Review Article

Commensal Microbiome Promotes Resistance to Local and Systemic Infections

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Abstract

Objective: In this review, to illustrate the resistance mechanism for pathogen insult, we discussed the role of the intestinal microbiome in promoting resistance to local gastrointestinal tract infections and to respiratory tract infections.
Data Sources: The review was based on data obtained from the published research articles.
Study Selection: A total of 49 original articles were selected in accordance with our main objective to illustrate the resistance mechanism(s) by which commensal microbiota can contribute to host defense against local and systemic infections.
Results: Diverse microorganisms colonize human environmentally exposed surfaces such as skin, respiratory tract, and gastrointestinal tract. Co-evolution has resulted in these microbes with extensive and diverse impacts on multiple aspects of host biological functions. During the last decade, high-throughput sequencing technology developed has been applied to study commensal microbiota and their impact on host biological functions. By using pathogen recognition receptors pathway and nucleotide binding oligomerization domain-like receptors pathway, the commensal microbiome promotes resistance to local and systemic infections, respectively. To protect against the local infections, the microbiome functions contain the following: the competing for sites of colonization, direct production of inhibition molecules or depletion of nutrients needed for pathogens, and priming immune defenses against pathogen insult. At the same time, with the purpose to maintain homeostasis, the commensal bacteria can program systemic signals toward not only local tissue but also distal tissue to modify their function for infections accordingly.
Conclusions: Commensal bacteria play an essential role in protecting against infections, shaping and regulating immune responses, and maintaining host immune homeostasis.

Key words: Commensal Microbiota; Gut Microbiota; Nucleotide Binding Oligomerization Domain-like Receptors Pathway; Pathogen Recognition Receptors Pathway; Respiratory Microbiome; Toll-like Receptors

Introduction

The human microbiota is the aggregate of microorganisms. These microorganisms reside on human respiratory tract, gastrointestinal tract, and other mucosal surfaces, on which they constantly contact with invasive pathogens. The huge number of resident microorganisms, identified by modern high-throughput sequencing technology, is called commensal microbiome. Commensal microbiota is primarily comprised of indigenous bacteria, most of which are known to be symbiotic or beneficial. It plays an essential role in protection from infections, nutrient acquisition, immune maturation, and neurological function.[1-3] Co-existence and co-evolution with the host in a mutually beneficial relationship, microbe uses commensal-derived signals, named pathogen-associated molecular patterns (PAMPs), to trigger a rapid defense program to eliminate local pathogens. And at the same time, it directly modulates appropriate adaptive immune responses for combating the invasive pathogen. With the purpose to maintain tissue homeostasis, the commensal bacteria can program systemic signals toward local tissue but also distal tissue to modify their function accordingly. Consequently, interactions between the immune system and the resident microbiota govern host resistance or susceptibility to infections and disease pathogenesis. This review will focus on the contribution of commensal microbiota in promoting host resistance against local mucosal and systemic infections.

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Intestinal Microbiome Promotes Resistance to Pathogen and Immune Modulations for Infections

Intestinal microbiome promotes resistance to pathogen

The intestinal microbiota promotes protection against

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enteric infection at least at three levels. First, it can promote host resistance against pathogen by competing for sites of colonization and direct production of inhibition molecules and depletion of nutrients to prevent pathogens expansion and dissemination.[4,5] Experiments in germ-free mice demonstrated that gut microbiota plays a role in clearing the pathogenic bacterium *Citrobacter rodentium* and the clearance was found to be mediated by the enhanced glycan acquisition capabilities of the transferred bacteria.[5] Other recent studies revealed that certain gut pathogens, e.g. *C. rodentium*, *Campylobacter jejuni*, and *Salmonella enteric* serovar Typhimurium (*S. typhimurium*) can compete commensal microbes by actively triggering and increasing intestinal inflammation.[5-7] Moreover, *S. typhimurium* exploits this deficiency in colonization resistance to establish infection and causes disease.[8]

