START CENTER
STRATEGIC ANALYSIS,
RESEARCH & TRAINING CENTER

GUT HEALTH DIGEST

UNIVERSITY OF WASHINGTON STRATEGIC ANALYSIS, RESEARCH & TRAINING (START) CENTER

REPORT TO THE BILL & MELINDA GATES FOUNDATION

JANUARY 9, 2017

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1. **Systemic inflammation, growth factors, and linear growth in the setting of infection and malnutrition** {abstract & UW comment} {full article}
    - A case-control study evaluating relationships between low levels of systemic inflammation, growth factors, and anthropometry in underweight and normal weight children in northern Brazil.

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4. **Impact of the gut microbiota on enhancer accessibility in gut intraepithelial lymphocytes** {abstract & UW comment} {full article}
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5. **Dynamics and Trends in Fecal Biomarkers of Gut Function in Children from 1-24 Months in the MAL-ED Study** {abstract & UW comment} {full article}
    - Trends in the concentrations of three biomarkers, myeloperoxidase (MPO), neopterin (NEO), and α-1-antitrypsin (AAT) in a cohort study of 2,076 children 0-24 months of age.

6. **Influence of early life exposure, host genetics and diet on the mouse gut microbiome and metabolome** {abstract & UW comment} {full article}
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7. **Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease** {abstract & UW comment} {full article}
    - Link between gut microbiome inflammation and neuroinflammation in a mouse model of Parkinson's Disease.

8. **The Role of Fibronectin in the Adherence and Inflammatory Response Induced by Enteroaggregative Escherichia coli on Epithelial Cells** {abstract & UW comment} {full article}
    - A study of fibronectin-mediated adherence of an enteric pathogen to epithelial cells and the effect on pro-inflammatory gene expression.

9. **Persistent microbiome alterations modulate the rate of post-dieting weight regain** {abstract & UW comment} {full article}
    - A mouse-model study demonstrating the effect of a persistent intestinal microbiome signature after successful dieting of obese mice.

10. **Diet-Microbiota Interactions Mediate Global Epigenetic Programming in Multiple Host Tissues** {abstract & UW comment} {full article}
    - A study of host histone acetylation and methylation in multiple tissues by the host gut microbiota in a mouse model.

DETAILS OF ARTICLES

1. Systemic inflammation, growth factors, and linear growth in the setting of infection and malnutrition
   Mark D. DeBoer M.D., M.Sc., M.C.R., Rebecca J. Scharf M.D., M.P.H., Alvaro M. Leite M.D., Alessandra Férrer R.N., Alexandre Havt Ph.D., Relana Pinkerton Ph.D., Aldo A. Lima M.D., Ph.D. and Richard L. Guerrant M.D.
   Nutrition, 2017-01-01, Volume 33, Pages 248-253. PMID: 27712965

ABSTRACT
Objectives: Deficits in weight gain and linear growth are seen frequently among children in areas where malnutrition and recurrent infections are common. Although both inflammation and malnutrition can result in growth hormone (GH) resistance, the interrelationships of infection, inflammation, and growth deficits in developing areas remain unclear. The aim of this study was to evaluate relationships between low levels of systemic inflammation, growth factors, and anthropometry in a case–control cohort of underweight and normal weight children in northern Brazil.
Methods: We evaluated data from 147 children ages 6 to 24 mo evaluated in the MAL-ED (Interactions of Malnutrition and Enteric Disease) case–control study following recruitment from a nutrition clinic for impoverished families in Fortaleza, Brazil. We used nonparametric tests and linear regression to evaluate relationships between current symptoms of infections (assessed by questionnaire), systemic inflammation (assessed by high-sensitivity C-reactive protein [hsCRP]), the GH insulin-like growth factor-1 (IGF-1) axis, and measures of anthropometry. All models were adjusted for age and sex.
Results: Children with recent symptoms of diarrhea, cough, and fever (compared with those without symptoms) had higher hsCRP levels; those with recent diarrhea and fever also had lower IGF-1 and higher GH levels. Stool myeloperoxidase was positively associated with serum hsCRP. hsCRP was in turn positively associated with GH and negatively associated with IGF-1 and IGFbinding protein-3 (IGFBP-3), suggesting a state of GH resistance. After adjustment for hsCRP, IGF-1 and IGFBP-3 were positively and GH was negatively associated with Z scores for height and weight.
Conclusions: Infection and inflammation were linked to evidence of GH resistance, whereas levels of GH, IGF-1, and IGFBP-3 were associated with growth indices independent of hsCRP. These data implicate complex interrelationships between infection, nutritional status, GH axis, and linear growth in children from a developing area.

