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Review

The Microbiota and Evolution of Obesity

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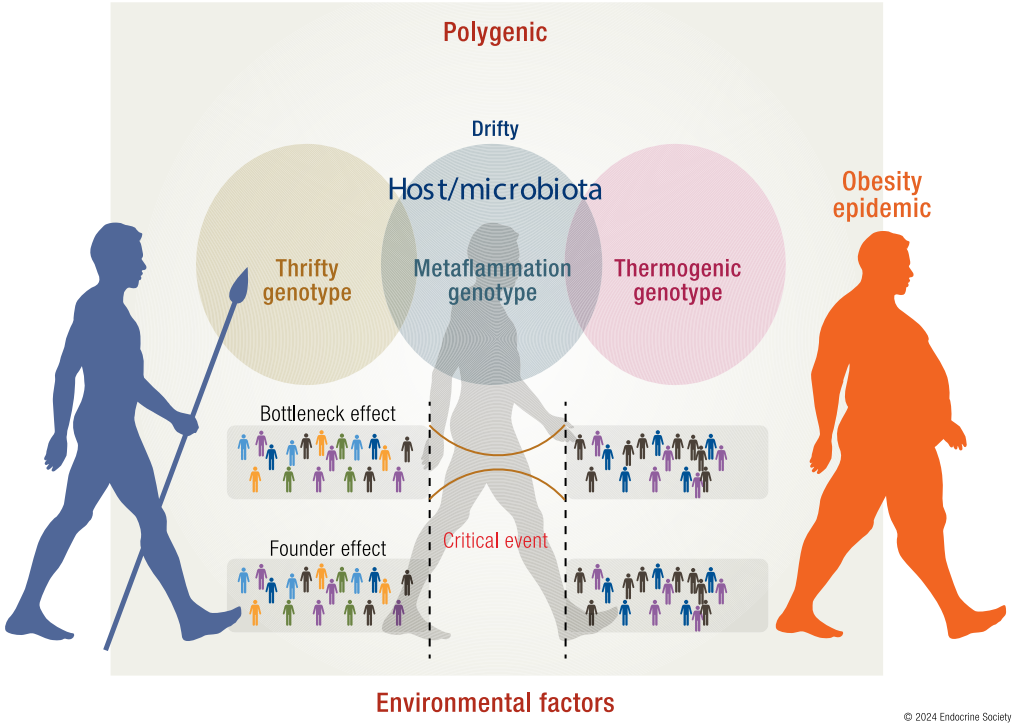
Abstract

Obesity is a major global concern and is generally attributed to a combination of genetic and environmental factors. Several hypotheses have been proposed to explain the evolutionary origins of obesity epidemic, including thrifty and drifty genotypes, and changes in thermogenesis. Here, we put forward the hypothesis of metaflammation, which proposes that due to intense selection pressures exerted by environmental pathogens, specific genes that help develop a robust defense mechanism against infectious diseases have had evolutionary advantages and that this may contribute to obesity in modern times due to connections between the immune and energy storage systems. Indeed, incorporating the genetic variations of gut microbiota into the complex genetic framework of obesity makes it more polygenic than previously believed. Thus, uncovering the evolutionary origins of obesity requires a multifaceted approach that considers the complexity of human history, the unique genetic makeup of different populations, and the influence of gut microbiome on host genetics.

Graphical Abstract



Key Words: gut microbiota, obesity, evolution, metaflammation, drift and thrifty

Abbreviations: BMI, body mass index; GWAS, genome-wide association studies; SNP, single-nucleotide polymorphism.

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ESSENTIAL POINTS

- Various hypotheses have been suggested for the evolutionary origins of obesity
- Metaflammation suggests that pathogen defense genes could lead to modern obesity
- Immune genes may influence obesity via immune and energy storage system interactions
- Gut microbiota genetics add to obesity's polygenic complexity
- Obesity's origins require considering history, genetics, and the gut microbiota

Over the past 4 decades, the obesity epidemic has rapidly escalated in Western societies. While obesity clearly has many environmental drivers including the changing nature of diets, it also has a substantial genetic component; tracing the evolutionary origins of this genetic history remains an important challenge (1-3).

Charles Darwin and Alfred Wallace revolutionized the understanding of how different environmental exposures in previous generations shaped biological diversity in today's generation. Their theory of natural selection proposed that species evolve, giving rise to new species, while sharing a common ancestry (4), and that this evolution is driven by natural selection, which favors traits that enhance the fitness of the species (5-7). However, it was not until the late 19th century that modern genetics emerged with the rediscovery of Mendel's work, laying the foundation for modern evolutionary synthesis.

Throughout history, humans have faced ever-changing environmental and social conditions, both before and after their migration out of Africa. Factors such as predation, famine, infectious diseases, and climate adaptation have shaped human evolution. However, with the rapid changes in lifestyle in recent years, the levels of daily activity and type/quality of food intake have become maladaptive. Applying these evolutionary concepts to explain the modern epidemics of obesity and type 2 diabetes have traditionally focused on genetic traits. With the completion of the Human Genome Project, our understanding of the genetic traits has advanced considerably (8). Indeed, over the last 15 years, researchers investigating the genetics of obesity using large populations and the genome-wide association studies (GWAS) approach have identified more than 1000 genetic loci linked to obesity (9). Despite such advancements, the exact driver genes of the most common types of obesity and their mechanism of action are not yet fully understood (9). It is possible that integrating these modern genetic studies with the hypothesis of the evolutionary origins of obesity can be one path to shed light on the role of genetics in obesity.

In this review, we revisit the existing hypotheses that, to some extent, explain the evolutionary basis of recent obesity epidemics, including the thrifty and drifty genotypes (1, 2) and the thermogenic hypothesis (3). Due to the intense selection pressures caused by environmental pathogens, we have put forward an additional metaflammation hypothesis in which modern-day obesity may also be driven in part from natural selection to favor specific genes that promote strong immune defense against epidemics and/or infectious diseases in our ancestors. Considering the close connection between the immune and energy storage systems (10), these genes might allow for efficient fat storage during food-abundance periods, allowing more resilience in times of stress. In today's constant food availability environment, however, this inflammatory genotype or metaflammation promotes excessive fat storage and obesity. However, it is essential to emphasize that the origins of obesity are complex and cannot be explained by a single theory.

Thus far, the effect of the interplay between host and microbial genetic variation on host evolution has received little attention in the study of obesity. Most of the research on obesity has largely neglected the microbiome's influence on the genetic basis and evolution of the host. Here we propose investigating how genetic variations in the microbiome can increase the genetic diversity of the host genome, affect the heritability of host traits, and ultimately influence the evolution of obesity in humans. Integrating data from the GWAS and the microbiome into these previous hypotheses, we explore the need to consider the changing nature of microbiota in the critical process of evolution that converges to our modern epidemic of obesity.

