HHS Public Access

Author manuscript

J Immunol. Author manuscript; available in PMC 2022 April 01.

Published in final edited form as:

J Immunol. 2021 October 01; 207(7): 1710–1718. doi:10.4049/jimmunol.2100215.

A modern world view of host–microbiota–pathogen interactions

Chin Yee Tan[#*,†], **Zeni E. Ramirez**[#*,†], **Neeraj K. Surana**[*,†,‡]

[*]Division of Infectious Diseases, Department of Pediatrics, Duke University School of Medicine, Durham, NC 27710

[†]Department of Molecular Genetics and Microbiology, Duke University School of Medicine, Durham, NC 27710

[‡]Department of Immunology, Duke University School of Medicine, Durham, NC 27710

[#] These authors contributed equally to this work.

Abstract

The microbiota—the diverse set of commensal microbes that normally colonize humans—represents the first line of defense against infectious diseases. In this review, we summarize the direct and indirect mechanisms by which the microbiota modulates susceptibility to—and severity of—infections, with a focus on immunological mechanisms. Moreover, we highlight some of the ways that modern-world lifestyles have influenced the structure–function relationship between the microbiota and infectious diseases. Ultimately, understanding how the microbiota influences infectious risks will facilitate development of microbiota-derived therapeutics that bolster host defenses.

The incidence of infectious diseases decreased dramatically throughout the 20th century owing to improvements in sanitation, advances in vaccinology, and the development of antimicrobials and other infectious disease control measures (1); however, infections still accounted for 3 of the top 10 causes of death worldwide in 2019 (2). Because of this importance of infections to public health, there has been intense investigation over the past century to better understand how pathogens cause disease and what can be done to stop this process. Ever since Pasteur published his germ theory in the mid-19th century, there has been an almost singular focus on studying pathogens. This view was further reinforced over the next ~125 years with the introduction of Koch's postulates and Falkow's molecular postulates (3, 4), which focused on identifying the microbe and/or microbial gene(s) that caused infectious diseases and provided the conceptual backdrop for most microbial pathogenesis research in the 20th century.

Even in Pasteur's time, though, there was disagreement regarding the relative importance of the pathogen and the context of the host–pathogen interaction. Antoine Béchamp, a contemporary of Pasteur, argued that the "terrain" and "internal milieu" of the body was critical for the development of disease after infection by the pathogen (5). Although Pasteur's germ theory carried the day, Pasteur, shortly before his death, recognized the

Corresponding author: Neeraj K. Surana, neil.surana@duke.edu, 919-613-8742 (phone).

strength of Béchamp's argument by stating: "Béchamp was right—the microbe is nothing. The terrain is everything" (6). Although Béchamp was incorrect to ignore the importance of the pathogen itself, there is now growing appreciation for his central tenet that the general landscape in which the infection occurs is also important. This concept has more recently been expanded upon with the damage response framework and the idea of disease tolerance (7, 8). Both of these paradigms invoke the notion that the host response—along with attributes of the pathogen itself—is necessary to determine whether, and how severely, disease may develop or whether the host is able to tolerate the infectious challenge. This idea of a context-dependent nature to infection that started with Béchamp and continues to evolve into the 21st century must now also integrate the microbiota, the diverse collection of host-associated microorganisms that regulates host physiology, into the concept of "terrain".

The intricate interactions between these three factors—the host, pathogen, and microbiota—determine the outcome of an infection. However, the microbiota itself is incredibly dynamic. In addition to intra- and inter-individual variability (9–12), there are notable changes to the microbiota associated with modernization, whether it be related to dietary shifts (13, 14), technological and medical advancements (15, 16), or increases in lifestyle-associated diseases (17, 18). Given that the microbiota, virulence strategies of pathogens, and host-specific defense mechanisms have individually been reviewed extensively (19–22), this review focuses on the mechanisms underlying how the microbiota modulates infectious diseases (Figure 1). Given the numerous studies in this area, it is challenging to be truly comprehensive. As such, we highlight exemplar vignettes of how the microbiota regulates infections, with a general focus on immune mechanisms.

