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Review Article

Mechanisms and Triggers of Pathogenic Transformation in Human Commensal Microbiota

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Abstract

The human commensal microbiota is a complex community of bacteria that lives in many parts of the body, including the gut, skin, and mucosal surfaces. It plays a crucial part in ensuring that the host remains healthy and resilient. These microbiotas engage in a wide variety of beneficial interactions with their host, including assisting in digestion, synthesising important nutrients, and providing protection against pathogenic invaders. On the other hand, these commensal bacteria have the potential to transform into pathogenic species under specific circumstances, consequently making a significant contribution to the aetiology of disease. The purpose of this in-depth review is to investigate the myriads of processes and stimuli that are accountable for the pathogenic alteration of human commensal microbiota. The most important methods of transformation are genetic mutations and horizontal gene transfer, both of which have the potential to increase the pathogenicity of microorganisms and their resistance to the defences of the host. A number of environmental factors, including dietary choices, exposure to antibiotics, and changes in lifestyle, have the potential to severely alter the stability of the microbial ecosystem, hence creating settings that are permissive to pathogenic conditions. These disturbances frequently cause a shift in the delicate equilibrium that exists between the populations of microorganisms and the host, which ultimately results in dysbiosis. Dysbiosis is a condition that is linked to a number of disorders, including metabolic syndrome, obesity, and inflammatory bowel disease. In addition to that, elements that are associated with the host have a significant contribution to this change. In a situation where an inadequate immune response can lead to unregulated microbial proliferation and pathogenic transformation, the immune system of the host is delicately shaped and modulated by the microbiota. In addition, the integrity of epithelial barriers serves as a first line of defence; a breach in this barrier can make it easier for pathogenic shifts and microbial translocations to occur. When it comes to designing targeted therapy techniques that attempt to restore and preserve microbial equilibrium, having a solid understanding of these transformation mechanisms is absolutely necessary. Prebiotics, probiotics, and synbiotics are all examples of what might be included in this category. Additionally, personalised dietary treatments that are aimed to support a healthy microbiome can also be included. New understandings have been gained on the ways in which these transformations can be predicted, prevented, and managed as a result of advancements in genetics and microbiome research.

Keywords: *Commensal Microbiota, Pathogenic Transformation, Dysbiosis, Genetic Mutations, Horizontal Gene Transfer, Antibiotic Resistance, Environmental Factors, Host Immune Response, Epithelial Barrier Integrity, Microbial Homeostasis, Human Microbiome, Virulence Factors, Prebiotics, Probiotics, Microbial Balance, Microbial Ecosystem, Inflammatory Diseases, Gut Flora, Microbial Interactions, Nutrient Synthesis*

1. Introduction

Microbes colonize every surface on earth. The surfaces are exposed to the air, water, skin, mucosal surfaces, and barrier organs. Commensal microbiota colonizes and takes part in forming the body's boundary surfaces starting from birth. Specific conditions and the increase in age shape the strength binding commensal microbiota and host animal. There are innumerate unique commensal species that live co-dependent and in co- existence with multicellular organisms to gain the potential from one another. With the advances in high-throughput next generation sequencing technology, it is now possible to analyze host microbiota with higher resolution and deeper understanding. Host-specific microbiomes have been identified in mammalian systems and other larger higher organisms by considering the mutual benefits. Commensal systems have adapted to the bio-ecological conditions since long term evolution and enhanced their support to the physiology of their hosts. The best-studied factor is the balanced presences of the microbiota that contributes to the formation of a protective barrier to pathogen colloquially referred to as “colonization resistance”. Microbiota the non-invasive bacteria strongly inhibits the replication of invasive bacteria and accompanies them to overcome the host immune system. Pathogens enhance the invasiveness and virulence when they manage to overcome the wall and break the ecologic competition with the microbiota. Commensal species can occupy spaces that pathogens can colonize and it becomes impossible for the pathogens to interact with the human cells (1).

2. Overview of Human Commensal Microbiota

The microbiota is the set of all microorganisms residing in an environment, their relationships with this environment, and with the host in the case of multicellular organisms (2). The microbiota capable of colonizing the human body is known as human microbiota. It is a stable and relatively long-term microbial community, which varies greatly among different body locations. Despite residence of a stable community of commensal species, the entire human microbiota, displaying over 100 times more species and genes than the number of eukaryotic cells, is in a state of metabolic and immunological equilibrium with the host (3). Under these circumstances, the microbial community can also be defined as a commensal microbiota.

This interacts with the host not only as individuals, but also as a holobiont comprising its metazoon host, or a metabiome involving the metapopulation of its microbial symbionts. When commensal species acquire or evolve towards pathogenicity or virulence, they become pathogens of the host. The colonization and onset of conflicts as a consequence of such pathogenic transformations in the microbiota sub-community are supported by certain triggers. These environmental, genetic, epigenetic or stochastic factors have long been studied mainly in the context of bacterial colonization, occurring during or shortly after parturition, or in the case of early immunity establishment.

2.1 Definition and Importance

Introduction: Microbiota is the collective assembly of microbial members that share a common environment, and commensal microbiota is the assemblage of beneficial bacteria housed by a eukaryotic host. Human commensal microbiota harbors a diverse collection of bacterial species and colonization of different sites generates remarkably distinct microbiomes. Commensals exert wide ranging beneficial effects, including competition with bacterial pathogens, training of the host immune system and aiding digestion by encoding enzymes that liberate substrates otherwise indigestible to the host. Metagenomic and metabolomic analyses demonstrate that common predicted functions of the human microbiome often vary between individuals, suggesting commensals can fulfill the same beneficial roles using distinct biochemical strategies. Although extensive efforts have been directed towards determining the impact of human microbiomes on human health, less is known about the predisposing conditions and triggers that allow commensals to cause disease (1).

Gut microbiota are essential for host physiology including production of essential amino acids and vitamins, energy harvesting, and protection against enteric pathogens. The gut epithelium separates the abundant and diverse microbiota from internal host tissues. Breakdown in intestinal barrier function allows direct contact between Enterococcus faecalis strains and the fly circulatory system, leading to systemic infection. Such events highlight the potential of normally benign members of the microbiota to cause disease if they bypass mucosal defenses and gain access to the normally protected internal tissues of the host. These phenomena necessitate a clearer understanding of the genetic and physiological states that underpin commensal pathogenicity to facilitate monitoring and ultimately therapeutic intervention.