Under conditions in which direct competition is insufficient to limit pathogen invasion, commensal microbes can use the strategy by inducing host immune response to further promote resistance to infection. These protections include both barrier immunity and priming immune defenses against pathogen insult. Moreover, commensal microbiome primes barrier immunity by driving expression of mucin, immunoglobulin A (IgA), and antimicrobial peptides that further prevents pathogen contact with host mucosa. Disruptions of the microbiota resulting in a breakdown of barrier immunity are highly susceptible to opportunistic infection with enteric bacterial pathogens, such as vancomycin-resistant enterococcus (VRE) and *S. typhimurium*.[9,10] Similar to *Clostridium difficile*, VRE is a common cause of antibiotic-associated diarrhea, which is exceedingly difficult to treat by antibiotics. It has been recently shown that the clearance of this pathogen can be restored by re-introducing the normal microbiota or bacteria-derived products, such as lipopolysaccharide (LPS), in antibiotic-treated mice.

Finally, once barrier resistance fails, the microbiota can function by enhancing host immune responses to invading pathogens. Microbiota promotes host to express certain pro-inflammatory cytokines, such as interleukin-1β (IL-1β), which promotes recruitment of inflammatory cells into the site of infection, and IL-22 expression by mononuclear phagocytes, which is specifically activated following pathogen insult and increases epithelial resistance against infection.[11]

Meanwhile, pathogen-induced inflammation in host adversely affects the composition of microbiota, by altering the number and proportion of beneficial bacteria. *S. typhimurium*-induced inflammation, as part of the infectious process, has been shown to reduce the number of symbiotic bacteria.[8] In addition to bacterial pathogens, viruses can also use microbiota-mediated inflammation to induce intestinal immune injury.[12] Indeed, a recent study using a mouse model found that respiratory influenza infection made the composition of intestinal microbiota changed and the change was mediated by interferon-γ (IFN-γ) produced by lung-derived $CCR9^+$ $CD4^+$ T-cells recruited into the small intestine. Even lymphocytes derived from the respiratory mucosa specifically migrated into the intestinal mucosa and destroyed the intestinal microbiota homeostasis in the small intestine, finally leading to intestinal immune injury.[12]

Immune modulation of intestinal microbiome protects host from infections

As the same as pro-inflammatory properties, specific groups of gut microbiota also regulate acquired immunity of the host. The intestinal mucosa contains large numbers of $CD4^+$ T-cells including T helper 17 (Th17) cells and $Foxp3^+$ regulatory T-cells (Tregs). Experimental colonization of mice with *Clostridium* spp. induced $CD4^+$ Tregs in the intestine and ameliorated intestinal inflammation in a murine model of inflammatory bowel disease (IBD).[13] Bacterial polysaccharide (PSA) from the gut microorganism *Bacteroides fragilis* expanded $CD4^+$ T-cells and corrected the systemic $CD4^+$ T-cell deficiency and imbalance in T-cell cytokine production in germ-free mice. PSA of *B. fragilis* is found to function as a symbiosis factor, and this molecule also protected against inflammatory colitis.[14] Recently, *B. fragilis* PSA has been shown to signal through toll-like receptor 2 (TLR2) directly on regulatory T-cells to promote immunological tolerance.[15] Another example is that segmented filamentous bacteria (SFB) colonization in germ-free mice is important for the induction of Th17 cells to protect against the *C. rodentium*. The frequency of Th17 cells was significantly elevated with the absence of commensal bacteria.[16] The gut microbiota has been implicated in intestinal immune developments, and commensal bacteria-derived signals are responsible for differentiation of Th17 cell and promotion Tregs effectors in other chronic inflammations.[17-19]

Commensal-derived Signal Pathway and its Resistance to Local and Systemic Infectious Diseases

Signals from commensal bacteria can act as an adjuvant, augmenting immune responses after intestinal bacterial infections. Immune modulation by the microbiota occurs through commensal-derived signals, called PAMPs. PAMPs are recognized by host pathogen recognition receptors (PRRs), such as TLRs, nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), retinoic acid-inducible gene-I-like receptors (RLRs), and C-type lectin receptors (CLRs).

