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THE HOST–MICROBIOME COEVOLUTION AND MODERN THERAPEUTIC IMPLICATIONS

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ABSTRACT

The human gut microbiome is a complex microbial ecosystem composed of trillions of bacteria, archaea, viruses, and fungi that has coevolved with humans over millions of years. This long-term evolutionary association has played a fundamental role in human digestion, nutrient absorption, immune system development, metabolism, and even the maturation of the nervous system. Many researchers now regard the human body as a **holobiont**, in which the host and its associated microbiome together constitute an integrated evolutionary unit. This prolonged coevolutionary relationship has been particularly important in shaping the human immune system. Beneficial gut microorganisms educate and regulate immune responses, enhance resistance against pathogens, and contribute to the control of inflammation. However, in the modern era, excessive antibiotic use, heightened hygiene practices, urbanization, and profound dietary changes have partially disrupted this coevolved relationship. Accumulating evidence suggests that such disruption is associated with an increased risk of allergies, inflammatory bowel disease, obesity, type 2 diabetes, and other chronic disorders. Collectively, the human gut microbiome is far more than a community of commensal microorganisms; it is an integral component of human evolution. Understanding the coevolution of humans and their gut microbiome is therefore essential for elucidating the mechanisms underlying long-term health, physiological adaptation, and the future trajectory of human evolution.

KEYWORDS: Gut microbiome; Coevolution; Holobiont; Immune system; Gut–brain axis; Dysbiosis; Pharmacomicrobiomics.

INTRODUCTION

Although the human body is traditionally regarded as a single organism, it is more accurately viewed as a complex biological consortium—or **holobiont**—comprising the host and its diverse microbial inhabitants. Large populations of bacteria, archaea (e.g., *Methanosphaera* spp.), fungi, viruses, and other microorganisms permanently colonize the skin, oral cavity, respiratory tract, urogenital tract, and, most abundantly, the gastrointestinal tract. The collection of microorganisms residing in the gut is referred to as the **gut microbiota**, whereas the microbiota together with their collective genomes constitute the **gut microbiome**.

Current estimates indicate that the gastrointestinal tract of a healthy adult harbors approximately 38 trillion (3.8×10^{13}) microorganisms, a number roughly comparable to the total number of human cells in the body.[1] Even more remarkable is the enormous genetic repertoire encoded by these microbial communities. The collective microbiome contains more than one hundred times as many genes as the human genome. Specifically, the human gut microbiome is estimated to harbor approximately 2–3 million microbial genes, whereas the human genome contains only about 20,000 protein-coding genes. Consequently, the functional genetic capacity of the gut microbiome exceeds that of the human genome by approximately 100–150-fold, substantially expanding the metabolic and physiological capabilities of the human host.[2]

The relationship between humans and their gut microorganisms is the product of millions of years of **coevolution**. Throughout this prolonged evolutionary history, a mutually beneficial (mutualistic) symbiosis has emerged, in which the host provides microorganisms with a stable habitat and a continuous supply of nutrients. In return, gut microbes contribute to food digestion, the metabolism of complex polysaccharides and dietary fiber, the production of short-chain fatty acids (SCFAs)—including butyrate, acetate, and propionate—the biosynthesis of vitamin K and several B vitamins, the metabolism of bile acids and numerous pharmaceuticals, and the maintenance of the intestinal epithelial barrier.[3, 4] In addition, the gut microbiome plays an indispensable role in the postnatal maturation of the immune system, the establishment of immune tolerance, and the development of effective defense mechanisms against pathogenic microorganisms.[5]

Research conducted over the past two decades has demonstrated that the gut microbiome is not confined to the gastrointestinal tract but interacts extensively with the host's metabolic, endocrine, nervous, and immune systems, thereby contributing to the maintenance of overall physiological homeostasis. In particular, through the **gut–brain axis**, intestinal microorganisms can influence neural development, neurotransmitter production, stress responses, behavior, and cognitive function.[6, 7] Consequently, the gut microbiome has been described as a functional "forgotten" or "virtual organ" of the human body.[8]

Conversely, disruption of the composition and functional balance of the gut microbial community—a condition known as **dysbiosis**—has been associated with a wide range of non-communicable and chronic diseases. Alterations in the gut microbiome have been linked to inflammatory bowel disease (IBD), obesity, type 2 diabetes, allergic disorders, cardiovascular disease, colorectal cancer, as well as several neurological and psychiatric conditions.[9,10] Although the causal relationships underlying many of these associations remain an active area of investigation, growing evidence indicates that a healthy gut microbiome is a fundamental determinant of human health and disease prevention.

