Development of the Microbiome: Early Life Events

David A. Relman, MD, Stanford University

Gut Microbiome Conference 2015
Huntington Beach, Sept 26, 2015
Questions, Challenges

• Sources, assembly of microbiota?
• History of maternal landscape?
• Relative roles of environmental selection vs. historical or stochastic effects on microbiota in early life?
• What governs early community shifts?
• Impacts on subsequent health, risks of immune-mediated disease?
• Enhanced clinical management of primary ecological succession?
• We are born ~100% human, but die >90% bacterial…

• What are the features of early microbial colonization in the human body?
Variation in the Overall Density of Fecal Bacteria During the First Year of Life
Early Days: Evidence of Opportunistic Exposures

Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns

Maria G. Dominguez-Bello,1,*, Elizabeth K. Costello,1,*, Monica Contreras,*, Magda Me gris,*, Gilda Hidalgo,*, Noah Fierer,† and Rob Knight*‡

1Department of Engineering, University of Puerto Rico, San Juan, Puerto Rico 00931; Departments of Chemistry and Biophysics, *Department of Ecology and Evolutionary Biology, and ‡Cooperative Institute for Research in Environmental Sciences, University of Colorado, Boulder, CO 80309; *Center for Wastewater and Urban Environment, *Department of Environmental Science, University of California, Santa Barbara, CA 93106, †Department of Biology, University of California, Los Angeles, CA 90024, ‡Howard Hughes Medical Institute, University of Colorado, Boulder, CO 80309.
The Mode by Which You Leave Your Mother Affects the Assembly of Your Microbiota

...so, What About Recent past History of the Maternal Landscape?
Microbiome and Landscape Prior to Birth

- Vertical transmission, prior generations
- Maternal history prior to conception
- Onset of pregnancy?
- Effects of pregnancy
- Maternal exposures during pregnancy
- Fetal encounters and development?
Possible Prior Influences on Early Childhood Microbiome

• Delivery mode
• Maternal microbiome during pregnancy
• Maternal health state, diet, lifestyle
• Maternal exposures (e.g., drugs, infections) before, during pregnancy
• Prior generations of family
### Microbes in Amniotic Fluid: Four 'Great Obstetrical Syndromes'

<table>
<thead>
<tr>
<th></th>
<th>Culture</th>
<th>PCR + Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence</td>
<td>Diversity</td>
</tr>
<tr>
<td>SGA (n=52)</td>
<td>0.0%</td>
<td>0</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>1.6%</td>
<td>1</td>
</tr>
<tr>
<td>(n=62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spont PL (n=166)</td>
<td>9.6%</td>
<td>11</td>
</tr>
<tr>
<td>PPROM (n=204)</td>
<td>34.0%</td>
<td>14</td>
</tr>
</tbody>
</table>

### Culture vs. PCR + Culture

<table>
<thead>
<tr>
<th>Condition</th>
<th>Culture Prevalence</th>
<th>Culture Diversity (# taxa)</th>
<th>PCR + Culture Prevalence</th>
<th>PCR + Culture Diversity (# taxa)</th>
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<tbody>
<tr>
<td>SGA (n=52)</td>
<td>0.0%</td>
<td>0</td>
<td>6.0%</td>
<td>3</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>1.6%</td>
<td>1</td>
<td>9.6%</td>
<td>6</td>
</tr>
<tr>
<td>Spont PL (n=166)</td>
<td>9.6%</td>
<td>11</td>
<td>15.0%</td>
<td>18</td>
</tr>
<tr>
<td>PPROM (n=204)</td>
<td>34.0%</td>
<td>14</td>
<td>50.0%</td>
<td>46</td>
</tr>
<tr>
<td>Term (n=115)</td>
<td>0%</td>
<td>0</td>
<td>0.9%</td>
<td>1</td>
</tr>
</tbody>
</table>

Preterm, Premature ROM: Bacterial Diversity as Revealed By: PCR Only, Culture Only, or Both

