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Of mice and men and women: Sexual dimorphism of the gut microbiome

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ABSTRACT

The gut microbiome plays a critical role in developing and educating our immune system. Therefore, its now well-established role in autoimmunity and immune disorders is in some ways not surprising. However, it is well-documented in the literature that there is a female predisposition to autoimmune disorders, while sexual dimorphisms in the human microbiome have been confined largely to areas outside of the gut. Herein, we will review the evidence of sexual dimorphism in the gut microbiome in both mice and humans, how this differs in animal models versus humans, and how such dimorphisms may be established and influenced by both host and environmental factors. We will conclude with a discussion on how these aspects of the gut microbiome may contribute to both the study and pathogenesis of gender-specific autoimmunity and immune disorders.

Contents

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What is known about the gut microbiome?

- The gut microbiome plays a critical role in developing and educating our immune system.
- We examined evidence of sex differences in the gut microbiome of both mice and humans and how they can contribute to the pathogenesis of gender-specific autoimmunity.

What is new from this article as messages for women?

- Current data support sexual dimorphism of the gut microbiome in animals; however, it has been difficult to determine its role in humans due to notable differences between human and animal studies.
- Autoimmune diseases demonstrate a strong female predisposition, yet they are managed in a gender-neutral manner.
- Future studies should be aimed at ways to tailor treatment strategies that sufficiently address the sex differences that drive the pathogenesis of immune disorders.

Lessons learned from mice

The behavior of microbial communities in either conventionally colonized or gnotobiotic animal models (which possess a defined or no microbiome) can sometimes closely parallel that of the human microbiome while diverging strikingly from other phenotypes (Chung et al., 2012; Stappenbeck and Virgin, 2016). The latter is notably the case for sexual dimorphism, because the gut microbiome in essentially any host is influenced by a wide range of host and environmental factors. In humans, it is difficult to tease out the influence of each factor on the structural and functional configurations of the gut microbiome, and everything from diet to lifestyle is potentially confounded by biological sex. In mice, controlled experiments allow us to gain a better understanding of how each factor influences the abundance, composition, and diversity of the gut microbiome, but at the cost of sometimes emphasizing or exacerbating differences not present in typical human populations.

Overall microbial community differences

In mice, several studies have observed sex differences in overall gut microbial profiles between males and females, although dependent on each specific experimental design, and it can still be difficult to disentangle these from environmental effects (e.g., housing). As with many mouse microbiome studies, baseline microbial communities can differ among facilities. In some C57BL/6 wild-type mice, for example, there is a higher relative abundance of Muribaculaceae in males compared to females and a lower relative abundance of many common gut clades (Bacteroidaceae, Rikenellaceae, Lactobacillaceae, and Verrucomicrobiaceae; Bridgewater et al., 2017).

A near-opposite result was observed in B6.129S wild-type mice at a different facility, where males had a higher relative abundance of gut-typical Ruminococcaceae and *Anaerostipes*, whereas females had a higher relative abundance of less-characteristic Peptostreptococcaceae (Kozik et al., 2017). In a broader experiment, across 89 different inbred strains of mice, some gut microbial sex differences were consistent, but the majority of the differences were host-specific (and thus potentially environment-specific; Org et al., 2016). Most commonly, members of the Actinobacteria and Tenericutes phyla were more abundant in males than females, in addition to *Allobaculum*, *Anaeroplasma*, and *Erwinia*. *SMB53* from the family Clostridiaceae and *Dorea*, *Coprococcus*, and *Ruminococcus* from the Lachnospiraceae were more abundant in female mice—a notable mixture of clades that in some cases do not even occur abundantly in human guts but are present in murine contexts.

Finally, in an observation that also recurs in humans, some sexual dimorphisms occurred specifically after puberty, such as changes in simple α-diversity (i.e., the number of species per sample).

Diet

Differences in the gut microbiome in response to dietary changes are also typically much stronger in mice than in humans, and previous studies have demonstrated that male and female mice exhibit different gut microbial shifts in response to the type of diet (e.g., standard chow vs. high-fat, high-sucrose diet). Although such differences are only extreme in certain unique human populations (e.g., hunter-gatherers; Smits et al., 2017), simple ordination analysis was enough to show large interactions between sex and diet on the mouse gut microbiome subsequent to a chow versus high-fat, high-sucrose diet for 8 weeks (Org et al.. 2016). Thus, in the sense of a formal statistical interaction, both sex and diet affected the murine gut microbiome in this setting, and those effects differed by the sex–diet combination.

