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THE ROLE OF BACTERIA IN HUMAN HEALTH AND DISEASE: FRIEND OR FOE

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Introduction

Human beings are complex, multicellular organisms that cooperate with trillions of microbial symbionts, accounting for almost 90% of the total number of cells. These symbiotic microorganisms, mainly bacteria, fungi, viruses, and archaea, inhabit different human body sites, including the gut, skin, oral cavity, respiratory tract, and urogenital tract. In recent decades, advances in DNA sequencing technologies have revealed the human microbiome's elaborate structure and its eventual impact on human health and disease. The role of bacteria in human health and disease may be curious. The emergence of antibiotics and bacteriophages highlights the pathogenic role of bacteria, which infect various human tissues, destroy host cells, and spread systemic infection. A growing body of evidence demonstrates that commensal bacteria promote tissue homeostasis in various organs of model animals. These findings in animals with a simple microbiome necessitate elucidating the effects of the microbiome's complexity arising from food intake, environment, and lifestyle, especially in social animals, including humans. Unfortunately, a significant gap remains in understanding the overall role of bacteria (both commensal and pathogenic) in human health and disease in association with bacterial cohabitation and competition. [1][2]

The germ is nothing; the terrain is everything. This phrase partly reflects how the role of bacteria in human health, as an environment in which evidence supports more benefits than harm, gradually shifts to disease upon certain dysbiosis. The microbiome contributes to environmental structures, body structures, metabolism, and immunity. The perturbation of terrain profoundly impacts health, and remediation of beneficial bacteria is probable for treatment. By contrast, pathogenic bacteria are commonly harmful due to their competitive destruction of inert structures and more aggressive structured biotopes. The emergence of threatening biotopes dominates the thoughts on bacterial pathogenicity and disease treatment. [3]

The advent of next-generation sequencing has yielded abundant genetic data on bacterial populations in human tissue. Similar taxonomic approaches have been utilized to elucidate the role of fungi and viruses, leading to the concept of a fungal microbiome and viral microbiome. On the other hand, high-throughput cultivation approaches offer a wealth of genetic data on cultivated bacteria. Thus, the study of symbiotic relationships between bacteria and multicellular organisms is yielding a bounty of evidence and fostering mathematicians to investigate co-development and interaction scenarios between relatively simple low-order organisms and their envoys or competitors. [4]

1.1. Background and Significance

Colonization by the body's natural flora is crucial to normal metabolic, immunological, and physiological functions. Over the past decade or so, advances in molecular biology and bioinformatics have allowed the identification of a complex and diverse intestinal microbiota in humans, which is suspected to play a role in metabolic disorders. The normal bacterial flora of humans is remarkably complex, consisting of 10 to 10 times as many microbial cells as are present in human cells. Recent advances in sequencing technology have allowed the first detailed characterizations of the bacterial flora in humans and a wealth of information about its diversity and potential metabolic capacity. Although the majority of normal human intestinal microbes are obligate anaerobes, numbers of gram-positive Lactobacillus and Bifidobacterium are usually determined in the gastrointestinal tract and feces. In addition, members of the Bacteroides and Eubacterium genera also belong to the considered normal flora. The innate immune system provides a first line of defense against invading pathogens and is highly sophisticated. The innate immune system has evolved to provide immediate resistance to a wide variety of infectious agents through barriers. The skin and epithelial cells are additional parts of the innate immune system. The mucus layer of the intestinal tract is a first physical barrier between the host and gut microbiota. Secretory immunoglobulin A is the principal antibody class at mucosal surfaces and plays a major role in the regulation of gut barrier functions. Members of the phylum Firmicutes are the most abundant groups of protozoans in the human gut, representing about half of the identified species. Bacterial members of the genus Lactobacillus also belong to the endogenous microbial flora. In addition, anaerobic Bacteroides and Clostridia species have been assigned to the endota. The ability of the cultured microbiota to degrade, transform, and otherwise metabolize dietary polysaccharides, other macromolecules, and polysaccharide metabolites was examined. The human microbiome is reported to consist of more than 500 prokaryotic and 100 eukaryotic species, mostly bacteria and yeast. Once established, the gut bacterial communities of individuals remain remarkably stable throughout adult life and respond conservatively to gut antibiotics, specific dietary changes, or pathogen infections. Such a large bacterial community can be expected to play an important role in human health. [5][6][7]

2. Historical Perspective

The origin of the modern concept of bacterial disease evolved from the extraordinary evolution in the field of bacteriology over the almost 300 years since the first description of bacteria under a microscope. This pre-microbiological conceptual period extended over thousands of years and included the generation of a rich array of speculative notions about the origins of life and disease through to the era when the tiny living objects were first described and issued an immortal declaration stating, "There are people who assert that these animalcules occur through spontaneous generation. If such a phenomenon bestows these little creatures on stagnant water, that confirmatory evidence would be lacking of a specific cause proceeding from a general cause." At the time, the major speculative systems were those of antiquity, such as the physiological theories of Thales and Anaximander and the allegorical explanations of Democritus, mythology icons like the famous Saint Anthony's fire, where the skin appears to be burned by proximity to an individual with skin inflammation. [8]

2.1. Discovery of Bacteria

We, in the 21st century, live in a very complex world. Our society, technology, economics, politics, and health issues are quite complex. Humans have advanced in their understanding and sophistication in all these areas, but our understanding of microbiology is still developing and has a very long and exciting way to go. The first people to report the existence of bacteria were the great scholars of the ancient world. They felt that everything living emanated some vapor and that living systems containing this vapor would decay if the system was not kept fresh. The scientists at the turn of the 19th century applied principles of chemistry to their discipline of medicine, and it was they who postulated that disease was a result of living raucous. The deductions by these pioneers no doubt resulted in the development of the germ theory and the ability of chemists to prepare antibiotics. [9]

As early as the 3rd millennium BC, populations practicing medicine were recognizing that some fevers of unknown origin, which may have been caused by bacteria, were not spread from person to person. The first report of infectious diseases as a natural event was made by the Egyptians, who recognized the existence of grazing animals with “foot rot,” a disease today that is caused by bacteria. It appears that the ancient Egyptians did not communicate their findings to the Greeks or any other civilization for that matter. The lack of communication in those ancient days did not help in advancing the knowledge of microbiology. The word “bacteria” was first used in 1828, but it was Anton Van Leeuwenhoek, a microscope manufacturer and amateur scientist, who, almost a century before, was the first to see these smallest of creatures. By chance, he discovered, as he called them, “scurf” or “animalcules” living in our environment. [10]