Evolutionary Hypothesis of Obesity

Thrifty Genotype

The oldest hypothesis, proposed by Neel in 1962, suggests that diabetes and obesity may have originated from natural selection to favor a "thrifty genotype" in our ancestors (1). This genotype would allow for efficient fat storage during food-abundance periods, which was advantageous when surviving food shortages. However, in today's constant food availability environment, this thrifty genotype would promote excessive fat storage and obesity (11-22).

One of the many criticisms of the hypothesis is that the causes of mortality are complex during times of famine, with significant factors being infectious disease and diarrhea (23), suggesting that mechanisms of immune defense against infection need to be included in the search for genotypes with evolutionary advantages associated with the thrifty genotype. Further weakening the thrifty genotype is the dearth of genetic studies supporting this hypothesis (24-26). Moreover, Wang and Speakman (27), who searched for genetic evidence of the thrifty genotype in the positive selection signatures at 115 single-nucleotide polymorphisms (SNPs) linked to obesity found no selection evidence, and thereby no support for the thrifty genotype as a major evolutionary driver for obesity.

Drifty Hypothesis

The drifty hypothesis, proposed by Speakman, challenges the concept of the thrifty genotype to explain obesity (2). Based on this hypothesis, it is suggested that early hominids underwent a process of stabilizing selection favoring body fatness, while obesity was selected against due to the increased risk of predation. However, around 2 million years ago, the risk of predation diminished substantially with the development of social behavior, weapons, and fire control. As a result, the population distribution of body fatness began to alter due to random mutations and genetic drift (2, 28, 29).

In essence, the drifty hypothesis suggests that once our ancestors became skilled hunters and discovered fire, the risk

of predation reduced and was nearly nonexistent. This removal of predation as a selection pressure meant that the upper limit or "point of intervention" for body weight status was no longer beneficial. Thus, the genes that promote adiposity and increased body weight were no longer being removed by natural selection, as they had been when predation posed a severe threat to survival. This hypothesis differs notably from the previous one by suggesting that the genetic predisposition to obesity has never been advantageous to humans (11, 16, 20, 28-32).

The hypothesis also explains why most individuals in society are not obese. Potential genetic alterations that cause upper body weight limits to be exceeded are presumed to have randomly occurred rather than being selected for. Therefore, individuals who have not experienced this genetic drift remain nonobese (2). Critics of this hypothesis argue that it fails to consider factors such as population size, gene-gene and gene-environment interactions, population bottlenecks and expansions, migration and founder effects, and population subdivision (33). Additionally, the hypothesis does not address certain genetic traits, such as type 2 diabetes and polycystic ovary syndrome, which are highly detrimental in our environment and cannot be solely explained by random mutations (34).

Thermogenic Capacity Hypothesis

Compelling evidence now suggests that modern humans embarked on a remarkable journey out of Africa approximately 70 000 years ago (35-45). As our ancestors ventured into colder regions (Europe and Northeast Asia), they faced unique environmental challenges that shaped their genetic makeup. Over time, natural selection favored genes that facilitated cold adaptation over heat adaptation (3, 46).

It is worth noting that modern humans reached Europe around 45 000 years ago and inhabited it at a time of the last glacial period when vast stretches of Europe were engulfed by ice. Around 40 000 years ago, Europe experienced a climatic deterioration that reduced mammalian species diversity. Ethnographic data and observations on mammalian species and fluctuating resources indicate a subsequent decline in human population densities, and suggest that population bottlenecks, genetic drift, and gene flow have more prominent roles in human evolution during this period than population replacement.

As a result, populations that remained in Africa were well adapted to hot climates and local savannah environments—features found even in modern times in individuals of African descent, including a larger surface area to body mass ratio, longer limbs, increased skin pigmentation, reduced body hair, more sweat glands, lower body temperature, and decreased metabolic rate, all of which would have helped protect individuals against solar radiation and overheating (47, 48). In contrast, indigenous populations with ancestors from China and Japan successfully settled in Arctic and subarctic regions, showcasing their evolutionary adaptation to cold climates (49-51). It is believed that natural selection has played a role in favoring cold-adaptation genes in these populations, influencing energy expenditure in these individuals with diverse ancestries (3). These studies have found that basal metabolic rates are highest in Arctic individuals, intermediate in White Europeans, and lowest in African Americans (52-54). These findings underpin a thermogenic capacity hypothesis (55-61), which suggests that the lineages of early humans who remained in Africa and those who migrated to other tropical environments retained heat-adaptation genes (3). As a result, modern African Americans, whose ancestors did not require such efficient energy expenditure, showed lower aerobic capacity and energy expenditure, which, when combined with sedentary Western lifestyles, increased obesity rates (52, 62). Indeed, total daily energy expenditure is lower in African American compared with White individuals, most of which is due to a lower resting metabolic rate (52, 62). Conversely, the lineages of those who migrated to colder regions acquired genes for cold adaptation (3, 63). Despite sedentary lifestyles and ultraprocessed foods, populations adapted to cold temperatures and with a propensity to efficient energy expenditure have less chance of developing obesity when compared with populations in hot climates.

Thus, the thermogenic capacity hypothesis highlights the profound influence of historical human migration on the modern obesity pandemic. The journey of our ancestors out of Africa, coupled with unique climatic challenges, has shaped distinct genetic adaptations in different populations. In accordance with this hypothesis, there are some gene variants associated with latitude, obesity, and brown adipose tissue thermogenesis, such as *UCP1*, *PRDM16*, *THADA*, *ADRB3*, *TBX15/Wars2*, and *TRIB2* (58). While the hypothesis provides valuable insights into human evolution and its effect on metabolic rates and obesity, as noted later, further research is needed to determine how differences and changes in gut microbiota might contribute to these differences and reinforce the hypothesis.

