Published in final edited form as:

Curr Opin Microbiol. 2013 February ; 16(1): 4–9. doi:10.1016/j.mib.2012.12.002.

The dynamic influence of commensal bacteria on the immune response to pathogens

Michael C. Abt¹ and David Artis^{1,2,3}

¹Department of Microbiology and Institute for Immunology, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

²Department of Pathobiology, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

Abstract

Alterations in the composition of commensal bacterial communities are associated with enhanced susceptibility to multiple inflammatory, allergic, metabolic and infectious diseases in humans. In the context of infection, commensal bacteria-derived signals can influence the host immune response to invasive pathogens by acting as an adjuvant to boost the immune response to infection or by providing tonic stimulation to induce basal expression of factors required for host defense. Conversely, some pathogens have evolved mechanisms that can utilize commensal bacteria to establish a replicative advantage within the host. Thus, examining the dynamic relationship that exists between the mammalian host, commensal bacteria and invasive pathogens can provide insights into the etiology of pathogenesis from an infection.

Keywords

commensal bacteria; intestinal microbiota; virus; bacteria; infection; immune response

Introduction

Microbial colonization of mammalian barrier surfaces, including the skin, mouth, nasopharynx, vaginal, and gastrointestinal tracts begins immediately following birth and a symbiotic relationship is established between the colonizing bacterial communities and the host organism [1-4]. Dysbiosis of commensal bacterial communities, however, is linked to various disease states in humans, such as obesity [5], inflammatory bowel disease [6], cancer [7,8], and atopic disorders [9]. These clinical observations highlight the need to better understand how commensal bacterial communities shape susceptibility to disease. Studies using murine model systems demonstrate that manipulation of commensal bacterial communities can alter immune cell development and homeostasis, and that specific commensal bacteria-derived products can shape immune cell differentiation and function both within the intestinal tract and in peripheral tissues [10,11]. As the role of commensal bacteria in shaping immune cell function in the steady-state has been extensively discussed by several recently published reviews [11-14], the focus of this review article will be to

© 2013 Elsevier Ltd. All rights reserved.

³CORRESPONDENCE: David Artis, dartis@mail.med.upenn.edu 215.898.7920 (P), 215.573.7945 (F).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

describe the impact of commensal bacteria-derived signaling on the immune response to invading bacterial, parasitic and viral pathogens. The review will discuss the different roles commensal bacteria have in shaping the immune response to pathogens located within the intestinal microenvironment, at other barrier surfaces, and in peripheral tissues.

Commensal bacterial communities influence the immune response to infection

Early studies employing various infection models in the germ-free (GF) mouse system identified significantly impaired host immune responses to pathogens in the absence of commensal bacteria [15]. However, the cause for the diminished immune response in these studies remained unclear due to inherent developmental and maturation defects in the immune system of GF mice. To better understand whether commensal bacterial communities have ongoing roles in orchestrating immune responses required for defense against pathogens, recent studies have employed antibiotic (ABX) -mediated manipulation of commensal bacteria in adult mice born and reared in the presence of normal commensal bacterial communities. These approaches have demonstrated that commensal bacteria can directly interact with both immune cells and pathogens, creating a dynamic relationship that contributes to determining the pathogenesis and outcome of infection. Whether these interactions benefit the host or pathogen is dependent on a combination of factors including the nature of commensal bacterial-derived signals, the class of pathogen and the anatomical location of the infection.