WEB: 10.1016/j.nut.2016.06.013
IMPACT FACTOR: 2.839
CITED HALF-LIFE: 8.3

UW EDITORIAL COMMENT: Figure 1 provides a detailed conceptual model of the effect of inflammation on regulation of growth. Although the results of the study are preliminary, the findings suggest significant downstream effects of systemic inflammation and malnutrition in children. The authors note

several limitations to the study, including: difficulties in controlling for confounders (such as current infections that could affect the observed association between inflammation and growth), assessments of height as a cross-sectional measure instead of over time, and use of crude markers of nutritional status.

2. Environmental Enteric Dysfunction and the Fecal Microbiota in Malawian Children
Ordiz M, Stephenson K, Agapova S, Wylie KM, Maleta K, Martin J, Trehan I, Tarr PI, Manary M.
Am J Trop Med Hyg. 2016 Dec 12. pii: 16-0617. PMID: 27956653

ABSTRACT
Environmental enteric dysfunction (EED) is often measured with a dual sugar absorption test and implicated as a causative factor in childhood stunting. Disturbances in the gut microbiota are hypothesized to be a mechanism by which EED is exacerbated, although this supposition lacks support. We performed 16S ribosomal RNA gene sequencing of fecal samples from 81 rural Malawian children with varying degrees of EED to determine which bacterial taxa were associated with EED. At the phyla level, Proteobacteria abundance is reduced with severe EED. Among bacterial genera, Megasphaera, Mitsuokella, and Sutterella were higher in EED and Succinivibrio, Klebsiella, and Clostridium_XI were lower in EED. Bacterial diversity did not vary with the extent of EED. Though EED is a condition that is typically believed to affect the proximal small bowel, and our focus was on stool, our data do suggest that there are intraluminal microbial differences that reflect, or plausibly lead to, EED.

WEB: 10.4269/ajtmh.16-0617
IMPACT FACTOR: 2.453
CITED HALF-LIFE: 9.9

UW EDITORIAL COMMENT: A major limitation of this study is the use of 16S rRNA gene sequencing to assess bacterial diversity since the bacteria sequenced are largely from the colon, rather than the proximal bowel. Bacteria of interest to EED may not have been abundant enough to be detectable using these methods. This methodology was chosen because an invasive endoscopy procedure was deemed inappropriate for measuring bacterial composition of asymptomatic children.

3. Environmental Enteric Dysfunction and Growth Failure/Stunting in Global Child Health
Owino V, Ahmed T, Freemark M, Kelly P, Loy A, Manary M, Loechl C.
Pediatrics. 2016 Dec;138(6). pii: e20160641. Epub 2016 Nov 4. PMID: 27940670

ABSTRACT
Approximately 25% of the world's children aged <5 years have stunted growth, which is associated with increased mortality, cognitive dysfunction, and loss of productivity. Reducing by 40% the number of stunted children is a global target for 2030. The pathogenesis of stunting is poorly understood. Prenatal and postnatal nutritional deficits and enteric and systemic infections clearly contribute, but recent findings implicate a central role for environmental enteric dysfunction (EED), a generalized disturbance of small intestinal structure and function found at a high prevalence in children living under unsanitary conditions. Mechanisms contributing to growth failure in EED include intestinal leakiness and heightened permeability, gut inflammation, dysbiosis and bacterial translocation, systemic inflammation, and nutrient malabsorption. Because EED has multiple causal pathways, approaches to manage it need to be multifaceted. Potential interventions to tackle EED include: (1) reduction of exposure to feces and contact with animals through programs such as improved water, sanitation, and hygiene; (2) breastfeeding and enhanced dietary diversity; (3) probiotics and prebiotics; (4) nutrient

supplements, including zinc, polyunsaturated fatty acids, and amino acids; (5) antiinflammatory agents such as 5-aminosalicyclic acid; and (6) antibiotics in the context of acute malnutrition and infection. Better understanding of the underlying causes of EED and development of noninvasive, practical, simple, and affordable point-of-care diagnostic tools remain key gaps. "Omics" technologies (genomics, epigenomics, transcriptomics, proteomics, and metabolomics) and stable isotope techniques (eg, ^{13}C breath tests) targeted at children and their intestinal microbiota will enhance our ability to successfully identify, manage, and prevent this disorder.

WEB: 10.1542/peds.2016-0641
IMPACT FACTOR: 5.196
CITED HALF-LIFE: 8.6

UW EDITORIAL COMMENT: This EED literature review was prepared based on information presented at a technical meeting held in October 2015. It details the pathobiology of EED and its link to stunting, providing an overview of factors that contribute to growth failure while also acknowledging that the mechanisms are poorly understood and likely involve multiple biological pathways. The review also lists biomarkers for the disease, available diagnostic tests, and postulates the potential for -omics technologies for future diagnostics. Finally, the authors list emerging approaches for the prevention and treatment of EED, specifically in low resource settings.