3. Bacterial Diversity

Bacteria are the most diverse and abundant group of organisms on Earth. There are approximately 10^31 individual bacteria on Earth, which exceed the total number of stars in the universe by several orders of magnitude. Bacteria encompass an enormous diversity of species, spanning an astonishing range of shapes and sizes, from the longest bacterium at 26 mm in length to the smallest at 0.2 mm in diameter. Mammals harbor a rich diversity of bacteria, with approximately 1,000 different species in the human gut alone. This taxonomic diversity is accompanied by an extraordinary metabolic capability, allowing exploitation of widely divergent environmental niches. For example, certain bacteria can degrade hydrocarbons at the deep-sea ocean floor and in human oil spills, while others can oxidize toxic hydrogen sulfide to harmless sulfate in the oxygen-depleted ocean anoxic basins and in the gut of animals. Bacterial diversity is not an accumulated byproduct of evolution but the virtuous basis of life on Earth. It is the worldwide effort to uncover this amazing diversity that sparked the development of molecular methods for exploring microbes by ribosomal RNA phylogeny. Bacteria are diverse and ubiquitous, existing in enormous numbers in practically every niche on Earth. They colonize the air, soil, oceans, and living organisms, thereby exerting a profound impact on both ecological and biogeochemical processes. Facilities have been developed for cultivation-independent studies of the diversity of 16S rRNA genes in diverse environments, including oceans, groundwater, sewage treatment plants, and the human gut. As a result of these efforts, the discovery of previously unknown bacterial lineages has fundamentally changed the view of microbial diversity on Earth. [11][12]

Bacteria are unicellular organisms and the simplest and most abundant forms of life. A simple description of bacteria is a single cell filled with cytoplasm and genetic material and surrounded by an outer membrane. However, the structures of bacterial cells vary widely. For example, the sizes of bacteria range from less than 0.5 microns to several millimeters. The shapes of bacterial cells can be rod-shaped, spiral, or oval. Some bacterial cells swim by the rotation of long filaments called flagella, while others remain immobile. Certain bacterial species contain unusual organelles, such as magnetosomes or intracellular membranes involved in the oxidation of sulfur or carbon dioxide fixation. In addition to the

massive morphological diversity, bacteria are taxonomically very diverse, with more than 60 different phyla currently described. Each phylum contains a wide variety of morphological and physiological characteristics. In recent years, a number of rare phyla largely represented by environmental sequences have been discovered. Some of them are only represented by a few clone sequences from limited environments. Most of these phyla have a few cultivation efforts under certain environmental conditions, while many of them remain completely uncultured. [13][14]

3.1. Classification and Structure

Bacteria are highly diverse prokaryotic microorganisms that inhabit numerous ecological niches on Earth. Prokaryotes are organisms that lack a membrane-bound nucleus and membrane-bound organelles. In addition to bacteria, this group of organisms includes archaea. All prokaryotes are single-celled organisms, but many eukaryotes, which have a membrane-bound nucleus and membrane-bound organelles, can also be unicellular, multicellular, and colonial. Eukaryotes include animals, plants, fungi, and protists. In this essay, discussions will focus on the classification, structure, and function of bacteria, and the roles of beneficial and pathogenic bacteria in human health and disease. [15]

Traditionally, bacteria were classified based on morphology and staining characteristics, such as Gram staining. However, recent advances in biochemistry and molecular biology have enabled the classification of bacteria into two domains, Bacteria and Archaea, based on ribosomal RNA sequences. Despite the diversity of form and function among bacteria, the basic structural and functional unity remains. The smallest bacteria, such as Mycoplasma, have a diameter of 0.1 to 0.5 µm, while the largest bacteria, such as Epulopiscium fishelsoni, can be 600 x 80 µm in size. Based on shape, bacteria can be classified as cocci (spherical), bacilli (rod-shaped), vibrio (comma-shaped), spirilla (coiled), and spirochete (flexible corkscrew). [16]

In addition to differences in shape, bacteria can also vary in the arrangement of cells after division. These arrangements include single (no arrangement), diplo (two in a pair), strepto (chain-like), staphylo (clusters), and sarcina (cubical packet of eight). Understanding bacterial classification and structure is essential for the exploration of their diverse ecological interactions and functions, effects on human health, and applications in biotechnology and medicine. [17]

4. Bacterial Metabolism

Nutrient Processing and Energy Production

Bacteria possess diverse metabolic pathways that have adapted to their environment and an individual's requirement for bioenergetics, biosynthesis, and maintenance of homeostasis. Typically, bacteria grow quite rapidly, and thus they have evolved metabolic pathways that are highly efficient in processing the available substrates. [18]

Organic nutrient degradation to simpler basic components or small molecules by specialized extracellular enzymes is the initial step in the assimilation of organic nutrients. Absorption of simple compounds over the cell surface explains the rapid utilization of organic nutrients. Uptake of low-molecular-weight compounds involves transport systems conserving energy in the form of electrochemical gradients of H+, Na+, or other cations where translocation of compounds occurs. The energy required for active transport can also be supplied by the hydrolysis of high-energy phosphate bonds of ATP in the case of the ABC transporters. [19]

For bacteria dwelling inside a host, membrane transport systems have evolved, forming a chain of interdependent interactions occurring with high specificity. Later, bacteria bypass the time-consuming energy released by the breakdown of polymeric substrates, instead absorbing preformed transport substrates of high molecular weight and low ionized compounds. Transport through the outer membrane,

as well as through the cell wall of Gram-negative bacteria, is demonstrated along with translocation into the periplasm and transport across the inner membrane. [20]

Microbial polysaccharides are essential in the interaction between bacteria and their environment. They mediate the formation of biofilms, are involved in adhesion processes, cell-cell recognition for controlling bacterial pathogenicity, and have important implications in host defenses. Bacterial enzymes participate in complex biochemical processes producing mono- and oligosaccharides and releasing ions. Recently, a detailed model of the overall composition, structure, and properties of the cell wall of Gram-negative bacteria was proposed, which predicts the relationships between growing and non-growing bacteria, acknowledging their surface-bound constituents. Thus, there are basically six homogeneous regions accounting for Gram-negative bacteria: the outer membrane composed of three strata forming a coating on the cell envelope; the peptidoglycan layer; and the inner membrane. [21]

Considering its length, the polysaccharidic glycocalyx or exocellular polysaccharide layer impedes random diffusion. Thus, EPS bacteria are subjected to flow velocity, which is proportional to the distance away from the surface and the gradient of concentration as a function of time. Bacterial EPS may also provide a surface to which contaminants can attach and consequently protect cells against toxic compounds. Thus, EPS bacteria remove contaminants from a liquid medium, sequestering and concentrating them at the cell wall. Despite the neutral and negative ionization at physiological pH, the cell envelope of Gram-negative bacteria possesses a polycharged solid surface directly in contact with the aquatic medium. This solid surface displays highly heterogeneous surface electrostatic potential gradients, interfacial pH with respect to the bulk aqueous phase, and anionic sites isolated outside the matrix structure, fundamentally obeying the Gouy-Chapman-Stern electrochemistry theory as a dielectric. [22]

The mature biofilm phenotype denotes an organism’s alternative growth mode, frequently in association with a surface or other organisms. The ability to form biofilms is widespread among bacterial species, including those associated with chronic infections. As biofilms grow, they excrete expanses of extracellular polysaccharide matrix that enables polysaccharide-encased communities of cells to mature. Bacterial polysaccharides play central roles in biofilm formation and involvement in Gram-negative biofilm development. [23]