Another study subjected mice to chow versus a high-fat diet for 81 days, during which the high-fat diet altered the microbiota composition dramatically (Bridgewater et al., 2017). The changes in the microbial composition again differed significantly between males and females, also demonstrating that diet (and, in principle, other environmental perturbations) can interact with biological sex with respect to microbiome influences. Bolnick et al. (2014) also demonstrated that in male mice, *Lactobacillus*, *Alistipes*, Lachnospiraceae, and *Clostridium* were more abundant on a high-fat rather than a chow diet, while in females, these genera were less abundant on a high-fat diet (Bolnick et al., 2014). Taken together, these findings show that under sufficiently extreme conditions revealed by well-controlled murine environments, diet can have divergent effects on the gut microbiome based on sex.

Sex hormones

Particularly in mice, a logical hypothesis for one of the mechanisms underlying these differences is in the biochemistry of circulating sex hormones, either directly or indirectly affecting gut microbes. Even when considering only host immunity, sex hormones play a key role in the pathogenesis of gender-specific autoimmunity and immune disorders (Elderman et al., 2018; Gomez et al., 2015). Indeed, animal studies have demonstrated that castration of males leads to disease progression in systemic lupus erythematosus and type 1 diabetes (T1D), two autoimmune disorders with a female predisposition (Fox, 1992; Johnson et al., 2020). In reverse, supplementation of females with androgens offers protection from these diseases.

To study the influence of sex hormones on the development of the gut microbiome, Yurkovetskiy et al. (2013) compared the gut microbiota of mice before and after puberty. Before puberty, there was no sex difference in the gut microbiota between males and females. After puberty, there was an overall decrease in microbial diversity in the gut in males compared to females. This was the result of a surprisingly wide range of clade enrichments in males compared to females, including members of the Porphyromonadaceae, Veillonellaceae, Kineosporiaceae, Peptococcaceae, and Enterobacteriaceae. Interestingly, many of these differences were reversed by male castration, unlinking the changes from at least some of the environmental and housing confounders raised above.

Org et al. (2016) also demonstrated that gut microbiota composition is partly mediated by sex hormones in three mouse strains:

C57BL/6J, C3H/HeJ, and DBA/2J. Using gonadectomy, they showed that the abundance of family Ruminococcacea was different between gonadectomized males and control males, while *Akkermansia* was more abundant in female controls than in gonadectomized females. Upon administration of testosterone after gonadectomy, the gonadectomy-associated microbiota changes were mostly reversed in male mice. While it is difficult to determine from these experiments whether these particular effects are mouse- or facility-specific, they are arguably some of the most direct demonstrations that sex hormones in isolation can themselves influence gut microbial composition.

Bidirectionally, the gut microbiota can also modulate estrogen cycles and testosterone levels. Germ-free (GF) nonobese diabetic (NOD) male mice devoid of the commensal gut microbiota had lower testosterone levels than conventional mice with a full complement of the gut microbiota (Markle et al., 2013). Moreover, in female mice, removing the gut microbiota increased the circulating level of testosterone. In contrast, the level of testosterone decreased in antibiotic-treated male mice whose gut microbiota were depleted. Moreover, colonization of GF NOD mice with defined gut microbiota overrepresented in male mice changed the circulating levels of sex hormones in the recipient mice. These studies demonstrate that certain gut microbial species may participate in regulating the levels of sex hormones and to some degree differentiate the competing effects of environment, live microbial colonization, and microbial biochemical activity and products. For example, after fecal transplant, the gut microbiome of antibiotic-depleted recipient mice was able to predict the donor's testosterone levels, implying that sex signature of the donor informs the gut microbiome of the recipient (Mayneris-Perxachs et al., 2020).

