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Symbiosis and cohabitation

Bacterial interspecies quorum sensing in the mammalian gut microbiota☆,☆☆

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ABSTRACT

The mammalian gastrointestinal tract harbors a diverse and complex resident bacterial community, which interacts with the host in many beneficial processes required for optimal host health. We are studying the importance of bacterial cell-cell communication mediated by the interspecies quorum-sensing signal autoinducer-2 (AI-2) in the beneficial properties of the gut microbiota. Our recent work provided the first evidence that AI-2 produced by *Escherichia coli* can influence the species composition of this community in the mouse gut. We showed that, under conditions of microbiota imbalances induced by antibiotic treatments, *E. coli*, which increases intestinal AI-2 levels, not only had an effect on the overall structure of the microbiota community, but specifically favored the expansion of the Firmicutes phylum. Because the Firmicutes are very important for many gut functions and were the group of bacteria most severely affected by antibiotic treatment with streptomycin, we are addressing the possibility that AI-2 can influence the balance of the major bacterial groups in the gut and promote recovery of gut homeostasis. Overall, we want to understand how bacterial chemical signaling shapes the multi-species bacterial communities in the mammalian gut and how these communities affect host physiology.

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1. Introduction

Recent advances in microbiology are leading to a revolution in biology. Researchers across many disciplines are discovering the importance of microbes that live on and within our bodies for our health and development. The mammalian gastrointestinal tract, in particular, harbors a diverse and complex resident bacterial community. This community interacts with the host in many processes required for the host's health, including nutrition, development of the immune system and even human behavior. However, despite the large body of literature supporting the beneficial properties of the gut microbiota community to the human host, most of the evidence substantiating this claim is primarily based on correlations. Our understanding of the molecular mechanisms responsible for the beneficial properties of the mammalian microbiome is still very limited.

The mammalian gut contains hundreds of different species that need to co-exist and interact with each other and with the host. Until now, our knowledge pertains primarily to the type of bacteria present in this complex environment. We understand the diversity of this ecosystem in terms of species composition, but we know very little about the mechanisms involved in the establishment, maintenance and resilience of this community. How many of the microbiota species cohabitating with each other and the mammalian host are important for host development and health? Which species are interacting with other

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species and which are the key players in these networks of interactions? What are the important functional properties of these microbes and how are these functions regulated? These are only some of the many questions that remain to be answered.

2. Towards the manipulation of bacterial quorum sensing to shape the microbiome

Based on studies of bacterial cell–cell interactions in laboratory systems, we know that bacteria are capable of exchanging chemical signalling molecules to communicate and to regulate their behaviors. This bacterial chemical lexicon seems to be particularly important when bacteria are interacting at high cell densities. It is therefore likely that the exchange of these signals plays an important role in the dense bacterial communities present in the mammalian gut. Many of the chemical signals exchanged by bacterial populations are involved in a process called *quorum sensing* [1,2]. This process of cell-cell signalling involves production, secretion and sensing of chemical signals, called autoinducers [3]. In laboratory cultures at low cell densities, the signals diffuse away and are not detected by the bacteria. At high cell densities, the signals accumulate and are detected by cellular protein receptors, which trigger a response at the level of gene expression, enabling the bacterial population to synchronize gene expression and engage in-group behaviors. Therefore, it is thought that bacteria use quorum sensing to monitor the density of their populations and to regulate gene expression accordingly. Typically, behaviors activated by autoinducers and quorum sensing are group behaviors that are productive when bacteria are present at high cell densities and are not productive when bacteria are present at low densities. These bacterial group behaviors include: production of bioluminescence, by bacteria living in symbiosis with marine animals, biofilm formation in human pathogens and secretion of pectolytic enzymes by plant pathogens that degrade plant tissues [1,2]. Importantly, the behaviors regulated by quorum sensing are important in many microbe-host interactions and can be either hostile or beneficial.