### PCR-Based Microbial Analysis of Amniotic Fluid from Healthy Subjects at Mid-Trimester

<table>
<thead>
<tr>
<th>Total subjects</th>
<th>Number positive by PCR</th>
<th>Percent Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>1027</td>
<td>15</td>
<td>1.46%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No.</th>
<th>Sample</th>
<th>Taxon</th>
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<tbody>
<tr>
<td>1</td>
<td>MT022</td>
<td>S. agalactiae</td>
</tr>
<tr>
<td>2</td>
<td>MT064</td>
<td>Staphylococcus sp., Lactobacillus sp.</td>
</tr>
<tr>
<td>3</td>
<td>MT100</td>
<td>Candida sp.</td>
</tr>
<tr>
<td>4</td>
<td>MT142</td>
<td>Ureaplasma sp.</td>
</tr>
<tr>
<td>5</td>
<td>MT209</td>
<td>Streptococcus sp.</td>
</tr>
<tr>
<td>6</td>
<td>MT243</td>
<td>Candida sp.</td>
</tr>
<tr>
<td>7</td>
<td>MT358</td>
<td>Candida sp.</td>
</tr>
<tr>
<td>8</td>
<td>MT388</td>
<td>Candida sp.</td>
</tr>
<tr>
<td>9</td>
<td>MT407</td>
<td>S. agalactiae</td>
</tr>
<tr>
<td>10</td>
<td>MT535</td>
<td>Sneathia sp.</td>
</tr>
<tr>
<td>11</td>
<td>MT611</td>
<td>M. hominis</td>
</tr>
<tr>
<td>12</td>
<td>MT613</td>
<td>S. agalactiae</td>
</tr>
<tr>
<td>13</td>
<td>MT667</td>
<td>Candida sp.</td>
</tr>
<tr>
<td>14</td>
<td>MT713</td>
<td>Sneathia sp.</td>
</tr>
<tr>
<td>15</td>
<td>MT718</td>
<td>Candida sp.</td>
</tr>
</tbody>
</table>
The Placenta Harbors a Unique Microbiome

Kjersti Aagaard,1,2,3* Jun Ma,1,2 Kathleen M. Antony,1 Radhika Ganu,1 Joseph Petrosino,4 James Versalovic5

Humans and their microbiomes have coevolved as a physiologic community composed of distinct body site niches with metabolic and antigenic diversity. The placental microbiome has not been robustly interrogated, despite recent demonstrations of intracellular bacteria with diverse metabolic and immune regulatory functions. A population-based cohort of placental specimens collected under sterile conditions from 320 subjects with extensive clinical data was established for comparative 16S ribosomal DNA–based and whole-genome shotgun (WGS) metagenomic studies. Identified taxa and their carriage patterns were compared to other human body site niches, including the oral, skin, airway (nasal), vaginal, and gut microbiomes from nonpregnant controls. We characterized a unique placental microbiome niche, composed of nonpathogenic commensal microbiota from the Firmicutes, Tenericutes, Proteobacteria, Bacteroidetes, and Fusobacteria phyla. In aggregate, the placental microbiome profiles were most akin (Bray-Curtis dissimilarity <0.3) to the human oral microbiome. 16S-based operational taxonomic unit analyses revealed associations of the placental microbiome with a remote history of antenatal infection (permultiple multivariate analysis of variance, \( P = 0.006 \)), such as urinary tract infection in the first trimester, as well as with preterm birth <37 weeks (\( P = 0.001 \)).

What Does Microbial Nucleic Acid Mean, in a Relatively Privileged Site?

• Intact cells? Viable? Only components?
  – Current vs. past?

• Source/origins?
  – Environmental contamination?
  – Local tissues (uterus, cervix, vagina
    • (e.g., local invasion)?
  – Distant host site (hematogenous)?

