HHS Public Access

Author manuscript

Crit Rev Immunol. Author manuscript; available in PMC 2020 July 15.

Published in final edited form as:

Crit Rev Immunol. 2019 ; 39(5): 313–328. doi:10.1615/CritRevImmunol.2019033233.

Impact of the Microbiome on the Immune System

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Abstract

Higher organisms are all born with general immunity as well as with, increasingly, more specific immune systems. All immune mechanisms function with the intent of aiding the body in defense against infection. Internal and external factors alike have varying effects on the immune system, and the immune response is tailored specifically to each one. Accompanying the components of the human innate and adaptive immune systems are the other intermingling systems of the human body. Increasing understanding of the body's immune interactions with other systems has opened new avenues of study, including that of the microbiome. The microbiome has become a highly active area of research over the last 10 to 20 years since the NIH began funding the Human Microbiome Project (HMP), which was established in 2007. Several publications have focused on the characterization, functions, and complex interplay of the microbiome as it relates to the rest of the body. A dysfunction between the microbiome and the host has been linked to various diseases including cancers, metabolic deficiencies, autoimmune disorders, and infectious diseases. Further understanding of the microbiome and its interaction with the host in relation to diseases is needed in order to understand the implications of microbiome dysfunction and the possible use of microbiota in the prevention of disease. In this review, we have summarized information on the immune system, the microbiome, the microbiome's interplay with other systems, and the association of the immune system and the microbiome in diseases such as diabetes and colorectal cancer.

Keywords

microbiome; innate immunity; adaptive immunity; microbiome interplay

I. INTRODUCTION

All organisms are ingrained with barriers that allow them to protect themselves from their external environment, clear pathogens and other foreign material, and regulate their internal environments by the disposal of dysfunctional cellular components. This type of general immunity becomes more complex the higher one goes on the evolutionary chain. Humans and other higher organisms are all born with a general immunity as well as increasingly

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more specific and diverse immune systems. The divergence of immune functions exists even among species that are closely related, likely due to the need to keep pace with the evolutionary rate of pathogens.[1] There is a high amount of redundancy among the many components of the human immune system. This redundancy provides insurance against the failure of one component to compensate in the presence of a pathogen; such compensation becomes evident upon the inactivation of a defense pathway and the subsequent activation of another.[2]

II. IMMUNE SYSTEM COMPONENTS

The redundancy of the immune system arises from the ability of each of its various components to protect the body. Most immune system components are able to differentiate in order to achieve more specific functions or signal to other constituents for the overall production of an immune response. These variable functions of the immune system, specifically the innate and adaptive immune systems, overlap to provide general immunity for the body.

The immune system comprises interactive lymphoid organs, humoral constituents, and cells.[3] The components of the immune system are mostly derived from internal organs that each provide specific individual elements. The primary organs of the immune system are the bone marrow, where leukocytes are produced from pluripotent hematopoietic stem cells, and the thymus, where T cells mature and differentiate. The main secondary organs of the immune system include the spleen, which recycles red blood cells and also stores some macrophages and other various defense cells, and lymph nodes and vessels, which drain fluid and traffic antigens and immune cells (Fig. 1).

The first defenses of the immune system are mechanical barriers such as the integumentary system, acidic pH in the stomach, mucous membranes, and tears and sweat. These nonspecific components work as basic anatomical obstacles against the external environment. The skin has both tight junctions that block pathogen entry and antimicrobial peptides that are activated by proteolytic cleavage, like cathelicidins and β-defensins that combat pathogens in a variety of ways.[4,5] Both the skin and the gastrointestinal (GI) system have differing pH levels that are incompatible with the survival of most invading pathogens. Mucous membranes, like those present in the respiratory and GI tracts, trap small molecules.

The most apparent effect of the microbiome on the mechanical systems of the immune system is in the GI tract, where there are two mucus layers, one firmly adherent and the other loosely adherent. The layers are made of mucins (MUCs) with various glycosylation patterns and structures: the firm layer is attached to the epithelium; the loose layer provides a nutrient source for bacteria and is where the bacteria of the gut are found.[6] Since bacteria are absent in the firm layer, the loose layer is the site of microbiome shifts in relation to the body's fluctuations in the face of disease. Tears help physically remove material from the eyes and contain lysozymes—hydrolytic enzymes that cleave glyosidic bonds in N-acetylmuramic acid and N-acetylglucosamine—which break down peptidoglycan in the cell walls of bacteria.[7] If a foreign molecule is able to make it past these initial barriers, then the immune system must respond accordingly.