Microbe–microbe interactions

The members of the microbiota exist in a delicate ecological balance with one another. Within these networks, numerous microbe–microbe interactions occur that enable persistence of some species (i.e., cross-feeding interactions) and exclusion of others (23). One major mechanism by which the microbiota protects against infections is by simply occupying the same niche that the pathogen would normally colonize. Seminal studies performed in the 1950's and 1960's demonstrated that the intestinal microbiota protected animals against infection (24–27). This manner of protection, later coined "colonization resistance" (28), could be abrogated by antibiotic treatment and restored with supplementation of commensal microbes. It has been known since the 1970's that this protection is largely reliant on anaerobic organisms (28, 29), and the subsequent half-century has been spent trying to identify the specific microbe(s) involved (30). In addition to niche competition, the microbiota can also produce molecules, such as bacteriocins, that directly antagonize would-be pathogens (discussed in more detail below). Moreover, there is precedence for microbiota-derived quorum-sensing molecules to impact infection: expression of luxS [autoinducer 2 (AI-2) synthase] by *Ruminococcus obeum* induces repression of several of *Vibrio cholerae* colonization factors (31). Although the precise mechanism for this repression is unknown, it does not require the *V. cholerae* AI-2 sensor, luxP. Importantly, though, this example highlights that commensal bacteria can "talk" to pathogens as a means to protect against infection. Although the host and microbiota normally exist in a mutualistic state of détente, slight perturbations to this equilibrium

result in inflammation, which subtly changes the redox state of the intestine in a way that favors pathogens and results in a bloom of Enterobacteriaceae (32, 33). The inability of the microbiota to adequately deal with these increases in reactive oxygen and nitrogen species predisposes the host to enteric infection.

Beyond these interbacterial interactions, bacteria–virus interactions have recently been demonstrated to be important as well. Intriguingly, some enteric viruses (e.g., poliovirus, reovirus, mouse mammary tumor virus) require the presence of commensal bacteria for pathogenicity (34, 35). In these cases, the viruses bind bacterial surface molecules (e.g., lipopolysaccharide, peptidoglycan), thereby triggering Toll-like receptor (TLR) responses that promote viral infectivity and enhancing receptor binding (34, 35). Interestingly, the specific bacterial requirements may vary for different viruses, even those that are closely related (36). In a more complex interaction, the microbiota differentially influences the pathogenicity of norovirus infections in a region-specific manner (37, 38). Biotransformation of bile acids in the proximal small intestine primes the type III interferon response and inhibits norovirus infection; in contrast, the microbiota stimulates norovirus infection in the distal gut (37). Finally, bacteriophages—viruses that are specific for bacteria—can also influence infections. While there is less robust data regarding the role of endogenous bacteriophages in preventing infection, there has recently been resurging interest in the clinical use of bacteriophages for treatment of infections that are otherwise medically recalcitrant (39, 40). Although these reports are still at the case report level, it underscores the important role that bacteriophages may play in modulating susceptibility to various infections.

Microbe-host interactions

Timing and memory of microbial exposures

The first glimpse of the microbial world begins in utero. Although the existence of a placental microbiome remains controversial (41), it is widely established that maternal transfer of antibodies and microbe-derived metabolites—both of which occur prenatally and via breast milk—provides passive immunity against neonatal infections and augments neonatal immune development (42–45). In some cases, these maternal antibodies are induced by the microbiota, cross-react with pathogens, and confer protection against infection to the offspring (46). Neonatal acquisition of specific commensal bacterial taxa, such as clostridial species, is necessary for protection against infection (47). Conversely, the neonatal microbiota is required for the development of immunosuppressive $CD71^{+}$ erythroid cells, which protect against excessive commensal microbe-induced inflammation but also leaves neonates more susceptible to infections (48). Moreover, some of the immunoregulatory changes induced in early postnatal life (e.g., invariant NK T cells, regulatory T cells, lymphoid tissue inducer-like cells) have life-long consequences that may similarly impact susceptibility to infection later in life (49–51). Considered together, the microbiota orchestrates host defenses against infections beginning in the prenatal period and provides multiple layers of transient protection during neonatal windows of vulnerability, which may also have lasting effects. It is likely that this process is disrupted due to peri-

and postpartum antibiotic exposure and may contribute to elevated rates of sepsis observed in antibiotic-exposed infants (52, 53).