Host - commensal bacteria - pathogen interactions within the gastrointestinal microenvironment

Intestinal commensal bacterial communities have a significant role in host defense by colonizing the intestinal lumen and competing with other potentially pathogenic organisms for the environmental niche [15,16]. Loss or perturbation of intestinal commensal bacterial communities can lead to improved infectivity by pathogenic bacteria. For example, GF mice infected with the murine enteropathogenic bacterium *Citrobacter rodentium* do not clear the bacteria, an observation attributed to the ability of *C. rodentium* to fill an environmental niche in the lumen of the intestine that is otherwise occupied by indigenous commensal bacteria [17]. This phenomenon is not unique to the GF mouse system, as several studies have reported that pre-treatment with antibiotics can increase the ability of invasive bacterial pathogens such as *Salmonella* and *C. rodentium* to establish an infection, resulting in increased host susceptibility and more severe infection-induced intestinal inflammation [18-21]. These findings are mirrored in clinical settings where long-term antibiotic treatment can lead to outgrowth of antibiotic-resistant, life-threatening, invasive bacteria such as vancomycin-resistant *Enterococcus* or *Clostridium difficile* [22-25]. Thus, maintaining a diverse composition of commensal bacteria in the intestine is important in limiting the potential for invasive bacterial pathogens to establish infections within the intestinal microenvironment.

In addition to preventing colonization by pathogenic bacteria, signals derived from commensal bacterial communities can enhance expression of host defense genes within the intestinal tract. In a series of studies by Hooper and colleagues, commensal bacteria-derived signals were found to be critical for expression of RegIII γ , an antimicrobial lectin that is secreted into the intestinal lumen by epithelial cells and kills Gram-positive bacteria by binding to peptidoglycans exposed on the surface of the bacteria [26-28]. Loss of commensal bacteria-induced RegIII γ expression led to increased bacterial dissemination and susceptibility to bacterial pathogens such as *Salmonella typhimurium* [29] or

vancomycin-resistant *Enterococcus* [30]. Further, commensal bacteria-derived products can stimulate immune cells and boost the magnitude of the immune response against an intestinal pathogen. For example, segmented filamentous bacteria (SFB), a class of commensal bacteria that drives CD4⁺ T_H17 cell differentiation in the intestine [31], has a protective role following infection with *C. rodentium* [31]. Clearance of *C. rodentium*, which induces a robust T_H17 immune response [32], was enhanced in mice colonized with SFB compared to mice lacking SFB as part of their natural intestinal microbiota. Thus, commensal bacterial stimulation of immune and non-immune cells along the intestinal tract results in the mutually beneficial consequence of limiting expansion of invasive bacteria, which are potential competitors with non-invasive commensal bacteria in the intestinal environmental niche.

Commensal bacteria can also augment the ongoing immune response to intestinal parasitic infections. Belkaid and colleagues observed that mice depleted of commensal bacterial communities via oral ABX treatment exhibited a diminished CD4⁺ T cell response and increased parasite burden following infection with the intestinal protozoan, *Encephalitozoon cuniculi* [33]. The immune response and ability to clear the protozoa were restored in the ABX-treated mice by supplementing mice with commensal bacterial-derived DNA or the TLR9 ligand CpG, indicating that commensal bacteria-derived products can have an adjuvant-like effect on the immune response and aid in formation of protective immunity to protozoans [33]. ABX-mediated depletion of commensal bacteria also revealed a critical role for commensal bacteria-driven stimulation of intestinal dendritic cells that are important in priming protective CD4⁺ T_H1 cell immune response following intestinal infection with *Toxoplasma gondii* [34]. Collectively, these studies suggest that commensal bacteria communities can act as a natural adjuvant that augments the immune response to intestinal infection and thereby enhances the quality of the immune response and accelerates pathogen clearance.