4.1. Nutrient Processing and Energy Production

Bacteria are crucial to the human gut ecosystem due to their ability to degrade complex polysaccharides and oligosaccharides. Microbial fermentation that occurs in the gut is a result of bacterial processing of these substrates, resulting in the production of various metabolites that contribute to human health. This is particularly important in adult humans as dietary fiber makes up a significant portion of their diet. Microbial fermentation converts dietary fiber into various short-chain fatty acids in the intestine, with butyrate acting as the preferred energy source for colonocytes and proposed to be protective against colon cancer. Acetate and propionate are utilized by the liver and peripheral tissues, achieving energy balance by feeding different tissues with short-chain fatty acids. [24]

Bacterial glucose metabolism has been explored extensively in cultured and sequenced gut bacteria. Such studies reveal different aspects of glucose and its derivatives metabolism in these bacteria, including variations in transporters and enzymes. In certain bacteria, two bioinformatic approaches, systems biology and genomic comparison-based enzyme classification suggest different metabolic pathways and efficiency for glucose and other sugars. There are also observations on how some bacteria use both residual glucose and acetate as carbon and energy sources during the diauxic growth on glucose and acetate mixtures. In parallel, genomic comparisons lead to the discovery of two classes of xylosidases

that are supposed to attack xylobiose, the major microbial product of xylose fermentation in non-growing xylanase-controlled fermentation conditions. [25]

To uncover the fermentative and respiratory metabolism of human gut strict anaerobe bacteria in a straightforward yet quantitative manner, a gut Firmicutes bacterium strain was chosen as a model organism. This Gram-positive bacterium ferments mucin as carbon and energy sources, resembling glycoprotein hydrolysis by mucus-degrading bacteria. Mucin metabolism is accompanied by H2 accumulation that can be utilized by H2-using bacteria through interspecies hydrogen transfer. This H2-using bacterium was isolated from human feces and bioinformatically predicted to utilize lactate, ethanol, and formate as substrates, and could grow on H2, butyrate, acetate, or propionate as carbon sources. The model organism was found to possess a hydrogenase with an ordered sequential mechanism for H2 oxidation. [26]

5. Bacterial Interactions with the Human Body

The human body is home to a staggering number of microbes, with bacteria serving as the predominant members of this vast community. Each individual harbors a unique microbiome, shaped by a variety of genetic, environmental, lifestyle, and dietary factors. While substantial differences exist in the composition of microbiomes across populations, certain veritable species, referred to as core species, are maintained among healthy individuals. The gut microbiome is the most well-studied and best understood of the human microbiomes. [27]

A growing body of literature highlights the relevance of the gut microbiome's compositional and functional alterations to various health and disease states. Notably, certain diseases, such as diabetes, colitis, and obesity, have been linked to shifts in microbiome composition and function. Though many bacterial species whose abundance or activity changes in these diseases have been identified, the actual roles and underlying mechanisms of these bacteria remain largely unknown. Recent research strategies focused on the resident gut microbiome members in mouse models have provided new insights into how these bacteria affect mammalian physiology. [28]

While much of the initial research efforts in this field were expended on understanding bacterial associations with the intestine, other bacterial populations outside of the gut and their relevance to health and disease are currently being studied. The interindividual differences in the microbiome are as extensive and complex as the individual genetic and phenotypic differences between humans. Since the microbiome is shaped by both intrinsic and extrinsic factors, it is not surprising that even populations living in a similar environment and under similar lifestyles can harbor very different bacterial compositions. There are major differences in both composition and function between the microbiomes of different body sites. Though the most well-studied and publicly accessible datasets focus on the bacterial sequences of these microbiomes, certain archaeal species and eukaryotes are also associated with specific microenvironments. [29]

5.1. Microbiome Composition and Function

The microbiome refers to the collection of microorganisms, including bacteria, that inhabit various environments in and on the human body. Bacteria are the most numerous and diverse members of the human microbiome, and as such, the microbiome is often thought of as the bacterial metagenome of the human body. Within the broad field of microbiome research, there is a particular focus on bacterial interactions with the human host and on the interplay between the microbiome and human health and disease. [15]

Historically, the sea was thought to be the most biodiverse environment on Earth until the discovery of the human microbiome. It was first documented that there are ten times more microbial cells living in and

on the human body than human cells. The overwhelming majority of the microbiome is composed of bacteria, and thus the human microbiome is often simply referred to as the human 'microbiota.' [15]

The composition of the microbiome varies widely from person to person, and this population is relatively stable throughout life. These unique populations can be referred to as a person's 'microbial signature.' However, the composition is also dynamic, as the microbiome is affected by other factors including diet, environment, and antibiotic use. [30]

The human microbiome is composed of more than 1,000 different bacterial species, with almost half of the bacterial genera comprised of only a single species. The broadest classification of the human microbiome is into five groups known as 'phyla.' The vast majority of the bacterial microbiome is composed of four phyla: Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. Most of the bacteria that associate with the human body are Gram-positive, which stain with crystal violet in the Gram-staining procedure. Gram-positive bacteria are characterized by a thick peptidoglycan layer, which gives them structural integrity and shapes. In contrast, Gram-negative bacteria are found to have an outer membrane, causing them to stain red during the Gram-staining procedure. Gram-negative bacteria are generally more resistant to antibiotics owing to this outer membrane barrier. Of the four main phyla, Firmicutes and Actinobacteria are Gram-positive, while Bacteroidetes and Proteobacteria are Gram-negative. [31]

6. Bacterial Pathogenesis

The human body serves as a diverse habitat for a multitude of bacterial species. Bacteria can colonize every part of the body, primarily those surfaces in contact with the environment, such as the skin, oral cavity, and gastrointestinal tract. Most of these bacterial species coexist peacefully with the host, establishing a symbiotic relationship and providing beneficial attributes. However, a limited number of bacteria may also invade the host tissue and cause disease; this in turn becomes detrimental to the human host. [32] [1]

Bacterial infection mainly involves the following processes: bacteria gain entry into the host, and subsequently multiply and spread within the host. Pathogenic bacteria have evolved various strategies to facilitate their invasion into the host tissue. These strategies can be classified into two major groups: i) bacteria initially attach to the surface of specific host cells or tissues, then invade cells or tissues by subverting host-cell signaling pathways, and ii) bacteria initially invade non-phagocytic host cells, then replicate inside membrane-bound vacuoles. In both cases, pathogenic bacteria may exploit various host molecules as receptors for bacterial attachment and uptake, including glycoproteins, glycolipids, and glycosaminoglycans that form the glycocalyx on the host-cell surface. After bacterial invasion into tissues, most pathogenic bacteria proliferate in the interstitial space and disseminate to other tissues. To resist phagocytosis by innate immune cells at the initial site of infection, some pathogenic bacteria deploy type IV pili. Type IV pili can also serve as [33][34]

6.1. Mechanisms of Infection

Bacterial pathogens possess a diverse arsenal of virulence factors that enhance their ability to colonize and infect a host, evade the immune system, replicate, and disseminate to new hosts. Many virulence factors also have other important functions in bacteria, such as essential cellular processes or nutrient uptake systems. Pathogenicity islands are examples of large blocks of DNA that contain virulence factors. They are considered to have been horizontally transferred from other organisms to confer virulence inside the bacterial genus. Pathogenicity islands are primarily present in pathogenic strains, and similar pathogenicity islands can be found in diverse pathogens. [35]

