The Microbiome in Infectious & Non-infectious Colitis

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When balance is lost...
Diseases characterized by gastrointestinal inflammation

- Infectious
  - Bacterial
  - Viral
  - Fungal
  - Parasitic

- Non-infectious
  - Inflammatory Bowel Disease
    - Crohn's disease
    - Ulcerative colitis
  - Drug induced
  - Ischemic
  - Radiation-induced
  - GVHD
  - Vasculitis-associated
  - Diverticulitis
Gaps/Needs & Challenges

- We must move from associations between disease states and specific microbiota community structures towards an understanding of the **functional consequences** of these community alterations.

- Results from experimentation with **model microbial communities** need to be validated and correlated with human subjects.

- There is a need for the development and validation of analytic methods to process data derived from “**multi-omic” datasets**.

- Results from microbiome studies need to be developed into **novel therapeutics**, which will require the ability to cultivate specific members of the microbiota and a deeper understanding of how to administer cultivars as potential therapies.
Inflammatory Bowel Disease (IBD)

- Idiopathic condition affecting 1-2% of people in developed nations
- Characterized by sustained, abnormal inflammatory response involving the gastrointestinal mucosa
- Evidence point to a crucial role of the intestinal microbiota in the pathogenesis of IBD
“Dysbiosis” in IBD

Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases

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Spatial Organization and Composition of the Mucosal Flora in Patients with Inflammatory Bowel Disease

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Contributed by Norman R. Pace, July 16, 2007 (sent for review June 7, 2007)
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y=Bfra  r=Erec  g=Eub

Crohn’s disease  self-limited colitis  no colitis
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Linking microbiome structure to microbiome function

ORIGINAL ARTICLE

Connecting dysbiosis, bile-acid dysmetabolism and gut inflammation in inflammatory bowel diseases

Henri Duboc,1,2,3 Sylvie Rajca,1,2,3 Dominique Rainteau,1,2,4 David Benarous,5 Marie-Anne Maubert,1,2,4 Elodie Quervain,1,2 Ginette Thomas,1,2,4 Véronique Barbu,4 Lydie Humbert,1,2,4 Guillaume Despras,2 Chantal Bridonneau,6 Fabien Dumetz,6 Jean-Pierre Grill,1,2 Joëlle Masliah,1,2,4 Laurent Beauperie,1,2,3 Jacques Cosnes,1,2,3 Olivier Chazouillères,7 Raoul Poupon,7 Claude Wolf,1 Jean-Maurice Mallet,2 Philippe Langella,6 Germain Trugnan,1,2,4 Harry Sokol,1,2,3 Philippe Seksik1,2,3

What are the new findings

- Fecal dysmetabolism of BAs is observed in IBD.
- This dysmetabolism is linked to IBD-associated dysbiosis.
- High rates of sulphated BAs is found in faeces of IBD patients.
- Dysmetabolism of BAs could impact on inflammatory loop in IBD.

How might it impact on clinical practice in the foreseeable future?

- BAs dysmetabolism could be used as a surrogate marker of IBD.
- Modulation of gut microbiota and/or BAs content could impact on IBD clinical course.

IBD

Bile acids liver secretion

Dysbiosis

Lower microbiota enzymatic activity

Lower desulfation (bacterial sulfatases)

Sulfation (epithelium sulfotransferase)

Primary BA

Secondary BA

Sulfated BA

Inflammation loop

Gut epithelium

TGR5 signaling

TGR5 signalling inhibits the production of pro-inflammatory cytokines by \textit{in vitro} differentiated inflammatory and intestinal macrophages in Crohn’s disease

TGR5 G-protein coupled BA receptor

lamina propria mononuclear cells from CD patients
More functions:
Loss of microbiota fermentation in Inflammatory Bowel Disease

Poster P41: Marius Vital et al.
“Investigating the role of butyrate-producing bacterial communities in the development of ulcerative colitis”

Additional challenge: how do you keep/form such interdisciplinary teams?
THE FATAL ENTERIC CHOLERA INFECTION IN THE GUINEA PIG, ACHIEVED BY INHIBITION OF NORMAL ENTERIC FLORA

ROLF FRETER*

From the Department of Microbiology, The University of Chicago, Chicago 37, Illinois

pigs. In this respect it might be worthwhile to consider the possibility of inhibitory action on the part of the normal human enteric flora as a factor in the resistance of humans to enteric diseases. This theory has—to the knowledge of the author—first been discussed by Nissle (1916). Following this line of
Case