These microbial exposures are important not only in shaping the acute response against infection, but they are also critical for the development of immunological memory after an infection. For example, the microbiota is required for the generation of virus-specific $CD8^+$ memory T cells (54, 55). Moreover, gastrointestinal infection with *Toxoplasma gondii* causes a loss of tolerance to the microbiota, with microbiota-specific $CD4^+$ T cells forming memory cells that are phenotypically similar to pathogen-specific T cells (56). Notably, these studies did not directly demonstrate that these microbiota-induced memory T cells actually confer protection against a secondary infectious challenge. More recent work has demonstrated that enteric infection causes an expansion of taurine-metabolizing bacterial species in the microbiota that confers greater resistance to subsequent infection (57).

Conceptually analogous to this idea that the microbiota influences the immune response after an active infection, it can also modulate the response to vaccines, which attempt to mimic immunologically key aspects of infection. Indeed, murine experiments have demonstrated that microbiota–TLR 5 interactions are required for a robust vaccine response (58, 59), though this appears to be more apparent for non-adjuvanted viral subunit vaccines (e.g., inactivated influenza, inactivated polio) and not live or adjuvanted vaccines (e.g., live attenuated yellow fever, Tdap/alum). In humans, disruption of the microbiota with antibiotics resulted in attenuated responses to influenza vaccination (60), findings that indicate the microbiota also potentiates vaccine responsiveness in humans. However, in some cases, the gut microbiota has been observed to distract vaccine-induced immunity, thereby leading to a poorer response (61). Furthermore, it has long been noted that many oral vaccines (e.g., polio, cholera, rotavirus) have lower immunogenicity in low- and middle-income countries as compared to high-income countries (62, 63). Although the exact reasons for this disparity remain unknown, it is thought to relate to differences in the intestinal milieu, including dysbiosis of the microbiota and higher incidence of environmental enteric dysfunction (63, 64). Taken together, these data suggest that the microbiota may serve as an adjuvant for certain vaccine types and could lead to novel microbiome-based methods for improving vaccine efficacy.

Local versus distant effects

In addition to the timing of microbial exposure, the location of these host–microbe interactions may also be important. In thinking about location, one must consider not only the macroenvironment (e.g., the organ or even the specific region of a given organ) but also the microenvironment (e.g., intestinal crypt or villus). This is true in all anatomic sites, as it is known that microbial communities in adjacent anatomic regions may be vastly different from one another (10, 65). These spatial differences, which reflect variability in physicochemical characteristics and immune effectors among other things, result in microbes selectively occupying locations suited to their adaptations (65–67).

Intuitively, it makes sense that spatial proximity may be required for the commensal microbiota to influence susceptibility to infectious diseases. For example, the gastric microbiota regulates clearance of *Helicobacter pylori* from the stomach by inducing local

production of immunoglobulin A (68). However, it is now clear that the microbiota can also exert its effects across long distances. For example, segmented filamentous bacteria (SFB), which is most abundant in the distal ileum and largely absent from the colon, is known to induce ileal Th17 cells; however, it also protects against colonic infection with *Citrobacter rodentium* (69). That said, SFB also induces colonic expression of IL-17 (70), which may explain this apparent dichotomy between the site of a commensal bacteria and location of its effects. Furthermore, intestinal SFB protects against pneumonia due to *Staphylococcus aureus* (71), a finding that further highlights the distant effects conferred by the microbiota. Indeed, this notion of the gut microbiota impacting infections in distant organs has now been demonstrated for multiple sites, including the liver, lungs, and brain among others (71–75). However, virtually nothing is known about how microbial signals from the intestines are transmitted to these distant sites. Possibilities include that bacteria translocate across the intestinal epithelium and travel to these remote sites, that immune cells educated in the intestines travel to other organs (76, 77), that bacterial factors and/or metabolites produced in the gut are somehow ferried to distant areas (42, 78), or that there is a direct hard-wired connection (e.g., the vagus nerve for the gut–brain axis) (79). None of these possibilities has conclusively been demonstrated as necessary or sufficient for modulating extra-intestinal infectious diseases.