Activation of PRRs and PAMPs triggers a cascade of signals leading to the production of pro-inflammatory cytokines and transcription of type I IFN genes. Expression and localization of PRRs by the epithelial cells are influenced by the bacterial colonization of the gut. However, in germ-free mice, the expression of defensins and other antimicrobial proteins

is deficient. By reorganization of ligand and the receptor, the bacteria drive epithelial production of mucin, secretion of IgA, and expression of antimicrobial peptides, to resist against pathogen invasion. Another example is that PSA of *B. fragilis* can reduce the severity of intestinal inflammation in mouse models of IBD.[20] However, several recent studies have also found that commensal bacteria can increase viral infectivity in the gastrointestinal microenvironment.[21,22] Thus, commensal-derived PAMPs signals are capable of limiting or exacerbating infection in the intestinal microenvironment. Moreover, PRR signaling can also induce intestinal lymphoid tissue genesis, as shown by one study that recognition of peptidoglycan, from gut-residing Gram-negative bacteria, was both necessary and sufficient to induce the generation of lymphoid follicles in the small intestine, whereas maturation of lymphoid follicles required subsequent signaling via PRRs.[23]

Toll-like receptors and nucleotide binding oligomerization receptors signaling pathway

Toll-like receptors are transmembrane PRRs that comprise an ectodomain containing leucine-rich repeats for PAMP recognition. NLRs constitute a family of intracellular receptors that detects PAMPs and endogenous molecules. The NLRs family members, NOD1 and NOD2, recognize intracellular bacterial products. It is known that TLRs and NLRs play a key role in recognition of extracellular and intracellular bacteria and control of the inflammatory response. The activation of TLRs and NLRs by their respective ligands activates downstream signaling pathways that converge on activation of transcription factors, such as nuclear factor-kappa B (NF-κB), activator protein-1 or IFN regulatory factors, leading to expression of inflammatory cytokines and antimicrobial molecules.

In viral infection of the respiratory tract, recognition of influenza virus by NLRs plays a central role in generating of immune responses. *In vivo* experiments carried out in mice demonstrated that inflammasome activation and the induction of downstream cytokines through NLRs pathway are important in innate and adaptive immune defense against influenza virus infection.[24] More recently, antiviral defense against the respiratory syncytial virus was found to be dependent on NOD2 signaling pathway, which could interact with viral ssRNA to induce production of type I IFNs.[25] It has been shown that NLRs respond to a broad variety of bacteria and are activated by the lung pathogenic microorganisms.[24,25]

Retinoic acid-inducible gene-I-like receptors and C-type lectin receptors Signaling Pathway

The RLR family contains three RNA helicases. Unlike those TLRs that recognize viruses in the endosomal compartment, the RLRs are located in the cytoplasm and mediate the responses to viruses that replicate inside the cell. All RLRs transmit their signal through a common adaptor protein, IFN promoter stimulator-1, to activate NF-κB, mitogen-activated protein kinases (MAPKs), and IFN regulatory factors for induction of type I IFNs and other inflammatory cytokines.

