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Sex, Puberty, and the Gut Microbiome

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Abstract

In humans, the gut microbiome is strongly implicated in numerous sex-specific physiological processes and diseases. Given this, it is important to understand how sex differentiation of the gut microbiome occurs and how these differences contribute to host health and disease. While it is commonly believed that the gut microbiome stabilizes after 3 years of age, our review of the literature found considerable evidence that the gut microbiome continues to mature during and after puberty in a sex-dependent manner. We also review the intriguing, though sparse, literature on potential mechanisms by which host sex may influence the gut microbiome, and vice versa, via sex steroids, bile acids, and the immune system. We conclude that the evidence for the existence of a sex-specific gut microbiome is strong but that there is a dearth of research on how host-microbe interactions lead to this differentiation. Finally, we discuss the types of future studies needed to understand the processes driving the maturation of sex-specific microbial communities and the interplay between gut microbiota, host sex, and human health.

In Brief

Sex differences in the gut microbiome may impact multiple aspects of human health and disease. We review the evidence for microbial sex differences in puberty and adulthood and discuss potential mechanisms driving differentiation of the sex-specific gut microbiome.

Keywords

steroid hormones; bile acid; puberty; gut microbiome

Introduction

Next-generation sequencing (NGS) has revolutionized our understanding of the human gut microbiome. The combination of NGS, multiplex-library construction, and bioinformatics has revealed gut microbial diversity to be temporally dynamic and highly variable among both populations and individuals. Moreover, the gut microbial community collectively

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contains two orders of magnitude more genes than the human genome (Zhu, Wang, and Li 2010; Falony et al. 2016; Huttenhower et al. 2012; Levy et al. 2020). Variation in abiotic (pH, oxygen levels, nutrition) and biotic factors (immune surveillance, signaling molecules) create numerous niches along the alimentary tract that select for highly differentiated communities of microorganisms (Barlow, Bogatyrev, and Ismagilov 2020). Conversely, the microbes in the mammalian gut influence a broad range of host physiological parameters ranging from metabolism (Acharya et al. 2019; Baars et al. 2018; Colldén et al. 2019), to immunity (Vatanen et al. 2016; Candon et al. 2015; Markle et al. 2014), to the nervous system (Desbonnet et al. 2015; Heinzel et al. 2021; Murray et al. 2020), and to the reproductive system (Arroyo et al. 2019; Acharya et al. 2019).

The human gut microbiome develops rapidly after birth, when the alimentary canal is seeded by the mother and environmental microbiomes (Breitbart et al. 2008; Helve et al. 2019; Bäckhed et al. 2015; Ferretti et al. 2018; Dominguez-Bello et al. 2016; Song et al. 2021). Studies showed that the infant gut microbiome rapidly increases in diversity and begins to resemble adult gut microbiome taxonomic composition and functional pathways by 2 to 3 years of age (Koenig et al. 2011; Bokulich et al. 2016; Yatsunenko et al. 2012; Kurokawa et al. 2007). Based on these initial studies, the gut microbiome of young children was thought to be fully mature by age three. However, the gut microbiomes of children can be readily distinguished from adults (Agans et al. 2011; Yatsunenko et al. 2012; Ringel-Kulka et al. 2013; Hollister et al. 2015; Dominianni et al. 2015).

Many important and profound changes in human physiology occur during puberty, which may also be the case with the gut microbiome. In humans, sex-specific processes have been linked to the gut microbiome, including cognition and anxiety (Desbonnet et al. 2015; Murray et al. 2019), liver metabolism (Bhat et al. 2021; van Keulen et al. 2020), immunity (Wilharm et al. 2021; Shepherd et al. 2021), and menstrual regularity (Wang, Zhang, et al. 2020). In addition, diseases which emerge during and after puberty have been linked to changes in gut microbial composition, often in a sex-specific manner. These include inflammatory bowel disease (IBD) (Franzosa et al. 2019; Ferguson and Sedgwick 1994), type I diabetes (T1D) (Markle et al. 2013; Yurkovetskiy et al. 2013), lupus (Young et al. 2014; He et al. 2016), obesity (Joriba et al. 2019), polycystic ovary syndrome (PCOS) (Torres et al. 2018; van Hooff et al. 1999; Jobira et al. 2020), and endometriosis (Svensson et al. 2021; Yuan et al. 2018). In addition to playing a role in the etiology and pathophysiology of various diseases, emerging differences in gut microbiota during puberty may lead to variable responses to drug treatments. Understanding the development of sex differences in the gut microbiome may be critical for designing and optimizing therapeutic approaches to treat gut microbiome-related diseases. Given the number of sex-specific diseases related to the gut and the potential for these sex differences to impact drug therapies, it is worth reviewing what is currently known about sex differentiation of the gut microbiome and the processes that drive maturation of the sex-specific gut microbial community.

Sex Differences and the Gut Microbiome

A survey of the literature investigating the relationship of sex and the gut microbiome strongly supports the hypothesis that human and rodent gut microbiomes differentiate during

puberty and that this differentiation results in sex-specific communities by adulthood. While early data from the Human Microbiome Project (HMP) did not detect sex differences in the gut microbiome (Huttenhower et al. 2012), subsequent studies have consistently identified distinct gut microbial communities between males and females. Numerous studies in both mice and humans have found sex differences in gut microbiome beta-diversity (between-sample taxonomic composition) (Fig 1) (Takagi et al. 2019; Markle et al. 2013; Sinha et al. 2019; Dominianni et al. 2015; Mayneris-Perxachs et al. 2020; Org et al. 2016; Sheng et al. 2017; Ding and Schloss 2014; Li et al. 2008; Falony et al. 2016; Gao et al. 2018; Borgo et al. 2018; Santos-Marcos et al. 2018; Mueller et al. 2006; Cui et al. 2021; Peters et al. 2022). Multiple studies have also shown that alpha diversity (within-sample taxonomic diversity) tends to be higher in adult females than adult males, though these differences are less pronounced in older adults (Takagi et al. 2019; de la Cuesta-Zuluaga et al. 2019; Sinha et al. 2019; Falony et al. 2016; Borgo et al. 2018; Gao et al. 2018; Peters et al. 2022). Sex was also among the ten factors that most explained variability in human gut microbial composition (Falony et al. 2016).