2.2 Composition of Commensal Microbiota

The human body is populated by thousands of distinct bacterial species, whose genomes are collectively known as the human microbiome (2). The majority of these commensal species reside in the gut, where they are involved in important metabolic and immune functions. This makes them potential pathogenic reservoirs in particular situations. Recent studies have improved our understanding of the variability of human commensal microbiota and of the factors that determine susceptibility to colonization and amplification by potentially pathogenic species. However, the processes that trigger the pathogenic transformation (PT) of commensals are still largely unknown.

The commensal species that populate the gut are usually present at approximate population levels and are therefore ineffective in competitive exclusion of incoming potential pathogens. Nevertheless, recent studies of ecological modeling of multispecies microbiota suggest that high biodiversity is associated with a more effective exclusion of new species. The concept of diversity is broad and in ecology it is usually quantified by assuming an overall measure that considers both the number of species and the uniformity of their abundances. Although this work has mainly focused on the human commensal microbiota, unveiling the dynamics of species-wise colonization and expansion in the human gut, the data suggest that a similar ecological interpretation of competing pressures due to members of the commensal flora can also be made for extraintestinal pathobionts. The sequence of ecological events associated with the PT appears to be more complex than a simple unbalance of competition forces.

2.3 Role in Human Health

In the healthy state, specific commensal species and beneficial consortiums regulate the host’s immune responses. It is also an important player in the development of the host’s immune system. A bacterial consortium that represents immune development is composed of a wide variety of species. It is important to know the operation mechanisms and triggers of immune responses induced by commensal bacteria consortiums to understand their effects on human health. Unlike parallel studies based on certain specific keystone species, a member of human commensal microbiota, consortia made up of multiple commensal species must be used to understand human microbiota as a whole and overcome limitations related to the living form, which exists as a community (1). As a result, this study will be helpful in understanding the relationship between human health and the immune responses of human commensal microbiota. This provides detailed realization of how human commensal microbiota consortiums induce host immune responses, and helps generate new knowledge about the immune education of the host by commensal microbiota, which can be helpful for regulating immune responses under certain conditions.

3. Pathogenic Transformation: An Overview

The commensal human microbiota protects against pathogens, aids digestion, and helps develop the immune system. Commensals establish symbiotic relationships with the host, keeping growth under control and fostering functions supportive of the host. However, under specific circumstances, commensals can turn hostile and cause pathology (1). Several mechanisms and triggers of the pathogenic transformation of human commensal microbiota have been identified. Changes in immune system and metabolic disorders, often caused by the western, high-fat diet, are the most prominent host-related triggers of the pathogenic transformation of commensal microbiota. Meanwhile, only a few triggers implicated in the control of human commensal microbiota pathogenic transformation have been discovered to date. It is believed that a more comprehensive understanding of the causes of the transformative events in commensals would enable the development of strategies to prevent and possibly treat numerous common diseases. At the same times, the potential role of other, yet undiscovered triggers remains to be determined. Of note, the existence of multiple pathobions duking similar pathological states in different patients likely reflects the presence of alternative triggers of the pathogenic transformation of microbiota (4). Given the vital role of commensal microbiota in health and disease, it is essential to investigate the mechanisms and triggers of the harmful switch in commensals. Knowledge of these phenomena would allow the development of strategies for recovering a healthy microbiota state or for preventing pathogenic transformation in the high-risk population.

3.1 Definition of Pathogenic Transformation

The human gut harbors abundant commensal bacteria that have co-evolved with the host for millions of years. The gut commensals have been shown to perform a wide range of beneficial functions for the host, while there is also growing awareness that the commensal microbiota may become pathogenic under certain conditions. Traditionally, commensals are considered as non-pathogenic due to the lack of virulence factors and this view is profoundly supported by the recent advances in experimental culture conditions to isolate a large number of commensals. However, it is increasingly realized that the commensals have been underestimated by focusing on a small number of well- adapted strains or species (5). Donor microbiota, as a complex bacterial community containing bacteria that are not used to each other, would by definition need some time to reach a steady-state; emphasis should be put on the development of investigative models to study community dynamics between many co-existing bacteria. For these reasons, as interest in host-microbiota interactions has grown, the notion of well-behaved commensals has been challenged by increasing evidence supporting a new hypothesis for pathogenic transformation (1).

Pathogenic transformation, or pathogenicization, denotes the changes in host-commensal interaction that normally cause commensals to opportunistically become pathogenic. Pathogenic transformation is a general phenomenon, rather than a single clear-cut event, and could be triggered by diversified mechanisms, so it is a continuously evolving process instead of a permanent state. With increasing insight of the human commensals identified, “pathogenic transformation” refers to the features of commensals that display pathogenicity in specific human hosts. A key benefit of the probiotic strategy is the potential for directed, safe induction of mucosal immune responses, which commensals do not elicit. Probiotics also provide colonization of the intestine by organisms that possess advantageous properties such as interference with commensal pathogen attachment sites, thus enhancing colonization resistance to pathogenic species. Since most commensals are delivered in food matrices, the opportunity for delivery of known and characterized commensals is possible, whereas the application of antibiotics that kill beneficial as well as pathogenic bacteria is likely to cause the overgrowth of pathogenic bacteria due to disruption of the intestinal flora.

3.2 Historical Perspectives

The human microbiota includes a rich combination of bacteria. Commensal bacteria are defined as bacteria found on body surfaces exposed to the exterior world colonizing humans postnatally and living in mutualistic relationship with the host. They provide vitamins, educate the immune system, improve digestion, and protect against potential pathogens. However, it is becoming evident that certain features of commensal human microbiota promote disease. The borders between opportunistic pathogens, pathobionts, and commensals are increasingly blurred, and specific targets for manipulation are becoming elusive. This study focuses on the functions of host-associated bacterial communities colonizing body surfaces exposed to the exterior world, not including endosymbionts, archaea, protists, fungi, or non-bacterial members of microbiota that have the potential to cause disease and proposes the term “pathogenic function (pathofunction)”. The concept of pathofunctions is presented via three distinct examples: the formation of trimethylamine, secondary bile acids, and hydrogen sulfide, as these bioactive compounds are linked to the development of common non-communicable diseases, including cardiovascular disease, atherosclerosis, hypertension, and hepatic steatosis. These three pathofunctions were ubiquitously present in samples and always with increased abundances in the patient group. At the same time, the three pathofunctions were not detected in control subjects, which includes healthy individuals and patients before the onset of a certain disease. All three pathofunctions were enriched in low mean concentrations. The three pathofunctions encompassed a high number of different taxa. The three pathofunctions were formed by various bacteria, and this formed compound was the same.

