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MINIREVIEW

Protective Role of Gut Commensal Microbes against Intestinal Infections

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The human gastrointestinal tract is colonized by multitudes of microorganisms that exert beneficial effects on human health. Mounting evidence suggests that intestinal microbiota contributes to host resistance against enteropathogenic bacterial infection. However, molecular details that account for such an important role has just begun to be understood. The commensal microbes in the intestine regulate gut homeostasis through activating the development of host innate immunity and producing molecules with antimicrobial activities that directly inhibit propagation of pathogenic bacteria. Understanding the protective roles of gut microbiota will provide a better insight into the molecular basis that underlies complicated interaction among host-pathogen-symbiont. In this review, we highlighted recent findings that help us broaden our knowledge of the intestinal ecosystem and thereby come up with a better strategy for combating enteropathogenic infection.

Keywords: gut microbiota, enteropathogenic bacterial infection, colonization resistance

Introduction

The gut microbiota is comprised of microorganisms such as bacteria, archaea, fungus, and viruses that are distributed from the duodenum to the rectum (Backhed *et al.*, 2005; Nava and Stappenbeck, 2011; Clemente *et al.*, 2012; Yoon *et al.*, 2013). In the case of healthy humans, over 1,000 species and about 10^{11}–10^{14} CFU/g of bacteria co-exist in an individual, representing 10 times more cells and approximately 100 times more genetic information than a human body (Guarner and Malagelada, 2003; Eckburg *et al.*, 2005). The role of the gut commensal was revealed by a comparison of conventionally raised and germ-free (GF) mice. In general, GF mice are more susceptible to infection than conventional mice. The susceptibility to infection was decreased when GF mice were transplanted with fecal microbiota derived from conventional mice (Shanahan, 2002; Guarner and Malagelada, 2003; Hooper *et al.*, 2012). The physiological differences between GF and conventional mice are listed in Fig. 1 (Shanahan, 2002; Sekirov *et al.*, 2010; Tanoue *et al.*, 2010). Gut microbiota induces secretory IgA production and affects the structural development of intestinal epithelial cells (IEC) by forming firm tight junctions and developing intestinal immune system (Conte *et al.*, 2006; Khachatryan *et al.*, 2008). Furthermore, gut microbiota can effectively defend the host against pathogenic bacterial infections by producing molecules, such as bacteriocin, short-chain fatty acids (SCFAs), and hydrogen peroxide, and also, by competing with pathogens for habitats and nutrients (Guarner and Malagelada, 2003; Fujimura *et al.*, 2010; Brown *et al.*, 2013; Buffie and Pamer, 2013; Kamada *et al.*, 2013).

Intestinal infections are caused by various bacterial species, such as enterohaemorrhagic *Escherichia coli* (EHEC) (Mundy *et al.*, 2005), *Vibrio cholerae* (Bari *et al.*, 2012), *Salmonella enterica* (Seong *et al.*, 2012), and *Staphylococcus aureus* (Kwon *et al.*, 2013). However, it gets removed by 'colonization resistance' in a few days in most cases (Ferreira *et al.*, 2011; Hooper *et al.*, 2012; Kamada *et al.*, 2012; Buffie and Pamer, 2013). The mechanism by which pathogenic microbes are removed from the gut is not clearly defined, but the role of gut

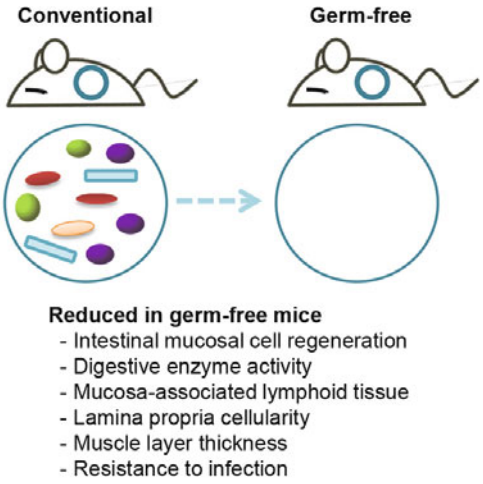

Fig. 1. The differences between germ-free mice and conventionally raised mice.

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microbes has been considered important based on the fact that host immune systems, such as complement-mediated killing, opsonophagocytosis, and T-cell-mediated toxicity, are quite ineffective in the gut environment (O'Hara and Shanahan, 2007). The gut microbes that inhabit on the mucus layer of enterocytes express a "barrier effect" that controls excessive growth of minor gut microbes and competitively inhibits colonization of foreign microbes (Ismail and Hooper, 2005). In order to have the barrier effect, gut microbes inhibit proliferation of pathogenic bacteria and promote growth of beneficial microbes using various means, such as (i) preferential occupation of the colonization site in gut, (ii) nutritional competition, (iii) production of antibacterial molecules, such as bacteriocin, (iv) inhibition of virulence factor production, and (v) induction of inflammatory responses by producing signal transducers or (vi) decreasing intestinal pH by producing organic acids through digestive conversion of macromolecules (O'Hara and Shanahan, 2007; Cerf-Bensussan and Gaboriau-Routhiau, 2010; Gareau *et al.*, 2010; Clemente *et al.*, 2012). The capabilities of the gut microbes to control infections in the host can be divided into two mechanisms; indirect inhibition through modulation of host immune systems and direct inhibition by commensal-pathogen interaction (Table 1 and Fig. 2).