• Nucleic acid or other components alone can have local biological consequence!
Bacterial DNA in AF During Preterm Labor Predicts Earlier Delivery

Community Stability Landscape

Shift in community state variables

Shift in environmental parameters

Pregnancy-Associated Microbiome

- **Aim:** Characterize the temporal dynamics of the pregnancy-associated microbiome (vaginal, distal gut, oral, skin), and host environment, in order to identify stereotypic features associated with preterm labor and birth (useful “biomarkers”, interventions)

- **Methods:** Prospective longitudinal sampling of four body habitats; taxonomic, gene content, transcriptomic and metabolomic compositional analysis of microbiota; host gene expression and immune responses
Sampling Strategy and Specimens Collected to Date

To date, 274 subjects enrolled (Stanford)…

- Self-collected specimens: ~54,000
- Blood specimens (maternal, cord, neonatal): ~3,800
- Delivery specimens (placenta, amniotic fluid): ~1,300
- Total specimens / time points: ~59,000
Initial ‘discovery’ dataset (16S; 454)
3767 samples from 40 subjects (29 term, 11 preterm)
>26M raw reads

‘Validation’ dataset (16S; Illumina):
246 vaginal samples from 9 subjects (5 term, 4 preterm)
>50M raw reads
# Characteristics of 49 Subjects in Initial Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Term delivery</th>
<th>Preterm delivery</th>
<th>TOTAL</th>
</tr>
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<tr>
<td></td>
<td>First Group</td>
<td>Second Group</td>
<td>First Group</td>
</tr>
<tr>
<td></td>
<td>(n=29)</td>
<td>(n=5)</td>
<td>(n=11)</td>
</tr>
<tr>
<td>Mean maternal age (range)</td>
<td>30 (19-41)</td>
<td>31.8 (29-37)</td>
<td>28 (19-39)</td>
</tr>
<tr>
<td>Race:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>18 (62%)</td>
<td>4 (80%)</td>
<td>4 (36%)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (10%)</td>
<td>1 (20%)</td>
<td>1 (9%)</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>1 (3%)</td>
<td>0</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>American Indian</td>
<td>1 (3%)</td>
<td>0</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (3%)</td>
<td>0</td>
<td>1 (9%)</td>
</tr>
<tr>
<td>Others</td>
<td>5 (17%)</td>
<td>0</td>
<td>1 (9%)</td>
</tr>
<tr>
<td>Ethnicity:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-hispanic</td>
<td>17 (59%)</td>
<td>4 (80%)</td>
<td>9 (82%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>11 (38%)</td>
<td>1 (20%)</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>Declined to state</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>4 (14%)</td>
<td>5 (100%)</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>Mean BMI, kg/m²</td>
<td>26.7</td>
<td>22.5</td>
<td>31.9</td>
</tr>
<tr>
<td>(range)</td>
<td>(18.2-36.8)</td>
<td>(20.1-24.6)</td>
<td>(22-39.7)</td>
</tr>
<tr>
<td>Gestational Diabetes</td>
<td>4 (14%)</td>
<td>1 (20%)</td>
<td>2 (18%)</td>
</tr>
</tbody>
</table>
## Characteristics of 15 Subjects with Preterm Delivery