A. Innate Immunity and Components

The two arms of the immune system are the innate arm and the adaptive arm. There is a high degree of crossover between them (Table 1). The innate immune system can be broadly described as the mechanical barriers, but usually it is described as the rapid response elements. The most important function of the innate immune system is to respond and recruit other immune cells quickly to the site of infection or inflammation. The components of innate immunity are outlined in Fig. 2. This recruitment is done through the secretion of cytokines, like interleukins, interferons, and tumor necrosis factor (TNF), and chemokines, named on the basis of their cysteine separation: CL/CR, one cysteine in the N-terminus; CCL/CCR, adjacent cysteines; CXCL/CXCR, the cysteines are one amino acid apart; and CX3L/CX3CR, the cysteines are three amino acids apart.[8]

Cytokines are small proteins that, upon secretion, regulate functions of cells that have the associated receptors. They are essential to the effectiveness of immune response, but can have negative effects. Cytokine dysregulation has been linked to many autoimmune disorders. This is likely due to their rapid self-amplification. For example, type I interferons (IFN-α, IFN-β, IFN-ω, IFN-ε, and IFN-κ) have links to systemic autoimmune diseases like lupus erythematosus and sclerosis.[9] Chemokines are a distinct class of cytokines that chemoattract other cells and prompt their migration. Typical chemokines target specific cell receptors and promote leukocyte migration. Chemokines have also been measured and implicated in diseases such as cancers, autoimmune disorders, and inflammatory diseases like chronic obstructive pulmonary disease, where the constant influx of inflammatory immune system components has an exacerbating effect on the lungs.[10,11] Cytokines and chemokines are critical components in the movement and activation of innate and adaptive immune responses.

1. Macrophages—Macrophages are formed from differentiated monocytes and reside in tissues. A macrophage's primary role is the phagocytosis of pathogens and the release of cytokines and chemokines after recognition of the pathogen-associated molecular patterns of invading pathogens via their own pattern recognition receptors. Macrophages are considered the first line of defense in the innate immune response and recognize pathogen-associated molecular patterns through the action of toll-like receptors, scavenger receptors, Dectin-1, mannose receptors, and complement receptors, all culminating in pathogen phagocytosis.[12] Once phagocytosed, the combination of the phagocytic vesicle and internal lysosomes results in the phagolysosome, where foreign material is degraded via a respiratory burst, pH alterations, and other enzymatic mechanisms.

Signaling to other immune system components is the other major function of macrophages; once activated they release cytokines and chemokines in order to initiate the inflammatory response and assist in the extravasation of leukocytes to the site of infection. Like most immune cells, macrophages vary in function upon contact with a pathogen; secretion of IL-10, which can inhibit cytokine synthesis in monocytes, and secretion of IL-12 by macrophages have been known to vary in the presence of *Lactobacillus* strains. *Lactobacillus* is a prominent bacteria present in gut microbiota.[13,14] The variation in

cytokine production in the presence or absence of *Lactobacillus* can alter the effector function of macrophages in the gut.

The exact mechanisms that allow macrophages to recognize the normal flora of the gut microbiome as self are elusive, but they seem to acquire inflammation anergy, allowing the absence of an inflammation response, through the up- and down-regulation of certain cytokines.[15] Macrophages are also known to present antigen to T cells, allowing them to have a function in adaptive immunity.[12,16]

2. Neutrophils—Neutrophils are both phagocytes and granulocytes—that is, cells containing granules that hold a variety of pathogen-attacking molecules, including myeloperoxidase, defensins, and other related cytotoxic enzymes.[17] All granulocytes are derived from a common myeloid progenitor. Neutrophils flow freely in the circulation and are the most abundant leukocytes in the body, with an estimated 100 billion produced daily.[17] They are the first to arrive at the site of infection by recognizing a chemokine signal. They then attach to various selectins and roll on to the endothelial cell surface until the integrins bind and hold them firmly in place. Next, they bind inter-cellular adhesion molecules (ICAMs)[17,18] and move across the endothelial cell, following the chemokine gradient toward the infection. The passage of neutrophils and other circulatory components through the endothelial cells is termed *diapedesis*.

At the site of infection, neutrophils recognize and phagocytose pathogens, triggering degranulation that results in the pathogen's termination. In the presence of HIV infection, certain *Lactobacillus* spp. show the ability to increase neutrophil apoptosis, possibly by inhibiting NF-κB, which results in a decrease in inflammatory cytokines.[19,20]

3. Eosinophils—Eosinophils, also granulocytes, mainly target large extracellular parasites and have a role in promoting allergic responses, where they have been seen to potentiate basophil and mast cell responses.[21] Eosinophils reside mostly in the GI tract and as such are in the best position to respond to parasites. Since large parasites—namely, helminths, which infect nearly every third person[22]—cannot be phagocytosed, they are destroyed by the granulocytic action of eosinophils. Cytotoxic granule products like major basic protein, eosinophil-derived neurotoxin, eosinophil cationic protein, and eosinophil peroxidase, along with other enzymes, promote the degradation of invading parasites.[23] IL-25, an inducer of eosinophil, basophil, and mast cell expansion, is mediated by healthy gut microbiota.[24] In the presence of *Clostridium difficile* infection (CDI), IL-25 was reduced in infected mice but their counterparts that had IL-25 replenished saw lower CDI mortality rates, indicating that microbiota-regulated IL-25 increases eosinophil response to CDI.[25]

