シンポジウム基調講演

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Positions

1995–1996	Undergraduate Research (DJ Klionsky, Advisor), University of California—Davis
1996–2003	PhD Student in Biomedical Sciences Graduate Program (A Varki, Advisor), University of California—San Diego
2003–2006	Research Associate, Department of Molecular Biology & Pharmacology and Center for Genome Sciences (JI Gordon, Mentor), Washington University School of Medicine, St. Louis, Missouri
2006–2008	Instructor, Department of Molecular Biology & Pharmacology and Center for Genome Sciences (JI Gordon, Mentor), Washington University School of Medicine, St. Louis, Missouri
2008–pres	Assistant Professor, Department of Microbiology and Immunology, Stanford University School of Medicine, Stanford, California

Honors

1995	Presidential Undergraduate Fellowship
1996	Lucille P. Markey Fellowship in Biomedical Sciences
2004–2006	W.M. Keck Fellowship
2008	Stanford Digestive Disease Center (DDC), Named Investigator
2008	Beckman Center for Molecular and Genetic Medicine, Start-up award
2009	NIH Director's New Innovator Award

Selected Peer-reviewed Publications

1. Tomashek JJ, Sonnenburg JL, Artimovich JM, Klionsky DJ. Resolution of subunit interactions and cytoplasmic subcomplexes of the yeast vacuolar proton-translocating ATPase. J. Biol. Chem. 1996; 271(17): 10397–404.
2. Chammas R, Sonnenburg JL, Watson NE, Tai T, Farquhar MG, Varki NM, Varki A. De-N-acetyl-gangliosides in humans: unusual subcellular distribution of a tumor antigen. Cancer Res. 1999; 59(6): 1337–46.
3. Brinkman-Van der Linden ECM, Sonnenburg JL, Varki A. Effects of sialic acid substitutions on recognition by sambucus nigra agglutinin and maackia amurensis hemagglutinin. Analytical Biochem. 2002; 303(1): 98–104.
4. Sonnenburg JL, Van Halbeek H, Varki A. Characterization of the acid stability of glycosidically-linked neuraminic acid: use in detecting De-N-acetyl-gangliosides in human melanoma. J. Biol. Chem. 2002; 277(20): 17502–10.
5. Sonnenburg JL, Altheide TK, Varki A. A uniquely human consequence of domain-specific functional adaptation in a sialic acid-binding receptor. Glycobiology. 2004; 14(4): 339–46.
6. Sonnenburg JL, Angenent LT, Gordon JI. Getting a grip on things: how do communities of bacterial symbionts become established in our intestine? Nat Immunol. 2004; 5(6): 569–73.
7. Westover BP, Buhler JD, Sonnenburg JL, Gordon JI. Operon prediction without a training set. Bioinformatics. 2005 Apr 1; 21(7): 880–8.
8. Sonnenburg JL, Xu J, Leip DD, Chen CH, Westover BP, Weatherford J, Buhler JD, Gordon JI. Glycan foraging in vivo by an intestine-adapted bacterial symbiont. Science. 2005; 307(5717): 1955–9.
9. Sonnenburg ED, Sonnenburg JL, Manchester J, Hansen E, Chiang H, Gordon JI. A hybrid two-component system protein of a prominent human gut symbiont couples glycan sensing in vivo to carbohydrate metabolism. PNAS. 2006; 103(23): 8834–9. PMC1472243.
10. Sonnenburg JL, Chen CTL, Gordon JI. Genomic and metabolic studies of the impact of probiotics on a model gut symbiont and host. PLoS Biol. 2006; 4(12): e413. PMC1661682.
11. Lecuit M, Sonnenburg JL, Cossart P, Gordon JI. Functional genomic studies of the intestinal response to a foodborne enteropathogen in a humanized gnotobiotic mouse model. J. Biol. Chem. 2007; 282(20): 15065–72.
12. Moon K, Sonnenburg JL, Salyers AA. Unexpected effect of a Bacteroides conjugative transposon, CTnDOT, on chromosomal gene expression in its bacterial host. Mol. Micro. 2007; 64(6): 1562–1571. PMC1976400.
13. Marco ML, Peters THF, Bongers RS, Molenaar D, van Hemert S, Sonnenburg JL, Gordon JI, Kleerebezem M. Lifestyle of Lactobacillus plantarum in the mouse caecum. Environ. Micro. 2009; 11(10): 2747–57. PMCID: not applicable.
14. Sonnenburg ED, Zheng H, Joglekar P, Higginbottom SK, Firbank SJ, Bolam DN, Sonnenburg JL. Specificity of polysaccharide use in intestinal bacteroides species determines diet-induced microbiota alterations. Cell. 141(7) pp. 1241–1252, June 25, 2010. PMCID: PMC2900928.

