis* may be associated with sexual dimorphism in RA. To our knowledge, however, no previous study has clarified this phenomenon of sexual dimorphism directly from the perspective of the microbiome. Therefore, we considered whether the mechanism of bacterial vaginitis, which is closely related to *Gardnerella*, might provide some clues. Fortunately, a new review of *Gardnerella* and vaginal health revealed that *Gardnerella* spp are related to female vaginal infection and also appear in other types of infection.⁸ More notably, these other types of infections include conditions such as acute hip arthritis, hip swelling, disc space infection, discitis, spinal osteomyelitis, joint infection and reactive arthritis.⁸ Although these phenomena were described only in certain clinical cases, the data were sufficient to suggest an association of *Gardnerella* with severe RA symptoms in female patients. However, we did not know whether the above relationship was direct or indirect. The relevant literature mentioned a mutually beneficial relationship between *Gardnerella* and *Prevotella bivia*.⁹ More precisely, specific amino acids produced by *Gardnerella* could be used by *P. bivia*, thus enhancing the growth of the latter species.⁹ This led to the bold speculation of an unknown homoplastic link between certain strains of *Gardnerella* and *Prevotella*. In other words, an interaction of *Gardnerella* with *Prevotella* may contribute to the onset of RA. The different concentrations of *Gardnerella* in male and female humans would eventually lead to sexual dimorphism in RA. In this regard, a single strain of *Gardnerella* could be isolated, cultured and transplanted into germ-free mice to verify the existence of a direct relationship with RA. *Prevotella* should also be isolated, cultured and transplanted into germ-free mice together with *Gardnerella*. A single homologous *Prevotella* strain should also be transplanted into germ-free mice as an experimental control. Such an experiment may roughly prove that *Gardnerella* directly influences the onset of RA by interacting with *Prevotella* spp.

In addition, relevant reports have mentioned that sex hormone levels may support the expansion of some selected microbial lineages via a positive feedback mechanism, which would contribute to the sexual dimorphism phenomenon observed in autoimmune diseases.^{10,11} In other words, changes in the compositions of some microbial lineages may be affected by sex hormone levels, and in turn, regulation of the composition of some microbial lineages may contribute to changes in sex hormone levels. Again, this expands our speculation that *Gardnerella* may also indirectly lead to sexual dimorphism in RA by influencing the levels of sex hormones.

Regardless, more specific scientific research regarding this issue is needed. Although some of the aforementioned conjectures or speculations may fail to provide further experimental verification, we still hope to discuss our ideas through this short article and hope that our colleagues in the field of RA will pay slightly more attention to *Gardnerella*.

Dongsong Liu,^{1,2} Feng Zhang,^{3,4} Hong Cao,³ Xuesong Wang^{1,2}

¹Department of Orthopedics, Affiliated Hospital of Jiangnan University, Wuxi, Jiangsu, China

²Medical College of Nantong University, Nantong, Jiangsu, China

³Clinical Study Center of Functional Foods, Affiliated Hospital of Jiangnan University, Wuxi, Jiangsu, China

⁴Wuxi Institute of Integrated Traditional Chinese and Western Medicine, Affiliated Hospital of Jiangnan University, Wuxi, Jiangsu, China

Correspondence to Professor Xuesong Wang, Department of Orthopedics, Affiliated Hospital of Jiangnan University, Wuxi, Jiangsu, China; biovictorwxs@163.com

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ORCID iD

Xuesong Wang <http://orcid.org/0000-0002-3686-333X>

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