4. Molecular Mechanisms of Transformation

The human commensal microbiota is a complex microbial community that resides on the epithelial surfaces and in the lumen of the gastrointestinal (GI) tract. As such, this bacterial flora needs to coexist with the host defense systems, participate in physiological digestion and maintain gut homeostasis. It is increasingly recognized that commensal bacteria can become pathogenic, but the mechanisms of this transformation are not completely understood. Aiming to clarify the molecular triggers of pathogenic transformation in gut commensal microbiota, in vitro high-throughput screening was performed on clinically isolated Enterobacteriaceae strains using novel experimental approaches.

Extracellular DNA (eDNA) is a ubiquitous environmental factor, yet there is only scarce information on its possible role in horizontal gene transfer (HGT) in natural environments. The results raise the possibility, that eDNA may be a previously overlooked factor in HGT between bacteria from the gut, the aquatic environment, and other habitats. Bacteria living in natural environments, and also as commensals on the body surfaces of humans and other animals, are important due to their potential transfer of antibiotic resistance and/or other genes to pathogenic bacteria. The most overlooked field in this respect is how genetic material, the principal driver of bacterial evolution, disseminates among the environmental bacteria. This type of HGT can take place between pathogens and commensals, and vice versa, on the human skin or mucosal surfaces. During the last 60 y, many articles and reviews were published on transformation in laboratory glassware. This research was initiated to verify eDNA as a source of DNA in naturally transformable strains (6). Within the gut, the commensal microbiota has beneficial effects on the host, whereas pathogens provoke stimulatory responses. Avenue of alteration may allow one subpopulation to dynamically change from commensal to pathogenic, which might benefit from reduced defense systems in a host.

4.1 Genetic Changes

The draft includes an experimentally confirmed GEM with broad and potentially harmful effects. Worrying questions are raised about possible negative effects of GEMs on the commensal intestinal microbiome, its bacteriophages and its regulating immune response, with resultant adverse consequences to public health. Insertions of composite transposon Tn1000 carrying ampicillin or tetracycline resistance genes recently established evolution experiments where one out of five commensal E. coli lineages (CCMG1-5 strains) become pathogenic. The progressive acquisition of phenotypes relevant during host colonization is consistent with parallel colonization of different gastrointestinal tract regions by genomically distinct lineages. Bibliography includes primarily partially shared and four personally created publications and editorials, letters or replies related to them. These fifth articles or responses are about potential implications or GEM effects on the mammalian intestinal microbiome and the interplay between engineered microorganisms, conjugative plasmids and high-range bacterial genomic diversity. More than three years have passed since the first publication in this category, and, considering the critical concerns raised, this is the most plausible delay to get responses. As the results presented in the 2024 publication are, therefore, the most reliable for scientific discussion, an effort is made to compensate for shortcomings using new bibliographic references outside the collection (7).

4.2 Virulence Factors

Virulence factors are molecules produced by bacteria that contribute to disease by enhancing the ability of a microbe to enter a host, obtain nutrients, communicate with other bacteria, and evade immune defenses. By contrast, some bacteria elicit extensive inflammation and disease using mechanisms that do not appear to be specifically required for theirreplication (AR Webb & M Kahler, 2008). Reflecting the immense advances in our understanding of bacterial pathogenesis that have accrued since the coining of the term in the 19th century, the most current understanding of virulence factors includes a wide array of factors that do not conform to Koch’s postulates or the traditional notions of the term virulence factor. Thus, although professional boilerplate definitions of “virulence factors” abound, they miss the point. In other words, it is exceedingly difficult to define in simple terms what a virulence factor is. Most definitions of virulence factors do not take this into account. Rather, the first line of these definitions is usually some variant of “molecules that enable bacteria to cause disease.” However, this preeminent definition misses the point that many organisms are extremely virulent pathogens in the right host but do not have a traditional set of virulence factors (9).

4.3 Biofilm Formation

Biofilms were first described by Antony van Leeuwenhoek in 1674, after examining dental plaque under a simple microscope (Luis Souza dos Santos et al., 2018). Subsequently, biofilms are defined as communities of properly organised microorganisms attached to an inert or living substrate and embedded in a self-produced extracellular matrix. The chemical constituents of the extracellular matrix - proteins, glycoproteins, exopolysaccharides, eDNA, lipids, and a few other compounds - are responsible for maintaining the biofilm architecture, stabilising it through a network of intermolecular interactions, and creating a continuous, spatially differentiated structural framework of microbial cells, empty water-filled channels, and other void structures (Gerald Buret et al., 2019). Such architectural features illustrate the organisational complexity of biofilms and determine a series of biological properties that include microbial survival, adhesion, transport, communication, cooperation, competition, and persistent (chronic) infections.

The microbial proliferation within the biofilm matrix leads these communities to initiate an evolutionary pattern, establishing and increasing the commensal pathogenic load (infestation), which additionally inhibits the host inflammatory response and antiseptic methods. Uptake can also be ascertained at the site of previously formed biofilms, during the following transplantation (seeding) of the inflamed, dysbiosed microbiota.

