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The role of intestinal flora in the immune system

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Abbreviations
SCFAs, short-chain fatty acids; SFB, segmented filamentous bacteria; DCs, dendritic cells; Th17, T helper 17; Tregs, T regulatory cells; TJ, tight junction; FMT, fecal microbiota transplantation; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; AID, activation-induced cytidine deaminase; VRE, vancomycin-resistant enterococcus; GI, gastrointestinal; Ahr, aryl hidrocarbon receptor; IL-22, interleukin 22; 2,3,7,8-TCDD, 2,3,7,8 -tetrachlorodibenzo-p-dioxin; APCs, antigen-presenting cells; CNS, central nervous system; ROS, reactive oxygen species; OS, oxidative stress; GF, germ-free; CNS OS, central nervous system oxidative stress; IL-17, interleukin 17; IL-23, interleukin 23; NOD, non-obese diabetic; SPF, specific pathogen-free.
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Abstract
The intestinal tract is the body's biggest digestive organ. Many microbes, including bifidobacteria, *Lactobacillus*, *Escherichia coli*, *Enterococcus*, *Clostridium perfringens*, and *Pseudomonas*, are always present in the intestinal tract. The digestive tract has evolved localized immunological features to defend the body from potential invaders. Its structure, function, and milieu are considerably distinct from common central and peripheral immune organs and account for these characteristics. The intestinal flora and its products provide a microenvironment in the gut that has a significant impact on the area's immune function. In turn, various disorders regulate and alter the kinds of gut microorganisms. The gut flora and immune system are constantly communicating with one another. Additionally, the intestinal microenvironment may be reconstructed with probiotics or microbiota transplantation. This assists in restoring immunological homeostasis and treating or preventing illness.

This manuscript examines how the intestinal flora influences the development and spread of illnesses, which in turn impacts intestinal immunity. We also discuss how improved immune function influences the general and particular immune systems. As a method of disease prevention and treatment, we also discuss how modifying the microenvironment affects the proliferation, differentiation, and release of immune cells in the intestinal region. Finally, we discuss how human behaviors influence gut microorganisms.

Keywords: gut flora; immunity; gut-brain; microbiota; antibiotics; autoimmunity; inflammation

Background

Intestinal bacteria and other microbes significantly aid food digestion. Biotin and vitamin K are made by bacteria in the gut, among other things. The good bacteria in the digestive tract are called "intestinal flora" [1]. Dhar and Mohanty [2] say that the billions of bacteria in a person's intestinal flora (gut microbiota) help make vitamins, keep intestinal cells healthy, build the immune system, and eliminate toxins. Schoeler and Caesar [3] say that the microbiota is at the center of stimulating, shaping, and releasing the host's immune system. Over time, the immune system has changed to protect the host's relationship with many microorganisms that are always changing [4, 5]. When it works right, this partnership between the immune system and microbiota allows the activation of protective responses to pathogens and the maintenance of regulatory pathways that help keep tolerance to harmless antigens.

Researchers Witkowski et al. [6] and Lazar et al. [7] found that overuse of antibiotics, changes in diet, and the loss of important partners like worms have all led to microbiota in high-income countries lacking the resilience and variety needed to develop balanced immune responses. Research by Zheng et al. [8] has led to the idea that this is partly to blame for the huge rise in autoimmune and inflammatory diseases in parts of the world where our symbiotic relationship with the microbiota has been most damaged. The immune system is made up of innate and adaptive parts and has an amazing ability to change and adapt to new situations [9]. Together, the cells in this network are a powerful regulator of host homeostasis. This means that after being exposed to microbes and the environment, tissues can be kept in good shape and fixed.

Intestinal flora and immune homeostasis

The development of different arms of the immune system, especially those related to adaptive immunity, happens simultaneously with the development of complex microbiota. This supports the idea that a lot of this equipment has evolved to keep symbiotic relationships with these very different microbial communities. According to research by Tang et al. [10], the microbiota, in turn, help the immune system and fine-tune it. At birth, the immune system is exposed to microbiota for the first time. The embryonic gastrointestinal tract is normally considered sterile [11, 12]. People think that these first contacts shape the mucosal immune system and the immune system as a whole. Vieira Borba et al. [13] say that some of these early responses to commensals are caused by things in the mother's milk. But scientists still don't know much about how new tissues adapt to the difficult task of microbial colonization.