While commensal bacteria can enhance immunity against enteric bacterial and protozoan pathogens, other classes of pathogens have evolved to incorporate commensal bacteria-derived signals as a critical component of the pathogen's replication and transmission life cycle. In the case of the parasitic helminth, *Trichuris muris*, the hatching of embryonated eggs is partially dependent on type I fimbriae from commensal bacteria binding to proteins on the surface of the egg. Further, the establishment of *T. muris* infection in the large intestine of mice is impaired following ABX-mediated disruption of commensal bacterial communities [35]. In addition, two seminal studies have demonstrated that successful establishment of enteric viral infection is dependent on the presence of intestinal commensal bacteria [36,37]. GF or ABX-treated mice orally challenged with mouse mammary tumor virus (MMTV) [36], poliovirus or reovirus [37] exhibited reduced viral infectivity and pathogenesis compared to conventionally-reared (CNV) mice. Pfeiffer and colleagues demonstrated that virus binding to polysaccharides derived from commensal bacteria was necessary to establish a productive infection in the intestinal tract [37]. Further, in the case of MMTV infection, Kane et al. suggested that commensal bacteria-driven induction of IL-10 via the TLR-4/MyD88 signaling pathway created an environment permissive to MMTV transmission, indicating that immunoregulatory signals from commensal bacteria can be used by pathogens to evade immune defense mechanisms [36]. Dependence on signals derived from commensal bacteria to establish a viral infection appears to be restricted to the intestinal microenvironment as systemic inoculation of the virus resulted in an equivalent infection between CNV and GF mice [36]. Thus, some invasive intestinal pathogens have evolved to utilize commensal bacterial-derived signals to gain a competitive advantage over the host immune response. Collectively, these reports demonstrate the dynamic role commensal bacterial communities have in balancing infectious disease pathogenesis in the gastrointestinal microenvironment (Figure 1).

Host - commensal bacteria - pathogen interactions at other barrier surfaces

Commensal bacterial communities located at extra-intestinal barrier surfaces can also modulate the immune response to pathogens that infect at distinct anatomical locations. For example, GF mice infected with *Leishmania major* fail to heal skin lesions and exhibit increased parasite burden compared to CNV mice [38]. Belkaid and colleagues determined that immunity to *L. major* infection was restored in GF mice following colonization with a skin-resident commensal bacteria but not following colonization with intestinal bacterial communities, demonstrating that commensal bacterial communities residing at distinct anatomical locations can influence host-pathogen interactions [39]. Skin-resident commensal bacteria-driven activation of the IL-1 signaling pathway mediated induction of the CD4⁺ T_H1 cell response and mediated protection following infection [39]. Commensal bacteria-driven IL-1 β production via inflammasome activation may be a common mechanism through which commensal bacteria influence the immune response to infection. ABX-mediated disruption of commensal bacterial communities led to an impaired innate immune response following influenza virus infection, characterized by diminished induction of proinflammatory cytokines and chemokines critical in initiating the host's antiviral immune response, including inflammasome-dependent IL-1 β [40,41]. These defects in the early innate immune response to influenza virus infection in ABX-treated mice had a cascading effect that led to a diminished influenza-virus specific adaptive immune response, delayed viral clearance, exacerbated pulmonary damage and ultimately increased host mortality [40,41]. The composition of commensal bacterial communities of the upper respiratory tract, as well as the intestinal tract, was dramatically altered following antibiotic treatment [40,41]. However, whether protective immunity against influenza virus infection is dependent on signals derived from commensal bacteria of the upper respiratory tract, the intestine, or a combination of both remains to be determined. These reports demonstrate that commensal bacterial communities are important in mediating immunity to infection at multiple barrier surfaces such as the skin and lung, in addition to the intestinal mucosa.

Host - commensal bacteria interactions calibrate the immune response to systemic pathogens

The important role of commensal bacterial communities in shaping the immune response to systemic pathogens that are not in direct contact with commensal bacteria has only recently been appreciated, and the mechanisms through which commensal bacteria elicit this effect remain incompletely understood. For example, GF mice were reported to exhibit impaired clearance of *Listeria monocytogenes* from the spleen, liver and peritoneal cavity, however, the underlying mechanisms for increased susceptibility remain unclear [42]. The impaired ability of GF mice to clear systemic *L. monocytogenes* may be partially explained by a recent report demonstrating that neutrophils elicited from the bone marrow of GF or ABX-treated mice exhibit a reduced capacity to phagocytize bacteria *ex vivo* [43]. In this study, bacterial peptidoglycans were detected in the blood following bacterial colonization of GF mice suggesting that commensal bacterial-derived products can translocate across the intestinal barrier, enter the circulation, and stimulate immune cells [43] (Figure 2).