What we know in humans

The Human Microbiome Project (HMP) was one of the earliest large-scale surveys of the body-wide human microbiome in a sizable population, spanning 18 body sites in 300 healthy individuals (Human Microbiome Project Consortium, 2012). As expected from prior, more targeted studies, the largest differences in microbial community structure arose between different body sites, with differences between subjects at the same body site still quite substantial. Notably, in a healthy population lacking overt perturbations from diseases, pharmaceuticals, or major lifestyle changes, other intrinsic factors that can influence the microbiome (including genetics) proved to have relatively little effect (Kolde et al., 2018).

This was true for sex-linked differences as well. Although some 960 microbial, enzymatic, or pathway features were associated with $\geq$1 of 15 phenotypes including age, sex, and body mass index (BMI), the degree of associations with sex was far smaller compared with that with body site, individual, or other demographic factors, such as race and ethnicity (Lloyd-Price et al., 2017). Intriguingly, however, some of the most consistent sex-related microbiome effects occurred within the vaginal microbiome across phenotypes, such as vaginal pH, indicating the importance of factors such as sex hormones in other habitats outside of the gut (Human Microbiome Project Consortium, 2012; Ravel et al., 2011).

Abundance, composition, and diversity

Apropos, other early population-wide studies in humans also failed to demonstrate significant sex differences in the gut microbiome (Jaggar et al., 2020). For example, in 2005, a study evaluated 91 subjects of northern European origin, and showed no difference in the gut microbiome based on biological sex according to Principal Coordinate Analysis (PCoA) (Lay et al., 2005). The same finding remained true in the HMP, despite its expansion to include additional data collected over 12 to 18 months after the initial visit, and more samples were deeply shotgun sequenced to increase resolution (Lloyd-Price et al., 2017). Of several thousand combinations of metagenomic taxonomic and functional features tested using updated statistical methods in this larger dataset, only one taxon, *Clostridium leptum*, and 11 pathways remained significantly different between men and women in the gut microbiome after multiple test corrections (and similarly low numbers at most other body sites). As per subsequent, more specific studies discussed below, this does not mean that no differences exist between male and female gut microbiomes in humans. Rather, these differences can be of very small effect size relative to other sources of microbial variation and/or they are highly context-dependent.

This limited range of sex-linked human gut microbial differences has been borne out of a variety of research. In 2006, an early study using targeted 16S rRNA gene fluorescence in situ hybridization probes found borderline significantly higher levels of the *Bacteroides-Prevotella* group primers among males in France and Germany compared with females of the same countries, but no biological sex effect was detectable for species-specific probes or other microbial groups (Mueller et al., 2006). In 2008, a Chinese study utilizing group-specific denaturing gradient gel electrophoresis profiling within a single human family (7 individuals) demonstrated higher abundances of *Bacteroides thetaiotaomicron* in males compared to females, although obviously with a variety of strongly confounding influences in such a small population (Li et al., 2008).

Another study also suggested that *Ruminococcus* was more abundant among Chinese women compared with men (Gao et al., 2018). In most cases, reports of substantial gut microbial differences between the sexes in typical human populations have arisen due to technical artifacts, such as the application of statistical methods that are inappropriate for microbial profiles (e.g., *t* tests; Takagi et al., 2019).

Large cohort studies with good control of potential confounding factors have generally been able to report more reliable sex-linked human gut microbiome changes, but typically at very low effect sizes that are only detectable under such circumstances. Two examples include the Belgian Flemish Gut Flora Project and Dutch LifeLines-DEEP studies, both of which suggested that women have a very slightly greater gut α-diversity compared with men (Falony et al., 2016; Zhernakova et al., 2016). A subsequent cohort study drawing subjects from four distinctive geographical regions (United States, United Kingdom, Colombia, and China) also corroborated this slightly greater α-diversity in women compared with men, although again without disentangling potential sex-confounded factors (de la Cuesta-Zuluaga et al., 2019). In agreement with the HMP, all of these studies suggest that such differences might persist only after adolescence and through middle age. In the study above, the difference in α-diversity disappeared after the average age of 40 years and was eliminated in another study after the average age of 60 years (Haro et al., 2016).