Colostrum and breast milk have live bacteria, metabolites, IgA, immune cells, and cytokines [14, 15]. These things work together to make a baby's microbiota and the host's response to it [16]. For example, the presence of metabolites like oligosaccharides in breast milk helps certain microbiota grow, like *Bifidobacterium*. Maternal IgA limits immune activation and microbial attachment by binding to nutritional and microbial antigens [17, 18]. Since bacterial translocation from the mouse gut is increased during pregnancy and breastfeeding, it has been thought that bacterial-loaded dendritic cells in the milk contribute to the immunological imprinting of the newborn by changing the type of immune response to commensal antigens [19].

To understand how the microbiota affects the immune system, you must remember that pathogenicity often depends on the situation [20]. The activation state of the host, the genetic predisposition of the host, and where the specific microbe is located all play important roles in a microbe's ability to cause or spread illness. This includes microbes that are part of the microbiota [21]. The ways the immune system keeps working with the microbiota are very similar to how harmful pathogens are stopped from spreading. Nell et al. [22] said that one of the main things the immune system does on its own is keeping track of our relationship with the microbiota. This means that the immune cells are most concentrated in the parts of the body where commensals live, like the skin and the gastrointestinal (GI) tract. Researchers Pickard et al. [23] found that one-way hosts keep their microbiota in check is by reducing the interactions between microbes and the epithelial cell surface. This keeps tissue inflammation and microbial translocation to a minimum and keeps microbes from moving around. According to Pickard et al. [23], most commensals live in the digestive tract, so epithelial cells, mucus, IgA, antimicrobial peptides, and immune cells all work together to keep them apart.

The body's immune system stops pathogens and illnesses. Nobody knows what microorganisms in the gut do [24]. Our knowledge of how microbes and people interact has changed greatly in the last few decades. "Holobiont" is where multiple species live with a host animal like us [24, 25]. Since bacteria can be put into eukaryotic cells, we can study how human cells and microbes evolved in symbiosis (human and animal). The bacteria in your gut and your immune system are linked. Most of the microbiome and 70–80% of the immune system are in the digestive tract [25]. They are made to keep the body from getting sick [25]. During birth, bacteria from the birth canal get into the body. Abbas et al. [26] say that the immune system affects the microbiota, while the gut affects the health and development of the immune system. Gut flora is affected by what a person eats, where they live, and what they do. A healthy gut and immune system help a healthy body.

The microbiota in the gut watch over and teach us. T-cells are taught to tell the difference between foreign tissue and their own. According to Thaiss et al. [27], cell-mediated immunity is how T-cells kill infected cells when antibodies can't get to viruses that have attacked our cells. Normal stomach function helps develop favorable immune responses. In return, the immune system helps the microbiome get settled. When these two work together, the body can fight dangerous infections while tolerating harmless bacteria. This keeps the immune system from being attacked and healthy at its best. Sickness has been linked to gut flora problems and how immune cells talk to each other [28]. Due to the strong link between the immune system and gut microbiota, a reduction in the intestinal flora may affect immunity if the body is exposed to bacteria-stripping stimuli (such as a poor diet, antibiotics, surgeries, heavy metals, or chemotherapy). When there are more bad bacteria in your gut than good ones, your body suffers [29].

Intestinal flora and autoimmunity

Since the gut microbiota has a big effect on innate and adaptive immune systems, it is not surprising that some members of the gut microbiota have been linked to autoimmune diseases. Much attention has been paid to the role of the gut microbiota in autoimmune diseases that affect the digestive tract [30]. As we have seen, the gut microbiota affects more than just the immune system. It also affects other parts of the immune system. This has led to much new research on how the microbiota outside the intestines affects different diseases. As per Xu et al. [30], particular attention is paid to research that shows how changes in either a single microbial species or worldwide commensal ecosystems can tip the balance between a pathogenic and protective immune response, changing the course of autoimmune disorders.

Epidermal cells line the skin, mouth, nose, genital, respiratory, and gastrointestinal tracts of animals, including humans, from birth until microbial colonization [30]. The community of microorganisms that live in a person's digestive tract is called the gut microbiota. These microorganisms help their host in many ways. The gut microbiota is where microbes that can be good or bad for health are found. Also, about two-thirds of the human microbial commensal population [30] lives in the gut microbiota, which is the part of the body with the most contact with the outside world. Disrupting the formation and maintenance of healthy microbiota composition in early childhood may negatively affect health and immunological homeostasis later in life [31]. In early childhood, the gut microbiome goes through three different stages: the developing stage (months 3–7), the normal stage (15–30), and the sound stage (months 31–46) [31]. When it comes to

the microbiome, breastfeeding is the most important thing.