Accordingly, the gut microbiome has emerged as one of the most important areas of research in modern biology, evolutionary biology, medicine, and nutritional science. A comprehensive understanding of its composition, functional diversity, and long-term coevolution with the human host is essential for elucidating the mechanisms underlying human health, disease susceptibility, immune function, and long-term evolutionary adaptation.

Coevolution of Humans and the Gut Microbiome

The relationship between humans and their gut microbiome is not a recent phenomenon; rather, it is the product of millions of years of **coevolution**. Since the early evolution of mammals, hosts and their resident intestinal microorganisms have been subjected to reciprocal selective pressures, leading to mutual adaptation that benefits both partners. [4,11]

Importantly, several human genes have evolved in ways that strengthen this mutually beneficial association by promoting the maintenance of beneficial microbes while simultaneously enhancing defense against pathogens. Notable examples include genes encoding Toll-like receptors (TLRs)**,** NOD-like receptors (NODs)**,** FUT2**,** MUC2**,** human leukocyte antigen/major histocompatibility complex (HLA/MHC) molecules, and components of the immunoglobulin A (IgA) pathway. The evolution of these genes demonstrates that the human immune system has evolved not only to eliminate infectious agents but also to establish and maintain a mutually beneficial relationship with the commensal gut microbiota.

One of the strongest lines of evidence supporting host–microbiome coevolution is that the composition of the gut microbiota across mammalian species closely reflects their evolutionary relationships (phylogeny). Even among species with similar diets or habitats, closely related hosts tend to harbor more similar microbial communities than distantly related species. This pattern indicates that host evolution has profoundly influenced the evolution of the gut microbiome, a phenomenon known as **phylosymbiosis.**[12]

Nevertheless, this relationship is not immutable. Dietary changes, antibiotic exposure, modern lifestyle, and environmental influences can disrupt the normal composition of the gut microbiome—a condition known as **dysbiosis**. Dysbiosis has been associated with an increased risk of obesity, inflammatory bowel disease, type 2 diabetes, and numerous other chronic disorders. Consequently, modern evolutionary biology increasingly views humans not as isolated organisms but as integrated biological entities comprising both the host and its associated microorganisms, a concept referred to as the **holobiont.**[13]

Although substantial evidence supports the coevolution of humans and their microbiome, most evolutionary biologists do not currently regard the **hologenome** as a universal unit of natural selection. This is because the majority of gut microorganisms are not transmitted exclusively through vertical inheritance from parent to offspring but are also continually acquired from diet and the environment. Therefore, while the holobiont provides a valuable conceptual framework for understanding host–microbe interactions, the hologenome theory remains a subject of ongoing scientific debate.[14, 15]

Birth and Maternal Transmission of the Microbiome

The establishment of the human microbiome begins at birth and continues during the early postnatal period through the transfer of beneficial microorganisms from the mother to the infant, a process known as maternal

microbiome transmission. This early microbial colonization plays a pivotal role in the development of the infant's immune system, metabolic functions, and normal intestinal maturation.

Maternal microbiome transmission occurs through several complementary routes: 1.Vaginal delivery- During vaginal birth, the newborn is exposed to the mother's vaginal and intestinal microbiota. These microorganisms colonize the infant's skin, oral cavity, and gastrointestinal tract, forming the foundation of the neonatal gut microbiome. 2.Cesarean delivery- In contrast, infants born by cesarean section have limited exposure to the maternal vaginal microbiota. Instead, their initial microbial colonization is dominated by microorganisms from the maternal skin and the hospital environment. Consequently, the early gut microbiome of cesarean-delivered infants differs from that of vaginally delivered infants, although these differences may diminish over time. 3.Breastfeeding- Human breast milk provides far more than nutrition. It supplies beneficial bacteria (particularly *Bifidobacterium* spp.), **human milk oligosaccharides (HMOs)**, antibodies, and numerous other bioactive compounds. HMOs are complex carbohydrates composed primarily of glucose, galactose, *N*-acetylglucosamine, fucose, and sialic acid. Although infants cannot digest HMOs directly, these molecules selectively promote the growth and persistence of beneficial gut bacteria, thereby acting as natural prebiotics.