<table>
<thead>
<tr>
<th>Preterm Subject</th>
<th>Subject Group</th>
<th>Race</th>
<th>Hispanic Ethnicity</th>
<th>Prior Preterm Delivery</th>
<th>Gest. Weeks at Delivery</th>
<th>pPROM‡</th>
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</thead>
<tbody>
<tr>
<td>10029</td>
<td>First</td>
<td>Pacific Islander</td>
<td>No</td>
<td>Yes</td>
<td>21 4/7</td>
<td>No</td>
</tr>
<tr>
<td>10542</td>
<td>Second</td>
<td>Asian (Thai)</td>
<td>No</td>
<td>Yes</td>
<td>23</td>
<td>Yes</td>
</tr>
<tr>
<td>10031</td>
<td>First</td>
<td>White</td>
<td>Yes</td>
<td>No</td>
<td>29 6/7</td>
<td>No</td>
</tr>
<tr>
<td>19009</td>
<td>First</td>
<td>Black</td>
<td>No</td>
<td>No</td>
<td>30 1/7</td>
<td>No</td>
</tr>
<tr>
<td>10013</td>
<td>First</td>
<td>White</td>
<td>Yes</td>
<td>Yes</td>
<td>34 6/7</td>
<td>No</td>
</tr>
<tr>
<td>10532</td>
<td>Second</td>
<td>White</td>
<td>No</td>
<td>NA</td>
<td>34 6/7</td>
<td>No</td>
</tr>
<tr>
<td>10011</td>
<td>First</td>
<td>Amer. Indian</td>
<td>No</td>
<td>Yes</td>
<td>35 2/7</td>
<td>No</td>
</tr>
<tr>
<td>10036</td>
<td>First</td>
<td>White</td>
<td>No</td>
<td>No</td>
<td>35 6/7</td>
<td>Yes</td>
</tr>
<tr>
<td>10018</td>
<td>First</td>
<td>Amer. Indian</td>
<td>No</td>
<td>Yes</td>
<td>36 1/7</td>
<td>No</td>
</tr>
<tr>
<td>19007</td>
<td>First</td>
<td>Pacific Islander</td>
<td>No</td>
<td>Yes</td>
<td>36 2/7</td>
<td>No</td>
</tr>
<tr>
<td>10527</td>
<td>Second</td>
<td>White</td>
<td>No</td>
<td>NA</td>
<td>36 2/7</td>
<td>No</td>
</tr>
<tr>
<td>10530</td>
<td>Second</td>
<td>White</td>
<td>Yes</td>
<td>Yes</td>
<td>36 2/7</td>
<td>No</td>
</tr>
<tr>
<td>10055</td>
<td>First</td>
<td>Other</td>
<td>No</td>
<td>Yes</td>
<td>36 3/7</td>
<td>No</td>
</tr>
<tr>
<td>10014</td>
<td>First</td>
<td>Asian-unspec.</td>
<td>No</td>
<td>No</td>
<td>36 6/7</td>
<td>No</td>
</tr>
<tr>
<td>10101</td>
<td>First</td>
<td>White</td>
<td>No</td>
<td>Yes</td>
<td>36 6/7</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Pregnancy-Associated Microbiota, by Body Site
N= 40 Subjects (29 Term; 11 Preterm), 3766 Samples

Pregnancy-Associated Microbiota, by Body Site
N= 40 Subjects (29 Term; 11 Preterm), 3766 Samples

PC2 (17%)

Vagina (n=996)
Stool (n=851)
Saliva (n=988)
Tooth/Gum (n=931)
Relative Stability of Phylogenetic Composition During Pregnancy

Vaginal Microbiota Over Time
n= 40 subjects (29 term; 11 preterm), 996 samples

PC1 (32%)

Term birth
(n=29 subjects)

Preterm birth
(n=11 subjects; GAD 22-36 wks)
Relative Abundances of 20 Most Abundant OTUs in Vaginal Communities
(N=761 Samples from 40 Women)

Timeline of Vaginal CSTs
(N=761 Samples from 40 Women)
# Vaginal CST 4 Was Associated with Preterm Delivery (N=761 Samples from 40 Women)

<table>
<thead>
<tr>
<th>CST</th>
<th>Term</th>
<th>Preterm</th>
<th>Very Preterm</th>
<th>Marginal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>232 (82%)</td>
<td>28 (9.9%)</td>
<td>[0]</td>
<td>23 (8.1%)</td>
</tr>
<tr>
<td>2</td>
<td>36 (75%)</td>
<td>0</td>
<td>[0]</td>
<td>12 (25%)</td>
</tr>
<tr>
<td>3</td>
<td>201 (80%)</td>
<td>10 (4%)</td>
<td>[10 (4%)]</td>
<td>39 (16%)</td>
</tr>
<tr>
<td>4</td>
<td>35 (32%)</td>
<td>68 (62%)</td>
<td>[33 (30%)]</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>5</td>
<td>67 (96%)</td>
<td>1 (1.4%)</td>
<td>[0]</td>
<td>2 (2.8%)</td>
</tr>
</tbody>
</table>

Vaginal CST 4 and Preterm Delivery
(N=33 Subjects Providing ≥10 Samples During Gestation)

CST 4 exhibited a dose-response relationship with preterm birth. An increase in proportion of time points in diverse state correlated with lower gestational age at delivery.