In the biomedical field, biofilms “are an asphalt in the road to good health”. Over 80% of infectious diseases in the human body are attributed to biofilms, which are believed to be a substantial causative agent of microbial resistance to antibiotics. Biofilms serve as shelters to multidrug-resistant bacteria. Furthermore, such communities showed anaerobiosis survival inside the superficial layers of the matrix when exposed to a bactericidal gentamicin concentration. Efficacy of antibiotics for biofilms is 1000 times less. The effects of certain antibiotics were even found to be reversible on treatment cessation. Disseminated biofilm-associated infections are also known to be incurable by systematic administration of antibiotics and surgical intervention. In light of these findings, this phenomenon could be postulated as one of the immunity evasive mechanisms of commensal infestants. Unsolved therapeutic aspects of established infections are acute or chronic undercurrents, creating positive feedback loop ecosystem instabilities, such as inflammation, effects on the binding of microorganisms, pathogens, and proteopathogens, and significant dysbacteriosis, which in turn can lead to detrimental pathogenic transformation, including oncogenicity. Unequivocal data on commensal biofilm communities could contribute to understanding the mechanisms of such transformations. Subsequent oncopathy was shown at the site of established biofilms, which included inhibited apoptosis, persistent proliferation (with oncogenation), transformation, and abnormal distribution of the genetic material.

5. Environmental Triggers

In the contemporary world, the quality of life expects diverse personal standards. The environmental and lifestyle factors that have a significant effect in disease status are collectively known as the exposome. These sickening elements possibly modify commensal strains to the pathobionts, which may include infectious agents, disease- causing microbes as well as the health disorders that affect host physiology but are devoid of generalized etiological agents. The dynamic with host habits of the bacteria, generally with gut ecological habitat, are the residing pathobionts (4). Exposomally bacterially habited risk trajectories are smelled on the validity of the biologically based Allocation Half model and the Stability of Essential Hors d'Oeuvres model. Thus, the smelling bacterial expenditure risk menu of the pathobiontic exposition includes background appetizers, evolutionary additives, discriminatory main-course meals, and balance. Further understanding of individual pathobiontics and heightened vigilance by the individual host will help in preventing life-threatening pathobiontic accidents. The exposomal factors are environmental triggers, encompassing a variety of living situations, including air pollution, diet patterns, physical activities, stress levels, pathological conditions, antibiotics, and medications, radiation and chemotherapies, and infections in the gut. This exposure set of environmental triggers conveys that living conditions play a crucial role in the microbial homeostasis of the host equation as well as in the alteration of the co-evolutionary adhesive systems of the microbe–host equation.

5.1 Antibiotic Use

Antibiotics have successfully treated a vast spectrum of bacterial infections for decades. However, antibiotic use also has deleterious side effects on the gut microbial community and has been associated with a range of post-antibiotic health risks (12). This is achieved through a variety of mechanisms, such as pathogenic transformation of commensal bacteria, antibiotic tolerance of formerly antibiotic susceptible bacteria, the ability of commensal bacteria to act as stealth pathogens or colonization resistant clostridia and competition for infection-relevant resources (K. Gough, 2022). Antibiotic use in the human population has become widespread since the last century, resulting in comprehensive and increasingly thorough research on health risks associated with the use of antibiotics on humans. Antibiotics have historically been paired with Nobel prized laurels as magic bullets, capable of exterminating virulent pathogens such as anthrax and tuberculosis with matched precision without damaging the host. This magic bullet hope largely overshadowed and preempted the consideration of antibiotic-induced collateral damage on the gut microbiota. Consequently, the microbial impacts of antibiotics are not prioritized in the development and application of antibiotics, and antibiotic-induced post-antibiotic microbial health risks are not neutralized. The advent of the era of post-antibiotic emergence characterizes the rise antibiotic-resistant (AR) bacteria and constitutes a deleterious impact of antibiotics on apparently commensal bacteria outside of the target pathogen, stoking a fervent and widespread quest for alternative drugs and therapeutic strategies.

5.2 Dietary Influences

The human gut microbiota encodes a wide variety of proteins with potent peptidase activity and is able to process, among others, ingested food proteins into bioactive peptides. The cardiovascular health of patients is associated with consumption of long- grain rice instead of conventional rice, as evidenced by monitoring the metabolic products produced by the gut microbiota in an advanced three-stage in vitro model of the upper gastrointestinal tract and in an intervention clinical trial with humans. Food peptides derived from long-grain rice accumulate in the bloodstream and reach the heart, where they promote angiogenesis and protect mice from suffering ischemia-induced experimental infarction. Supporting data from the in vitro digestion of human samples and an interventional clinical trial with a low daily dose for overweight and controlled obese participants demonstrate its clinical interest. Therefore, nutritional strategies together with the modulation of peptidase activity of commensal microbiota could offer hitherto unexploited possibilities to improve the use of bioactive peptides in physiologically relevant prevention or therapeutic interventions. Besides accumulated scientific evidence, an updated view on the pathways and triggers involved in the assignment of beneficial commensal microbiota into pathogenic transformation is provided.

5.3 Host Immune Response

The knowledge regarding mechanistic and trigger of pathogenic transformation in human commensal bacteria is still limited in comparison with plant bacterial microbiota. Mechanistic understanding of dysbiosis is always based on host immunity level. This section will only review studies linking the early stage of dysbiosis caused by commensal bacteria and the host immune response. Therefore, pathogen infection-caused dysbiosis development that does not directly associate with host immunity responses are not included.

Immune dysregulation is thought to be one route by which the gastrointestinal microbiota can predispose to pathology. The immune system must manage an always-dangerous task: for example, knowing when to raise an inflammatory response against a potentially pathogenic organism is crucial. The gastrointestinal tract is the largest interface between a host organism and the external environment and the site of an enormous microbial load. Commensal bacteria may influence the immune system’s interaction with pathogens, as well as immune development and tolerance to commensals. Therefore, they are thought to be key controllers of host immunity (13).

Commensal microorganisms have a symbiotic relationship with the host, providing biological functions e.g. host nutrient absorption enhancement, supplementing essential nutrients and competes with potential pathogenic microbes. These functions, highly collaborative with the host, are defined as indirect factors for niche protection. Therefore, most gut commensal bacteria are obligate anaerobes, being predominant in the colon where the oxygen level is low. However, in certain times or physiological states, commensals may directly compromise host immune response and become pathogens. Those are defined as direct factors for bacterial pathogenic transformation (José Barbosa Silva et al., 2015).

The host immune response to commensal bacteria is usually applied to avoid injuries to both sides. 1) The host immune system activates immune response suppressor i.e., FOXP3 gene-based T regulatory cells. Tregs’ active compounds suppress effector cells functions e.g., anti-inflammatory IL-10 and TGF-β immunosuppressive cytokines. 2) Commensal bacteria also avoid tissue invasion by down-regulate the immune response. The latter was usually triggered by the bacterial surface component i.e., the lipopolysaccharides.