4. Basophils—Basophils, the least prominent granulocytes, also respond to parasitic invasions and have a more prominent role in the allergic response than eosinophils. Basophils are mainly found in the blood stream and are recruited to infection sites.[22] They can augment allergic responses by feeding back into the allergic response and inducing more inflammation. Also, like eosinophils, they attack large parasites that cannot be phagocytosed. Basophils respond to parasites through chemokine recognition and degranu-

late similarly to eosinophils; these granules contain histamine and cytotoxic-associated enzymes that participate in immunoglobulin E (IGE-) –mediated response.[26–28]

5. Mast Cells—Mast cells are mostly viewed as the primary cells in allergic responses. They are present in peripheral tissues and release cytokines and granules containing histamine that produce inflammation through IgE-mediated interactions. Mast cells and basophils have a high affinity for FcεRI receptors, which promote the release of cytokines and degranulation through their interactions with IgE.[29] T mast cells (mucosal) contain only trypsin; connective tissue mast cells contain both trypsin and chymotrypsin.[30] Mast cell activation leads to nasal irritation, mucus production, and asthma in the upper and lower airways of the respiratory tract. It also causes increased local inflammation but can be problematic if the release of histamine and other products is systemic, which can lead to anaphylactic shock.

6. Natural Killer Cells—Natural killer (NK) cells arise from common lymphoid progenitors, like B and T cells, but are a part of the innate immune system. They do not function like most other innate immune components that attack pathogens directly; instead, they lyse cells in order to stop the spread of already infected cells. NK cells are an area of interest in immunotherapy because they exhibit a cytolytic function against tumors and virally infected cells. They express a wide variety of activating and inhibitory receptors on their cell surface, and it is the balance of signals from these receptors that determines the outcome of NK cell activity.[31–33]

NK cell cytolytic functions include the pathways of perforin granule exocytosis and Fas/Fas ligand interaction. NK cells can also contribute to targeted cell death indirectly by secreting proinflammatory cytokines like IFN-γ and TNF-α. Innate immune cells are thought to have no memory capability, but recent studies have shown that NK cells may acquire immunological memory through cytokine and viral antigen pre-exposure.[34,35] The microbiota effects on NK cells are minimally described, but the consumption of probiotics, mainly *Bifidobacterium lactis*, has been shown to increase NK cell production in elderly populations.[36]

7. Complement System—The complement system, or complement cascade, consists of a variety of proteins that circulate when inactive. Upon activation they induce an enzyme cascade that eventually leads to a large complement response. The complement system has three pathways of activation—classical, alternative, and mannose-binding lectin—that all converge on a C3 convertase. Differentiation of the C3 protein leads to three mechanisms that assist the immune response: opsonization of pathogens for phagocytic and adaptive immune component recognition, recruitment of other immune components to the site of infection, and formation of the membrane attack complex (MAC), which forms pores in bacterial membranes, contributing to their lysis.[37]

The complement system's main advantage is its amplification in support of an immune response. Its role in clearing microbes and its amplification mean that it has a large amount of contact and responsibility in the clearance of bacteria and other pathogens. As such, it is a prime example of the interplay between the immune system and microbiota. If the

complement system recognizes normal microbiota as pathogenic, it induces a large immune response resulting in a myriad of health issues. Dysfunctions of the complement system, including inactivation of receptors and up- or down-regulation of the C3 convertase, have been indicated in preterm births, multiple skin disorders, and colitis.[38–40]

8. Dendritic Cells—Dendritic cells (DCs) are the bridge between innate and adaptive immune responses and are produced from both common myeloid progenitors and common lymphoid progenitors, with the former being about 10-fold more prevalent than the latter.[41] Dendritic cells are the main antigen-presenting cells (APCs) of the immune system, phagocytosing and bringing processed antigen and peptide material from the site of inflammation to the draining lymph nodes. Up-regulation of chemokines, namely CCR7, helps direct dendritic cells away from the site of inflammation and toward lymphatic vessels and nodes.[42] Once DCs enter the lymph node through the afferent lymph, they activate naïve B and T cells by finding antigen-specific cells directed by the major histocompatibility complex (MHC), which allows for antigen loading and presentation.[43,44] This contributes to specificity in the adaptive immune response, aiding in the clearing of infections and in turn assisting the innate immune system.

Dendritic cells that are in contact with commensal bacteria need a way to distinguish self from nonself to prevent inappropriate maturation and presentation of normal microbiota as pathogenic. The mechanisms that underlie the recognition of resident microbiota are not clearly understood. Dendritic cells recognize self by differing expression of pattern recognition receptors (PRRs), but some form of conditioning or secondary signaling must be involved in the recognition of bacteria and microorganisms in the microbiome although none have been specifically identified.[45,46]

B. Adaptive Immune System and Components

The adaptive immune system diagrammatically follows the innate immune response, but it feeds back into the innate response so the two arms have indistinguishable timelines in the human body. Both B and T cells originate in the bone marrow from the common lymphoid progenitors, but while B cells mature there, T cells mature in the thymus. Adaptive immunity is associated with immunological memory and long-term immune system effects. It uses both cell-mediated and humoral immunity to provide protection against intracellular pathogens.[47] Generally, B cells are involved in the production of antibodies and T cells are involved in the propagation of B cells, directly attacking pathogens, and general regulation of an immune response.

