Introduction to the Human Microbiome and NIH’s Human Microbiome Project

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(+ the work of thousands of scientists in US and abroad)

OARAC
April 6, 2017
Everywhere we look, we find microbes* associated with healthy human tissues.

<table>
<thead>
<tr>
<th>Body site</th>
<th>Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouth (total)</td>
<td>$10^{10}$</td>
</tr>
<tr>
<td>Lungs</td>
<td>$\sim 10^9$/ml</td>
</tr>
<tr>
<td>Breastmilk (prelim.)</td>
<td>$\sim 10^9$/L</td>
</tr>
<tr>
<td>Skin (total)</td>
<td>$10^{12}$</td>
</tr>
<tr>
<td>GI tract (total)</td>
<td>$10^{14}$</td>
</tr>
<tr>
<td>Vagina</td>
<td>$\sim 10^7$ to $10^9$/ml</td>
</tr>
<tr>
<td>Placenta (prelim.)</td>
<td>$\sim 10^5$/g tissue</td>
</tr>
</tbody>
</table>

*microbe = microbial life (bacteria, eukaryotic viruses, bacteriophage, fungi)  
*microbiome = all microbial life and their genomic/metabolic capabilities

- Adult gut microbiome weighs about 3-5 lbs (same as the brain).
- Metabolic capacity of gut microbiome equivalent to liver.
1) Infants obtain inoculum from mother or environment.
2) Microbial succession over ~1-2 yrs.
3) Microbiome becomes “adult-like” in ~1-2 yrs.
Human milk oligosaccharides (HMOs):
1) microbial food for the developing microbiome
2) protects against invading pathogens

100s of different kinds of HMOs

HMOs as molecular decoys
<table>
<thead>
<tr>
<th>newborn</th>
<th>three month old</th>
<th>one year old</th>
<th>six years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternally-acquired (passive) immunity</td>
<td>Adaptive immunity</td>
<td>Antibodies at 15-20% of adult levels.</td>
<td>Normal antibody levels.</td>
</tr>
</tbody>
</table>

- Infant begins producing antibodies.
- Maternal immune properties transferred in utero.
Microbiota and host *interact* to regulate human health.

- ‘educates’ the immune system to recognize self from nonself,
- digests the ‘indigestables’ (ex. plant material, host cells, mucous),
- produces energy substrates for host cells (ex. SCFAs),
- metabolizes drugs,
- produces beneficial compounds (ex. vitamins, antimicrobials)
- produces signaling molecules which interact with the host,
- communicates with the brain
The human microbiome augments or extends the human genome

Each of us host ~4000 bacterial species, which include ~4,000,000 bacterial genes.

Human genome? 20,000-23,000 genes

~100s of times more bacterial genes than human genes
Practices in modern society may be leading to an impoverished microbiota.

Contemporary practices:
- sanitation
- fresh food
- cooking
- clean water
- bathing
- antibiotic use
- caesarean birth
- formula feeding
- Hg amalgams
- diet changes
- etc.

"Healthy Brazilian Amerindians and African Malawians have 30% more microbes in their microbiomes than so-called healthy Americans" (M. G. Dominguez-Bello, NYU 2014)

Postulated systematic loss of microbiota inocula each generation.
And, the list of postulated microbiome-associated diseases/disorders is growing....

Brain/behavior: general brain function, epilepsy, Alzheimer’s, psychiatric disorders

Heart: cardiovascular diseases

Gut: irritable bowel disease (IBD), ulcerative colitis, Crohn’s disease, GERD, necrotizing enterocolitis (NEC)

Cancers: esophageal cancer, colorectal cancer, Hodgkin’s lymphoma, cervical cancer, liver cancer, gastric cancer

Systemic: obesity, metabolic syndrome, rheumatoid arthritis, multiple sclerosis, autism, type 1 diabetes, type 2 diabetes

Skin: eczema, psoriasis, acne

Lung: asthma, cystic fibrosis

Vagina: bacterial vaginosis, preterm birth

Liver: non-alcoholic liver disease (NAFLD), alcoholic steatosis
Catalysts for the NIH Human Microbiome Project

Follow on to Human Genome Project

~1400 human pathogens

vs.