6. Case Studies of Pathogenic Transformation

The idea that biologically similar roles in different organisms can be encoded by analogous genes is as ancient as the biological sciences themselves. Carl Linnaeus, the founder of modern taxonomy in the Collective Categories of the Forma Genomica, stipulated that similar purposes should be accomplished in a similar manner. Indeed from the perspective of systems biology commensals and pathogens share similar functions. They inhabit hostile environments created by their hosts and must adapt similar strategies to life in a community. When commensals from the natural communities of Lepidoptera or Drosophila are experimentally transferred to a popular lab genetic model, a major switch in their lifestyle occurs with a single generation: they immediately become pathogens of D. melanogaster or of the caterpillars Galleria. A similar outcome occurs conversely when food-borne pathogenic bacteria are isolated and re-colonize the new gut of a Lepidoptera caterpillar. Again, a change of lifestyle occurs, and these bacteria establish themselves as commensals.

From the same hosts where they were pathogenic, some bacterial strains display high effectiveness in protection against pathogenic attack observed in life-long experiments in clonally identical hosts.

2. Mechanisms of Commensal to Pathogen Transformation The cognition of how a commensal turns into a pathogen encompasses many levels of complexity. First, the same molecule or the same reaction from one taxa can do harm to another host population. Second, metabolic pathways can be associated with particular taxa that are usual in the host living in the natural communities in which they are found; in other hosts they may have not been encountered over their evolutionary path and display novel pathogenic functions. Third, pathogenic functions may come from consortial gradients of molecules flowing along interacting bacterial partners. Fourth, redundancy in gene pathways across evolutionary distinct taxa. Finally, the same function can be accomplished by clusters of paralogs, homopolymers, and orthologs that have sufficiently high potential to lead to common outcomes but are cryptic from a sequence alignment perspective.

3. The Last Frontier of Bacterial Evolution In ecosystems saturated with bacteria undergoing thousands of daily stress events that could be life-threatening, but rarely so, a few outliers become problematic for homeostasis. They begin to cross-react and attack the host, normally an event, only entertained after perplexing immunological breaches and the accumulation of rare hand-made or synthetic mutants. This bottleneck could be, indeed, a reason for infection at the dawn of the animals since the divergence of the basic metazoans, as bacteria likely were sheltered through the coevolution of basic immunity.

6.1 Escherichia coli

Escherichia coli consists of both commensal and pathogenic strains. As a commensal bacterium, E. coli colonizes the host gut soon after birth, and is responsible for maintaining mucosal and immune homeostasis. It is also considered to be a gatekeeper of the intestine owing to its ability to outcompete exogenous pathogens for both the colonization niche and nutrients. However, pathogenic strains of the bacterium can cause various diseases, depending on their colonization sites in the human body (15).

Pathogenic strains of E. coli are also known to induce inflammation in host cells, resulting in the production of inducible nitric oxide synthase by the host innate immune cells. Once released, Nitric Oxide (NO) can block the microbial oxidative stress response, and rapidly impair DNA synthesis and induce DNA damage. Specifically, Uropathogenic E. coli (UPEC), newborn meningitic E. coli (NMEC), and Severe sepsis (SeS) strains have been reported to follow a commensal-to-pathogen transformation during adaptation to the urinary tract, newborn gut and meningitis infection, respectively. UPEC strains are equipped with type I fimbriae, AfA/Dr adhesins and pyelonephritis-associated pili (PAP) that enable them to colonize and infect the urinary tract. Strains that colonize the urinary tract display pathotypes, colonization sites, antimicrobial sensibility and virulence gene sets very different from commensal strains. The same occurs to other E. coli pathotypes, which are armed with sets of genes and operons that enable them to evade the host immune system. Differential utilization of nutrients is another way in which pathogenic strains of E. coli can overcome the resistance mounted by the commensal strains. It has been shown that newborn meningitic E. coli has the ability to use glycerol as a carbon source and commensal K-12 strains do not. Conversely, commensal E. coli strains are resistant to lysozyme overload damages, while some pathogenic strains are sensitive. For example, enterohemorrhagic E. coli (EHEC) are particularly sensitive to lysozyme, as demonstrated by a series of EHEC LEE mutants. Instead, when in contact with lysozyme TG2P, commensal E. coli growth is arrested. Additionally, EHEC LEE mutants, which fail to activate the innate immune cells as wild-type bacteria do, are no longer sensitive to both indole. In contrast, EHEC are still sensitive to only one signal molecule, HA, pointing to a variety of escape divergence strategies developed by different pathogenic strains.

6.2 Staphylococcus aureus

All bacterial infections occur within a polymicrobial environment. Here it is shown that the virulence of the leading human pathogen, Staphylococcus aureus, is significantly augmented through interactions with melanin-producing commensals that are commonly found in the polymicrobial spectrum of human nasal flora. In a polymicrobial environment, a pigment produced by one species within the community, in this case, Staphylococcus lugdunensis, shielded S. aureus from host immune clearance and antibiotics. The presence of S. lugdunensis generally enhanced pathogenesis of polymicrobial infections, including bacterial densities in vivo and infection-induced skin pathology. The addition of the melanin compound itself significantly protected Staphylococcus aureus from ex vivo killing by human neutrophils. There is no further increase in S. aureus pathogenesis when a S. lugdunensis mutant strain unable to produce melanin is introduced in a murine nasal infection model.

Understanding the mechanisms utilized by commensals to compete with pathogens may reveal new ways to develop treatments that do not rely on antibiotics. For example, the discovery that S. lugdunensis commonly produces melanin has led to experiments aimed at inhibiting the production of melanin in this commensal, as opposed to directly targeting other pathogens with melanin. It is likely that many commensals produce yet-unknown compounds or have genera/strain-specific characteristics which protect the host. A better understanding of these protective mechanisms can yield new therapeutic approaches (16).