Since multiple studies support the idea that there are sex differences in the adult gut microbiome, it follows that there must be a point during development where the gut microbiome differentiates by sex. While initial studies reported that the microbial community in young children (1–3 years of age) resembled that of adults (Yatsunenko et al. 2012; Kurokawa et al. 2007), follow-up studies showed significant differentiation of beta diversity between child and adult microbiomes (Ringel-Kulka et al. 2013; Hollister et al. 2015; Agans et al. 2011). A study of human dizygotic twins found no differentiation in gut microbial beta diversity between male and female infant twins, but did find differentiation between male and female pubertal twins (Yatsunenko et al. 2012). Similarly, another study revealed no sex differentiation in gut microbial beta diversity in pre-pubertal children, but did show differentiation by sex in pubertal subjects (Yuan et al. 2020). Moreover, beta diversity of pubertal male and female microbiomes was more similar to adult microbiomes of the same sex the further along the child was in puberty (Korpela et al. 2021). Similar patterns occurred in mouse studies: sex differences in alpha and beta diversity in mouse gut microbiomes were not observed before puberty but became evident after puberty (Markle et al. 2013; Yurkovetskiy et al. 2013). While some taxonomic differences between sexes in puberty were noted (Yuan et al. 2020; Korpela et al. 2021), there have been too few studies with small sample sizes to make strong conclusions about pubertal-specific taxonomic differences. Collectively, these studies support the idea that the mammalian gut microbiome differentiates during puberty, resulting in sex differences in adulthood.

Despite a consistent pattern of community-level sex differentiation in the gut microbiome, the specific taxa differentiated by sex varies among studies. For example, early work suggested that the ratio of the common gut phyla, Bacteroidetes and Firmicutes, differed between male and female gut microbiomes (Huttenhower et al. 2012; Gomez et al. 2012). However, follow-up studies found no difference in the Bacteroidetes to Firmicutes ratio, indicating that it is not a reliable indicator of sex differences (Takagi et al. 2019; Santos-Marcos et al. 2018; Singh and Manning 2016; Elderman et al. 2018). The abundances of specific bacterial genera or species have also not been reliable markers of sex differentiation. While individual studies identified bacterial taxa associated with microbiome

sex-differentiation, the same taxa did not change consistently in all studies. The reasons for the lack of consistency are unclear, but may partly be due to external factors influencing the microbial gut composition in the various study populations (e.g., geography, age, and diet) (Valeri and Endres 2021; Kim et al. 2019; Jaggar et al. 2020). This inconsistency may also be a result of functional redundancy in the gut microbiome. So far, most studies of gut microbiome sex differentiation have employed 16S rRNA bacterial gene sequencing which cannot directly analyze gene function (Fig. 1). Future studies applying techniques such as metagenomics, transcriptomics or metabolomics to study gut microbiome function could be useful in determining the precise nature of gut microbiome sex differentiation.

Sex steroids and the Gut Microbiome

Sex steroids are produced by the gonads during puberty in response to activation of the hypothalamic-pituitary-gonadal axis (Fig 2). Observational studies in humans and studies in rodent models collectively suggest a linkage between sex steroids and the gut microbiome. For example, several studies manipulating sex steroid levels in mice indicated that estrogen and testosterone influenced gut microbial diversity and function. Gonadectomy of male and female mice shifted the gut community composition in both sexes and resulted in lower levels of sex differentiation as measured by beta diversity (Org et al. 2016; Kaliannan et al. 2018; Harada et al. 2016; Gao et al. 2021; Choi et al. 2017). Since gonad removal affects more than just the production of sex steroids, gonadectomy plus steroid replacement studies are necessary to discern whether sex steroids are responsible for a certain phenotype. One such study showed that treatment of ovariectomized female mice with estradiol shifted gut microbiome beta diversity to be more like intact females (Kaliannan et al. 2018). Another study demonstrated that treating castrated male mice with dihydrotestosterone shifted the gut microbiome beta diversity to be more like intact males (Gao et al. 2021).

In addition to studies with gonadectomized mice, which results in steroid insufficiency, other studies have employed steroid excess to study the relationship between sex steroids and the gut microbiome. For example, studies have shown that treatment of pubertal female mice or rats with the aromatase inhibitor letrozole, which elevates testosterone and decreases estrogen (Kauffman et al. 2015) results in a shift in gut bacterial alpha and beta diversity (Kelley et al. 2016; Guo et al. 2016). Treatment of female rats with dihydrotestosterone (a non-aromatizable androgen) was also found to alter the gut microbiome (Zheng et al. 2021; Rodriguez Paris et al. 2022). Interestingly, letrozole treatment affected the gut microbiome and metabolic phenotype of pubertal females differently than adult females, indicating that puberty may be a sensitive period for effects of steroids on the gut microbiome as well as the host (Torres, Skarra, et al. 2019; Arroyo et al. 2019; Torres, Ho, et al. 2019). Moreover, cohousing letrozole- and placebo-treated mice, in which mice exchanged gut microbiota through coprophagy, reduced testosterone levels and ameliorated reproductive and metabolic phenotypes in letrozole-treated mice (Torres, Ho, et al. 2019; Ho et al. 2021). This potential bidirectional relationship between host sex steroids and the gut microbiome was also suggested by another study which showed that maternal high-fat diet induced metabolic dysregulation, early puberty, and infertility could be partially reversed in female offspring cohoused with healthy females (Wang, Zhang, et al. 2020).

