How the Human Microbiome Influences Arthritis

Blake Hanson
Jackson Laboratory for Genomic Medicine
Farmington, CT

Wisconsin Rheumatology Association 2017
March 18th, 2017
Terminology

Microbiome: the ecological communities of microorganisms that share our body
Incidence of "Microbiome" in Scientific Papers

Year


Papers

0  500  1000  1500  2000  2500  3000  3500  4000  4500  5000
There are more bacteria in your mouth than there are people on the earth.
Salivary microbiome

You have more bacterial genes in your body than human genes

Human microbiome
1,000,000+ genes

Human genome
23,000 genes
Terminology

Microbiome:
the ecological communities of microorganisms that share our body

Metagenome:
The collective genomes of the microbiota

The Scientist, 4/2/2001
‘Ome Sweet ‘Omics – A Genealogical Treasury of Words
Microbiome analysis
What microbes are in the sample?

Sample

Nucleic acid extraction

Sequencing

<table>
<thead>
<tr>
<th>Organism (or genes)</th>
<th>Amt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteroides</td>
<td>574</td>
</tr>
<tr>
<td>Prevotella</td>
<td>64</td>
</tr>
<tr>
<td>Ruminococcus</td>
<td>7</td>
</tr>
<tr>
<td>Clostridia</td>
<td>231</td>
</tr>
<tr>
<td>Escherichia</td>
<td>4</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>57</td>
</tr>
<tr>
<td>Faecalibacterium</td>
<td>32</td>
</tr>
</tbody>
</table>
Revolution in DNA sequencing enables metagenomics

What is the human microbiome?

The human microbiome is the community of native bacteria that live in and on the human body.

There are 10x more bacterial cells in and on the human body than there are human cells.

Different bacteria are found at different body sites, and these bacteria perform different functions.

The microbiome plays a major role in human health and disease and represents an understudied diagnostic and therapeutic target.
Xochitl et al. Trends in Genetics 2012, 51-58

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Community classes in specific sites

Zhou et al. Genome Biology 2014, 15:R66
Novel Bacterial Taxa in the Human Microbiome

Kristine M. Wylie¹, Rebecca M. Truty²,⁎, Thomas J. Sharpton², Kathie A. Mihindukulasuriya¹,
Yanjiao Zhou¹, Hongyu Gao¹, Erica Sodergren¹, George M. Weinstock¹, Katherine S. Pollard²,⁎
¹The Genome Institute, Washington University School of Medicine, St. Louis, Missouri, United States of America, ²Gladstone Institutes, University of California San Francisco, San Francisco, California, United States of America, ³Division of Biostatistics, Institute for Human Genomics, University of California San Francisco, San Francisco, California, United States of America

The early infant gut microbiome varies in association with a maternal high-fat diet

Derrick M. Chu¹,²,³, Kathleen M. Antony¹, Jun Ma¹, Amanda L. Prince¹, Lori Showalter¹, Michelle Moller¹
and Kierstil M. Aagaard¹,²,³,⁴,⁎

Metagenomic Approach for Identification of the Pathogens Associated with Diarrhea in Stool Specimens

Yanjiao Zhou,⁎⁎ Kristine M. Wylie⁎, Rana E. El Feghaly,⁎ Kathie A. Mihindukulasuriya,⁎ Alexis Elward,⁎ David B. Haslam,⁎
Gregory A. Storch,⁎ George M. Weinstock⁎⁎
Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri, USA; Department of Pediatrics, University of Mississippi Medical Center, Jackson, Mississippi, USA; McDonnell Genome Institute, Washington University School of Medicine, St. Louis, Missouri, USA; Division of Infectious Disease, Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio, USA.
The Holy Grail of Microbiome Research:

Identify Specific Causative Microbes
A microbiome disease: 
*Clostridium difficile* associated diarrhea