6.3 Candida albicans

Candida species are responsible for the majority of human infections caused by fungal pathogens. The most frequent cause of these opportunistic infections is Candida albicans. As a commensal existing in the oral, gastrointestinal, and genital tracts of approximately 40–70% of the human population, C. albicans colonizes these human anatomical niches asymptomatically, forming part of the human mycobiome. Upon perturbation of the integrity of the epithelial barrier and/or the host immune responses, however, C. albicans, and some biochemically related species along with it, can manage to migrate through the epithelium and reach the underlying deep-seated anatomical niches to cause infection. In humans, Candida species are responsible for the majority of infections caused by fungal pathogens. In general, most of these infections occur in hosts with underlying inflammatory or immune perturbations. The most frequent cause of infections in humans among Candida species is C. albicans. It is estimated that C. albicans is part of the healthy normal microbiota in 40–70% of the human population. Other Candida species, such as Candida dubliniensis, Candida tropicalis, Candida glabrata or Candida parapsilosis, may also be part of the host–fungus commensal relationship. Under certain cellular and chemical conditions, which can particularly be found during treatment with chemical antibiotics, the overgrowth of these Candida species can lead to mucosal or systemic infection.

7. Impact of Pathogenic Transformation on Health

1. Introduction and definitions

ECDC definition: “an invasive infection where the bacterium is resistant to ß-lactam antibiotics (3rd generation cephalosporins). Carbapenem-resistant strains of this bacteria are included.” Feral animal definition: “animals naturally living in the wild or night life long captive state, but which have either escaped, been released or lost either its owner (including abandonment or straying), and now live in the wild.” Note: New species or orientation of received species, acquisition of new resistance including colonization or end of spread in a new ecological niche, spread between countries, any other significant event or publication.

2. Descriptions of publications, events, or reports

Antibiotic resistance and feral animals in the COVID-19 era List of recent events or reports Antibiotic resistance in SARS-CoV-2 mutations Proposal for wild animal sampling: low altitude HCHC hospital helicopter “new high rise” paddy field. Do a WHO antibiotics swab study of animals, people, and water in the China Basin training class. A look towards the future: Things to pick up

3. Reporting on resistant feral animals

Yemen cholera strains in Australian gulls. Note: This is the first report of low-frequency blaCTX M-14 carrying extra-intestinal E. coli isolated from the wild birds, indicative of a possible Transmission from a Colonized Feral Bird to an intense Human: Environment (Live bird market)-Animal chain. Requirements for annual reports: Demonstrated transmission dynamics between feral animals and humans carrying major ESBL genes for 2022-4.

7.1 Infections and Disease

Microbial infections are a primary cause of human disease. Bacteria, viruses, fungi, and parasites that colonize the human body as pathogens can escape their natural niche and cause local or systemic disease. These diseases come in many kinds and are often distinctive for a particular pathogen (5). Localization of pathogens to a particular tissue or organ can involve microbial factors such as adhesion molecules or toxins, or colonization may be driven by host-specific changes in the environment at a particular site. Host factors can contribute to infections: molecular and cellular components of human immunity such as antibodies, phagocytes, cytokines, and various metabolites that can limit pathogen growth or clear infections completely.

Spatiotemporal colonization dynamics of the human microbiota in different body sites are complex and vary in time, and involve many different species. Some members of the human microbiota can cause disease in specific conditions. The reasons and consequences for the transformation of commensal microbes into virulent pathogens are multiple and diverse. The presence of a commensal microbe in the host can contribute to protection against infection. Commensal microbes can compete with a pathogen for limited space and nutrients. The colonization resistance hypothesis states that commensal microbes may provide resistance to pathogens by allowing them to compete for space, nutrients, and/or to modulate signaling or the immune response of the host.

7.2 Healthcare Costs

Introduction to the healthcare costs analysis, the costs involved in vertical columns, patient-related transformed healthcare costs for diarrhoea, Guillain Barré syndrome and invasive non-typhoidal salmonellosis in Gondar, Ethiopia are taking into account. A transformed cost is defined as the changed costs for a healthcare facility relative to the estimate for a same type primary healthcare unit as the distance increases to the 10th percentile together with affected demographic variables (17). Linear regression was then applied to estimate the relative contribution of each healthcare facility type to each category of transformed costs in order to enable estimation of the patient-related transformed healthcare costs at an unsampled healthcare facility. Across all years and health facilities, vertical costs show a chaotic pattern relative to the primary type. Lower horizontal costs for the cost-ambulance and cost- laboratory types are observed compared to the primary type health facility at short and medium distances.

The analyses are carried out on the patient-related transformed healthcare costs at Gondar administrative town (GAT) and 4 other common districts (ANC, KIR, WOG and TEL) in Gondar zuriya wereda (GZW) with care providers in Gondar city as well as 4 other districts (BAS, ARA, SIM and AAB) in Gondar awraja (GAW). The patient-related healthcare costs analyses involve 3 steps (direct medical, direct non-medical and patient-related transformed costs) and require a wealth of data. Estimates of the presence of a community-acquired infection have been recently made available for the majority of commensal bacteria. The cosmopolitan human pathogen Salmonella enterica is estimated to cause about 192 million Gastroenteritis cases each year globally (1% prediction interval: 85 – 435 million) of which an estimated 47,400 additional cases (1% prediction interval: 21,000 – 149,900) per year are GBS (Guillain Barré syndrome) related.

7.3 Public Health Implications

In light of the impressive beneficial interactions between commensal bacteria and the human body, the abundance of certain human commensal microbiota dramatically drops due to the pathogenic transformation triggered by exogenous genetic elements. Key safety features are introduced along with desired modules combating potential fallacies aiming to cast light on this danger in order to guarantee the safe use of nonpathogenic microorganisms. The unique safety hurdles that consumers and scientists need to be aware of are also proposed. So it is urgent to inspect the safety disciplines of in vivo synthetic biocircuits as a measure to avoid unintended chronic microbial colonization in humans and animals. Since the discovery of penicillin during the first half of the 20th century, antibiotics have saved countless lives, led to significant reductions in morbidity and mortality, and facilitated the management of diverse infectious diseases. Unfortunately, antibiotics also perturb the composition of the host gut microbiota, resulting in a range of unintended and undesired consequences including promoting inflammatory and allergic diseases, rendering the host more susceptible to and/or rendering pathogens more virulent and (in some cases) promoting the development and transmission of multi-drug resistant organisms. These unintended consequences of antibiotic therapy underscore the urgent need for novel approaches to mitigate the risks associated with dysbiotic and declining commensal communities in the antibiotic era. Importantly, recent studies provide several benchmarks for the maintenance and restoration of a healthy microbiota. This offers the long-awaited rationale for establishing appropriate strategies to prevent or reduce the dysbiosis caused by antibiotics and, thereby, the adverse effects of antibiotics on health (1).

