Published in final edited form as:

J Public Health Emerg. 2017 March ; 1: . doi:10.21037/jphe.2017.03.08.

“Nature versus Nurture” and the indigenous microbiome

Richard A. Hickman¹, Liying Yang¹, and Zhiheng Pei^{1,2}

¹New York University School of Medicine, New York, NY, USA

²Department of Veterans Affairs New York Harbor Healthcare System, New York, NY, USA

The human microbiome represents the total aggregate of microorganisms within the human body and is recognized as a significant player in human health and disease. The total number of bacteria in humans is nearly 4×10^{13} and although recalculated appraisals of the ratio between human cells and microorganisms has now been reduced and approximates 1:1, the vast quantity of bacteria has an enormous impact in host physiology (1). Healthy development and disease states are closely entwined with the microbiome and examples include obesity, cancer, and also include conditions outside the gastrointestinal tract, such as neurologic and psychiatric illness (2–6). Therefore, understanding the influences on the microbiome is critical to appreciating possible preventative and therapeutic measures for disease.

There is a large body of evidence implicating a role for the environment in shaping the microbiome which can have long-lasting consequences. At birth, the mode of delivery (Cesarean section versus vaginal delivery) is one of the earliest environmental factors in determining the gastrointestinal microbiome (7). Oral antibiotic regimens radically alter the gastrointestinal microbiome, in some cases causing overgrowth of bacteria that can be harmful, as in *Clostridium difficile* in pseudomembranous colitis (8,9). Likewise, an individual's diet has a huge impact in modifying the microbiome (10).

The article by Bonder et al., describes how differences in host genetics are associated with the differences in the residential microbiota (11). Using three Danish cohort studies and metagenomic shotgun sequencing, the group analyzed the fecal microbiome in 1,514 human subjects after receiving a matched blood sample that was genotyped. Enrolled subjects were examined for single nucleotide polymorphisms (SNP) that had a minor allele frequency >0.05 and this was compared with their respective fecal microbial taxonomies. Fifty-eight SNPs at 9 loci were associated with specific microbial taxa. Of note, the authors showed a significant association with the *Blautia* genus and the *Methanohacteriaceae* family, which

Correspondence to: Zhiheng Pei, MD, PhD, FASCP. Department of Veterans Affairs New York Harbor Healthcare System, 423 East 23rd Street, Room 6001W, New York, NY 10010, USA. Zhiheng.Pei@nyumc.org.

Conflicts of Interest: Z Pei is a Staff Physician at the Department of Veterans Affairs New York Harbor Healthcare System. The other authors have no conflicts of interest to declare.

Publisher's Disclaimer: *Disclaimer:* The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, the U.S. Department of Veterans Affairs or the United States Government.

Provenance: This is a Guest Commentary commissioned by the Editor-in-Chief: Baoli Zhu (Jiangsu Province Center for Disease Control and Prevention, Nanjing, China).

Comment on: Bonder MJ, Kurilshikov A, Tigchelaar EF, et al. The effect of host genetics on the gut microbiome. *Nat Genet* 2016;48:1407-12.

has been implicated in inflammatory bowel disease, obesity and dyslipidemias (12). Other genetic associations that were discovered included the species *Dialister invisus*, which has a role in gut inflammation, and *Sutterellaceae* abundance (13). Furthermore, they showed that there were specific loci that were associated with certain microbial metabolic pathways, specifically in the degradation of plant sterols and bile acid metabolism. These functional units are believed to have roles in obesity, type 2 diabetes and the metabolic syndrome. Interestingly, the genetic variants that were associated with these metabolic pathways were not the same variants involved in microbiota taxonomic differences, suggesting that different host loci influence taxonomic differences and functional pathways largely independently. Focused analyses examining specific genes involved in immunity found associations with IBD-associated bacteria, notably *Proteobacteria* and *Coprococcus comes*. Similar approaches to metabolic loci also demonstrated associations, including *Lactococcus* and an SNP involved in fat distribution.

One of the most interesting aspects of the study was associations between different microbiota with specific loci of C type lectin receptors. C type lectin receptors, along with other receptors have a critical role in immunity and inflammation. Specific polymorphisms in *CLEC7A* gene have been associated with more severe inflammatory disease in ulcerative colitis (14).