~10 million microbial species on Earth, most which are beneficial
Sequence Technologies and Computational Analyses
Coming of Age...

- Isolate microorganism
- Extract DNA
- 16S rRNA PCR
- Sequence
- 16S rRNA gene sequencing
- Analyse
- Whole-Genome sequencing
- Metagenomic sequencing

Specific marker for bacteria in samples
Single microbial genomes
Total microbial communities

And... proteomics, metabolomics, other ‘omics

Building a community resource
Human Microbiome Project, Phase One: *a community resource*
(http://commonfund.nih.gov/hmp)

Phase 1 ($185M): Survey of the microbiome in humans
(Funding from Common Fund + NHGRI, NIAID, NCI, NIDDK, NIDCR, NCCAM, ODS)

“Who’s there?”

**Healthy cohort study**

**Clinically healthy**
- 300 male/female
- 18-40 y.o.
- 5 major body regions (18 body sites)
- Up to 3 visits in 2 yrs
- No antibiotics, probiotics, immunomodulators

**Microbiome-associated conditions**

**Skin**: eczema, psoriasis, acne

**GI/oral**: esophageal adenocarcinoma, necrotizing enterocolitis, pediatric IBS, ulcerative colitis, Crohn’s Disease

**Urogenital**: bacterial vaginosis, circumcision, sexual histories
In healthy American adults, the microbial community composition in each part of the body is unique.

- For each person, est. 1,000 bacterial species and 2,000,000 bacterial genes.
- Total pool, est. 10,000 species and 8,000,000 genes.

Human Microbiome Project Consortium (2012a)
In general though, microbial composition of healthy adult microbiomes is highly variable.

Yet, metabolic potential of each microbiome is less variable.

Microbial composition of each body site community

A ‘core’ microbial composition may not correlate with host phenotype.

However, a ‘core’ metagenomic and/or functional profile may correlate with host phenotype.

Human Microbiome Project Consortium (2012b)
Relationship between microbial properties and time

Microbial property to be measured dependent on question

RNA: Gene expression

Protein: Synthesis, Enzyme activity

Cell: Metabolism, Reproduction

Niches & Microbial community:
Population and community structure & metabolism, Microbial products, HGT, AR, etc.

days/weeks/mons/ys

mins/hrs/days

mins/hours

secs/mins

stimulus
The metagenome alone is only the genetic “blueprint” for the biology of the microbiome.

What biological properties do we need to study to understand the microbiome’s role in humans?

Gene expression profiles
Protein profiles
Metabolomes
Human Microbiome Project, Phase Two: a community resource (http://ihmpdcc.org)

Phase 2 (to date, ~$35M): Integrative HMP “iHMP”
(Funding from Common Fund + NIDDK, NICHD, ORWH, NCCIH, ODS)

“What are they doing?”

Analyse biological properties of both microbiome & host over time to look for biomarkers of health and disease.

Three “model” microbiome-associated conditions:

1. Pregnancy & Preterm Birth
   - Multi-Omic Microbiome Study: Pregnancy Initiative (MOMS-PI)
2. Inflammatory Bowel Disease
   - Characterizing the gut microbial ecosystem for diagnosis and in therapy in IBD
3. Prediabetes
   - Microbiome and host changes during respiratory and other stress conditions in individuals at risk for type 2 diabetes
## iHMP: Dynamics of Pregnancy and Preterm Birth

(http://vmc.vcu.edu/momspi)

### Subjects

- 2000 Pregnant women
- 2000 Neonates

### Sample Collection

- **Subjects**
  - Buccal
  - Nostril
  - Chest
  - Palm
  - Vagina
  - Cervix
  - Rectum
  - Stool
  - Cord blood
  - Amniotic fluid
  - Antecubital fossa
  - Blood - plasma
  - Blood - whole blood
  - Blood -uffy coat
  - Respiratory secretions
  - Membranes