Healthy Microbiome

Antibiotic Treatment

*C. difficile*
Antibiotic resistant
Toxigenic

Diarrhea Disease

How to treat an antibiotic resistant infection?
Microbiome Therapy Headlines

Fecal transplants beat antibiotics for curing diarrhea caused by C. difficile

Fecal transplants cure most cases of C. difficile

Faecal transplants succeed in clinical trial

From me, to poo, to you: The faecal transplants fighting C. difficile
Effectiveness of fecal transplant

- Patients enrolled following 1st *C. difficile* recurrence
- Randomized to three groups:
  - Vancomycin treatment (500 mg orally 4 times a day, 4 days)
  - Vancomycin + bowel lavage
  - Vancomycin + bowel lavage + fecal transplant

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Cure Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>30.8%</td>
</tr>
<tr>
<td>Vancomycin + Bowel Lavage</td>
<td>23.1%</td>
</tr>
<tr>
<td>Vancomycin + Bowel Lavage + Fecal Transplant</td>
<td>93.8%</td>
</tr>
</tbody>
</table>

Figure 3. Microbiota Diversity in Patients before and after Infusion of Donor Feces, as Compared with Diversity in Healthy Donors.

Microbiota diversity is expressed as Simpson’s Reciprocal Index of diversity in fecal samples obtained from nine patients before and 14 days after the first infusion of donor feces, as compared with their donors. The index ranges from 1 to 250, with higher values indicating more diversity. The box-and-whisker plots indicate interquartile ranges (boxes), medians (dark horizontal lines in the boxes), and highest and lowest values (whiskers above and below the boxes).
The microbiome and immunology

Gut microbiota, metabolites and host immunity

Michelle G. Rooks & Wendy S. Garrett

Affiliations | Corresponding author


Temporal and spatial interplay of microbiota and intestinal mucosa drive establishment of immune homeostasis in conventionalized mice FREE

Sahar El Aidy, Peter van Baarlen, Muriel Derrien, Dicky J Lindenbergh-Kortleve, Guido Hooiveld, Florence Levenez, Joël Doré, Jan Dekker, Janneke N Samsom, Edward E S Nieuwenhuis and Michiel Kleerebezem
Mucosal Immunology 5: 567-579; Published online, 23 May 2012; doi:10.1038/mi.2012.32

The Macro Influence of the Microbiome

Pamela J. Fink

J Immunol January 15, 2017, 198 (2) 553; DOI: https://doi.org/10.4049/jimmunol.1690022

The Microbiome, Timing, and Barrier Function in the Context of Allergic Disease

Duane R. Wosemann, Cathryn R. Nagler

DOI: http://dx.doi.org/10.1016/j.immuni.2016.02.002 | CrossMark

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Proposed gut-joint axis mechanism

Differentiating RA patients from controls

The microbiome as a diagnostic for RA

- Stool: AUC: 0.940, Sensitivity: 0.922, Specificity: 0.838
- Dental Plaque: AUC: 0.870, Sensitivity: 0.860, Specificity: 0.800
- Saliva: AUC: 0.814, Sensitivity: 0.814, Specificity: 0.702

Microbiome is predictive of response to treatment

The lung microbiome in early RA and sarcoidosis

Differential bacteria in RA and sarcoidosis

The future

- Microbial communities throughout the body
  - New class of diagnostics
- Assess metabolomics
  - Look towards the metabolites produced by the host and microbes
- Microbiome-based therapies
  - Manipulate the microbiome (e.g. diet)
  - Single organism probiotics
  - Whole microbiome transplants
- Preventative measures
  - Track the microbiome
  - Make life-style adjustments
Additional diseases and conditions under study

- Rheumatoid arthritis
- Ankylosing spondylitis
- Enthesitis-related arthritis
- Psoriatic arthritis
- Psoriasis
- Lupus
- Sjögren’s syndrome
- Behçet’s disease
- Giant Cell arteritis
- Kawasaki disease
Inflammatory arthritis microbiome consortium

- Based in the UK
- Formed in 2016
- International consortium utilizing DNA and RNA sequencing
- Looking to identify host-microbiota interactions specific to inflammatory arthritis

https://www.kennedy.ox.ac.uk