It is noteworthy that oligosaccharides are present in the milk of all mammals; however, human milk contains an exceptionally high abundance and remarkable structural diversity of HMOs**,** representing a significant evolutionary adaptation in our species. These unique glycans contribute to the establishment of a healthy gut microbiome, facilitate immune maturation, inhibit pathogen colonization, and reduce the long-term risk of metabolic disorders and allergic diseases.

It is also important to distinguish human milk oligosaccharides (HMOs**)** from colostrum. Colostrum is the thick, yellowish milk produced during the first 2–5 days after childbirth and is exceptionally rich in immunoglobulins, particularly secretory IgA, along with numerous antimicrobial proteins and immune factors. In contrast, HMOs are specialized carbohydrate molecules that function primarily as prebiotics and are present throughout lactation, although their composition changes over time.

In summary, maternal microbiome transmission represents a direct form of biological inheritance through which mothers pass not only their genes but also a beneficial microbial community to their offspring. This early microbial inheritance constitutes a fundamental foundation for healthy growth, normal immune development, and long-term physiological well-being.

The Origin of the Microbiome

The earliest forms of life on Earth, which emerged approximately 3.5–4.0 billion years ago, were bacteria and archaea (including methanogenic archaea). These microorganisms represented the first living organisms on the planet and remained its only inhabitants for nearly two billion years, forming the foundation of Earth's earliest biosphere. Multicellular organisms evolved much later. According to the widely accepted **endosymbiotic theory**, an ancestral bacterium established a permanent intracellular association within another primitive cell and eventually evolved into the **mitochondrion**. Similarly, the origin of chloroplasts in plants resulted from a comparable endosymbiotic event. These evolutionary transitions represent some of the earliest and most profound examples of long-term symbiosis between microorganisms and their hosts.

Following the emergence of multicellular animals approximately 800–600 million years ago, diverse microorganisms gradually colonized the skin, gastrointestinal tract, and other body surfaces of their hosts. Natural selection favored these mutually beneficial associations, leading to increasingly stable and functionally integrated host–microbe relationships.

The intestinal microbial communities of human ancestors began to develop tens of millions of years ago, approximately 60 million years ago, during the evolution of early primates. In modern humans, microbial colonization begins at birth through exposure to the mother's birth canal, skin, breast milk, and subsequently through diet and environmental contact, resulting in the establishment of a complex and relatively stable microbiome, as discussed earlier. Humans and their microbiome have coevolved for more than 300,000 years. As a consequence of this prolonged coevolution, the microbiome has become indispensable for numerous physiological functions, including digestion, vitamin synthesis, immune system development and regulation, metabolism, and even nervous system function.

Thus, the origin of the microbiome was not a chance event but rather the outcome of a continuous evolutionary process extending back to the earliest history of life on Earth. Consequently, the human body is now increasingly viewed not simply as an assemblage of human cells, but as a **holobiont**—an ecological and evolutionary unit comprising both the host and its associated microbial communities. Within this framework, the host and its microbiota function together as a highly integrated biological system.

Evolution of the Microbiome and the Gut–Brain Axis

Throughout animal evolution, a close and mutually beneficial relationship has developed between the host and its intestinal microorganisms. This long-term coevolution has given rise to a sophisticated bidirectional communication network—the **gut–brain axis**—that links the gastrointestinal tract and the central nervous

system through neural pathways (particularly the **vagus nerve**), endocrine signaling, immune mechanisms, and microbially derived metabolites.[6, 16]

Beneficial gut microorganisms produce **short-chain fatty acids (SCFAs)**, neurotransmitters (Serotonin, GABA, Dopamine etc.), and neurotransmitter precursors that influence brain development, behavior, stress responsiveness, and immune function.[7] These microbial metabolites interact with specific receptors on vagal afferent nerve endings within the intestinal wall, triggering electrical signals that are transmitted directly to the brainstem. In this way, information regarding intestinal health, inflammation, and metabolic status is continuously conveyed from the gut to the brain.