Two recent studies reported a conserved immune calibration mechanism in which tonic signaling of circulating innate immune cells by commensal bacteria-derived signals can modulate the immune response against systemic viral infections [41,44]. The loss of commensal bacterial-derived signaling led to an impaired virus-specific CD8⁺ T cell response and prolonged viremia following systemic Lymphocytic Choriomeningitis virus (LCMV) infection [41], while defective natural killer cell cytotoxicity of viral infected target cells were reported in GF or ABX-treated mice following murine cytomegalovirus or LCMV infection [44]. These independent studies identified a specific defect in the early

induction of type I Interferons (IFN) and IFN response genes following viral infection in mice with altered commensal bacterial communities [41,44]. The early defects suggest an inherent role for commensal bacterial-derived signaling in calibrating responsiveness of innate immune cells to systemic viral pathogens. Indeed, macrophages from ABX-treated mice exhibited reduced basal expression of antiviral defense genes in the steady-state and an impaired ability to respond to IFN stimulation and control viral replication [41]. Similarly, in the absence of commensal bacterial-derived signals, dendritic cells exhibited an impaired ability to produce type I IFN following stimulation with the TLR ligands polyinosinic:polycytidylic acid (poly I:C) or lipopolysaccharide (LPS) [44]. The defect in IFN production by dendritic cells was likely due to epigenetic modification at the *Ifnb* gene locus that limited gene accessibility, resulting in reduced binding of phosphorylated transcription factors to the *Ifnb* gene promoter region and diminished initiation of gene transcription [44]. Due to the central importance of type I IFN in the antiviral immune response network [45-47], altering accessibility to this key hub gene could have multiple downstream effects on the magnitude and quality of the immune response to viruses. Thus, these studies suggest that commensal bacteria-derived signals can influence the gene expression profile of multiple cell types via epigenetic modifications of innate immune defense genes thereby creating a dynamic transcriptional state that enables basal expression of host-defense factors and rapid responses upon encounter with a pathogen (Figure 2).

Concluding Remarks

It is evident that commensal bacteria-derived signals are critical in regulating host-defense mechanisms to both mucosal-associated and systemic pathogens. In the absence of commensal bacteria-derived signals, the immune machinery for host defense against infection, while functionally intact, may be in an inactive state. This inactive state can be perilous for the host if the invading pathogen establishes a replicative advantage before the host immune response is initiated. Therefore, it is beneficial for an organism's immune system to be in a state of constitutive readiness, producing host defense factors to prophylactically limit infection and ensure the organism's fitness for survival and reproduction. By engaging with surrounding commensal bacterial communities and utilizing commensal bacteria-derived signals as an immuno-rheostat, the immune system can calibrate itself for efficient and rapid responses to potential dangers. This calibration mechanism would give an organism a distinct evolutionary survival advantage by establishing basal protection against a threat that has yet to be encountered and thus cannot be predicted, in terms of type, timing and location. Therefore, the immune system may have evolved to incorporate signals from commensal bacterial communities as part of its repertoire of host defense mechanisms, as important to host defense as any other arm of the immune system.

Future studies are required to identify specific bacterial products that have immunomodulatory effects as well as the mechanisms through which these products are interacting with immune cells at different anatomical locations. As indicated by Clarke et al. [43], commensal bacterial products may translocate across the intestine to directly stimulate circulating immune cell populations. Conversely, interactions between commensal bacteria and hematopoietic and/or non-hematopoietic cells at barrier surfaces could elicit secretion of factors into circulation to indirectly modulate peripheral immune cells (Figure 2). Further, the mechanisms through which commensal bacterial-derived signaling may be involved in chromatin remodeling remains unknown and the extent to which commensal-driven epigenetic modification contribute to immune readiness needs further exploration. Understanding the specific signals and mechanisms through which commensal bacteria regulate the immune response to infectious pathogens will be essential to harness the therapeutic potential of commensal bacteria in infectious disease settings.