Evidently, the microbiota is both influenced by host genetics and environmental exposures. This study highlights how SNP correlates with differences in the GI microbiome as determined from fecal samples. Whilst the subjects' diet was recorded in the study, exactly how this was controlled for is not clear and whether microbiota differences could have manifest through dissimilar dietary intakes is a possibility. This is also true with other environmental influences on the microbiome, which may not have been controlled for, such as smoking and exercise (15,16).

Certainly, the issue of host genetics on the microbiota is complex and large-scale studies are required to overcome the small effect sizes that individual SNP may have on the microbiota. Extension of this work into examining the microbiota of the skin, vagina, oral and nasal cavities would be worthwhile to further document the role of host genetics in the microbiota at these sites. With more investigation of host genetics and their interaction with the microbiome, we will be able to better understand complex diseases and provide therapeutic options against harmful dysbiosis.

Acknowledgements

Funding: This work was supported in part by the Department of Pathology, New York University Langone Medical Center, National Cancer Institute, National Institute of Allergy and Infectious Diseases, and National Institute of Dental and Craniofacial Research of the National Institutes of Health under award numbers U01CA182370, R01CA159036, R01AI110372, and R21DE025352.

References

1. Sender R, Fuchs S, Milo R. Revised Estimates for the Number of Human and Bacteria Cells in the Body. *PLoS Biol* 2016;14:e1002533. [PubMed: 27541692]

2. Hickman RA, Hussein MA, Pei Z. Consequences of Gut Dysbiosis on the Human Brain In: Mozsik PG. editor. The Gut Microbiome - Implications for Human Disease. InTech, 2016.
3. Petschow B, Doré J, Hibberd P, et al. Probiotics, prebiotics, and the host microbiome: the science of translation. *Ann NY Acad Sci* 2013;1306:1–17. [PubMed: 24266656]
4. Yang L, Lu X, Nossa CW, et al. Inflammation and intestinal metaplasia of the distal esophagus are associated with alterations in the microbiome. *Gastroenterology* 2009;137:588–97. [PubMed: 19394334]
5. Yang L, Chaudhary N, Baghdadi J, et al. Microbiome in reflux disorders and esophageal adenocarcinoma. *Cancer J* 2014;20:207–10. [PubMed: 24855009]
6. Turnbaugh PJ, Hamady M, Yatsunenko T, et al. A core gut microbiome in obese and lean twins. *Nature* 2009;457:480–4. [PubMed: 19043404]
7. Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci U S A* 2010;107:11971–5. [PubMed: 20566857]
8. Blaser MJ. Antibiotic use and its consequences for the normal microbiome. *Science* 2016;352:544–5. [PubMed: 27126037]
9. Ianiro G, Tilg H, Gasbarrini A. Antibiotics as deep modulators of gut microbiota: between good and evil. *Gut* 2016 [Epub ahead of print].
10. Turnbaugh PJ, Ridaura VK, Faith JJ, et al. The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. *Sci Transl Med* 2009;1:6ra14.
11. Bonder MJ, Kurilshikov A, Tigchelaar EF, et al. The effect of host genetics on the gut microbiome. *Nat Genet* 2016;48:1407–12. [PubMed: 27694959]
12. Locke AE, Kahali B, Berndt SI, et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature* 2015;518:197–206. [PubMed: 25673413]
13. Martinez I, Lattimer JM, Hubach KL, et al. Gut microbiome composition is linked to whole grain-induced immunological improvements. *ISMEJ* 2013;7:269–80.
14. Iliev ID, Funari VA, Taylor KD, et al. Interactions between commensal fungi and the C-type lectin receptor Dectin-1 influence colitis. *Science* 2012;336:1314–7. [PubMed: 22674328]
15. Biedemann L, Zeitz J, Mwinyi J, et al. Smoking cessation Journal of Public Health and Emergency, 2017 induces profound changes in the composition of the intestinal microbiota in humans. *PLoS One* 2013;8:e59260. [PubMed: 23516617]
16. Bressa C, Bailen-Andrino M, Perez-Santiago J, et al. Differences in gut microbiota profile between women with active lifestyle and sedentary women. *PLoS One* 2017;12:e0171352. [PubMed: 28187199]