In humans, the evidence for a relationship between sex steroids and the gut microbiome comes from various observational studies with postmenopausal women or women using oral contraceptives. Two gut microbiome studies of women using oral contraceptive pills (estrogen and progesterone) found they had lower alpha diversity, differentiated beta diversity, and distinct gut microbial metabolic pathways compared with women not using oral contraceptives (Mihajlovic et al. 2021; Hua et al. 2022). Other studies showed that urinary estrogens and their metabolites were negatively correlated with gut microbiota alpha diversity in postmenopausal females but not premenopausal females (Fuhrman et al. 2014; Flores et al. 2012). In postmenopausal women, estrone levels and the ratio of parent estrogens to estrogen metabolites were associated with an increased relative abundance of specific bacterial taxa (Fuhrman et al. 2014; Flores et al. 2012). A metagenomics study also found significant differences in the taxonomic and functional pathway beta diversity of postmenopausal women compared to premenopausal women (Zhao et al. 2019). Interestingly, the one study we found that investigated changes in the gut microbiome directly within the intestinal tract, namely the duodenum, also showed a relationship between sex steroids and the microbiome. Specifically, Leite et al. reported that the duodenal microbiome of postmenopausal women treated with hormone replacement therapy was more like premenopausal women than postmenopausal women not taking hormone replacement therapy (Leite et al. 2022).

Another link between sex steroids and the gut microbiome was identified in women with PCOS with elevated testosterone levels (hyperandrogenism). Studies of gut microbial diversity found that women and adolescent girls with PCOS had lower alpha diversity and differences in beta diversity compared to healthy women and adolescent girls (Torres et al. 2018; Lindheim et al. 2017; Qi et al. 2019; Liu et al. 2017; Jobira et al. 2020; Garcia-Beltran et al. 2021). Testosterone levels in women with PCOS also correlated with alpha diversity and the abundance of specific members of the gut microbial community [reviewed in (Rizk and Thackray 2020)]. Intriguingly, Qi et al. reported that female mice transplanted with stool from women with PCOS developed metabolic and reproductive dysregulation (Qi et al. 2019) suggesting that changes in the gut microbiome may be sufficient to induce PCOS-like phenotypes.

Microbial Modifications of Sex Steroids

Several key studies support the hypothesis that gut bacteria play a critical role in enterohepatic circulation of sex steroids (Fig 3). Studies in humans and rats demonstrated that antibiotic treatment dramatically increased the ratio of conjugated to deconjugated estrogens excreted in urine and feces (Adlercreutz et al. 1984; Goldin and Gorbach 1984; Flores et al. 2012). Moreover, Colldén et al. found negligible deconjugation of testosterone glucuronide in the intestinal tract of germ-free male mice (Colldén et al. 2019). This study also showed that the concentration of androgen glucuronide in normal mice was high in the small intestine and low in the cecum and colon, indicating that microbial deconjugation of androgen glucuronide (and presumably other steroids) occurs largely in the small intestine.

While gut bacteria facilitate enterohepatic cycling of sex steroids, the role of specific bacterial species in this process is not well understood. Studies have shown that a

bacterial enzyme, β-glucuronidase, is primarily responsible for the deconjugation of steroid glucuronides (Pellock and Redinbo 2017; Sui, Wu, and Chen 2021) and that β-glucuronidase homologs are present and active in many common gut bacteria in mice and humans (Lombardi et al. 1978; Dabek et al. 2008; McIntosh et al. 2012; Winter and Bokkenheuser 1987; Gloux et al. 2011; Gadelle, Raibaud, and Sacquet 1985). β-glucuronidase homologs were found in members of many common gut bacterial families, including *Ruminococcaea, Lachnospiraceae, Clostridiaceae, Bacteroidaceae*, and *Tannerellaceae*. Many studies have demonstrated *E. coli* deconjugation of various estrogen-glucuronides (Buehler, Katzman, and Doisy 1951; Graef, Furuya, and Nishikaze 1977; Lombardi et al. 1978; Legler et al. 2002), though studies on androgen glucuronides are lacking. Recently, Ervin et al. reported deconjugation of estrogen glucuronides by β-glucuronidases isolated from other gut bacteria, including *Faecalibacterium prausnitzii, Roseburia* species, and *Clostridium* species (Ervin et al. 2019). As β-glucuronidase genes are not present in all gut microbes, possession of this gene could provide a competitive advantage during puberty. Phylogenetic and structural diversity analyses of bacterial β-glucuronidase genes indicate that microbial β-glucuronidases are substrate specific and fall into functional classes (Biernat et al. 2019; Little et al. 2018; Ervin et al. 2019). The fact that many common gut bacteria possess β-glucuronidase activity with different substrate specificity provides a potential mechanisms by which sex steroids could differentiate the gut microbiome. In support of this idea, glucuronidase genes in gut metagenomes were reported to be higher in premenopausal women than in postmenopausal women and adult men (Peters et al. 2022).