Abbreviations used

ABX	antibiotic
CNV	conventionally-reared
IFN	interferon
LCMV	Lymphocytic Choriomeningitis virus
TLR	toll-like receptor
GF	germ-free

References

1. Clemente JC, Ursell LK, Parfrey LW, Knight R. The impact of the gut microbiota on human health: An integrative view. *Cell*. 2012; 148(6):1258–1270. [PubMed: 22424233]
2. Dethlefsen L, McFall-Ngai M, Relman DA. An ecological and evolutionary perspective on human-microbe mutualism and disease. *Nature*. 2007; 449(7164):811–818. [PubMed: 17943117]
3. Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. *Nat Rev Immunol*. 2009; 9(5):313–323. [PubMed: 19343057]
4. Ley RE, Peterson DA, Gordon JI. Ecological and evolutionary forces shaping microbial diversity in the human intestine. *Cell*. 2006; 124(4):837–848. [PubMed: 16497592]
5. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature*. 2006; 444(7122):1027–1031. [PubMed: 17183312]
6. Ott SJ, Musfeldt M, Wenderoth DF, Hampe J, Brant O, Folsch UR, Timmis KN, Schreiber S. Reduction in diversity of the colonic mucosa associated bacterial microflora in patients with active inflammatory bowel disease. *Gut*. 2004; 53(5):685–693. [PubMed: 15082587]
7. Moore WE, Moore LH. Intestinal floras of populations that have a high risk of colon cancer. *Appl Environ Microbiol*. 1995; 61(9):3202–3207. [PubMed: 7574628]
8. Karin M, Lawrence T, Nizet V. Innate immunity gone awry: Linking microbial infections to chronic inflammation and cancer. *Cell*. 2006; 124(4):823–835. [PubMed: 16497591]
9. Marra F, Marra CA, Richardson K, Lynd LD, Kozyskyj A, Patrick DM, Bowie WR, Fitzgerald JM. Antibiotic use in children is associated with increased risk of asthma. *Pediatrics*. 2009; 123(3):1003–1010. [PubMed: 19255032]
10. Macpherson AJ, Harris NL. Interactions between commensal intestinal bacteria and the immune system. *Nat Rev Immunol*. 2004; 4(6):478–485.
11. Littman DR, Pamer EG. Role of the commensal microbiota in normal and pathogenic host immune responses. *Cell Host Microbe*. 2011; 10(4):311–323. [PubMed: 22018232]
12. Honda K, Littman DR. The microbiome in infectious disease and inflammation. *Annu Rev Immunol*. 2012; 30
13. Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. *Science*. 2012; 336(6086):1268–1273. [PubMed: 22674334]
14. Blumberg R, Powrie F. Microbiota, disease, and back to health: A metastable journey. *Sci Transl Med*. 2012; 4(137):137rv137.
15. Smith K, McCoy KD, Macpherson AJ. Use of axenic animals in studying the adaptation of mammals to their commensal intestinal microbiota. *Semin Immunol*. 2007; 19(2):59–69. [PubMed: 17118672]
16. Hooper LV, Gordon JI. Commensal host-bacterial relationships in the gut. *Science*. 2001; 292(5519):1115–1118. [PubMed: 11352068]
17. Kamada N, Kim YG, Sham HP, Vallance BA, Puente JL, Martens EC, Nunez G. Regulated virulence controls the ability of a pathogen to compete with the gut microbiota. *Science*. 2012; 336(6086):1325–1329. [PubMed: 22582016] * This study observed that commensal bacteria help

prevent colonization of *C. rodentium* by outcompeting *C. rodentium* for energy sources in the intestinal lumen.