Activation of host innate immune system

Gut microbes stimulate host intestinal immune system by activating the secretion of antimicrobial molecules (AMs). Defensins, LL-37 (cathelicidins), and C-type lectins can suppress microbial propagation in the intestine (Cash *et al.*, 2006; Hooper *et al.*, 2012; Tsai *et al.*, 2014). Paneth cells (PCs), located at the crypts of the small intestines, produce various kinds of AMs in response to the interaction with microbial products (Guarner and Malagelada, 2003). In particular, LL-37 expression was found to be increased by the presence of SCFAs, such as acetate (Fukuda *et al.*, 2011). Defensin, processed from pro-defensin was activated by matrilysin, a matrix metalloproteinase produced by PCs. The synthesis of matrilysin was elevated, when GF mice were colonized with *Bacteroides thetaiotaomicron* (Wilson *et al.*, 1999; Lopez-Boado *et al.*, 2000) further suggesting the role of gut commensals in activating intestinal defense system. C-type lectin, RegIIIγ, has been considered as an important determinant for intestinal innate immunity against invasive. The expression of RegIIIγ was activated, when gut microbes, isolated from conventional mice, were transplanted into GF mice and the secreted RegIIIγ exerted antimicrobial effects by binding to mannon of bacterial peptidoglycan through hip/pap (hepatocarcinoma intestine pancrease/pancreatic associated protein) (Cash *et al.*, 2006). It was shown that *Listeria monocytogenes* infection was antagonized by secretory products of commensals belonging to the genus of *Lactobacillus* and *Bifidobacterium*. Especially, these two probiotics may regulates the local immune response to *L. monocytogenes* by modulating the production of pro-inflammatory and anti-inflammatory cytokines (Corr *et al.*, 2007). In addition, *L. acidophilus* inhibited the formation of brush border lesions, caused by diarrheagenic Afa/Dr diffusely adhering *E. coli* (Afa/Dr DAEC). The number of Afa/Dr DAEC was effectively decreased when Caco-2/TC7 cells were treated with the supernatant of *L. acidophilus*. This finding was proposed to be related with an increase in F-actin, sucrose-iso-

Table 1. Summary of inhibitory effects by commensal microbes

Barrier effects	Role	Microbe	Function	References
Indirect effects	Colonization resistance	*L. rhamnosus* GG, *L. plantarum* 299v	Stimulate mucin secretion	Mack *et al.* (1999)
		L. plantarum	Strengthen tight junction integrity	Karczewski *et al.* (2010)
		SFB	Inhibit colonization of *Salmonella enteritidis* in Peyer's patches	Garland *et al.* (1982)
	Nutrition competition	*B. thetaiotaomicron*	Decrease the availability of monosaccharide for pathogen utilization	Kamada *et al.* (2012)
	Immune system development	*Lactobacillus*	Activate DC and NK cell	Corr *et al.* (2007)
		L. acidophilus	Strengthen brush border	Lievin-Le Moal *et al.* (2002)
	Inhibition of adhesion	*L. acidophilus* La-5	Inhibit EHEC O157:H7 by modulate F-actin production	Medellin-Peña and Griffiths (2009)
		SFB	Activate Th-17 cell and RegIIIγ production to repress *C. rodentium* infection	Collins *et al.* (2014)
Direct effects	Production of antimicrobial molecules	*R. gnavus* FRE1	Produce ruminococcin C to inhibit *C. perfringenes* infection	Crost *et al.* (2011)
		B. thuringiensis	Produce thuricin CD to Inhibit *C. difficile* infection	Rea *et al.* (2010)
		Lactobacillus, Bifidobacterium	Produce SCFAs to lower pH	Qin *et al.* (2010)
		Bacterial products (flagellin, LPS)	Inhibit VRE by increment of RegIIIγ	Cash *et al.* (2006)
		Bifidobacteria sp.	Activate production of LL-37	Makras and De Vuyst (2006)
		B. thetaiotaomicron	Produce matrilysin to Inhibit *S. typhimurium*	Wilson *et al.* (1999)
	Quorum sensing inhibition	*R. obeum*	Repress colonization of *V. cholerae* on intestinal mucus layer	Hsiao *et al.* (2014)

Detailed description is provided in the text. Abbreviations: Muc2, Mucin 2; *C. rodentium*, *Clostridium rodentium*; LPS, lipopolysaccharide; VRE, Vancomycin-resistant Enterococcus; RegIIIγ, Regenerating islet-derived 3 gamma; DC, Dendritic cells; NK cell, Natural killer cell; F-actin, actin filaments; LL-37, cathelicidin-derived antimicrobial peptide; Th-17 cell, T helper 17 cell.