1. T Cells—T cells, or T lymphocytes, are generated in the bone marrow and then mature in the thymus. While in the thymus, they undergo antigen receptor rearrangement and positive and negative selection to determine whether they will commit to becoming a cluster of differentiation (CD) cells, CD4+, or CD8+ T cells, and whether they will exit the thymus for peripheral circulation. T cell receptors undergo α-and β-chain rearrangement during somatic recombination of their variable, diversity, and junctional genes. The enzymes RAG 1 and RAG 2 and terminal deoxynucleotidyl transferase are involved in the recombination

process, which results in a wide range of possible T cell antigen receptor combinations that culminate in diverse pathogen recognition.[48]

Prior to leaving the thymus, T cells go through positive and negative selection. Positive selection involves T cell receptor interaction with a variety of MHCs in order to determine coreceptor expression; CD8+ T cells are MHC class I restricted, while CD4+ T cells are MHC class II restricted.[49] If a T cell has no affinity for self MHC, it will die off due to neglect. Negative selection induces apoptosis of cells that bind with high affinity to self MHC. The possible repertoire of T cell combinations is large, but it is estimated that, through positive and negative selection, almost 90% of T cells do not become immunocompetent in circulation.[50,51] The CD4+ and CD8+ T cells that do make it to circulation can induce multiple effects in the immune response. CD8+ T cells are cytotoxic and target cancerous and pathogen-infected cells. CD8+ T cells secrete granules similar to NK cells and induce apoptosis of targeted cells. They also release cytokines, like IFN-γ and TNF-α, which activate macrophages.[52]

Short-chain fatty acids, like butyrate, are a common product of gut microbiota which potentially enhance the antipathogenic function of CD8+ T cells via up-regulation of IFN-γ.[53] CD4+ T cells are helper cells that regulate immune responses through the release of cytokines and activation of other immune components. CD4+ T cells, with the help of dendritic cells, activate CD8+ T cells by the up-regulation of CD40 and Interleukin-2, which increases the level of activity in CD8+ T cells.[54,55] CD4+ T cells in the form of T follicular helper cells (T_{FH}s) induce class switching in B cells. T_{FH}s release a myriad of cytokines that bind to receptors on B cells, activating them and leading to proliferation and differentiation.[56]

Th17, another differentiated CD4+ T cell, has been shown to produce IL-22, which has been implicated in the destruction of goblet cells in the gut by the up-regulation of the MUC1, MUC3, MUC10, and MUC13 genes.[57] This enhancement of cell degradation by Th17 in the gut is an example of T cell and subsequent cytokine effects on the resident microbiota of the gut in colitis. Memory T cells, which are different from cytotoxic T cells, have an important function in immunological memory. They differ from memory B cells in that they recruit other immune components in response to an earlier encounter, while B cells produce antibodies on the basis of encounters with pathogens. Helper T cell function is schematically presented in Fig. 3.

2. B Cells—The main function of B cells is the secretion of antibodies, and thus they play a role in humoral immunity. Antibodies opsonize, neutralize, and activate the complement system; their production of antibodies ($< 10^{11}$) is through recombination.[58] When B cells are activated upon antigen binding on their receptors, they differentiate into plasma cells, which are responsible for the secretion of antibodies. B cells enhance the immune response through antibody secretion and the release of cytokines that sensitize pathogens, allowing other components of the immune system to respond more efficiently in the event of pathogenic encounters. B cells stimulate and present antigens to CD4+ T cells and also produce cytokines like IL-6, TNF-α, and Interleukin-10.[59] They have been seen to be the dominant APC in some situations.[60]

Contact with differing microbial compositions in the gut can affect the differentiation and subsequent repertoire of antibodies produced from B cells; diversity in the gut microbiota can regulate levels of IgE.[61] Early exposure to ubiquitous microorganisms can lead to increased microbiota diversity and increased immune system efficacy against some diseases. IgA coats most of the bacteria in the gut and can affect its composition and function, as seen in IgA deficiencies that reduce microbiota diversity.[62]

III. CRITICAL FACTORS FACING THE IMMUNE SYSTEM

The immune system is in flux in its active state and can be affected by multiple factors, including internal and external environments, age, sex, diet, and exercise. Aging is associated with a decrease in immune cell signaling and reduced B and T cell production.[63] Aging is also associated with chronic inflammation; as cellular function declines, the risk for age-related diseases increases.[64] Sex is another major determinant of susceptibility to diseases; sex differences have been shown to have an effect in cardiomyopathies, heart disease, hypertension, certain cancers (e.g., renal, gastric, bladder, pancreatic), and Alzheimer's.[65] Diet and exercise have been shown to affect the immune system as well. Frequent exercise and good nutritional practices have long been associated with better health outcomes. Even moderate exercise has been associated with better immunosurveillance and more effective immune responses.[66] Malnutrition, over-, and undernutrition are leading causes of immunodeficiency and represent a large global health burden; on the other hand, regulated nutritional intake has been shown to have positive effects on the immune system and may help to prevent some immune dysfunctions.[66,67]

Internal and external environmental factors can play a huge role in the efficiency of the immune system. Chemicals, pollution, radiation, genetic variations, consistent infections, and allergies are just a few of these. One emerging internal factor having a diverse role throughout the body is the microbiome, which has been an incredibly active area of research for almost two decades.

