Published in final edited form as:
Cell Host Microbe. 2019 August 14; 26(2): 160–162. doi:10.1016/j.chom.2019.07.018.

The Gut Feeling: GPCRs Enlighten the Way

Shubhi Pandey[1], **Jagannath Maharana**[1], **Arun K. Shukla**[1,*]

[1]department of Biological Sciences and Bioengineering, Indian Institute of Technology, Kanpur 208016, India

Abstract

Host-microbiome interactions affect host physiology, but the underlying mechanisms are not well understood. Recent papers from Chen et al. (2019) and Colosimo et al. (2019) in this issue of Cell Host & Microbe demonstrate that metabolites produced by several members of the gut microbiota can efficiently activate host G protein-coupled receptors and influence host physiology.

Host-microbiome interplay and crosstalk are now well established as a key paradigm in the modulation and fine-tuning of host physiology at multiple levels. It is now also being integrated into strategies for designing novel therapeutics. Human gut microbiota in particular, which harbors a wide range of microorganisms and produces a broad spectrum of metabolites, has come to the center stage, in terms of directly influencing the host physiological responses. Understanding the mechanisms of action of the metabolites produced by gut microbiota is of utmost importance to delineate the specifics of their crosstalk with the host. Previous focused studies have indicated that microbiota-derived molecules may act as ligands for specific G protein-coupled receptors (GPCRs) and influence, for example, gastrointestinal physiology (Cohen et al., 2017; Husted et al., 2017). In two recent studies, screening of a large number of metabolites produced by several members of the gut microbiota against nearly all non-olfactory GPCRs identified several metabolites as GPCR agonists capable of triggering distinct host physiological responses (Chen et al., 2019; Colosimo et al., 2019) (Figure 1).

GPCRs constitute a large class of seven transmembrane receptors that are activated by a diverse range of ligands. They are critically involved in nearly every physiological process in our body, making them an important class of drug targets (Sriram and Insel, 2018). These receptors couple to two distinct transducers, namely the heterotrimeric G proteins and β-arrestins (βarrs) (Lefkowitz and Shenoy, 2005). As there are several subtypes of G proteins, each with a distinct downstream response, screening of a large set of molecules across the entire GPCRome to identify potential agonists requires multiple assays. On the other hand, there are only two isoforms of βarrs, both of which directly interact with nearly every GPCR (Srivastava et al., 2015). Therefore, GPCR-βarr interaction can be utilized as a streamlined readout for identification of agonists across the entire repertoire of GPCRs. Accordingly, Chen et al. used a recently described transcriptional outcome-based βarr recruitment assay, referred to as PRESTO-Tango (Kroeze et al., 2015), to screen the metabolites produced by

*Correspondence: arshukla@iitk.ac.in.

Europe PMC Funders Author Manuscripts

individual cultures of more than 100 different bacterial isolates against the entire non-olfactory GPCRome (Chen et al., 2019). These bacterial isolates were derived from the gut microbiota of patients with inflammatory bowel disease (Palm et al., 2014).

Interestingly, the metabolite mixtures produced by these bacterial isolates were able to stimulate a broad set of GPCRs, although a clear correlation between the bacterial phylogeny and subfamily of the activated receptors was not apparent, except for a few selected examples. A number of metabolite mixtures appear to activate several different aminergic GPCRs, including the dopamine and histamine receptors. Nevertheless, some metabolites appear to exhibit preferential selectivity toward different receptor subtypes. For example, the metabolite mixture produced by *Morganella morganii* efficiently activated dopamine receptor subtypes 2–4 (DRD2–4) but failed to activate the other two subtypes, i.e., DRD1 and DRD5. Metabolomic analysis revealed a major enrichment of PEA (phenethylamine) over dopamine and tyramine in the supernatant *M. morganii*, and indeed purified PEA showed the same subtype selectivity pattern as observed with the supernatant.

