In sickness and health: Effects of gut microbial metabolites on human physiology

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The connection between intestinal microbes and human health has been appreciated since the 1880s with Theodor Escherich’s investigation of Escherichia coli and other fecal bacteria. Escherich hypothesized that indigenous microorganisms play roles in both digestion and intestinal diseases [1]. In the last century, our understanding of the bacteria, viruses, archaea, and eukaryotes that normally inhabit the gut has expanded alongside the rest of the field of microbiology, and numerous fundamental roles have been established for this community, now termed the microbiome. As speculated by Escherich, these roles definitively include nutrient digestion [2, 3] and protection from invading pathogens [4] but also extend to short- and long-term instruction of the immune system [5–7] and production of a wide range of metabolites that are unable to be produced by human physiology. Although the gut microbiome is typically described as being composed of nonharmful or beneficial microorganisms, it is now appreciated that both individual species [8] or multiple community members acting together [9, 10] can exert pathogenic effects, which are often more subtle than those of classical pathogens. Indeed, the presence of common intestinal microorganisms with discrete virulence factors (e.g., enterotoxins, genotoxins) that may only manifest in diseases like colorectal cancer or inflammatory bowel disease (IBD) over long periods of time or in certain host genetic backgrounds obscures the definition of pathogen.

Accelerated in the 2000s by the “-omics” revolution, along with a recent resurgence of cultivation [11–13], countless studies in the past 2 decades have implied or established connections between altered gut microbiomes and many diseases. These studies have demonstrated the malleability (or fragility) of the microbiome in the face of environmental and dietary perturbations encompassing antibiotic use [14], geography [15], immigration [16], and dietary changes, including fiber deprivation [17, 18]. Although Escherich’s original ideas were logically predicted with respect to microbiome effects in the gut, less-anticipated connections between gut microbes and health have extended to neurobiology [19–22] and systemic immune responses that impact allergy [23]. Emerging studies, often extending from omics-based observations, are providing causal and mechanistic understanding of the relationships that connect host responses with changes in the microbiome and its metabolism. Here, we look at recent examples that illustrate how the gut microbiome can augment or perturb host physiology through complementary or novel metabolism often initiating or modifying disease trajectories. The studies we highlight provide details that underscore the importance of gut microbes in human health, which Escherich postulated long ago.

The impact of gut bacterial metabolites on host physiology

The collective diversity of microbial species that compose the gut microbiome harbor approximately 10 million unique, annotated genes [24]—probably many more [25]—that are not
present in the human genome. Through our individual microbiomes, each of us has a personalized subset of this gene repertoire that substantially exceeds the genes in our human genome. With this unique genetic potential, our microbiomes are equipped to produce an astonishing array of microbiome-produced products (MPPs): metabolites and other cellular products like polysaccharides and curli fibers, which, in many cases, do not remain confined to the gut. The impacts of specific MPPs and the presence/absence of individual species/strains that produce them have been implicated in a wide range of diseases both in the gastrointestinal tract and beyond (Fig 1). Effects in the gut include preventing pathogen invasion through bile salt modifications [26], mucus layer erosion when the host lacks dietary fiber [27], and accelerating DNA damage that promotes tumor formation [9, 10]. More surprisingly, studies have drawn connections to neurological conditions such as Parkinson’s disease (PD) [22, 28], depression [29, 30], and autism spectrum disorder (ASD) [31–33], suggesting that certain bacteria and their MPPs (e.g., curli fibers in PD; the metabolites, 4-ethylphenylsulfate, p-cresol, taurine, and 5-aminovaleric acid in ASD) can contribute to these states (Fig 1).