As with factors such as diet, sex-linked human microbiome differences can be more apparent in less Westernized populations, however, in which both environmental factors and gender roles are more consistent and dimorphic. Indigenous Mexican children, for example, were found to have significantly greater differences in male versus female diversity compared with urban children (Sánchez-Quinto et al., 2020). Outside of the gut, the greatest differences in human body-wide microbial communities have been linked, perhaps unsurprisingly, to age by way of sexual development. These include sometimes rapid and (relatively) dramatic changes in the skin microbiome during puberty (Jo et al., 2016; Oh et al., 2012; Park et al., 2021), and shifts in the vaginal microbiome both during onset of menarche and later during menopause (Gliniewicz et al., 2019; Hickey et al., 2015).

Sex hormones

Relatedly, this variation in sex differences with aging supports a hypothesis that sex hormones may play a role in human gut microbial dimorphisms despite their differences relative to mice. While under typical circumstances, this may manifest only indirectly or weakly in the gut, it is clear both that gut microbes can theoretically interact with sex hormones chemically and that hormone-induced immune changes could, in principle, induce gut microbial effects (Donova and Egorova, 2012).

To date, only a few studies in humans have examined the influence of sex hormones on the gut microbiome. Very preliminary work by Santos-Marcos et al. (2018) suggests that levels of estradiol may positively correlate with broad groups such as the Gammaproteobacteria, but this result is weak and dependent on questionable statistical tests in a small population . More directly, administration of exogenous sex hormones (e.g., oral contraceptives) has shown to weakly, but directly, impact the composition of the gut microbiome (Sinha et al., 2019). Similarly, the modest, but clearly causal, elimination of female sex hormones via ovariectomy caused an alteration of the gut microbiome as well (Sinha et al., 2019).

As can be inferred from these examples, and as also occurs in the vaginal microbiome, one of the strongest sex-associated effects on the gut microbiome arises during periods of substantial hormonal shifts, specifically menopause in women. Compared with postmenopausal women, premenopausal women have a higher abundance of generally short chain fatty acid-producing bacteria (Santos-Marcos et al., 2019). In particular, *Prevotella*, *Ruminococcus*, and *Roseburia*, which are among the most typical fastidiously anaerobic gut residents in healthy individuals, have all been shown to depend on both sex and menopausal status (Santos-Marcos et al., 2019). Mayneris-Perxachs et al. (2020) even suggested that the gut microbiota from postmenopausal women was more similar to that of men than to premenopausal women. However, as another reminder of the extreme subtlety of such differences, functional pathways of the gut microbiome did not differentiate between postmenopausal women and men. The gut microbiota of premenopausal women was only enriched in a small subset of genes from steroid biosynthesis and degradation pathways that could be associated with plasma levels of testosterone and progesterone.

Diet and obesity

In most human populations, dietary differences have similarly modest effects on the gut microbiome, despite its perception as one of the most ubiquitous environmental influences on our gut. However, diet remains of great interest as an intriguing therapeutic option for improving health outcomes, as it can be (relatively) easily altered. Most diet-microbiome interaction effects have been investigated in rodent models, since diet and lifestyle are heavily confounded with sex and environmental factors in humans in generally noncausal ways. Bolnick et al. (2014) observed diet-sex interaction effects in mice and fish, for example, and suggested that these might occur in certain rare clades (e.g., Fusobacteriaceae) in humans as well. Because several such animal studies have shown that these diet–sex interaction effects can occur in animals, it is notable that in many human populations they rarely do. However, this remains to be studied in more diverse, non-Westernized settings (Smits et al., 2017).

Changes in the gut microbiome during the development of obesity also follow a very similar pattern because they manifest quite strongly in animal models but only modestly in most human populations. Some of the earliest studies in animal models demonstrated that obesity is linked to a higher ratio of Firmicutes to Bacteroidetes, for example, which has replicated surprisingly well among different mice but barely at all among humans (Magne et al., 2020; Sze and Schloss, 2016; Turnbaugh et al., 2006).

The study by Haro et al. (2016) is one of few studies of the gut microbiome explicitly as a function of sex and BMI in humans. In 39 men and 36 postmenopausal women with similar diet, matched by age and stratified by BMI, the *Bacteroides* genus was lower in men than in women only when BMI was greater than 33. While the genus was negatively correlated with BMI in men, it remained unchanged in women regardless of BMI. However, again, these changes reflect only a few percent abundance in a small number of individuals.