Do these observations recorded *in vitro* have a direct *in vivo* correlation? Colonization of germ-free mice with a specific *M. morganii* strain C135, which produces histamine, resulted in enhanced levels of histamine in the intestine and serum. Moreover, these mice exhibited significantly higher fecal output, a measure of intestinal motility, compared to control mice, which were colonized with bacterial isolates not able to produce histamine. Interestingly, the patients suffering from Crohn's disease display not only a higher level of histamine but also an enrichment of histidine decarboxylase gene encoded by *M. morganii*, an enzyme that catalyzes the conversion of histidine to histamine. It is particularly noteworthy because the enhanced level of histamine in Crohn's disease patients was previously thought to be derived primarily from the host. Colonization of mice with *M. morganii* also resulted in an increase in the levels of PEA, a DRD2-4 selective G protein-biased ligand, although its detection required inhibition of monoamine oxidases (MAOs), which may metabolize biogenic amines including PEA. Increased levels of PEA led to lethargy and mortality in mice within a few days, and this may be a potential mechanism to explain a significant variability among patients who are prescribed MAO inhibitors as anti-depressants.

In addition to a direct interplay of metabolites produced by specific bacteria with the host physiology, a crosstalk among different bacterial species constituting the gut microbiota may also play an important role. For example, one bacterial species can convert metabolites produced by other bacteria into new derivatives, which can directly influence the host physiology. Such metabolic exchanges between two bacterial species, or possibly even among several species, may encode a broader diversity of microbiota metabolites depending on dynamic distribution of microbiota population. Chen et al. discover a specific strain of *Bacteroides thetaiotaomicron* (B. *theta*) that produces the essential amino acid phenylalanine (L-Phe), which not only serves as an agonist for adhesion GPCRs (GPR56 and GPR97) but can also be processed by *M. morganii* into PEA, which is a dopamine receptor agonist as described earlier. This interesting observation in mice colonized with defined bacterial species hints at a larger picture of metabolic exchanges in gut microbiota taking place *in vivo*, which may significantly influence and fine-tune host physiology under normal and disease conditions.

Europe PMC Funders Author Manuscripts

Another study by Colosimo et al. in this issue of *Cell Host & Microbe* employs a similar approach to identify several bacterial metabolites that are capable of activating a diverse set of GPCRs (Colosimo et al., 2019). This study carries out a functional screening of metabolites produced by seven different bacterial species that constitute a small group referred to as the simplified human microbiomes (SIHUMIs) (Kovatcheva-Datchary et al., 2019). This study also uses βarr recruitment as the primary readout against more than 200 GPCRs and then follows up by purifying the selected metabolites and characterizing their chemical structures. Once again, a number of neurotransmitter receptors are found to be activated by bacterial metabolites, highlighting an interplay along the gutbrain axis, which is likely to have immense therapeutic implications. Furthermore, colonization of germ-free mice with SIHUMI strains resulted in an enrichment of those metabolites, which were identified from monocultures of these individual strains *in vitro*, providing a strong *in vivo* corollary for the findings.

An interesting aspect of both studies is the identification of microbiota metabolites as agonists for orphan GPCRs, for example, the members of adhesion GPCR subfamily such as BAI1, GPR56, and GPR97. Considering the importance of GPCR deorphanization from a drug-discovery point of view, these studies have far-reaching implications and suggest that looking outside the box may be key going forward. It is also important to note that metabolites analyzed in the initial screening process are collected from individual cultures of the bacterial isolates. It is plausible that there are specific qualitative and quantitative variations in the metabolites produced by the gut microbiota under *in vivo* conditions, a potential aspect that can be addressed in future. Moreover, allosteric modulation of GPCRs continues to be an intense focus of investigation from a therapeutic perspective, and therefore, it is tempting to speculate that screening the microbiota metabolites as allosteric modulators may reveal even further surprises and interesting leads.

In conclusion, these studies firmly establish a direct connection between metabolites produced by the gut microbiota and their ability to influence host physiology through GPCRs. Considering the widespread expression pattern of GPCRs in the body and their diverse role in human physiology, a comprehensive conceptual and experimental framework of host-microbiome interaction may significantly contribute in GPCR targeted novel drug discovery efforts.

