How Biological Sex Influence the Microbiome

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The Microgenderome?

Gender, microbes, and disease

At puberty (in mice), the composition of the gut microbiota of male and female animals diverged

Impact of sexual maturation and changing hormones on the gut microbiota

Ability of gut microbiota to positively affect hormonal and immune pathways (T1D susceptibility)


The Microgenderome?

Gender, microbes, and disease

The ‘microgenderome’ provides a paradigm shift that highlights the role of sex differences in the host-microbiota interaction relevant (so far) for autoimmune and neuro-immune conditions.

The bidirectional communication between the gut microbiome and the brain has emerged as a factor that influences immunity, metabolism, neurodevelopment and behavior and that in the context of sex differences

Applied and mechanistic research needs to consider sex-interactions when examining the composition and function of human microbiota.

The Estrobolome

Gender, microbes, and disease

Estrobolome, the aggregate of enteric bacterial genes whose products are capable of metabolizing estrogens.

Sex specific metabolic effects of residential organisms leading to distant diseases (i.e., malignancies)

The Vaginal Microbiota Through the Lifespan

**Birth**
Sterile then rapidly colonized by *Lactobacillus* (maternal estrogen)

**Pre-puberty**
Loss of *Lactobacillus* - strict anaerobes

**Puberty**
Increased estrogen; *Lactobacillus* dominates

**Reproductive age**
Estrogen, glycogen and production of lactic acid
*Lactobacillus* dominates

**Menopause**
Decreased estrogen, less glycogen, less lactic acid
Loss of *Lactobacillus* mainly aerobes

**Pregnancy**
High estrogen
The Gut-Vagina Axis?
The Vaginal Microbiota

~5,000 samples from over 800 women

Seven major community state types that differ in their microbial composition and abundance

Community state types IV-A and IV-B lack significant number of *Lactobacillus* - higher diversity
Vaginal Microbiota Longitudinal profiles

160 women
Daily sampling
10-week study
The rate of community change is affected by time in the menstrual cycle (natural change) and sexual activities to some extent.
CST IV: an normal state that carry risks?

At any given time, >25% of women are in a non-Lactobacillus dominated state.

This state is associated with higher Nugent scores and higher pH

High Nugent scores are strongly associated with increased risk of sexually transmitted infection, including HIV

These women could be asymptomatic and apparently healthy, but potentially at increased risk of STI or other adverse outcomes

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**Critical need to review the management of this asymptomatic condition and explore ways to restore a Lactobacillus-dominated microbiota**


Effect of male circumcision on penile microbiome

HIV-negative adult men (age 18-64)

Randomization

Control Arm (n = 77)

Intervention Arm (n = 79)

Baseline

No circumcision

Male circumcision

Year-1

Year-1

MC alters penile microbiome

Decreases cytokine & chemokine production

Decreases HIV target cell activation & recruitment

Decreases HIV susceptibility in men
16S Sequencing

Pan-bacterial qPCR

Absolute abundance of $A$ =

Proportional abundance of $A \times$ total bacterial density
DS axis 2

Intervention

nMDS axis 2

Baseline

Year-1

Control

Liu et al mBio 2013
Baseline
Year-1
Control
Baseline
Year-1
Intervention
Baseline
Year-1
Liu et al mBio 2013
Male circumcision reduces absolute abundance of anaerobes
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Major decrease in anaerobes

Prevotella = ~25,000
Porphyromonas = ~14,000
Finegoldia, Anaerococcus, Peptoniphilus = ~1,300

Liu et al mBio 2013
Male circumcision reduces absolute abundance of anaerobes

Major decrease in anaerobes
*Prevotella* = ~25,000
*Porphyromonas* = ~14,000
*Finegoldia, Anaerococcus, Peptoniphilus* = ~1,300

Minor increase in non-anaerobes
*Corynebacterium* = ~3,000
*Staphylococcus* = 250

Liu et al mBio 2013
Penile microbiome, inflammation, and risk of HIV seroconversion