Modulation of epithelial cell physiology

Epithelial cells are a critical partner to the microbiota in regulating susceptibility to infection as they can sense and quickly respond to changes in microbial signals delivered by commensal organisms. Two key defense mechanisms that provide direct protection against pathogens include establishing and maintaining a mucus barrier as well as expressing a variety of antimicrobial peptides (e.g., lysozyme, Reg3 proteins, defensins). Both of these features are regulated by the microbiota (80, 81). The importance of mucus in protecting the host against infection has been shown in the lungs and gut (82–86). In the large intestine, each crypt opening is guarded by a sentinel goblet cell, which is able to detect TLR ligands only when their concentrations are high as occurs during breaches of the mucus layer (87). In addition to increasing their own mucus secretion, these sentinel goblet cells generate an intercellular gap junction signal that activates adjacent goblet cells to also increase mucus secretion (87). Antimicrobial peptides help maintain a bacteria-free zone adjacent to epithelial cells and have critical roles in protecting against infection due to a variety of pathogens (88–91). The mechanism for microbiota-induced antimicrobial peptide expression has been best studied for Reg3γ, where the working model holds that two independent pathways are simultaneously required (92): luminal microbe-associated molecular patterns (e.g., lipopolysaccharide) signal through intestinal epithelial cell TLRs and a MyD88-dependent pathway to increase Reg3γ expression while group 3 innate lymphoid cell secretion of IL-22 in the lamina propria is also required for Reg3γ expression (93–96). However, while MyD88 signaling is required for Reg3γ expression in the colon, it is not required in the ileum (97). Moreover, it is less likely that TLR agonists are generically able to stimulate Reg3γ expression in the small intestine given that very few bacterial species have this capacity (80, 98). Finally, mice deficient in IL-22 still express Reg3γ (99), an observation that indicates that IL-22 is not absolutely required for Reg3γ expression. Although exogenously administered IL-22 leads to increased Reg3γ expression (100), this

could be through a pathway distinct from commensal-induced Reg3γ. Taken together, while Reg3γ expression—and antimicrobial peptide expression more generally—is dependent on the microbiota, the specific mechanisms underlying induction may differ among commensal microbes.

In addition to these mechanisms that directly protect against infection, the microbiota also helps regulate stem cell activity (101–103), which is crucial for maintaining barrier integrity in the setting of infection (104, 105). Finally, epithelial cells are also able to process signals from commensal bacteria to modulate the underlying immune system. For example, commensal bacteria regulate MHCII expression on intestinal epithelial cells such that they can present antigens to immune cells in the lamina propria (106). SFB represents a specific illustration of this, where SFB proteins are endocytosed, processed, and presented by intestinal epithelial cells to induce Th17 cells (107). Moreover, commensal organisms can alter cytokine production by epithelial cells, which results in a different immune microenvironment that is less permissive to invading microbes (108, 109). A conceptually similar example involves clostridial regulation of retinoic acid levels in intestinal epithelial cells, which results in regulating IL-22 responses and colonization by pathogens (110). While the vast majority of studies examining how the microbiota regulates host epithelial cell biology focus on commensal bacteria, there is an increasing appreciation for the importance of other microbial classes. For example, *Tritrichomonas musculis*, a murine commensal protist, has been shown to protect against enteric infection by inducing IL-18 in epithelial cells (111) Taken together, these examples highlight how microbiota–epithelial cell interactions help modulate susceptibility to infections through both direct and indirect mechanisms.