- **2000 Pregnant women**
  - Vagina
  - Blood - plasma
  - Amniotic fluid

- **2000 Neonates**
  - Vagina
  - Cheek
  - Respiratory secretions

### Assays

- **Microbes: 16S rRNA gene profiling**
  - 30,400 samples

- **Microbes: Bacterial cultivation / seq**
  - 30,400 samples

- **Host: Lipidomic profiling**
  - 8000 samples

- **Host: Cytokine assays**
  - 8000 samples

- **Microbes: Metatranscriptome**
  - Host
  - 60 samples

- **Microbes: Interactome maps**
  - Host
  - Pilot study

- **Microbes: Metagenome**
  - Host
  - 60 samples

### Study Sites

- VCU Medical Center (5 Clinics)
- GAPPs Seattle (5 Clinics)
- Mom Samples
- Baby Samples

*de-identification*
iHMP: Dynamics of IBD Onset
(http://ibdmdb.org)
iHMP: Dynamics of Type 2 Diabetes Onset

(http://med.stanford.edu/ipop.html)
NIH consists of 27 Institutes, Centers and Offices (ICOs)

By 2012, 18 ICOs invested in the human microbiome research
Trans-NIH Microbiome Working Group (TMWG)

established 2012

Extramural program staff only, membership from 18 ICOs

LM Proctor (NHGRI), TMWG chair

Mission: Forum for microbiome-related investments at NIH

- Identify, gaps, needs, challenges and opportunities
- Share upcoming FOAs, develop joint FOAs; coordinate joint funding of applications
- Develop microbiome review panel at CSR
- Organize NIH-wide meetings
- Serve as central resource for external community

TMWG (external page):
www.commonfund.nih.gov/hmp/related_activities
NIST*- NIH Workshop:
Standards for Microbiome Measurements
(http://www.nist.gov/mml/microbiome-standards.cfm)

Details:
Start Date: Tuesday, August 9, 2016
End Date: Wednesday, August 10, 2016
Location: NIST, 100 Bureau Drive, Gaithersburg, Md.

Special issue in prep.,
BMC Standards in Genomic Sciences

The webcast recording posted online http://go.usa.gov/cw8dT.

*NIST = Natl. Institute of Standards & Technology
“The Human Microbiome: Emerging Themes at the Horizon of the 21st Century”

- NIH-wide human microbiome workshop, organized by TMWG
- 40+ speakers, 500 participants; August 16-18, 2017
- Workshop closes with joint Agency Panel: NIH, FDA, CDC, DOD, VA, NIST, USDA
- Workshop goals: Identify knowledge gaps, technical challenges, new approaches needed to advance field in the next ten years
$922M

**NIH** 56%

**DOE** 15%

**USDA** 4%

**DOD** 4%

**NASA** 3%

**EPA** 1%

**FDA** 2%

**NOAA** <1%

**DOI** 1%

**NSF** 11%

**USAID, CDC, Smithsonian** <1%

**FTAC-MM**

- OSTP charter
- FY12-14 data call
- Microbiome ‘writ large’
- 6 Departments (16 agencies), 4 Independent Agencies, 1 quasi-governmental entity

**Data call results:**

- $922M over FY12-14
- NIH comprised 56% of this total
- NSF and DOE comprised an additional 26% of this total

**2016 Nature Microbiology paper:**

[http://dx.doi.org/10.1038/nmicrobiol.2015.15](http://dx.doi.org/10.1038/nmicrobiol.2015.15)
Announcing the National Microbiome Initiative

MAY 13, 2016 AT 6:00 AM ET BY JO HANDELSMAN

Summary: The new National Microbiome Initiative aims to advance microbiome science in ways that will benefit individuals, communities, and the planet.

16-agency Microbiome Interagency Working Group (MIWG):
Developing federal strategic plan
MIWG Federal Strategic Plan

✓ Initiate, coordinate and expand activities in:
  • computational biology and bioinformatics
  • reference databases and biorepositories
  • standardized protocols and high-throughput tools
  • longitudinal and functional studies
  • interdisciplinary research
  • microbiome/metagenomics training
  • international collaborations

✓ Plan over short term (2-5 yrs) and long term (10+ yrs)

✓ MIWG timeline:
  2016-2017: Develop outline of plan
  New Administration: Seek approval to execute plan
  If approved: flesh out short term and long term plan
Questions?

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