Association between CST 4 and preterm birth was observed relatively early in gestation.

Dynamics of Vaginal CSTs (N=40 Subjects) Represented as a Markov Chain

Fig. 2. Proposed mechanisms of disease implicated in spontaneous preterm labor. Genetic and environmental factors are likely contributors to each mechanism.

Possible Links Between Microbiome and Prematurity?

• Aberrant assembly or function of microbiome during pregnancy provokes local/systemic inflammatory or inappropriate immune response?

• Fails to resist invasion by pathogens?

• Disturbed community allows breakdown of normal mucosal barrier, leakage of indigenous microbes, toxins, metabolites into circulation?
Alpha Diversity of Vaginal Communities Pre- and Post-Delivery in the First Subject Group (N=22 Subjects with ≥1 Post-Delivery Sample)
Optimal Sampling Frequency?

- Depends on the question being asked
- In our cohort, we observed the following:

<table>
<thead>
<tr>
<th>Vaginal CST</th>
<th>Persistence Time (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48.1</td>
</tr>
<tr>
<td>2</td>
<td>40.5</td>
</tr>
<tr>
<td>3</td>
<td>7.5</td>
</tr>
<tr>
<td>4</td>
<td>2.6</td>
</tr>
<tr>
<td>5</td>
<td>5.4</td>
</tr>
</tbody>
</table>

- Therefore, sampling at a frequency less than weekly would have disproportionately impacted the ability to detect excursions into CST 4
Conclusions

1. Microbiota community taxonomic composition and alpha- and beta-diversity remained remarkably stable at all four body sites during pregnancy (p>0.05 for trends over time)
2. Prevalence of a *Lactobacillus*-poor vaginal community (CST 4) inversely correlated w/ GAD (p=0.0039)
3. Risk for preterm birth more pronounced for subjects with CST 4 accompanied by elevated *Gardnerella* or *Ureaplasma* abundances
4. Most women experienced postdelivery disturbance in vaginal community characterized by decrease in *Lactobacillus* species and an increase in diverse anaerobes such as *Peptoniphilus, Prevotella*, and *Anaerococcus* species
At Each Time Point, Multiple Body Sites Were Sampled Using Non-Invasive Techniques

n = 4,150 unique samples

Mom’s samples:
- skin surface (ear creases)
- oral cavity (dorsal tongue)
- breast milk (as available)
- distal gut (fecal sample)
- vagina

Baby’s samples:
- oral cavity (dorsal tongue)
- skin surface (ear creases)
- distal gut (fecal sample)
### Early Development of Microbiome: An Ongoing Study of Healthy Mother-Infant Dyads

<table>
<thead>
<tr>
<th>Baby</th>
<th>Birth-weight (kg)</th>
<th>Sex</th>
<th>Delivery mode</th>
<th>No. antibiotic courses (from birth to age 2y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.71</td>
<td>M</td>
<td>C-section</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>3.20</td>
<td>F</td>
<td>vaginal</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>3.71</td>
<td>M</td>
<td>C-section</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>2.07</td>
<td>F</td>
<td>C-section</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>3.71</td>
<td>M</td>
<td>vaginal</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>3.01</td>
<td>M</td>
<td>vaginal</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>3.03</td>
<td>F</td>
<td>vaginal</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>3.23</td>
<td>M</td>
<td>vaginal</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>2.50</td>
<td>M</td>
<td>vaginal</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>3.29</td>
<td>F</td>
<td>C-section</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>3.37</td>
<td>M</td>
<td>vaginal</td>
<td>3</td>
</tr>
<tr>
<td>12</td>
<td>3.03</td>
<td>M</td>
<td>vaginal</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>2.78</td>
<td>F</td>
<td>vaginal</td>
<td>1</td>
</tr>
<tr>
<td>14</td>
<td>3.01</td>
<td>M</td>
<td>vaginal</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>2.21</td>
<td>M</td>
<td>C-section</td>
<td>0</td>
</tr>
</tbody>
</table>