Microbiota-derived molecules that modulate infectious diseases

Commensal microbes produce chemicals at a diversity that rivals that of any other microbial ecosystem (112, 113), a feature that attests to their vast potential in modulating host physiology, including susceptibility to infection. The molecules can either be produced directly by commensal microbes (i.e., microbial products) or result from microbe-mediated modification of host compounds (i.e., microbial metabolites). Regardless of how they are produced, these microbiota-derived molecules can influence infections by either modulating the host response or directly impacting pathogens.

Microbial products

The first century of microbiology largely focused on pathogens, with attempts to clarify the molecular basis for how they cause disease. A wide variety of virulence factors have been identified, and one major class includes pattern recognition receptor (PRR) ligands, such as lipopolysaccharide, lipoteichoic acid, and peptidoglycan (114). Just as these molecules help pathogens shape the host response to infection, the host immune system is similarly guided by the TLR agonists expressed by commensal bacteria. NOD1 recognition of microbiota-derived peptidoglycan enhances neutrophil function to help protect against pneumococcal sepsis (115), and glycolipids from various *Bacteroides* species induce interferon β that leads to protection against infection with either influenza virus or vesicular stomatitis

virus (116). It is not clear what drives these divergent responses across different bacteria, though it may relate to subtle—yet important—structural variations in the bacterial products. Moreover, the context of how these molecules are delivered is also critical. *Bacteroides fragilis* polysaccharide A, the archetypal immunomodulatory molecule from a commensal bacterium, is required for abdominal abscess formation but also promotes immunoregulatory changes in other disease settings (117). In contrast to direct production of PRR ligands impacting infection severity, *Enterococcus faecium* produces a peptidoglycan hydrolase, SagA, that protects against *Salmonella* and *Clostridiodes difficile* infection in a MyD88- and NOD2-dependent fashion (118, 119).

Beyond expression of PRR ligands that modulate host immunity, commensal microbes also produce molecules that can directly antagonize pathogens, a function that helps them maintain their niche in an ecologically dense environment. One manner in which bacteria accomplish this is through the secretion of bacteriocins, which are peptide-based toxins that target and kill other bacteria. In many cases, these bacteriocins specifically target similar or closely related species, such as observed with microcin-producing *Escherichia coli* protecting against infection with adherent-invasive *E. coli* and *Salmonella* (120). In some cases, the bacteriocin confers protection against more distantly related species: a *Blautia producta*-produced lantibiotic reduces colonic colonization of vancomycin-resistant enterococci (121). Finally, gassericin A, a bacteriocin expressed by *Lactobacillus gasseri* that targets various food-borne pathogens, confers resistance to diarrhea by binding to keratin 19 in the plasma membrane of intestinal epithelial cells and enhancing fluid absorption (122), a finding that demonstrates bacteriocins can also directly affect the host.

Microbial Metabolites

Some of the best studied microbiota-derived metabolites include short chain fatty acids (SCFAs), bile acids, and tryptophan breakdown products. There are a growing number of examples where each of these classes of molecules help protect against infection. Commensal bacteria differ in their capacity and propensity to produce SCFAs, with differences also present in which specific SCFAs are made; however, multiple SCFAs have been shown to reduce infections. Microbiota-derived butyrate, particularly from clostridial organisms, helps maintain the intestinal barrier integrity and protects against *Salmonella* infection (123, 124); acetate produced by *Bifidobacterium longum* can improve intestinal defense and protect against enteropathogenic infection (125); and succinate generated by *Tritrichomonas*, a protozoan, induces small-intestinal remodeling and limits infection by other helminths (126). Furthermore, SCFAs help acidify the proximal colon and directly facilitate clearance of a variety of aerobic pathogens by eliminating the benefit of their O_2 and NO_3 respiration (127). More broadly, SCFAs offer a dual-pronged defense against infection by also promoting host antimicrobial immune responses (126, 128–131). In the case of bile acids, many commensal bacteria are able to hydrolyze primary bile acids into free bile acids, but only a small subset are able to dehydroxylate them into secondary bile acids (132). Generation of secondary bile acids by *Clostridium scindens* has been shown to protect against *C. difficile* and *Entamoeba histolytica* (133, 134). Moreover, colonization resistance to *Vibrio cholerae* is mediated via microbiome-derived bile salt hydrolase activity, and the abundance of this enzyme in the fecal microbiota of humans correlates with