Another mechanism by which sex steroids may impact bacterial communities is via bacterial metabolism of unconjugated (free) steroids. Metabolism of free androgens and estrogens, including redox reactions and partial cleavage of steroids, has been reported in human fecal cultures (Lombardi et al. 1978; Eriksson and Gustafsson 1971). These studies indicated that free steroids were not broken down completely by bacteria, so this activity may be for detoxifying steroids rather than for energy or anabolism. Indeed, free testosterone was shown to be toxic to gut bacteria such as *E. faecalis* and *E. coli*, suggesting that high concentrations of steroids may be toxic to some bacteria but not others (Plotkin et al. 2003). On the other hand, additional studies showed that estrogen and progesterone were completely degraded when added to fecal cultures (Coombes et al. 2020; Li et al. 2018). Collectively, these studies provide evidence that gut microbes metabolize sex steroids, and that this metabolism could potentially influence the composition of the gut microbial community in a sex-specific manner. However, the mechanisms by which this might occur are poorly understood and many more studies are needed to determine if and how these processes occur.

Bile acids and the Gut Microbiome

While direct interaction of sex steroids with gut microbiota may lead to a sexually dimorphic gut microbiome, this is not the only possible mechanism. Sex steroids may also indirectly influence the gut microbial community by regulating host production and secretion of bile acids, which may then modulate the gut microbiota. Bile acids are important for emulsifying fats during digestion and as signaling molecules in glucose and lipid metabolism (Perino et al. 2021). In humans, the liver produces cholic acid (CA), and chenodeoxycholic acid

(CDCA) from cholesterol (Russell 2003). Muricholic acid (MCA) is produced instead of CDCA in mice. Bile acids are conjugated with either taurine or glycine, then secreted as primary bile acids through the bile duct into the small intestine. Like sex steroids, bile acids circulate between the liver and the intestine through enterohepatic circulation (Fig 3). Once secreted into the small intestine, microbial bile salt hydrolase (BSH) deconjugates bile acids with glycine or taurine. 70–90% of bile acids are reabsorbed from the ileum and transported to the liver through the hepatic portal vein (Angelin et al. 1982; Wahlström et al. 2016). The BSH gene is present in most major gut microbiome phyla (Firmicutes, Bacteroidetes, Actinobacteria, Fusobacteria, and Proteobacteria), and BSH enzymes in different phyla have different substrate specificity for glycine- or taurine-conjugated bile acids (Jones et al. 2008; Song et al. 2019). The widespread presence of BSH among members of the gut microbiota suggests that it could confer a competitive advantage by providing resistance to bile acid detergent toxicity (Jones et al. 2008). Another transformation of bile acids by gut microbiota is 7α-dehydroxylation, which produces the secondary bile acids deoxycholic acid (DCA) and lithocholic acid (LCA; MDCA in mice) (Lucas et al. 2021). 7α-dehydroxylase activity is less widespread among human gut bacteria than BSH activity, which may lead to niche specialization by species with this activity (Lucas et al. 2021). Less common transformations of bile acids include dehydroxylation, epimerization, isomerization, and oxidation (Eyssen et al. 1983; Degirolamo et al. 2014). As secondary bile acids have varying levels of toxicity to different microbes, producing more secondary bile acids may provide a competitive advantage for bacteria able to tolerate this toxicity and a mechanism for the host to influence the gut microbial community (Tian et al. 2020).

Multiple reviews indicate that microbial bile acid metabolism is widespread within the gut microbiota and that it creates a large diversity of bile-acid derived metabolites (Wahlström et al. 2016; Foley et al. 2019; Winston and Theriot 2020). However, apart from BSH activity, the prevalence of these functions within gut microbiota is unknown (Winston and Theriot 2020). While some effects of secondary bile acids on the host are known, such as anti-inflammatory properties, much remains to be discovered about how microbial transformation of bile acids affects host physiology (Ward et al. 2017; Lajczak-McGinley et al. 2020). A growing body of literature indicate that bile acids have a profound effect on host biology. For instance, both primary and secondary bile acids bind to host receptors such as farnesoid X receptor (FXR), G Protein-Coupled Bile Acid Receptor 1, pregnane X receptor, vitamin D receptor, and retinoid-related orphan receptor, and regulate metabolic and immune functions (Fiorucci et al. 2021; Chiang 2013). FXR, specifically, has been widely studied and implicated in glucose metabolism, lipid homeostasis, inflammation, and permeability of the intestinal barrier (Ding et al. 2015).

Sex differences and Bile Acids

In humans, the bile acid profiles of newborn infants (infants less than 48 hours old) were largely composed of primary bile acids and were markedly different from adult bile acid profiles (Wang, Chen, et al. 2020). In mice and rats, the gut microbiota and bile acid pool both diversify rapidly after birth. Interestingly, the diversity of secondary bile acids appears to increase until puberty after which time it stabilizes (van Best et al. 2020; Morris, Little, and Lester 1983). During and after puberty, studies have shown that primary and secondary

bile acid levels are higher in female than male rodents (Morris, Little, and Lester 1983; Li-Hawkins et al. 2002; Schwarz et al. 2001; Turley et al. 1998; Jahnel et al. 2015; Baars et al. 2018). Ma et al. also identified differences in secondary bile acid levels between young and older adult mice, and determined that these differences were reduced by cohousing, indicating that the gut microbiome influences bile acid levels (Ma et al. 2020).