Current evidence therefore supports the concept that animals and their microbiomes have coevolved as **holobionts**, with this integrated biological partnership contributing significantly to host health, physiological adaptation, and reproductive fitness.[17]

Influence of Diet on the Evolution of the Gut Microbiome

The human gut microbiome has evolved in parallel with changes in dietary habits over both evolutionary and relatively short ecological timescales. A substantial body of research now demonstrates that diet profoundly influences the composition, diversity, and functional capacity of the gut microbiome.[18]

The dietary patterns of human ancestors have undergone multiple transitions during the past 6–7 million years, and each dietary shift has been accompanied by corresponding adaptations of the gut microbiome. Early hominins, like modern great apes, consumed diets rich in fruits, tubers, leaves, and other high-fiber plant foods. Over time, the consumption of animal-derived foods increased. Approximately 10,000–12,000 years ago, the advent of agriculture introduced cereal grains and dairy products as major dietary components. Following the Industrial Revolution, the widespread consumption of ultra-processed foods, refined sugars, and saturated fats increased dramatically. Each of these dietary transitions has reshaped the composition, diversity, and metabolic functions of the intestinal microbiota.

Studies have shown that populations consuming traditional high-fiber diets typically harbor greater abundances of *Prevotella* species, exhibit higher microbial diversity, and produce larger quantities of short-chain fatty acids (SCFAs), particularly butyrate, which plays a critical role in maintaining intestinal health.[19] In contrast, individuals consuming a typical Western diet generally exhibit higher abundances of *Bacteroides*, reduced populations of fiber-degrading bacteria, decreased microbial diversity, and increased numbers of inflammation-associated microorganisms.[18] These microbiome alterations influence not only digestive processes but also immune regulation, metabolic homeostasis, nervous system function, and overall health. Accordingly, the prevailing view is that humans and their gut microbiome constitute a coevolved biological unit, with diet serving as one of the principal evolutionary forces shaping this intricate host–microbiome relationship**.**

The Influence of the Microbiome on the Immune System

The human immune system did not evolve solely to defend the body against pathogenic microorganisms; it also evolved to maintain a balanced symbiotic relationship with the beneficial microorganisms inhabiting the gastrointestinal tract.[17] This long-term coevolution between the host and its microbiome forms one of the fundamental bases of the highly efficient and well-regulated immune system of modern humans. The major influences of the microbiome on the immune system include the following.

1. Immune System Maturation

Beneficial gut microorganisms begin to "educate" the immune system immediately after birth, facilitating the proper development of both innate and adaptive immune responses.[20] The gut microbiota trains the immune system to distinguish harmful pathogens from beneficial commensal microorganisms and to mount immune responses of appropriate magnitude and timing. In the absence of this microbial education, the immune system may become either insufficiently responsive, increasing susceptibility to infection, or excessively reactive, predisposing the host to allergies and autoimmune diseases. Pattern-recognition receptors, particularly Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors, play central roles in this process.[21, 22]

2. Discrimination Between Harmful and Beneficial Microorganisms

Through millions of years of coevolution, the immune system has acquired the ability to tolerate beneficial resident microorganisms (immune tolerance) while simultaneously mounting effective immune responses against pathogenic microbes. This discrimination is based on multiple factors, including microbial localization, behavior, tissue damage, and inflammatory signals. Pattern-recognition receptors (PRRs), regulatory T cells (Tregs), and secretory immunoglobulin A (IgA) are key components responsible for maintaining this delicate balance.

3. Maintenance of Immune Homeostasis

The gut microbiota promotes the development and function of regulatory T lymphocytes and other immune cell populations that suppress excessive inflammatory responses and reduce the risk of autoimmune diseases. By maintaining immune homeostasis, the microbiome contributes to long-term health and protection against immune-mediated disorders.

4. Evolutionary Adaptation of Immune Genes

Prolonged interactions between humans and their microbial communities have exerted strong selective pressures on numerous immune-related genes. In particular, genes encoding Toll-like receptors (TLRs), NOD-like receptors, and major histocompatibility complex (MHC)/human leukocyte antigen (HLA) molecules have undergone adaptive evolution through natural selection, enhancing the host's capacity to recognize pathogens while maintaining tolerance toward beneficial microbes.

5. Advantages for Health and Survival

Host–microbiome coevolution has enabled humans to develop more effective defenses against infectious diseases while simultaneously benefiting from the metabolic and nutritional functions of commensal microorganisms. These mutualistic interactions have substantially improved survival and reproductive fitness throughout human evolutionary history.

