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STRATEGIC ANALYSIS, RESEARCH & TRAINING CENTER

GUT HEALTH DIGEST

UNIVERSITY OF WASHINGTON STRATEGIC ANALYSIS, RESEARCH & TRAINING (START) CENTER
REPORT TO THE BILL & MELINDA GATES FOUNDATION

JULY 31, 2017

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    - Metaproteomic study of the microbial colonization of the infant gut.

9. **(Dis)Trust your gut: the gut microbiome in age-related inflammation, health, and disease.** {Abstract & UW comment} {Full article}
    - Review of recent evidence on the role of the microbiome in age-related health.

10. **Longitudinal development of the gut microbiome and metabolome in preterm neonates with late onset sepsis and healthy controls.** {Abstract & UW comment} {Full article}
    - Case-control study of the neonatal gut microbione in neonates with late onset sepsis using multi-omic analysis.

DETAILS OF ARTICLES

1. Patterns of Early-Life Gut Microbial Colonization during Human Immune Development: An Ecological Perspective
   Laforest-LaPointe I, Arrieta MC.
   Frontiers in Immunology. 8:788. 2017 July 10.

ABSTRACT
Alterations in gut microbial colonization during early life have been reported in infants that later developed asthma, allergies, type 1 diabetes, as well as in inflammatory bowel disease patients, previous to disease flares. Mechanistic studies in animal models have established that microbial alterations influence disease pathogenesis *via* changes in immune system maturation. Strong evidence points to the presence of a window of opportunity in early life, during which changes in gut microbial colonization can result in immune dysregulation that predisposes susceptible hosts to disease. Although the ecological patterns of microbial succession in the first year of life have been partly defined in specific human cohorts, the taxonomic and functional features, and diversity thresholds that characterize these microbial alterations are, for the most part, unknown. In this review, we summarize the most important links between the temporal mosaics of gut microbial colonization and the age-dependent immune functions that rely on them. We also highlight the importance of applying ecology theory to design studies that explore the interactions between this complex ecosystem and the host immune system. Focusing research efforts on understanding the importance of temporally structured patterns of diversity, keystone groups, and inter-kingdom microbial interactions for ecosystem functions has great potential to enable the development of biologically sound interventions aimed at maintaining and/or improving immune system development and preventing disease.

WEB: 10.3389/fimmu.2017.00788
IMPACT FACTOR: 3.35
CITED HALF-LIFE: N/A

UW EDITORIAL COMMENT: Figure 1 presents a temporal diagram of succession events that occur within the bacterial microbiome from in utero through introduction of solid foods and gives comparisons of bacterial composition between a variety of factors including pre-term vs. full-term, vaginal vs. cesarean birth, and breastmilk vs. formula. The authors note that increases or decreases in bacterial community diversity may not be adequate indicators of gut disruption and rather community compositions and functions should be considered.

2. Microbiota metabolite short-chain fatty acid acetate promotes intestinal IgA response to microbiota which is mediated by GPR43.
   Wu W, Sun M, Chen F, Cao A T, Liu H, Zhao Y, et al.
   Mucosal Immunology. 10, 946-956. 2017 July.

ABSTRACT
Intestinal IgA, which is regulated by gut microbiota, has a crucial role in maintenance of intestinal homeostasis and in protecting the intestines from inflammation. However, the means by which microbiota promotes intestinal IgA responses remain unclear. Emerging evidence suggests that the host can sense gut bacterial metabolites in addition to pathogen-associated molecular patterns and that recognition of these small molecules influences host immune response in the intestines and beyond. We reported here that microbiota metabolite short-chain fatty acid acetate promoted intestinal IgA

responses, which was mediated by "metabolite-sensing" GPR43. GPR43-/- mice demonstrated lower levels of intestinal IgA and IgA+ gut bacteria compared with those in wild type (WT) mice. Feeding WT but not GPR43-/- mice acetate but not butyrate promoted intestinal IgA response independent of T cells. Acetate promoted B-cell IgA class switching and IgA production in vitro in the presence of WT but not GPR43-/- dendritic cells (DCs). Mechanistically, acetate-induced DC expression of Aldh1a2, which converts Vitamin A into its metabolite retinoic acid (RA). Moreover, blockade of RA signaling inhibited the acetate induction of B-cell IgA production. Our studies thus identified a new pathway by which microbiota promotes intestinal IgA response through its metabolites.

