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Editorial

A Crucial Factor in the Development of Therapeutic Approaches: Microgenderome?

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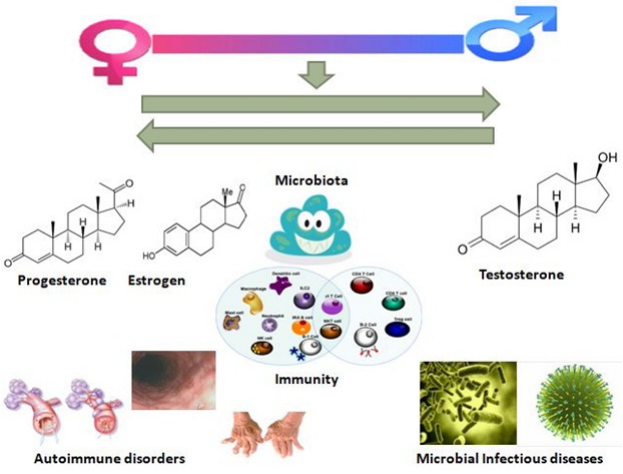
A close association of microbiota in human health continues to emerge. Microbiota has been implicated in autoimmune disorders such as type I diabetes mellitus, inflammatory bowel disease, rheumatoid arthritis and multiple sclerosis.[1] This is pointing out that early-life microbial exposure could be linked to later-life susceptibility to immune-mediated disorders. From the experimental models related to autoimmune disorders, it is known that tissue injury is prevented by alteration in microbiota or in germ-free condition. Therefore, microbial alteration can be beneficial during autoimmune disorders. However, several lines of evidence suggest the role of gender-bias, (regulation of sex-hormones by microbiota) in numerous diseases. This editorial aims to throw light on the novel, emerging triangular relationship between host microbiota, sex hormones (testosterone, progesterone and estrogen) and immune responses cumulatively termed as "Microgenderome".

Microgenderome is an interaction between microbiota, sex-hormones and immune responses of the host (Figure 1). Growing body of evidence suggest that gender-bias observed in numerous diseases is numerous diseases was host-intrinsic factor adding to severity and susceptibility of the disease. In patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, gut microbiota played a dual role in protection and exacerbation of disease.[2] This cross-sectional report and faecal microbiota data in 274 patients revealed sex-specific interactions between gut commensals, neurological and immunological responses. This was also observed in case of type I diabetes mellitus.[3] Authors showed the role of early-life microbiota influence on puberty and sex-hormonal levels in a non-obese diabetic model. When mice were made germ-free, the circulatory testosterone levels were higher in female mice than in male mice. In contrast, protection from type I diabetes mellitus was lost in germ-free mice, where testosterone levels were also found to be low to untraceable. This study provides the evidence of bi-directional relation between sex-hormones and microbiota during autoimmune diseases.

Figure 1. *Microgenderome and its Role in Autoimmune Diseases and Microbial Infections*



Interestingly, this interaction and/or communication between microbiota and sex-hormones is referred to as "interkingdom signaling". This type of signaling is commonly used by microbes during bacterial or viral infections to modulate the outcome of the infection.[4] Numerous studies have reported that males are more susceptibility to microbial infections than females. This elevated susceptibility in males could be due to differential modulation of immune response by sex-hormones compared to females, indicating the role of sex-hormones in host-microbial interactions. However, the exact mechanism on how sex-hormones modulate immune responses in microbial interactions is still unclear. To investigate this issue, Fransen and group used an animal model where the gut microbiota from conventional males or females was transferred to germ-free mice of same or opposing gender.[5] Interestingly, the type I interferon (pro-inflammatory cytokine) levels were already elevated in intestine of germ-free females. Presence of certain bacteria in male microbiota induced weight loss and inflammation in female mice after transfer. The study revealed presence of sex-specific microbial composition and their expansion in absence of innate immune responses thereby demonstrating the link between gut microbes, gender and immunity. Taken together, authors suggested gender should be considered as an important variable in developing therapeutic strategies to target gut microbiota in various disorders.

A close association of sex-hormones, gut microbiota and immune response was observed in experimental models studying trabecular bone loss. Under germ-free condition, sex-hormone deficiency increase gut permeability and upregulated inflammatory cytokines.[6] Estrogen deficiency-associated bone loss is microbiota dependent and is prevented by probiotics. Consistent with this study, it was also observed that certain lactobacilli probiotic modulated gut microbiota, downregulated inflammation and prevented trabecular bone loss in ovariectomized mice.[7] From these studies, it is understood that depletion of sex-hormones increases the gut permeability and alters the microbial composition leading to increase in osteoclastogenic inflammation. Supplementing with certain probiotic bacteria ameliorated bone loss by repopulating microbiota and down streaming the associated inflammatory cytokines.[8,9]

Taken together, these observations suggest a pivotal role of microgenderome in human health.[8] Human clinical research should consider sex comparison as an important variable. Future studies should consider measuring sex hormone levels to extend the current knowledge on triangular relation between microbes, sex hormones and related immune responses.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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