The Microbiome and the Effects of Medications

Although antibiotics represent one of the greatest achievements of modern medicine, they eliminate not only pathogenic bacteria but also beneficial members of the gut microbiota. Consequently, antibiotic treatment often reduces microbial diversity, disrupts the normal microbial ecosystem (dysbiosis), promotes the proliferation of opportunistic pathogens such as *Clostridioides difficile*, and increases the risk of antimicrobial resistance. Excessive antibiotic exposure during early childhood is of particular concern because it may interfere with normal immune system development and have long-lasting health consequences.[23, 24]

Recent research has demonstrated that numerous non-antibiotic medications also influence the gut microbiome. For example, proton pump inhibitors (PPIs) alter gut microbial composition and may increase susceptibility to enteric infections. Non-steroidal anti-inflammatory drugs (NSAIDs) can impair intestinal barrier integrity and promote intestinal inflammation. In contrast, metformin has been shown to increase the abundance of beneficial bacteria and enhance the production of short-chain fatty acids, thereby contributing to its therapeutic efficacy in type 2 diabetes.[25, 26] In addition, anticancer drugs, immunosuppressants, psychotropic medications, antifungal agents, and antiviral drugs have all been shown to alter the composition and functional activity of the gut microbiome.[27]

The relationship between medications and the microbiome is bidirectional. On the one hand, drugs alter the composition and function of the gut microbiota; on the other hand, the microbiome influences drug absorption, metabolism, efficacy, and toxicity. Gut microorganisms are capable of activating, inactivating, or chemically modifying numerous pharmaceutical compounds, thereby contributing to interindividual variability in drug responses. This rapidly expanding field of research is known as **pharmacomicrobiomics.**[28]

Drug-induced dysbiosis has been associated with an increased risk of inflammatory bowel disease, obesity, type 2 diabetes, allergic disorders, autoimmune diseases, and gastrointestinal infections. However, although these associations are increasingly well documented, the precise causal mechanisms underlying many of these relationships remain incompletely understood and require further investigation.

CONCLUSION

The human gut microbiome is now recognized as an integral component of human biology rather than merely a collection of commensal microorganisms. Over millions of years of host–microbiome coevolution, these complex microbial communities have become indispensable for immune system development, metabolic homeostasis, protection against pathogens, and overall health. Conversely, disruptions of the gut microbiota (dysbiosis), whether caused by antibiotics, other medications, dietary changes, or environmental factors, have been associated with an increased risk of numerous infectious, metabolic, inflammatory, and autoimmune disorders.

Accumulating evidence further demonstrates that the relationship between the microbiome and pharmaceuticals is inherently bidirectional: medications reshape the composition and function of the gut microbiota, while microbial communities influence drug absorption, metabolism, efficacy, and toxicity. This reciprocal interaction has established **pharmacomicrobiomics** as a rapidly emerging discipline with important implications for clinical practice and drug development.

Host genetic variation also contributes significantly to microbiome diversity and disease susceptibility. Polymorphisms in genes involved in microbial recognition and host–microbe interactions, including **TLR**, **NOD2**, and **FUT2**, influence the composition of the intestinal microbiota, the regulation of immune responses, and individual susceptibility to a wide range of diseases. Understanding the complex interplay among host genetics, the microbiome, environmental exposures, and pharmacological interventions will therefore be essential for advancing both evolutionary biology and modern medicine.

Looking ahead, the integration of genomic, microbiome, metabolomic, and clinical data is expected to transform **precision medicine**. Comprehensive characterization of an individual's genetic profile and gut microbiome may enable more accurate prediction of disease risk, earlier preventive interventions, optimization of drug selection and dosing, and the development of personalized therapeutic strategies. Continued interdisciplinary research into host–microbiome interactions will not only

deepen our understanding of human evolution but also pave the way for more effective, individualized, and microbiome-informed healthcare in the future.

CONFLICT OF INTEREST: I declare that I have no conflict of interest.

Abbreviations

HMO – Human Milk Oligosaccharide
SCFA – Short-chain Fatty Acid
TLR – Toll-like Receptor
NOD – Nucleotide-binding Oligomerization Domain
PRR – Pattern Recognition Receptor
IBD – Inflammatory Bowel Disease
HLA – Human Leukocyte Antigen
MHC – Major Histocompatibility Complex
IgA – Immunoglobulin A
PPI – Proton Pump Inhibitor
NSAID – Non-steroidal Anti-inflammatory Drug

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