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Review

Microbiota in a Long Survival Discourse with the Human Host

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Abstract: The relationship between human health and gut microbiota is becoming more apparent. It is now widely believed that healthy gut flora plays a vital role in the overall well-being of the individual. There are spatial and temporal variations in the distribution of microbes from the esophagus to the rectum throughout an individual's lifetime. Through the development of genome sequencing technologies, scientists have been able to study the interactions between different microorganisms and their hosts to improve the health and disease of individuals. The normal gut microbiota provides various functions to the host, whereas the host, in turn, provides nutrients and promotes the development of healthy and resilient microbiota communities. Thus, the microbiota provides and maintains the gut's structural integrity and protects the gut against pathogens. The development of the normal gut microbiota is influenced by various factors. Some of these include the mode of delivery, diet, and antibiotics. In addition, the environment can also affect the development of the gut microbiota. For example, one of the main concerns of antibiotic use is the alteration of the gut microbiota, which could lead to the development of multidrug-resistant organisms. When microbes are disturbed, it can potentially lead to various diseases. Depending on the species' ability to adapt to the human body's environment, the fate of the microbes in the host and their relationship with the human body are decided. This review aims to provide a comprehensive analysis of microbe, microbes-host immune interactions, and factors that can disturb their interactions.

Keywords: Microbiota; Microbiome; Adhesions; Pili; Curli; Enterotoxins

Introduction

Although humans are bone germless, our body starts colonizing with several microbial species soon after birth. As an estimate, the number of microbial species residing in and out of the human body outnumbers the human cells themselves. Most of this makeup what we call the normal microbiota of the human body. These reside in and outside the human body in symbiotic or commensal associations. Also, the microbial species associated with infection or those which are "foreigners" to the body share a parasitic relationship with the human body. These interactions confer an array of various physiological and biochemical implications to the human body. Recent advances in metagenomics have elevated the levels of understanding of the composition of the human microbiota, its relationship with the human host, and their possible mechanisms of interactions. The Human Microbiome Project was established by the NIH's Common Fund in 2007. The objective of the project was to create a community-focused resource for the research community that would allow them to collect and analyze large datasets related to the human microbiome. The project's goal was to create various tools that would enable researchers to study the microbiome in different populations and diseases. The human microbiome is regarded as an essential part of our health. The project's first phase collected a reference dataset of the various types of microbes that live in the human body. It identified five specific body regions: the skin, oral cavity, gastrointestinal tract, and airways. Using DNA sequencing technology, the researchers analyzed the various types of microbes that live in the human body. They also identified the factors that could potentially lead to multiple diseases. The reference dataset was additionally used to determine the different microbes associated with different conditions. Various approaches have been used to study the interactive capabilities

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of human host-microbe interactions, their composition, genomic, metabolic, and biochemical influences on the human host, and the mechanisms underlying the establishment and maintenance of such complex microbial communities within and outside the human body in the presence of the host immune system, and their pathophysiological role in the event of disease progression. The present review deals with the composition of the human microbiota, particularly concerning their interaction with the human host and the prevalent mechanisms involved.

The Human Microbiome Project

The human microbiome is composed of all the microorganisms that live in and outside the human body. Trillions of microbes have evolved and continue to live in humans; the trillions of microorganisms that live in humans are known to play a vital role in developing and maintaining human health. The human microbiota, composed of the gut microbiota, is considered an essential organ. It carries around 150 times more genes than the entire human genome **([i])**. The human microbiota is known to play a role in various biological processes **([ii])**, such as regulating the development of epithelial cells **([iii])** and the regulation of the metabolic phenotype **([iv], [v])**. Some of the chronic diseases that are associated with the presence of this organism include diabetes, obesity, and atherosclerosis **([vi], [vii])**. For instance, Vamanu et al., 2016 demonstrated that the prevalence of cardiovascular diseases and diabetes is known to affect the human gut microbiome **([viii])**. Their study revealed that the diabetes group had significantly increased the number of aerobic bacteria and decreased the *bifidobacteria*. Additionally, their cardiovascular group's microbiota showed many similarities to that of their control group. They showed that in the cardiovascular patients and controls, each colonic segment showed a distinct microbial fingerprint, whereas, in the diabetics, the gene profile occurred in all three segments. They revealed that the variety of beneficial bacteria was diminished in patients with nutritional or cardiovascular disease. Thus, their work demonstrated that diabetes and cardiovascular disease are associated with changes in the colonic microbial fingerprint. Additionally, they inferred that the presence of ammonium, a microbial byproduct associated with colonic cancer, additionally increased the levels of Gram-positive bacteria. There were additionally significant numbers of *Clostridia*.

New technologies have allowed us to collect more data on the human host's interactions between gut microbiota and metabolites. In contrast, the number of these microorganisms is around 10 times greater than that of human cells. Most of the gut microbes are also part of the human body's microbiome and are known to carry over 150 times more genes than are found in the entire human genome **(1)**. More so, to understand the various factors that contribute to the development of the human microbiome, the NIH launched the Human Microbiome Project (HMP) **([ix])**. The Human Microbiome Project is a multi-disciplinary community resource that is funded by the NIH. It aims to improve the understanding of the human microbiome. The goal of the HMP is to use high-throughput methods to thoroughly study the human microbiome. It also seeks to identify the possible link between various health conditions and the changes in the microbiome. Through the HMP, the scientific community has been able to thoroughly study the ethical, social, and legal aspects of research on the human microbiome. The ultimate goal of the project is to demonstrate that there are potential applications for manipulating the microbiome. Thus, the project aims to study the interactions between different types of microorganisms in four significant sites—the interactions between humans and their microbes and how much they influence various physiological processes. To understand the role of the human microbiome in maintaining a healthy and normal environment, the project is focused on analyzing the interactions between different types of microorganisms. Through genome-wide analysis, the project aims to identify the core microbiome of the human body **([x])**. To provide an overview of the interactions between the human body's microbiome and its host and to identify the various diseases that are caused by these interactions, we summarize works done in the area of the human microbiota. Some of these include research carried out on liver diseases, respiratory diseases, mental health disorders, etc. This work also reviews the latest techniques used in studying the human microbiome. These include the use of metabolomics, DNA sequencing, and computational methods. Due to the increasing number of studies on the human microbiota, the scope of the research has also become more sophisticated. This section aims to provide a comprehensive view of the interactions between the host and the microorganisms. These studies could help develop new treatment strategies and improve the quality of life for people with diseases. The HMP is additionally dedicated to

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advancing the understanding of the human microbiome by providing the necessary tools and resources to scientists to study its role in health and disease. It will also help them develop effective interventions. The HMP is launched at a time when the cost of DNA sequencing has significantly decreased. This technological change has led to the development of new methods that can be used to study the human microbiome. HMP's efforts to establish standards for the use of these new technologies will help pave the way for the development of future microbiome research. As shown in Figure 1, the distribution by body site of bacteria that have been sequenced under the HMP as at the early 2000s is graphically depicted.

