Why is the Microbiome Important in Environmental Health?

Vincent B. Young, MD/PhD
Department of Internal Medicine/Infectious Diseases
Department of Microbiology and Immunology
University of Michigan Medical School, Ann Arbor
Young lab research interests

- Role of the gut microbiota in human inflammatory bowel disease
- Murine models of inflammatory bowel disease
- Role of the microbiota in mediating colonization resistance against pathogenic organisms
- Antibiotic-associated colitis due to *Clostridium difficile*
- Role of complex microbial communities in the lung pathology of patients with cystic fibrosis
- Lung microbiome in HIV-infected patients
Health Consequences from Xenobiotic - Gut Microbiome - Host Interactions
Superfund Research Program

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What is Environmental Health?

Environmental health is the branch of public health that is concerned with all aspects of the natural and built environment that may affect human health.
Natural and built environments
Oral Cavity

Skin

Respiratory Tract

Gastrointestinal Tract

GU Tract

Where are the Bugs?
Gastrointestinal Tract

Oral Cavity
- gingivitis, peridontitis
- halitosis, caries

Respiratory Tract
- COPD, cystic fibrosis
- otitis media, sinusitis
- asthma, allergic rhinitis

GU Tract
- bacterial/fungal vaginosis, urethritis

Skin
- psoriasis, cellulitis

Gastrointestinal Tract
- IBD, AAD, IBS
- infectious gastroenteritis
- obesity, GI cancer
How to think about microbes?

- The only good microbe is a dead microbe...
Koch’s postulates (1882)

- The pathogen must be found in all cases of disease
- The pathogen must be isolated from the host and grown in culture
- The pathogen must recreate disease when given to susceptible host
- Pathogen must be isolated from experimental host
Case

- 56 year old man with chronic obstructive pulmonary disease
- Admitted with a probable pneumonia (seen on CXR)
- Treatment with piperacillin/tazobactam, levofloxacin
- Hospital day three, develops abdominal pain, diarrhea, hypotension
Clostridium difficile
Clindamycin-Associated Colitis Due to a Toxin-Producing Species of
Clostridium in Hamsters

John G. Bartlett, Andrew B. Onderdonk, Ronald L. Cisneros, and Dennis L. Kasper

From the Infectious Disease Research Laboratory, Boston Veterans Administration Hospital; the Department of Medicine, Tufts University School of Medicine; and the Channing Laboratory and Department of Medicine, Harvard Medical School, Boston, Massachusetts

Clindamycin-associated enterocolitis in hamsters was studied to detect and characterize a transmissible agent. It was found that the disease could be transferred by cecal contents and filtrates of cecal contents (pore size of filter, 0.02 μm) obtained from animals after administration of clindamycin. Subsequent work showed that enterocolitis could be produced with broth cultures of a species of Clostridium recovered from cecal contents of animals with clindamycin-induced disease. The cell-free supernatant of this strain also caused enterocolitis. Cecal contents from animals with clindamycin-induced disease incubated with gas gangrene antitoxin failed to cause intestinal lesions. These experiments indicate that clindamycin-associated colitis in hamsters is due to a clindamycin-resistant, toxin-producing strain of Clostridium.
**Clostridium difficile**

- Anaerobic, gram-positive, spore-forming, toxin producing bacterium
- Spores: environmentally stable reservoir of the organism
- Can be detected in a small minority of the normal population
C. difficile and the indigenous gastrointestinal microbiota

**Theory:** the indigenous microbiota can prevent colonization by C. difficile or it can control the population size in colonized patients

**Corollary:** antibiotics disturb the indigenous microbiota, allowing colonization or overgrowth and toxin production
“community thinking”

- Thinking outside of Koch’s postulates
- Rather than looking for a single “bad bug” need to consider the possibility that there exists “good” and “bad” communities of microorganisms
- Restoring balance or preventing imbalance can be novel treatments
Functions of the microbiota

- Metabolism of luminal contents
- Colonization resistance
- Immune signaling
- Synthesis (e.g., vit K)
Paradigm #1: Host immunity and indigenous microbiota

Immune system

Microbiota
Specific Microbiota Direct the Differentiation of IL-17-Producing T-Helper Cells in the Mucosa of the Small Intestine

Ivaylo I. Ivanov,1 Rosa de Llanos Frutos,5 Nicolas Manel,1 Keiji Yoshinaga,3,7 Daniel B. Rifkin,3,4 R. Balfour Sartor,6 B. Brett Finlay,5 and Dan R. Littman1,2,4

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Paradigm #2: Host immunity and indigenous microbiota

Microbiota → Immune system

Pathogenic microbe
LETTERS

Vancomycin-resistant enterococci exploit antibiotic-induced innate immune deficits

Katharina Brandl†, George Plitas², Coralia N. Mihu†, Carles Ubeda¹, Ting Jia¹, Martin Fleisher³, Bernd Schnabl†, Ronald P. DeMatteo² & Eric G. Pamer¹,³
Paradigm #3: Microbiota influences on host physiology

Microbiota → Cytochrome P450 → Metabolism of xenobiotics
Paradigm #3: The tail wagging the dog

Colonization-Induced Host-Gut Microbial Metabolic Interaction

Sandrine P. Claus, a,* Sandrine L. Ellero, b,* Bernard Berger, c Lutz Krause, c Anne Bruttin, c Jérôme Molina, d Alain Paris, d Elizabeth J. Want, a Isabelle de Waziers, b Olivier Cloarec, a Selena E. Richards, a Yulan Wang, a, * Marc-Emmanuel Dumas, a Alastair Ross, c Serge Rezzi, c Sunil Kochhar, c Peter Van Bladeren, c John C. Lindon, a Elaine Holmes, a and Jeremy K. Nicholson a

Biomolecular Medicine, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, London, United Kingdom; INSERM, Unité Mixte de Recherche 775, Université Paris Descartes, IFR des Saints Pères, Paris, France; Nestlé Research Centre, NESTEC Limited, Vers-Chez-les-Blancs, Lausanne, Switzerland; and 4 UMR 1089-Xénobiotiques, INRA, Toulouse, France

* Present address: Sandrine P. Claus, Department of Food and Nutritional Sciences, The University of Reading, Reading, United Kingdom; Sandrine L. Ellero, Division of Analytical Biosciences, LACDR, Leiden University, Leiden, Netherlands; Lutz Krause, Genetics and Population Health, Queensland Institute of Medical Research, Brisbane, Queensland, Australia; Yulan Wang, State Key Laboratory of Magnetic Resonance and Atomic and Molecular Physics, Wuhan Centre for Magnetic Resonance, Wuhan Institute of Physics and Mathematics, The Chinese Academy of Sciences, Wuhan, People’s Republic of China.

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Weight gain in ex-germ free mice
Cytochrome P450 expression

Germ Free

Day 20 post conventionalization
Are paying for assaults on several billion of our closest friends?

- Antibiotics as an evolutionary driver
- Death by a thousand cuts
- Microbiota of other vertebrates
Hygiene hypothesis

Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

In Panel A, data concerning infectious diseases are derived from reports of the Centers for Disease Control and Prevention, except for the data on hepatitis A, which are derived from Joussem et al. In Panel B, data on immune disorders are derived from Swarbrick et al., Dubois et al., Tuomilehto et al., and Pugliatti et al.

Summary

- The indigenous microbiota of the gut is part of a complex, balanced ecosystem.
- Disturbances in this balance may underlie disease states.
- Understanding the close relationship between the microbiota and host can provide insight into the effect of environmental stressors on host health via microbial action.
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