A. The Microbiome

The microbiome is the collection of bacteria, viruses, fungi, and other microorganisms that live in and on all mammalian organisms.[68] The ratio of this community of microorganisms to normal cells in the body is about 1.3 to 1.[69] The interplay between the microbiome and the body is elucidated by ongoing research, which is revealing the microbiome's innumerable effects. The highest concentration of microbes and lymphoid tissue is in the GI tract, where the immune system and the microbiota have a symbiotic relationship.[70,71] The immune system benefits from the microbiome as it provides pathogen colonization resistance. However, the microbiota can also alter the body's response to a pathogen and lessen the efficiency of drugs and the immune system.[70]

A crucial step toward understanding the importance of the microbiome in humans was the development of gnotobiotic, or germ-free (GF), animals, which allow study of immune responses in the absence of microbiota.[72] Mice with a functioning microbiome tend to have greater macrophage digestive ability and a more rapid immune response when compared to GF mice.[73] The microbiome of the GI tract has been shown to secrete antimicrobial peptides

termed *bacteriocins*, which are proteins produced by bacteria that are active against related strains of bacteria and exhibit bactericidal and bacteriostatic effects.[71,74] This allows some pathogens to be disposed of within the microbiome itself instead of relying on a classic immune response.

Microbiota have been linked to multiple immune functions, including the production of cytokines, maintenance of homeostasis, T cell production, and regulation of the immune system.[75–77] The microbiome is involved in heavy interplay with the immune system and is affected to a great degree by environmental factors through birth and infancy.[78] It has also been identified as a potential player in the development of certain immune system components such as myeloid cell derivatives,[79] suggesting that the microbiota have various roles in the differentiation and efficacy of immune responses.

The microbiome is significantly affected by antibiotics and diet. Diet can potentially alter the microbiota and, in turn, alter T cell responses to microbes.[80] Antibiotics decrease the level and diversity of the microbiota, reducing the efficacy of the immune response, as mentioned. This is why probiotics should be prescribed along with high-dose antibiotics.[81]

B. Microbiome-Associated Diseases

A large number of diseases arise from a dysfunctional microbiome. As discussed earlier, the microbiome has varying effects on the immune response. A few conditions that the microbiome has been associated with are inflammatory bowel disease (IBD), type 1 diabetes, multiple sclerosis, HIV, and even some cancers.[82–86] The overarching term for microbiota imbalance is *dysbiosis*, or loss of beneficial microbiota, overgrowth of harmful microorganisms, and/or loss of microbial diversity.[87] Dysbiosis can occur from overuse of antibiotics, an unhealthy lifestyle, recurrent or serious infections, and the like.

1. Diabetes—Type 1 diabetes (T1D) is an autoimmune disorder in which pancreatic beta cells are attacked by effector T cells. This renders the pancreas incapable of producing insulin for use in metabolic regulation. Patients with T1D inject insulin in order to combat rising blood glucose levels, which result in high blood sugar levels or hyperglycemia if unchecked. There is currently no cure for T1D, and insulin injection is the only effective treatment.

Because of the variability in microbiota composition, it is difficult to find a specific link between exact microbiota changes and any disease; however, the gut microbiome of infants has been observed in order to establish a connection between it and the onset of T1D. A study conducted in Finland and Estonia suggest that infants predisposed to T1D-susceptible human leukocyte antigen (HLA) alleles and later diagnosed with early-onset diabetes show lower gut microbiota diversity along with higher levels of human beta-defensin 2.[88] This finding demonstrate that infants predisposed to T1D may have proinflammatory and less diverse microbiota when compared to other infants. Since the microbiota go through a dynamic change through birth and infancy, this period could be a highly relevant area of research on connections between the microbiota and T1D. There could also be specific compositional differences in the microbiota of people diagnosed with T1D. Diabetic children have shown an increase in *Bacteroidetes* and a subsequent decrease in

Actinobacteria and *Firmicutes* when compared against healthy children.[89] The link between bacterial composition and T1D should continue to be investigated in order to find better diagnoses and treatment options.

2. Colorectal Cancer—Colorectal cancer (CRC) is a slow, progressive cancer that begins as benign polyps in either the colon or the rectum. Estimates of new cases of CRC, colon, and rectal cancers for 2019 were 145,600, and estimated deaths due to CRC were 51,020, which places colorectal cancer as one of the major causes of cancer deaths in the United States.[90] Since the gut has the highest concentration of microorganisms that contribute to the microbiome of the host, there is great likelihood that a correlation can be made between the microbiome and colorectal and other digestive system cancers. The microbiome of the host may play a role in tumor development due to interaction between the tumor and its surrounding environment. Microbiota composition has been associated with certain aspects of tumor differentiation in CRC, including *Bifidobacterium*, that can be linked to inhibition of CRC carcinogenesis.[91]

Some research is seeking to take advantage of these bacteria in the gut. Both *in vitro* and *in vivo* studies have revealed that prebiotics contribute to the inhibition of aberrant crypt foci, which are a precursor to colorectal polyp formation.[92] Other microorganisms may contribute to conditions in the microbiome that drive the tumorigenesis of CRC tumors. Bacteria such as *Fusobacterium nucleatum*, *Coriobacteridae* spp., and *Faecalibacterium* spp., have been shown to be overrepresented in CRC tissues when compared to surrounding tissue.[93,94] While these bacteria apparently increase in relation to CRC, further investigations need to be conducted before they can be specifically indicated as drivers of CRC.