Colonization is the first step in bacterial infection. Most pathogens enter and colonize a host at mucosal surfaces that are protected by a layer of epithelial cells. Epithelial cell surfaces facing the environment are coated by mucins, large glycopolymers secreted by specialized epithelial cells. Mucins are highly O-glycosylated, and their dense branched glycan structures confer gel-forming properties that trap bacteria, limiting their access to epithelial cells. Mucins also contain anti-microbial peptides that permeabilize and kill bacteria. The sheer forces generated by the movement of ciliated epithelial cells flush out bacteria and mucus towards the gastrointestinal tract. [36]

Pathogenic bacteria overcome the protective role of mucins and penetrate the epithelial cell layer by using different strategies. One of them is to adhere to the mucus layer by directly binding glycoproteins or using auto-aggregative properties. Furthermore, bacteria can also subvert the innate immune response triggered by epithelial cells. Epithelial cells utilize pattern recognition receptors to detect host-derived signals or pathogen-associated molecular patterns to identify invading microorganisms. Pattern recognition receptors include secreted C-type lectins, clade 4, and clade 2 membrane-bound receptors that recognize β-glucans, peptidoglycan, chitin, and mannans. Epithelial cells also produce pro-inflammatory cytokines that recruit immune cells to destroy pathogens more efficiently. Many pathogens express polysaccharides mimicking host glycoproteins that evade the glycosylation patterns of the host. [37]

7. Bacterial Diseases

Bacteria have been recognized as pathogenic agents for many centuries. The Golden Age of Microbiology in the late nineteenth century witnessed the discovery of specific bacteria responsible for diseases. These discoveries laid the foundation of bacteriology and provided insight into the germ theory of disease. Since then, bacteria have been identified as causal factors of a large variety of infectious diseases in humans, animals, and plants. These infections can be life-threatening or at least greatly impact the quality of life in affected individuals. More recently, the knowledge of bacteria as pathogens expanded to include certain viruses, fungi, and protists as well. However, bacteria remain the most abundant and diverse group of pathogens, and a variety of diseases caused by bacteria are still a global health burden. [38]

Although most of the interactions between bacteria and humans are benign or beneficial, some bacteria are able to colonize the host and evade the immune system, ending up inflicting harm on the host. Notable examples of common bacterial infections include bacterial pneumonia, tuberculosis, and streptococcal disease. One of the most famous examples is a Gram-positive encapsulated bacterium residing asymptomatically in the nasopharynx of 20-60% of adults. However, it can invade the respiratory epithelium and cause severe pneumonia and sepsis in susceptible individuals, including children, the elderly, and those with impaired immune defense. A close relative is also a well-known opportunistic pathogen and the causal factor of diseases such as strep throat, skin infections, and severe necrotizing fasciitis. It is remarkable that the very same bacteria that can be benign members of the healthy microbiota can also be responsible for life-threatening infections. [39]

Averaging over a wide variety of different species, pathogenic bacteria share certain strategies to promote their ability to colonize, evade the immune system, and replicate within the host. Many of these mechanisms are well studied, such as the production of toxins that target host cellular structures or signal transduction pathways, or the differentiated production of surface structures promoting adherence to epithelial cells. In recent years, further progress in our understanding of the molecular and cellular basis of infection has been made at the systems level. Analysis of the entire pathogen-host interaction at the systems biology level has helped to get a holistic view of bacterial diseases and their impact on human health. [40]

7.1. Common Infections and Their Impact

Bacterial infections are the most common infectious diseases of humans and often do not receive prompt medical attention. Untreated, they can lead to serious or fatal complications. However, there are also mild acute bacterial infections that the body's own defenses can usually overcome without the use of chemical drugs. Epidemic entry of new strains of bacteria can result in larger populations being infected and hence an increased chance of serious consequences. Bacteria are highly adept at adapting to any new environment, and rapidly evolving strains may arise, making them resistant to previously effective treatments. Such resistant strains may spread to the general population and form new endemic strains. Due to the widespread overuse of antibiotics to treat bacterial infections and as food additives in farming, many new strains of bacteria have recently arisen that are resistant to all known antibiotics. Normal strains of bacteria are harmless but may opportunistically take advantage when the immune system is severely compromised, for example, due to hospital procedures or chronic disease. [41][42]

Common Infections and Their Impact

Some common types of infection caused by bacteria, with their current treatments, are given below:

Pharyngitis, or sore throat, is usually caused by streptococci bacteria. Most sore throats are viral in origin and resolve without treatment within a week. However, strep throat may cause serious complications: infection of the heart valves, inflammation of the kidney, or rheumatic fever, which can affect the joints and heart and cause permanent damage to the heart valves. In the USA, a commonly used standard for determining whether a sore throat can be treated with chemical drugs is available. Otherwise, it should resolve within 7 days. If it does not, it is advisable to test for strep throat, and if there is a positive result, to consult a doctor for possible laboratory analysis of the strain and treatment with penicillin or its derivatives. [43]

Otitis media, or middle ear infection, is also usually caused by streptococci bacteria, although among children it may also be caused by more virulent bacteria such as staphylococci or meningococci bacteria. The immune system usually resolves the infection within 1-3 weeks. However, repeated infections or a failure to resolve after 8 weeks may affect hearing and development and warrant the insertion of tubes in the ear to allow drainage of fluid, allowing the body's defenses to recover. After 3 days, it should be tested for strep and, if positive, treated with amoxicillin or a wider spectrum drug if there are repeated infections; otherwise, it should resolve within 7 days. If not, this may indicate a more dangerous infection with meningococci bacteria. [44]

8. Antibiotics and Bacterial Resistance

Antibiotics are compounds that have the ability to kill bacteria. They have different mechanisms of action that help them control the growth or replication of different bacteria. Therefore, antibiotics are widely used for both the domestication of bacteria, scientific experimentation, and therapeutic purposes. The downside of using antibiotics so widely is the development of resistance by the bacteria. This happens when a bacterial population changes its genetic makeup to render the antibiotic useless. For example, the antibiotic capability of penicillin revolves around its shape and the recognition it uses to inhibit the transpeptidase cell wall enzyme. Some bacteria might develop modifications to this enzyme such that penicillin might not recognize it, as the transpeptidase might have a different shape than what is stereotypical of all transpeptidase enzymes. [45]

8.1. Development and Mechanisms of Resistance

The overuse of antibiotics in human and veterinary medicine and in agriculture has caused tremendous selection pressure on bacteria that goes together with the development of resistance. These bacteria are able to lower the impact of the antibiotic in different ways, such as modification of the target structure or

increased expression of a cell membrane protein that eliminates the antibiotic from the cell. The individual strategies that bacteria use to cope with the effects of these compounds are highly conservative, and the mechanisms of resistance are found in different groups of bacteria. Resistance can develop in single bacteria but also on a chromosomal, as well as on an extrachromosomal level. The responsible gene can be located in the same unit that shows the effect of the antibiotic, but also in a different unit that is closely or not at all linked to the target gene. Since 1996, the situation has become even worse with the appearance of examples of horizontal gene transfer of resistance determinants from one group of bacteria to another, resulting in the rapid spread of diverse resistance genes in bacterial populations. Major factors in the development of antibiotic resistance are the degree of resistance and therefore the suitable concentration of the antibiotic, the percentage of the bacterial population that is exposed to the antibiotic, the rate of spontaneous mutations among the exposed bacteria, and the susceptibility of the bacteria to horizontal gene transfer. [46][47]