A New Hypothesis: The Metaflammation Hypothesis

Due to intense selection pressures exerted by pathogens, the immune system has become our primary interface with the environment (64-66). Devastating historical epidemics, such as the Black Death in Europe, viruses that decimated Native Americans in Peru and Mexico, and the influenza pandemic of 1919, have had a significant effect on population sizes and genetic selection (66). Disparities in obesity rates exist among different populations, with African Americans, Hispanic Americans, and Pacific Islanders having higher rates when compared to European Americans (67). Together, these observations lead us to propose a metaflammation hypothesis, which proposes that obesity rate differences between populations reside, at least in part, in the differences in the immune system (which is linked to the energy storage system) and are the consequences of genetic selection induced by infectious diseases or epidemics. Thus, populations that stayed in Africa and lived a more primal lifestyle, hunting in tropical rainforests where they were exposed to various parasites and pathogens carried by insects, birds, and animals, have developed a robust immune system (68, 69). By contrast, populations that migrated out of Africa were exposed to lower pathogen levels, thereby reducing the need for strong and energy-costly proinflammatory signals (70, 71).

In favor of this hypothesis, it has been shown that individuals of African descent, including African Americans, express more genes linked to strong inflammation, increased cytokine secretion, and bactericidal activities when compared to other populations (65, 72). There are more than 250 such genes with evidence of recent natural selection, for example, variants of the *IL1A* and *IL1B* genes (65, 72). Macrophages

are required to fight infections and in individuals of African ancestry, macrophages respond more strongly to infections, as assessed by expression of genes related to inflammatory responses (65). These findings suggest that Africans and African Americans have more efficient inflammatory responses and may better control bacterial infections.

Recent studies have shown that Hispanic Americans, who have a high prevalence of obesity, have inherited stronger immune systems from their Native American ancestors, possibly because the latter had survived epidemics of infectious disease. Research has also shown that African American and Hispanic American women have higher circulating C-reactive protein levels when compared to European American women. This phenomenon is linked to a specific protein variant (TREM2) which is expressed in myeloid cells (73).

Another population with a high obesity prevalence, which likely experienced selective pathogen pressure, are the Pima Indians. GWAS studies conducted in this population have identified multiple SNPs associated with body mass index (BMI), including SNPs in *A2BP1*, *TMEM18*, *TCF7L2*, *MAP2K3*, and *LPGAT1* (74-77). Although these genes had many different cellular functions, most of these are expressed in macrophages and/or code for proteins that can modulate the immune responses or are related to endoplasmic reticulum stress (76, 78-80). Thus, these genes could have roles in subclinical inflammation in obesity and also serve as connections between inflammatory genotypes and weight gain.

In the 19th century, infectious diseases such as measles, whooping cough, and influenza caused approximately 75% mortality in some East Polynesian populations (81), and potentially exerted a considerable effect on genetic diversity in modern populations. In GWAS of obese populations from the Pacific Islands, strong associations were observed with *Insig2* and *CREBRF* genes (82, 83), which, while not uniquely related to the immune system, have relevant roles in inflammation or endoplasmic reticulum stress directly linked to inflammatory responses (84, 85).

Although less prevalent than in African Americans and Hispanic Americans, Europeans and European Americans also have a high prevalence of obesity. While most GWAS in obese populations of European ancestry have not reported correlations between BMI and immune system genes, a more careful search can identify possible links. For example, two of the most significant GWAS-identified and widely replicated obesity loci are the *FTO* (9, 86) and *MC4R* genes (9, 87, 88). Although several mechanisms have been proposed to explain why these loci modulate body weight, including the central nervous system–mediated control of food intake (9), it is important to note that both *FTO* (89-98) and *MC4R* (99-102) have important roles in macrophage activation and inflammatory responses, suggesting some effect on immune response modulation. Moreover, reexamination of a study examining the genetic factors contributing to BMI variations in 339 000 individuals (103) (predominantly of European descent) using GWAS and metabochip meta-analysis to successfully identify 97 BMI-associated loci, which accounted for approximately 2.7% of the variance in BMI, revealed many expected pathways, including substantial central nervous system involvement, but also revealed 56 novel loci associated with BMI in a European meta-analysis, of which at least 90% had roles in macrophage/inflammatory processes, indicating potential connections between BMI and immune genotype composition (104-137).

While it is commonly believed that subclinical inflammation is caused by obesity in response to cytokines secreted from macrophage/adipose tissue, epidemiological studies have shown that inflammation can precede and promote weight gain (138-141). At molecular levels, precise control mechanisms exist between insulin signaling/resistance and pathways in immune cells that may contribute to weight gain. In primary infections or excess nutrient conditions, innate immune system activation (toll-like receptor [TLR], inducible nitric oxide synthase, JNK, and nuclear factor κB) causes posttranscriptional protein modifications in insulin signaling. This causes insulin resistance, which is specific to the liver, muscle, and hypothalamus, while adipose tissue remains insulin sensitive or less resistant thereby favoring weight gain (141-144). Inflammation may also contribute to increased weight gain via reduced energy expenditure, secondary to M1 macrophage infiltration in brown adipose tissue, thereby increasing degradation or impairing sympathetic neuron-mediated norepinephrine signaling in this tissue (145, 146).

In summary, our metaflammation hypothesis suggesting that genes that promote a strong defense against infectious diseases could also be responsible for the increasing prevalence of obesity in modern society. This hypothesis could also shed light on the evolutionary origins of the obesity epidemic, but further studies of the connections between genes linked to obesity and the immune system and inflammation must be explored.

Microbiota, Obesity, and Evolution

Environment Factors and Microbiota

The environment is a determinant factor in the establishment of the obesity pandemic observed in recent years. Nevertheless, the increase in obesity cannot be entirely ascribed to individual choices for high-calorie diets or decreased energy expenditure resulting from contemporary sedentary lifestyles. This viewpoint overemphasizes personal responsibility for obesity, failing to acknowledge the broader systemic factors that contribute to the creation of inequitable obesogenic environments. For instance, the unique characteristics of Latin American countries render their populations particularly susceptible to these factors, which may elucidate the substantial increase in obesity rates observed in the region (147-149). These factors include the physical environment, food exposure, economic and political interests, social inequity, limited access to scientific knowledge, cultural influences, contextual behavior, and genetics (147, 150-153). While some factors are related to individual behavior, most are systemic, significantly affecting obesity trends by limiting individual freedom of choice. Additionally, the reduced selective pressure resulting from medical advancements and food abundance may allow individuals with a genetic predisposition to obesity to survive and reproduce, potentially increasing obesity prevalence in future generations (154).