IV. MICROBIOTA IN DIAGNOSIS AND TREATMENT

The identification of different roles for bacteria in specific diseases should lead to the recognition of microbiota as agents of disease therapy and diagnosis. Many avenues for microbiota involvement in treatment being explored involve the use of prebiotics. Fecal microbiota transplantation (FMT) has been used as a treatment for CDI, a major nosocomial diarrheal infection that is often recurrent and represents a large clinical burden in healthcare.[95] CDI is now widely recognized as being related to an imbalance in the microbiome of the gut and, as such, is a target for microbiota-based therapies. FMT is the transfer of fecal material from a healthy patient to a patient in a state of gut dysbiosis.[96] FMT delivered by colonoscopy has been highly effective in the treatment and staving off of CDI. It has been shown to decrease proinflammatory cytokines such as IL-6 and TNF-α and increase anti-inflammatory bacteria like *Lactobacillaceae* and *Ruminococcaceae*, thus restoring microbiota balance in the recipient.[97]

Further study of FMT is required to test its safety and its ability to impact other diseases. Interestingly, the microbiome has also been associated with allergies in which the immune system is modulated by microbiota, possibly resulting in allergic responses.[98,99] Treatment for some allergies may be as simple as prebiotics, probiotics, and synbiotics,[98] which, when combined, can be simple preventative measures to regulate the resident microbiome in order

to increase diversity and normalize the gut flora.[100] Treatments can be as simple as altering dietary intake in order to diversify existing microbiota.

While probiotics and prebiotics can be effective, they are not yet known to be specific for any one bacterium and therefore their disease effects are relatively unknown. Targeting pathogenic bacteria or bacteria that are overrepresented in microbiome-associated diseases by bacteriophages is another potential treatment option. Studies have shown that bacteriophages can specifically target and knock down bacteria in gut microbiota, but also indicate that they affect off-target bacteria.[100,101] The off-target cascade of effects in the microbiome is to be expected due to the high degree of interactivity among microbiota in the gut and elsewhere.

Since the microbiome has been closely associated with the development and response of the immune system in the gut, it may play a role in the systemic response to vaccines.[102] Microbiota may thus be a potential target to increase vaccine efficacy. Studies have shown that *Bifidobacteria* have a positive relation to CD4+ T cell response to certain vaccines; bacillus Calmette-Guerin, oral polio vaccine, tetanus toxoid, and hepatitis B vaccine; *Pseudomonadales*, *Enterobacteriales*, and *Clostridiales* have been associated with lower vaccine responses.[103,104] More understanding of the interaction between microbiota and vaccine efficacy will help in enhancing immunological memory and offer better protection against viral infections. Treatment involving the microbiome will continue to evolve as our understanding of the ecological principles that govern the system evolves.

V. FUTURE PERSPECTIVES

Limited studies have only begun to offer insight into the microbiome's interplay with the systems of the body. Research so far confirms the role of dysbiosis in multiple diseases and host health. There is a need for studies to discover biomarkers or different levels of microbiota composition in the body in order to further diagnostic tools for dysbiosis-related diseases. The most studied example of the microbiota's use as a marker is in IBD, where the bacterial composition of the gut signals the active state of the disease.[105] The bacterial composition of the microbiome and prominent bacteria located at three major microbiome sites are depicted in Fig. 4.[106–108] Diagnostic advancements such as this are critical in the clinical setting as early detection is paramount in most diseases.

Additionally, studies have shown that specific bacteria can be either harmful or beneficial in various diseases. In order to further understand the role of certain bacteria in relation to disease, studies manipulating the makeup of the microbiome in controlled conditions, such as in gnotobiotic mice, may prove critical in defining the relationship between microbiota and various disease presentations.

Targeting specific groups of bacteria and microorganisms of the microbiota and studying their fluctuation in diseases will surely aid the development of efficient means of combating disease within the context of the microbiome, as with FMT and CDI. One obstacle in the eventual application of microbiome research is the variability from one host to another due to genetic polymorphisms and environmental factors. Identification of microbiota

involvement in disease and their potential use in therapy will likely need to be personalized in order to be effective. Future human research and trials will have to take into account population sampling in order to accurately measure responsiveness in the face of variations among individuals.