Acknowledgments

The research program in our laboratory is supported by an Intermediate Fellowship of the Wellcome Trust/DBT India Alliance Fellowship (grant number IA/I/14/1/501285) awarded to A.K.S., Department of Biotechnology, Department of Science and Technology, LADY TATA Memorial Trust, and IIT Kanpur. A.K.S. is an EMBO Young Investigator and Joy Gill Chair Professor.

References

Chen H, Nwe PK, Yang Y, Rosen CE, Bielecka AA, Kuchroo M, Cline GW, Kruse AC, Ring AM, Crawford JM, Palm NW. A forward chemical genetic screen reveals gut microbiota metabolites that modulate host physiology. Cell. 2019; 177:1217–1231.e18. [PubMed: 31006530]

Cohen LJ, Esterhazy D, Kim SH, Lemetre C, Aguilar RR, Gordon EA, Pickard AJ, Cross JR, Emiliano AB, Han SM, et al. Commensal bacteria make GPCR ligands that mimic human signalling molecules. Nature. 2017; 549:48–53. [PubMed: 28854168]

Colosimo DA, Kohn JA, Luo PM, Piscotta FJ, Han SM, Pickard AJ, Rao A, Cross JR, Cohen LJ, Brady SF. Mapping interactions of microbial metabolites with human G-protein-coupled receptors. Cell Host Microbe. 2019; 26:273–282. [PubMed: 31378678]

Husted AS, Trauelsen M, Rudenko O, Hjorth SA, Schwartz TW. GPCR-mediated signaling of metabolites. Cell Metab. 2017; 25:777–796. [PubMed: 28380372]

Kovatcheva-Datchary P, Shoaie S, Lee S, Wahlstrom A, Nookaew I, Hallen A, Perkins R, Nielsen J, Backhed F. Simplified intestinal microbiota to study microbe-diet-host interactions in a mouse model. Cell Rep. 2019; 26:3772–3783.e6. [PubMed: 30917328]

Kroeze WK, Sassano MF, Huang XP, Lansu K, McCorvy JD, Gigufbre PM, Sciaky N, Roth BL. PRESTO-Tango as an open-source resource for interrogation of the druggable human GPCRome. Nat Struct Mol Biol. 2015; 22:362–369. [PubMed: 25895059]

Lefkowitz RJ, Shenoy SK. Transduction of receptor signals by beta-arrestins. Science. 2005; 308:512–517. [PubMed: 15845844]

Palm NW, de Zoete MR, Cullen TW, Barry NA, Stefanowski J, Hao L, Degnan PH, Hu J, Peter I, Zhang W, et al. Immunoglobulin A coating identifies colitogenic bacteria in inflammatory bowel disease. Cell. 2014; 158:1000–1010. [PubMed: 25171403]

Sriram K, Insel PA. G protein-coupled receptors as targets for approved drugs: how many targets and how many drugs? Mol Pharmacol. 2018; 93:251–258. [PubMed: 29298813]

Srivastava A, Gupta B, Gupta C, Shukla AK. Emerging functional divergence of β-arrestin isoforms in GPCR function. Trends Endocrinol. Metab. 2018; 26:628–642.