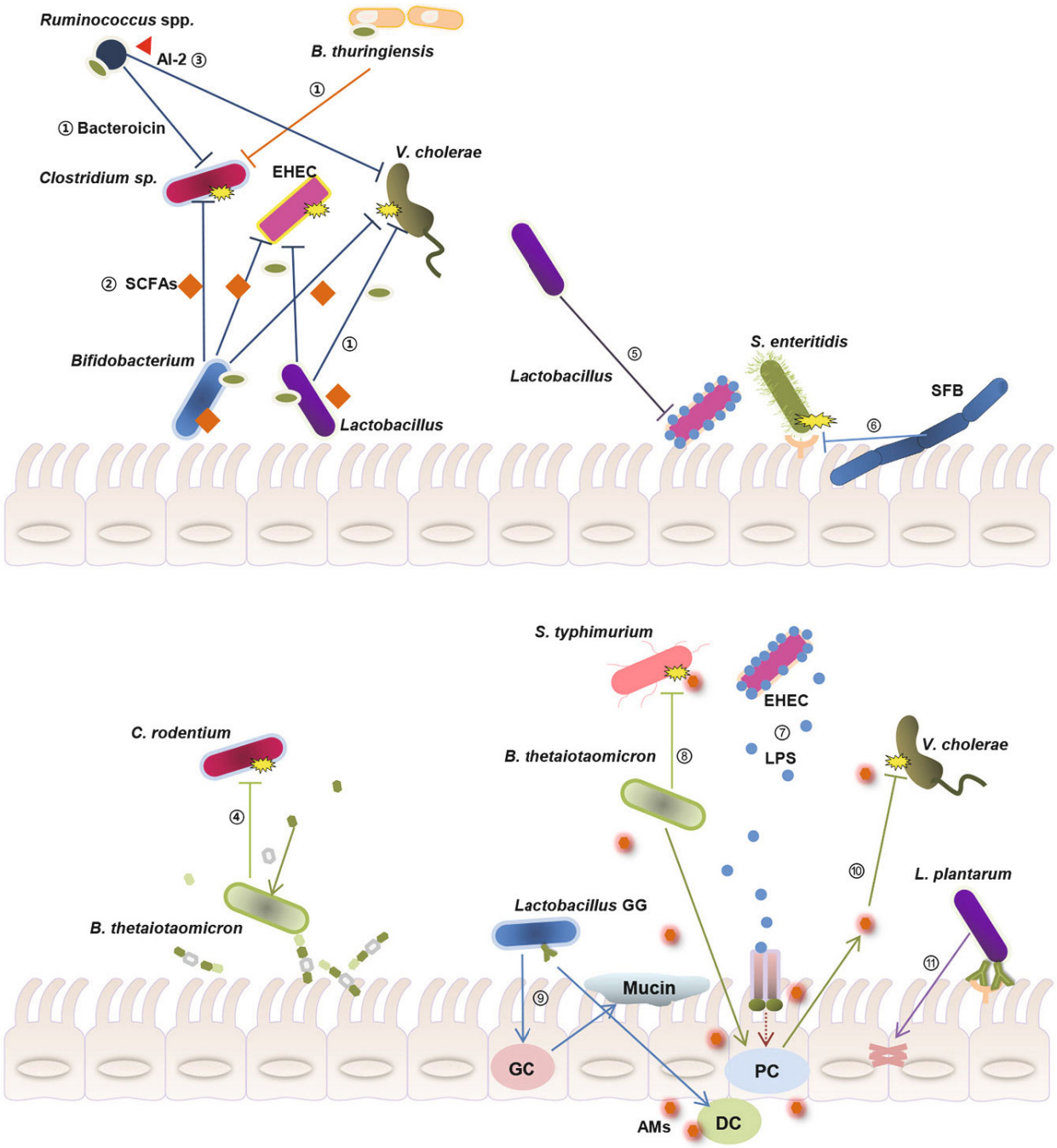

Fig. 2. Indirect and direct inhibitions of pathogen colonization by gut commensal microbes. The intestinal microbiota enhances resistance for colonization of intestinal pathogens by both direct and indirect (immune-mediated) mechanisms. Commensal microbiota prevents the proliferation and colonization of exogenous pathogens through multiple mechanisms. For examples, the microbiota produces bacteriocins and short-chain fatty acids in order to inhibit the growth of pathogens directly (① and ②). *B. thuringiensis* secretes a bacteriocin that directly targets Gram-negative bacteria and *Clostridium difficile*. Quorum sensing (QS) signals, also, inhibit the pathogen infections by regulating the QS signal transduction system of pathogens. For an instance, AI-2 of *R. obeum* represses the *V. cholerae* colonization (③). The alterations in virulence expression in the pathogens are obtained by suppressing their growth by the metabolites of gut commensal microbiota and consuming residual nutrition (④). The gut microbes, also, inhibit pathogen colonization by competing for attachment sites on epithelial cells and nutrients derived from host (⑤ and ⑥). SFB inhibits the colonization of *S. entertidis* by physically removing the pathogen from mucosa of ileum (⑥). Commensal microbiota facilitates mucosal barrier function through modulation of the host immune system. For example, *B. thetaiotaomicron* enhances expression of the peptidoglycan-binding C-type lectin, which has an antimicrobial activity (⑧). *B. thetaiotaomicron* may inhibit colonization of pathogenic bacteria through multiple mechanisms. *Lactobacillus* inhibits attachment of pathogenic *E. coli* by enhancing mucin secretion (⑨). Microbial products, such as lipopolysaccharide (LPS) and flagellin, stimulate dendritic cells (DCs) to enhance epithelial expression of REGIIIγ, which impairs colonization by *V. cholera* (⑩). *L. plantarum* induces the barrier tension by localization of tight junction-associated proteins, such as zonula occludens (ZO)-1 and occludin (⑪). Microbial LPS activates immune defenses, including nucleotide-binding oligomerization domain 2 (NOD2)-dependent cryptdin expression and extension of transepithelial dendrites. These processes enhance resistance to EHEC (⑦) and *V. cholera* (⑩). Abbreviations: GC, goblet cell; PC, paneth cell.