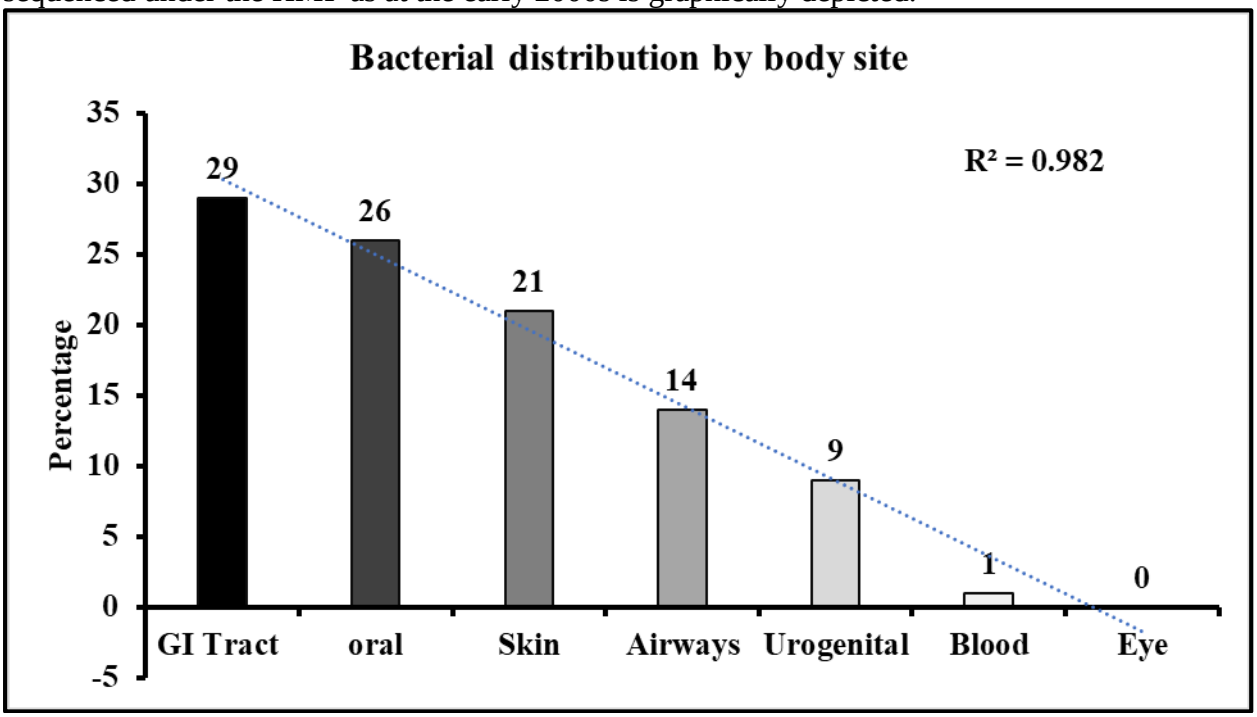

Figure 1. This histogram shows the distribution by body site of bacteria that was sequenced at the early 2000s under the HMP. Data adopted from the NIH Human Microbiome Project **(9)**.

The Gut Microbiota

The relationship between gut microbiota and human health is becoming more widely acknowledged. It is believed that healthy gut flora can help maintain a person's overall health **([xi])**. As shown in Figure 2, the normal gut flora of humans consists of several bacterial bacteria strains belonging to two types of phyla, namely the *Firmicutes and Bacteroidetes*. Although the gut microbiota in infants appears haphazard, by age 3, it can start resembling the adult flora. There are spatial and temporal variations in the distribution of microbes from the esophagus to the rectum throughout an individual's life span. Through genome sequencing technologies, scientists have been able to study the interactions between different microbes and their host communities to improve the quality of life for individuals **([xii])**. The normal gut microbiota provides various functions to its host communities, such as maintaining the structural integrity of the gut barrier, protecting against pathogens, and regulating the metabolism of nutrients. Various factors influence the development of the normal gut microbiota. Some of these include the mode of delivery, the diet, and antibiotics **([xiii])**. In addition, the environment can also affect the development of the gut microbiota. One of the most common factors that can affect gut microbiota development is exposure to antibiotics which can lead to the transfer of resistant genes from one organism to another.

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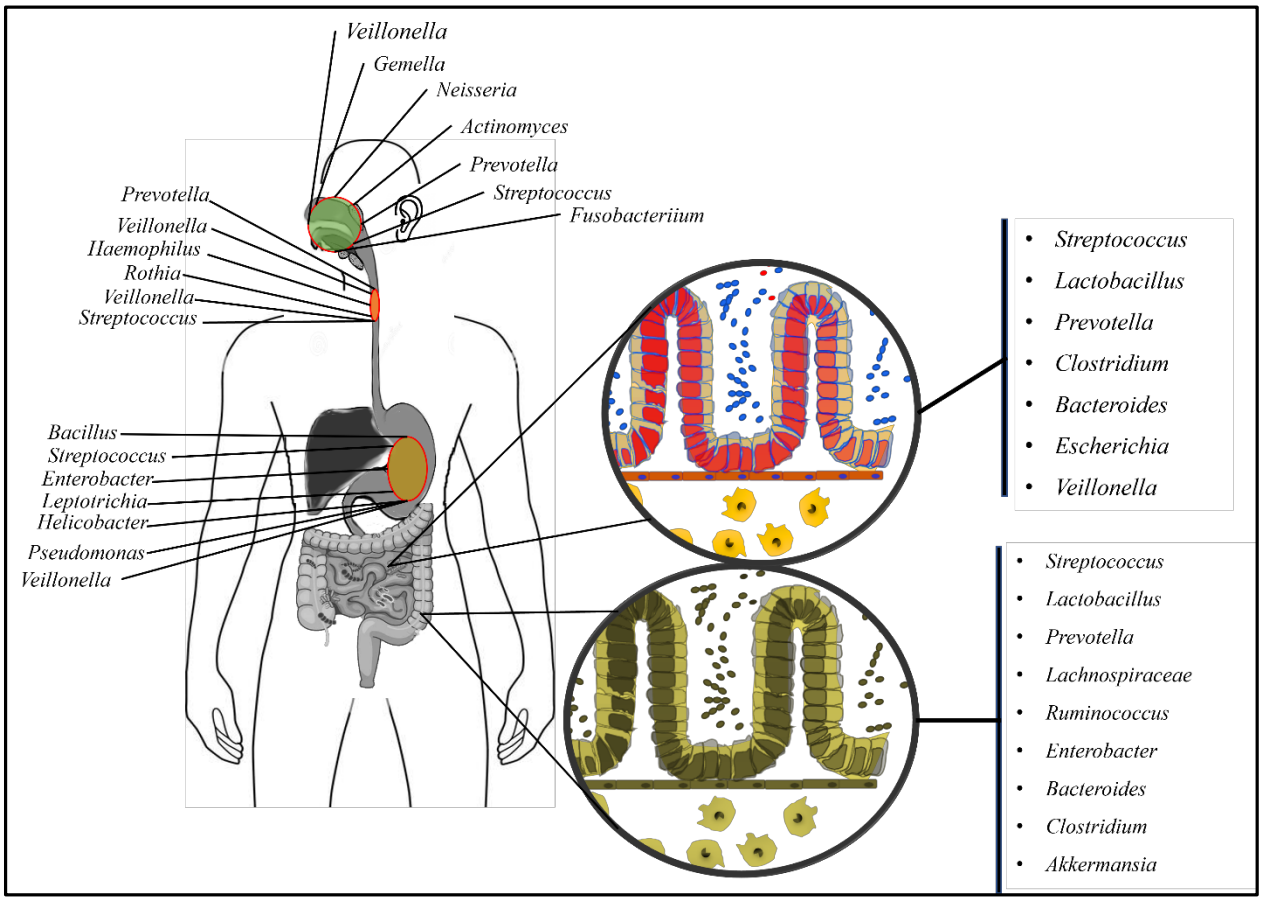

Figure 2. The distribution of the gut microbiota

The gut microbiota changes over time

The gut microbiota is a diverse group of microorganisms that can be distinguished from other pathogenic human microbes by the two divisions - *Firmicutes* and *Bacteroidetes* **([xiv])**. The complex microenvironment of the gut may explain the multiple factors that contribute to its diversity **([xv])**. Although the various factors that influence the composition of the microbiota are known to contribute to its unique characteristics, the exact mechanisms by which these factors interact with each other, and the environment are still poorly understood **([xvi])**. Only species that can cross these barriers and be associated with the human gut are considered pathogens. New computational methods, genome sequencing, and metagenomics have allowed for studying the interactions between the host microbes and their pathogens. These studies can help understand the mechanisms by which these organisms develop and function. Understanding the changes in the gut microbiota of older individuals is becoming increasingly important as we create a more accurate understanding of their clinical phenotypes. This framework allows us to identify the factors that influence the development of these conditions and develop a strategy to improve the health of older adults. The human infant's gut is relatively sterile until birth and takes in bacteria from its mother and environment **([xvii])**. As a result, the composition of its microbiome differs from that of an adult gut **([xviii])**. An infant's microbiome begins to develop at around three years of age, gradually changing to become more diverse as they age **([xix])**. Both cell culture-dependent and independent studies suggest that the gut microbiota of older individuals differs from that of younger individuals **([xx])**. Although the composition of the microbiota does not change with age, it changes with time because a chronological threshold does not trigger the changes in the gut microbiota; instead, they occur gradually **(20)**. Studies have classified the gut microbiota into specific groups based on age, long-term care, habitual diet, and retention of a core microbiome.