4. Impact of the gut microbiota on enhancer accessibility in gut intraepithelial lymphocytes.
Nicholas P. Semenkovich, Joseph D. Planer, Philip P. Ahern, Nicholas W. Griffin, Charles Y. Linc, and Jeffrey I. Gordon . *Proc Natl Acad Sci* USA. 2016 Dec 20;113(51):14805-14810. PMID: 27911843.

ABSTRACT
The gut microbiota impacts many aspects of host biology including immune function. One hypothesis is that microbial communities induce epigenetic changes with accompanying alterations in chromatin accessibility, providing a mechanism that allows a community to have sustained host effects even in the face of its structural or functional variation. We used Assay for Transposase-Accessible Chromatin with high-throughput sequencing (ATAC-seq) to define chromatin accessibility in predicted enhancer regions of intestinal $\alpha\beta^+$ and $\gamma\delta^+$ intraepithelial lymphocytes purified from germ-free mice, their conventionally raised (CONV-R) counterparts, and mice reared germ free and then colonized with CONV-R gut microbiota at the end of the suckling–weaning transition. Characterizing genes adjacent to traditional enhancers and super-enhancers revealed signaling networks, metabolic pathways, and enhancer-associated transcription factors affected by the microbiota. Our results support the notion that epigenetic modifications help define microbial community-affiliated functional features of host immune cell lineages.

WEB: 10.1073/pnas.1617793113
IMPACT FACTOR: 9.423
CITED HALF-LIFE: 8.7

UW EDITORIAL COMMENT: The authors found that gut colonization status does not fundamentally affect lineage-specific regulatory genes but affects the accessibility of the enhancer elements. The researchers note that these results differ from previous published literature on the topic, possibly because the previous study used a heterogeneous population of intestinal epithelial cells, which could have attenuated any measurable variation in expression due to differential access to enhancer

segments. The results of this study suggest a significant effect of gut microbiota on the epigenetic state of intraepithelial lymphocytes and suggest enhancers and pathways that are impacted by colonization. Further characterization of these impacts is needed.

5. Dynamics and Trends in Fecal Biomarkers of Gut Function in Children from 1-24 Months in the MAL-ED Study.
   McCormick BJ, Lee GO, Seidman JC, Haque R, Mondal D, Quetz J, Lima AA, Babji S, Kang G, Shrestha SK, Mason CJ, Qureshi S, Bhutta ZA, Olortegui MP, Yori PP, Samie A, Bessong P, Amour C, Mduma E, Patil CL, Guerrantl RL, Lang DR, Gottlieb M, Caulfield LE, Kosek MN; MAL-ED Network. *Am J Trop Med Hyg*. 2016 Dec 19. pii: 16-0496. PMID: 27994110.

ABSTRACT
Growth and development shortfalls that are disproportionately prevalent in children living in poor environmental conditions are postulated to result, at least in part, from abnormal gut function. Using data from The Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development (MAL-ED) longitudinal cohort study, we examine biomarkers of gut inflammation and permeability in relation to environmental exposures and feeding practices. Trends in the concentrations of three biomarkers, myeloperoxidase (MPO), neopterin (NEO), and α-1-antitrypsin (AAT), are described from an unparalleled number of fecal samples collected during the first 2 years of each child's life. A total of 22,846 stool samples were processed during the longitudinal sampling of 2,076 children 0-24 months of age. Linear mixed models were constructed to examine the relationship between biomarker concentrations and recent food intake, symptoms of illness, concurrent enteropathogen infection, and socioeconomic status. Average concentrations of MPO, NEO, and AAT were considerably higher than published references for healthy adults. The concentration of each biomarker tended to decrease over the first 2 years of life and was highly variable between samples from each individual child. Both MPO and AAT were significantly elevated by recent breast milk intake. All three biomarkers were associated with pathogen presence, although the strength and direction varied by pathogen. The interpretation of biomarker concentrations is subject to the context of their collection. Herein, we identify that common factors (age, breast milk, and enteric infection) influence the concentration of these biomarkers. Within the context of low- and middle-income communities, we observe concentrations that indicate gut abnormalities, but more appropriate reference standards are needed.