maltase, dipeptidylpeptidase IV, alkaline phosphatase, and fructose transporters in the cell (Lievin-Le Moal *et al.*, 2002). Gut microbes regulate the immune response through pattern-recognized receptors (PRRs), which exist in enterocytes (Kelly *et al.*, 2004). GF mice exhibited decreased expression of Nod-containing protein-2 (Nod-2) in the ileum compared to conventional mice, but the expression of Nod2 was recovered to normal levels when mice were treated with *L. plantarum* and *E. coli* Nissle 1927. This proves that the normal flora of the intestine can positively regulate the expression of Nod-2 (Philpott and Girardin, 2004; Petnicki-Ocwieja *et al.*, 2009). Eighteen percent of genes present in *B. thetaiomicron* genome were annotated to be involved in polysaccharide utilization, which helps the bacteria to catabolize indigestible carbohydrates to SCFAs (Sonnenburg *et al.*, 2005). The SCFAs, produced by *Lactobacillus* spp. and *Bifidobacteria* spp. can regulate signal transduction and induce anti-inflammatory responses through neutrophil and eosinophil regulation (Maslowski *et al.*, 2009). Together, these findings clearly demonstrate the critical role of commensal microbes in shaping intestinal immune system.

Inhibition of pathogen colonization

Upon infection with pathogenic bacteria, the commensal gut microbes start to compete with them for intestinal colonization. Pathogens can establish persistent infection, when normal composition of gut microbiota was compromised, even in the presence of functional immune responsiveness (Isolauri, 2003; Kamada *et al.*, 2013). Secretory IgA (sIgA) displays a specific response to O-antigen of Gram-negative bacteria inhibiting the colonization of pathogens on the intestinal mucus layer. However, sIgA alone cannot exhibit sufficient inhibitory effects, when balanced composition of gut microbiota was disrupted (Synnott *et al.*, 2009). Therefore, commensal microbes are essentially required for colonization resistance. The sIgA can also modulate gut microbiota composition. For example, intestinal colonization of specific pathogens was increased in the sIgA-deficient mice and this was likely due to the change in gut microbiota population. The composition of the gut microbiota was recovered to normal, when sIgA production was supplemented (Endt *et al.*, 2010). This indicates that production of the immunological substance by gut-associated lymphoid tissue (GALT) is closely related with the balanced maintenance of gut microbes. Commensal bacteria belonging to the genus of *Lactobacillus* and *Bifidobacterium* can effectively colonize enterocytes by secreting glycoproteins and therefore contribute to control the colonization of pathogenic bacteria (He *et al.*, 2001). Segmented filamentous bacteria (SFB) in the ileum control the attachment of *Salmonella enteritidis* by physically interfering with its attachment to Peyer's patches (Garland *et al.*, 1982).

Some bacterial species, isolated from the gut, can enhance the intestinal defense against pathogens by promoting the production of mucin (Johansson *et al.*, 2008). The well-known probiotic strains, *Lactobacillus rhamnosus* GG and *Lactobacillus plantarum* 299v inhibit adherence of pathogenic *E. coli* on enterocytes (HT-29 cells), but not on squamous epithelial cells (HEp-2 cells). The HT-29 cells secreted the specific mucin proteins, MUC2 and MUC3 and *L. plantarum* 299v was reported to increase the expression of genes coding for these proteins (Mack *et al.*, 1999) suggesting that probiotic-induced enhancement of mucin production is necessary for the optimal colonization resistance. The commensals, such as *E. coli* and *B. thetaiotaomicron* are capable of inhibiting *C. rodentium* infection. These two probiotic strains were found to compete with *C. rodentium* for structurally similar carbohydrates, thereby suggesting that *C. rodentium* infection can be controlled by the elevated abundance of commensals that exhibit analogous metabolic capabilities with *C. rodentium* (Kamada *et al.*, 2012). Pathogenic microbes often produce exotoxins during intestinal invasion, which can destroy the tight junctions between epithelial cells. Some commensal microbes, however, protect epithelial barrier function by making tight junctions even tighter. In healthy human subjects treated with *L. plantarum*, production of zonula occludens (ZO)-1 and occludin, two protein components forming the paracellular seal between intestinal epithelial cells, was significantly increased (Karczewski *et al.*, 2010).

Production of antimicrobial substances

Some gut microbes produce various antimicrobial substances, such as organic acids, hydrogen peroxide and bacteriocin that can effectively inhibit Gram-positive and -negative bacterial growth (Cerf-Bensussan and Gaboriau-Routhiau, 2010; Brown *et al.*, 2013). These substances not only inhibit growth of pathogens, but also control metabolism and toxin production of pathogens. For instance, gut microbes that belong to the genus of *Bifidobacterium* or *Lactobacillus* can alter the intestinal pH environment by producing organic acids including SCFAs, lactic acid, propionic acid, and butyric acid (Gareau *et al.*, 2010; Fukuda *et al.*, 2011; Kim *et al.*, 2014). It was revealed that acetate produced by *Bifidobacterium* species plays a critical role in protecting mouse from lethal infection by *E. coli* O157:H7 (Fukuda *et al.*, 2011). Such a protection was mediated by bacterial capability to inhibit shiga toxin (Stx) transport from intestinal lumen to the blood and was not observed when using a mutant strain defective in acetate production.