WEB: 10.1038/mi.2016.114
IMPACT FACTOR: 5.53
CITED HALF-LIFE: 3.10

UW EDITORIAL COMMENT: Authors contribute to the evidence base of the role of IgA in maintaining intestinal homeostasis by demonstrating that acetate, one of many short-chain fatty acids, can promote intestinal IgA responses. Figure 2 gives visual representations of differences of IgA production between the group of mice that was fed acetate in addition to antibiotics and the group that was fed only antibiotics. It can be seen in Figure 2a that there was a significant increase in IgA production within the acetate-fed mice.

3. Lactobacillus acidophilus/Bifidobacterium infantis probiotics are associated with increased growth of VLBWI among those exposed to antibiotics
   Härtel C, Pagel J, Spiegler J, Buma J, Henneke P, Zemlin M, et al.
   Scientific Reports. 7:5633. 2017 July 17.

ABSTRACT
We performed an observational study with very-low-birth weight infants (VLBWI) ≤33 weeks of gestation born in centers of the German Neonatal Network (GNN; (total n = 8534, n = 6229 received probiotics). The primary objectives of our study were (a) to assess the effect of *Lactobacillus acidophilus*/*Bifidobacterium infantis* probiotics on growth in VLBWI during primary stay in hospital and (b) to determine whether this effect is modified by antibiotic exposure. In linear regression models the administration of probiotics was independently associated with improved weight gain [g/d; effect size B = 0.62 (95% CI: 0.37–0.87), p < 0.001], and higher growth rates for body length [(mm/d; B = 0.06 (95% CI: 0.04–0.08), p < 0.001] and head circumference [mm/d; B = 0.03, 95% CI: 0.02–0.04, p < 0.001]. This effect was pronounced in infants with postnatal exposure to antibiotics; i.e. weight gain [g/d; B = 0.66 (95% CI: 0.32–1), p < 0.001], growth rate body length [(mm/d; B = 0.09 (95% CI: 0.06–0.12), p < 0.001] and head circumference [mm/d; B = 0.04, 95% CI: 0.02–0.06, p < 0.001]. In the small subgroup that was available for analysis at 5-year-follow-up (with probiotics: n = 120 vs. without probiotics: n = 54) we noted a sustained effect of probiotics in infants who received postnatal antibiotics. Probiotics may improve growth in antibiotic-treated infants which needs to be confirmed in randomized-controlled trials.

WEB: 10.1038/s41598-017-06161-8
IMPACT FACTOR: 5.47
CITED HALF-LIFE: 1.70

UW EDITORIAL COMMENT: The results demonstrate that the potential synergistic effect of probiotics and antibiotics on growth may depend on timing of antibiotic administration. There was no growth promoting effect of probiotics among those VLBW infants whose mothers were exposed to antenatal antibiotics only, while there was an effect present in those infants who received postnatal antibiotic exposure. Additionally, the authors highlight the need for large randomized-controlled trials to overcome the limitations of observational studies such as this one. In this case, the study was limited by its ability to overcome confounding variables that may have biased results, in addition to a small sample size for the long follow up group. However, the study does contribute to the evidence base around the role of antibiotics and probiotics, and specifically their synergistic effect on growth promotion.