The microbiota plays a key role in keeping the host's nutrition, metabolism, detoxification, vitamin synthesis, and immune system balanced, in addition to the more obvious role it plays in keeping the gastrointestinal tract balanced [31]. Even though viruses, fungi, protozoa, archaea, and bacteria are part of the gut microbiota [32], bacteria have been studied the most. They have a relationship with the mutually beneficial host. Most of the microbiota in the gut are obligate anaerobic organisms, which are different from other bacteria in the gut because they can't live in oxygen. There are more than 1,014 different kinds of microbes in the human body. The largest colony is in the gut [32]. The main types of gut microbiota in the human intestinal lumen are Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. Over the last ten years, thanks to the widespread use of high-throughput deep-sequencing technologies, it has been found that the gut microbiome contains 3.3 million genes, which is 100 times more than the number of human genes [32]. Because of this, the microbiome in a person's digestive tract has been called the "human second genome". The gut microbiota is divided into three functional groups: helpful commensal microorganisms, possibly sensitive pathogens, and pathogenic bacteria.

The "beneficial" commensal microbes in the gut microbiota do more than keep the host healthy. They also interact with host tissues in a mutually helpful and not harmful way. Illness happens when the balance of "sensitive" microorganisms is upset. "Pathogenic" bacteria cause the illness, while "therapeutic" microorganisms may help bring things back to normal [32]. Diet, age, gender, and location are just some of the things that can change the gut microbiota [33]. The colon has the most species and most of them than any other part of the digestive tract. Rapid diet changes, antibiotics or probiotics, and many different diseases can change a person's microbiota as they grow up.

Changes to the complex gut microbiota have many effects on the host. The wide variety of microbes in the human gut is closely linked to growth, development, drug metabolism, and immune system function [30]. Beneficial microbiota species play important roles in several processes, such as digestion, maintaining the homeostasis of the immune system, helping the immune system fight infections, and controlling lipid metabolism [34]. In particular, gut microbiota composition may affect how well the intestine works, how strong the barrier is, and how well it regulates permeability. All of these things have been linked to the immune response and the development of inflammatory illness afterward. There is evidence that high numbers of Prevotella copri are linked to the low gut microbiota, which is linked to the ability to control the immune system [34]. The gut microbiota may also be affected by what we eat, making cell-based treatments more useful there. For example, Xu et al. [30] showed that transferring the porphyrin utilization locus to an outside *Bacteroides* strain could change the number of strains in the mouse intestines by many orders of magnitude. The aryl hidrocarbon receptor (AhR) signaling system may change the microbiome's composition in the small intestine. According to Xu et al. [30], microbiota profiling has shown differences between AhR (+/+) and AhR (-/-) mice that were fed either a diet rich in a certain AhR ligand or a diet without any known AhR ligands. Short-chain fatty acids (SCFAs) are one microbiome metabolite that can affect AhR and the genes it controls in the gut [30].

In the future, changes to the gut microbiome may be made to improve clinical outcomes across a wide range of genetic backgrounds. This is promising because an imbalance of the gut microbiota may be at the root of many human diseases, including immune, metabolic, cardiovascular, and neurological disorders. With the help of gut flora, it may be possible to make more accurate predictions about things like blood sugar levels and obesity [30]. Compared to medications, food, and body mass index, host genetic variables don't affect the microbiome's makeup [35]. Epidemiological evidence suggests that hospitalizations may be caused by the tendency for harmful bacteria to spread from one person to another [30]. AhR is a multifunctional part of the gut microbiota that you should keep in mind. After 18 days of genotypic segregation, Xu et al. [30] used cohoused littermates of the C57BL6/J AhR (-/+) and AhR (-/-) mice strains and found big changes in the gut microbiota, especially for Verrucomicrobia and segmented filamentous bacteria (SFB). When AhR (-/-) microbiota was transferred to wild-type germ-free mice, the number of Verrucomicrobia and the level of inflammation went up. This shows that AhR (-/-) depends on microbes [30]. Targeting AhR could also treat GI tract barrier dysfunction caused by antibiotics. AhR could make interleukin 22 (IL-22), control anti-inflammatory signals, and control how immune cells differentiate, multiply, and become active [30]. This makes it a possible therapeutic target for diseases caused by immune system problems.