Europe PMC Funders Author Manuscripts

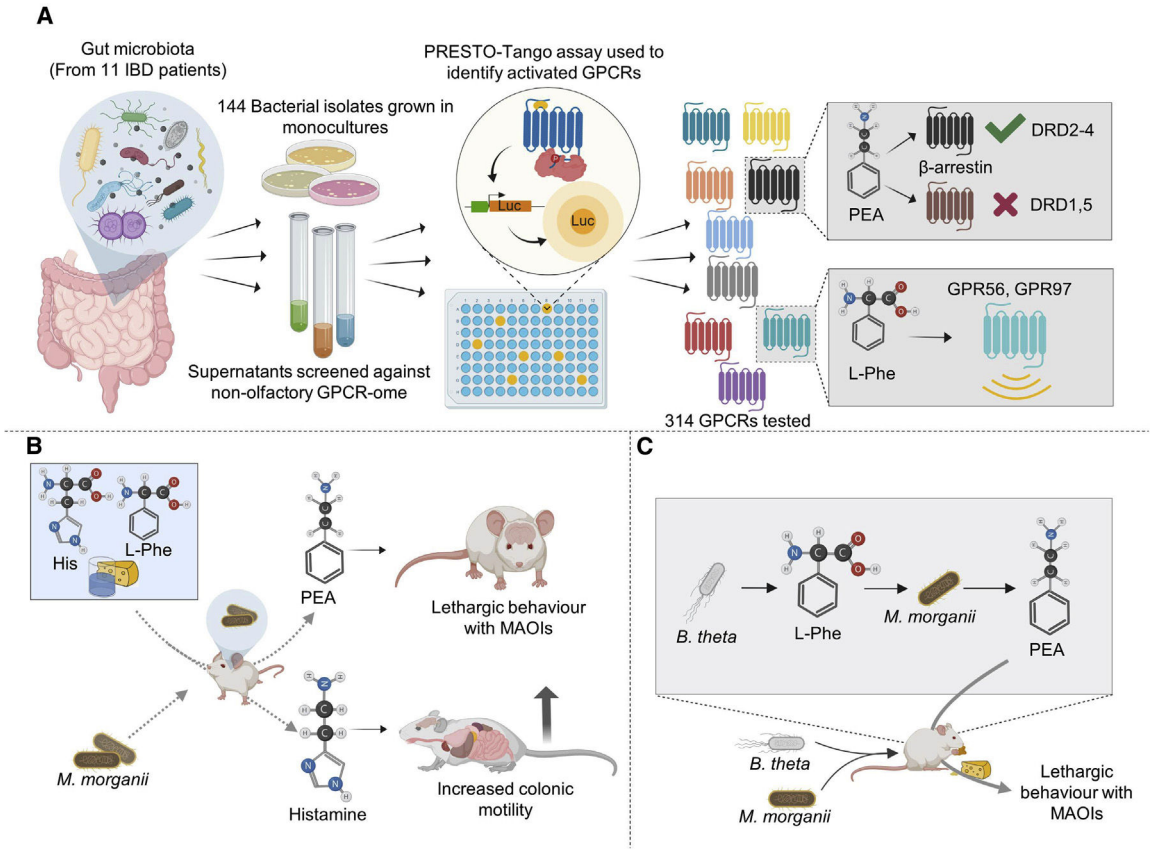

Figure 1. Microbiota Metabolites Influence Host Physiology through G Protein-Coupled Receptors

(A)Screening of metabolites produced by the individual members of human gut microbiota identifies several GPCR agonists. Chen et al. used culture supernatants from 144 unique bacterial isolates to measure the activation of non-olfactory GPCRs using GPCR-βarr interaction as readout. Microbiota metabolites activate a diverse spectrum of GPCRs with a predominant effect on aminergic receptors. Interestingly, some of the metabolites exhibit receptor subtype selectivity as well as functional selectivity. Moreover, bacterial metabolites such as L-Phe (phenylalanine) also activate orphan GPCRs belonging to the adhesion subfamily such as GPR56 and GPR97.

(B)The ability of isolated bacterial cultures to produce GPCR agonists is recapitulated *in vivo.* Germ-free mice colonized with *Morganella morganii* (*M. morganii*) display enhanced levels of histamine and L-Phe (phenylalanine). Feeding *M. morganii* monocolonized mice with L-His(histidine), a precursor of histamine, further substantiates histamine levels and results in increased colonic motility in mice. Furthermore, *M. morganii* colonization also results in enhanced level of PEA and leads to lethargic behavior in mice treated with MAO (monoamine oxidase) inhibitor.

(C)Metabolic exchange between two bacterial isolates is observed in mice colonized with defined bacterial species. Germ-free mice were colonized with *Bacteroides thetaiotaomicron* (*B. theta*) and *Morganella morganii (M. morganii).* L-Phe (pheylalanine) produced by *B. theta* can be processed into PEA (phenethylamine), a dopamine receptor agonist, by *M. morganii* and leads to lethargic behavior in mice treated with monoamine oxidase (MAO)

inhibitor. This figure is designed based on the findings described recently by Chen et al. (2019).

Europe PMC Funders Author Manuscripts