Also in this field of evolutionary biology, recent evidence suggests that the study of human evolution is incomplete without due consideration of the human microbiota (155-159). The gut microbiota is a complex ecosystem of gastrointestinal microorganisms, including bacteria, viruses, fungi, protozoa, and archaea. More than a trillion microorganisms, including normal commensal bacteria in various compartment of the body, influence the functioning of the human body (160-162). Of these, gut bacteria have been studied the most. In addition to maintaining normal intestinal function, intestinal microbiota also influences the overall health of the host (160-169). Bacterial cells from the gut microbiota possess an

astounding number of genes that surpasses the entire human genome (160, 162, 170-172). As a result, they have gained the moniker "second genome" or "extended genotype." This secondary genetic system can account for an overwhelming 99% of the genetic information in our bodies, providing us with augmented genetic diversity compared to our genome (Fig. 1). Moreover, it facilitates accelerated evolutionary processes and grants us the remarkable capability of exchanging microorganisms with our surroundings, along with their genes and associated functionalities (173, 174). These attributes hold immense potential in contributing to the adaptability of the host organism, making the second genome an appealing target for natural selection.

Diet and lifestyle choices substantially influence the gut microbiota (175-183) and have profound implications on the evolutionary journey toward obesity. Vertebrates, including humans, modulate their intestinal microbiota in response to acute and chronic dietary changes (175, 177, 178, 184, 185). This adaptation enables greater flexibility and efficiency in digesting a wide range of nutrients, promoting survival even under extreme dietary conditions. Evidence indicates the existence of diurnal oscillations in the gut microbiota of mice and humans, corresponding to feeding rhythms (185-187), as well as long-term adaptations that provide a mechanism for responding to changing environments and providing evolutionary influence on the host. This is exemplified by comparison of gut microbiota between populations from the United States, Malawi, and the Amazon and their adaptation to differing dietary components (188). People in America have adapted to a high-protein and high-fat diet, whereas individuals from Malawi and the Amazon have adapted to digest complex carbohydrates.

Horizontal gene transfer represents another adaptation of the human microbiota with substantial implications in evolution (see Fig. 1). This transfer involves changes in the composition of bacteria within the gut and subsequent alterations in gene content (189). Furthermore, it has been demonstrated that human-associated bacteria have a substantially higher rate of gene transfer than bacteria in other environments, because horizontal gene transfer occurs frequently within an individual's gut microbiome, with higher frequencies of transfer in industrialized populations (190).

In addition to diet, various environmental factors, including early-life antibiotic use, treatment with antipsychotic medications, smoking cessation, reduced physical activity, and numerous other conditions, have been shown to affect the composition of gut microbiota, potentially favoring weight gain (191-207). Host genetic variation also contributes to shape the microbial ecosystem (208-214). This interaction between host genetics and the gut microbiome can potentially affect the host's phenotype. Understanding the complex interplay between human genetics, environment, and gut microbiota provides valuable insights into the evolutionary origins of obesity and its underlying mechanisms.

Gut Microbiota and Obesity

Extensive research has shed light on the critical role of intestinal microbiota in the development of obesity (162, 215-219). In a now classic study, it was found that germ-free mice were comparatively protected against diet-induced obesity and exhibited reduced adiposity, improved glucose tolerance, and enhanced insulin sensitivity, all linking the microbiome to obesity and metabolic syndrome (217). Transplantation of the microbiota from ob/ob mice to lean mice increased adiposity in the recipients, even though they did not carry the obesity genes (219). Indeed, multiple studies in different mice models suggest the causal role of microbiota as an important variable in the induction of weight gain (220, 221), and indicate that intestinal microbiota may overcome genetic protection against insulin resistance, inducing weight gain and metabolic syndrome (222).

In humans, the composition and biodiversity of gut bacteria substantially differ between obese and healthy individuals (196, 223-241). Compared to lean individuals, obese individuals show reduced bacterial diversity. A systematic review showed that the most consistent phylum associated with obesity is Proteobacteria, and the association between the Bacteroidetes/Firmicutes ratio is dubious (241). In obesity, various genera, such as Lactobacillus and Fusobacterium, are also enriched. On the other hand, Faecalibacterium, Akkermansia, and Alistipes are considered to be lean-associated genera (242-244). In a metagenome-wide association study, researchers have found 1358 significant associations between bacterial SNPs and host body mass index (BMI) using gut metagenomic samples from a cohort of more than 7000 healthy individuals (245). The researchers also identified BMI associations in SNPs related to inflammatory pathways in Bilophila wadsworthia and energy metabolism functions in the *Faecalibacterium prausnitzii* genome, highlighting the significance of nucleotide-level diversity in microbiome studies.

Gut Microbiome Expands the Host's Evolutionary Capacity

The microbiome plays an important role in the host's evolutionary potential by expanding its genetic repertoire (156-158, 246-248). The interaction of the microbiome with the host phenotype is crucial in shaping the distribution of host phenotypes. It enhances the host's response to natural selection and influences its evolutionary trajectory. Microbial effects on host evolution depend on how microbes are transferred to the host species. Previously, only vertically transmitted microbes were recognized as inheritable; however, hosts can acquire microbes through different transmission modes (249) (see Fig. 1). Recent research has revealed that host genetic variation significantly contributes to the relative abundance of microbes in hosts that acquire microbiome directly from the environment (209, 250, 251). On the other side, despite the complex inheritance of the microbiome, microbial variation explains considerable phenotypic variance that can rival the contribution of host genetic, suggesting that the microbiome's fidelity of inheritance may also influence host phenotypic variance (208, 209).

The microbiome can modulate the host's evolutionary potential in two common scenarios (252). First, microbial variation may shift the mean phenotype of the population, facilitating local adaptation (173, 252, 253). Second, microbial diversity has the potential to stabilize and enhance phenotypic variability within a host population. These two patterns often coexist and significantly influence how hosts navigate their adaptive journey (253, 254). By harnessing the abilities of microbes, hosts can acquire specific adaptive traits tailored to their local environment, thereby maximizing their chances of survival and reproductive success in rapidly changing ecological landscapes (156).