Bifidobacterium is a genus of nonmotile gram-positive bacteria that lives in mammals' gastrointestinal tract and mouth **([xxi])**. Although strains of these bacteria have been isolated from the vagina and mouth, they are still considered to be common inhabitants of the gut. Some *bifidobacteria* are also known to be beneficial for the health of humans **([xxii])**. However, over time, the variability in the genotypes of *Bifidobacterium* can make them

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less stable compared to adults. Children and infants under 3 years old have low levels of diversity in their microbiome bacteria, but they are more diverse than adults. This is due to the reduction of *Bifidobacterium* in the diet and the increase in solid food intake. Oligosaccharides found in human milk are not broken down by human digestive enzymes and remain in the digestive tract until they reach the colon where, they are then broken down by the microbiota (**[xxiii]**). Bifidobacterium species *Bifidobacterium bifidum*, *Bifidobacterium longum*, and *Bifidobacterium breve* contain genes that can hydrolyze some of these oligosaccharides **([xxiv])**. These genes are also present in higher numbers in breast-fed infants **(24)**.

Gut Metabolome

Studies have shown that certain gut microbes are important for the survival of the gut **([xxv])**. These communities have two sets of genes that are required for their survival. One of these is called the minimal gut genome, a set of genes designed to guide the development and maintenance of the gut microbiome **([xxvi])**. The other is called the Gut Metagenome, a group of genes designed to maintain the homeostasis of the whole gut ecosystem **([xxvii])**. The first set of functions includes the housekeeping functions of the various components of the metabolic pathway—an example of such functions includes carbon and amino acid synthesis and DNA and RNA polymerase. The second set of functions consists of the interactions between the host proteins and their nutrients. These include the generation of nutrients from the epithelial cells and the adhesion to the host tissues. It has also been known that certain gut microbes can biodegrade complex sugars and glycans that are produced from the host diet and the intestinal lining. Some of these sugars, such as sorbitol and pectin, are known to be difficult to absorb by humans. However, certain gut microbes can degrade these sugars, which are not harmful to humans **([xxviii])**. The capacity to ferment is also a crucial part of the functional aspects of the metagenome. And it has been shown that both the diversity and abundance of these microbes are essential for developing and maintaining a normal gut microbiome. It is also important to point out that the host's role in the degradation of complex sugars is also as crucial. Early childhood changes can have lasting effects, such as the development of allergic reactions and other conditions related to the immune system. It has been shown that the gut microbiome can affect the development of these conditions. For instance, a study on children at risk for developing celiac disease revealed that the metabolome of infants below six months old was dominated by sugars, such as glucose and lactose **([xxix])**. However, after six months, the levels of these nutrients and amino acids started to change. The study also noted that the changes in the metabolome of infants at two years old were similar to those of adults. In another study employing the 16S amplicon, researchers proved that infants' microbiota could resemble that of adults as they get older **([xxx])**. It also suggests that the child's intestinal microbiota can convert breast milk into nutrients. Different *Bifidobacterium* species have genome sequences enriched with genes involved in the processing of human milk oligosaccharides **([xxxi])**. These species might have a competitive advantage over other organisms in the intestine.

The Gut-Microbe Interaction

The diversity of the gut microbiota is becoming increasingly recognized as a vital component of human health and disease. However, it is not easy to determine the exact cause of these interactions due to the complexity of the genome-wide sequencing studies and the interspecies differences. Recent advances in the development of microbes with colonic and intestinal epithelia have led to the development of new models of organoids and organs-on-chips **([xxxii])**.

Interactions Among Host, Microbiota, and Metabolites

The gut microbiota can be perceived as a complex organism that can convert various substrates into metabolites that can affect the host's peripheral vascular system. For instance, therapeutic agents can be inactivated, reducing their effectiveness. On the other hand, drugs can be converted to derivatives that have non-target effects. The changes in the substrates that are used in the production of these nutrients can affect the metabolomic profile of the gut. This can result in different effects on the host. In addition, the presence of a new host phenotype can influence the development of the microbial community. As shown in Table 1, several microbiota functions positively or otherwise affect the human body via synthesizing or modifying specific metabolites.

Functions	Metabolites	Bacteria	References

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Inhibits CNS functions, decreases weight loss, promotes diuresis and hypotension	Gamma aminobutyric acid (GABA)	*Lactobacillus paracasei*, *Lactobacillus brevis*	[xxxiii]
Lower blood pressure	butyric acid	*Lachnospiraceae*, *Acidaminococcaceae*, and *Ruminococcaceae* families	[xxxiv]
Cofactor: Enzymatic reactions, regulate cell proliferation, enhance immune function.	Vitamins: vit. B, K, biotin, riboflavin, folate, thiamine	*Lactobacilli*, *Bifidobacterium*	[xxxv,xxxvi]
Cell growth, apoptosis, increased calcium ion accumulation in mitochondria	Polyamines: cadaverine, spermine, spermidine, putrescine	*Clostridium saccharolyticum*, *Campylobacter jejun*	[xxxvii]
Improve intestinal permeability, decrease host fat mass and body weight, bile acid and production.	Acylglycerols, conjugated fatty acids, cholesterol, sphingomyelin, phosphatidylcholine, triglycerides	*Clostridium*, *Bifidobacterium*, *Lactobacillus*, *Enterobacter*, *Roseburia*	[xxxviii]
Increase blood pressure	Propionic acid, indole-3-propionic acid	*Salmonella*, *Bacteroides*, *Veillonella*, and *Roseburiainulinivorans*	[xxxix, xl]
Ceases cytokines levels, decreased neutrophil infiltration, host immune modulation.	Polysaccharide A and B, Exopolysaccharides	*Lactobacillus acidophilus*, *Bacteroids frag*	[xli]
Maintenance of intestinal barrier functions enhance lipid absorption, bile acid accumulation by some Bifidobacteria.	Bile acids: glycocholate, cholate, etc.	*Clostridium*, *Bifidobacterium*, *Lactobacillus*, *Enterobacter*, *Bacteroids*	[xlii, xliii, xliv]
Attenuates hepatic steatosis	acetic acid	*Desulfovibrio vulgaris* *Streptococcus spp.*, *Prevotella spp.*, *Bifidobacterium spp.*, *Clostridium spp.*	39, [xlv]
Protection against stress induced GI epithelial damage	Indole derivative	*Clostridium sporogenes*, *E-coli*	[xlvi]

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Lower the colonic pH, lower the level of cholesterol, pathogen inhibition, stimulate Na and H2O absorption	Short chain fatty acids (SCFAs): acetate, hexanoate, butyrate, propionate, isobutyrate	*Clostridium, Bifidobacterium spp, coprococcus, roseburia*	**([xlvii])**
Neurotransmission, methyl transfer, cell membrane functioning	Choline metabolites: betaine, dimethylglycine, methylene, dimethyline, dimethyline	*Firmicutes, Actinobacteria, Proteobacteria, Bifidobacterium, Faecalibacterium prausnitzii*	**([xlviii])**
Chronic diabetes and hepatitis, asthma indication (urinary 3-Nitrotyrosine and 3-Nitro4-hydroxyphenylacetic acid), obesity and hypertension biomarkers in humans.	Phenyl derivatives, benzoyl, phenol	*Lactobacillus, Bifidobacterium, Clostridium difficile, F. prausnitzii*	**([xlix])**

Table 1. Metabolites from gut microbiota and their effects.