Fifteen Mother-Infant Pairs (Dyads) Participated In & Completed Our 2-Year Study of Healthy Mother-Infant Dyads
Development of Microbiota in First Two Years of Life: 15 Infant-Mom Dyads, 4150 Samples

Babies, postnatal day (gradient)

Moms + babies, body site

PC1 (18%)

PC2 (8%)

Gut (baby)
Mouth (baby)
Skin (baby)

Gut (mom)
Mouth (mom)
Skin (mom)
Community 'Matures' in Gut and Mouth

Distal gut

Dyad #14 (Antibiotic Naive)

Mouth

Skin

Postnatal day
Community 'Matures' in Gut and Mouth

Dyad #14 (Antibiotic Naive)

- **Distal Gut**
  - PC1 (28%)
  - PC2 (14%)
  - Baby14
  - Mom14

- **Mouth**
  - PC1 (28%)
  - PC2 (10%)
  - Baby14
  - Mom14

- **Skin**
  - PC1 (21%)

Postnatal day

Dyad #15 (Antibiotic Naive)

- **Distal Gut**
  - PC1 (30%)
  - PC2 (8%)
  - Baby15
  - Mom15

- **Mouth**
  - PC1 (34%)
  - PC2 (8%)
  - Baby15
  - Mom15

- **Skin**
  - PC1 (30%)
  - PC2 (7%)

Liz Costello
Baby 4: Female, Vaginal Delivery, Breast Fed, No Antibiotics
Many Vaginally-Delivered Infants Are Colonized from Birth with *Bacteroides* at High Abundance

- Many, but not all; exposure to fecal bacteria (e.g., *Bacteroides*) is more likely during vaginal delivery, but not guaranteed
Baby 1: Male, C-Section, Breast Fed, 10d Amoxicillin at 5 Mo
Baby 12: 4 samples around first abx course—E. coli “A” bloom, B. longum resilience
Later Days: Emergence of Individuality
(Within- and Between-Baby Pairwise Correlation Scores, ~165,000)
Human gut microbiome viewed across age and geography

Tanya Yatsunenko, Federico E. Rey, Mark I. Manary, Indi Trehan, Maria Gloria Dominguez-Bello, Monica Contreras, Magda Magris, Clara Hidalgo, Robert N. Baldassano, Andrey P. Anokhin, Andrew C. Heath, Barbara Warner, Jens Reeder, Justin Kuczynski, J. Gregory Copas, Catherine A. Llorupone, Christian Linfer, Jose Carlos Clemente, Dan Knights, Rob Knight, and Jeffrey I. Gordon

Maturation of distal gut taxonomic composition

Fecal Microbiomes of Babies Enriched in Genes for Folate Biosynthesis—Whereas in Adults, Genes for Folate Metabolism

Genes for biosynthesis of cobalamin, thiamine, biotin enriched in adults

Colonization of the Newborn

• Rapid, early increase in population density
• Extreme early temporal variability, reflects accidental exposures (many “healthy patterns”)
• Later, postnatal differentiation of body habitats
• Frequent temporary equilibria; relative stability over time, interrupted by dramatic shifts
• After first few months, individuality emerges, as well as convergence towards a “generic” adult profile (by 1-3 years of age)
• Distinct health outcomes based on different trajectories? Key functional features?
Clinical Implications

• Importance of…
  – Early days (re: intervention)
  – Maternal landscape, prior history
  – Windows of susceptibility, opportunity
    • (site-specific?)
  – Strains, community-wide functions
    • (e.g., cooperative synthetic activities)
  – Individuality
Study of the Human Microbiome: Challenges

• Tracking, understanding sources of variation
• Getting at function
• Assessing possible causation

...But learning about human biology, health and disease
Park Management Plan (For Human Microbial Ecosystem)

- Habitat restoration
- Promotion of native species
- Targeted removal of invasive species
- Ecosystem service providers?
- Community and host context?
- Adaptive management: system monitoring to inform decisions

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