4. Introducing the sporobiota and sporobiome.
   Tetz G, Tetz V.
   Gut Pathogens. 9:38. 2017 June 30.

ABSTRACT
Unrelated spore-forming bacteria share unique characteristics stemming from the presence of highly resistant endospores, leading to similar challenges in health and disease. These characteristics are related to the presence of these highly transmissible spores, which are commonly spread within the environment and are implicated in host-to-host transmission. In humans, spore-forming bacteria contribute to a variety of pathological processes that share similar characteristics, including persistence, chronicity, relapses and the maintenance of the resistome. We first outline the necessity of characterizing the totality of the spore-forming bacteria as the sporobiota based on their unique common characteristics. We further propose that the collection of all genes of spore-forming bacteria be known as the sporobiome. Such differentiation is critical for exploring the cross-talk between the sporobiota and other members of the gut microbiota, and will allow for a better understanding of the implications of the sporobiota and sporobiome in a variety of pathologies and the spread of antibiotic resistance.

WEB: 10.1186/s13099-017-0187-8
IMPACT FACTOR: 3.4
CITED HALF-LIFE: 3.4

UW EDITORIAL COMMENT: Genomic-based workflows, like the one represented in Figure 2 of the article, that combine traditional culture approaches with more innovative genetic strategies will be crucial to the understanding of the sporobiome. Figure 2 provides a phylogenetic representation of global sporobiome families that allows for identification of novel sporobiota families and further understanding of the complex sporobiome.

5. Potential and active functions in the gut microbiota of a healthy human cohort.
   Tanca A, Abbondio M, Palomba A, Fraumene C, Manghina V, Cucca F, et al.
   Microbiome. 5:79. 2017 July 14.

ABSTRACT
BACKGROUND: The study of the gut microbiota (GM) is rapidly moving towards its functional characterization by means of shotgun meta-omics. In this context, there is still no consensus on which microbial functions are consistently and constitutively expressed in the human gut in physiological

conditions. Here, we selected a cohort of 15 healthy subjects from a native and highly monitored Sardinian population and analyzed their GMs using shotgun metaproteomics, with the aim of investigating GM functions actually expressed in a healthy human population. In addition, shotgun metagenomics was employed to reveal GM functional potential and to compare metagenome and metaproteome profiles in a combined taxonomic and functional fashion.
RESULTS: Metagenomic and metaproteomic data concerning the taxonomic structure of the GM under study were globally comparable. On the contrary, a considerable divergence between genetic potential and functional activity of the human healthy GM was observed, with the metaproteome displaying a higher plasticity, compared to the lower inter-individual variability of metagenome profiles. The taxon-specific contribution to functional activities and metabolic tasks was also examined, giving insights into the peculiar role of several GM members in carbohydrate metabolism (including polysaccharide degradation, glycan transport, glycolysis, and short-chain fatty acid production). Noteworthy, Firmicutes-driven butyrogenesis (mainly due to *Faecalibacterium* spp.) was shown to be the metabolic activity with the highest expression rate and the lowest inter-individual variability in the study cohort, in line with the previously reported importance of the biosynthesis of this microbial product for the gut homeostasis.
CONCLUSIONS: Our results provide detailed and taxon-specific information regarding functions and pathways actively working in a healthy GM. The reported discrepancy between expressed functions and functional potential suggests that caution should be used before drawing functional conclusions from metagenomic data, further supporting metaproteomics as a fundamental approach to characterize the human GM metabolic functions and activities.

WEB: 10.1186/s40168-017-0293-3
IMPACT FACTOR: 9.85
CITED HALF-LIFE: N/A

UW EDITORIAL COMMENT: In addition to summarizing an in-depth analysis of gut microbiota of a cohort of healthy humans, the authors discuss the benefit of using both omic approaches (shotgun metaproteomics and shotgun metagenomics) in a complementary fashion— metagenomics allows for a complete history of the functions of traveling gut microbiota, while metaproteomics allows for a snapshot look at the gut microbiota at a specific time or location.

6. More than just a gut feeling: constraint-based genome-scale metabolic models for predicting functions of human intestinal microbes.
   van der Ark K, van Heck R, Martins Dos Santos V, Belzer C, Vos W.
   Microbiome. 5:78. 2017 July 14.