Autoimmune diseases are caused by genetic polymorphisms, geographic location, patient exposure, immune system problems, and viral infections, among other things. AhR may play a role in autoimmune diseases by turning outside and inside signals into cellular responses. It binds to various ligands from food, cells, and microbes. Xu et al. [30] found that AhR-deficient animals had lower levels of innate IL-22. This allowed the immune activator commensal SFB to grow and cause Th17 cells to multiply. As we have discussed before [36], the natural expression of AhR protects against experimental colitis caused by T cells by stopping the growth of harmful Th17 cells.

Also, AhR ligands and important commensals showed therapeutic promise by significantly controlling the host response to 2,3,7,8 -tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) [36]. This was because SFB was in the microbiome of the gut. A change in the gut microbiota called dysbiosis has been linked to autoimmune diseases. But it's still unclear what role microbiota plays in developing these diseases in humans, and other factors may be at play. The gut microbiota may have a mechanistic role in autoimmunity by altering autoantigens after they are produced. This is because living gut bacteria can get past a broken gut barrier and interact directly with immune and tissue cells, which then sets off systemic autoimmunity [30].

The link between an imbalance of gut microbiota and autoimmune disorders could be caused by several things that affect the immune system and how it works. In this way, antigen presentation and cytokine production can be triggered by changing the host's immune response and activating antigen-presenting cells (APCs) like dendritic cells (DCs), which can then affect how T cells develop and work [30]. The effect also throws off balance between T helper 17 (Th17) cells and T regulatory cells (Tregs). Autoimmunity is made worse by pathogen-derived autoreactive T and B cells and activated when foreign antigens are similar to self-antigens. This is called antigenic mimicry [30]. But tight junction (TJ) protein expression changes how the intestinal mucosa lets things in and out.

There is a lot of evidence that gut microbiota plays a role in how people with autoimmune disorders get sick and how sick they get. Antigenic mimicry, an immune response from the host caused by microbiota, effects on the permeability of the intestinal mucosa, and molecular mimicry are all possible mechanisms [30]. Changes in the microbiota of the gut have been linked to autoimmune disorders. Gut microbiota may play a role in autoimmune diseases by affecting or interfering with the immune system's ability to tell itself from other things [30]. People with autoimmune diseases often have weak gut barriers, making them vulnerable to their immune system. A breakdown in mucosal immunological tolerance can also lead to abnormal and harmful immune responses to the gut microbiota, which can worsen a disease.

Recent studies have shown that antibiotics, prebiotics, antimicrobial interventions, fecal microbiota transplantation (FMT), and selective probiotics can be used to control gut microbiota [37]. But changes in the gut microbiota have been linked to the improper use of antibiotics and even to human-targeted drugs that are not antibiotics. There is more and more evidence from both lab and real-life settings that a gut microbiome with dysbiosis plays a big role in developing autoimmune diseases by causing a persistent inflammatory response [38]. Germ-free animal models are better for studying the role of the host microbiome in the start and spread of many diseases [38]. The microbiota may cause autoimmunity in people genetically more likely

to get it, or it may keep others from getting it.

Autoimmune illness that does not depend on the intestinal flora

Both genes and the environment often cause autoimmune diseases, but this isn't always the case. In some cases, the start of an illness has nothing to do with the environment or how a person lives [39]. So, it's important to remember that the presence or absence of commensal bacteria does not change the severity of certain autoimmune diseases in mice that lack the autoimmune regulator. Mutations in the Aire protein cause autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in humans. The Aire protein is a transcriptional regulator essential for T cell tolerance induction in the thymus. The Aire/mouse is a good example of an animal that can be used to study this condition. Re-deriving the mice into a germ-free (GF) condition or crossing them into a MyD88/background did not affect the disease phenotype of Aire/ mice [40]. This suggests that the loss of central tolerance in the thymus alone can lead to autoimmunity that overrides peripheral tolerance mechanisms without needing microbial stimulation [39].

The MRL/lpr mouse model of human systemic lupus erythematosus and activation-induced cytidine deaminase (AID) defective mice, which are a model of autoimmune gastritis, have much in common with the GF disease [40]. These results show that these mice's autoimmune diseases are mostly caused by their genes and not by living organisms that live with them. These results don't rule out the possibility that the lack of environmental signs of illness in GF mice is caused by low levels of microbial-derived products in their food, which turns the immune system [41].