18. Crosswell A, Amir E, Tegatz P, Barman M, Salzman NH. Prolonged impact of antibiotics on intestinal microbial ecology and susceptibility to enteric salmonella infection. *Infect Immun*. 2009; 77(7):2741–2753. [PubMed: 19380465]
19. Sekirov I, Tam NM, Jogova M, Robertson ML, Li Y, Lupp C, Finlay BB. Antibiotic-induced perturbations of the intestinal microbiota alter host susceptibility to enteric infection. *Infect Immun*. 2008; 76(10):4726–4736. [PubMed: 18678663]
20. Garner CD, Antonopoulos DA, Wagner B, Duhamel GE, Keresztes I, Ross DA, Young VB, Altier C. Perturbation of the small intestine microbial ecology by streptomycin alters pathology in a salmonella enterica serovar typhimurium murine model of infection. *Infect Immun*. 2009; 77(7): 2691–2702. [PubMed: 19433544]
21. Wlodarska M, Willing B, Keeney KM, Menendez A, Bergstrom KS, Gill N, Russell SL, Vallance BA, Finlay BB. Antibiotic treatment alters the colonic mucus layer and predisposes the host to exacerbated citrobacter rodentium-induced colitis. *Infect Immun*. 2011; 79(4):1536–1545. [PubMed: 21321077]
22. Donskey CJ, Chowdhry TK, Hecker MT, Hoyer CK, Hanrahan JA, Huger AM, Hutton-Thomas RA, Whalen CC, Bonomo RA, Rice LB. Effect of antibiotic therapy on the density of vancomycin-resistant enterococci in the stool of colonized patients. *N Engl J Med*. 2000; 343(26): 1925–1932. [PubMed: 11136263]
23. Fridkin SK, Edwards JR, Courval JM, Hill H, Tenover FC, Lawton R, Gaynes RP, McGowan JE Jr. The effect of vancomycin and third-generation cephalosporins on prevalence of vancomycin-resistant enterococci in 126 U.S. Adult intensive care units. *Ann Intern Med*. 2001; 135(3):175–183. [PubMed: 11487484]
24. Johnson S, Samore MH, Farrow KA, Killgore GE, Tenover FC, Lyras D, Rood JJ, DeGirolami P, Baltch AL, Rafferty ME, Pear SM, et al. Epidemics of diarrhea caused by a clindamycin-resistant strain of clostridium difficile in four hospitals. *N Engl J Med*. 1999; 341(22):1645–1651. [PubMed: 10572152]
25. Gaynes R, Rimland D, Killum E, Lowery HK, Johnson TM 2nd, Killgore G, Tenover FC. Outbreak of clostridium difficile infection in a long-term care facility: Association with gatifloxacin use. *Clin Infect Dis*. 2004; 38(5):640–645. [PubMed: 14986246]
26. Hooper LV, Wong MH, Thelin A, Hansson L, Falk PG, Gordon JI. Molecular analysis of commensal host-microbial relationships in the intestine. *Science*. 2001; 291(5505):881–884. [PubMed: 11157169] * References [26–28] demonstrates that commensal bacteria-driven secretion of the anti-microbial peptide RegIII γ helps maintain a physical separation between intestinal epithelial cells and bacterial communities.
27. Vaishnava S, Yamamoto M, Severson KM, Ruhn KA, Yu X, Koren O, Ley R, Wakeland EK, Hooper LV. The antibacterial lectin RegIII γ promotes the spatial segregation of microbiota and host in the intestine. *Science*. 2011; 334(6053):255–258. [PubMed: 21998396]
28. Cash HL, Whitham CV, Behrendt CL, Hooper LV. Symbiotic bacteria direct expression of an intestinal bactericidal lectin. *Science*. 2006; 313(5790):1126–1130. [PubMed: 16931762]
29. Vaishnava S, Behrendt CL, Ismail AS, Eckmann L, Hooper LV. Paneth cells directly sense gut commensals and maintain homeostasis at the intestinal host-microbial interface. *Proc Natl Acad Sci U S A*. 2008; 105(52):20858–20863. [PubMed: 19075245]
30. Brandl K, Plitas G, Mihu CN, Ubeda C, Jia T, Fleisher M, Schnabl B, DeMatteo RP, Pamer EG. Vancomycin-resistant enterococci exploit antibiotic-induced innate immune deficits. *Nature*. 2008; 455(7214):804–807. [PubMed: 18724361]
31. Ivanov II, Atarashi K, Manel N, Brodie EL, Shima T, Karaoz U, Wei D, Goldfarb KC, Santee CA, Lynch SV, Tanoue T, et al. Induction of intestinal Th17 cells by segmented filamentous bacteria. *Cell*. 2009; 139(3):485–498. [PubMed: 19836068]
32. Mangan PR, Harrington LE, O'Quinn DB, Helms WS, Bullard DC, Elson CO, Hatton RD, Wahl SM, Schoeb TR, Weaver CT. Transforming growth factor-beta induces development of the Th17 lineage. *Nature*. 2006; 441(7090):231–234. [PubMed: 16648837]