We think that these same types of quorum sensing molecules are likely to be regulating important bacterial behaviors in the mammalian gut. By understanding how bacteria among the gut microbiota are interacting and which bacterial processes are being regulated at high densities, we expect to identify the mechanisms controlling bacterial behaviors in the mammalian gut and determine the most important bacterial group behaviors that benefit the host. To begin addressing the importance of quorum sensing in the mammalian gut, we have established a model to manipulate interspecies quorum sensing in the mouse gut. The only quorum-sensing signal that is known to foster interspecies bacterial communication across distantly related bacterial species is autoinducer-2 (AI-2) [4]. This signal is a small 5-carbon molecule that was first discovered in the vibrios, but has been found to be produced and sensed by a wide range of bacterial species across the bacterial kingdom [5,6]. Since its discovery, many studies have shown that AI-2 regulates a variety of behaviors that are typically regulated by quorum sensing such as bioluminescence in *Vibrio harveyi*, biofilm formation and virulence in *Vibrio cholerae*, formation of oral biofilms in *Streptococcus gordonii*, phage dispersal in *Enterococcus faecalis* and motility and cell aggregation in *Escherichia coli* [7–9]. For the most part, these behaviors have been studied in single species settings that do not address the potential of AI-2 as an interspecies signal that can influence the behavior of poly-species communities.

To address the function of AI-2 and interspecies quorum sensing in the poly-species gut microbiota communities, we took advantage of a natural system in the bacterium, *Escherichia coli*, to manipulate the extracellular levels of AI-2. We constructed a collection of engineered *E. coli* strains, which upon colonization of mouse intestines could either increase AI-2 or scavenge AI-2 produced by other members of the microbiota. We next used these strains to ask if AI-2 could influence the species composition of the microbiota during conditions of microbiota imbalance (dysbiosis) [10].

We showed that in mice, a prolonged antibiotic treatment with streptomycin added to drinking water leads to very strong gut dysbiosis characterized by an imbalance in the proportion of Bacteroidetes and Firmicutes. In mice treated with streptomycin for one month, the composition of gut microbiota was dominated by bacteria belonging to the Bacteroidetes phylum, while the bacteria which belong to the Firmicutes were almost cleared from the gut. The Bacteroidetes and the Firmicutes phyla are the two most predominant phyla in the mammalian gut. A healthy mammalian gut microbiota is composed of an almost equal proportion of Bacteroidetes and Firmicutes. Shifts in the microbiota affecting the balance between these two phyla are associated with several disease states including obesity, inflammation and pathogenic infections [11–13]. Our results showed, that under conditions of microbiota imbalance induced by prolonged streptomycin treatment, mice colonized with the *E. coli* strain engineered to increase intestinal levels of AI-2 had a different overall structure of the microbiota community. Specifically, the Firmicutes were the bacteria that were significantly decreased by antibiotic treatment. However, increasing AI-2 levels favored the expansion of the Firmicutes in the antibiotic-treated microbiota, while hindering the Bacteroidetes, demonstrating that AI-2 counteracted the dysbiosis induced by long-term antibiotic treatment [10]. Because the Firmicutes are very important for many gut functions and were the group of bacteria that responded more positively to AI-2, we are exploring alternative strategies to potentiate the effect of the AI-2 produced by *E. coli* to influence the balance between the Firmicutes and the Bacteriodetes and so recover gut homeostasis. In other dysbiotic conditions, such as those described in patients suffering from inflammatory bowel diseases such as Crohn's disease, the balance between the Firmicutes and Bacteriodetes is affected in the opposite direction. Under such conditions, strategies that favor the Bacteriodetes are expected to help ameliorate disease symptoms. In these cases, strategies that decrease intestinal levels of AI-2, which should favor the Bacteriodetes, could be tested [14].

3. Future perspectives and conclusions

Overall, our studies on the effect of manipulating interspecies quorum sensing showed that AI-2 can influence the species composition of the microbiota community in the mouse gut. We are now pursuing these studies to determine which of the AI-2-mediated interactions are direct and which microbiota functions are influenced by AI-2. With this knowledge, we expect to devise better strategies to take advantage of the bacterial language in the mammalian gut to shape these important bacterial communities. Importantly, we learned that although we know many of the quorum sensing molecules produced by the Firmicutes, almost half of the gut microbiota community is composed of Bacteroidetes, and only about 20% of the bacteria belonging to this phylum are potential AI-2 producers [10]. Moreover, homologues to the other quorum sensing signal synthases are absent in the genome sequences of the Bacteroidetes. Because these bacteria engage in many functions that are often regulated by quorum sensing in other bacteria, we expect that a whole new lexicon of chemical signals remains to be discovered.