8. Preventive Strategies

Antibiotic resistance genes are abundant in the thermophilic anaerobic bacteria typically isolated from animals used for food production. They are less prevalent in both commensal bacteria isolated from people outside the areas of high antibiotic use, and in ambient bacteria isolated from outside of farms.

For example, the BlaTEM gene is abundant in the guts of poultry in Ecuador but nearly absent in fecal samples from people living there as compared to the United States. Intriguingly, there is a higher density of bacterial 16S DNA in the people despite a nearly identical sample size.

Despite the low to no occurrence of the BlaTEM transposon in commensal bacteria from the population, in vitro conjugation experiments demonstrated that it can be readily transferred. These results underscore the importance of commensals in potentially exacerbating the dissemination of antibiotic resistance on a global scale and the benefit of isolating productive commensals away from farm and treatment environments at a minimum (18). Eighteen major antibiotics are currently used in cattle. Incorporating these antibiotics into microbiota growth media at sub-minimum inhibitory concentration levels allowed for the creation of 13 distinct resistomes spanning six major bacterial phyla involved in food production. The resistomes created under these conditions display remarkable differences in the net number of resistance genes compared to controls and in the resistome composition. There is a 13-fold increase in measured resistance between the resistomes. Moreover, these differences are apparent within the first eight days of culture despite the high sequence enrollment and the ambient prevalence of the recorded resistance genes in the original fecal samples. Therefore, given the known global epidemiology and commensal lifecycles of ANE resistant bacteria, greater insight into and stewardship of commensal bacteria would be invaluable in mitigating the emergence and spread of antibiotic resistance genes.

8.1 Probiotics and Prebiotics

In health and nutritional sciences, the human gut microbiota is often considered to be pivotal in the health of the host. However, the majority of research assertion come from studies carried out on so-called “diseased models”. It has been discovered that the human commensal microbiota can be pathogenically transformed, regardless of any state of health. Despite the current literature, a new perspective on a balance between “pathogenically transformed” and “protective” human commensal microbiota is necessary, involving the proposal of both possible mechanism and triggers of such transformation. This may open up new areas of research with far-reaching importance for molecular diagnosis and the therapy of diseases correlated with the pathogenic transformation of human commensal microbiota. Analysis of the mechanism and triggers of pathogenic transformation in human commensal microbiota represents a shift in the existing paradigm of microbiome research. It envisions a commensal microbiota in terms of the extent of its health beneficial potential, implementation of which can be pivotal in dietary intervention strategies.

In a classical view, human commensal microbiota was considered to provide beneficial metabolic and protective functions to its host. These functions were exerted through different diverse mechanisms, such as metabolic activities, competition for colonization sites, or stimulation of the formation of mucosal immunity. At each moment, microorganisms in the gut are in a dynamic homeostasis with their human host. The recent progress in metagenomic and culturomic assay revealed that a classical view of gut microbiota as being composed of commensal microorganisms intimately connected with the host is simplistic and incorrectly limited. There are in excess of 1000 different species of bacteria, representing about 9.5 million unique genes in the human GI tract. Aside from bacteria, other microorganism groups are present in the human commensal microbiota, such as fungi and viruses. In total, the human gut may contain a community of 4 × 10^13 microorganisms, constituting a complex ecosystem. This ecosystem colonizes the gastrointestinal tract and plays a crucial role in the health of the subject (19).

8.2 Antimicrobial Stewardship

Fighting drug-resistant commensal pathogens in human gut microbiota requires a broad set of methods and approaches. Future research in this area naturally divides into three sections: (1) the search for possibilities and prediction of the mechanisms and/or triggers of commensal gut microbiota conversions into pathogens in human body; (2) finding ways to prevent such changes; (3) aiding the former commensal microbiota to return to its original state after acquiring pathogenic features.

Most people have experienced antibiotic treatment more than once in their life. Bacteria naturally present in the human organism, which are not separated from the pathogenic ones by any internal barriers, are being killed en masse. It makes the pathogenic ones to experience less competition, and could also acquire the genes and mutations that encode resistance to the given antibiotic. Resistance again, is paradoxically, hereditary, that is, its carriers propagate faster and outcompete those who lack it, at least under prolonged antibiotic treatment. But killing all pathogens is in fact unlikely, even with a half-dozen drugs taken simultaneously, and different pathogens might require different antibiotic types anyway.

As a result, the population of gut and other tissues after the treatment often hosts those bacteria who now carry multiple antibiotic resistance genes against many otherwise effective antibiotics. Aided by the factors such as widespread prescription, essentially non-regulated or regulated in paper only antibiotics usage throughout the world, the result is that very often the most powerful antibiotic known to medical science will not work by the time a patient, a potential host, becomes a reservoir of such bacteria.

How different this patient is from that of a pre-antibiotic era, who could be culled of the vast majority of potential pathogens throughout the whole course of antibacterial treatment, one that is impossible, at least for more complex life forms, for the host to take itself. Subsequent loss of lives is estimated to be between 10 million and 100 million worldwide every year (20). As antibiotic resistance genes (ARGs) are often carried by transposons, which can shuttle between bacterial species, the commensal and pathogenic population of a human gut could be expected to exchange genes more efficiently than an average two- to three-billion-old bacterial genetic exchange which are themselves might be thwarted by a range of defense mechanisms, e.g. restriction- modification systems. Broad-spectrum antibiotic treatment of a human gut is certainly a pressure strong and ubiquitous enough to make a number of recipients share their genetic load of ARGs with those, who have none but badly need them.