Microbes belonging to the genus of *Lactobacillus* can inhibit various pathogens by lactic acid production. The *Lactobacillus* species also produces various antimicrobial substances besides lactic acid. The supernatant of the *L. acidophilus* strain La-5 inhibited colonization of *E. coli* O157:H7 by altering the F-actin at the adhesion site and affected transcription of genes involved in quorum sensing (Medellin-Pena and Griffiths, 2009). Further, it was often observed that bacteriocin produced by gut commensals exerted bactericidal activity against invading pathogens. *Ruminococcus guavas* FRE1 produces ruminocuccin A, a lantibiotic bacteriocin, which can perturb the settlement of *Clostridium perfuringens* (Gomez *et al.*, 2002). It is of particular interest that the ruminicussin A is resistant to the proteolytic action of trypsin. This unique property clearly shows that *R. guavas* can adapt to the host environment in order to antagonize the infectivity of pathogens (Marcille *et al.*, 2002).

Regulation of gut microbiota community by quorum sensing

Quorum sensing (QS) is a cell-density dependent gene reg-

ulatory mechanism in bacteria (Yang *et al.*, 2012; Zhao *et al.*, 2013). QS is mediated by chemical compounds called autoinducer (AI) (Lee *et al.*, 2011) and it regulates both intra-species and inter-species communication (Bassler, 1999). It remains unclear whether or not QS plays a role in maintaining a complex multi-species microbial community in the intestine. Host-derived hormones, such as epinephrine (EPI) or norepinephrine (NE) were reported to affect various physiological status of commensal microbes (Sperandio *et al.*, 2003). In EHEC, expression of the locus of enterocyte effacement (LEE) gene, an important genetic determinant for virulence is promoted by AI-3, a QS regulator. Furthermore, its expression was found to increase due to the interaction with host EPI and NE through QseC and QseE, known adrenergic receptors (Sperandio *et al.*, 2003; Clarke *et al.*, 2006).

Pathogenic bacteria can also employ QS to assess relative abundance of other commensal species in the intestine. For example, EHEC can recognize AHLs produced by other bacteria using SdiA, a transcription factor involved in QS. Moreover, *E. coli* Nissle 1917 produces AI-2 in the gut (Jacobi *et al.*, 2012). The AI-2 was reported to inhibit expression of IFN-γ in mice with gastritis (Sperandio, 2010). On the other hand, it was also reported that a Gram-positive bacterium, *Bacillus* sp. 240B1, can degrade the AHL of the Gram-negative bacteria, *Erwinia caratovora* (Dong *et al.*, 2000). Recently, in mice infected with *V. cholerae*, increased abundance of *Ruminococcus obeum* was observed. AI-2 synthase, *luxS* expression levels and AI-2 production of *R. obeum* were significantly increased with *V. cholerae* invasion. The AI-2 repress several *V. cholerae* colonization factors via a novel pathway of *V. cholerae* QS system (Hsiao *et al.*, 2014). Together, QS appears to play a role in regulating gut microbiota populations and disturbance of a particular QS system can lead to the community change.

Conclusions

An unbalanced composition of gut microbiota is known to cause IBD, such as Crohn's disease or ulcerative colitis (UC) and absence of or improperly balanced gut microbiota seem to be the major cause of decreased defense against external pathogens (Conte *et al.*, 2006). The defense mechanisms against invaders consist of three major systems, (i) gut microbiota, (ii) mucosa of the intestines, and (iii) intestinal epithelial cells (Brown *et al.*, 2013). Therefore, it is very important to understand the defense mechanisms of gut microbiota, but it is still unknown how these mechanisms form, and how effective they are for defense. According to recent studies, non-pathogenic microbes effectively control pathogens by antimicrobial substance production, competition for nutrition and space, proper regulation of the host immune system and so on, while dwelling inside of the host's GI tract. This defense mechanism occurs through close interaction with the immune system of the enterocytes (Cerf-Bensussan and Gaboriau-Routhiau, 2010; Clemente *et al.*, 2012). Interestingly, *E. coli* can act as a member of the normal flora, but can be pathogenic at the same time (Kamada *et al.*, 2013). In addition, understanding the phenomenon and etiology can be a clue to understand the interaction between pathogens and gut microbes. It is important to study the competition and mutual cooperation among gut microbiota and their control mechanisms to understand the causes and conditions of infectious disease. Therefore, future research on the interactions between pathogens, hosts, and gut microbiota should focus on predicting proper therapies for infectious diseases. Understanding the tripartite interactions between the host immune system, gut microbes and pathogens will be crucial when developing effective therapies for the enteric infections.

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References

Backhed, F., Ley, R.E., Sonnenburg, J.L., Peterson, D.A., and Gordon, J.I. 2005. Host-bacterial mutualism in the human intestine. *Science* **307**, 1915–1920.

Bari, W., Lee, K.M., and Yoon, S.S. 2012. Structural and functional importance of outer membrane proteins in *Vibrio cholerae* flagellum. *J. Microbiol.* **50**, 631–637.

Bassler, B.L. 1999. How bacteria talk to each other: Regulation of gene expression by quorum sensing. *Curr. Opin. Microbiol.* **2**, 582–587.

Brown, E.M., Sadarangani, M., and Finlay, B.B. 2013. The role of the immune system in governing host-microbe interactions in the intestine. *Nat. Immunol.* **14**, 660–667.

Buffie, C.G. and Pamer, E.G. 2013. Microbiota-mediated colonization resistance against intestinal pathogens. *Nat. Rev. Immunol.* **13**, 790–801.