Our present understanding of how different species of bacteria in the mammalian gut interact with each other and what functions they regulate, is in its infancy. However, we expect that by understanding how the bacterial chemical lexicon shapes multi-species bacterial communities in the mammalian gut, we will be able to better understand how these communities contribute to host physiology.

References

[1] C.M. Waters, B.L. Bassler, Quorum sensing: cell-to-cell communication in bacteria, Annu. Rev. Cell Dev. Biol. 21 (2005) 319–346 (PMID: 16212498).

[2] K. Papenfort, B.L. Bassler, Quorum sensing signal-response systems in Gram-negative bacteria, Nat. Rev. Microbiol. 14 (2016) 576–588 (PMID: 27510864).

[3] C. Fuqua, E.P. Greenberg, Listening in on bacteria: acyl-homoserine lactone signaling, Nat. Rev. Mol. Cell Biol. 3 (2002) 685–695. , http://dx.doi.org/10.1038/nrm907 (PMID: 12209128).

[4] K.B. Xavier, B.L. Bassler, Interference with AI-2-mediated bacterial cell-cell communication, Nature 437 (7059) (2005) 750–753 (PMID: 16193054).

[5] X. Chen, et al., Structural identification of a bacterial quorum-sensing signal containing boron, Nature 415 (2002) 545–549 (PubMed).

[6] S.T. Miller, K.B. Xavier, S.R. Campagna, M.E. Taga, M.F. Semmelhack, B.L. Bassler, et al., *Salmonella typhimurium* recognizes a chemically distinct form of the bacterial quorum-sensing signal AI-2, Mol. Cell. 15 (5) (2004) 677–687 (PMID: 15350213).

[7] C.S. Pereira, J.A. Thompson, K.B. Xavier, AI-2-mediated signalling in bacteria, FEMS Microbiol. Rev. 37 (2013) 156–181 (PubMed).

[8] F.S. Rossmann, T. Racek, D. Wobser, J. Puchalka, E.M. Rabener, M. Reiger, et al., Phage-mediated dispersal of biofilm and distribution of bacterial virulence genes is induced by quorum sensing, PLoS Pathog. 11 (2) (2015) e1004653, http://dx.doi.org/10.1371/journal.ppat.1004653 (eCollection, PMID: 25706310).

[9] L. Laganenka, R. Colin, V. Sourjik, Chemotaxis towards autoinducer 2 mediates autoaggregation in *Escherichia coli*, Nat. Commun. 7 (2016) 12984, http://dx.doi.org/10.1038/ncomms12984 (PMID: 27687245).

[10] J.A. Thompson, R.A. Oliveira, A. Djukovic, C. Ubeda, K.B. Xavier, Manipulation of the quorum sensing signal AI-2 affects the antibiotic-treated gut microbiota, Cell Rep. 10 (11) (2015) 1861–1871 (PMID: 25801025).

[11] C. Ubeda, V. Bucci, S. Caballero, A. Djukovic, N.C. Toussaint, M. Equinda, et al., Intestinal microbiota containing *Barnesiella* species cures vancomycin-resistant *Enterococcus faecium* colonization, Infect. Immun. 81 (3) (2013) 965–973. , http://dx.doi.org/10.1128/IAI.01197-12 (PubMed PMID: 23319552; PubMed Central PMCID: PMCPMC3584866).

[12] D.N. Frank, A.L. St Amand, R.A. Feldman, E.C. Boedeker, N. Harpaz, N.R. Pace, Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases, Proc. Natl. Acad. Sci. USA 104 (34) (2007) 13780–13785. , http://dx.doi.org/10.1073/pnas.0706625104 (PubMed PMID: 17699621; PubMed Central PMCID: PMCPMC1959459).

[13] R.E. Ley, P.J. Turnbaugh, S. Klein, J.I. Gordon, Microbial ecology: human gut microbes associated with obesity, Nature 444 (7122) (2006) 1022–1023. , http://dx.doi.org/10.1038/444 (PubMed PMID: 17183309).

[14] J.A. Thompson, R.A. Oliveira, K.B. Xavier, Chemical conversations in the gut microbiota, Gut Microbes 7 (2) (2016) 163–170. , http://dx.doi.org/10.1080/19490976.2016.1145374 (PMID: 26901101).