Although a variety of host pattern recognition receptors (PRRs) directly sense microbial “danger” signals, including those from microbiome symbionts, emerging evidence also
supports the idea that we interact directly with microbes through additional cellular receptors. A recent study using a forward chemical genetics screen showed that MPPs from several dozen bacteria promote direct interactions with G-protein coupled receptors (GPCRs), a broad class of receptors important for physiological responses spanning mood regulation, immune function, and intestinal peristalsis [34]. This included a strain of *Morganella morganii* that converts L-phenylalanine into phenethylamine, a psychoactive compound that can be fatal in individuals taking monoamine oxidase inhibitor drugs [34]. Studies have also shown that the bacteria that convert tryptophan to tryptamine stimulate the colonic-restricted GPCR, 5HT4R, resulting in increased intestinal transit time [35]. Additionally, bacterial production of *N*-acyl amides regulates glucose homeostasis and possibly appetite [36]. MPPs also interact with other receptors, such as the aryl-hydrocarbon receptor (AhR). For example, production of AhR ligands, such as indole 3-aldehyde by *Lactobacillus reuteri*, leads to increased IL-22 production and a mucosal immune response against *Candida albicans* [37]. Just as the effects of potentially pathogenic bacteria can be altered because of the content of pathogenicity islands and other accessory gene content, studies like the ones noted previously often reveal variable effects from strains of the same species. This is an important consideration when formulating potential probiotics or other live bacterial therapeutics. A recent example of this is the implication of *L. reuteri* (strain SP-C2-NA0070) as an exacerbator of systemic lupus erythematosus (SLE) symptoms in a TLR7-dependent manner, an effect that is not attributable to other *Lactobacilli* [38].

Another class of molecules, which have previously been well-studied in pathogenic bacteria, the cyclic di- and trinucleotides (CDNs/CTNs), are also emerging as molecules that interact with host sensors. The structural diversity of these compounds has expanded from purine-based to include pyrimidine-based molecules [39]. Although not definitively linked to aspects of host health and disease, some of these CDNs can activate host immune pathways through PRRs, such as stimulator of interferon genes (STING) and reductase-controlling NF-κB (RECON) protein. Homologs of CDN synthesis operons are widespread in both commensal and pathogenic bacteria, including the prevalent *Bacteroides* genus. A recent study suggests that bacteria have evolved new ways of evading/enhancing host PRR recognition through synthesis of unique CTNs or modified CDNs not efficiently sensed by host PRRs [39].

A final group of MPPs that are just beginning to be explored are bacterial capsular polysaccharides (CPS), which are enriched and highly diversified in several lineages of gut bacteria [40]. For example, just 14 sequenced strains of the common gram-negative symbiont *Bacteroides thetaiotaomicron* harbor 47 different configurations of gene clusters for producing CPS [41]. Expression of some of these CPS alters the way this bacterium is sampled by macrophages and presented to T cells [42]. A subset of zwitterionic CPS, first discovered in *Bacteroides fragilis* but present in other species, has immunomodulatory properties, as do CPS and extracellular polysaccharides produced by members of different phyla, the Actinobacteria [43], Proteobacteria [44], and Firmicutes [45, 46]. These bacterial surface coatings are likely to be under intense pressure to diversify their glycan structures, perhaps to evade host immune responses, bacteriophages, and microbe-mediated killing. In the process, they have fortuitously synthesized chemical structures that interact with the host epithelium and immune system (*Fig 1*), providing additional advantages during colonization and also opportunities for researchers to exploit these molecules for potential drug development [47].

Collectively, the studies highlighted previously illustrate how host cells have evolved to sense and interact with a variety of metabolites or products that are uniquely microbial, which is the basis of much innate immune recognition and of central importance in the tolerance of the dense human gut microbiome [48]. Better understanding of these interactions may prove
helpful in leveraging these existing chemical relationships to design new drugs that alter immune responses or other aspects of host cellular biology.

**Metabolism of drugs and other xenobiotics by gut microbes**

Just as members of the microbiome produce novel molecules that interact with human physiology, they also have the capacity to modify exogenous chemicals (xenobiotics), many of which are the drugs used to treat diseases. Two prominent examples are inactivation of the cardiac drug digoxin by *Eggerthella lenta* [49] and related plant-derived cardenolides [50] and the ability of several species to convert the common dietary compound choline to trimethylamine (TMA), which is subsequently converted by the host to harmful trimethylamine-N-oxide (TMAO), which promotes cardiovascular disease (Fig 1) [51–53]. Another process that has been characterized mechanistically is drug reactivation following β-glucuronic acid conjugation in the liver and biliary secretion back into the gut. This process is catalyzed by gut bacterial β-glucuronidases, which are widely present in gut bacteria [54] and have broad substrate specificities [55, 56] that allow them to reactivate toxic drugs like the chemotherapeutic irinotecan. This process may be circumvented by drugs that, in turn block, β-glucuronidases to halt drug retoxification.