The CLRs are transmembrane PRRs. CLR signaling is mainly mediated by a spleen tyrosine kinase (Syk)-dependent activation of MAPKs and NF-κB with the resultant generation of pro-inflammatory cytokines in intestinal inflammation. Members of CLRs consist of dectin-1, mannose-binding lectin (MBL), macrophage-restricted C-type lectin (MCL), macrophage galactose-type lectin, RegIII lectins family, and some SIGNR molecules. They recognize carbohydrate-binding domain, which is present on a cell wall component of commensal fungi or intestinal microbiota. They are mainly expressed by the antigen presenting cells, such as monocytes, macrophages, and dendritic cells (DCs). Recent studies have shown that mice deficient with dectin-1 or MBL or some SIGNR molecules, respectively, exhibited an increased susceptibility to chemically induced colitis.[26] This was due to an altered response to commensal intestinal fungi, which are recognized by dectin-1 and SIGNR molecules.[26] Moreover, in the human a polymorphism dectin-1 gene is associated with ulcerative colitis. MBL in humans was reported to ameliorate the excessive inflammation during IBD. Although MCL acts as an activating receptor that can mediate phagocytosis, respiratory burst, and inflammatory cytokine production, recent studies revealed that mice lacking MCL only exhibited a slightly increased disease severity based on either clinical symptoms or histopathology.[27] The antibacterial lectin RegIII family limits direct contact between bacteria and the intestinal epithelium, and thus promotes tolerance to the intestinal microbiota by spatial segregation.[9,28] Taken together, these results indicated that members of CLRs play a crucial role in the regulation of intestinal immune homeostasis and colon inflammation.

Host recognition of the intestinal microbiota is essential in shaping local immune responses and contributing to host defense for infections

Germ-free animals have extensive deficits in the development of the gut-associated lymphoid tissues (GALT) and defects in antibody production.[29,30] Compared to animals housed under specific pathogen-free conditions, germ-free mice have underdeveloped GALT including Peyer's patches and mesenteric lymph nodes. A recent report has shown that germ-free animals display impaired development and maturation of isolated lymphoid follicles.[23]

It is known that the interaction between the host and the gut microbiota is highly dynamic and has a profound impact on the immune system locally and systemically. For example, the absence of commensal bacteria was found to have a systemic effect on T- and B-cell zones in spleens and secondary lymphoid organs.[14] And germ-free mice have fewer germinal centers, plasma cells, and Igs systemically. Furthermore, these mice have systemic $CD4^+$ T-cell deficiency in the spleen and aberrant Th1/Th2 cytokine production in response to *in vitro* stimulation. However, the aberrant production of cytokines could be restored by the injection of purified bacteria product, e.g., LPS, from specific

commensal bacteria.[14] Additionally, immune modulation by intestinal microbiota can prime systemic inflammation. Colonization of the intestine with SFB is associated with increased frequencies of intestinal $CD4^+$ Th17 cells and exacerbated experimental autoimmune inflammation in murine models of encephalomyelitis, arthritis, multiple sclerosis, obesity, and diabetes, further demonstrating that defined commensal species can promote inflammatory diseases.[19,31-33]

Resistance to respiratory infection is programmed by signals from gut microbiome

The mucosal immune system is a system-wide organ. With the purpose to maintain tissue homeostasis, the gut commensal bacteria can program systemic signals towards local intestine but also distal tissue to modify their function accordingly.

Antibacterial activity in lung is programmed systemically by signals from the intestine

Recently, Clarke has shown that the antibacterial activity in the lung of mice was programmed systemically by signals from the intestine. In his experiments, germ-free mice treated by LPS were found to be resistant to pulmonary *Klebsiella pneumoniae* infection, had abrogated IL-10 production and restored tumor necrosis factor-α production and neutrophil mobilization into lungs of the infected germ-free mice through activation of TLR-dependent pathways.[34,35] But, in early defenses against respiratory infection by *K. pneumonia* were enhanced by bacterial peptidoglycan, which were recognized by NLRs, but not TLRs. Further, this signal was noticed to come from the gastrointestinal tract, but not from the upper respiratory tract. And these intestine-derived signals promoted the production of reactive oxygen species in alveolar macrophages.[35,36] Another example is gut dysbiosis, which refers to the microbial imbalance inside gastrointestinal tract induced by antibiotic treatments, not only can cause overgrowth of particular fungal species in the gut, but further promotes allergic airway inflammation by shifting macrophage polarization in the lung toward the alternatively activated M2 macrophage.[37] These changes in function of alveolar macrophages were shown to be due to increased prostaglandin E2 levels.[37]

Gastrointestinal microbiome is required for supporting respiratory influenza infection