ABSTRACT
The human gut is colonized with a myriad of microbes, with substantial interpersonal variation. This complex ecosystem is an integral part of the gastrointestinal tract and plays a major role in the maintenance of homeostasis. Its dysfunction has been correlated to a wide array of diseases, but the understanding of causal mechanisms is hampered by the limited amount of cultured microbes, poor understanding of phenotypes, and the limited knowledge about interspecies interactions. Genome-scale metabolic models (GEMs) have been used in many different fields, ranging from metabolic engineering to the prediction of interspecies interactions. We provide showcase examples for the application of GEMs for gut microbes and focus on (i) the prediction of minimal, synthetic, or defined media; (ii) the prediction of possible functions and phenotypes; and (iii) the prediction of interspecies interactions. All

three applications are key in understanding the role of individual species in the gut ecosystem as well as the role of the microbiota as a whole. Using GEMs in the described fashions has led to designs of minimal growth media, an increased understanding of microbial phenotypes and their influence on the host immune system, and dietary interventions to improve human health. Ultimately, an increased understanding of the gut ecosystem will enable targeted interventions in gut microbial composition to restore homeostasis and appropriate host-microbe crosstalk.

WEB: 10.1186/s40168-017-0299-x
IMPACT FACTOR: 9.85
CITED HALF-LIFE: N/A

UW EDITORIAL COMMENT: The authors highlight the usage of genome-scale metabolic models in the design of defined culture media. Three case studies are provided to exemplify this point: 1) using a GEM to investigate the metabolic capabilities and fermentation behavior of *Lactobacillus plantarum* WCFS1, which is used in industrial food processes and probiotics, 2) constructing a GEM of *Lactococcus lactis* IL1403 to design a minimal medium for physiological studies and determine essential amino acids for growth, and 3) designing a GEM to investigate the essential amino acids for *Staphylococcus aureus* N315.

7. Formula diet driven microbiota shifts tryptophan metabolism from serotonin to tryptamine in neonatal porcine colon.
   Saraf M, Piccolo B, Bowlin A, Mercer K, LeRoith T, Chintapalli S, et al.
   Microbiome. 5:77. 2017 July 14.

ABSTRACT
BACKGROUND: The gut microbiota of breast-fed and formula-fed infants differ significantly, as do the risks for allergies, gut dysfunction, and upper respiratory tract infections. The connections between breast milk, various formulas, and the profiles of gut bacteria to these childhood illnesses, as well as the mechanisms underlying the effects, are not well understood.
METHODS: We investigated distal colon microbiota by 16S RNA amplicon sequencing, morphology by histomorphometry, immune response by cytokine expression, and tryptophan metabolism in a pig model in which piglets were sow-fed, or fed soy or dairy milk-based formula from postnatal day (PND) 2 to 21.
RESULTS: Formula feeding significantly ($p < 0.05$) altered the colon microbiota relative to the sow feeding. A significant reduction in microbial diversity was noted with formula groups in comparison to sow-fed. *Streptococcus, Blautia, Citrobacter, Butrycimonas, Parabacteroides, Lactococcus* genera were increased with formula feeding relative to sow feeding. In addition, relative to sow feeding, *Anaerotruncus, Akkermansia, Enterococcus, Acinetobacter, Christensenella,* and *Holdemania* were increased in milk-fed piglets, and *Biliophila, Ruminococcus, Clostridium* were increased in soy-fed piglets. No significant gut morphological changes were noted. However, higher cytokine mRNA expression (BMP4, CCL11, CCL21) was observed in the distal colon of formula groups. Formula feeding reduced enterochromaffin cell number and serotonin, but increased tryptamine levels relative to sow feeding.
CONCLUSIONS: Our data confirm that formula diet alters the colon microbiota and appears to shift tryptophan metabolism from serotonin to tryptamine, which may lead to greater histamine levels and risk of allergies in infants.

WEB: 10.1186/s40168-017-0297-z
IMPACT FACTOR: 9.85

CITED HALF-LIFE: N/A

UW EDITORIAL COMMENT: Authors demonstrate associations between a formula diet and colon microbiota and serotonin levels in pigs— however, results should be interpreted with caution as environmental factors such as the housing environment may have played an important role in the microbiome compositions. Further, linkages to human infants in regards to these results should be made with caution.