9. Probiotics and Prebiotics

There are many potentially probiotic fermentative or saccharolytic non-pathogenic gut bacteria currently available. Most of them are members of the genera Bifidobacterium and Lactobacillus, and a smaller number of others are isolated from otherwise "natural" intestinal bacterial populations. Several suspected pathogens have been used as probiotics in a variety of animal models of intestinal disease. Intake of antibiotics, poor diet, stress, surgery, or certain diseases can lead to colonization of the intestinal tract with pathogenic bacteria. This condition is called dysbiosis. When the balance of the normal intestinal microbiota is disrupted, several mechanisms can be used to perturb it to a greater or lesser level. A shift in the composition of the normal microbiota can occur, leading to the predominance of a normally underrepresented species or closer relation to the input bacteria. [48]

Feeding an individual with large amounts of one of the normal gut microbiota genera, usually Lactobacillus or Bifidobacterium, may help to restore the balance of the microbiota since these bacteria can favorably colonize the intestine. If this shift in balance negatively impacts an individual, then those members of the conventional microbiota that are enhanced through prebiotic effects can be called upon to counteract the unwanted effects. The ideal situation is to utilize bacteria consumption to create a favorable individual environment, both competitively in the intestine itself or extra-intestinally as part of a large "arsenal" to be deliberately or coincidentally consumed by an impacted individual. When used with conventional therapies in treating challenging gastrointestinal issues, beneficial microbiota can increase an individual's quality of life, substantially reduce costs, and sharply decrease the likelihood that any one approach may fail. [49]

9.1. Health Benefits and Mechanisms

The relationship of humans with commensals has long been recognized, and some of this interaction has been rationalized into direct benefits for humans, e.g., purification of food; synthesis of vitamins; suppression of harmful microorganisms; and modulation of the development of the immune system. The host support associated with some of these is considered in the context of the present hypothesis, and examples of each are to be found. There are probiotic, immunomodulation, other favorable effects, and chronic diseases-related beneficial effects from gut commensals. In general, when disease-resistance methods were limited, pre-modern humans either avoided or coped with the health problems that were caused by beneficial agents in the environment. The development of germ theory during the 19th century prompted consideration of prevention and resolution by enemy reduction and, more recently, beneficial effects that could demonstrate probiotics. [50]

The resident commensals also deliver homeostatic signals to the mucosal immune system of the host. Modulation of the immune system is one of the co-evolved advantages associated with dietary

supplementation that is achievable after digestive stress, while suppression of problematic organisms selects diet-dependent physiological benefits. Competition between various commensals for colon resources will contribute to keeping them at an immunomodulation non-stimulatory level, thereby maintaining the balance by limiting overall stimuli. Bacterial community profiling has shown that there are commensal population parameters that can be associated with health and disease status. Conventional in vivo quantitation tools and next-generation sequencing technologies have identified a number of different populations that are related to health and others with disease associations. These gut microbial ecosystem revelations have raised a host of questions, such as what are the practical effects of the shifts reported, what drives them, and what are the structural and functional impacts on health, disease, and metabolism? Ongoing and future coherent, inclusive, and testable human, animal, cell line, and in silico studies are necessary to functionally understand these associations at the organismal and molecular level. [51]

10. Bacteria as Therapeutic Agents

Bacteria have been increasingly recognized for their potential therapeutic applications in various fields of medicine, including cancer therapy, metabolic diseases, immune disorders, and inflammatory bowel diseases. Advances in genetic manipulation techniques have enabled the engineering of bacteria with desired functions for the treatment of diseases. A major application of bacteria in medicine is in the field of cancer therapy. Scientists have engineered bacteria to specifically target and undergo lysis in tumors, delivering therapeutic genes that kill tumor cells. Live, attenuated bacteria have also been used as adjuvants to potentiate antitumor immunity. The choice of bacterial strains for tumor targeting is critical and involves considering bacterial host factors, intrinsic tumor characteristics, and the tumor microenvironment. In animal models, various types of bacteria, such as attenuated Salmonella typhimurium, Listeria monocytogenes, and Bifidobacterium, have been shown to target and colonize tumors, leading to antitumor effects. Phase I clinical trials have demonstrated the safety and feasibility of using live bacteria in cancer therapy. [52][53][54]

Another important application of bacteria in medicine is in the treatment of metabolic diseases, particularly obesity and type 2 diabetes. Researchers have engineered bacteria to specifically sense and degrade dietary L-Phe, a precursor of the satiation hormone PYY. This approach has been shown to lead to cascading effects and a reduction in food intake and body weight. By tuning the sensing and degrading abilities of commensal bacteria, it is possible to achieve the desired gut-host physiological effects. The absence of unwanted side effects is an additional advantage of using bacteria for therapeutic purposes.Bacteria are also being applied in the treatment of immune disorders, with a focus on inflammatory bowel diseases. Probiotics and commensals are known to exhibit immunoregulatory properties, and engineering a commensal bacterium with a therapeutically effective cytokine has been shown to ameliorate colitis in colitic mice. Bacteria can be designed to prevent the onset or attenuate the severity of immune disorders by controlling their dosage, timing, and virulence. [55][56]

In summary, bacteria have demonstrated great potential as therapeutic agents for various diseases. Research into the engineering and applications of bacteria in medicine is ongoing and is expected to lead to novel treatments with great promise.

10.1. Applications in Medicine

The human body harbors at least 100 trillion microorganisms, mostly bacteria. For more than 100 years, bacteria have been used to alleviate human suffering by curing diseases. The role of bacteria in health and disease is beautifully understated in the quotes 'Bacteria are our friends' and 'Bacteria are dangerous germs.' The destructive nature of pathogenic bacteria has been understood during the last two centuries. The virulence factors of these bacteria, like toxins, proteases, polysaccharides, capsules, endotoxins, and

exotoxins, are understood in detail. Nevertheless, a comprehensive understanding of friendly bacteria, the probiotics, is still elusive. Several bacteria exhibit probiotic potential, but Lactobacillus and Bifidobacterium species dominate the probiotic field. [57]

During the last 30 years, probiotic applications in medicine have surged due to the increased understanding of gut bacteria and their beneficial roles. Probiotics have been reported to prevent or treat several adult and childhood diseases, including diarrheal diseases, allergies, cancers, diabetes, autoimmune diseases, obesity, and other ailments. However, many probiotic applications in medicine are not fully explored or understood. Prior to the probiotic explosion, beneficial bacteria were used to cure diseases for centuries. The efficacy of several types of milk fermented with Lactobacillus bulgaricus to alleviate digestive and nutritional diseases was reported 1,700 years ago. Similarly, extensive use of fermented foods, especially milk, to combat intestinal diseases has been documented in ancient civilizations. A specific type of yogurt fermented with Lactobacillus bulgaricus and Streptococcus thermophilus was granted a patent in the USA in 1929 to treat and prevent gastroenteritis in infants. The use of friendly bacteria to treat diseases has been documented since 1899 when the physician proposed the use of buttermilk fermented with Bacillus bulgaricus for promoting longevity and health. The experiments laid the foundation of 'favorable bacteriotherapy' or friendly bacteria, the probiotics. [58][59]