There is also evidence for sex differences in bile acids in humans. Multiple studies have determined that total bile acid concentrations and levels of bile acid synthesis are higher in males than females (Xiang et al. 2012; Frommherz et al. 2016; Steiner et al. 2012; Gälman, Angelin, and Rudling 2011; Bennion et al. 1978). Since mice show the opposite pattern, this difference is important to consider when using mice as a model for the effects of bile acids on physiology. While there are consistent sex differences in the total bile acid pool in humans, the reported sex differences in terms of the types of primary and secondary acids varies among studies (Wang, Chen, et al. 2020; Fisher and Yousef 1973; Bennion et al. 1978). In addition, little is known about how age interacts with sex differences in primary and secondary bile acid metabolism although one study indicated that sex steroids, which change in concentration throughout the lifespan, may indirectly affect secondary bile acid metabolism (Ridlon, Kang, and Hylemon 2010).

Interplay between Bile Acids, Gut Microbiome, and PCOS

Ho et al. found a relationship between gut microbiota and secondary bile acids in mice. In this study, letrozole treatment of female mice during puberty resulted in changes to secondary bile acid levels, gut microbiota abundances, metabolism, and the reproductive axis (Ho et al. 2021). In humans, women with PCOS were reported to have different levels of specific secondary bile acids compared to healthy controls, and higher levels of BSH genes in their gut microbial metagenomes (Yang, Wu, et al. 2021; Qi et al. 2019; Zhang et al. 2019). Transplantation of stool from women with PCOS into adult female mice resulted in impaired fertility and glucose and insulin sensitivity, potentially modulated by the secondary bile acids tauroursodeoxycholic acid and glycoursodeoxycholic acid (Qi et al. 2019). Another study with fecal microbiome transplantation from women with PCOS to adult female mice showed decreased expression of the FXR receptor in the ileum and impaired insulin sensitivity (Yang, Zhou, et al. 2021). These studies indicate a potential influence of the gut/liver axis on metabolic dysregulation and vice versa.

The Immune System, Sex, and the Gut Microbiome

The immune system differentiates in a sex-specific manner during puberty and remains sexually dimorphic in adulthood (Rizzetto et al. 2018; Hooper, Littman, and Macpherson 2012; Fuhler 2020). Since both innate and adaptive immunity shapes many of the interactions in the gut microbiome and vice versa (Hooper, Littman, and Macpherson 2012; Foster et al. 2017; Shi et al. 2017; Wiertsema et al. 2021), the sexually dimorphic nature of the immune system creates another possible mechanism for generating a sex-specific gut microbiome (Whitacre et al. 1999; Lamason et al. 2006; Sharma et al. 2018; Klein and Flanagan 2016). The immune system is known to influence the gut microbiome through a number of mechanisms, such as preventing infiltration of the gut microbiota

into host tissues (Gallo and Hooper 2012), secreting mucins and antimicrobial compounds into the intestine, and propagating microbial signals to other immune cells (Abreu 2010; Peterson and Artis 2014). Adaptive immune cells also surveil the gut microbiota and alter community composition through immunoglobulin secretion (Zhang et al. 2015; Fransen et al. 2015). In turn, the gut microbiome affects differentiation of T and B cells and pro-and anti-inflammatory cytokine levels (Zhao and Elson 2018; Fujimura et al. 2016; Luu et al. 2018; Sampson et al. 2016; Li et al. 2019; Lajczak-McGinley et al. 2020).

Given the importance of the immune system in regulating the gut microbiome, sex-specific differences in the immune system could shape the gut microbiome in a sex-specific manner. This idea is supported by studies showing an association between the gut microbiome and autoimmune disorders. Ulcerative colitis, a form of IBD, is diagnosed more frequently in females, while Chron's disease, another form of IBD, is diagnosed more often in males (Hayter and Cook 2012; Herzog et al. 2014; Henderson et al. 2011). Studies indicate that the gut microbiome is a major factor in IBD incidence and severity. Microbiome and metabolome composition in patients with IBD was different from healthy patients and associated with gut inflammation levels (Franzosa et al. 2019; Dong et al. 2019; Clooney et al. 2019). Gut microbiota may affect severity of IBD directly through activation of immune cells through pattern recognition receptors or immunoglobulin binding or indirectly through bile acid signaling (Ding et al. 2015; Schirmer et al. 2019). Additionally, fecal microbiome transplantation is an effective treatment for many patients, though differences in effectiveness by donor and recipient are not well understood (Zhou et al. 2021; Mańkowska-Wierzbicka et al. 2020; Cheng et al. 2021). While differences in gut microbiome composition between patients with ulcerative colitis or Crohn's disease were reported, sex differences were not observed (Clooney et al. 2019; Dong et al. 2019). However, since sex differences in IBD patients or their microbiomes are often not analyzed or reported, it is possible that sex differentiation of the gut microbiome may contribute to differences in the development and pathology of the IBD subtypes and warrants future investigation. Given that sex-specific immune responses to bacterial metabolites are a candidate for how the gut microbiome contributes to sex differences in the incidence of IBD (Murray et al. 2019; Murray et al. 2020; Bhattarai et al. 2020; Spichak et al. 2021), it may also be important to determine if the sex of the donor and recipient needs to be considered in fecal microbiome transplantation for IBD treatment.