8. Genome-resolved metaproteomic characterization of preterm infant gut microbiota development reveals species-specific metabolic shifts and variabilities during early life.
   Xiong W, Brown C, Morowitz M, Banfield J, Hettich R.
   Microbiome. 5:72. 2017 July 10.

ABSTRACT
BACKGROUND: Establishment of the human gut microbiota begins at birth. This early-life microbiota development can impact host physiology during infancy and even across an entire life span. However, the functional stability and population structure of the gut microbiota during initial colonization remain poorly understood. Metaproteomics is an emerging technology for the large-scale characterization of metabolic functions in complex microbial communities (gut microbiota).
RESULTS: We applied a metagenome-informed metaproteomic approach to study the temporal and inter-individual differences of metabolic functions during microbial colonization of preterm human infants' gut. By analyzing 30 individual fecal samples, we identified up to 12,568 protein groups for each of four infants, including both human and microbial proteins. With genome-resolved matched metagenomics, proteins were confidently identified at the species/strain level. The maximum percentage of the proteome detected for the abundant organisms was ~45%. A time-dependent increase in the relative abundance of microbial versus human proteins suggested increasing microbial colonization during the first few weeks of early life. We observed remarkable variations and temporal shifts in the relative protein abundances of each organism in these preterm gut communities. Given the dissimilarity of the communities, only 81 microbial EggNOG orthologous groups and 57 human proteins were observed across all samples. These conserved microbial proteins were involved in carbohydrate, energy, amino acid and nucleotide metabolism while conserved human proteins were related to immune response and mucosal maturation. We identified seven proteome clusters for the communities and showed infant gut proteome profiles were unstable across time and not individual-specific. Applying a gut-specific metabolic module (GMM) analysis, we found that gut communities varied primarily in the contribution of nutrient (carbohydrates, lipids, and amino acids) utilization and short-chain fatty acid production.
CONCLUSIONS: Overall, this study reports species-specific proteome profiles and metabolic functions of human gut microbiota during early colonization. In particular, our work contributes to reveal microbiota-associated shifts and variations in the metabolism of three major nutrient sources and short-chain fatty acid during colonization of preterm infant gut.

WEB: 10.1186/s40168-017-0290-6
IMPACT FACTOR: 9.85
CITED HALF-LIFE: N/A

UW EDITORIAL COMMENT: Authors note that, in comparison to adults, infant gut metaproteomes are more unstable and individual-unspecific, as evidenced by this study. They attributed this to the infant gut being less mature and more susceptible to environmental factors. Figure 2 provides four side-by-side

boxplots comparing proteome coverage among the 4 infants analyzed in this study, which provides a visual representation of microbial variations throughout the initial weeks of life.

9. (Dis)Trust your gut: the gut microbiome in age-related inflammation, health, and disease.
   Buford, T.
   Microbiome. 5:80. 2017 14 July.

ABSTRACT
Chronic inflammation represents one of the most consistent biologic features of aging. However, the precise etiology of persistent low-grade increases in inflammation remains unclear. Recent evidence suggests that the gut microbiome may play a key role in age-related inflammation. Indeed, several studies have indicated that older adults display an altered composition of the gut microbiota, and early evidence indicates that this dysbiosis is associated with the presence of several key circulating inflammatory analytes. The present review summarizes knowledge on age-related inflammation and discusses how potential relationships with gut dysbiosis may lead to novel treatment strategies in the future.

WEB: 10.1186/s40168-017-0296-0
IMPACT FACTOR: 9.85
CITED HALF-LIFE: N/A

UW EDITORIAL COMMENT: Authors point out a significant research gap in regards to the association between the microbiome and aging, especially around the specific etiologic explanations for these age-related changes. In addition to a lack of research, studies that have investigated this association are not all consistent; Table 1 provides a summary of the studies that have been performed in this area and highlights the direction (increase/decrease) of change of microbiota in each study, if present.