Apart from the use of probiotics, the deliberate use of bacteria to treat diseases has been practiced for nearly 100 years. Staphylococcus aureus, Salmonella typhi, Agrobacterium tumefaciens, Clostridium botulinum, and other bacteria have been widely used for producing vaccines. Extracts of Mycobacterium vaccae displayed remarkable ability in treating allergic and autoimmune diseases and for enhancing the antitumor efficacy of vaccines. Mycobacterium vaccae was initially discovered in the soil of mountain regions, where people lived a healthy life and did not develop allergic diseases. Further studies revealed that the bacteria could modulate the immune response and induce the production of anti-inflammatory cytokines. Subsequently, the bacteria were tested on asthmatic children, where a significant decline in the allergic symptoms and an increase in the levels of cytokines in serum were observed. [60]

11. Ethical Considerations

Fundamental to the concept of replacing pathological bacteria with their normal physiological flora is the embracing of the philosophy and values that govern most probiotic uses, namely the rejection of non-beneficial bacteria. Disease treatment with non-pathogenic microbes, like disease prevention with beneficial microbes, is predicated upon the fundamental quality of the agent, rather than the characteristics of the bacteria affecting the syndromes. Two key principles should guide our caution in using non-pathogenic bacteria: (1) The characteristics of the natural flora that are to be displaced or eclipsed are as important as the displaced or eclipsing pathogens, (2) Using only the "virtuous" non-pathogenic microflora as replacement agents for evicted opponents is more desirable than selecting or genetically modifying bacteria to exclude bacterial antagonists. Replacement therapy, which disarms a major host-pathogen barrier system, cannot be undertaken cavalierly and is an error-prone clinical procedure. Radical reconstitution with discontinued (or new) residents can provoke deleterious alterations in the host. Under normal circumstances, the composition of the microflora host system is not primarily determined by competition between bacterial residents. Overgrowth of a few members of the normal microflora epidemiologically correlates with an ephemeral lessening of host resistance. Similarly, mass absence of natural microflora does not improve host competence, yet reconstitution invariably returns host resistance with its original efficiency. [61]

11.1. Research and Treatment Ethics

Unlike in the field of cancer, where clinical research for new treatments cannot be tested on healthy subjects, infectious disease research includes the use of healthy subjects in research. To what extent can

an individual volunteer for research to be infected with an agent when there is no specific cure for the disease or infection that will ensue? When new asymptomatic infections or unexpected sequelae of therapeutic interventions appear, treatments in development can suddenly reduce the population of potential research volunteers. Volunteer studies, by their nature, rarely include sufficient controlled samples to answer all the important medical questions, and thus large numbers of infected subjects may be required. Society must balance this increased-risk potential benefit and compensate the participants appropriately. Should these prospective patients and participants be the same subjects, and what institutional and regulatory mechanisms can be put in place to ensure adequate ethical 'firewalls' to prevent undue influence or interest upon the rights and safety of these individuals? Especially with the current public and global threat of bioterrorism, should the risk and reward relationships be affected or intensified? These are not exclusively scientific concerns, but they are vitally important in the design, outcome value, and ethical limitations of individual and population-based infectious disease research initiatives. Current hypervigilance on topics related to biosafety and biosecurity is affecting the recruitment or ability to conduct the very necessary research efforts to develop more optimal strategies for diagnosis, control, and treatment of many important human diseases. Addressing these questions and more will require the broadest and most transparent academic, political, social, legal, research, and public participation within a true global socioethical framework. [62][63]

12. Conclusion

In this analysis, the role of bacteria in both human health and human disease has been explored in detail. It has been shown how a vast majority of bacteria focus on the symbiotic relationship with humans, being friends rather than foes. The diversity of species of bacteria is one of the greatest assets of the microbial world, creating enormous biochemical capabilities within the host for its own benefit. Important functional roles have been discussed, for instance, of flagged pathogenic bacteria at colonic sites, shaping the initial host immune response in the gut. Important activities of microbial communities within the female reproductive tract and placenta on maternal-fetal health have been outlined as well. This beneficial cooperation of bacteria can also be established artificially, and proves to be of fundamental significance during the first years of life, as well as after antibiotic consumption or other pathogenic insults.

Alongside its beneficial role, there is a variety of scenarios of host-bacteria interactions that can lead to diseases. Sometimes bacteria can directly invade the cells. Bacteria can induce cell death, such as toxin-producing bacteria, which are dangerous not only in the intestines but also for neurological effects in muscle intoxications. As a special case of harmful interactions usually followed by the cohabitation of other microbial species in the gut, dysbioses have been presented. These relatively common phenomena in modern societies are well characterized but poorly understood, as they do not necessarily imply an increase in pathogenic bacteria. They are lethal for more than just one type of antibiotic treatment, the prospect of which appears to be a dead end. Dysbioses of numerous pathogens wipe out the entire microbiota population.

Therefore, there remains a great unknown of unexplored bacteria on the borderline between friend and foe. These bacteria are poorly characterized at the genomic level, and their roles during a disease state remain unexplored. Collaborating with a high-resolution monitoring technique, they might provide important data for a better understanding of host-bacteria interactions. With such knowledge, artificial approaches might be designed to steer interaction outcomes, in some cases changing foes into friends for the host and uplifting the protection from infectious phenomena.