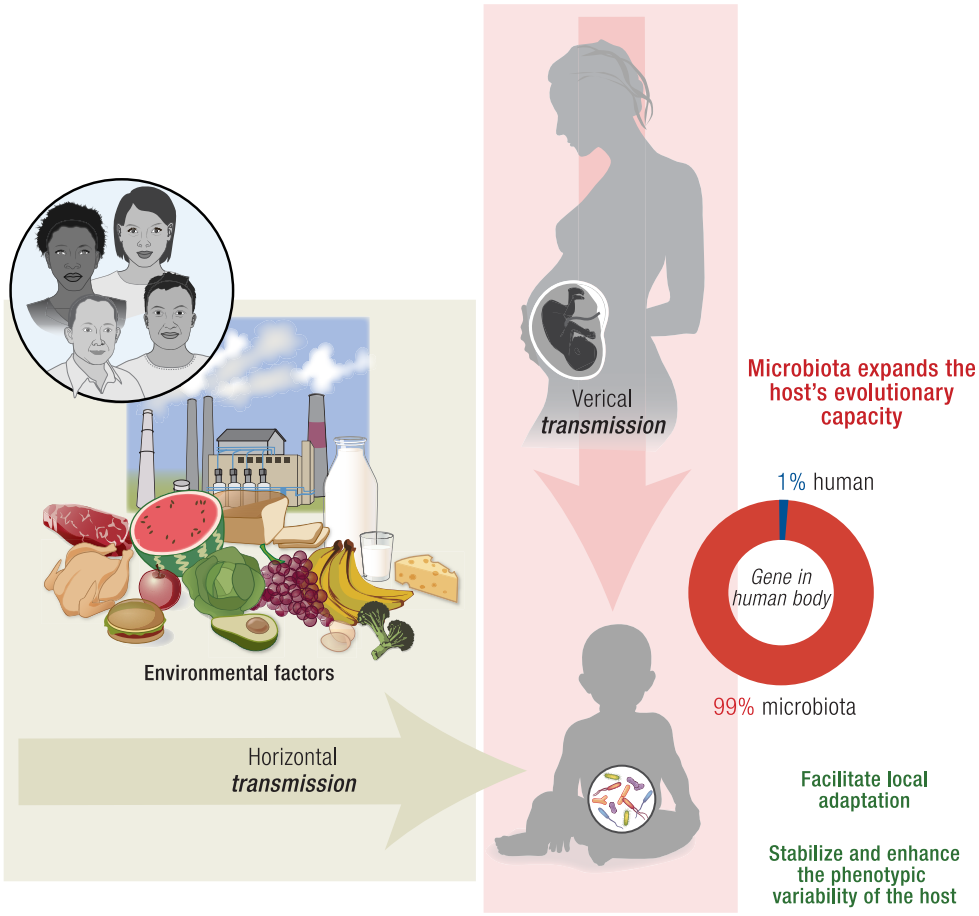

Figure 1. The gut microbiome expands the host's evolutionary capacity. The study of human evolution is incomplete without considering the human microbiota. Bacterial cells in gut microbiota possess 99% of the genetic information in our bodies, providing us with augmented genetic diversity compared to our genome and facilitating accelerated evolutionary processes through generations. Previously, only vertically transmitted microbes were recognized as inheritable, but hosts can also acquire gut microbiota through horizontal gene transfer. The microbiome can modulate the host's evolutionary potential in 2 common scenarios: First, microbial variation may shift the population's mean phenotype, facilitating local adaptation, and second, microbial diversity can stabilize and enhance phenotypic variability within a host population. The effect of the microbiome on host genetics needs to be considered in the hypotheses of the evolutionary origin of obesity.

The assembly process of intestinal microbiota introduces chance and priority effects, resulting in microbial variation among hosts within a population. Therefore, it increases phenotypic variability and creates new opportunities for host exploration within the fitness landscape. This alteration in evolutionary trajectories has important implications for hosts. Thus, changes in the distribution of phenotypic traits within the microbiome affect the host's response to natural selection, leading to tractable signatures of selection in the host's genome over time. The interplay between microbial variation and host phenotypic diversity plays a crucial role in the dynamics of evolutionary processes. These findings highlight the critical role of the microbiome in shaping the adaptive potential of host populations and provide valuable insights into the intricate interdependencies between microbes and their hosts.

While locally adaptive microbes may help facilitate short-term host trait evolution, their long-term evolutionary outcomes are still unknown. If these microbes prove beneficial, hosts may develop mechanisms to maintain locally adaptive microbes and their effects on host traits or environmental stress mitigation, similar to genetic accommodation or niche construction (253). Thus, hosts may increase their frequency within the population, improving the host's ability to adapt to the environment.

Specifically looking at the immune system, protective symbionts potentially shape immune system evolution in multiple ways. One possibility is that host immune responses, when coupled with protective symbionts, reduce the need for redundant immune mechanisms. In contrast, symbionts may also help develop host immune responses by providing sufficient protection, thereby enabling hosts to persist and adapt. Immune system evolution is likely to differ, depending on factors such as the type of immunity, how symbionts are transmitted, and the cost benefits associated with immune system functions. Ultimately, the effect of beneficial symbiosis on immunity evolution will rely on the intricate interactions between the host immune system and symbionts, with specific interactions potentially alleviating the pressure for immune system maintenance, while others may create constraints (255).

Reconciling the Evolutionary Hypothesis of Obesity With the Changing Landscape of Gut Microbiota

Host/Microbiota Thrifty Hypothesis

The discovery of the important and changing role of gut microbiota in the development of obesity provides a new