WEB: 10.4269/ajtmh.16-0496
IMPACT FACTOR: 2.453
CITED HALF-LIFE: 9.9

UW EDITORIAL COMMENT: Measured concentrations of fecal biomarkers were highly variable over the first two years of life, likely due to a combination of gut physiological changes and immune system development in early childhood. The authors note that all three biomarkers in this study had high average concentrations relative to published references for healthy individuals (of individuals in high-income countries), which they attribute to differences in breastfeeding behavior between high and low resource countries. Breast milk is known to affect immune system biomarkers and therefore the authors assert that better reference data is needed for biomarker concentrations in healthy breastfeeding infants in order to adequately identify biomarkers of enteropathy.

6. Influence of early life exposure, host genetics and diet on the mouse gut microbiome and metabolome
   Antoine M. Snijders, Sasha A. Langley, Young-Mo Kim, Colin J. Brislawn, Cecilia Noecker, Erika M. Zink, Sarah J. Fansler, Cameron P. Casey, Darla R. Miller, Yurong Huang, Gary H. Karpen, Susan E. Celniker, James B. Brown, Elhanan Borenstein, Janet K. Jansson, Thomas O. Metz & Jian-Hua Mao. *Nature Microbiology*. 2016 November 28. *2:16221.* PMID: 27892936

ABSTRACT
Although the gut microbiome plays important roles in host physiology, health and disease, we lack understanding of the complex interplay between host genetics and early life environment on the microbial and metabolic composition of the gut. We used the genetically diverse Collaborative Cross mouse system to discover that early life history impacts the microbiome composition, whereas dietary changes have only a moderate effect. By contrast, the gut metabolome was shaped mostly by diet, with specific non-dietary metabolites explained by microbial metabolism. Quantitative trait analysis identified mouse genetic trait loci (QTL) that impact the abundances of specific microbes. Human orthologues of genes in the mouse QTL are implicated in gastrointestinal cancer. Additionally, genes located in mouse QTL for Lactobacillales abundance are implicated in arthritis, rheumatic disease and diabetes. Furthermore, Lactobacillales abundance was predictive of higher host T-helper cell counts, suggesting an important link between Lactobacillales and host adaptive immunity.

WEB: 10.1038/nmicrobiol.2016.221
IMPACT FACTOR: 24.727
CITED HALF-LIFE: n/a

UW EDITORIAL COMMENT: The investigators compared mouse strains raised in two distinct built environments (a pathogen-free facility and a barrier facility that removed screened infectious agents). Microbiomes of mice raised in the pathogen-free facility versus the barrier facility were significantly different and these compositional differences were maintained in a second generation of mice born and raised together in a third pathogen-free facility. The authors conclude that the gut microbiome is shared between parents and offspring in early life history and is persistent, even in a new environment. Additional analyses of gut microbiome composition indicated modest associations between bacterial composition and B-cell counts, body weight, and rotarod performance. Figure 2 provides results of a genome wide association analysis identifying host genetic loci that impact gut microbiome composition and abundances.

7. Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease
   Timothy R. Sampson, Justine W. Debelius, Taren Thron, Stefan Janssen, Gauri G. Shastri, Zehra Esra Ilhan, Collin Challis, Catherine E. Schretter, Sandra Rocha, Viviana Gradinaru, Marie-Francoise Chesselet, Ali Keshavarzian, Kathleen M. Shannon, Rosa Krajmalnik-Brown, Pernilla Wittung-Stafshede, Rob Knight, and Sarkis K. Mazmanian. *Cell*. 2016 Dec; 167:1469-1480. PMID: 27912057

ABSTRACT
The intestinal microbiota influence neurodevelopment, modulate behavior, and contribute to neurological disorders. However, a functional link between gut bacteria and neurodegenerative diseases remains unexplored. Synucleinopathies are characterized by aggregation of the protein a-synuclein (aSyn), often resulting in motor dysfunction as exemplified by Parkinson's disease (PD). Using mice that overexpress aSyn, we report

herein that gut microbiota are required for motor deficits, microglia activation, and aSyn pathology. Antibiotic treatment ameliorates, while microbial re-colonization promotes, pathophysiology in adult animals, suggesting that postnatal signaling between the gut and the brain modulates disease. Indeed, oral administration of specific microbial metabolites to germ-free mice promotes neuroinflammation and motor symptoms. Remarkably, colonization of aSyn-overexpressing mice with microbiota from PD-affected patients enhances physical impairments compared to microbiota transplants from healthy human donors. These findings reveal that gut bacteria regulate movement disorders in mice and suggest that alterations in the human microbiome represent a risk factor for PD.