10. Longitudinal development of the gut microbiome and metabolome in preterm neonates with late onset sepsis and healthy controls.
    Stewart C, Embleton N, Marrs E, Smith D, Fofanova T, Nelson A, et al.
    Microbiome. 5:75. 2017 July 12.

ABSTRACT
BACKGROUND: Late onset sepsis (LOS) in preterm infants is associated with considerable morbidity and mortality. While studies have implicated gut bacteria in the aetiology of the disease, functional analysis and mechanistic insights are generally lacking. We performed temporal bacterial (*n* = 613) and metabolomic (*n* = 63) profiling on extensively sampled stool from 7 infants with LOS and 28 matched healthy (no LOS or NEC) controls.
RESULTS: The bacteria isolated in diagnostic blood culture usually corresponded to the dominant bacterial genera in the gut microbiome. Longitudinal changes were monitored based on preterm gut community types (PGCTs), where control infants had an increased number of PGCTs compared to LOS infants (*P* = 0.011). PGCT 6, characterised by Bifidobacteria dominance, was only present in control infants. Metabolite profiles differed between LOS and control infants at diagnosis and 7 days later, but not 7 days prior to diagnosis. Bifidobacteria was positively correlated with control metabolites, including raffinose, sucrose, and acetic acid.
CONCLUSION: Using multi-omic analysis, we show that the gut microbiome is involved in the pathogenesis of LOS. While the causative agent of LOS varies, it is usually abundant in the gut. Bifidobacteria dominance was associated with control infants, and the presence of this organism may

directly protect, or act as a marker for protection, against gut epithelial translocation. While the metabolomic data is preliminary, the findings support that gut development and protection in preterm infants is associated with increased in prebiotic oligosaccharides (e.g. raffinose) and the growth of beneficial bacteria (e.g. *Bifidobacterium*).

WEB: 10.1186/s40168-017-0295-1
IMPACT FACTOR: 9.85
CITED HALF-LIFE: N/A

UW EDITORIAL COMMENT: The study has a small sample size and a limited number of infants on which metabolomics was performed, weakening the strength of the association. Nevertheless, the article is consistent with prior evidence that prebiotic oligosaccharides and beneficial bacteria, such as Bifidobacterium, play a role in protection against late onset sepsis in preterm infants.

ARTICLE ARCHIVE (JAN 2016-PRESENT)

EED Biology & Review Articles

Parasitic protozoa and interactions with the host intestinal microbiota.

Gastrointestinal inflammation by gut microbiota disturbance induces memory impairment in mice.

New insights into environmental enteric dysfunction.

Tropical Enteropathies.

Age and Sex Normalization of Intestinal Permeability Measures for the Improved Assessment of Enteropathy in Infancy and Early Childhood: Results from the MAL-ED Study.

Infant Nutritional Status and Markers of Environmental Enteric Dysfunction are Associated with Midchildhood Anthropometry and Blood Pressure in Tanzania.

Biomarkers to Stratify Risk Groups among Children with Malnutrition in Resource-Limited Settings and to Monitor Response to Intervention

Association between Enteropathogens and Malnutrition in Children Aged 6-23 mo in Bangladesh: a Case-Control Study.

Causal Pathways from Enteropathogens to Environmental Enteropathy: Findings from the MAL-ED Birth Cohort Study.

Biomarkers of Environmental Enteric Dysfunction: The good, the bad and the ugly.

Application of penalized linear regression methods to the selection of environmental enteropathy biomarkers.

Environmental enteropathy is associated with cardiometabolic risk factors in Peruvian children.

Biomarkers of Environmental Enteric Dysfunction Among Children in Rural Bangladesh.

Environmental Enteric Dysfunction is Associated with Carnitine Deficiency and Altered Fatty Acid Oxidation.

Determinant Variables, Enteric Pathogen Burden, Gut Function, and Immune-Related Inflammatory Biomarkers Associated with Childhood Malnutrition: A Prospective Case-Control Study in Northeastern Brazil.