Earlier studies have shown that microbiota had the potential to protect certain viral infections. It is known that germ-free mice are more susceptible to influenza virus, Coxsackie virus, and Friend leukemia virus.[38] The finding of a recent study has identified the neomycin-sensitive bacteria in the gastrointestinal tract required for supporting immune responses to respiratory influenza infection. And the bacterial species, *Wolbachia*, can confer protection against respiratory viral infections in Drosophila.[39] To explore the mechanism(s) by which commensal microbiota contributes to host defense against these viruses, several recent studies have focused on crosstalk between the microbiota and the immune system and the requirement for inflammasome-mediated cytokine release for triggering adaptive immune responses against influenza virus.[36,40] These studies demonstrated that gut microbiota supports respiratory immunity against influenza virus by releasing low levels of PRR ligands in circulation. Upon flu infection, direct PRR activation or the induction of host factors as a result of PRR signaling could provide the immediate source for inflammasome-mediated cytokine release, such as IL-1β and IL-18, in the lung at steady-state. Further, after influenza virus infections, which in turn modulate the ability of respiratory DCs to become professional antigen-presenting cells for the activation of adaptive immune defense against influenza viruses. On the other hand, recent studies also highlighted the importance of the signals derived from commensal bacteria which can calibrate the activation threshold of innate immunity. The results obtained from these studies[40] reveal a previously unrecognized interplay between commensal and antiviral IFN signaling pathways, in which low-level tonic signaling by commensal bacteria, regulates the steady-state readiness of antiviral pathways in macrophages, involved in responses to bacteria, cytosolic oligomers, and respiratory infection with influenza A virus.[36,40,41] This finding that macrophages isolated from antibiotic-treated mice are deficient in signaling of type I and II IFNs suggested that signals dependent on commensal-derived can maintain the fitness of antiviral pathways in macrophages.[36,40] Moreover, the observations that splenic mononuclear cells, isolated from germ-free mice are deficient in expressing pro-inflammatory cytokines when stimulated with only purified PAMPs, also provided a sound explanation for the commensal-antiviral immune fitness axis at the transcriptional level.[41]

In contrast, studies also showed that respiratory influenza infection could cause intestinal disease. Influenza infection altered the intestinal microbiota composition, which was mediated by IFN-γ produced by lung-derived $CCR9^+$ $CD4^+$ T-cells recruited into the small intestine.[42] And latent influenza virus infections can render mice less susceptible to bacterial challenge, an effect attributed to basal macrophage activation.[42]

Cutaneous Microbiome Influences Pathogen Infection at Colonization Sites

Cutaneous inflammatory disorders such as psoriasis, atopic dermatitis, and rosacea have been found to be associated with dysbiosis in the cutaneous microbiota.[43,44] Although development and differentiations of the effectors and regulatory T lymphocytes are tightly controlled by gut flora signals,[19] skin T-cell differentiations, such as Th1, Th17, and IL-17^+γδ-T-cell are dependent on signals from skin microbiota through PAMP-driven IL-1β signals, rather than gut microbiota.[45] Germ-free mice experiments also demonstrated IFN-γ and IL-17A, produced by functional T-cell effectors, were significantly reduced in their skin tissues.[45] Furthermore, protective immunity against parasite

Leishmania was found to be critically dependent on the skin commensal *Staphylococcus epidermidis*.[45]

Nasopharyngeal Microbiome and its Diversity in Chronic Rhinosinusitis

In normal nasal cavity and sinus cavity, the commensal microbiota includes *Firmicutes*, *Actinobacteria,* and *Staphylococcaceae* families.[46] Compared with normal commensal, *Staphylococcus aureus*, *P. aeruginosa,* and anaerobic species were present in adult chronic rhinosinusitis (CRS) patients, using conventional culture and biofilm detection.[47,48] And these presences were also confirmed by more sensitive pyrosequencing technology targeting of bacterial 16S rRNA genes.[49] The highly discriminatory techniques further identified and differentiated other members of bacterial pathogens, including *Corynebacterium*, *Lachnospiraceae, Ralstoniaceae, Mycobacteriaceae,* and *Helicobacteriaceae*.[49] The study also showed that certain bacterial taxa or species, such as *Lactobacillales* and the species *Lactobacillales sakei*, may be protective against the development of CRS. Moreover, CRS patients' microbiome is characterized by less richness, evenness, and diversity compared to normal.[49]