WEB: 10.1016/j.cell.2016.11.018
IMPACT FACTOR: 28.71
CITED HALF-LIFE: 9.0

UW EDITORIAL COMMENT: The authors found evidence of inflammation in the brains of mice with typical microbiota but not in mice treated with antibiotics to reduce gut microbial community. When the antibiotic-treated mice were fed short-chain fatty acids (microbial metabolites) the animals developed inflammation, α-synuclein aggregates, and motor deficits. Based on this evidence, the authors propose a mechanistic link between PD and the production of short-chain fatty acids by gut microbiota. This is a very limited study of microbiomes from just six PD patients and six controls, but suggests a clear biological link between gut microbiome inflammation and Parkinson's Disease.

8. The Role of Fibronectin in the Adherence and Inflammatory Response Induced by Enteroaggregative Escherichia coli on Epithelial Cells.
   Yáñez D, Izquierdo M, Ruiz-Perez F, Nataro JP, Girón JA, Vidal RM, Farfan MJ.
   Front Cell Infect Microbiol. 2016 Dec 8;6:166. PMID: 28008386

ABSTRACT
Enteroaggregative *Escherichia coli* (EAEC) infections are still one of the most important etiologic pathogens of diarrhea in children worldwide. EAEC pathogenesis comprises three stages: adherence and colonization, production of toxins, and diarrhea followed by inflammation. Previous studies have demonstrated that EAEC strains have the ability to bind to fibronectin (FN); however, the role this extracellular matrix protein plays in the inflammatory response induced by EAEC remains unknown. In this study, we postulated that FN-mediated adherence of EAEC strains to epithelial cells increases the expression of pro-inflammatory genes. To verify this hypothesis, we infected HEp-2 and HT-29 cells, in both the presence and absence of FN, with EAEC reference strain 042. We quantified IL-8 secretion and the relative expression of a set of genes regulated by the NF-κB pathway. Although FN increased EAEC adherence, no changes in IL-8 protein secretion or *IL8* gene expression were observed. Similar observations were found in HEp-2 cells transfected with FN-siRNA and infected with EAEC. To evaluate the involvement of AAF/II fimbriae, we infected HEp-2 and HT-29 cells, in both the presence and absence of FN, with an EAEC 042*aafA* mutant strain transformed with a plasmid harboring the native *aafA* gene with a site-directed mutation in Lys72 residue (K72A and K72R strains). No changes in IL-8 secretion were observed. Finally, SEM immunogold assay of cells incubated with FN and infected with EAEC revealed that AAF fimbriae can bind to cells either directly or mediated by FN. Our data suggests that FN participates in AAF/II fimbriae-mediated adherence of EAEC to epithelial cells, but not in the inflammatory response of cells infected by this pathogen.

WEB: 10.3389/fcimb.2016.00166
IMPACT FACTOR: 5.218
CITED HALF-LIFE: 2.5

UW EDITORIAL COMMENT: Figure 1 shows levels of IL-8 secretion (a marker used to evaluate inflammation response to pathogens) in EAEC infected cultures with and without the presence of fibronectin. While the addition of fibronectin did increase adhesion of EAEC to epithelial cells, there was no subsequent difference in IL-8 secretions. Collectively, the findings of this study suggest fibronectin does not play a critical role in the activation of the inflammatory response against EAEC infections.

9. Persistent microbiome alterations modulate the rate of post-dieting weight regain
Christoph A. Thaiss, Shlomik Itav, Daphna Rothschild, Mariska T. Meijer, Maayan Levy, Claudia Moresi, Lenka Dohnalová, Sofia Braverman, Shachar Rozin, Sergey Malitsky, Mally Dori-Bachash, Yael Kuperman, Inbal Biton, Arieh Gertler, Alon Harmelin, Hagit Shapiro, Zamir Halpern, Asaph Aharoni, Eran Segal & Eran Elinav. *Nature*. 540, 544–551. PMID: 27906159

ABSTRACT
In tackling the obesity pandemic, significant efforts are devoted to the development of effective weight reduction strategies, yet many dieting individuals fail to maintain a long-term weight reduction, and instead undergo excessive weight regain cycles. The mechanisms driving recurrent post-dieting obesity remain largely elusive. Here, we identify an intestinal microbiome signature that persists after successful dieting of obese mice, which contributes to faster weight regain and metabolic aberrations upon re-exposure to obesity-promoting conditions and transmits the accelerated weight regain phenotype upon inter-animal transfer. We develop a machine-learning algorithm that enables personalized microbiome-based prediction of the extent of post-dieting weight regain. Additionally, we find that the microbiome contributes to diminished post-dieting flavonoid levels and reduced energy expenditure, and demonstrate that flavonoid-based 'post-biotic' intervention ameliorates excessive secondary weight gain. Together, our data highlight a possible microbiome contribution to accelerated post-dieting weight regain, and suggest that microbiome-targeting approaches may help to diagnose and treat this common disorder.