33. Hall JA, Bouladoux N, Sun CM, Wohlfert EA, Blank RB, Zhu Q, Grigg ME, Berzofsky JA, Belkaid Y. Commensal DNA limits regulatory t cell conversion and is a natural adjuvant of intestinal immune responses. *Immunity*. 2008; 29(4):637–649.
34. Benson A, Pifer R, Behrendt CL, Hooper LV, Yarovinsky F. Gut commensal bacteria direct a protective immune response against toxoplasma gondii. *Cell Host Microbe*. 2009; 6(2):187–196. [PubMed: 19683684]
35. Hayes KS, Bancroft AJ, Goldrick M, Portsmouth C, Roberts IS, Grecnis RK. Exploitation of the intestinal microflora by the parasitic nematode trichuris muris. *Science*. 2010; 328(5984):1391–1394. [PubMed: 20538949] * The authors show that the parasitic helminth *T. muris* fails to establish an infection following antibiotic depletion of commensal bacteria.
36. Kane M, Case LK, Kopaskie K, Kozlova A, MacDermid C, Chervonsky AV, Golovkina TV. Successful transmission of a retrovirus depends on the commensal microbiota. *Science*. 2011; 334(6053):245–249. [PubMed: 21998394] ** This study found that mouse mammary tumor virus was not transmissible from mother to pups in the absence of commensal bacteria.
37. Kuss SK, Best GT, Etheredge CA, Pruijssers AJ, Frierson JM, Hooper LV, Dermody TS, Pfeiffer JK. Intestinal microbiota promote enteric virus replication and systemic pathogenesis. *Science*. 2011; 334(6053):249–252. [PubMed: 21998395] ** The authors demonstrate impaired establishment of enteric viral infections in mice depleted of commensal bacterial communities.
38. Oliveira MR, Tafuri WL, Afonso LC, Oliveira MA, Nicoli JR, Vieira EC, Scott P, Melo MN, Vieira LQ. Germ-free mice produce high levels of interferon-gamma in response to infection with leishmania major but fail to heal lesions. *Parasitology*. 2005; 131(Pt 4):477–488. [PubMed: 16174412]
39. Naik S, Bouladoux N, Wilhelm C, Molloy MJ, Salcedo R, Kastenmuller W, Deming C, Quinones M, Koo L, Conlan S, Spencer S, et al. Compartmentalized control of skin immunity by resident commensals. *Science*. 2012 ** This study was the first to identify resident skin commensal bacteria to be important in regulating the immune response to *L. major* infection.
40. Ichinohe T, Pang IK, Kumamoto Y, Peaper DR, Ho JH, Murray TS, Iwasaki A. Microbiota regulates immune defense against respiratory tract influenza a virus infection. *Proc Natl Acad Sci U S A*. 2011; 108(13):5354–5359. [PubMed: 21402903] ** The authors demonstrate that ABX-mediated depletion of commensal bacteria in mice lead to impaired inflammasome activation and a reduced adaptive immune response to influenza virus infection.
41. Abt MC, Osborne LC, Monticelli LA, Doering TA, Alenghat T, Sonnenberg GF, Paley MA, Antenus M, Williams KL, Erikson J, Wherry EJ, et al. Commensal bacteria calibrate the activation threshold of innate antiviral immunity. *Immunity*. 2012; 37(1):158–170. [PubMed: 22705104] ** This reference demonstrates tonic commensal bacteria-derived signals can modulate expression of antiviral defense genes in peripheral macrophages in the steady state thereby altering susceptibility to viral infection.
42. Inagaki H, Suzuki T, Nomoto K, Yoshikai Y. Increased susceptibility to primary infection with listeria monocytogenes in germfree mice may be due to lack of accumulation of l-selectin+ cd44+ t cells in sites of inflammation. *Infect Immun*. 1996; 64(8):3280–3287. [PubMed: 8757865]
43. Clarke TB, Davis KM, Lysenko ES, Zhou AY, Yu Y, Weiser JN. Recognition of peptidoglycan from the microbiota by nod1 enhances systemic innate immunity. *Nat Med*. 2010; 16(2):228–231. * The authors find bone marrow derived neutrophils from GF or ABX-treated mice are less efficient at phagocytizing bacteria than neutrophils from conventionally-reared mice
44. Ganai SC, Sanos SL, Kallfass C, Oberle K, Johnner C, Kirschning C, Lienenklaus S, Weiss S, Staeheli P, Aichele P, Diefenbach A. Priming of natural killer cells by nonmucosal mononuclear phagocytes requires instructive signals from commensal microbiota. *Immunity*. 2012; 37(1):171–186. [PubMed: 22749822] ** The authors demonstrate that commensal-derived signals imprint epigenetic modification on interferon response defense genes in peripheral mononuclear phagocytes maintaining the gene in an open, active state.
45. Trinchieri G. Type i interferon: Friend or foe? *J Exp Med*. 2010; 207(10):2053–2063. [PubMed: 20837696]
46. Muller U, Steinhoff U, Reis LF, Hemmi S, Pavlovic J, Zinkernagel RM, Aguet M. Functional role of type i and type ii interferons in antiviral defense. *Science*. 1994; 264(5167):1918–1921. [PubMed: 8009221]