Clinical implications in autoimmune diseases

It is thus at present difficult to determine whether sex-linked differences of immune conditions in humans are an emergent consequence of these small changes in the gut microbiome or derived from other (e.g., host) factors. In general, autoimmune disease is a consequence of an abnormal, hyperactive immune response against the self. It is well-documented that there is a higher female than male prevalence of autoimmune diseases; females are 2 to 10 times more susceptible than males to develop rheumatoid arthritis (RA), multiple sclerosis (MS), systemic lupus erythematosus, myasthenia gravis, Sjogren's syndrome, and Hashimoto's thyroiditis (Fish, 2008; Zandman-Goddard et al., 2007) The pathogenesis of autoimmunity is complex and is driven by a combination of genetic predisposition and environmental factors, such as diet, smoking, and other lifestyle factors—all, of course, in combination with the microbiome (gut and otherwise).

T1D is among the autoimmune conditions of most interest with respect to sexual dimorphism and the microbiome due to its sex-linked epidemiology in humans (Gale and Gillespie, 2001) and the demonstrable dependence of this phenotype on sex in mouse models (King and Sarvetnick, 2011; Kriegel et al., 2011; Yurkovetskiy et al., 2013). Similar to other autoimmune diseases, T1D occurs more frequently in women than men, with a ratio of 3:2 in populations of European descent (Gale and Gillespie, 2001). However, as previously stated, the relationship of this with the gut microbiome is only clear in mice: NOD mice develop diabetes spontaneously with a strong female predisposition (Yurkovetskiy et al., 2013). GF NOD mice develop diabetes more frequently than specific pathogen-free NOD mice, demonstrating that the gut commensals provide a protective role against the development of diabetes. In addition, the sex predisposition for diabetes is completely abolished in GF NOD mice, in contrast with specific pathogen-free NOD mice. Although neither gut microbial changes nor sexual dimorphism in human populations with T1D are anywhere near as apparent, these observations support the hypothesis that the sexual dimorphism of the gut microbiome can, at least in principle, be a contributor to establishing sex-specific autoimmune responses.

RA follows a similar pattern, in which no human gut microbial sexual dimorphism is typically apparent, but in which there are striking differences in mice. A humanized RA mouse model, DRB1*0401, develops arthritis in a female-to-male ratio of 3:1. Using the mouse model, Gomez et al. (2012) demonstrated a significant difference in gut microbiota composition between arthritis-susceptible and -resistant mice, specifically an increased abundance of *Clostridiales* in the susceptible mice and *Bifidobacteria* in the resistant mice. However, *Bifidobacteria*, the protective genus, was significantly more enriched in the resistant females than resistant males, but significantly more enriched in the susceptible males than females. These observations suggest that the genetic susceptibility establishes the unbalanced gut microbiomes, but initiation of RA may be driven by the impact of sex hormones on the development of the gut microbiome over time, at least under the

right (or arguably wrong) circumstances in a fragile ecology, such as laboratory mice.

The impact of sex hormones on modulating the gut microbiome is further demonstrated by experiments in a mouse model of MS, a chronic, immune-mediated demyelinating disease of the central nervous system (Benedek et al., 2017). MS has a greater prevalence among women. Interestingly, women with MS tend to experience improvement of clinical symptoms during pregnancy, implicating a therapeutic role of sex hormones in autoimmune disorders (Runmarker and Andersen, 1995). In a mouse model, pretreatment with high levels of 17-β-estradiol prevented the onset and progression of experimental autoimmune encephalomyelitis (an MS analog; Benedek et al., 2017). In this system, 17-β-estradiol also affected the microbiota composition prior to and during experimental autoimmune encephalomyelitis induction with a significant increase in the relative abundances of Lactobacillaceae (Benedek et al., 2017). Although they are not typically common in the adult human gut, the enrichment of this family is associated with host immune regulation, particularly by inducing proliferation of regulatory B cells and anti-inflammatory macrophages in the mesenteric lymph nodes of the mouse (Benedek et al., 2017).