WEB: 10.1038/nature20796
IMPACT FACTOR: 38.138
CITED HALF-LIFE: >10

UW EDITORIAL COMMENT: The authors developed a mouse model of recurrent obesity through cycles of feeding high-fat and normal diets and compared it to mice continuously fed on either a high fat or normal diets. The authors also determined that the addition of celastrol, a weight loss drug, exacerbated the metabolic derangements of the weight-cycling mice. With successive cycles of high to normal fat diets, the mice exhibited exacerbated weight gain beyond those on the consistently high fat diet, suggesting obesity-dieting cycles progressively accelerate susceptibility to weight gain. Metabolic profiling revealed that oxygen, food, and drink consumption returned to baseline during the normal diet phases of the cycle but the mice's microbiota were significantly altered, even after metabolic normalization. Using fecal transplants into germ-free recipient mice, the authors confirmed that compositional differences between microbiota from weight-cycling mice and controls persisted beyond the diet cycling (even when the transplant recipient mice were maintained on a normal diet).

10. Diet-Microbiota Interactions Mediate Global Epigenetic Programming in Multiple Host Tissues
Krautkramer KA, Kreznar JH, Romano KA, Vivas EI, Barrett-Wilt GA, Rabaglia ME, Keller MP, Attie AD, Rey FE, Denu JM. Mol *Cell*. 2016 Dec 1;64(5):982-992. PMID: 27889451

ABSTRACT
Histone-modifying enzymes regulate transcription and are sensitive to availability of endogenous small-molecule metabolites, allowing chromatin to respond to changes in environment. The gut microbiota produces a myriad of metabolites that affect host physiology and susceptibility to disease; however, the underlying molecular events remain largely unknown. Here we demonstrate that microbial colonization regulates global histone acetylation and methylation in multiple host tissues in a diet-dependent manner: consumption of a "Western-type" diet prevents many of the microbiota-dependent chromatin changes that occur in a polysaccharide-rich diet. Finally, we demonstrate that supplementation of germ-free mice with short-chain fatty acids, major products of gut bacterial fermentation, is sufficient to recapitulate chromatin modification states and transcriptional responses associated with colonization. These findings have profound implications for understanding the complex functional interactions between diet, gut microbiota, and host health.

WEB: 10.1016/j.molcel.2016.10.025
IMPACT FACTOR: 13.958
CITED HALF-LIFE: 7.2

UW EDITORIAL COMMENT: The authors evaluated the effects of high fat, high-sucrose diet (low fiber "Western diet") on microbiota-mediated regulation of gene expression in a mouse model. The results demonstrated that the mice fed the low fiber diet produced fewer short-chain fatty acid metabolites (which act as messenger molecules to affect the gene expression in other tissues). In observing other body tissues, the researchers found differences in global histone acetylation and methylation based on which diet the mice consumed. However, further study is required to elucidate the mechanism by which the metabolites elicit epigenetic changes in other body tissues.

ADDITIONAL ARTICLES OF INTEREST (DECEMBER PUBLICATIONS)

Formation of propionate and butyrate by the human colonic microbiota.

Microbiome, Growth Retardation, and Metabolism: Are they related?

Xenobiotic Receptor-Mediated Regulation of Intestinal Barrier Function and Innate Immunity.

Linking Dietary Patterns with Gut Microbial Composition and Function.

The Association Between Fecal Biomarkers of Environmental Enteropathy and Rotavirus Vaccine Response in Nicaraguan Infants.

Impacts of resistant starch and wheat bran consumption on enteric inflammation in relation to colonic bacterial community structures and short-chain fatty acid concentrations in mice.

Impact of prebiotics on metabolic and behavioral alterations in a mouse model of metabolic syndrome.

Starter formula enriched in prebiotics and probiotics ensures normal growth of infants and promotes gut health: a randomized clinical trial.

Identifying species of symbiont bacteria from the human gut that, alone, can induce intestinal Th17 cells in mice

Microbiota Diurnal Rhythmicity Programs Host Transcriptome Oscillations

ARTICLE ARCHIVE (JAN-NOV 2016)

EED Biology & Review Articles

Environmental enteropathy.

Environmental Enteropathy: Elusive but Significant Subclinical Abnormalities in Developing Countries.

Endomicroscopic and Transcriptomic Analysis of Impaired Barrier Function and Malabsorption in Environmental

Environmental Enteric Dysfunction in Children.

Environmental Enteric Dysfunction Includes a Broad Spectrum of Inflammatory Responses and Epithelial Repair Processes.