VI. CONCLUSION

The microbiome interacts with other body systems, especially the immune system, and its effects on the microenvironment of this interaction are largely unknown. The mechanisms that underlie the microbiome's systemic effects are in need of further study in order to be applied in therapeutic settings. Microbiota have been shown to potentiate or interfere with disease progression, and studies are beginning to show the benefits of identifying and using this information in order to provide clinical tools other than antibiotics alone to treat disease. The microbiome has the potential to play a massive role in personalized medicine in the future and greatly improve detection, treatment, and prognosis of multiple diseases.

ACKNOWLEDGMENTS

R.B., S.M., and U.T.S. are supported by grants from the National Cancer Institute (P20CA233355-01); R.B. and U.T.S. are also supported by the National Institute on Minority Health and Health Disparities (U54 MD006882-06). K.P. and S.S. are supported by the National Heart, Lung, and Blood Institute (R25HL125447).

ABBREVIATIONS:

CD	cluster of differentiation
CDI	*clostridium difficile* infection
CRC	colorectal cancer
CXCL	chemokine ligand
CXCR	chemokine receptor
FMT	fecal microbiota transplantation
GI	gastrointestinal
HLA	human leukocyte antigen
IBD	inflammatory bowel disease
IF	interferon
IgE	immunoglobulin E
ILC	innate lymphoid cell
MHC	major histocompatibility complex
MUC	mucin
NK	natural killer

PRRs	pattern recognition receptors
TNF	tumor necrosis factor

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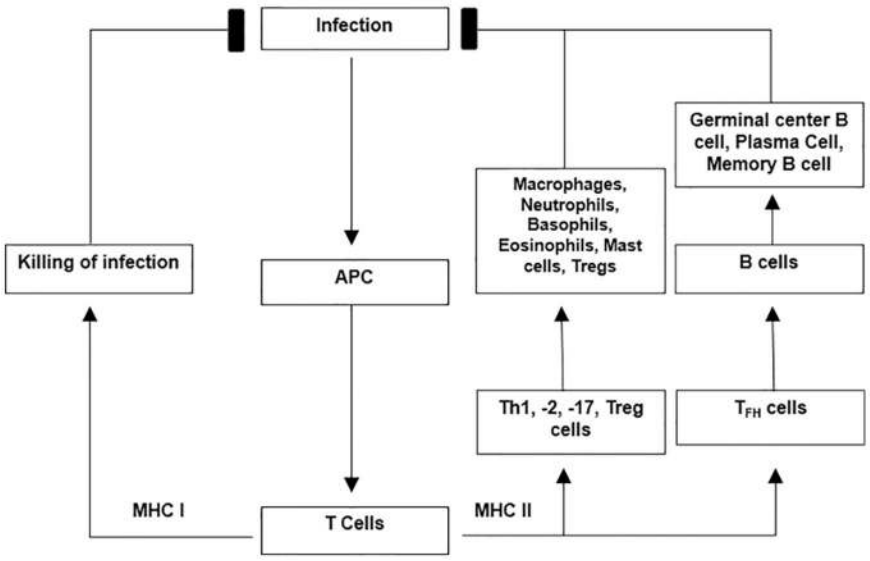

FIG. 1:

Infection course in adaptive immunity. An APC recognizes antigen of an invading pathogen, processes it, and brings it to the draining lymph nodes. In the lymph nodes, the presentation of antigen on MHC class I or class II occurs. CD8+ T cells are MHC-I restricted and CD4+ T cells are MHC-II restricted. Further differentiation of CD4+ T cells helps to activate the immune components and, with the CD8+ T cells (cytotoxic T lymphocytes), the CD4+ T cells attack the original infection.

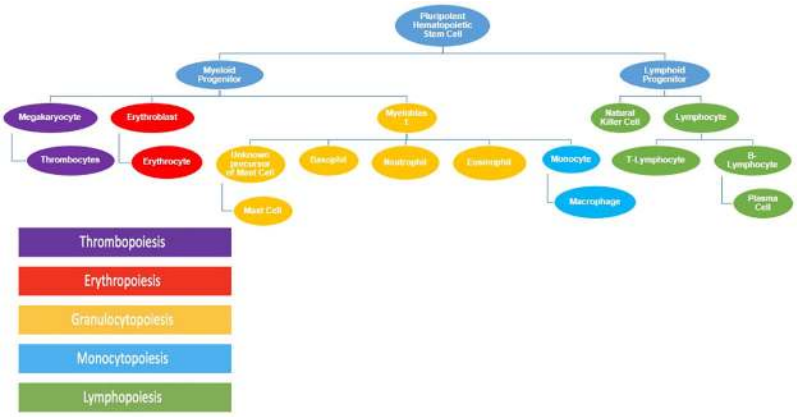

FIG. 2:

Hematopoietic stem cells are multipotent precursor cells with the ability to differentiate into all cells of the blood. Thrombopoiesis is the formation of platelets, the cells involved in primary hemostasis, and platelet plug formation. Erythropoiesis is the formation of erythrocytes, the cells involved in oxygen and CO_2 transport in the blood. Granulocytopoiesis is the formation of granulocytes (neutrophils, basophils, and eosinophils), the cells involved in the immediate response of the innate immune system. Monocytopoiesis is the formation of monocytes; these cells further differentiate into macrophages, which are involved in the innate immune response as well as the adaptive immune response as APCs. Lymphopoiesis is the formation of B and T lymphocytes as well as NK cells. B and T-lymphocytes are involved in the adaptive immune response while NK cells are involved in the innate immune system.