Conclusions

Commensal bacteria play an essential role in protecting against infections, shaping and regulating immune responses, and maintaining host immune homeostasis. The high-throughput genomic sequencing analysis of the microbiota has revealed a previously unknown diversity and functions of the commensal microbiome in humans. Given the essential functions of the commensal microbiome in shaping and developing innate and adaptive immunity, increasing number of studies have examined its therapeutic potential for infections. There are convincing data to support the use of certain probiotics in treating intestinal inflammations including IBD, necrotizing enterocolitis, and prevention of antibiotic-associated diarrhea including those caused by *C. difficile*. Clearly, further understanding of the role of microbiota in promoting resistance to infections has important implications for human health and disease.

References

1. Kau AL, Ahern PP, Griffin NW, Goodman AL, Gordon JI. Human nutrition, the gut microbiome and the immune system. Nature 2011;474:327-36.
2. Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. Nat Rev Immunol 2009;9:313-23.
3. Rhee SH, Pothoulakis C, Mayer EA. Principles and clinical implications of the brain-gut-enteric microbiota axis. Nat Rev Gastroenterol Hepatol 2009;6:306-14.
4. Reid G, Howard J, Gan BS. Can bacterial interference prevent infection? Trends Microbiol 2001;9:424-8.
5. Kamada N, Kim YG, Sham HP, Vallance BA, Puente JL, Martens EC, *et al.* Regulated virulence controls the ability of a pathogen to compete with the gut microbiota. Science 2012;336:1325-9.
6. Lupp C, Robertson ML, Wickham ME, Sekirov I, Champion OL, Gaynor EC, *et al.* Host-mediated inflammation disrupts the intestinal microbiota and promotes the overgrowth of *Enterobacteriaceae*. Cell Host Microbe 2007;2:204.
7. Sekirov I, Tam NM, Jogova M, Robertson ML, Li Y, Lupp C, *et al.* Antibiotic-induced perturbations of the intestinal microbiota alter host susceptibility to enteric infection. Infect Immun 2008;76:4726-36.
8. Stecher B, Robbiani R, Walker AW, Westendorf AM, Barthel M, Kremer M, *et al. Salmonella enterica* serovar typhimurium exploits inflammation to compete with the intestinal microbiota. PLoS Biol 2007;5:2177-89.
9. Vaishnava S, Yamamoto M, Severson KM, Ruhn KA, Yu X, Koren O, *et al.* The antibacterial lectin RegIIIgamma promotes the spatial segregation of microbiota and host in the intestine. Science 2011;334:255-8.
10. Brandl K, Plitas G, Mihu CN, Ubeda C, Jia T, Fleisher M, *et al.* Vancomycin-resistant enterococci exploit antibiotic-induced innate immune deficits. Nature 2008;455:804-7.
11. Franchi L, Kamada N, Nakamura Y, Burberry A, Kuffa P, Suzuki S, *et al.* NLRC4-driven production of IL-1ß discriminates between pathogenic and commensal bacteria and promotes host intestinal defense. Nat Immunol 2012;13:449-56.