Another notable example of sex-specific differences in the immune system-gut microbiome relationship occurs in the non-obese diabetic (NOD) mouse model for the autoimmune disorder, T1D. In the NOD mouse model, T1D incidence after 30 weeks of age is ~80% in females and 20% in males, although this ratio varies depending on the mouse colony (Makino et al. 1980; Yurkovetskiy et al. 2013; Pozzilli et al. 1993). Intriguingly, castration of NOD males results in a T1D incidence similar to females, indicating that gonadal sex steroids may be important in protecting male mice from T1D (Makino et al. 1981). Additionally, Markle et al. found no sex differences in T1D in NOD mice raised in a germ-free environment, indicating that the gut microbiome was required for the sex differences in T1D incidence (Markle et al. 2013). This and other studies also showed that the male microbiome was protective against T1D and that delivery of male gut microbiota to female mice via fecal transplantation was protective against T1D (Markle et al. 2014; Markle et

al. 2013; Yurkovetskiy et al. 2013). Altogether, this evidence suggests that host-microbe interactions may play a key role in modulating sex differences in autoimmunity.

Conclusions and Future Perspectives

Our review of the current literature on the relationship of sex to the gut microbiome in humans and in rodent models showed that a sex-specific gut microbiome develops during puberty and continues into adulthood. The majority of these studies relied on NGS of bacterial 16S rRNA gene amplicon libraries due to its cost-effectiveness and its ability to taxonomically identify both cultured and uncultured bacteria across all phyla. However, while the 16S gene provides useful information about gut bacterial diversity, it reveals little about the function of gut microbes. Metagenomic, metabolomic, and transcriptomic approaches can inform us about microbial gene content and expression, and metabolite production, and can identify changes in archaea, fungi, and viruses in addition to bacteria. Future studies employing these approaches will be needed to understand comprehensively how sex and sex steroids regulate the composition and function of gut microbial communities along the alimentary canal.

Understanding the role of gut microbiota in sex-specific human health and disease will require better knowledge of how sex steroids affect the gut microbiome, and vice versa. In humans, there is a lack of clinical studies investigating the relationship between sex steroids and the gut microbiome in men. Given that men commonly experience hypogonadism due to factors such as age, disease (e.g. obesity and type 2 diabetes), or drug treatment, e.g. GnRH agonist for prostate cancer (Zarotsky et al. 2014; Mittan et al. 2002), future studies are needed to discern the relationship between sex steroids and the gut microbiome in men. Since gender-affirming care for transgender individuals often involves hormone therapy, study of the gut microbiome in individuals receiving cross sex steroid treatment is also important.

While many studies in humans and rodents have established correlations between sex differences and factors such as sex steroids, bile acids and the immune system, few studies have investigated causal relationships and mechanisms. More studies are needed to investigate how microbiome manipulation affects sex steroid levels (e.g., via antibiotics, cohousing, or fecal transplants) and how sex steroid manipulation affects the gut microbiome (e.g., via gonadectomy and steroid replacement). Additionally, research should be undertaken to measure levels of both conjugated and unconjugated steroids in males and females, especially when paired with gut microbiome manipulation. The use of germ-free or antibiotic-depleted mice will be key in establishing which sex-specific diseases require the presence of the gut microbiome and which disease phenotypes can be recapitulated by fecal microbiome transplantation.

Since there is growing evidence that there are sex differences in bile acid production in the liver, future research should investigate when sex differences in primary and secondary bile acid levels emerge in humans and rodents and how the gut microbiome contributes to these differences. Gut microbiota manipulation may provide insight into how the gut microbiome affects sex-specific bile acid metabolism and signaling. Altering

host bile acid levels through host genetic knock-outs in the bile acid pathway or through diet supplementation could potentially be used to determine how sex-specific bile acid levels affect gut microbiota composition. Deciphering this relationship may be essential to understand how gut microbiota contribute to sex-specific metabolic disorders like PCOS and type 2 diabetes.

Finally, given the number of sex-specific autoimmune diseases, understanding the relationship between the gut microbiome and the immune system is likely to be important for developing microbial-based preventative measures and therapeutics for these disorders. Studies manipulating the immune system are needed to understand how the immune system shapes the sex-specific gut microbiome. Likewise, more studies are required to provide insight into how gut microbiota manipulation affects development of sex-specific autoimmune diseases like IBD and type I diabetes. Understanding how sex steroids, bile acids, the immune system, and the gut microbiome interact to create and maintain sex differences in microbiome-related diseases may have far-reaching implications especially since the gut microbiome is increasingly being considered a therapeutic target.