Before the emergence of multicellular life, eukaryotic cells had formed an alliance with microbes. One of the most significant features of this relationship was the establishment of the endosymbionts in the cell. These are capable of providing the necessary metabolic and biochemical capabilities **([l])**. In an environment that is conducive to the development of beneficial microbes, the interactions between the host and the microbes can be beneficial **([li])**. For instance, the nutrients provided by the cell can help the microbes maintain a stable environment and compete against non-beneficial microbes **([lii])**. The development of plankton microbes eventually led to the establishment of the complex lytic enzymes needed by the host. For instance, it has been shown that the gut microbiota (because of the enzymes they produce) is a crucial player in the host development and physiology and vice versa; thus, the development of the gut and the energy sources used by the host can both direct the development and evolution of the gut microbial species that provide these complex enzymes **([liii])**. These are then used to help the host's metabolic processes and provide the nutrients and shelter that the microbes need.

Reactive oxygen species in the gut

It has been shown that induction of AMP is only necessary for host survival when the bacteria present in the environment encounter certain types of reactive oxygen species (ROS). This suggests that AMP plays an important role in the microbicidal actions of certain bacteria **([liv])**. The gut IMD-AMP pathway is down-regulated by various negative regulatory systems to maintain the health and community of the bacteria in the environment. Studies have shown that the presence of reactive oxygen species (ROS) in the gut is a major factor that contributes to the development of microbicidal effects. It was first observed that these compounds were produced in the gut of flies without a secretory form of catalase **([lv])**. In flies, reduced expression of the IMD-AMP pathway is known to be a risk factor for gut infection **(54)**. Biochemical studies have revealed that the activity of the catalase in converting H_2O_2 to H_2O is triggered by the presence of an inflammatory environment. Overexpression of this enzyme can help rescue the dying flies from gut infection **([lvi])**. When gut bacteria are infected with dead microbes, the death rate is likely caused by the accumulation of reactive oxygen species in the gut. However, it is not the over-proliferation of microbes that causes the issue. These observations suggest that the presence of an antioxidant system in the gut is essential during gut infection **([lvii])**.

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The presence of a robust reactive oxygen generation system in the gut suggests that the bacteria are able to recognize and activate this system. The role of reactive oxygen species in innate immunity is most apparent in professional phagocytes **([lviii])**. In phagosomes, organisms produce superoxide from molecular oxygen. This substance is then converted to H_2O_2 through a process known as deoxidization. This process can be performed by an enzyme known as MPO. In this process, H_2O_2 is then converted to microbicidal HOCl **([lix])**.

The role of NF-κB pathway in gut epithelia

Adenosine monophosphate-activated protein kinase (AMPK) is a key component of energy metabolism homeostasis that regulates the regulation of various metabolic processes **([lx])**. It is also involved in developing metabolic syndrome, a chronic inflammation that can affect tissue **(54)**. The role of the NF- κB-AMP system in the development of systemic immunity has been well-documented. However, its role in the regulation of gut epithelia is not clear. Oral consumption of various microbes can lead to the development of gut infections, thus prompting the need to determine the role of the AMP system in the development of gut epithelia. Despite the presence of certain types of bacteria, the AMP is rarely triggered. The repression of the NF- κB –AMP system is required to maintain the presence of these bacteria. The loss of the NF-κB-AMP system can lead to the development of a modified community structure in the gut. Cad-mediated AMP repression is required for a healthy commensal community. AMP-overexpressing Cad-knockdown re-shapes the healthy commensal community structure to an unhealthy community structure, and eventually provokes elevated gut apoptosis and host death **(54)**.

Gut Microbiota–miRNA Interactions

Many different types of cancer, such as breast cancer, have arisen from the dysregulation of specific miRNAs **([lxi])**. These are known to play a role in the development and maintenance of the disease **([lxii])**. In addition to cancer, other conditions such as inflammation and gastric cancer also significantly impact individuals' health **([lxiii])**. The interactions between the gut microbiota and various types of miRNAs are known to play a role in the development and maintenance of cancer since these miRNAs are said to be the epicenter of intestinal homeostasis **(63)**.

Gut Microbiota and High blood pressure

High blood pressure is known to be the most preventable cause of the cardiovascular disease **([lxiv])**. Therefore, it is also crucial that people with this condition take practical steps to reduce their risk of cardiovascular disease. Studies have shown that the gut microbiota can play a role in the development of metabolic disorders **([lxv],[lxvi])**. In addition, studies have shown that the presence of gut microbiota can influence blood pressure regulation **([lxvii])**. In animal studies, gut microbiota was linked to elevated blood pressure. Antibiotic treatment also increased blood pressure, suggesting that the gut microbiota could be involved in controlling blood pressure **(67)**. In rats with high blood pressure, a significant decrease in the diversity and microbial richness in the gut was observed **([lxviii])**. This condition is known to be caused by vasoconstriction and vascular resistance **([lxix])**. The reduction in the gut microbiota was also linked to the increase in the ratio of *Brachoidetes* and *Firmicutes* **(68)**.

The effects of angiotensin II on blood pressure were observed in germ-free mice, suggesting that the gut microbiota plays a role in regulating blood pressure. Although the mechanism by which the gut microbiota regulates blood pressure is not fully understood, it is believed that this condition could be a contributing factor to the development of hypertension **([lxx])**. Specific gut microbial metabolites, known as SCFAs, in the blood pressure levels of these animals could be a contributing factor to the development of hypertension. These include butyrate, propionate, acetate, and b-lactone. It is also believed that some gut bacteria use substrates other than polysaccharides to produce these metabolites **([lxxi], [lxxii])**. Some of the most common gut bacteria that produce acetic acid are *Streptococcus* spp., *Prevotella*, *Bifidobacterium*, and *Clostridium* spp. Propionic acid is produced by different types of bacteria such as *Salmonella*, *Bacteroides*, *Veillonella*, and *Roseburiainulinivorans* **(39)**. The *Lachnospiraceae*, *Acidaminococcaceae*, and *Ruminococcaceae* families produce butyric acid in the gut **(34)**. The abundance of these bacteria in pregnant women with obesity is known to lower their blood pressure levels. In addition, the presence of acetate and fiber in the diet can improve gut dysbiosis.

Gut Microbiota and appetite regulation

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Studies on the role of SCFAs in regulating energy intake and appetite have been presented in detail [lxxiii, lxxiv]. They show that these compounds can also affect the activity of the peripheral and central nervous systems It is unclear if a single SCFA drives these findings or if a combination of these compounds can be utilized. Although there are currently limited studies supporting the role of fermentable fiber in appetite regulation [lxxv,73], it is believed that increasing the daily fiber intake in the range of 16 to 35 g/d can help improve this regulation [lxxvi]. This suggests that the effects of this compound can be influenced by the animal's equivalent fiber loadings. Although the exact role of SCFAs in appetite regulation is not yet clear, it is believed that their production can be influenced by the pathways that are involved in this regulation. Studies revealed that the presence of SCFAs in humans can trigger short-term appetite regulation **(76)**. For instance, selective modulation of colonic propionate in humans demonstrated that propionate induces short-term appetite regulation though PYY and GLP-1 mediated mechanisms [lxxvii].