12.1. Summary of Key Findings

The human microbiota is a vast and intricate collection of approximately 100 trillion microorganisms that take up residence primarily in various parts of the gastrointestinal tract. These incredible symbionts play a crucial and indispensable role in human health, particularly in the maturation and fortification of the immune system, the metabolism of essential nutrients, and the development of a multitude of diseases. Recent ground-breaking advances in DNA sequencing technology have provided unprecedented insight into the complex composition of the microbiota and its profound influence on host physiology and intricate biochemistry. These remarkable and awe-inspiring discoveries represent a paradigm shift in the realm of healthcare, as they open up thrilling possibilities for manipulating the microbiota to effectively treat or even prevent a wide array of diseases, including but not limited to inflammatory bowel diseases, obesity, type 2 diabetes, and neurodegenerative disorders. However, it is important to acknowledge that, despite the immense potential, there exist certain technological barriers and gaps in our knowledge that must be diligently addressed before the full commercial potential of biotechnology related to the human microbiome can be actualized. In the gastrointestinal tract alone, the estimation is that an astonishing number of over 100 trillion microorganisms are present, predominantly dominated by bacteria, while also featuring the presence of fungi, viruses, archaea, and protozoa. These remarkable microorganisms have the unique ability to adhere to surfaces, and when different organisms colonize a specific surface, they come together to form what is known as a biofilm. Although the study of biofilms has primarily focused on individual species, with a particular emphasis on environmental biofilms or biofilms formed by bacteria that cause notoriously difficult-to-treat chronic infections, it is imperative to understand the complexity and dynamics of these biofilms within the context of the human microbiota. To delve even deeper into the intricacies of this fascinating field, it is crucial to establish a clear distinction between the terms "microbiota" and "microbiome." The microbiota can be defined as the vast collection of microorganisms that inhabit a particular environment, whereas the microbiome refers specifically to the entire collection of genes possessed by these microorganisms. Consequently, when we refer to the microbiome, we are essentially focusing on the functional aspects of the microbiota and its complex interactions within the host-microbiota-gene framework. This nuanced understanding provides a comprehensive comprehension of the dynamic relationships between the microbial communities and the host organism. From the very moment of birth and in the early stages of life, microorganisms commence colonizing the human body, and as a child grows and matures, the microbial composition undergoes constant change. There exist a multitude of factors that significantly influence the composition of the microbiota after birth, including the mode of delivery, diet, and various environmental factors such as the administration of antibiotics and other medications, hygiene and sanitation practices, lifestyle, and geographical location. Remarkably, population-based studies have demonstrated that lifestyle factors exhibit a more pronounced correlation with microbiota composition than host genetic variations, thereby emphasizing the substantial impact of external factors on the intricate microbial ecosystem residing within us. Compellingly, the microbiota composition exhibits the ability to adapt and transform in response to sudden and dramatic changes in the environment, as well as during the natural aging process. Additionally, certain microorganisms are absolutely indispensable for the normal development and functionality of the immune system. Consequently, any disruption in the delicate balance and colonization of these beneficial bacteria can lead to heightened susceptibility to infections and the onset of a range of diseases, including atopic diseases, metabolic syndrome, and autoimmune disorders. The astonishing discoveries surrounding the human microbiota have truly revolutionized our understanding of the intricate relationship between microorganisms and human health. With the rapid advancements in technology and the ongoing accumulation of knowledge, we are edging closer to unlocking the full potential of harnessing the power of our microbiome to improve human well-being and prevent disease.

The road ahead undoubtedly holds exciting possibilities as we continue to explore and unravel the mysteries of this captivating microbial world within us.

References:

1. S. Kitamoto, H. Nagao-Kitamoto, and R. Hein, "The bacterial connection between the oral cavity and the gut diseases," *Journal of dental*, 2020. nih.gov
2. T. Wein and R. Sorek, "Bacterial origins of human cell-autonomous innate immune mechanisms," Nature Reviews Immunology, 2022. weizmann.ac.il
3. D. Zheng, T. Liwinski, and E. Elinav, "Interaction between microbiota and immunity in health and disease," Cell research, 2020. nature.com
4. Y. Combarnous and T. M. D. Nguyen, "Cell communications among microorganisms, plants, and animals: origin, evolution, and interplays," International Journal of Molecular, 2020. mdpi.com
5. I. Khan, Y. Bai, L. Zha, N. Ullah, and H. Ullah, "Mechanism of the gut microbiota colonization resistance and enteric pathogen infection," *Frontiers in Cellular*, 2021. frontiersin.org
6. S. Taghizadeh, M. Asgharzadeh, and S. Dao, "Gut microbiota and human body interactions; its impact on health: a review," Current, 2022. researchgate.net
7. P. Belvoncikova, P. Splichalova, P. Videnska, and R. Gardlik, "The human mycobiome: colonization, composition and the role in health and disease," Journal of Fungi, 2022. mdpi.com
8. L. Bottalico, I. A. Charitos, M. A. Potenza, "The war against bacteria, from the past to present and beyond," *Expert Review of Anti*, 2022. [HTML]
9. N. Arning and D. J. Wilson, "The past, present and future of ancient bacterial DNA," Microbial Genomics, 2020. microbiologyresearch.org
10. A. R. A. Saied, A. A. Metwally, N. A. B. Madkhali, "Egypt's COVID-19 recent happenings and perspectives: a mini-review," Frontiers in Public Health, 2021. frontiersin.org
11. J. M. Kirsch, R. S. Brzozowski, D. Faith, "Bacteriophage-bacteria interactions in the gut: from invertebrates to mammals," Annual Review of ..., 2021. annualreviews.org
12. S. Runge and S. P. Rosshart, "The mammalian metaorganism: a holistic view on how microbes of all kingdoms and niches shape local and systemic immunity," Frontiers in Immunology, 2021. frontiersin.org
13. F. Baluška, W. B. Miller, and A. S. Reber, "Cellular and evolutionary perspectives on organismal cognition: from unicellular to multicellular organisms," Biological Journal of the ..., 2023. researchgate.net
14. S. G. B. Amyes, "Bacteria: a very short introduction," 2022. collectiveliberation.org
15. G. A. Ogunrinola, J. O. Oyewale, "The human microbiome and its impacts on health," International journal, 2020. wiley.com
16. O. Uluçay, "Microorganisms and Diversity of Bacteria," 2023. researchgate.net
17. B. Maier, "How physical interactions shape bacterial biofilms," Annual Review of Biophysics, 2021. [HTML]
18. A. K. Wani, N. Akhtar, F. Sher, A. A. Navarrete, "Microbial adaptation to different environmental conditions: molecular perspective of evolved genetic and cellular systems," Archives of …, 2022. ntu.ac.uk

19. Y. Xu, L. Sun, R. Lal, R. Bol, Y. Wang, X. Gao, "Microbial assimilation dynamics differs but total mineralization from added root and shoot residues is similar in agricultural Alfisols," Soil Biology and ..., 2020. [HTML]
20. J. C. Caruana and S. A. Walper, "Bacterial membrane vesicles as mediators of microbe–microbe and microbe–host community interactions," Frontiers in microbiology, 2020. frontiersin.org
21. S. Singh, S. Datta, and K. B. Narayanan, "Bacterial exo-polysaccharides in biofilms: role in antimicrobial resistance and treatments," Journal of Genetic, 2021. springer.com
22. K. U. Mahto, M. Priyadarshanee, and D. P. Samantaray, "Bacterial biofilm and extracellular polymeric substances in the treatment of environmental pollutants: beyond the protective role in survivability," Journal of Cleaner, 2022. [HTML]
23. F. A. Sadiq, M. Burmølle, M. Heyndrickx, "Community-wide changes reflecting bacterial interspecific interactions in multispecies biofilms," Critical Reviews in..., Taylor & Francis, 2021. [HTML]
24. Q. Song, Y. Wang, L. Huang, M. Shen, Y. Yu, and Q. Yu, "Review of the relationships among polysaccharides, gut microbiota, and human health," Food Research, 2021. [HTML]
25. N. Tsukuda, K. Yahagi, T. Hara, Y. Watanabe, "Key bacterial taxa and metabolic pathways affecting gut short-chain fatty acid profiles in early life," The ISME, 2021. oup.com
26. Y. Sun, S. Zhang, Q. Nie, H. He, and H. Tan, "Gut firmicutes: Relationship with dietary fiber and role in host homeostasis," *Critical reviews in*, 2023. researchgate.net
27. W. M. De Vos, H. Tilg, M. Van Hul, and P. D. Cani, "Gut microbiome and health: mechanistic insights," Gut, 2022. bmj.com
28. E. Z. Gomaa, "Human gut microbiota/microbiome in health and diseases: a review," Antonie Van Leeuwenhoek, 2020. [HTML]
29. L. M. Olsson, F. Boulund, S. Nilsson, M. T. Khan, "Dynamics of the normal gut microbiota: a longitudinal one-year population study in Sweden," *Cell Host & Microbe*, 2022. cell.com
30. M. S. Kennedy and E. B. Chang, "The microbiome: Composition and locations," in *Progress in Molecular Biology and Translational*, Elsevier, 2020. nih.gov
31. S. Naud, A. Ibrahim, C. Valles, and M. Maatouk, "Candidate phyla radiation, an underappreciated division of the human microbiome, and its impact on health and disease," Clinical Microbiology, Am Soc Microbiol, 2022. nih.gov
32. H. J. Lee and M. Kim, "Skin barrier function and the microbiome," International journal of molecular sciences, 2022. mdpi.com
33. E. J. Stevens, K. A. Bates, and K. C. King, "Host microbiota can facilitate pathogen infection," PLoS pathogens, 2021. plos.org
34. J. S. Ramírez-Larrota and U. Eckhard, "An introduction to bacterial biofilms and their proteases, and their roles in host infection and immune evasion," Biomolecules, 2022. mdpi.com
35. I. Jurado-Martín, M. Sainz-Mejías, and others, "Pseudomonas aeruginosa: An Audacious Pathogen with an Adaptable Arsenal of Virulence Factors," International Journal of…, 2021. mdpi.com
36. K. K. Selwal, M. K. Selwal, and Z. Yu, "Mucolytic bacteria: prevalence in various pathological diseases," World Journal of Microbiology, Springer, 2021. [HTML]