8.3 Vaccination Approaches

Humans start their life harboring a gamut of diverse microbial communities that have co- evolved with the host for mutual benefit. During fetal development, newborns are also exposed to facultative pathogens from the mother and/or birth environment. In the first weeks of life, the virulent population of bacteria quickly colonizes and establishes an adult-like community structure. Present in all exposed surfaces of the human body and also in internal tissues, the resident microbiota exerts numerous beneficial effects. In the human gastrointestinal tract, the microbiota is involved in nutrient absorption, metabolism, immune tolerance, and the stimulation and development of the immune system. Additionally, commensal bacteria deter pathogen invasion and colonization by competition for nutrients, adhesion sites, and the secretion of inhibitory compounds. In contrast to pathogenic bacteria, the majority of the commensal microbiota is in direct contact with the lumen and there are anatomical and functional barrier mechanisms that prevent excessive interactions between our body and these bacteria under normal physiological conditions. In response to a variety of stimuli, commensal bacteria can gain access to privileged internal compartments and cause severe abnormalities, leading to the development of inflammatory diseases with immunopathological features, particularly Crohn's disease and ulcerative colitis. As a consequence, most bacteria ingested with the diet or those that accidentally cross barriers such as mucus, stimulate or modulate the immune response. In general, the mammalian host recognizes microbes indirectly through microbial associated molecular patterns which are specific of groups of microorganisms and are common components of the structural molecules forming part of these microorganisms.

9. Future Directions in Research

Alterations in the intestinal microbiota have been associated with a variety of pathological conditions including metabolic disorders, inflammatory chronic diseases, allergies, neurodegeneration, and cancer. Injured host tissues can elicit specific virulence reactions from some commensals, although phyla such as Firmicutes and Bacteroidetes demonstrate significant metagenomic characterization — The profiles of dysbiotic microbial communities: the gut microbiota of children inadequately fed shows a differential repertoire of genes between health and different disease conditions.

Findings from recent research on the role of feeding practices and host genetics in influencing the gut microbiota of young children from an impoverished urban setting are reviewed. The gut microbiota of children younger than 2 years, who were either healthy or affected by varying degrees of kwashiorkor, other severe forms of acute malnutrition, or hypertension, were characterized using a metagenomic approach based on direct extraction of microbial DNA and whole-community shotgun sequencing. Infants more important solely from the standpoint of undernutrition, revealing that the microbiota of blood group A individuals exhibited a differential repertoire of genes important for the synthesis of glycan structures compatible with the A-type antigen. To expand upon known human microbiota alterations related to different pathological conditions — Problems with the concept of gut microbiota dysbiosis.

9.1 Emerging Technologies

Historically Longer-Culturable Microbial Community in Human Medical Literature and Technologies of the 21st Century Also Allow Rapid Monitoring of Microbial Compositions Microbial community consisting of different prokaryote and other cellular organisms have been detected or evidenced in any ecosystem and living macro-organism by using 21st Century technologies though they were not culturable on artificial media before the 19th century (4). Their physiological and molecular activities producing beneficial and detrimental effects have been recorded by natural historians, microscopists, and physicians for over three millennia, while other disciplines in which they were specialized also emerged.

The collection of medical literature on such microbes and microbe-host interactions, although strongly fragmented and institutionally based, perhaps predates that of other disciplines in some pre-modern societies, and has been maintained continuously until present.

Considerable interest and concern with microbial cells due to their past, present, and potential threat which serve as a transformative agent of various pathogens resulting in emerging infectious disease, is recorded in ancient Indian texts known as Vedas. These texts documented that microorganisms could be higher resistant than unicellular for some time from trying to kill lethal factors outside the cell while starving until they develop resistant factor in the cell, and harmful mutations also appear faster in microorganisms under these conditions. This “strategic resistance” against higher cells, such as humans distinguished by lack of their acq-ins factors, is successfully used by the pathogenic wild- type variants of today’s commensals for the survival behind the antibiotic bombardment of humans, livestock, and agriculture. This theory is well confirmed on the model of laboratory device called microbial growth device functioning according to physical laws defining the features of growth of all cells, be higher or unicellular.

9.2 Interdisciplinary Approaches

Engineering transformative approaches to integrate disciplines of biological and medical research on human commensal microbiota, mainly on cutaneous (skin) and mucous membrane (nasopharynx, oral, gut, and urogenital) microbiota, to investigate mechanisms and triggers of pathogenic transformation coming from within (endogenous) and also from its environment, is needed. Anthroposphere (inhabited and manmade environments) exerts selective pressures that drive microbiota to develop pathogenic functions. Ultimately, impacts are expected on modern medical science. Pathogenic microbiota (pathobionts, symbionts, and the pathogenic core of discrete microbiome host communities) are likely exhibitors of evolutionary releasers due to the microbiota/microbiome evolutionary “arms races” rooted in pathogenicity refinement (co-evolution of specialised hosts and their pathogens/parasites). Locomotion of rampantly peaking “harmful” microbiota among trade networks was proposed to be one of the factors contributing to the collapse of the Late Bronze Age civilisations. A full comprehension of mechanisms mediating adverse effects of pathogenic transformation of the human microbiota is obligatory for mitigating risks and leveraging the potential benefits of microbiota. In 2015, Thomas J. Sharpton published attempt to model (i.e. understand) the context-dependent associations between the gut microbiome, its environment, and host health. These mathematical model-based frameworks provide insight into the mechanisms through which microbiomes operate and will likely be essential in developing a comprehensive view of how hosts and their microbiomes interact (21).

10. Conclusion

The human microbiome has become an ever more popular topic of research and health care development in the last decades. Current research suggests the importance of the human microbiome not only for the gastrointestinal tract, but also for the function of the entire immune system. At the same time, research related to the human microbiome now implies its connection to numerous diseases. This text is focused on the functions of the human commensal microbiota that can be signalled in the host response without any assessment. Several mechanisms and triggers of the pathogenic transformation of the human commensal microbiota and the consequent risks of forming the emerging pathogens are analyzed. The human commensal microbiota is now encoding numerous virulence factors, such as lipopolysaccharide, porins, and peptide hormones. Noteworthy activation of the dust cleaning functions for home, food, hygiene, and health applied in the human environment proximities blurs the contact density of the commensal microbiota with the human host. The convenient aid and food means applied for the maternal and baby health care in domestic animals enhance the risks of the pathogenic transformation of the commensal microbiota in the human body of infants too. Undifferentiated care of the home, food, hygiene, and health is pro-dangerous.

Declaration of competing interest

The author declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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