A recent example highlights how the common gut commensal *Bacteroides thetaiotaomicron* and related Bacteroidetes metabolize a range of xenobiotics using previously undescribed mechanisms. One of these involves degradation of the nucleoside-based antiviral drugs brivudine and sorivudine to the hepatotoxic compound bromovinyluracil (BVU) through the action of a nucleoside phosphorylase [57]. Homologs of this gene are found in many members of the phylum, suggesting that toxic BVU could accumulate at faster rates based on which members of the microbiota are present or their abundance. Another study expanded the repertoire of drugs that can be metabolized by *B. thetaiotaomicron*, identifying 18 drugs that are modified by an additional 17 unique enzymes [58]. Further highlighting that multiple bacteria can work synergistically in the gut, a recent study discovered a pathway for enzymatic inactivation of the Parkinson’s drug, levodopa (L-dopa). This stepwise mechanism involves *Enterococcus faecalis*, which first decarboxylates L-dopa to active dopamine, followed by a dehydroxylase from *E. lenta* that inactivates L-dopa and produces *m*-tyramine [59]. These studies point to variations in the gut microbiome as often overlooked reasons why therapy fails, or patients have intolerable side-effects to treatments. Thus, the gut microbiome is another factor to consider during treatment of disease, which may eventually require integration of both microbiome sequencing and culture/biochemistry-based approaches.

Beyond commensal bacteria altering the effects of therapeutic drugs, recent studies involving *Clostridium difficile* (*Cd*) have potentially uncovered a link as to why patients taking calcium supplements, proton-pump inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs) may be predisposed to infection or have more severe outcome. The germination signal for *Cd* is known to be intestinal bile salts, such as taurocholate, with glycine acting as a co-germinant. However, recent studies in vitro [60] and in vivo [61] have identified a role for *Ca*²⁺, which circumvents the requirement for glycine and could be derived from dietary supplements or increased during malabsorption. The connection between *Ca*²⁺ and *Cd* germination suggests a plausible mechanism for why individuals with high intestinal *Ca*²⁺ due to diet or poor absorption due to proton-pump inhibitors or low vitamin D are at greater risk of *C. difficile* infection (CDI). NSAIDs were recently shown to alter the community structure of the microbiota, potentially creating an environment in which CDI is more severe [62]. Although the study only examined responses to the NSAID indomethacin, dysregulation of intestinal tight junctions was observed leading to more severe disease through translocation of *Cd* across the epithelium.
Some of the findings described previously can be leveraged to design tools to guide drug selection and therapeutic interventions. A recently developed in silico tool is being used to model interactions between drug classes and bacterial enzymes with activities against these drugs [63]. This approach was used to successfully predict 3 previously unknown xenobiotic metabolic pathways by gut microbes that were confirmed through in vitro studies [63]. As knowledge of microbiome–drug interactions expands, it is likely that future personalized medicine approaches will use these predictive tools coupled with in vitro and in vivo models to guide treatment regimes in a myriad of diseases.

A way forward in the search for better therapeutics

From the studies highlighted here, the concepts of commensal and mutualistic bacteria always being “neutral” or “beneficial” to host biology is almost certainly naive. Rather, commensals, and even mutualists, may exhibit pathogenic activities, albeit in more subtle ways. Whereas true pathogens are equipped with toxins and machinery that directly damages cells, our more numerous, nonpathogenic symbionts may not be as directly insidious. The means by which these commensal organisms exhibit pathogenic tendencies are contextually dependent on factors such as diet, host genetics, drug intake, and production of MPPs. Furthermore, when considering whether the presence of a species could be beneficial or detrimental based on metagenomic or 16S ribosomal DNA sequencing approaches, the unique accessory genome of each strain, and not just phylogeny, needs to be considered. The context-specific activities of our common symbiotic bacteria may have both transient (acute) and chronic (long-term) health effects that likely influence disease states across organ systems. Leveraging the results of functional studies that link the microbiome to these diseases will illuminate new paths to manipulate the potential deleterious effects of the gut microbiome on health.