Cash, H.L., Whitham, C.V., Behrendt, C.L., and Hooper, L.V. 2006. Symbiotic bacteria direct expression of an intestinal bactericidal lectin. *Science* **313**, 1126–1130.

Cerf-Bensussan, N. and Gaboriau-Routhiau, V. 2010. The immune system and the gut microbiota: friends or foes? *Nat. Rev. Immunol.* **10**, 735–744.

Clarke, M.B., Hughes, D.T., Zhu, C., Boedeker, E.C., and Sperandio, V. 2006. The QseC sensor kinase: A bacterial adrenergic receptor. *Proc. Natl. Acad. Sci. USA* **103**, 10420–10425.

Clemente, J.C., Ursell, L.K., Parfrey, L.W., and Knight, R. 2012. The impact of the gut microbiota on human health: An integrative view. *Cell* **148**, 1258–1270.

Collins, J.W., Keeney, K.M., Crepin, V.F., Rathinam, V.A.K., Fitzgerald, K.A., Finlay, B.B., and Frankel, G. 2014. *Citrobacter rodentium*: Infection, inflammation and the microbiota. *Nat. Rev. Microbiol.* **12**, 612–623.

Conte, M.P., Schippa, S., Zamboni, I., Penta, M., Chiarini, F., Seganti, L., Osborn, J., Falconieri, P., Borrelli, O., and Cucchiara, S. 2006. Gut-associated bacterial microbiota in paediatric patients with inflammatory bowel disease. *Gut* **55**, 1760–1767.

Corr, S.C., Gahan, C.G., and Hill, C. 2007. Impact of selected *Lactobacillus* and *Bifidobacterium* species on *Listeria monocytogenes* infection and the mucosal immune response. *FEMS Immunol. Med. Microbiol.* **50**, 380–388.

Crost, E.H., Ajandouz, E.H., Villard, C., Geraert, P.A., Puigserver, A., and Fons, M. 2011. Ruminococcin C, a new anti-*Clostridium*

perfringens bacteriocin produced in the gut by the commensal bacterium *Ruminococcus gnavus* E1. *Biochimie* **93**, 1487–1494.

Dong, Y.H., Xu, J.L., Li, X.Z., and Zhang, L.H. 2000. AiiA, an enzyme that inactivates the acylhomoserine lactone quorum-sensing signal and attenuates the virulence of *Erwinia carotovora*. *Proc. Natl. Acad. Sci. USA* **97**, 3526–3531.

Eckburg, P., Bik, E., Bernstein, C., Purdom, E., Dethlefsen, L., Sargent, M., Gill, S., Nelson, K., and Relman, D. 2005. Diversity of the human intestinal microbial flora. *Science* **308**, 1635–1638.

Endt, K., Stecher, B., Chaffron, S., Slack, E., Tchitchek, N., Benecke, A., Van Maele, L., Sirard, J.C., Mueller, A.J., Heikenwalder, M., and *et al.* 2010. The microbiota mediates pathogen clearance from the gut lumen after non-typhoidal *Salmonella* diarrhea. *PLoS Pathog.* **6**, e1001097.

Ferreira, R.B.R., Gill, N., Willing, B.P., Antunes, L.C.M., Russell, S.L., Croxen, M.A., and Finlay, B.B. 2011. The intestinal microbiota plays a role in *Salmonella*-induced colitis independent of pathogen colonization. *PLoS One* **6**, e20338.

Fujimura, K.E., Slusher, N.A., Cabana, M.D., and Lynch, S.V. 2010. Role of the gut microbiota in defining human health. *Expert Rev. Anti-infective Ther.* **8**, 435–454.

Fukuda, S., Toh, H., Hase, K., Oshima, K., Nakanishi, Y., Yoshimura, K., Tobe, T., Clarke, J.M., Topping, D.L., Suzuki, T., and *et al.* 2011. Bifidobacteria can protect from enteropathogenic infection through production of acetate. *Nature* **469**, 543–547.

Gareau, M.G., Sherman, P.M., and Walker, W.A. 2010. Probiotics and the gut microbiota in intestinal health and disease. *Nat. Rev. Gastroenterol Hepatol.* **7**, 503–514.

Garland, C., Lee, A., and Dickson, M. 1982. Segmented filamentous bacteria in the rodent small intestine: Their colonization of growing animals and possible role in host resistance to Salmonella. *Microb. Ecol.* **8**, 181–190.

Gomez, A., Ladiré, M., Marcille, F., and Fons, M. 2002. Trypsin mediates growth phase-dependent transcriptional regulation of genes involved in biosynthesis of ruminococcin A, a lantibiotic produced by a *Ruminococcus gnavus* strain from a human intestinal microbiota. *J. Bacteriol.* **184**, 18–28.

Guarner, F. and Malagelada, J.R. 2003. Gut flora in health and disease. *Lancet* **361**, 512–519.

He, F., Ouwehan, A.C., Hashimoto, H., Isolauri, E., Benno, Y., and Salminen, S. 2001. Adhesion of *Bifidobacterium* spp. to human intestinal mucus. *Microbiol. Immunol.* **45**, 259–262.

Hooper, L.V., Littman, D.R., and Macpherson, A.J. 2012. Interactions between the microbiota and the immune system. *Science* **336**, 1268–1273.

Hsiao, A., Ahmed, A.M.S., Subramanian, S., Griffin, N.W., Drewry, L.L., Petri, W.A., Haque, R., Ahmed, T., and Gordon, J.I. 2014. Members of the human gut microbiota involved in recovery from *Vibrio cholerae* infection. *Nature.* doi: 10.1038/nature13738.