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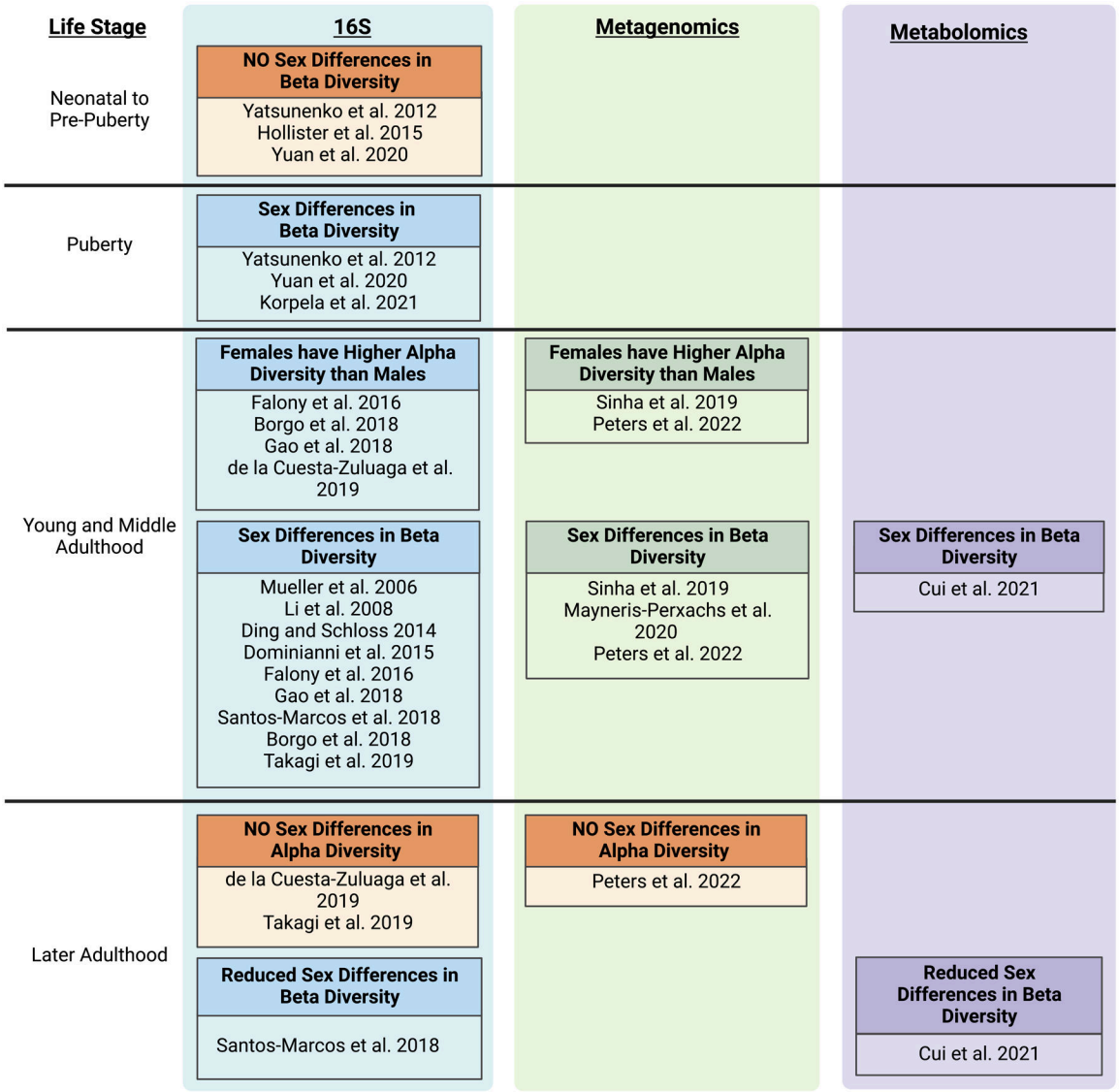

Figure 1.

Sex differences in the human gut microbiome arise during puberty. Studies providing evidence of sex differences are categorized by developmental stage, type of data analysis (eg. 16S rRNA gene sequencing, metagenomics, or untargeted metabolomics) and observed effect on the gut microbiome. Created with BioRender.com.

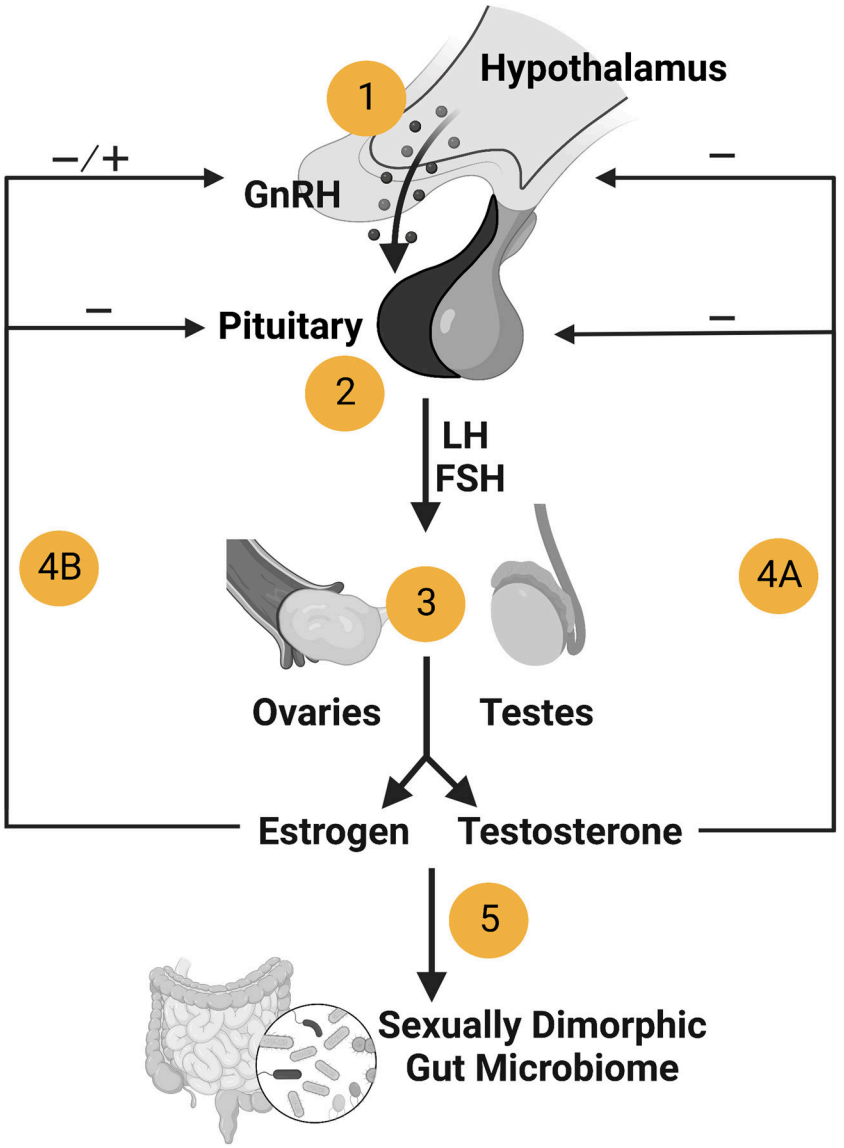

Figure 2.