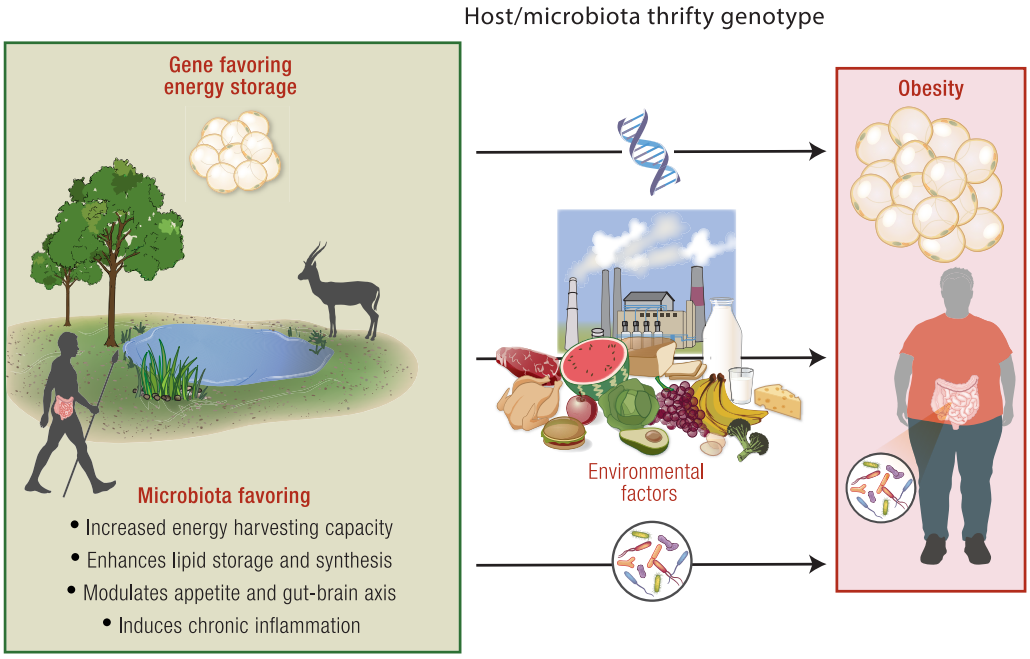

Figure 2. Host/microbiota thrifty genotype hypothesis. The host thrifty genotype proposes that genes that allowed for efficient fat storage during food abundance were advantageous for survival during periods of food shortage. Additionally, a microbiota able to induce energy storage and less energy expenditure, independent of whether it was installed more recently (favored by environmental factors) or was installed in our ancestors and passed through vertical transmission, can undoubtedly integrate the thrifty genotype. A possible microbiota thrifty genotype is a microbiota favoring a) an increase in digestible energy uptake while decreasing energy expenditure, leading to weight gain; b) an increase in lipid synthesis and storage, contributing to obesity; c) the control of appetite and feeding behavior and modulate the gut-brain axis to influence cravings and eating habits; d) the induction of a state of subclinical chronic inflammation, leading to tissue-specific insulin resistance with increased adipose mass. In today's environment of constant food availability, this host/microbiota thrifty genotype promotes excessive fat storage and obesity.

mechanism that must be considered in the context of the thrifty genotype hypothesis. Mechanisms, whereby gut microbiota can promote weight gain/energy storage, can be categorized into 4 key areas. First, gut microbiota disrupt energy homeostasis by increasing digestible energy uptake (increased capacity to energy harvest) (219), leading to weight gain. Second, gut microbiota may enhance lipid synthesis and storage, contributing to obesity (217). Furthermore, gut microbiota may affect control of appetite and feeding behavior and modulate the gut-brain axis to influence cravings and eating habits (256, 257). Last, gut microbiota may induce a state of subclinical chronic inflammation, leading to tissue-specific insulin resistance with increased adipose mass (141, 258-261). A gut microbiota with these characteristics is deemed to have a "thrifty genotype," which refers to its ability to efficiently induce fat storage in the host (141, 217, 219, 256-261), a trait that have been advantageous in our ancestors (Fig. 2).

Host/Microbiota Thermogenic Capacity Hypothesis

Previous data have shown that cold exposure can lead to a substantial shift in mouse microbiota composition, which researchers dubbed the "cold microbiota" (262). Intriguingly, when these microbiota were transplanted into germ-free mice, the animals showed improved insulin sensitivity and better cold tolerance effects that were partly due to white fat browning and increased energy expenditure with loss of white fat. Zietak et al (263) found that lowering the environmental temperature reduced diet-induced obesity in mice and was associated with increased thermogenesis and a plasma bile acid profile similar to their germ-free counterparts. The authors observed significant changes in microbiome composition at both the phylum and family levels within a day of cold exposure and after 4 weeks at lower temperatures. Interestingly, under these conditions, the gut microbiota showed higher levels of bacteria associated with leanness, such as *Adlercreutzia*, *Mogibacteriaceae*, *Ruminococcaceae*, and *Desulfovibrio*, while bacteria linked to obesity (*Bacilli*, *Erysipelotrichaceae*, and rc4-4) were reduced.

Taken together, these findings suggest that exposure to cold temperatures induce microbiota composition alterations that favor genera associated with leanness and suppress those linked to obesity (262, 264, 265). Thus, changes in microbiota can potentially explain, at least in part, White European and East Asian adaptation to cold climates and their resistance to obesity. Furthermore, in hot climates, microbiota modulation in the opposite direction, coupled with sedentary and Western lifestyles, may contribute to an obesity propensity among African and South Asian populations. This "host/microbiota thermogenic capacity genotype" adaptation may also contribute to relatively rapid obesity development when these populations migrate from cold to hot climates (Fig. 3). Such lifestyle changes may represent a promising avenue for further research in this field.

Host/Microbiota Metaflammation Hypothesis

The host and its commensal bacteria work together to resist pathogens, with cooperative efforts potentially favored by natural selection (266-269). Pathogen defenses are crucial microbiome functions in terms of evolution, and many symbionts that have colonized hosts are effective against a range of pathogens, making the benefits of pathogen resistance a