Gut Microbiota and lipid metabolism

The effects of SCFA on the metabolism and tissue of fat are known to be significant. In the liver, propionate can prevent the development of lipogenesis and cholesterogenesis. It is, therefore, important that the ratio of propionate to acetate is maintained to ensure the optimal contribution of colonic acetate to the lipid stores [lxxviii, lxxix]. Studies have shown that propionate can reduce liver fat and visceral fat [lxxx]. The effects of SCFA on adipocyte lipolysis are also known to be beneficial. First, it can prevent the accumulation of lipid in adipocytes by inhibiting the activity of the FARE 2 signaling [lxxxi, lxxxii]. It has been shown that acetate can stimulate the secretion of the hormone leptin in adipocytes. This critical signal regulates appetite and energy balance [lxxxiii]. Other studies have demonstrated that inhibiting lipolysis can reduce free fatty acids translocation from the adipocytes to the liver [lxxxiv].

In fatty liver disease, the accumulation of fat derived from the adipocytes is known to contribute 60% of the total fatty acids in the liver. On the other hand, the *de novo* lipogenesis contribution from the adipocytes is 26% **(84)**. Rectal infusion of propionate and acetate has shown a 40% reduction in serum fatty acid levels [lxxxv]. It is estimated that the contribution of gut microbiota to the whole-body acetate flux is around 44% [lxxxvi]. However, the exact contribution of these microbes to this flux is not known.

Host monitoring and Control Mechanisms

The interactions between animals and prokaryotic organisms can provide various physiologic benefits. In humans, this is especially important because the gastrointestinal tract is a significant area of the body where bacterial and animal cells can interact. By developing new conceptual and technical approaches, scientists have established the role of the human gut microbiota in human health and disease. The human host evolved from a normal microbiota to a complex immune system capable of controlling and monitoring its environment. These systems are essential in maintaining the gut's well-being [lxxxvii]. The development of these systems suggests that the gut's complex immune responses can contribute to developing a healthy and balanced environment. During the evolution of the bacterial microbiota, they have developed various mechanisms to influence the host. These mechanisms maintain their stable niche and promote a beneficial environment for the bacteria [lxxxviii]. The host control mechanism can be either microbicidal or microbistatic. The human body's innate and adaptive immune responses are designed to fight against various types of bacteria. These include the formation of antimicrobial peptides, which can be found in the gut epithelium. The Paneth cells also produce -defensins, which can be used to fight pathogens [lxxxix]. In addition to interacting with symbiotic bacteria, the human body also interacts with other microbes, thus aiding in the identification of the pathogenic microbes and modalities of fighting them. These effectors are highly conserved and can prevent the growth and proliferation of certain types of bacteria. This mechanism helps maintain the balance of the microbiota in the gut. However, other complex mechanisms help maintain the body's homeostasis [xc].

Furthermore, the gut is composed of various receptor types, such as the pattern recognition receptors (PRRS) and the intracytoplasmic and transmembrane receptors [xci]. These are capable of recognizing and binding specific microbial molecules, such as those that are known to be associated with forming protein-specific molecular patterns, such as flagellins, peptidoglycans, and lipopolysaccharides. The PRRS scans the extracellular space while the NLRs guard the cytoplasmic compartment [xcii, xciii]. In all multicellular

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organisms, PRRS is known to initiate and activate regulatory pathways, such as the nuclear factor-kB/Rel, the mitogen-activated protein, and the inflammasome. These pathways are also involved in regulating the interactions between microbes and humans. As a result, evolution has conserved the various mechanisms that are needed to detect and respond to the interactions between humans and microbes **(6, [xciv])**. The primary function of PRRS is to identify and monitor the different types of pathogens **([xcv], [xcvi])**. Sometimes, the difference between a symbiont and a pathogenic species can be due to the presence or absence of a specific type of cell. This is because the immune system can recognize pathogens through the structure of the lipopolysaccharide **([xcvii])**. Symbionts can alter the surface receptors of their cells to escape from the immune system. The gut has evolved to recognize and respond to bacterial threats. This process is carried out through the development of a pattern recognition receptor and an innate immune effector **([xcviii], [xcix])**.

Microbiota and Pathogenic microbes

The gut is a site that is inaccessible to the external communities, but various microbial species can access it through the fecal-oral route. Some common enteric pathogens that enter the gut include *Salmonella, Shigella*, and *E. coli*. Before the emergence of antibiotics, the infection was regarded as an invasion by foreign agents. However, due to the microbiota, which can resist these pathogens, the infection can be treated successfully. The increasing susceptibility of germ-free mice to various types of pathogens has led to the concept of colony resistance **([c])**. However, this is not the only mechanism by which this inhibition is mediated. In addition to the competition for adhesion, other mechanisms such as the communication between intra- and inter-specific cells are also involved. Due to the various mechanisms that are involved in the development of these inhibitions, pathogenic microorganisms can also escape from the immune system **([ci], [cii])**. Understanding the various processes involved in the development of microbes in humans is very important for developing effective strategies to prevent their spread. There are multiple stages in the development of these organisms; such steps include, among others, their entry into the host and avoidance of the innate defense system. The term virulence refers to the ability of microbes to cause an infection. These factors play a role in the development and transmission of infections, including the attachment and growth of pathogens. They also help in the escape from the host defenses. To further complicate matters, the host's inflammatory response can also contribute to the development of disease **([ciii])**.

The oral route is the most common pathway for the entry of pathogens into the human body **([civ])**. Usually, these pathogens enter the body through contaminated food or water. Once they have established themselves in the gut, they can start developing various mechanisms to promote their adhesion. One of the most critical factors that can be considered when developing a gut adhesion system is the presence of a class of microbial proteins known as adhesins **([cv])**.

Adhesins

Pathogenic and commensal bacteria commonly use the class of adhesive molecules known as adhesins to interact with eukaryotic cells. These molecules can also be used to facilitate the spread of pathogens to the host cell **([cvi], [cvii])**. Although this method may be beneficial for bacterial colonization, attaching the bacteria to the host cell is not always feasible due to the metabolic cost involved. Some pathogens have evolved ways to escape the body's immune system without compromising its primary function. These include the creation of an antiphagocytic surface layer composed of polysaccharides and the expression of adhesins on the outer surface of the cell **([cviii])**. Most microbes produce several adhesins directed towards specific multiple host receptors **([cix])**. Some of these adhesion factors are often redundant and serologically variable and are often utilized by microbes to facilitate the attachment to cells of their host bodies. These include the natural host protein receptor, which allows microbes to bind and enter cells. For instance, gram-negative bacteria commonly utilize fimbriae as a type of adhesion factor to attach to host tissues **([cx])**.

Pili or the fimbrial adhesions

Most studies on bacteria adhesions focus on the pili or fimbrial variants. However, over the years, various surface-bound proteins have been identified. Some of these can also reach the capsular layer. Initially, it was believed that these adhesions only prevented the bacteria cell from being taken away by the mucosal cells.