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

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

Environmental Enteric Dysfunction and the Fecal Microbiota in Malawian Children

Environmental Enteric Dysfunction and Growth Failure/Stunting in Global Child Health

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

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

Detrimental Impact of Microbiota-Accessible Carbohydrate-Deprived Diet on Gut and Immune Homeostasis: An Overview

Chronic consequences on human health induced by microbial pathogens: Growth faltering among children in developing countries.

The effects of micronutrient deficiencies on bacterial species from the human gut microbiota.

Gut microbiota interactions with the immunomodulatory role of vitamin D in normal individuals.

The association of serum choline with linear growth failure in young children from rural Malawi.

Starved Guts: Morphologic and Functional Intestinal Changes in Malnutrition.

Which dietary components modulate longitudinal growth?

Influence of diet on the gut microbiome and implications for human health.

Nopal feeding reduces adiposity, intestinal inflammation and shifts the cecal microbiota and metabolism in high-fat fed rats

Western diets, gut dysbiosis, and metabolic diseases: Are they linked?

Nutrition, infection and stunting: the roles of deficiencies of individual nutrients and foods, and of inflammation, as determinants of reduced linear growth of children

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

Linking Dietary Patterns with Gut Microbial Composition and Function.

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.

Diet-Microbiota Interactions Mediate Global Epigenetic Programming in Multiple Host Tissues

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

Early antibiotic exposure in low-resource settings is associated with increased weight in the first two years of life.

The path towards microbiome-based metabolite treatment.

Next-generation probiotics: the spectrum from probiotics to live biotherapeutics

Severity of pancreatitis- associated intestinal mucosal barrier injury is reduced following treatment with the NADPH oxidase inhibitor apocynin.

Targeting the gut microbiota with inulin-type fructans: preclinical demonstration of a novel approach in the management of endothelial dysfunction.

Interleukin-23 Increases Intestinal Epithelial Cell Permeability In Vitro

Pili-like proteins of Akkermansia muciniphila modulate host immune responses and gut barrier function.

The anti-inflammatory drug mesalamine targets bacterial polyphosphate accumulation

*Akkermansia muciniphila i*mproves metabolic profiles by reducing inflammation in chow diet-fed mice

Longitudinal change of selected human milk oligosaccharides and association to infants' growth, an observatory, single center, longitudinal cohort study

Abrupt suspension of probiotics administration may increase host pathogen susceptibility by inducing gut dysbiosis

Toward a Personalized Approach in Prebiotics Research

Dietary Fiber and Prebiotics and the Gastrointestinal Microbiota.

A microbial protein that alleviates metabolic syndrome

Can probiotics modulate human disease by impacting intestinal barrier function?

Human Milk Oligosaccharides Influence Neonatal Mucosal and Systemic Immunity.

Oral Microbiota in Infants Fed a Formula Supplemented with Bovine Milk Fat Globule Membranes - A Randomized Controlled Trial.

Dietary Prebiotics and Bioactive Milk Fractions Improve NREM Sleep, Enhance REM Sleep Rebound and Attenuate the Stress-Induced Decrease in Diurnal Temperature and Gut Microbial Alpha Diversity.

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.

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

Improving the detection of environmental enteric dysfunction: a lactulose, rhamnose assay of intestinal permeability in children aged under 5 years exposed to poor sanitation and hygiene.

Organs-on-chips with integrated electrodes for trans-epithelial electrical resistance (TEER) measurements of human epithelial barrier function.

A methodologic framework for modeling and assessing biomarkers of environmental enteropathy as predictors of growth in infants: an example from a Peruvian birth cohort.

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Engineered Regulatory Systems Modulate Gene Expression of Human Commensals in the Gut

MicrobiomeAnalyst: a web-based tool for comprehensive statistical, visual and meta-analysis of microbiome data.

Honeybee gut microbiota promotes host weight gain via bacterial metabolism and hormonal signaling.

Leading microbiome-based therapeutic falters in Phase II trial

Faecal microbiota transplantation—A clinical view.