infection (135). Similar to SCFAs, microbiota-derived tryptophan metabolites (e.g., indole and its derivatives) can act directly on bacterial and fungal pathogens, in this case by inhibiting virulence pathways and/or pathogen growth (136–140). Moreover, tryptophan metabolites also modulate the mucosal barrier function and the host immune response (most notably, levels of IL-22 and group 3 innate lymphoid cells) to impact bacterial and fungal infections (141–144). Intriguingly, indole-3-carbinol, a specific tryptophan metabolite that regulates the number of intestinal group 3 innate lymphoid cells, is vertically transmitted from mother to infant via breast milk (42), thereby providing a mechanism for microbiome-mediated multigenerational control of immune responses that can impact severity of infections (145, 146).

In addition to these widely studied metabolites, there is growing evidence of other bacterial metabolites that impact infection outcomes. Microbiome-mediated increases in taurine levels enhances NLRP6 inflammasome-induced colonic IL-18 secretion and downstream antimicrobial peptide expression, while histamine, spermine, and putrescine suppresses IL-18 secretion and antimicrobial peptide expression (147). While this study did not directly link these changes to infection severity, it is well established that antimicrobial peptides constitute a key host defense against infection. Finally, *Clostridium orbiscindens* metabolizes dietary flavonoids to produce desaminotyrosine, which induces type I interferon and protects against influenza virus (148). These examples, which highlight the range of potential microbiome-derived molecules and their effects, underscore how much more there is to be learned regarding bacterial metabolites. Efforts are ongoing to exhaustively catalog the genes and phenotypes of commensal microbes, which will undoubtedly unveil broader classes of metabolites that impact infection severity.

Modern world influences on the intestinal microbiota

As highlighted by the examples above, it is evident that the microbiota plays a critical role in modulating susceptibility to infection. It is important to note that medical and technological advancements over the past century have had profound impacts on the structure of the microbiota and risk of infections (Figure 2). For example, the advent of antibiotics has drastically reduced morbidity and mortality due to infectious diseases (1); however, these treatments have profound and lasting effects on the microbiome (15, 149). Even a quarter of drugs that are not conventional antimicrobials influence the growth of commensal microbes (150). While antibiotic treatment has clearly been linked to increased risk of subsequent infections, it is likely—but as of yet unproven—that some of these non-antimicrobial therapies similarly modify the microbiota in ways that alter susceptibility to infection. This concept of collateral damage to the microbiota has been incorporated into antimicrobial stewardship strategies, and it is likely that a similar consideration may be needed for other drugs as well. Other changes in medical practice beyond therapeutics also alter the microbiota and can impact infectious risk. Indeed, childbirth via Cesarean section, which has become much more common in modern times, is associated with a small, but statistically significant, increase in rates of enteric infections in children less than 5 years of age (151). This association between Cesarean sections and an altered microbiota in early life has given rise to attempts to normalize this dysbiotic microbial community (152), though it remains to be seen whether this sort of intervention alters health outcomes. A large-scale randomized

clinical trial, however, has shown that treatment of high-risk infants with a combination of prebiotics and probiotics resulted in a decreased incidence of sepsis (153), a finding that demonstrates modulation of the microbiota in early life can impact rates of infection.

Beyond changing medical practices, technological advancements have completely reshaped dietary habits such that the typical Western diet bears little resemblance to that of a hunter–gatherer (154). These changes have had a drastic impact on the microbiota as evidenced in both controlled and cross-sectional studies (12, 13, 155). Diets that contain low amounts of fiber—a hallmark of Western diets—are linked with thinner mucus layers, disrupted spatial localization of the microbiota, reduced SCFA production, and altered susceptibility to infections (85, 156–158). In addition, the increased protein content of Western diets leads to greater tryptophan intake, which may lead to functionally important differences in tryptophan metabolites and infection severity (144, 159). Of note, microbiota changes induced by dietary shifts impact many non-immune facets of host physiology, which may also impact the development of infectious diseases (160). These dietary effects on the microbiota have increased interest in developing dietary interventions and rational prebiotics that help shape the microbiota into beneficial states (161), though the specific intervention may need to be individualized (162).