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However, their complex functions have revealed that they can play a role in regulating the immune response and bacterial colonization **([cxi])**. Pilin is a major protein that plays a role in the formation of the pili, which are usually made up of a major protein subunit. Some strains of *E. coli* have a type 1 pili that is inhibited by the D-mannose receptor **([cxii], [cxiii])**. On the other hand, other strains have a type 1 pili capable of binding to digalactose residues on the human P blood group's surface **([cxiv])**. In some animal studies, the immunization with the FimH tip protein type 1 prevented the development of *E. coli* bladder infections. This is because the protein's receptors for enterocytes are located on the small bowel. These are known to be involved in the development of diarrheal diseases **([cxv])**. Additionally, pili are involved in developing various bacterial infections, such as *Neisseria meningitides, Moraxella*, and *Vibrio cholera* **(108)**. These organisms are known to adhere to surfaces by having a conserved and variable carboxyl- and amino-terminal region. For instance, the pili are also known to be involved in the attachment of cells to mucosal membranes. For some, the pili only play a partial role in the development of the cell's adherence to host tissues **([cxvi])**. In *Vibrio cholerae*, the cells use different types of pili to colonize their gastrointestinal tract **([cxvii])**. Uropathogenic *E. coli* is composed of two different pilus operons. The first one is known as type 1 pili- which is responsible for mannose-sensitive hemagglutination. The second type is type 1 pap-pili, accountable for the interaction between the digalactoside unit and the P-blood group antigen **([cxviii])**. The two adhesion domains are respectively accountable for the copolymerization and the carbohydrate-binding lectin domains. These adhesins follow the pathway that leads to the protein folding by an usher. The incomplete protein is then transported to the cell membrane through the SecA/Y pathway **(108)**.

Type IV Pili

Type IV pili are usually found in Gram-negative and Gram-positive pathogens, such as the *Neisseria* species and the *E. coli* genus. These include the pre-pilins co-transmitted across the inner membrane and cleaving into a mature pilin peptide. The inner-membrane pre-pilin peptidase then recognizes the pre-pilin and produces a new pilin peptide **([cxix])**. After the release of the pilin monomers from the inner membrane, the fiber is then assembled in the periplasmic region of the cell. This process is carried out by an unknown mechanism involving the addition of four proteins to the ATPase **([cxx], [cxxi])**. In the case of the *N. gonorrhoeae* species, the pilin structure has two post-translational modifications, which are characterized by the presence of an O-linked protein and glycosylation **([cxxii])**. Although the exact mechanism by which type IV pili is produced is not known, it is believed that this process can be triggered by the interaction between the inner-membrane peptidase and the pre-pilin. The type IV pili known as the *Neissserial* pili Pil C is known to recognize the CD46 cellular receptor. In recent studies, it has been shown that the protein interacts with the host cell in a way that is independent of CD46 **([cxxiii])**.

Curli

Some of the common enteric pathogens that cause diseases such as *E. coli* and *Salmonella* spp. are known to express a type of adhesion protein known as curli **([cxxiv])**. This protein is produced by the aggregation of the fimbriae. It is located on the inner membrane and can cross the outer membrane via a multi-layered outer membrane. This protein undergoes a change in its structure when it interacts with a surface bound CsgB subunit. This produces insoluble amyloid fibers, which are very sticky in nature and can only be expressed by organisms that have a specific type of ligand **([cxxv])**. *Mycobacterium tuberculosis* is also known to exhibit this condition **([cxxvi])**.

Autotransporter Adhesins

Some of the most common adhesins of gram-negative proteobacteria, such as *Yersinia enterobacteria* and *Neisseria meningitis*, are members of the Trimeric Autotransporter adhesins family **([cxxvii])**. The intra-inner membrane translocation of these autotransporter adhesins is sec-dependent **([cxxviii])**. After the translocation, the

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three adhesins' domains are placed into the outer membrane, which then allows for the transport of the linked passenger domains **([cxxix])**. These adhesins have the capability to form stable trimers on the surface of the bacterial cell **(127)**. The head-stalk-anchor architecture of these adhesins allows them to mediate attachment. They also interact with host cells and extracellular matrix proteins to promote invasion **(108,127)**. The first known instance of a pili in a Gram-positive bacterium was *Corynebacterium renale* **([cxxx])**. This type of pili has since been observed in other Gram-positive bacteria such as *Actinomyces naeslundii* and *Streptococcus pyogenes* **(130)**. The difference between the pili in Gram-positive and Gram-negative bacteria is that the former is made up of a combination of linked subunits (**130**). After the secretion of the pilins by the sec-mediated process, transpeptidases are able to link the pilins to each other and transfer them to the peptidoglycan cell wall **([cxxxi])**.

Adhesin-Receptor Interactions

In addition to the secretion of the proteins, adhesins are also known to initiate a signaling cascade involving physical contact with the host cell's surface. This process leads to the development of a mucosal response. This response is generated by the combined efforts of the non-associated adhesins and the associated pilus. These attachments are essential in the regulation of the secretion of effector proteins **(108)**.

Pilus-Associated Adhesins:

This is a type of adhesins that is commonly used in the UPEC-mediated treatment of urinary tract infections. They can trigger inflammation and a bacterial response **([cxxxii])**. Although the exact mechanism by which *E. coli* induces an inflammatory response in the bladder epithelium is unknown, it has been shown that this type of organism can be associated with acute cystitis. On the other hand, type 1-piliated *E. coli* does not cause an inflammatory response in the uroepithelium. In most studies, the proinflammatory response of the urinary tract after the use of adhesion-producing agents has been linked to the presence of a receptor known as TLR4 **(132)**. The activation of the receptor for the protein known as TLR4 by the *E. coli* papG adhesins is independent of the presence of lipopolysaccharide **([cxxxiii])**. A proposed mechanism is that the P-fimbriae's lipid receptors can recruit the receptor to their cells. In the absence of this signaling, the internalization process is significantly higher. The production of cAMP, which is a key component of the secondary messenger, helps to regulate the activity of the lipid raft-mediated bacterial invasion **([cxxxiv])**. When combined with the ability to replicate rapidly, the emergence of UPECs can lead to the formation of an environment characterized by a variety of bacterial communities protected from the effects of antibiotics and innate defenses. The development of bacterial communities within a biofilm can lead to various changes in the epithelium's morphology **([cxxxv])**. Bacteria have devised several mechanisms to avoid antibiotics, or antibacterial peptides **([cxxxvi], [cxxxvii], [cxxxviii], [cxxxix], [cxl], [cxli])**. In vitro, the bacteria regulate the production of type 1 pili by the piliation abrogates. This suggests that the presence of type 1 fimbriae in the formation of IBCs could play a role in the internalization process **(108)**. The biological effects of type 1 fimbriae are dependent on the presence of the adhesins, which are bound to mannose residues on the host cell's glycoproteins. This makes a wide variety of host cell glycoproteins potential targets for the FimH lectin. The mechanisms by which the FimH lectin is activated are also related to the lectin binding nature of the protein **(108)**.

The presence of curli in the host can trigger an inflammatory response. In *Salmonella* and *E. coli*, the release of bradykinin can induce various physiological conditions such as fever, pain, and fatigue **([cxlii])**. The CsgA protein, which is a component of the curli subunit, acts as a molecular pattern that can be used to identify the target of a specific immune response **([cxliii])**. As human pathogens, the *Gonorrheae* and the meningitides require to adhere to the surfaces of their hosts. The *Neisseriae* uses type IV pili for initial attachment. This type of pili is also known to cause a reduction in the activity of proapoptotic proteins **([cxliv])**. This condition can additionally lead to the formation of microcolonies that are dependent on this type of pili. The presence of curli in the host can trigger an inflammatory response. It can also lead to the development of a variety of cell membrane abnormalities and the formation of cortical plaques **(121),** suggesting that further signaling could be used to control the response.