References

1. Escherich T, Bettelheim KS. The Intestinal Bacteria of the Neonate and Breast-Fed Infant. Reviews of Infectious Diseases. 1988; 10: 1220–5. https://doi.org/10.1093/clinids/10.6.1220 PMID: 3060950
2. Koropatkin NM, Cameron EA, Martens EC. How glycan metabolism shapes the human gut microbiota. Nature reviews Microbiology. 2012; 10: 323–35. https://doi.org/10.1038/nrmicro2746 PMID: 22491358
3. Porter NT, Martens EC. The Critical Roles of Polysaccharides in Gut Microbial Ecology and Physiology. Annu Rev Microbiol. 2017; 71: 349–69. https://doi.org/10.1146/annurev-micro-102215-095316 PMID: 28657886
4. Britton RA, Young VB. Role of the intestinal microbiota in resistance to colonization by Clostridium difficile. Gastroenterology. 2014; 146: 1547–53. https://doi.org/10.1053/j.gastro.2014.01.059 PMID: 24503131
5. Nash MJ, Frank DN, Friedman JE. Early Microbes Modify Immune System Development and Metabolic Homeostasis-The “Restaurant” Hypothesis Revisited. Front Endocrinol (Lausanne). 2017; 8: 349.
6. Gollwitzer ES, Marsland BJ. Impact of Early-Life Exposures on Immune Maturation and Susceptibility to Disease. Trends Immunol. 2015; 36: 684–96. https://doi.org/10.1016/j.it.2015.09.009 PMID: 26497259
7. Chung H, Pamp SJ, Hill JA, Surana NK, Edelman SM, Troy EB, et al. Gut immune maturation depends on colonization with a host-specific microbiota. Cell. 2012; 149: 1578–93. https://doi.org/10.1016/j.cell.2012.04.037 PMID: 22726443
8. Hickey CA, Kuhn KA, Donermeyer DL, Porter NT, Jin C, Cameron EA, et al. Cologenic Bacteroides thetaiotaomicron Antigens Access Host Immune Cells in a Sulfatase-Dependent Manner via Outer Membrane Vesicles. Cell Host & Microbe. 2015; 17: 672–80.
9. Dejea CM, Fathi P, Craig JM, Boletj A, Taddese R, Geis AL, et al. Patients with familial adenomatous polyposis harbor colonic biofilms containing tumorgenic bacteria. Science. 2018; 359: 592–7. https://doi.org/10.1126/science.aah3648 PMID: 29420293
10. Tomkovich S, Dejea CM, Winglee K, Drewes JL, Chung L, Housseau F, et al. Human colon mucosal biofilms from healthy or colon cancer hosts are carcinogetic. J Clin Invest. 2019; 130: 1699–712. https://doi.org/10.1172/JCI124196 PMID: 30855275
11. Lagkouvardos I, Pukall R, Abt B, Foesel BU, Meier-Kolthoff JP, Kumar N, et al. The Mouse Intestinal Bacterial Collection (miBC) provides host-specific insight into cultured diversity and functional potential of the gut microbiota. Nat Microbiol. 2016; 1: 16131. https://doi.org/10.1038/nmicrobiol.2016.131 PMID: 27670113

12. Browne HP, Forster SC, Anonye BO, Kumar N, Neville BA, Stares MD, et al. Culturing of 'unculturable' human microbiota reveals novel taxa and extensive sporulation. Nature. 2016; 533: 543–6. https://doi.org/10.1038/nature17445

13. Lagier JC, Khelaifi S, Alou MT, Ndongo S, Dione N, Hugon P, et al. Culture of previously uncultured members of the human gut microbiota by culturomics. Nat Microbiol. 2016; 1: 16203. https://doi.org/10.1038/nmicrobiol.2016.203 PMID: 27819657

14. Dethlefsen L, Huse S, Sogin ML, Relman DA. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. PLoS biology. 2008; 6: e280. https://doi.org/10.1371/journal.pbio.0060280 PMID: 18386261

15. Smits SA, Leach J, Sonnenburg ED, Gonzalez CG, Lichtman JS, Reid G, et al. Seasonal cycling in the gut microbiome of the Hadza hunter-gatherers of Tanzania. Science. 2017; 357: 802–6. https://doi.org/10.1126/science.aan4834 PMID: 28839072

16. Vangay P, Johnson AJ, Ward TL, Al-Ghalith GA, Shields-Cutler RR, Hillmann BM, et al. US Immigration Westernizes the Human Gut Microbiome. Cell. 2018; 175: 962–72 e10. https://doi.org/10.1016/j.cell.2018.10.029 PMID: 30388453

17. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014; 505: 559–63. https://doi.org/10.1038/nature12820 PMID: 24997786

18. Sonnenburg ED, Smits SA, Tikhonov M, Higginbottom SK, Wingreen NS, Sonnenburg JL. Diet-induced extinctions in the gut microbiota compound over generations. Nature. 2016; 529: 212–5. https://doi.org/10.1038/nature16504 PMID: 26762459