Conclusions

Although the microbiota has long been known to provide colonization resistance against infections, it is now clear that it also modulates susceptibility to infectious diseases through a variety of mechanisms. Alterations in the microbiota, particularly those induced by modern world changes, influence and—in many cases—increase susceptibility to infections; however, this should not be seen as a call to revert back to a “simpler” lifestyle. Rather, careful consideration of how these changes impact microbiome-dependent infectious risks will highlight high-priority areas—some of which are detailed in this review—that can be exploited as therapeutic strategies. Ultimately, understanding the molecular mechanisms underlying how the microbiota impacts infectious risks and severity of infections will empower development of therapies that can shift this host–microbiota–pathogen balance back to a healthier state.

Grant Support:

C.Y.T. is supported by a National University of Singapore Development Grant. Z.E.R. is supported by the National Science Foundation grant DGE 1545220. N.K.S. receives support from The Hartwell Foundation, as a Translating Duke Health Scholar, and as a Whitehead Scholar.

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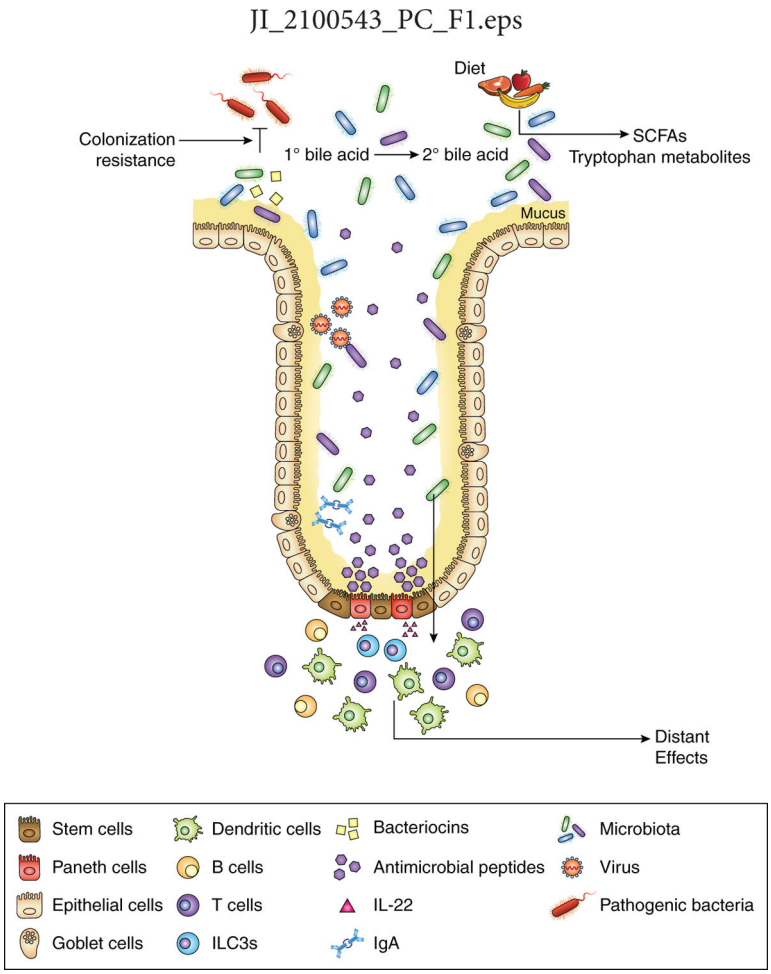

Figure 1. The microbiota impacts infectious diseases via multiple mechanisms.