12. Wang J, Li F, Wei H, Lian ZX, Sun R, Tian Z. Respiratory influenza virus infection induces intestinal immune injury via microbiota-mediated Th17 cell-dependent inflammation. J Exp Med 2014;211:2397-410.
13. Atarashi K, Tanoue T, Shima T, Imaoka A, Kuwahara T, Momose Y, *et al.* Induction of colonic regulatory T cells by indigenous *Clostridium* species. Science 2011;331:337-41.
14. Mazmanian SK, Liu CH, Tzianabos AO, Kasper DL. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. Cell 2005;122:107-18.
15. Round JL, Lee SM, Li J, Tran G, Jabri B, Chatila TA, *et al.* The Toll-like receptor 2 pathway establishes colonization by a commensal of the human microbiota. Science 2011;332:974-7.
16. Zaph C, Du Y, Saenz SA, Nair MG, Perrigoue JG, Taylor BC, *et al.* Commensal-dependent expression of IL-25 regulates the IL-23-IL-17 axis in the intestine. J Exp Med 2008;205:2191-8.
17. Rakoff-Nahoum S, Medzhitov R. Regulation of spontaneous intestinal tumorigenesis through the adaptor protein MyD88. Science 2007;317:124-7.
18. Rakoff-Nahoum S, Paglino J, Eslami-Varzaneh F, Edberg S, Medzhitov R. Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis. Cell 2004;118:229-41.
19. Ivanov II, Atarashi K, Manel N, Brodie EL, Shima T, Karaoz U, *et al.* Induction of intestinal Th17 cells by segmented filamentous bacteria. Cell 2009;139:485-98.
20. Mazmanian SK, Round JL, Kasper DL. A microbial symbiosis factor prevents intestinal inflammatory disease. Nature 2008;453:620-5.
21. Kane M, Case LK, Kopaskie K, Kozlova A, MacDearmid C, Chervonsky AV, *et al.* Successful transmission of a retrovirus depends on the commensal microbiota. Science 2011;334:245-9.
22. Kuss SK, Best GT, Etheredge CA, Pruijssers AJ, Frierson JM, Hooper LV, *et al.* Intestinal microbiota promote enteric virus replication and systemic pathogenesis. Science 2011;334:249-52.
23. Bouskra D, Brézillon C, Bérard M, Werts C, Varona R, Boneca IG, *et al.* Lymphoid tissue genesis induced by commensals through NOD1 regulates intestinal homeostasis. Nature 2008;456:507-10.
24. Ichinohe T, Lee HK, Ogura Y, Flavell R, Iwasaki A. Inflammasome recognition of influenza virus is essential for adaptive immune responses. J Exp Med 2009;206:79-87.
25. Sabbah A, Chang TH, Harnack R, Frohlich V, Tominaga K, Dube PH, *et al.* Activation of innate immune antiviral responses by Nod2. Nat Immunol 2009;10:1073-80.
26. Eriksson M, Johannssen T, von Smolinski D, Gruber AD, Seeberger PH, Lepenies B. The C-type lectin receptor SIGNR3 binds to fungi present in commensal microbiota and influences immune regulation in experimental colitis. Front Immunol 2013;4:196.
27. Hütter J, Eriksson M, Johannssen T, Klopfleisch R, von Smolinski D, Gruber AD, *et al.* Role of the C-type lectin receptors MCL and DCIR in experimental colitis. PLoS One 2014;9:e103281.
28. Mukherjee S, Zheng H, Derebe MG, Callenberg KM, Partch CL, Rollins D, *et al.* Antibacterial membrane attack by a pore-forming intestinal C-type lectin. Nature 2014;505:103-7.