Optimization of metabolomics of defined in vitro gut microbial ecosystems

Community dynamics drive punctuated engraftment of the fecal microbiome following transplantation using freeze-dried, encapsulated fecal microbiota.

Challenges of metabolomics in human gut microbiota research

The Role of the Immune System in Metabolic Health and Disease

Optimization of metabolomics of defined in vitro gut microbial ecosystems.

An Intestinal Organ Culture System Uncovers a Role for the Nervous System in Microbe-Immune Crosstalks.

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Gut-Brain Cross-Talk in Metabolic Control

Dynamics of the human microbiome in inflammatory bowel disease

The human gut microbiome as source of innovation for health: Which physiological and therapeutic outcomes could we expect?

Tryptophan: A gut microbiota-derived metabolites regulating inflammation

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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.

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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

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

Chemical and pathogen-induced inflammation disrupt the murine intestinal microbiome.

Transient activation of mucosal effector immune responses by resident intestinal bacteria in normal hosts is regulated by interleukin-10 signalling.

Zinc Transporter SLC39A7/ZIP7 Promotes Intestinal Epithelial Self-Renewal by Resolving ER Stress.

Regulation of intestinal permeability: the role of proteases.

Foxp3 Reprograms T Cell Metabolism to Function in Low-Glucose, High-Lactate Environments

Bap180/Baf180 is required to maintain homeostasis of intestinal innate immune response in Drosophila and mice

Age-Associated Microbial Dysbiosis Promotes Intestinal Permeability, Systemic Inflammation, and Macrophage Dysfunction

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Molecular insight into Evolution of Symbiosis between Breast-Fed Infants and a Member of the Human Gut Microbiome Bifidobacterium longum

An insider's perspective: Bacteroides as a window into the microbiome

Antibiotics, Pediatric Dysbiosis, and Disease

Linking Gut Microbiota and Inflammation to Obesity and Insulin Resistance.

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Microbial Respiration and Formate Oxidation as Metabolic Signatures of Inflammation-Associated Dysbiosis.

A prominent glycyl radical enzyme in human gut microbiomes metabolizes trans-4-hydroxy-l-proline.

The Bactericidal Lectin RegIIIβ Prolongs Gut Colonization and Enteropathy in the Streptomycin Mouse Model for Salmonella Diarrhea.

Mining the Human Gut Microbiota for Immunomodulatory Organisms.

Feedback control of AHR signalling regulates intestinal immunity

Reinforcement of intestinal epithelial barrier by arabinoxylans in overweight and obese subjects: A randomized controlled trial: Arabinoxylans in gut barrier.

Changes in Intestinal Motility and Gut Microbiota Composition in a Rat Stress Model

Enteric Pathogens and Their Toxin-Induced Disruption of the Intestinal Barrier through Alteration of Tight Junctions in Chickens.

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Campylobacter jejuni and associated immune mechanisms: short-term effects and long-term implications for infants in low-income countries.

The Role of Fibronectin in the Adherence and Inflammatory Response Induced by Enteroaggregative Escherichia coli on Epithelial Cells.

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

The Gut Microbiome: Connecting Spatial Organization to Function

Intestinal, extra-intestinal and systemic sequelae of Toxoplasma gondii induced acute ileitis in mice harboring a human gut microbiota.

The shape of the microbiome in early life

Dysbiosis and the immune system.

Dysbiosis in intestinal inflammation: Cause or consequence

Discovery of Reactive Microbiota-Derived Metabolites that Inhibit Host Proteases

A purified membrane protein from Akkermansia muciniphila or the pasteurized bacterium improves metabolism in obese and diabetic mice

Microbiome-Modulated metabolites at the Interface of Host Immunity

Gastrointestinal Inflammation and Repair: Role of Microbiome, Infection, and Nutrition

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

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

Persistent microbiome alterations modulate the rate of post-dieting weight regain

Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease

Influence of early life exposure, host genetics and diet on the mouse gut microbiome and metabolome

Impact of the gut microbiota on enhancer accessibility in gut intraepithelial lymphocytes.

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