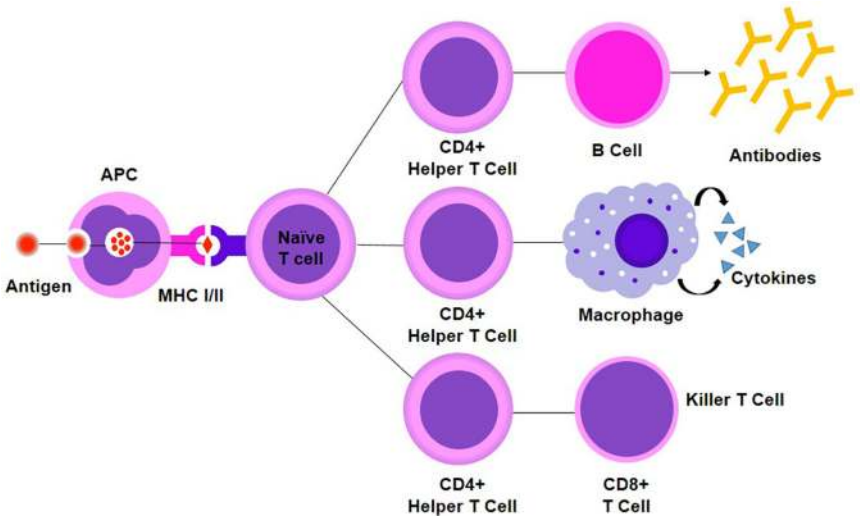

FIG. 3:

Effector T cell functions. Activation of CD4 helper T cells via recognition of antigens presented on MHC II molecules on an APC leads to a subsequent release of cytokines that stimulate the activity of B cells to differentiate into an antibody-secreting plasma cell. Activated CD4 helper T cells, upon contact with a macrophage engaged in the phagocytosis of bacteria, secrete cytokines that increase the microbicidal power of the macrophages by secretion of inflammatory cytokines. A naïve CD8 T cell can be activated directly by a virus-infected dendritic cell or indirectly by help from a CD4 helper T cell, which makes it a killer T cell.

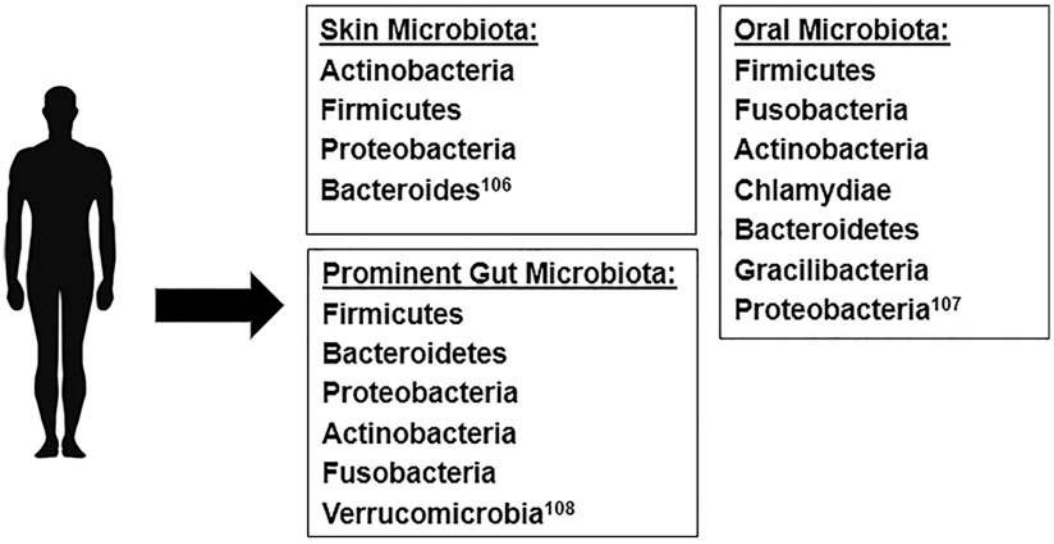

FIG. 4:

Bacterial composition of microbiota. The microbiome consists of varying bacterial compositions. The Human Microbiome Project and outside studies have worked to characterize the microbiome through 16S rRNA and metagenomic sequencing. Listed are a few of the prominent bacteria from three major sites of the microbiome. Similar families of bacteria are seen across most sites in the body, but vary in composition due to their role in certain environments.

TABLE 1:

Features of innate immunity vs. adaptive immunity

	Innate	Adaptive
Function	Immediate response upon antigen recognition	Induction of long-term effects and immunological memory
Components	Monocytes, macrophages, innate lymphoid cells (ILC), neutrophils, basophils, eosinophils, mast cells, NK cells, complement, dendritic cells	B cells, T cells, dendritic cells
Specificity	Nonspecific	Specific
Onset	Rapid	Slow