37. A. P. Rogers, S. J. Mileto, and D. Lyras, "Impact of enteric bacterial infections at and beyond the epithelial barrier," Nature Reviews Microbiology, 2023. [HTML]
38. G. Mancuso, A. Midiri, E. Gerace, and C. Biondo, "Bacterial antibiotic resistance: the most critical pathogens," Pathogens, 2021. mdpi.com
39. N. Mues and H. W. Chu, "Out-smarting the host: bacteria maneuvering the immune response to favor their survival," Frontiers in Immunology, 2020. frontiersin.org
40. L. Sharma, J. Feng, C. J. Britto, and C. S. Dela Cruz, "Mechanisms of epithelial immunity evasion by respiratory bacterial pathogens," Frontiers in immunology, 2020. frontiersin.org
41. H. Li, N. Terrando, and H. A. Gelbard, "Infectious diseases," in *Microglia: Physiology, Pathophysiology*, Springer, 2024. [HTML]
42. Y. Fu, Q. Yang, M. Xu, H. Kong, and H. Chen, "Secondary bacterial infections in critical ill patients with coronavirus disease 2019," *Infectious Diseases*, 2020. oup.com
43. K. M. Miller, J. R. Carapetis, and C. A. Van Beneden, "The global burden of sore throat and group A Streptococcus pharyngitis: A systematic review and meta-analysis," The Lancet, 2022. thelancet.com
44. M. Macaj, L. Perdochova, and J. Jakubikova, "Streptococcus pneumoniae as cause of acute otitis media (AOM) in Slovak children in the pneumococcal conjugate vaccine era (2008–2019)," Vaccine, 2023. sciencedirect.com
45. T. Li, D. Teng, R. Mao, Y. Hao et al., "A critical review of antibiotic resistance in probiotic bacteria," Food Research International, 2020. [HTML]
46. S. F. Nadeem, U. F. Gohar, S. F. Tahir, "Antimicrobial resistance: more than 70 years of war between humans and bacteria," Critical Reviews in ..., 2020. academia.edu
47. L. Serwecińska, "Antimicrobials and antibiotic-resistant bacteria: a risk to the environment and to public health," Water, 2020. mdpi.com
48. D. Dahiya and P. S. Nigam, "Antibiotic-therapy-induced gut dysbiosis affecting gut microbiota—brain axis and cognition: restoration by intake of probiotics and synbiotics," International journal of molecular sciences, 2023. mdpi.com
49. L. B. Olvera-Rosales, A. E. Cruz-Guerrero, et al., "Impact of the gut microbiota balance on the health–disease relationship: the importance of consuming probiotics and prebiotics," Foods, 2021. mdpi.com
50. Y. Chen, W. Cui, X. Li, and H. Yang, "Interaction between commensal bacteria, immune response and the intestinal barrier in inflammatory bowel disease," Frontiers in Immunology, 2021. frontiersin.org
51. O. Manor, C. L. Dai, S. A. Kornilov, B. Smith, "Health and disease markers correlate with gut microbiome composition across thousands of people," Nature, 2020. nature.com
52. D. Lin, X. Feng, B. Mai, X. Li, F. Wang, J. Liu, and X. Liu, "Bacterial-based cancer therapy: An emerging toolbox for targeted drug/gene delivery," Biomaterials, 2021. [HTML]
53. Z. Cao and J. Liu, "Bacteria and bacterial derivatives as drug carriers for cancer therapy," Journal of Controlled Release, 2020. [HTML]
54. X. Huang, J. Pan, F. Xu, B. Shao, and Y. Wang, "Bacteria-based cancer immunotherapy," Advanced ..., 2021. wiley.com

55. T. P. M. Scheithauer, E. Rampanelli, and M. Nieuwdorp, "Gut microbiota as a trigger for metabolic inflammation in obesity and type 2 diabetes," Frontiers in, 2020. frontiersin.org
56. L. Wang, X. Cheng, L. Bai, M. Gao, G. Kang, "Positive interventional effect of engineered butyrate-producing bacteria on metabolic disorders and intestinal flora disruption in obese mice," Microbiology, 2022. asm.org
57. P. M. Ergashevich, "WHAT YOU NEED TO KNOW ABOUT INFECTIOUS DISEASE," International Multidisciplinary Journal for Research & ..., 2023. ijmrd.in
58. A. Lopez-Santamarina, E.G. Gonzalez, and A. Lamas, "Probiotics as a possible strategy for the prevention and treatment of allergies. A narrative review," Foods, 2021. mdpi.com
59. B. A. Tegegne and B. Kebede, "Probiotics, their prophylactic and therapeutic applications in human health development: A review of the literature," Heliyon, 2022. cell.com
60. WP Gong, Y Liang, YB Ling, JX Zhang, YR Yang, "Effects of Mycobacterium vaccae vaccine in a mouse model of tuberculosis: protective action and differentially expressed genes," Military Medical, 2020. springer.com
61. R. Debray, R. A. Herbert, A. L. Jaffe, "Priority effects in microbiome assembly," Nature Reviews, 2022. nsf.gov
62. G. Molenberghs, M. Buyse, S. Abrams, and N. Hens, "Infectious diseases epidemiology, quantitative methodology, and clinical research in the midst of the COVID-19 pandemic: Perspective from a European …," Contemporary Clinical …, 2020. sciencedirect.com
63. D. Vinsensia, S. Amri, and J. Sihotang, "New Method for Identification and Response to Infectious Disease Patterns Based on Comprehensive Health Service Data," MATRIK: Jurnal, 2024. universitasbumigora.ac.id