Ismail, A. and Hooper, L. 2005. Epithelial cells and their neighbors. Iv. Bacterial contributions to intestinal epithelial barrier integrity. *Am. J. Physiol. Gastrointest Liver Physiol.* **289**, G779–G784.

Isolauri, E. 2003. Probiotics for infectious diarrhoea. *Gut* **52**, 436–437.

Jacobi, C., Grundler, S., Hsieh, C.J., Frick, J.S., Adam, P., Lamprecht, G., Autenrieth, I., Gregor, M., and Malfertheiner, P. 2012. Quorum sensing in the probiotic bacterium *Escherichia coli* Nissle 1917 (Mutaflor) - evidence that furanosyl borate diester (Ai-2) is influencing the cytokine expression in the DSS colitis mouse model. *Gut Pathog.* **4**, 8.

Johansson, M.E.V., Phillipson, M., Petersson, J., Velcich, A., Holm, L., and Hansson, G.C. 2008. The inner of the two Muc2 mucin-dependent mucus layers in colon is devoid of bacteria. *Proc. Natl. Acad. Sci. USA* **105**, 15064–15069.

Kamada, N., Chen, G.Y., Inohara, N., and Nunez, G. 2013. Control of pathogens and pathobionts by the gut microbiota. *Nat. Immunol.* **14**, 685–690.

Kamada, N., Kim, Y.G., Sham, H.P., Vallance, B.A., Puente, J.L., Martens, E.C., and Núñez, G. 2012. Regulated virulence controls the ability of a pathogen to compete with the gut microbiota. *Science* **336**, 1325–1329.

Karczewski, J., Troost, F.J., Konings, I., Dekker, J., Kleerebezem, M., Brummer, R.J., and Wells, J.M. 2010. Regulation of human epithelial tight junction proteins by *Lactobacillus plantarum in vivo* and protective effects on the epithelial barrier. *Am. J. Physiol. Gastrointest Liver Physiol.* **298**, G851–859.

Kelly, D., Campbell, J.I., King, T.P., Grant, G., Jansson, E.A., Coutts, A.G., Pettersson, S., and Conway, S. 2004. Commensal anaerobic gut bacteria attenuate inflammation by regulating nuclear-cytoplasmic shuttling of PPAR-gamma and RelA. *Nat. Immunol.* **5**, 104–112.

Khachatryan, Z.A., Ktsoyan, Z.A., Manukyan, G.P., Kelly, D., Ghazaryan, K.A., and Aminov, R.I. 2008. Predominant role of host genetics in controlling the composition of gut microbiota. *PLoS One* **3**, e3064.

Kim, J.E., Kim, M.S., Yoon, Y.S., Chung, M.J., and Yum, D.Y. 2014. Use of selected lactic acid bacteria in the eradication of *Helicobacter pylori* infection. *J. Microbiol.* **52**, 955–962.

Kwon, A.S., Lim, D.H., Shin, H.J., Park, G., Reu, J.H., Park, H.J., Kim, J., and Lim, Y. 2013. The N3 subdomain in a domain of fibronectin-binding protein B isotype I is an independent risk determinant predictive for biofilm formation of *Staphylococcus aureus* clinical isolates. *J. Microbiol.* **51**, 499–505.

Lee, K.M., Yoon, M.Y., Park, Y., Lee, J.H., and Yoon, S.S. 2011. Anaerobiosis-induced loss of cytotoxicity is due to inactivation of quorum sensing in *Pseudomonas aeruginosa*. *Infect. Immun.* **79**, 2792–2800.

Lievin-Le Moal, V., Amsellem, R., Servin, A.L., and Coconnier, M.H. 2002. *Lactobacillus acidophilus* (strain LB) from the resident adult human gastrointestinal microflora exerts activity against brush border damage promoted by a diarrhoeagenic *Escherichia coli* in human enterocyte-like cells. *Gut* **50**, 803–811.

Lopez-Boado, Y.S., Wilson, C.L., Hooper, L.V., Gordon, J.I., Hultgren, S.J., and Parks, W.C. 2000. Bacterial exposure induces and activates matrilysin in mucosal epithelial cells. *J. Cell Biol.* **148**, 1305–1315.

Mack, D.R., Michail, S., Wei, S., McDougall, L., and Hollingsworth, M.A. 1999. Probiotics inhibit enteropathogenic *E. coli* adherence *in vitro* by inducing intestinal mucin gene expression. *Am. J. Physiol.* **276**, G941–950.

Makras, L. and De Vuyst, L. 2006. The *in vitro* inhibition of Gram-negative pathogenic bacteria by bifidobacteria is caused by the production of organic acids. *Intl. Dairy J.* **16**, 1049–1057.

Marcille, F., Gomez, A., Joubert, P., Ladiré, M., Veau, G., Clara, A., Gavini, F., Willems, A., and Fons, M. 2002. Distribution of genes encoding the trypsin-dependent lantibiotic ruminococcin a among bacteria isolated from human fecal microbiota. *Appl. Environ. Microbiol.* **68**, 3424–3431.

Maslowski, K.M., Vieira, A.T., Ng, A., Kranich, J., Sierro, F., Yu, D., Schilter, H.C., Rolph, M.S., Mackay, F., Artis, D., and *et al.* 2009. Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. *Nature* **461**, 1282–1286.