- 56 year old man with chronic obstructive pulmonary disease
- Admitted with acute exacerbation of chronic bronchitis
- Treatment with cephalosporin and respiratory fluoroquinolone
- Hospital day three, develops abdominal pain, diarrhea, hypotension
normal microbiota → antibiotics → loss of colonization resistance → susceptible microbiota → C. difficile spores → germination → vegetative C. difficile → toxin production → clearance/asymptomatic colonization

recovery

recurrence cycle

CDI treatment (antibiotics) → C. difficile infection → CDI treatment (fecal transplant) → recurrent disease
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Interaction of *Clostridium difficile* and *Escherichia coli* with Microfloras in Continuous-Flow Cultures and Gnotobiotic Mice

KENNETH H. WILSON and ROLF FRETER

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Received 16 December 1985/Accepted 15 August 1986
Cefoperazone-treated mice as an experimental platform to assess differential virulence of *Clostridium difficile* strains

Casey M. Theriot, Charles C. Koupouras, Paul E. Carlson Jr., Ingrid I. Bergin, David M. Aronoff and Vincent B. Young

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[Image of a chemical structure] cefoperazone in drinking water then infect with *C. difficile*
% baseline weight vs. days post infection for control, CDI (well), and CDI (sick) groups.

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From molecular surveys to novel therapies

- Lachnospiraceae associated with protection/minimal disease
- *E. coli* associated with susceptibility/severe disease
- How to move from a 16S survey association to a cultivated organism?

Isolate Lachnospiraceae strain and *E. coli* strain from murine sources using 16S data to guide cultivation efforts.

Monoassociate germ free mice with each of these isolates.

Challenge with *C. difficile*.
VPI 10463 infection

% baseline weight

- C. diff
- Lachno D4/ C.diff
- E.coli/ C. diff

days post challenge

Systematic Review of Intestinal Microbiota Transplantation (Fecal Bacteriotherapy) for Recurrent *Clostridium difficile* Infection

Ethan Gough,1 Henna Shaikh,2 and Ameen A. Manges1,3

Departments of 1Epidemiology Biostatistics and Occupational Health, and 2Biology, McGill University, and 3 Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada

Targeted Restoration of the Intestinal Microbiota with a Simple, Defined Bacteriotherapy Resolves Relapsing *Clostridium difficile* Disease in Mice

Trevor D. Lawley1, Simon Clare1,2, Alan W. Walker1,3, Mark D. Stares1, Thomas R. Connor1, Claire Raisen1, David Goulding1, Roland Rad1, Fernanda Schreiber1, Cordelia Brandt1, Laura J. Deakin1, Derek J. Pickard1, Sylvia H. Duncan2, Harry J. Flint2, Taane G. Clark2, Julian Parkhill1, Gordon Dougan1

1 Wellcome Trust Sanger Institute, Hinxton, United Kingdom, 2 Rowett Institute of Nutrition and Health, Aberdeen, United Kingdom, 3 London School of Hygiene and Tropical Medicine, London, United Kingdom

Microbiome

**METHODOLOGY**

Stool substitute transplant therapy for the eradication of *Clostridium difficile* infection: ‘RePOOPulating’ the gut

Baine O Petrof1,2, Gregory B Gloor2, Stephen J Vanner3, Scott J Weese3, David Carter4, Michelle C Daigneault5, Eric M Brown6, Kathleen Schroeter2 and Emma Allen-Vercoe5
Models without a host

Poster P2 Jennifer Auchtung
“Studying interactions between C. difficile and complex microbial communities in human fecal bioreactors”
courtesy of Rob Britton/MSU

Monday, August 12, 2013
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“multi-‘omics” going from structure to function

Integrated Metagenomics/Metaproteomics Reveals Human Host-Microbiota Signatures of Crohn’s Disease

Alison R. Erickson¹,²,³, Brandi L. Cantarel³,⁴, Regina Lamendella⁴,⁵, Youssef Darzi⁵,⁶, Emmanuel F. Mongodin³, Chongle Pan¹, Manesh Shah¹, Jonas Halfvarson⁷, Curt Tysk⁷, Bernard Henrissat⁸, Jeroen Raes⁵,⁶, Nathan C. Verberkmoes¹, Claire M. Fraser³,⁵, Robert L. Hettich¹⁵, Janet K. Jansson⁴,⁵
Microbiome and metabolome state transitions of the gut microbiota after antibiotic treatment

Poster P37 **Casey Theriot**

“Antibiotic-mediated shifts in the gut microbiome and metabolome leads to susceptibility to *Clostridium difficile* infection”

Carbohydrates  Bile acids

- **R1**
- **R2**
- **R3**
- **Abx**
- **S1**

- 8 weeks
- 6 weeks
- 2 days

R: full colonization resistance
S: susceptible
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Acknowledgements

**MSU:** Robert Britton, Jennifer Auchtung, James Tiedje, Marius Vital

**U of M:** Gary Huffnagle, Thomas Schmidt

**BPC:** Mitchell Sogin

**UC:** Eugene Chang

**The Young Lab:** Angela Reeves, Casey Theriot, Judith Opp

DK070875, DK083993

AI30058, AI075396

HL098961, HL100809