What is clearer in humans as well, though, is that sex hormones play a pivotal role in the development of gender-specific autoimmunity independent of their interaction with the gut microbiome. β-estradiol, for example, has several functions on the intestinal mucosal surface (Gomez et al., 2015). It induces dendritic cells to produce IL-12 and INFγ, which subsequently activate inflammatory pathways mediated by IL-6 and IL-8 and polarization of T cells into Th1/Th17. It also promotes B-cell and polyclonal B-cell activation, leading to increased autoantibody production. Lastly, β-estradiol also participates in the increased gene expression involved in the Toll-like receptor pathway. In contrast, testosterone attenuates the aforementioned immune responses.

Taken together, this combination of host versus microbial and human versus mouse evidence presents a dramatically complex picture of sexual dimorphism in immune disease. Genetic factors, sex hormones, host phenotypes, sex-confounded diet, and environmental exposures, as well as the gut microbiome can all play roles, but the details and relative importance of those roles can vary greatly among settings and contexts. Not only do sex hormone phenotypes manifest (obviously) differently in mice than in humans, but the ecology of a free-living adult gut ecosystem evolved for tens of thousands of microbial generations also differs fundamentally from that of a young, isolated laboratory mouse. In both cases, genetic, environmental, hormonal, microbial, and immune factors all interact to determine health outcomes, but their individual consequences are not yet well-disentangled.

Sexual dimorphism in the skin microbiome?

In the context of this review, it is of interest to briefly touch on potential sexual dimorphisms of the skin microbiome as well because in some ways they have again demonstrated opposite effects in human versus animal models. On the skin, however, human microbial differences can sometimes exceed those of model systems, rather than the reverse. Oh et al. (2012) profiled the skin bacteria of four body sites (antecubital and popliteal fossae, volar forearm, and the nares) in relation to the Tanner stage of human development, identifying a variety of changes (particularly Actinobacteria enrichment) in adulthood. These differences were sexually dimorphic for matched ages, given the generally earlier Tanner progression of women (particularly in the nares).

Relatedly, when examining the fungal composition of the skin, *Malassezia* predominated in adults (age 18-39 years), but more diverse fungal communities colonized the skin of children (age <14 years) (Jo et al. 2016). Most recently, a longitudinal study was performed to investigate puberty-associated shifts in skin microbiota (Park et al., 2021). Twelve healthy children were followed every 6 to 18 months for up to 6 years. The skin microbiome transitioned to more adult-like microbiome during puberty, again with notable sex-specific differences. Female children shifted to greater *Cutibacterium* and *Malassezia* earlier, in agreement with their more rapid Tanner progression discussed above. In addition, the relative abundances of these taxa strongly correlated with serum sex hormone concentrations. These findings argue that the skin microbiome undergo a potentially more apparent maturation than the gut during development in a sex-dependent manner.

In contrast, according to the largest existing mammalian skin microbiome survey, biological sex has not been shown to be a significant factor in the skin microbiome of cats, dogs, and horses (Ross et al., 2018). However, in both wild and laboratory populations of house mice, biological sex has been demonstrated to play a significant role in the skin microbiome (Belheouane et al., 2020), although without close investigation of specifics (i.e., assigning overall beta-diversity shifts to individually correlated taxa). Of note, although a series of experiments have identified highly specific immune-microbial interactions on mouse skin, it is not yet clear whether these might be sexually dimorphic or, if so, how they relate to developmental processes or their human analogs (Naik et al., 2012; 2015).

Conclusion and future directions

Autoimmune diseases demonstrate a female predisposition. However, current management strategies for these conditions remain sex neutral, thereby unable to leverage the sex differences that drive pathogenesis. Although the microbiome has received great attention due to its underexplored contributions to inflammation and immunity, its role in the sexual dimorphism of these conditions has proven especially difficult to determine due to notable differences between findings in human versus animal studies and the limited data in humans. Future research should aim to delineate interactions between the sexual dimorphism of disease course (i.e., initiation, progression, and outcome) and the microbiome, focusing on health relevance in human populations in tandem with (but sometimes distinct from) potential underlying mechanisms in animal models. Identifying translationally meaningful biomarkers will not only allow clinicians to better monitor patients, but also potentially guide treatment protocols. Moreover, these biomarkers may allow researchers to develop tailored treatment strategies that sufficiently address the sex differences that exist in autoimmune diseases.

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