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Bacterial Adhesins Associated with Non-Pilus Surface Structures

The Adhesins belonging to the TAA family such as NhhA from *N. meningitidis*, UspA1 from *Moraxella catarhalis*, or YadA from enteropathogenic *Yersinia* share a common binding affinity with various components of the extracellular matrix **([cxlv])**. Some of these are involved in the invasion of the pathogens into the host cells. For instance, *H. influenza* strain HadA invades the host cells through the induction of a signaling event that occurs within the zippering bacteria **([cxlvi])**. Studies have shown that the flagella of Enterotoxigenic *E. coli* bacteria can be utilized by the pathogen to enter the host cells **([cxlvii])**. The EtpA-binding domain of the flagellin has been shown to be a flagellum mediated event. This is because the FliD cap protein complex can be easily accessed by the EtpA-binding domain **(147,[cxlviii])**. Besides providing the necessary mechanism for the induction of the invasion, flagella also play crucial role in the secretion of effector proteins by acting as a type III secretion **([cxlix])**. The exact structure of the bacterial secretion apparatus has been poorly studied. Different types of *Yersinia* species, which are known to be susceptible to the T3SS-dependent delivery of effector proteins, use the adhesins Ail, Aya, and Yad to enter the host cells. Other bacterial domains also utilize the flagellar proteins to enter the host cells **([cl])**.

Evasion of Innate Immune Responses

During the evolution of humans, microbes might have likely interacted with various surfaces, such as the mucus layer and the epithelial surface, which are known to be defense mechanisms against pathogens. The layer of mucus that's covered by the mucosal barrier helps keep harmful organisms from entering the body. Other processes that help remove them include coughing and urination. The gut is characterized by an acidic environment that is inimical to the survival of most pathogens. This environment also allows the development of microbes that can help prevent the spread of pathogens. However, to survive, these microbes must still face various factors, such as the endocytic, inflammatory, and phagocytic responses. Host genetic factors also play a role in determining the degree to which pathogens can grow. Also, the inhabitant microbiota of the gut constrains the growth of pathogens by interfering with the capacity of pathogens to take over and infect a host. Macrophages, neutrophils, and dendritic cells are known to play an important role in the activation of the innate immune response. However, bacteria have developed ways to avoid getting killed by these cells, which are then used to hide from the body's immune system **([cli])**. The ability of a symbiotic organism to maintain a network with its host can yet again be used by the bacteria to develop a response to the environment **([clii])**. For instance, the proteins known as FimH, A, and LPS are known to trigger the activation of a specific type of immune response. In addition to these two, other factors such as lectins and scavenger receptors are also involved in the clearance of the bacteria **(108)**. The interactions between the various types of immune cells and the bacterial polysaccharide are known to be well-characterized. These include the interactions between bacterial adhesins and the phagocytic cells, usually leading to the killing of the bacteria. Although phagocytosis is always considered beneficial to the host, it can also serve as a mechanism for the development of bacterial virulence. Once the microbes have established themselves in the gut epithelium, they need to multiply to develop full-blown infections. The nutrients they need to grow are then obtained from the host tissues. Some infectious processes that can be confirmed to follow this process include gonorrhea, gastrointestinal esophagitis, and urogenital esophagitis. Various factors can explain why certain pathogens are more likely to be specific to certain environments. One of these is their ability to obtain nutrients from these environments **([cliii])**. The firmicutes produced by a Gram-positive protein are known to produce head-stalk adhesins. The most important protein type known to be involved in this process is the SRRP family, which is composed of serine-rich repeat proteins. The amino-terminal region of these proteins is fundamental and a crucial component of the adhesion between the two glycoconjugates. The SRRPs of various bacterial species are known to play a role in developing endocarditis and colonizing multiple bacterial infections **(108)**. Sometimes, the host receptors are located on different cells within the mucus layer. Target cells such as epithelial cells lining the mouth's surfaces play a crucial role in host defense. A wide range of receptor types can trigger infection by microbes. Conversely, the loss of these receptors can confer natural resistance to an invading pathogen **([cliv],[clv])**.

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Microbial Effects on Inflammatory Signaling

The epithelial lining of human tissues has various mechanisms that regulate the activation of the antimicrobial arsenal. These include the dampening of the signaling of Toll-like receptor (TLR) and the limiting of the expression of this receptor **(87)**. The presence of individual microbiota can also influence the intensity of the signaling. Nonpathogenic organisms can also suppress the effects of inflammatory substances by interfering with the pathways that are involved in the regulation of the response **([clvi])**. For instance, the intestinal symbiont *Bacteroides thetaiotaomicron* can prevent the NF-kB pathway from being activated by regulating the p65 subunit's nuclear translocation **([clvii])**. One of the most common mechanisms that can be utilized to prevent the degradation of the target proteins is by ubiquitination. This process allows the pathogens to maintain their own resistance against the host immune cells **([clviii])**.

Microbial Regulation of Adaptive Immunity

When a microbe gets into the host, it needs to be able to escape or remain completely unaffected by the host's adaptive immunity. This is done through the gut/mucosal arm of the immune system. This system, which is composed of multiple cells and tissues, is designed to provide protection against antigens and luminescent organisms **([clix])**. The ability to ignore or respond to certain antigens is known as adaptive immunity. This system can develop this tolerance in response to certain stimuli that have been exposed to it in the past. For instance, repeated exposure to the same stimulus does not trigger the same response in a naive animal **([clx])**. The development of adaptive immunity can be attributed to the increasing complexity of the host's microbiota and the multiple cells and tissues it contains. This allows the host to tolerate a wide variety of microbes, which can expand its metabolic and immunologic roles **([clxi])**. The development of adaptive immunity can also be influenced by the various factors that affect the arrangement of the gut/mucosal arm of the immune system. The gut-associated lymphoid tissue (GALT) is the largest organ in the body, and most of it is composed of discrete structures known as Peye's patches. These structures are in the gut's lymph nodes and are characterized by their unique endocytotic properties **(87)**. The presence of a wide variety of microbes can also help develop the adaptive immune system by regulating the expression of certain genes. For instance, the development of TH17 CD4+ T cells can be influenced by the presence of a bacterial community **([clxii])**. The development of the adaptive immunity can also be influenced by the presence of a wide variety of microbes. For instance, the presence of a bacterial community can help develop the adaptive immune system by regulating the expression of certain genes. Another mechanism that can help develop the system's tolerance toward the microbiota is by stimulating the development of humoral immunity. This type of immunity is triggered by the presence of a specific type of IgA **(4, [clxiii])**.

Microbiota encounter with phagocytes, tissue invasion and tropism

Phagocytosis is a process that limits the spread and growth of pathogens. It can also trigger inflammation at the sites of infection. This process is carried out through the recognition receptors of the pathogens. A good pathogen has a strategy to avoid getting trapped by macrophages. For instance, the hemolysins of *Streptococcus* can kill or inhibit macrophages' chemotaxis. There are many ways a pathogen can avoid getting trapped by macrophages. These include non-recognition by macrophages, the inertness of the pathogen to lysosomal enzymes, and the formation of endolysosomal structures **([clxiv])**. One of the most common strategies microorganisms utilizes to survive after they have ingested a substance is to enter the macrophages. Inhibition of the fusion of the phagosome with the lysosome, which is composed of antimicrobial substances, allows certain pathogens, such as *Mycobacterium tuberculosis* and *S. typhi*, to survive **([clxv], [clxvi])**. Some organisms that can escape from the macrophages into the cytoplasm, such as *L. monocytogenes* **([clxvii])**, can then spread to other cells. Resistance to the killing of these organisms within the macrophage is critical to the successful infection of various types of viruses, such as those that are known to cause diseases such as measles, chickenpox, and poxvirus **([clxviii])**. In order to survive, certain types of bacteria, such as *Salmonella*, *Yersinia*,

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Legionella, Mycobacterium, Trypanosoma, Nocardia, Histoplasma, and R*ickettsia*. *Salmonella spp*. use a master regulatory system in which the Pho/PhoQ genes control other genes to enter and survive within cells, with intracellular survival entailing structural changes in the cell envelope LPS **(21)**. Intracellular bacterial penetration can occur through the uptake of epithelial cells or the penetration of denuded epithelial surfaces. Among the factors that contribute to the development and maintenance of bacterial populations are the outer membrane proteins **([clxix])**. For instance, the strains of *Staphylococcus* and *Streptococci* utilize various extracellular enzymes to break down the matrix and cellular structures **([clxx])**. These enzymes are important in allowing the bacteria to access deeper tissues and blood. Microbes that live in the gastrointestinal tract can readily translocate through the epithelium into the bloodstream. In conditions where the host defenses are inadequate, they can cause bacteremia.