The Impact of Environmental Enteropathy and Systemic Inflammation on Infant Growth Failure

Small Intestine Bacterial Overgrowth and Environmental Enteropathy in Bangladeshi Children.

Decoding Hidden Messages: Can Fecal Host Transcriptomics Open Pathways to Understanding Environmental Enteropathy?

Plasma Tryptophan and the Kynurenine–Tryptophan Ratio are Associated with the Acquisition of Statural Growth Deficits and Oral Vaccine Underperformance in Populations with Environmental Enteropathy

Malnutrition Is Associated with Protection from Rotavirus Diarrhea: Evidence from a Longitudinal Birth Cohort Study in Bangladesh

Nutrition/metabolism

Systemic inflammation, growth factors, and linear growth in the setting of infection and malnutrition.

Environmental Enteric Dysfunction is Associated with Altered Bile Acid Metabolism

Metabolic alterations in children with environmental enteric dysfunction.

Genetic and Metabolic Signals during Acute Enteric Bacterial Infection Alter the Microbiota and Drive Progression to Chronic Inflammatory Disease

Interactions between intestinal pathogens, enteropathy and malnutrition in developing countries.

Child Stunting is Associated with Low Circulating Essential Amino Acids.

Diet–microbiota interactions as moderators of human metabolism

Protein malnutrition impairs intestinal epithelial turnover: a potential mechanism of increased cryptosporidiosis in a murine model

A Comparison of Diarrheal Severity Scores in the MAL-ED Multisite Community-Based Cohort Study.

Metabolomic Changes in Serum of Children with Different Clinical Diagnoses of Malnutrition.

Mortality in children with complicated severe acute malnutrition is related to intestinal and systemic inflammation: an observational cohort study.

Steroid Administration and Growth Impairment in Children with Crohn's Disease.

Effects of a gut pathobiont in a gnotobiotic mouse model of childhood undernutrition

A Dietary Fiber-Deprived Gut Microbiota Degrades the Colonic Mucus Barrier and Enhances Pathogen Susceptibility

Microbiome Therapies

Diet-induced extinctions in the gut microbiota compound over generations

Microbiome: Eating for trillions

An important chapter in the infection-malnutrition story.

Lactobacillus plantarum strain maintains growth of infant mice during chronic undernutrition

Gut bacteria that prevent growth impairments transmitted by microbiota from malnourished children

Sialylated Milk Oligosaccharides Promote Microbiota-Dependent Growth in Models of Infant Undernutrition

Effects of bovine colostrum on recurrent respiratory tract infections and diarrhea in children.

Sialylated galacto-oligosaccharides and 2'-fucosyllactose reduce necrotising enterocolitis in neonatal rats

Rebooting the microbiome.

Fecal microbiota transplantation: in perspective.

Fecal Microbiota-based Therapeutics for Recurrent Clostridium difficile Infection, Ulcerative Colitis and Obesity

Microbial therapeutic interventions.

High-affinity monoclonal IgA regulates gut microbiota and prevents colitis in mice

Stable Engraftment of Bifidobacterium longum AH1206 in the Human Gut Depends on Individualized Features of the Resident Microbiome

Protein- and zinc-deficient diets modulate the murine microbiome and metabolic phenotype

Fecal Microbiota-based Therapeutics for Recurrent Clostridium difficile Infection, Ulcerative Colitis and Obesity

Overcoming the limited availability of human milk oligosaccharides: challenges and opportunities for research and application

Efficacy of Probiotics Versus Placebo in the Prevention of Necrotizing Enterocolitis in Preterm Very Low Birth Weight Infants: A Double-Blind Randomized Controlled Trial

Eosinophils, probiotics, and the microbiome.

A Combined Intervention of Zinc, Multiple Micronutrients, and Albendazole Does Not Ameliorate Environmental Enteric Dysfunction or Stunting in Rural Malawian Children in a Double-Blind Randomized Controlled Trial

Gut Health Diagnostics & Research

Biomarkers of Environmental Enteropathy, Inflammation, Stunting, and Impaired Growth in Children in Northeast Brazil.

Fecal Markers of Environmental Enteropathy and Subsequent Growth in Bangladeshi Children.

Etiology of Diarrhea, Nutritional Outcomes and Novel Intestinal Biomarkers in Tanzanian Infants: A Preliminary Study.

Co-culture of Living Microbiome with Microengineered Human Intestinal Villi in a Gut-on-a-Chip Microfluidic Device.

MiniBioReactor Arrays (MBRAs) as a Tool for Studying C. difficile Physiology in the Presence of a Complex Community.