Apoptosis, autophagy, oxidative stress, and the gut microbiota

Diabetic cardiomyopathy makes people's lives very difficult and sometimes threatens their lives. Numerous factors contribute to diabetic cardiomyopathy, and it is widely accepted that oxidative stress, inflammation, insulin resistance, apoptosis, and autophagy are all implicated. According to several studies, the microbiota in the gut has a significant influence on heart disease [42]. Controlling oxidative stress, inflammation, insulin resistance, apoptosis, autophagy, gut microbiota, and its metabolites may alter the development of diabetic cardiomyopathy [42]. The bacteria in the stomach may provide a novel treatment for diabetic cardiomyopathy.

The gut-brain axis is becoming more recognized as a crucial means by which the body communicates and is regulated. Gut bacteria seem to play a significant part in this. Oxidative stress is one of the leading causes of neurodegenerative illnesses such as Alzheimer's and Parkinson's, as well as acute disorders such as a stroke or brain injury [42]. A peculiar form of microbiota might increase the quantity of inflammation and reactive oxygen species in the brain and cause aberrant protein adhesion. On the other hand, brain injuries induced by various factors alter the microbiota and characteristics of the stomach [42]. These novel concepts might facilitate the discovery of novel treatments for various neurological disorders.

Through the microbiota-gut-brain axis, the bacteria and the host communicate extensively. This may have direct and indirect impacts on the central nervous system (CNS) operating system by altering the local amount of reactive oxygen species, reactive nitrogen species, and the CNS antioxidant system [42]. The creation of potentially neurotoxic chemicals such as lipopolysaccharides, amyloid proteins, and antibiotics, which may reach the CNS through the systemic circulation or the vagus nerve and trigger microglia to become active and create reactive oxygen species (ROS) and oxidative stress (OS), should be the subject of more study [42]. Identifying microbiome biomarkers associated with deleterious central nervous system oxidative stress (CNS OS) should also get more focus. The microbiota-gut-brain axis facilitates the development of novel treatments for various neurological illnesses.

The intervention of gut microbiota as a therapeutic target for immune-related diseases

How alterations in the microbiome might lead to or exacerbate a dysregulated immune response like that found in sepsis is not completely understood. According to Haak et al. [43], the more we understand various groups of microorganisms that reside in different sections of our bodies, the more we realize how delicate the processes are that these bacteria use to maintain the equilibrium of our bodies. In addition, microorganisms that reside in areas of the body other than the gut, such as the skin and the lungs, are likely to play an essential but understudied role in the everyday functioning of the immune system [44]. To further complicate matters, the current study indicates that eukaryotic viruses govern and are controlled by the host and other intestinal microorganisms [45]. These co-occupants consist of bacteria, bacteriophages, helminths, and fungi. They influence one another in various ways, known as "transkingdom interactions". This perspective on the human microbiome as a whole is novel and requires more testing in the context of sepsis.

Large human cohort studies that record the makeup of the microbiota before, during, and after an episode of sepsis are required to determine which commensals protect against sepsis and which may be associated with an increased risk of developing it and a worse prognosis. With these new concepts, it may be possible to identify bacterial groupings associated with robust immune systems. Then, these groupings might be used as possible indicators of vulnerability to sepsis or negative consequences. In addition, mechanistic animal studies, which should use older and "dirtier" mice [45] and better replicate the clinical condition by using antibiotics and other therapies often used in sepsis [43], are required to determine what may be driving the observed human phenotypes. These efforts have resulted in the identification and development of novel probiotics for the next generation that may treat particular diseases such as *C. difficile* and vancomycin-resistant enterococcus (VRE) [46]. It is believed that additional microbiota-targeted medicines might make it simpler to treat and prevent sepsis, even though many challenges can be solved.

Human practices that affect intestinal flora

Many habits that have grown up with humans have been shown to have a big effect on the bacteria in the gut. As this review shows, gut microbiota changes can affect autoimmune diseases' development. They can also affect many other health issues, like allergies and obesity, so they must be studied closely. For example, food is a big part of how gut bacteria are made up [39]. Researchers used GF mice with human gut microbiota fecal-transplanted into their digestive tracts. They found that the microbiome's composition changed in just one day from a low-fat, plant polysaccharide-rich diet to a high-fat, high-sugar diet [47]. By two weeks, the new diet had changed the mice's microbiota enough to make them fat.

