The NIH Human Microbiome Project: Catalyst for an Emerging Field

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National Human Genome Research Institute, NIH
(+ the work of thousands of scientists in US and abroad)

CHE webinar
May 24, 2016
Topics in this talk

1) Impetus for and goals of the HMP
2) Early findings about the human microbiome
3) Microbiome research beyond the HMP
4) National Microbiome Initiative
“microbiome”
“microbial organ”
“human superorganism”
“good germs”
“our second genome”
Society’s war against infectious disease

(bubonic plague, smallpox, scarlet fever, yellow fever, tuberculosis, malaria, diptheria, dysentery, leprosy, typhoid fever...)

[Image of a historical scene with a doctor administering a vaccine to a child.]
The **MAJORITY (>> 99%)** of microbes (bacteria, viruses, fungi) do not cause disease; many are beneficial. Microbes on Earth:

- Soil production/regeneration
- Oxygen production
- Base of food webs (ocean, forests, etc)
- Support plant, animal & human health

~1400 species of human pathogens vs.

~1 - 10 million microbial species on Earth

**Phase 1 ($181M)$: Survey of the microbiome in humans**

**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

**Demonstration Projects**

**case:control**
Human Microbiome Project, Phase Two: a community resource ([http://hmp2.org](http://hmp2.org))

Phase 2 (to date, ~$35M): Integrative HMP “iHMP”

“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:

- **Pregnancy & Preterm Birth**
  Multi-Omic Microbiome Study: Pregnancy initiative (MOMS-PI)

- **Inflammatory Bowel Disease**
  Characterizing the gut microbial ecosystem for diagnosis and in therapy in IBD

- **Prediabetes**
  Microbiome and host changes during respiratory and other stress conditions in individuals at risk for type 2 diabetes

*longitudinal studies*
Early findings about the microbiome
Microbiota acquired anew each generation.

1) Infants obtain inoculum from mother or environment.
2) Microbial succession over ~1-2 yrs.
3) Microbiome becomes “adult-like” in ~1-2 yrs.
Development of the immune system

<table>
<thead>
<tr>
<th>newborn</th>
<th>three month old</th>
<th>one year old</th>
<th>six years old</th>
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<tbody>
<tr>
<td>Maternally-acquired (passive) immunity</td>
<td>Adaptive immunity</td>
<td>Maternal immune properties transferred in utero.</td>
<td>Infant begins producing antibodies.</td>
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### Sources of microbes to the newborn, infant and child

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</thead>
<tbody>
<tr>
<td>Uterus</td>
<td>Breastmilk, food</td>
<td>Food</td>
<td></td>
</tr>
<tr>
<td>Amniotic fluid</td>
<td>Family members</td>
<td></td>
<td>Other humans</td>
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<tr>
<td>Vagina</td>
<td>Pets/animals</td>
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<td></td>
</tr>
<tr>
<td>Breastmilk</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Skin</td>
<td>Environment</td>
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*Images of newborn, infant, and child.*
We co-evolved with our microbiome: Immune system cannot mature without specific microbes.

Some bacteria induce host pro-inflammatory response to protect against infection.

Others bacteria induce host anti-inflammatory response to restore immune system balance.

Cross section of gut epithelium and bacterial community.
(blue = gut wall cells  green = mucous layer  yellow and fuschia = bacteria)

micrograph from Earle et al. (2015)
Each of us host ~4000 bacterial species, which include ~4,000,000 bacterial genes.

Human genome? 20,000-23,000 genes

100-200x more bacterial genes than human genes in human ecosystem.
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, mucus),
- produces energy substrates for host cells (ex. SCFAs),
- metabolizes drugs,
- produces beneficial compounds (ex. vitamins, antimicrobials)
- produces signaling molecules which communicate with the host,
- gut microbiota communicate with the brain
Though the human microbiome is a fixed feature, it is also a variable trait.

- Between generations
- Throughout our lifetimes
- Between health and disease

Unlike the human genome, the microbiome is naturally mutable.
Disturbances to our microbiomes and modern diseases?

From Center for Global Development
The list of potential microbiome-associated diseases/disorders is growing.

**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

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

**Skin:** eczema, psoriasis, acne

**Lung:** asthma, cystic fibrosis

**Vagina:** bacterial vaginosis, preterm birth

**Liver:** non-alcoholic liver disease (NAFLD), alcoholic steatosis
Microbiome research beyond the HMP
NIH consists of
27 Institutes, Centers and Offices (ICOs)
2012-2013: approx. $100-150M/yr invested in the human microbiome
Atmospheric microbiomes
Soil & plant microbiomes
Astronaut/ISS microbiomes
Livestock/poultry microbiomes
Warfighter microbiomes
Coral reef & oceanic microbiomes
Soil & plant microbiomes
Hospital & built environment microbiomes
Total Microbiome Research Funding FY12-14 by Agency

**Total Funding for FY12-14:** $921,786,776

- **USDA:** 4%
- **DOE:** 15%
- **NASA:** 3%
- **DOD:** 4%
- **NIH:** 56%
- **FDA:** 2%
- **USAID, CDC, Smithsonian:** <1%
- **DOI:** 1%
- **NSF:** 11%
- **NIST:** $225,000 (0.02%)
- **NOAA:** <1%
- **EPA:** 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

**Nature Microbiology paper:**
http://dx.doi.org/10.1038/nmicrobiol.2015.15
Microbiome research comes of age: The National Microbiome Initiative

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.

https://www.whitehouse.gov/blog/2016/05/13/announcing-national-microbiome-initiative
Questions?

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