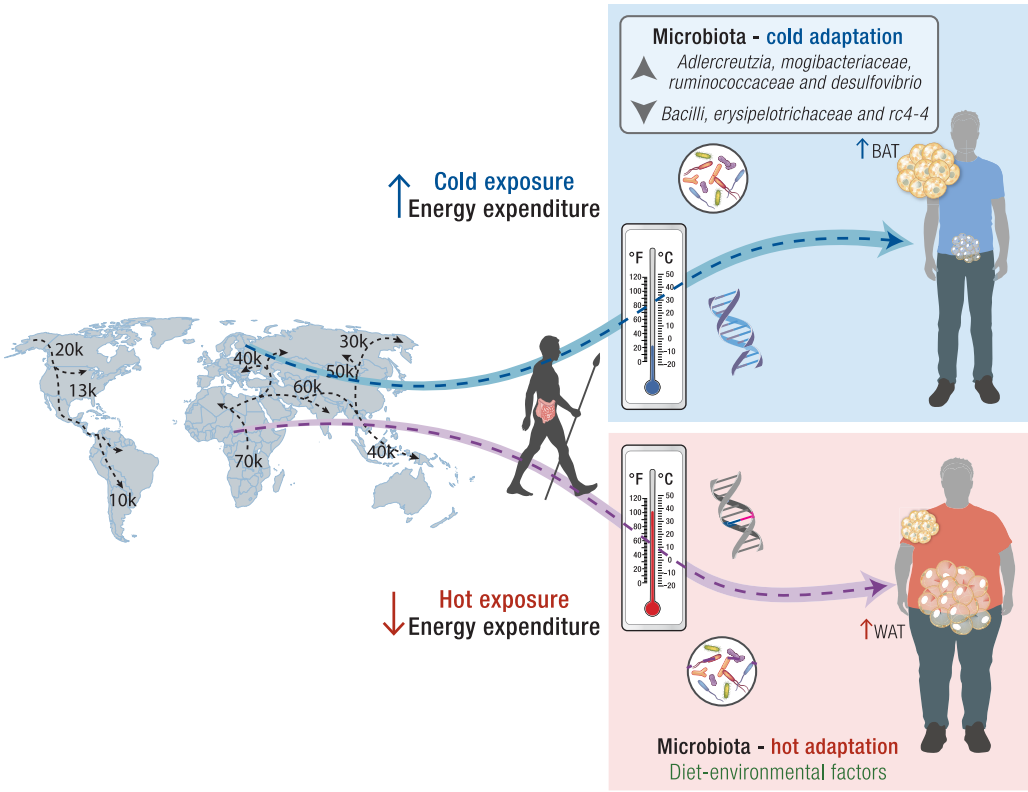

Figure 3. Host/microbiota thermogenic genotype hypothesis: The thermogenic capacity hypothesis suggests that the lineage of early humans who remained in Africa and those who migrated to other tropical environments retained genes for heat adaptation. Conversely, the lineage of those who migrated to colder regions acquired genes for cold adaptation. Nowadays, with a sedentary lifestyle and ultraprocessed food abundance, populations adapted to cold temperatures with a propensity to efficient energy expenditure have less chance to develop obesity compared with populations that were adapted to hot climates. In addition, it is essential to mention that exposure to cold temperatures induces alterations in the microbiota composition that favor genera associated with leanness and suppresses those linked to obesity. This leads to the hypothesis that the modulation of microbiota could potentially explain the adaptation of White and East Asian individuals to cold climates and their resistance to obesity. Furthermore, the opposite modulation of microbiota in hot climates may predispose descendants (coupled with sedentary and Western lifestyles) to obesity. This phenomenon can be identified as the "host/microbiota thermogenic capacity genotype" adaptation, which may also elucidate the relatively rapid development of obesity when these populations migrate from cold to hot climates, accompanied by lifestyle changes.

considerable advantage (255, 270). This is particularly important compared to other microbiota benefits, such as nutritive benefits or the thrifty microbiota genotype.

In this regard, a careful search using data from different sources shows that intestinal microbiota taxa considered protective against some infectious diseases are more prevalent in microbiota from obese individuals (240, 271, 272). There is a clear relationship between the gut microbiota and the sepsis outcome (273-275). A mendelian randomization investigation estimates that *Lentisphaerae*, *LachnospiraceaeUCG004*, and *Coprococcus* negatively correlated with sepsis severity. In addition, *Coprococcus* had a significant negative correlation with the risk of sepsis-related death, suggesting a protective effect of these taxa (271). Interestingly, all these taxa are more prevalent in obese individuals, suggesting that, at least in part, a more protective microbiota in sepsis is also present in obesity (147). A systematic review of malaria and microbiome showed a clear correlation between the phylum firmicutes and proteobacteria and the attenuation of malaria severity in mice and men (272), and these phyla are certainly more prevalent also in obesity (240). Although the microbiota of obese individuals might have a significant influence from diet and environment, we cannot exclude the possibility that part of it may have come from vertical transmission, which leads us to suggest that certain microbiota strains that have evolutionary advantages in fighting infectious diseases may also predispose the host to weight gain.

The colonization resistance induced by gut microbiota may involve direct mechanisms (interactions between microbial cells) and indirect mechanisms (through regulation of host physiology and largely host immune responses) (276). These indirect mechanisms, mainly activation of the innate immune system and cytokine production, may also mediate weight gain. Individuals with low gut bacterial diversity have low-grade inflammation due to innate immune system activation and are more likely to experience weight gain, dyslipidemia, and insulin resistance (277, 278). Also, specific bacterial strains associated with host inflammation, such as *Ruminococcus gnavus* and *Bacteroides* species, are more prevalent in obese individuals (178, 279). In contrast, strains with anti-inflammatory properties (*F prausnitzii*) are less common (192). Furthermore, a unique intestinal microbiome signature was shown to contribute to weight regain in obese mice following successful dieting (280). The molecular connections between microbiota-induced inflammation and obesity may be manifested through factors previously described, such as tissue-specific insulin resistance and reduced energy expenditure (141-146, 281-283), but other microbiota-related mechanisms are also likely at play. One additional potential mechanism involves fatty acid metabolism