Reverse Engineering Human Pathophysiology with Organs-on-Chips.

Human Microbiota-Associated Mice: A Model with Challenges

Contributions of microbiome and mechanical deformation to intestinal bacterial overgrowth and inflammation in a human gut-on-a-chip.

Optimization of Quantitative PCR Methods for Enteropathogen Detection

Use of quantitative molecular diagnostic methods to identify causes of diarrhoea in children: a reanalysis of the GEMS case-control study

Diagnostics: Filling in the missing pieces

Natural history of the infant gut microbiome and impact of antibiotic treatment on bacterial strain diversity and stability

Gut check

Population-level analysis of gut microbiome variation

Childhood undernutrition, the gut microbiota, and microbiota-directed therapeutics

Plasma Tryptophan and the Kynurenine-Tryptophan Ratio are Associated with the Acquisition of Statural Growth Deficits and Oral Vaccine Underperformance in Populations with Environmental Enteropathy

Environmental Enteric Dysfunction is Associated with Poor Linear Growth and Can be Identified by Host Fecal mRNAs

Commendation for Exposing Key Advantage of Organ Chip Approach

Biomarkers of Environmental Enteropathy are Positively Associated with Immune Responses to an Oral Cholera Vaccine in Bangladeshi Children

Shifts in *Lachnospira* and *Clostridium* sp. in the 3-month stool microbiome are associated with preschool age asthma

Other Gut Infections/Health

Early-life enteric infections: relation between chronic systemic inflammation and poor cognition in children.

GEMS extend understanding of childhood diarrhoea

Infectious disease: something in the water

Genomic diversity of EPEC associated with clinical presentations of differing severity.
Gene-microbiota interactions contribute to the pathogenesis of inflammatory bowel disease

Taking it Personally: Personalized Utilization of the Human Microbiome in Health and Disease
Enrichment of the lung microbiome with gut bacteria in sepsis and the acute respiratory distress syndrome

Giardia: a pathogen or commensal for children in high-prevalence settings?

Tuft Cells: New Players in Colitis.

PGE2 is a direct and robust mediator of anion/fluid secretion by human intestinal epithelial cells

Dysbiosis is not an answer

Epidemiology and Impact of *Campylobacter* Infection in Children in 8 Low-Resource Settings: Results From the MAL-ED Study

The microbiota and immune response during *Clostridium difficile* infection

Enterocyte Purge and Rapid Recovery Is a Resilience Reaction of the Gut Epithelium to Pore-Forming Toxin Attack

Microbiome & Infection

Universality of human microbial dynamics

Reparative inflammation takes charge of tissue regeneration

Intrinsic Defense Mechanisms of the Intestinal Epithelium

Lipocalin 2 Protects from Inflammation and Tumorigenesis Associated with Gut Microbiota Alterations

Gut Microbial Metabolites Fuel Host Antibody Responses

IFN-γ Hinders Recovery from Mucosal Inflammation during Antibiotic Therapy for Salmonella Gut Infection

Limited diversity sparks inflammation at the mucosal border

Rhythm and bugs: circadian clocks, gut microbiota, and enteric infections.

I'll have a turkey and cheese sandwich

A microbial perspective of human developmental biology

The microbiome and innate immunity

The microbiota in adaptive immune homeostasis and disease

Interactions between the microbiota and pathogenic bacteria in the gut

Microbiome-wide association studies link dynamic microbial consortia to disease

Host-microbe interaction: Rules of the game for microbiota

The Host Shapes the Gut Microbiota via Fecal MicroRNA

Another Reason to Thank Mom: Gestational Effects of Microbiota Metabolites

Preterm infant gut microbiota affects intestinal epithelial development in a humanized microbiome gnotobiotic mouse model.

Development of the gut microbiota and mucosal IgA responses in twins and gnotobiotic mice

Host Selection of Microbiota via Differential Adhesion
Tummy Time: The Infant Microbiota–IgA Connection

Antibiotics, birth mode, and diet shape microbiome maturation during early life

Integrated multi-omics of the human gut microbiome in a case study of familial type 1 diabetes

Host-Protozoan Interactions Protect from Mucosal Infections through Activation of the Inflammasome

Adaptive immune response in symptomatic and asymptomatic enteric protozoal infection: evidence for a determining role of parasite genetic heterogeneity in host immunity to human giardiasis

The Liver at the Nexus of Host-Microbial Interactions

Modeling human enteric dysbiosis and rotavirus immunity in gnotobiotic pigs.

Linking the Human Gut Microbiome to Inflammatory Cytokine Production Capacity

Culture of previously uncultured members of the human gut microbiota by culturomics