19. Cekanaviciute E, Yoo BB, Runia TF, Debelius JW, Singh S, Nelson CA, et al. Gut bacteria from multiple sclerosis patients modulate human T cells and exacerbate symptoms in mouse models. Proceedings of the National Academy of Sciences of the United States of America. 2017; 114: 10713–8. https://doi.org/10.1073/pnas.1711235114 PMID: 28893978

20. Hsiao EY, McBride SW, Chow J, Mazmanian SK, Patterson PH. Modeling an autism risk factor in mice leads to permanent immune dysregulation. Proceedings of the National Academy of Sciences of the United States of America. 2012; 109: 12776–81. https://doi.org/10.1073/pnas.1202556109 PMID: 22802640

21. Sharon G, Cruz NJ, Kang DW, Gandal MJ, Wang B, Kim YM, et al. Human Gut Microbiota from Autism Spectrum Disorder Promote Behavioral Symptoms in Mice. Cell. 2019; 177: 1600–18 e17. https://doi.org/10.1016/j.cell.2019.05.004 PMID: 31150625

22. Sampson TR, Challis C, Jain N, Moiseyenko A, Ladinsky MS, Shastri GG, et al. A gut bacterial amyloid promotes α-synuclein aggregation and motor impairment in mice. Elife, 2020; 9: e53111. https://doi.org/10.7554/eLife.53111

23. Feehley T, Plunkett CH, Bao R, Choi Hong SM, Culleen E, Belda-Ferre P, et al. Healthy infants harbor intestinal bacteria that protect against food allergy. Nat Med. 2019; 25: 448–53. https://doi.org/10.1038/s41591-018-0324-z PMID: 30643289

24. Li J, Jia H, Cai X, Zhong H, Feng Q, Sunaga S, et al. An integrated catalog of reference genes in the human gut microbiome. Nat Biotechnol. 2014; 32: 834–41. https://doi.org/10.1038/nbt.2942 PMID: 24997786

25. Pasolli E, Asnicar F, Manara S, Zolfo M, Karcher N, Armanini F, et al. Extensive Unexplored Human Microbiome Diversity Revealed by Over 150,000 Genomes from Metagenomes Spanning Age, Geography, and Lifestyle. Cell. 2019; 176: 649–62 e20. PMID: 30661755

26. Thanassery R, Winston JA, Thériot CM. Inhibition of spore germination, growth, and toxin activity of clinically relevant C. difficile strains by gut microbiota derived secondary bile acids. Anaerobe. 2017; 45: 86–100. https://doi.org/10.1016/j.anaerobe.2017.03.004 PMID: 28279860

27. Desai MS, Seekatz AM, Koropatkin NM, Kamada N, Hickey CA, Wolter M, et al. A Dietary Fiber-Dependent Gut Microbiota Degrades the Colonic Mucus Barrier and Enhances Pathogen Susceptibility. Cell. 2016; 167: 1339–53 e21. https://doi.org/10.1016/j.cell.2016.10.043 PMID: 27863247

28. Sampson TR, Debelius JW, Thron T, Janssen S, Shastri GG, Ilhan ZE, et al. Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson’s Disease. Cell. 2016; 167: 1469–80 e12. https://doi.org/10.1016/j.cell.2016.11.018 PMID: 27912057

29. Strandwitz P, Kim KH, Terekhova D, Liu JK, Sharma A, Levering J, et al. GABA-modulating bacteria of the human gut microbiota. Nat Microbiol. 2019; 4: 396–403. https://doi.org/10.1038/s41564-018-0307-3 PMID: 30531975
30. Valles-Colomer M, Falony G, Darzi Y, Tigchelaar EF, Wang J, Tito RY, et al. The neuroactive potential of the human gut microbiota in quality of life and depression. Nat Microbiol. 2019; 4: 623–32. https://doi.org/10.1038/s41564-019-0523-3 PMID: 31006530

31. Hosie S, Ellis M, Swaminathan M, Ramalhoosa F, Seger GO, Balasuriya GK, et al. Gastrointestinal dysfunction in patients and mice expressing the autism-associated R451C mutation in neurogin-3. Autism Res. 2019.