Uncircumcised men
Baseline coronal sulcus swabs

Seroconvert during 2-yr study
Cases (n = 46)

Controls (n = 136)
HIV-negative during 2-yr study

Liu et al, submitted
Anaerobe absolute abundance and risk of seroconversion

<table>
<thead>
<tr>
<th>Anaerobe</th>
<th>Odds Ratio (95% CI)</th>
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<tbody>
<tr>
<td><strong>Prevotella</strong></td>
<td>1.63 (1.23, 2.26)</td>
</tr>
<tr>
<td><strong>Porphyromonas</strong></td>
<td>1.47 (1.13, 1.98)</td>
</tr>
<tr>
<td><strong>Dialister</strong></td>
<td>1.57 (1.21, 2.10)</td>
</tr>
<tr>
<td><strong>Mobiluncus</strong></td>
<td>1.33 (1.11, 1.64)</td>
</tr>
<tr>
<td><strong>Negativicoccus</strong></td>
<td>0.94 (0.81, 1.10)</td>
</tr>
<tr>
<td><strong>Finegoldia</strong></td>
<td>1.54 (1.09, 2.29)</td>
</tr>
<tr>
<td><strong>Peptoniphilus</strong></td>
<td>1.57 (1.12, 2.30)</td>
</tr>
<tr>
<td><strong>Anaerococcus</strong></td>
<td>1.36 (0.95, 2.01)</td>
</tr>
<tr>
<td><strong>Murdochiella</strong></td>
<td>1.29 (1.05, 1.62)</td>
</tr>
<tr>
<td><strong>Peptostreptococcus</strong></td>
<td>1.30 (1.10, 1.61)</td>
</tr>
</tbody>
</table>
Penile Microbiota and Female Partner Bacterial Vaginosis

Penile Microbiota and Female Partner Bacterial Vaginosis

Men with CST4 to 7 were significantly more likely to have a female partner with a high Nugent score.

Female partner Nugent-BV is significantly associated with penile microbiota.

Explore the role of penile bacteria and inflammation in HIV susceptibility from a mechanistic angle (Price and Liu - R01)

Liu et al, MBio. 2015
Penile Microbiota and Female Partner Bacterial Vaginosis

Anaerobic dysbiosis may affect the risk of HIV acquisition in men.

A similar anaerobic dysbiosis occurs in women with bacterial vaginosis.

In men, this dysbiosis largely resolves in response to circumcision.

These anaerobic bacteria are correlated between sexual partners, indicating that the dysbiosis itself is sexually transmissible.
Sexually-transmissible dysbiosis that increases HIV susceptibility
Sexual transfer of microbial dysbiosis
Sexual transfer of microbial dysbiosis
Interaction between microbiota and cervicovaginal mucus

Collected CVM from 31 women using Instead Cups
Measure the mobility of HIV-1 virus-like particles in fresh CVM

Understand the contribution of the vaginal microbiota to these variations in the diffusional barrier properties of CVM samples against HIV - Important in the context of microbicide development

Interaction between microbiota and cervicovaginal mucus

CVM associated with *L. crispatus* appears protective, while CVM associated with *L. iners* is somewhat deficient in trapping HIV-1.
Conclusions

Biological sex, especially sex hormones are associated with differences in the composition of the gut microbiota and associated immune development and response

Mechanistic understanding of this relationship is not unresolved

The genital microbiota of men and women share similarities and dysbiosis can be transferred sexually - the silent STI

While sex hormones can affect the composition of the gut or genital microbiota and immunity, sex-specific microbiota affect physical barriers to infection

Research is needed to resolve the mechanism by which the microbiota interact with the host in a sex-specific manner and in the context of HIV
Model

Female host

Gut Microbiota

Vaginal Microbiota

Gut Environment

Cervicovaginal Environment

Male host

Penile Microbiota

Penile Environment

Gut Microbiota

Environment

HIV