Mechanistic Insight into Intestinal Microbiota Function and Manipulation

Justin L. Sonnenburg

Trillions of microbes live in our digestive tract and influence our biology in profound and diverse ways. Several diseases, including obesity and inflammatory bowel diseases, have been associated with large-scale shifts in microbiota composition. The ability to address basic questions concerning community function and plasticity are fundamental to understanding the extent of causal relationships between host biology and microbiota perturbations, and whether the microbiota is a viable therapeutic target. One of our long-term goals is to achieve a level of functional understanding that would allow us to accurately predict aspects of a microbial community's functional adaptation to a specific perturbation (e.g., dietary change).

To investigate how changes in the intestinal environment alter microbiota function, and how these changes, in turn, influence host biology we have characterized responses of simplified microbiotas living within the gut of gnotobiotic mice to changes in host diet, community membership, and host genotype. These studies have revealed the importance of finely-tuned systems of polysaccharide sensing and utilization in *Bacteroides* species. We are currently using a single polysaccharide utilization locus (PUL) dedicated to dietary fructan utilization of *Bacteroides* as a model to understand mechanisms underlying diet-induced changes in microbiota function and composition. These data have elucidated how *Bacteroides* species acquire and process this common class of dietary carbohydrates. Comparative genomic analysis revealed that the fructan PUL is conserved to varying extents among *Bacteroides* species, corresponding to a range of fructan utilization capability across the genus. Using model intestinal microbiotas living within gnotobiotic mice, we demonstrate that dietary fructan can have disparate effects on community composition, depending upon the fructan degrading capacity of members of the microbiota.

Analysis of >10 members of the *Bacteroides* genus has revealed that each species has specialized in use of either β2-1 (inulin)- or β2-6 (levan)-linked fructan, but no species is adept at using both linkages. Investigation of several *B. thetaiotaomicron* isolates has revealed that even closely related strains within the same species have differing specificities for the fructan linkage. We have set out to understand the genomic and molecular basis for these differences in fructan-use specificity suspecting that either lateral gene transfer or rapid evolution (i.e., positive selection) could explain the functional differences that we observe. Bi-associated gnotobiotic mice colonized with wild-type (wt) Bacteroides species, genetically modified Bacteroides species, and/or Bifidobacterium species have revealed how genomic sequence information can be translated to understand and predict community dynamics *in vivo*.

In addition to alterations in diet, differences in host genotype, antibiotics, orally acquired microbes, and numerous other factors can impact the microbiota. Understanding how variability in these environmental factors influence the composition, function, and interaction within the microbiota, and how these changes, in turn, affect our biology as hosts, is experimentally challenging due to the complexity of the community. We have used gnotobiotic mice harboring defined model communities or a completed human microbiota ('humanized') to unravel the complexity associated with the 'universe' of small molecules associated with microbiota-host interaction. Small molecule metabolites produced by the microbiota are important mediators of microbe-microbe and microbe-host interactions. New technology in mass-spectrometry offers the ability to perform extensive characterization of small molecule metabolites produced by the microbiota or via microbiota-host interaction. We are applying these metabolomic approaches to understand how alterations in the composition of the gut microbiota influence the metabolite profile of urine, blood or feces. Metabolomic analysis of these biofluids allows us to monitor the dynamics of microbial colonization and provides an instantaneous readout of gut microbiota functionality. We are also defining novel, biologically important compounds produced by members of the microbiota. Together these data set the stage for predicting, based on gene content or metabolite profile, how a microbiota will respond to changes in the nutrient environment and suggest how systems-level data could facilitate both the diagnostic potential and the personalized therapeutic manipulation of the intestinal microbiota.