Toxins and tissue damages

At the onset of bacteriology, it has been shown that certain microbes can cause disease by infecting a specific tissue. However, the molecular basis of this propensity is not as straightforward as it should be for viral pathogens. The presence of a particular receptor on a target tissue does not explain how these viruses can enter and disrupt normal tissue function. In treating endocarditis, the bacteria must first adhere to the surfaces of the cardiac valve before they can colonize it. The characteristics of the surface cells of the vascular system are known to influence the attachment of the bacteria to the cell. Studies have shown that Fibronectin can bind to bacterial strains, such as *Staphylococcus aureus* and the viridans *Streptococci*. However, Gram-negative organisms such as *E. coli* do generally not bind well to Fibronectin. The binding of *S. aureus* to the Fibronectin or endothelial cells has been shown to be dependent on the bacterial surface protein **([clxxi])**. In a study of *S. aureus*, the characterization of the interaction between the bacteria and the vascular system revealed that the ability of the bacteria to attach to the vascular system is influenced by the propensity to colonize cardiac tissues. Thus, specific receptor-ligand interactions clearly underlie the ability of certain microbes to enter cells within tissues and disrupt normal tissue function. Nonetheless, there is excellent complexity with regard to disease conditions due to the various factors that contribute to the disease development, such as the invasion and destruction of tissues, the elaboration of toxins, and the host response. Toxin production is a widely characterized molecular mechanism for the production of certain types of pathogens. Host factors such as inflammatory proteins and the activation of the complement system contribute to the severity of the disease **([clxxii])**.

Among the first infectious diseases to be understood were those due to toxin-elaborating bacteria. Diphtheria, botulism, and tetanus toxins are responsible for the conditions associated with local infections due to *Corynebacterium diphtheria, Clostridium botulinum*, and *Clostridium tetani*, respectively **([clxxiii])**. Enterotoxins produced *E. coli, Salmonella, Shigella, Staphylococcus*, and *V. cholera* contribute to diarrheal disease caused by these organisms. *Staphylococcus, Streptococcus, P. aeruginosa*, and *Bordetella* elaborate various toxins that cause or contribute to disease, including toxic shock syndrome toxin 1 (TSST-1); erythrogenic toxin; exotoxins A, S, and U; and pertussis toxin. A number of these toxins (e.g., cholera toxin, diphtheria toxin, pertussis toxin, E. coli heat-labile toxin, and *P. aeruginosa* exotoxin) have adenosine (ADP)-ribosyltranferase activity; i.e, the toxins enzymatically catalyze the transfer of the ADP-ribosyl portion of nicotinamide adenine diphosphate to target proteins and inactivate them. Loss or inactivation of this virulence system usually greatly reduces the capacity of a bacterial pathogen to cause diseases **(9, [clxxiv], [clxxv]).** This lipid A portion of gram-negative LPS has potent biologic activities that cause many clinical manifestations of gram-negative bacterial sepsis, including fever, muscle proteolysis, uncontrolled intravascular coagulation, and shock.

The effects of lipid A appear to be mediated by the production of potent cytokines due to LPS binding to CD14 and signal transduction via TLRs, particularly TLR4 **([clxxvi])**. Cytokines exhibit potent hypothermic activity through effects on the hypothalamus; they also increase vascular permeability, alter the activity of endothelial cells, and induce endothelial cell procoagulant activity **([clxxvii])**. As a part of the process of infecting a person, some harmful microbes are shed from the body and then turn infectious to the susceptible individuals.

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However, the transmissibility rate may not usually be high even if the disease is severe. Most pathogens that cause disease passes through similar routes such as respiratory, gastrointestinal, and reproductive organs; these routes are considered to spread through direct contact with the body; however, some of these microbes can also be acquired through indirect contact with the environment, such as through blood meal or water. Some of the factors that promote transmission are the presence of certain toxins. For instance, the presence of certain toxins, such as those that cause cholera, can help spread bacterial cells in large volumes of diarrheal fluids **([clxxviii])**. The interactions between host and microbial factors during the infectious process are complex and can result in disease. One of the most important factors contributing to disease development is the coordination of the multiple virulence factors **([clxxix])**. Therefore, developing effective treatment strategies for diseases and infections requires the availability of diverse elements that can be considered when it comes to identifying and preventing the spread of harmful microbes **(155)**.

Conclusions and future perspectives

The human body has a vast and diverse collection of microbes. These species are known to help maintain the health of the body and can cause various diseases. When these microbes are disturbed, it can lead to various health conditions. It has been known that the presence of certain types of microbes can affect our health. Several studies revealed that the presence of these organisms could lead to various health conditions. Although these microbes do not usually harm humans, they can interact with the body in a symbiotic manner. This review summarized the effects of the human microbiota on human health, the mechanisms underlying their mode of function, and in-depth consideration of the microbiota, the interactions between them and the human host, etc. The species' ability to adapt to the environment of the human body is also considered. The review also considered various microbes that live in the human gut microbiota. Microbiota can help prevent pathogens from entering the human body through the competitive exclusion system. Four decades ago, it was shown that antibiotics could cause competitive exclusion machinery to malfunction, leading to the emergence of *Salmonella* infection. One of the possible reasons for the sudden reduction in the diversity of the gut microbiota following antibiotic treatment is the loss of the interspecies interactions that allow for the growth of certain types of bacteria, such as those that cause diseases such as *Clostridium difficile* and *Salmonella typhimurium*. Even short-term use of antibiotics with a dominant anaerobic coverage has been known to cause a persistent non-recover of *Bacteroides*' diversity. For instance, in *H. pylori* eradication, a short course of treatment with clarithromycin can reduce the bacteria's diversity by a thousand-fold. Besides altering the gut microbiota's natural diversity, broad-spectrum antibiotics can also lead to developing resistant strains. This can be caused by transferring genetic information between different bacterial species. Bacteria can create and distribute genetic information through various mechanisms, such as natural transformation and conjugation.

Additionally, it is tempting to overlook the role of small molecules known as short chain fatty acids (SCFA) in regulating the microbiome and the metabolism of host cells. A growing body of evidence suggests that these molecules play a critical role in developing various cell functions, such as regulating the cell's response to environmental factors. This question should be further explored to determine if it can serve as the link between diet and health. The discovery of SCFA's role in the metabolism of the gut microbiome and the development of new tools to analyze the molecular biology of this axis are starting to provide substantial evidence of its central role. However, further studies are needed to confirm its role in developing other metabolic pathways.

Sometimes, the question of whether the microbiome is a passive degradation system or a signaling molecule involved in the crosstalk between the host and the bacteria is a crucial one that needs to be answered to enable our understanding of the role of the microbiome in the development of health. Currently, and in the future, through the use of metabolomics, it is and will be possible to identify the various signals involved in regulating the microbiome. Understanding the role of the gut microbiome in developing disease risk factors could help improve the development of effective interventions. Although it is widely believed that the presence of the microbiome can improve the development of health, studies on the effects of various types of prebiotics on the health of individuals have been inconsistent. The potential of the diet-gut-host metabolism axis to prevent chronic diseases such as diabetes and cancer remains to be seen. However, it is a promising step toward developing effective, relatively simple, and cost-efficient interventions.

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