The Vaginal Microbiota in Health and Disease

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The Human Microbiota

- Our adult bodies harbor ~10 times more microbial cells than human cells – a significant number of these species have not been successfully grown in culture.

- The importance of the human microbiota in health and disease is now well-established.

- The “human genome” is an amalgam of human genes and the genes of our microbial partners.

- Without understanding the interactions between our human and microbial genomes, it is impossible to obtain a complete picture of our biology.
**Common wisdom about the human vagina**

- *Lactobacillus* spp. are characteristic of vaginal microbiota in “normal” healthy reproductive age women.

- Growth of non-indigenous organisms, including pathogens, is restricted.

- The mechanisms are not well characterized:
  - low pH (≤4.5)
  - lactate
  - other organic acids
  - bacteriocins
  - others

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Albert Siegmund Gustav Döderlein, [German obstetrician and gynecologist, 1860–1941], first described the “Döderlein bacillus” in 1894.
Taxonomic Marker Genes - 16S rRNA gene

Microbial identification

- **16S rRNA gene - Universal**
  - 16S rRNA → Bacteria and Archaea

- **16S rRNA gene nucleotide sequence is phylogenetically informative** - One sequence - one species

- **cpn60 (Chaperonin-60, HSP60, GroEL)** or **recA** are also good alternatives

**454 Pyrosequencing**
The vaginal microbiota in asymptomatic women

- Cross sectional study of 410 asymptomatic healthy women

  - Four ethnic groups equally represented:
    - Caucasian, Black, Hispanic, Asian
  
  - Physician-collected mid-vaginal swabs
    - Vaginal pH measurements (Inverness VpH glove)
    - Nugent’s Gram stain scores
    - Questionnaire (health and sexual history, hygiene...)
  
  - Determine bacterial community composition by 454 pyrosequencing of barcoded V1-V2 16S rRNA gene

**Vaginal community state types (CST)**

- Five community state types that differ in their microbial composition and abundance
- Community state type IV lacks significant number of *Lactobacillus*

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Community state types and ethnic groups

Asian (96)  
- I: 19.8%  
- II: 25%  
- III: 42.7%  
- IV: 10.3%  
- V: 7.3%

White (97)  
- I: 26.8%  
- II: 8.2%  
- III: 26.8%  
- IV: 10.3%  
- V: 9.3%

Black (104)  
- I: 45.4%  
- II: 4.8%  
- III: 22.1%  
- IV: 9.3%  
- V: 1%

Hispanic (97)  
- I: 31.4%  
- II: 7.2%  
- III: 36.1%  
- IV: 38.1%  
- V: 4.1%

Ravel et al. The vaginal microbiome of reproductive age women. PNAS. 2011
The vaginal community space

A plot of principle component analysis (PCA) shows distribution of community states in 3-D space.

Graphics generated with inVUE (inVUE.sourceforge.net)
Conclusions

- Several microbial community states are found in human vaginas that differ in terms of bacterial species composition/abundance

- The frequency of each CST differs among women of different ethnicity

- At any given time, about 25% of women are in a non-lactobacillus state.
  - How long does this state persist over time? How frequently does the vaginal microbiota of a woman is in this state?

Longitudinal studies of the vaginal microbiota
33 women self-collected vaginal smears and swabs were obtained twice-weekly (1,107 samples total) for 16 weeks

Daily diaries mailed to the lab weekly

Analyze community composition by 454 pyrosequencing of barcoded 16S rRNA genes (V1-V2 region)

- 1063 samples extracted (out of 1,107)
- >3.5 million sequence reads of the V1-V2 region of 16S rRNA gene (avg. 240-316 bp)

Community State vs. Community State Type

Profile of Vaginal Community State Types

Vaginal Community Classes

Longitudinal profiles - relative high stability
Longitudinal profiles - low stability
Vaginal community dynamics

*L. crispatus* to *L. iners* to diverse group transition
Conclusions - Implications

- Microbiome is somewhat unique/personalized to a women (or group of women)
- Different women, different kinds of communities
- Different women, different changes over time
- Understanding these changes has major implications in increasing diagnosis accuracies, hence decrease disease prevalence, as well as predicting susceptibility and risk to infections.
  - Might have to rethink women’s health and treatments
  - Future: personalized treatment - use prior information and prescribe treatment
Acknowledgments

Pawel Gajer
Rebecca Brotman
Stacey McCulle
Guoyun Bai
Li Fu
Bishoy Michael
Arthur Brady
Anup Mahurkar
Owen White
Bing Ma
Doug Fadrosh
Sara Koenig
Joyce Sakamoto
Melissa Nandy
Hongqiu Yang
Elliot Drabek
Jonathan Crabtree

National Institutes of Health
NIAID U01 - AI070921 - R03-AI061131
NIAID UH2 - AI083264