The microbiota directly affects the ability of pathogens to colonize the host by niche exclusion (*colonization resistance*) and producing molecules (e.g., bacteriocins) that target pathogens. Bacterial products can both influence the infectivity of pathogens and also modulate the immune system. The microbiota indirectly alters the course of infection by modulating epithelial cell responses [e.g., mucus production, expression of antimicrobial peptides (AMPs), stem cell regeneration) and through the production of various bacterial metabolites. These various mechanisms can alter the course of infectious diseases locally and also at distant sites. Although these processes occur at all mucosal surfaces, the small-intestinal epithelium is depicted with enterocytes in yellow, goblet cells in purple, stem cells in brown, and Paneth cells in red.

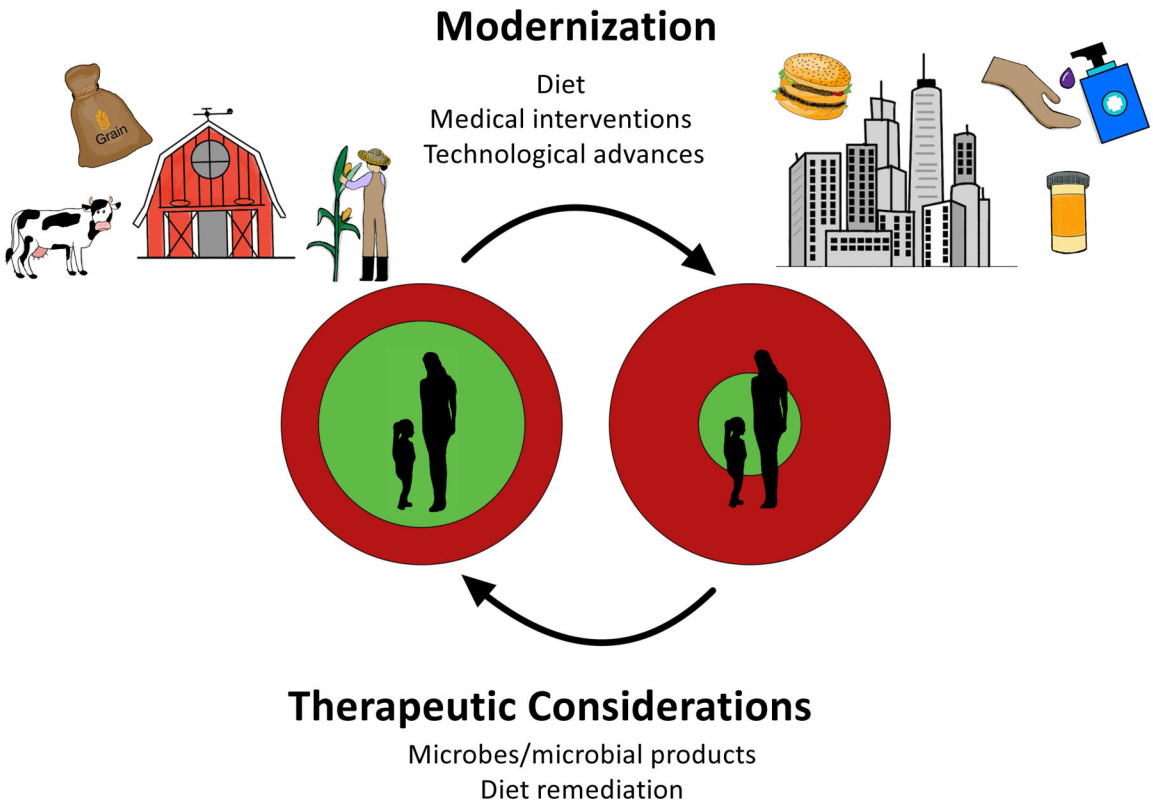

Figure 2. Modernization of lifestyles has altered the microbiota and infectious risks.

Although individuals benefit from the many conveniences of urbanization and technological developments, these same factors have altered the microbiota. In doing so, the protective "shroud" offered by the commensal microbiota (green circle) is insufficient to defend against pathogenic exposures (red circle; right side). With ongoing development of microbiome-based therapeutics—including prebiotics to alter the structure–function of the microbiome—there is an opportunity to restore the microbiome such that its protective shroud begins to cover the host again and provides balance to host–microbiota–pathogen interactions (left side).