Medellin-Peña, M.J. and Griffiths, M.W. 2009. Effect of molecules secreted by *Lactobacillus acidophilus* strain La-5 on *Escherichia coli* O157:H7 colonization. *Appl. Environ. Microbiol.* **75**, 1165–1172.

Mundy, R., MacDonald, T.T., Dougan, G., Frankel, G., and Wiles, S. 2005. *Citrobacter rodentium* of mice and man. *Cell. Microbiol.* **7**, 1697–1706.

Nava, G.M. and Stappenbeck, T.S. 2011. Diversity of the autochthonous colonic microbiota. *Gut Microbes* **2**, 99–104.

O'Hara, A.M. and Shanahan, F. 2007. Gut microbiota: Mining for therapeutic potential. *Clin. Gastroenterol. Hepatol.* **5**, 274–284.

Petnicki-Ocwieja, T., Hrncir, T., Liu, Y.J., Biswas, A., Hudcovic,

T., Tlaskalova-Hogenova, H., and Kobayashi, K.S. 2009. Nod2 is required for the regulation of commensal microbiota in the intestine. *Proc. Natl. Acad. Sci. USA* **106**, 15813–15818.

Philpott, D. and Girardin, S. 2004. The role of toll-like receptors and nod proteins in bacterial infection. *Mol. Immunol.* **41**, 1099–1108.

Qin, J., Li, R., Raes, J., Arumugam, M., Burgdorf, K.S., Manichanh, C., Nielsen, T., Pons, N., Levenez, F., Yamada, T., and *et al.* 2010. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* **464**, 59–65.

Rea, M.C., Sit, C.S., Clayton, E., O'Connor, P.M., Whittal, R.M., Zheng, J., Vederas, J.C., Ross, R.P., and Hill, C. 2010. Thuricin Cd, a posttranslationally modified bacteriocin with a narrow spectrum of activity against *Clostridium difficile*. *Proc. Natl. Acad. Sci. USA* **107**, 9352–9357.

Sekirov, I., Russell, S.L., Antunes, L.C.M., and Finlay, B.B. 2010. Gut microbiota in health and disease. *Physiol. Rev.* **90**, 859–904.

Seong, W.J., Kwon, H.J., Kim, T.E., Lee, D.Y., Park, M.S., and Kim, J.H. 2012. Molecular serotyping of *Salmonella enterica* by complete *rpoB* gene sequencing. *J. Microbiol.* **50**, 962–969.

Shanahan, F. 2002. The host–microbe interface within the gut. *Best Pract. Res. Clin. Gastroenterol.* **16**, 915–931.

Sonnenburg, J.L., Xu, J., Leip, D.D., Chen, C.H., Westover, B.P., Weatherford, J., Buhler, J.D., and Gordon, J.I. 2005. Glycan foraging *in vivo* by an intestine-adapted bacterial symbiont. *Science* **307**, 1955–1959.

Sperandio, V. 2010. SdiA sensing of acyl-homoserine lactones by enterohemorrhagic *E. coli* (EHEC) serotype O157:H7 in the bovine rumen. *Gut Microbes* **1**, 432–435.

Sperandio, V., Torres, A.G., Jarvis, B., Nataro, J.P., and Kaper, J.B. 2003. Bacteria–host communication: The language of hormones. *Proc. Natl. Acad. Sci. USA* **100**, 8951–8956.

Synnott, A., Ohshima, K., Nakai, Y., and Tanji, Y. 2009. IgA response of BALB/c mice to orally administered *Salmonella typhimurium* flagellin-displaying T2 bacteriophages. *Biotechnol. Prog.* **25**, 552–558.

Tanoue, T., Umesaki, Y., and Honda, K. 2010. Immune responses to gut microbiota-commensals and pathogens. *Gut Microbes* **1**, 224–233.

Tsai, P.W., Cheng, Y.L., Hsieh, W.P., and Lan, C.Y. 2014. Responses of *Candida albicans* to the human antimicrobial peptide ll-37. *J. Microbiol.* **52**, 581–589.

Wilson, C.L., Ouellette, A.J., Satchell, D.P., Ayabe, T., López-Boado, Y.S., Stratman, J.L., Hultgren, S.J., Matrisian, L.M., and Parks, W.C. 1999. Regulation of intestinal α-defensin activation by the metalloproteinase matrilysin in innate host defense. *Science* **286**, 113–117.

Yang, Y.X., Xu, Z.H., Zhang, Y.Q., Tian, J., Weng, L.X., and Wang, L.H. 2012. A new quorum-sensing inhibitor attenuates virulence and decreases antibiotic resistance in *Pseudomonas aeruginosa*. *J. Microbiol.* **50**, 987–993.

Yoon, M.Y., Lee, K.M., Yoon, Y., Go, J., Park, Y., Cho, Y.J., Tannock, G.W., and Yoon, S.S. 2013. Functional screening of a metagenomic library reveals operons responsible for enhanced intestinal colonization by gut commensal microbes. *Appl. Environ. Microbiol.* **79**, 3829–3838.

Zhao, Z.G., Yan, S.S., Yu, Y.M., Mi, N., Zhang, L.X., Liu, J., Li, X.L., Liu, F., Xu, J.F., Yang, W.Q., and Li, G.M. 2013. An aqueous extract of Yunnan Baiyao inhibits the quorum-sensing-related virulence of *Pseudomonas aeruginosa*. *J. Microbiol.* **51**, 207–212.