32. Grimaldi R, Gibson GR, Vulevic J, Giallourou N, Castro-Mejia JL, Hansen LH, et al. A prebiotic intervention study in children with autism spectrum disorders (ASDs). Microbiome. 2018; 6: 133. https://doi.org/10.1186/s40168-018-0523-3 PMID: 30071894

33. Hsiao EY, McBride SW, Hsien S, Sharon G, Hyde ER, McCue T, et al. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. Cell. 2013; 155: 1451–63. https://doi.org/10.1016/j.cell.2013.11.024 PMID: 24315484

34. Chen H, Nwe PK, Yang Y, Rosen CE, Bielecka AA, Kuchroo M, et al. A Forward Chemical Genetic Screen Reveals Gut Microbiota Metabolites That Modulate Host Physiology. Cell. 2019; 177: 1217–31 e18. https://doi.org/10.1016/j.cell.2019.03.036 PMID: 31006530

35. Bhattarai Y, Williams BB, Battaglioli EJ, Whitaker WR, Till L, Grover M, et al. Gut Microbiota-Produced Tryptamine Activates an Epithelial G-Protein-Coupled Receptor to Increase Colonic Secretion. Cell host & microbe. 2018; 23: 775–85 e5.

36. Cohen LJ, Esterhazy D, Kim SH, Lometre C, Aguilar RR, Gordon EA, et al. Commensal bacteria make GPCR ligands that mimic human signalling molecules. Nature. 2017; 549: 48–53. https://doi.org/10.1038/nature23874 PMID: 28854168

37. Zelante T, Iannitti RG, Cunha C, De Luca A, Giovanni G, Pieraccini G, et al. Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. Immunity. 2013; 39: 372–85. https://doi.org/10.1016/j.immuni.2013.06.003 PMID: 23973224

38. Zegarra-Ruiz DF, El Beidaq A, Iniguez AJ, Lubrano Di Ricco M, Manfredo Vieira S, Ruff WE, et al. Diet-Sensitive Commensal Lactobacillus Strain Mediates TLR7-Dependent Systemic Autoimmunity. Cell host & microbe. 2018; 23: 775–85 e5.

39. Porter NT, Canales P, Peterson DA, Martens EC. A Subset of Polysaccharide Capsules in the Human Symbiont Bacteroides thetaiotaomicron Promote Increased Competitive Fitness in the Mouse Gut. Cell host & microbe. 2017; 22: 494–506 e8.

40. Hsieh S, Porter NT, Donermeyer DL, Horvath S, Stout G, Saunders BT, et al. Polysaccharide capsules equip the human symbiont Bacteroides thetaiotaomicron to modulate immune responses to a dominant antigen in the intestine. J. Immunol. 2020; 204: 1035–1046. https://doi.org/10.4049/jimmunol.1901206 PMID: 31900343

41. Campos MA, Vargas MA, Regueiro V, Liompert CM, Alberti S, Bengoechea JA. Capsule polysaccharide mediates bacterial resistance to antimicrobial peptides. Infection and immunity. 2004; 72: 7107–14. https://doi.org/10.1128/IAI.72.12.7107-7114.2004 PMID: 15557634

42. Fanning S, Hall LJ, Cronin M, Zomer A, MacSharry J, Goulding D, et al. Bifidobacterial surface-exopolysaccharide facilitates commensal-host interaction through immune modulation and pathogen protection. Proceedings of the National Academy of Sciences of the United States of America. 2012; 109: 2108–13. https://doi.org/10.1073/pnas.1115621109 PMID: 22308390

43. Lee IC, Caggianiello G, van S II, Taverne N, Meijerink M, Bron PA, et al. Strain-Specific Features of Extracellular Polysaccharides and Their Impact on Lactobacillus plantarum-Host Interactions. Applied and environmental microbiology. 2016; 82: 3959–70. https://doi.org/10.1128/AEM.00306-16 PMID: 27107126

44. Remus DM, van Kranenburg R, van S II, Taverne N, Bongers RS, Wels M, et al. Impact of 4 Lactobacillus plantarum capsular polysaccharide clusters on surface glycán composition and host cell signaling. Microb Cell Fact. 2012; 11: 149. https://doi.org/10.1186/1475-2859-11-149 PMID: 23170998

45. Ramakrishna C, Kujawski M, Chu H, Li L, Mazmanian SK, Cantin EM. Bacteroides fragilis polysaccharide A induces IL-10 secreting S and T cells that prevent viral encephalitis. Nature communications. 2019; 10: 2153. https://doi.org/10.1038/s41467-019-09884-6 PMID: 31089128