Activation of the hypothalamic–pituitary–gonadal axis during puberty. 1) Gonadotropin-releasing hormone (GnRH) production is stimulated by kisspeptin secreted from neurons in the hypothalamus. 2) GnRH induces pituitary gonadotrope cells to produce and secrete the gonadotropins, follicle stimulating hormone (FSH) and luteinizing hormone (LH). 3) In males, LH signaling in testicular Leydig cells results in testosterone production, while in females LH stimulates testosterone production in ovarian theca cells, which is then converted to estrogen in granulosa cells by aromatase. 4A) Testosterone exerts negative feedback in the hypothalamus and pituitary, while 4B) estrogen exerts both negative and positive feedback. 5) Sex steroids may directly or indirectly modulate the gut microbiome to be sexually dimorphic. Created with BioRender.com.

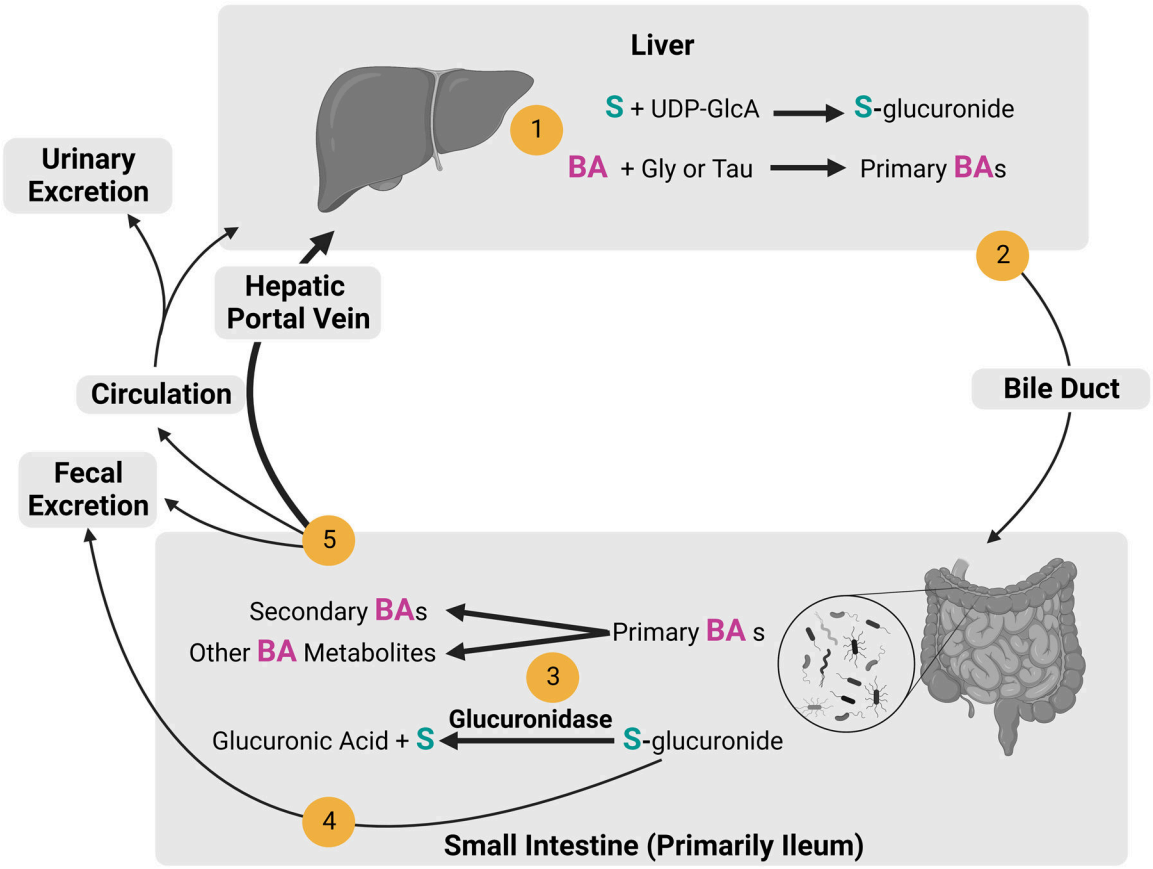

Figure 3.

Enterohepatic circulation of sex steroids and bile acids. 1) Sex steroids (S) are conjugated with glucuronide from uridine 5'-diphosphoglucuronic acid (UDP-GlcA) by liver enzymes. Bile acids (BAs) are synthesized and conjugated with glycine (Gly) or taurine (Tau) in the liver. 2) Sex steroid glucuronides (S-glucuronide) and primary bile acids are transported to the gallbladder and excreted into the small intestine via the bile duct. 3) Gut bacteria deconjugate S-glucuronide and transform BAs into secondary BAs or other BA metabolites. 4) S-glucuronides that are not deconjugated are excreted through the feces. 5) Secondary BAs, other BAs metabolites, and deconjugated sex steroids are primarily reabsorbed through the hepatic portal vein to the liver. Alternatively, they are excreted through feces or returned to circulation, to be reabsorbed by the liver or excreted through urine. Created with BioRender.com.