47. Hwang SY, Hertzog PJ, Holland KA, Sumarsono SH, Tymms MJ, Hamilton JA, Whitty G, Bertoncello I, Kola I. A null mutation in the gene encoding a type I interferon receptor component eliminates antiproliferative and antiviral responses to interferons alpha and beta and alters macrophage responses. *Proc Natl Acad Sci U S A*. 1995; 92(24):11284–11288. [PubMed: 7479980]

Highlights

- Commensal bacteria influence the immune response to local and systemic pathogens
- Mammalian hosts and pathogens have evolved to utilize commensal-derived signals
- Commensal-driven signaling on immune cells maintain defense genes in an open state
- Tonic commensal-driven stimulation enables a rapid host response to pathogens

Figure 1. Dynamic host – commensal bacteria – pathogen interactions in the intestinal microenvironment

Intestinal commensal bacteria communities limit intestinal infection by (1) competing for space and resources or (2) stimulating intestinal epithelial and immune cells. Epithelial cells can produce anti-microbial peptide, such as RegIII γ , that inhibit colonization of invasive bacteria. Resident innate immune cells can secrete cytokines that activate host-defense defense mechanisms and shape the quality and magnitude of the adaptive immune response to infection. Conversely, (3) some intestinal pathogens have evolved to utilize commensal bacterial-derived signals to improve infectivity.

Figure 2. Commensal bacteria-derived signals calibrate responsiveness of peripheral immune cells

Commensal bacteria can basally stimulate peripheral immune cells, eliciting epigenetic modification in host defense genes and maintaining these genes in an open, transcriptionally active state. Commensal bacteria may (1) directly, via translocation of commensal bacteria-derived products, or (2) indirectly, via stimulation of intestinal epithelial cells or resident immune cells to secrete factors into the circulation, modulate peripheral immune cells. This tonic stimulation by commensal bacteria facilitates rapid responsiveness by immune cells upon encounter with a pathogen.