46. Vitetta L, Vitetta G, Hall S. Immunological Tolerance and Function: Associations Between Intestinal Bacteria, Probiotics, Prebiotics, and Phages. Front Immunol. 2018; 9: 2240. https://doi.org/10.3389/fimmu.2018.02240 PMID: 30356736
49. Haiser HJ, Gootenberg DB, Chatman K, Sirasani G, Balskus EP, Turnbaugh PJ. Predicting and manipulating cardiac drug inactivation by the human gut bacterium Eggerthella lenta. Science. 2013; 341: 295–8. https://doi.org/10.1126/science.1235872 PMID: 23869020

50. Koppel N, Bisanz JE, Pandelia ME, Turnbaugh PJ, Balskus EP. Discovery and characterization of a prevalent human gut bacterial enzyme sufficient for the inactivation of a family of plant toxins. Elife. 2018; 7: e33953. https://doi.org/10.7554/eLife.33953 PMID: 29761785

51. Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, Dugar B, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature. 2011; 472: 57–63. https://doi.org/10.1038/nature09922 PMID: 21475195

52. Koppel N, Maini Rekdal V, Balskus EP. Chemical transformation of xenobiotics by the human gut microbiota. Science. 2017; 356: eaag2770. https://doi.org/10.1126/science.aag2770 PMID: 28642381

53. Martinez-del Campo A, Bodea S, Hamer HA, Marks JA, Haiser HJ, Turnbaugh PJ, et al. Characterization and detection of a widely distributed gene cluster that predicts anaerobic choline utilization by human gut bacteria. mBio. 2015; 6: e00042–15 https://doi.org/10.1128/mBio.00042-15 PMID: 25873372

54. Pollet RM, D’Agostino EH, Walton WG, Xu Y, Little MS, Biernat KA, et al. An Atlas of beta-Glucuronidases in the Human Intestinal Microbiome. Structure. 2017; 25: 967–77 e5. https://doi.org/10.1016/j.str.2017.05.003 PMID: 28578872

55. Dashnyam P, Mudududdla R, Hsieh TJ, Lin TC, Lin HY, Chen PY, et al. beta-Glucuronidases of opportunistic bacteria are the major contributors to xenobiotic-induced toxicity in the gut. Scientific reports. 2018; 8: 16372. https://doi.org/10.1038/s41598-018-34678-z PMID: 30401818

56. Biernat KA, Pellock SJ, Bhatt AP, Bivins MM, Walton WG, Tran BNT, et al. Structure, function, and inhibition of drug reactivating human gut microbial beta-glucuronidases. Scientific reports. 2019; 9: 825. https://doi.org/10.1038/s41598-019-36069-w PMID: 30696850

57. Zimmermann M, Zimmermann-Kogadeeva M, Wegmann R, Goodman AL. Separating host and microbiome contributions to drug pharmacokinetics and toxicity. Science. 2019; 363: eaat9931. https://doi.org/10.1126/science.aat9931 PMID: 30733391

58. Zimmermann M, Zimmermann-Kogadeeva M, Wegmann R, Goodman AL. Mapping human microbiome drug metabolism by gut bacteria and their genes. Nature. 2019; 570: 462–67. https://doi.org/10.1038/s41586-019-1291-3 PMID: 31158845

59. Maini Rekdal V, Bess EN, Bisanz JE, Turnbaugh PJ, Balskus EP. Discovery and inhibition of an interspecies gut bacterial pathway for Levodopa metabolism. Science. 2019; 364: eaau6323. https://doi.org/10.1126/science.aau6323 PMID: 31196984

60. Kochan TJ, Shoshiev MS, Hastie JL, Somers MJ, Plotnick YM, Gutierrez-Munoz DF, et al. Germinant Synergy Facilitates Clostridium difficile Spore Germination under Physiological Conditions. mSphere. 2018; 3: e00335–18. https://doi.org/10.1128/mSphere.00335-18 PMID: 30185513

61. Kochan TJ, Somers MJ, Kaiser AM, Shoshiev MS, Hagan AK, Hastie JL, et al. Intestinal calcium and bile salts facilitate germination of Clostridium difficile spores. PLoS Pathog. 2017; 13: 1006443.