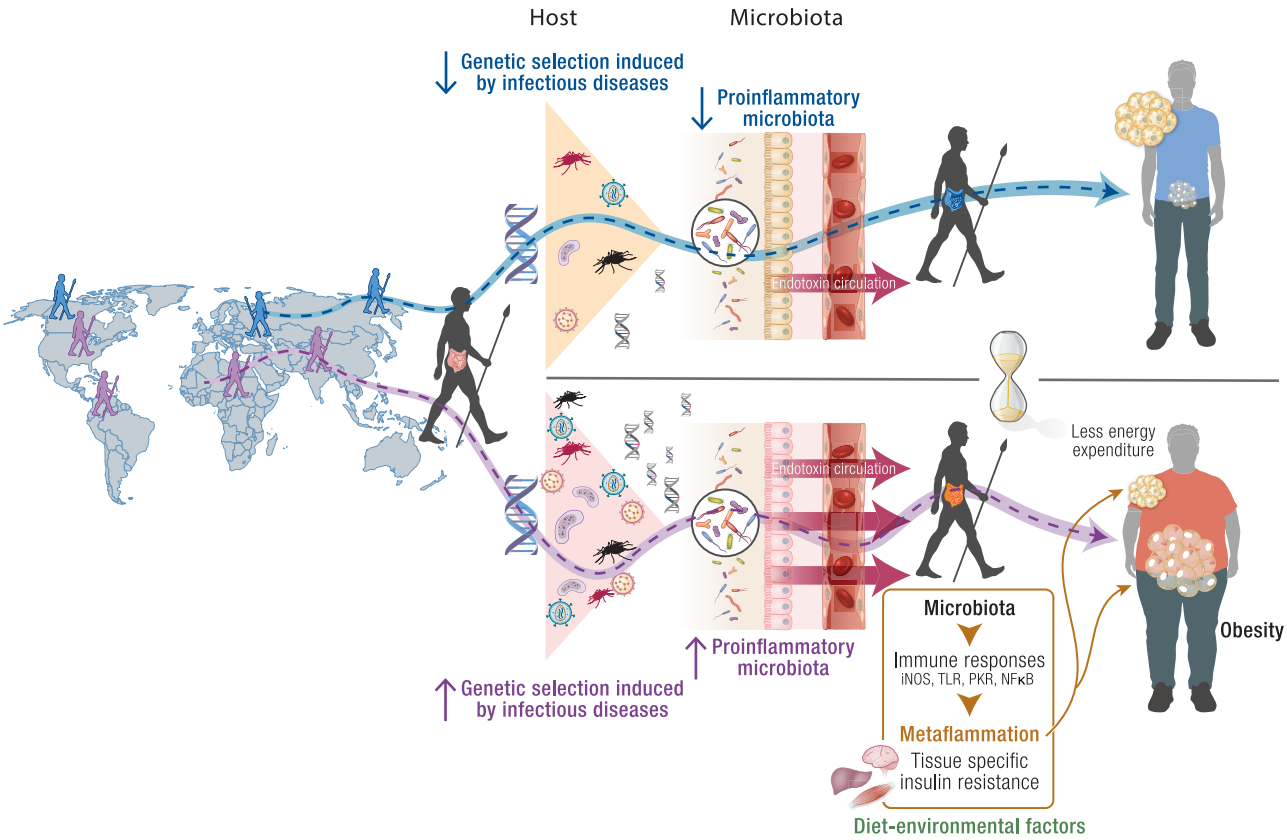

Figure 4. Host/microbiota metaflammation genotype hypothesis: There are disparities in obesity rates among different populations, with African Americans, Hispanic Americans, and Pacific Islanders having higher rates compared to European Americans. The differences in obesity prevalence between human populations may involve the immune response, which lies in the genetic selection induced by infectious diseases. As populations stayed in Africa, they lived and hunted in the tropical rainforest. They were exposed to various insect, bird, and animal parasites and pathogens and developed a more inflammatory genotype. As some humans migrated out of Africa to develop agriculture and animal husbandry, they encountered diverse pathogenic environments. This led to population-specific selection and adaptation to these new environments, with less pressure on infectious diseases and a less inflammatory genotype. Evidence shows that a genotype more prone to inflammation may predispose to obesity in today's constant food availability environment. Moreover, we suggest that certain strains of microbiota that possess evolutionary advantages in fighting infectious diseases may contribute to a more inflammatory phenotype, predisposing to weight gain, reinforcing the role of a more inflammatory microbiota in the evolutionary origins of obesity (microbiota metaflammation genotype). Taken together, we propose the integration of host and microbiota genotypes and call it the host/microbiota metaflammation genotype hypothesis.

by the gut microbiota and its effect on the obesity-inflammation axis. Research has shown that dietary and microbial factors influence specific fatty acid isomer levels in the gut, which modulate specific immune cells called CD4+ intraepithelial lymphocytes (284). These findings provide a new role for bacterial fatty acid metabolism in maintaining the immunological balance in the gut by modulating the relative number of CD4+ T cells that are CD4+ CD8αα+. These studies support the notion that distinct gut microbial signatures are associated with host inflammation and obesity. Taken together with these data, we can suggest that the microbiota exhibiting these characteristics can be identified as possessing a "metaflammation genotype," which is responsible for its ability to combat infections and promote fat storage in the host effectively (Fig. 4).

COVID-19 Pandemic and the Metaflamation Hypothesis

The recent COVID-19 pandemic needs to be analyzed considering this new metaflammation hypothesis. First, it is important to mention that the pandemic of the 21st century is very different from those of previous centuries, considering the availability of vaccines and medical and hospital resources, including intensive care, which are much more advanced today. However, some data from the COVID-19 pandemic seemingly support the metaflammation hypothesis. To begin with, the recent pandemic induced an acute pronounced inflammatory response in patients followed in some of them by a milder chronic inflammatory process, which has been termed "*long COVID*." In these patients, weight gain was observed in the months following the initial episode (285-289), confirming that a nonsevere but chronic inflammatory process can lead to weight gain through the mechanisms previously described (138-146). As expected, GWAS studies conducted in this population have identified multiple SNPs associated mainly with the immune system (290-295), again indicating the connection between the immune response and the energy storage system (adipose tissue).

Additionally, it is important to highlight that patients experiencing long COVID exhibit gut microbiota dysbiosis, characterized by a significant reduction in bacterial diversity. This includes a lower relative abundance of genera known to confer protection against obesity, particularly those that produce short-chain fatty acids, such as the *Eubacterium hallii* group, *Subdoligranulum*, *Ruminococcus*,

Dorea, *Coprococcus*, and the *Eubacterium ventriosum* group (296, 297). On the other side, the relative abundance of *Veillonella*, which is a genus abundant in individuals with a high inflammatory index (298), was higher compared to controls. A recent study (299) used summary statistics from GWAS and mendelian randomization analyses, aiming to explore the association between gut microbiota and long COVID. The meta-analysis findings indicated that the genus *Parasutterella* significantly elevated the risk of developing long COVID. In this context, previous research has demonstrated a positive correlation between *Parasutterella* and both BMI and type 2 diabetes, independent of the reduced microbiome alpha and beta diversity and the low-grade inflammation typically observed in obesity (300). Taking together these data, we can suggest that the immune response to an infection is a complex process that involves the genetic architecture of the immune system and the microbiota, and epidemics may select survivors with a more robust inflammatory response that can predispose to obesity even in future generations.

In summary, we are suggesting that the evolutionary hypotheses of obesity should be enriched with microbiota genotype, and even for the drifty hypothesis (a nonadaptive scenario), microbiota modulation, mainly by environmental and dietetic factors more recently, certainly contributes to explaining the increased obesity prevalence in the past 40 years. Moreover, adding the microbiota genotype increases the scope of the thrifty, the thermogenic, and the metaflammation hypotheses in the adaptive scenario. However, it remains uncertain whether this microbiota genotype, or at least a portion of it, originated in the ancestors of obese individuals long ago and provided evolutionary benefits or if it is a more recent adaptation to our food-rich environment. Nonetheless, this microbial genotype found in obese individuals can be inherited by future generations, giving rise to a microbiota-associated thrifty, thermogenic, and metaflammation genotype.

Conclusions

Human populations in different regions have unique genetic histories influenced by founder effects, genetic drift, admixture events, and various ecological challenges. These factors have collectively contributed to the genetic architecture of humans. It is crucial to acknowledge that models of the origin of obesity cannot be categorized as adaptive or nonadaptive. The origins of obesity are complex and cannot be explained by a single theory. Both natural selection and genetic drift likely influenced the genetic framework of obesity. There is an overlap of natural selection hypotheses that are not mutually exclusive. Natural selection may have increased the prevalence of beneficial alleles for survival, whereas genetic drift randomly affected the frequencies of other alleles. The combined effects of these forces and the modulation of microbiota under different circumstances may offer insight into the ethnogeographic variation in obesity. It is well accepted now that the common forms of obesity are polygenic, and incorporating the microbiota genotype in this complex genetic architecture certainly makes it more polygenic than previously thought. Thus, uncovering the evolutionary origins of obesity requires a multifaceted approach that considers the complexity of human history, the unique genetic makeup of different populations, and the influence of gut microbiome on host genetics. Exploring these factors together will open up new avenues for understanding the genetics of obesity and its evolution.

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The authors have nothing to disclose.

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