Another study looked at the gut microbiota of kids in rural Africa and Europe by looking at their poop [48]. While the Western diet is high in sugar, starch, and fat and low in fiber, the African diet is high in fiber, starch, and plant polysaccharides and low in fat and animal protein. Compared to the European cohort, the African cohort's microbiota showed a significant decrease in Firmicutes and an increase in Bacteroidetes. These bacteria are known to have the genes needed to break down plant polysaccharides. Also, the African group had a much higher level of chemicals that reduce inflammation, such as SCFAs. Also, animal research showed that the pro-inflammatory cytokines interleukin 17 (IL-17) and interleukin 23 (IL-23) were lower in the colons of non-obese diabetic (NOD) mice fed a soy-based diet, which led to a much lower rate of diabetes [49].

The gut microbiota can be changed by taking antibiotics, getting immunized, or even how clean you keep yourself. *Bacteroides* and *Bifidobacterium* were found to be less common in the intestines after antibiotic use, while *Campylobacter*, *Streptococcus*, *Leuconostoc*, and yeasts like *Candida albicans* were more common [50]. Because people are born without any bacteria in their bodies, bacterial colonization during and right after birth has a big effect on the gut microbiota

communities. So, the acquisition phase of the gut microbiota is greatly affected by things like whether or not the baby was born early, how the baby was born, and what the baby ate (e.g., breast milk, commercial formula, etc.). Those born vaginally were mostly colonized by bacteria communities similar to their mother's vaginal microbiota, such as *Lactobacillus*, *Prevotella*, or *Sneathia* spp. Those born via C-section were mostly colonized by bacteria communities similar to those on the skin's surface, such as *Staphylococcus*, *Corynebacterium*, and *Propionibacterium* spp. Also, *C. difficile* was the most common bacteria in babies born early [50]. Staphylococci, *Escherichia coli*, *Clostridium difficile*, *Bacteroides*, *Atopobium*, and *Lactobacillus* were often found in formula-fed babies, while *Bifidobacterium* species colonization was often found to be delayed in formula-fed babies. Changes to the microbiome during pregnancy, like C-sections, can increase the risk of asthma, allergies, and autoimmune diseases in later childhood.

Conclusion

The field of immunology is at an interesting turning point right now. In recent years, immunological research has moved away from focusing on lymphoid tissues to recognizing how important tissue microenvironments are in shaping immune responses. Research in this field shows us that microbiota is an important part of the immune system's work. In recent years, there has been a lot of research on the link between the microbiome, keystone bacterial species, products or metabolites made by commensal bacteria, and human illness. This is a once-in-a-lifetime chance for ecologists, dietitians, geneticists, microbiologists, biochemists, immunologists, and other scientists to work together with doctors and scientists to learn more about human health is connected. This interdisciplinary field tries to change or fix parts of the conversation between the immune system and microbiota. This is the key to improving or restoring human meta-organism health.

The effect of commensals on health and illness through changes in how the immune system works is a new field of study with important clinical implications. Recent developments in "next-generation" sequencing have sparked a revolution in making a method to describe gut microbial populations that don't need a culture and are complete. Changing the gut microbiota has been shown to affect autoimmune disorders inside and outside the gut, showing how important it is. The microbiota is not only shaped by genes but also by the environment. Through microbiota-mediated immunomodulation, bad habits like taking too many antibiotics can raise the risk of autoimmune diseases. Because of this, you should be careful around these things.

The next problem is to figure out if changes in the gut microbiota caused the illness or if they are a result of it. Animal models like GF animals, in which the gut flora can be changed, are a powerful tool for these mechanistic studies. We now know that even a small change in a single bacterial species in the gut can have a big effect on the immune system and pathology of the host. This makes it hard to predict how the intestinal microbiota will affect the results of every animal experiment because the microbiota can be different from one animal facility to the next. It will take more care to compare published research and determine the results. This step is important for comparing GF NOD mice get sick to how often NOD mice from other specific pathogen-free (SPF) facilities get sick. More and more evidence suggests dysbiosis of commensals contributes to the worrying rise in illnesses, including some immune disorders. This means that it is important to learn more about how gut microorganisms interact with the host's immune system.

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