62. Maseda D, Stacke JP, Trindade B, Kirk L, Roxas JL, Rogers LM, et al. Nonsteroidal Anti-inflammatory Drugs Alter the Microbiota and Exacerbate Clostridium difficile Colitis while Dysregulating the Inflammatory Response. mSphere. 2019; 10: e02282–18. https://doi.org/10.1128/mSphere.02282-18 PMID: 30622186

63. Guthrie L, Wolfson S, Kelly L. The human gut chemical landscape predicts microbe-mediated biotransformation of foods and drugs. Elife. 2019; 8: e42866. https://doi.org/10.7554/eLife.42866 PMID: 31184303

64. Lundmark K, Westermark GT, Olsen A, Westermark P. Protein fibrils in nature can enhance amyloid protein A amyloidosis in mice: Cross-seeding as a disease mechanism. Proceedings of the National Academy of Sciences of the United States of America. 2005; 102: 6098–102. https://doi.org/10.1073/pnas.0501814102 PMID: 15829582

65. Friedland RP, Chapman MR. The role of microbial amyloid in neurodegeneration. PLoS Pathog. 2017; 13: e1006654. https://doi.org/10.1371/journal.ppat.1006654 PMID: 29267402

66. Gandy KAO, Zhang J, Nagarkatti P, Nagarkatti M. The role of gut microbiota in shaping the relapse-remitting and chronic-progressive forms of multiple sclerosis in mouse models. Scientific reports. 2019; 9: 6923. https://doi.org/10.1038/s41598-019-43356-7 PMID: 31061496

67. Yuan J, Chen C, Cui J, Lu J, Yan C, Wei X, et al. Fatty Liver Disease Caused by High-Alcohol-Producing Klebsiella pneumoniae. Cell metabolism. 2019; 30: 675–88 e7. https://doi.org/10.1016/j.cmet.2019.08.018 PMID: 31543403

68. Llorente C, Jepsen P, Inamine T, Wang L, Blumel S, Wang HJ, et al. Gastric acid suppression promotes alcoholic liver disease by inducing overgrowth of intestinal Enterococcus. Nature communications. 2017; 8: 837. https://doi.org/10.1038/s41467-017-00796-x PMID: 29038503
69. Carr TF, Alkatib R, Kraft M. Microbiome in Mechanisms of Asthma. Clin Chest Med. 2019; 40: 87–96. 
https://doi.org/10.1016/j.ccm.2018.10.006 PMID: 30691719

70. Berni Canani R, Nocerino R, Terrin G, Frediani T, Lucarelli S, Cosenza L, et al. Formula selection for management of children with cow’s milk allergy influences the rate of acquisition of tolerance: a prospective multicenter study. J Pediatr. 2013; 163: 771–7 e1. https://doi.org/10.1016/j.jpeds.2013.03.008 PMID: 23582142

71. Stefka AT, Feehley T, Tripathi P, Qiu J, McCoy K, Mazmanian SK, et al. Commensal bacteria protect against food allergen sensitization. Proceedings of the National Academy of Sciences of the United States of America. 2014; 111: 13145–50. https://doi.org/10.1073/pnas.1412008111 PMID: 25157157

72. Caminero A, Galipeau HJ, McCarville JL, Johnston CW, Bernier SP, Russell AK, et al. Duodenal Bacteria From Patients With Celiac Disease and Healthy Subjects Distinctly Affect Gluten Breakdown and Immunogenicity. Gastroenterology. 2016; 151: 670–83. https://doi.org/10.1053/j.gastro.2016.06.041 PMID: 27373514

73. Wu S, Shin J, Zhang G, Cohen M, Franco A, Sears CL. The Bacteroides fragilis toxin binds to a specific intestinal epithelial cell receptor. Infection and immunity. 2006; 74: 5382–90. https://doi.org/10.1128/IAI.00060-06 PMID: 16926433

74. Haghi F, Goli E, Mirzaei B, Zeighami H. The association between fecal enterotoxigenic B. fragilis with colorectal cancer. BMC Cancer. 2019; 19: 879. https://doi.org/10.1186/s12885-019-6115-1 PMID: 31488085

75. Wu J, Li Q, Fu X. Fusobacterium nucleatum Contributes to the Carcinogenesis of Colorectal Cancer by Inducing Inflammation and Suppressing Host Immunity. Transl Oncol. 2019; 12: 846–51. https://doi.org/10.1016/j.tranon.2019.03.003 PMID: 30986689

76. Arthur JC, Perez-Chanona E, Muhlbauer M, Tomkovich S, Uronis JM, Fan TJ, et al. Intestinal inflammation targets cancer-inducing activity of the microbiota. Science. 2012; 338: 120–3. https://doi.org/10.1126/science.1224820 PMID: 22903521