Ground Zero – the impact of the gut microbiome on host epithelial functions and responses.

Eugene B. Chang, M.D.
Human Microbiome Science: A Vision for the Future
July 24, 2013

http://phenomena.nationalgeographic.com/2013/05/13
Examples of critical gut epithelial functions that are impacted by microbes

• Barrier function
  – Intestinal permeability (TJ mediated)
  – Mucus, AMPs
• Development and Adaptation
• Wound healing
• Innate immune functions
• Cytoprotection
• Nutrient/electrolyte/water transport
• Autophagy
• Proliferation/apoptosis
Gut microbes regulate mucosal development, proliferation, and apoptosis

Ki67 immunostaining (green)  
LGG-derived peptides (p40, p75)  
Prevent TNF-induced apoptosis

(Reikvam, et al PlosOne 2011)  
(Yan, et al Gastroenterology 2007)
Conditioned media from *Bifidobacterium breve* protects against ROS-induced barrier dysfunction.
Physiological expression of inducible Hsps by surface colonocytes is maintained by gut microbes
Metagenomic profiles of mucosa-associated microbiota from the healthy human colon

In Hsp70 KO mice, otherwise acute DSS colitis becomes chronic

Wild Type - normal

Hsp70 KO – chronic-like colitis

B.
Identified molecular mediators that affect gut epithelial function

- QSM (e.g. CSF of *B. subtilis*)
- Innate ligands (PAMPs, MAMPs)
  - PG, MDP
  - LPS, dsRNA
- SCFAs, Lactic acid
- H$_2$S
- Chemotactic peptides (nFMLP)
- Metabolites
Gaps in our knowledge of gut microbial-epithelial interactions

• Rudimentary knowledge and inventories of bioactive microbe-derived factors
• Incomplete understanding of the complexity and heterogeneity of gut epithelial functions, particularly as they relate to microbial selection, assemblage and region-specific interactions.
• Incomplete vetting and understanding of the above in the context of human biology and pathobiology
Challenges and Needs

Human Studies:
• Observational and associative
• People are different and difficult to study
• Disease classifiers are inadequate
• Technology-driven
• Bottom-up approach

Technical:
• Sampling, QC, SOPs
• Insufficient vetting (metatranscriptomes, metagenomes, etc)
  – Better toolbox

Experimental/data analysis
• Animal and experimental models of the human condition
• Integration of data sets (host and microbe, location).
• Incomplete inventories of microbial transcriptomes, proteomes, metabolomes, etc.
IBD are progressive diseases and natural histories differ among patients

Cosnes J et al. Inflamm Bowel Dis. 2002;8:244.
Location, location, location
Half empty, half full?

There is a solution to every problem
Surgical treatment of severe ulcerative colitis – total colectomy with ileal-anal pouch anastomosis

Why study pouchitis?
• Unique to UC
• Microbe-dependent
• >50% pts will develop it
• Prospective design
• Easy to sample
• Pts as their own controls
Developing a model that recapitulates conditions of the human ileal pouch

Self-Emptying (SE)

Self-Filling (SF)

Proximal Small Intestine

Loop

Cecum

Colon
Does stasis promote a colonic-like microbiota?
If UC never involves the small intestinal mucosa, why does pouchitis occurs?

H&E mucosal histology

Microarray heat map
Are colonic microbiota and metaplasia sufficient to cause disease?

IL-10-/- mouse
Self-filling loop

II-10-/- mouse
Self-emptying loop

Inflammation Score

Histologic Score

P < 0.01
Working model for UC pathogenesis:
The perfect storm

- Ulcerative colitis and pouchitis
- Colonic metaplasia
- Colonic Microbiota (dysbiosis?)
- Genetic Susceptibility
Challenge:
The gut mucosa is a multicellular

Laser capture microdissection

Enteroid
Acknowledgements

Folker Meyer, Dionysios Antonopoulos, Eugene Chang, Mitchell Sogin, James Tiedje, Vincent Young, Thomas Schmidt

NIH HMP, NIDDK, Helmsley Trust