29. Macpherson AJ, Harris NL. Interactions between commensal intestinal bacteria and the immune system. Nat Rev Immunol 2004;4:478-85.
30. Falk PG, Hooper LV, Midtvedt T, Gordon JI. Creating and maintaining the gastrointestinal ecosystem: What we know and need to know from gnotobiology. Microbiol Mol Biol Rev 1998;62:1157-70.
31. Kriegel MA, Sefik E, Hill JA, Wu HJ, Benoist C, Mathis D. Naturally transmitted segmented filamentous bacteria segregate with diabetes protection in nonobese diabetic mice. Proc Natl Acad Sci U S A 2011;108:11548-53.
32. Lee YK, Menezes JS, Umesaki Y, Mazmanian SK. Proinflammatory T-cell responses to gut microbiota promote experimental autoimmune encephalomyelitis. Proc Natl Acad Sci U S A 2011;108 Suppl 1:4615-22.
33. Wu HJ, Ivanov II, Darce J, Hattori K, Shima T, Umesaki Y, *et al.* Gut-residing segmented filamentous bacteria drive autoimmune arthritis via T helper 17 cells. Immunity 2010 25;32:815-27.
34. Fagundes CT, Amaral FA, Vieira AT, Soares AC, Pinho V, Nicoli JR, *et al.* Transient TLR activation restores inflammatory response and ability to control pulmonary bacterial infection in germfree mice. J Immunol 2012;188:1411-20.
35. Clarke TB. Early innate immunity to bacterial infection in the lung is regulated systemically by the commensal microbiota via nod-like receptor ligands. Infect Immun 2014;82:4596-606.
36. Ichinohe T, Pang IK, Kumamoto Y, Peaper DR, Ho JH, Murray TS, *et al.* Microbiota regulates immune defense against respiratory tract influenza A virus infection. Proc Natl Acad Sci U S A 2011;108:5354-9.
37. Kim YG, Udayanga KG, Totsuka N, Weinberg JB, Núñez G, Shibuya A. Gut dysbiosis promotes M2 macrophage polarization and allergic airway inflammation via fungi-induced PGE2. Cell Host Microbe 2014;15:95-102.
38. Smith K, McCoy KD, Macpherson AJ. Use of axenic animals in studying the adaptation of mammals to their commensal intestinal microbiota. Semin Immunol 2007;19:59-69.
39. Teixeira L, Ferreira A, Ashburner M. The bacterial symbiont *Wolbachia* induces resistance to RNA viral infections in *Drosophila* melanogaster. PLoS Biol 2008;6:e2.
40. Abt MC, Osborne LC, Monticelli LA, Doering TA, Alenghat T, Sonnenberg GF, *et al.* Commensal bacteria calibrate the activation threshold of innate antiviral immunity. Immunity 2012;37:158-70.
41. Lamkanfi M, Dixit VM. Modulation of inflammasome pathways by bacterial and viral pathogens. J Immunol 2011;187:597-602.
42. Barton ES, White DW, Cathelyn JS, Brett-McClellan KA, Engle M, Diamond MS, *et al.* Herpesvirus latency confers symbiotic protection from bacterial infection. Nature 2007;447:326-9.
43. Gallo RL, Nakatsuji T. Microbial symbiosis with the innate immune defense system of the skin. J Invest Dermatol 2011;131:1974-80.
44. Kong HH, Oh J, Deming C, Conlan S, Grice EA, Beatson MA, *et al.* Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. Genome Res 2012;22:850-9.
45. Naik S, Bouladoux N, Wilhelm C, Molloy MJ, Salcedo R, Kastenmuller W, *et al.* Compartmentalized control of skin immunity by resident commensals. Science 2012;337:1115-9.
46. Lemon KP, Klepac-Ceraj V, Schiffer HK, Brodie EL, Lynch SV, Kolter R. Comparative analyses of the bacterial microbiota of the human nostril and oropharynx. MBio 2010;1:e00129-10.
47. Psaltis AJ, Ha KR, Beule AG, Tan LW, Wormald PJ. Confocal scanning laser microscopy evidence of biofilms in patients with chronic rhinosinusitis. Laryngoscope 2007;117:1302-6.
48. Corriveau MN, Zhang N, Holtappels G, Van Roy N, Bachert C. Detection of *Staphylococcus aureus* in nasal tissue with peptide nucleic acid-fluorescence *in situ* hybridization. Am J Rhinol Allergy 2009;23:461-5.
49. Stephenson MF, Mfuna L, Dowd SE, Wolcott RD, Barbeau J, Poisson M, *et al.* Molecular characterization of the polymicrobial flora in chronic rhinosinusitis. J Otolaryngol Head Neck Surg 2010;39:182-7.

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