

Opinion

Do Vertebrate Gut Metagenomes Confer Rapid Ecological Adaptation?

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During times of rapid environmental change, survival of most vertebrate populations depends on their phenomic plasticity. Although differential gene-expression and post-transcriptional processes of the host genome receive focus as the main molecular mechanisms, growing evidence points to the gut microbiota as a key driver defining hosts' phenotypes. We propose that the plasticity of the gut microbiota might be an essential factor determining phenomic plasticity of vertebrates, and that it might play a pivotal role when vertebrates acclimate and adapt to fast environmental variation. We contemplate some key questions and suggest methodological approaches and experimental designs that can be used to evaluate whether gut microorganisms provide a boost of plasticity to vertebrates' phenomes, thereby increasing their acclimation and adaptation capacity.

The Gut Microbiota as a Fuel for Acclimation and Adaptation

Many vertebrate species that we are losing as part of the so-called sixth mass extinction [1] disappear because the rapid rate of environmental change prevents them from adapting to the novel conditions [2]. Genomic adaptive processes seem unlikely to provide a rapid enough solution for the majority of terrestrial vertebrates [3], as they require many generations to take effect. Hence, most populations principally depend on phenomic plasticity for their survival [4]. Phenomic plasticity has traditionally been defined as the capacity of a single genotype to alter its expression so as to exhibit different phenotypes (see [Glossary](#)) in response to environmental pressure [5]. However, a growing body of evidence suggests that in many situations, the physical and biochemical features that comprise the phenomes of organisms are not solely produced through direct interaction between a genome and the environment. Rather, the recently introduced hologenome concept posits that the biology and evolution of complex organisms cannot be understood without the contribution of their associated microorganisms [6]. Within that context, the phenomes of complex organisms such as vertebrates would be the result of the interactions between the hologenome—that is, the sum of their own genomes and the combined genomes of their symbiotic microorganisms (the metagenome)—and the environment [7]. At the same time though, the metagenome is determined by the host's phenome (e.g., biochemical composition of the gut, dietary behavior) and the external environment (e.g., microbial availability) [8,9], as well as microbial interactions that might be independent from host and environmental factors [10]. Examples of this complex circular relationship include how feeding behavior affects microbiota composition, while microbiota composition influences feeding behavior [11], or how the immune system affects microbiota composition and vice versa [12].

Trends

Recent studies highlight the large impact that gut microbiota has on host biology.

The vertebrate gut microbiota is a plastic element that can vary considerably as a response to environmental change. This variation can influence host phenomes.

Some gut microbiota changes have been demonstrated to confer benefits to their hosts, which might yield enhanced capabilities to acclimate and adapt to the novel conditions.

Measuring the impact of gut microbiota variation on the hosts' capacity to acclimate and adapt to novel environmental conditions will be necessary to assess the transcendence of gut microorganisms in the evolution of hosts.

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Box 1. Differences between the Host Genome and the Gut Metagenome

When studying how the host genome and its gut metagenome affect the host phenotype, it is necessary to think about their different properties. From a quantitative point of view, the number of genes encoded in the gut metagenome considerably exceeds the number of genes in the host genome. For example, around a thousand different bacterial species with more than 3 million genes have been identified in the human gut metagenome. This is about 150 times more genes than the human genome [15]. However, the main difference resides in the fundamental properties of the host genomes and the gut metagenomes [56]. While the host genome is directly transmitted from parents to offspring, the host's gut metagenome is mostly acquired from the environment. However, it is worth noting that recent evidence shows the importance of pseudo-vertical transmission of microorganisms, for instance, via vaginal contact, nursing, and feeding on parents' feces [57]. In addition, the gut metagenome is a much more labile element than the host's genome, since the gut microbiota continuously changes in response to the host's physiological variations and external environmental change. For instance, the relative abundances of different gut microorganisms can change [25], new gut microorganisms (thus new genes) can be acquired from the environment [58], and genes can be transferred horizontally between gut microorganisms [59], among other mechanisms. In addition, the generation time of the gut microorganisms is much shorter than the host's, allowing for genetic evolution over shorter periods.

The most influential community of vertebrate symbiotic microorganisms resides in the gut [13]. The influence of gut microorganisms on vertebrates has been recognized for over a century [14], and with the arrival of high-throughput DNA sequencing approaches, the cataloging of their taxonomical and functional elements has exploded [13,15,16]. Recent studies have shown that gut microorganisms influence host biology much more than previously expected. For example, gut microorganisms have been shown to affect, and even condition, host metabolism [17], nutrition [18], immunology [12], behavior [19], morphology [20], and development [21]. Furthermore, external environmental variations such as changes in food source [22], food abundance [23], and environmental temperature [24] produce fast and profound variations in the gut metagenome [25], due to the different biological properties of the gut microorganisms' metagenome compared with the host's genome (Box 1).

The host's phenotype is shaped by both the host's genome and the gut metagenome, although it must be emphasized that the relative influence of the gut metagenome is not constant for every phenomic character, but depends on the phenomic domain in question (Box 2). It is notable though that recent studies have indicated a high influence of the gut metagenome in several phenomic domains that are directly involved in providing means of survival when facing rapid environmental variation. For instance, it has been shown that the gut microbiota composition affects energy intake from food [26], as well as energy storage [27], and it is an important regulator of thermal homeostasis [24]. All these processes likely play a key role when acclimating and adapting to ongoing environmental changes such as deforestation, aridification, atmospheric warming, or spread of allochthonous species (Figure 1).

Box 2. The Gut Metagenome's Influence in Different Phenomic Domains

The phenotype of an organism is the composite of its observable or measurable characters from multiple domains such as morphology, development, physiology, and behavior. Although the gut metagenome seems to either directly or indirectly influence many phenomic characters, its impact differs considerably. Here we list the phenomic domains in which considerable influence of the gut metagenome has been reported (Figure 3).

- 1. **Nutrition:** one of the best-studied phenomic domains regarding the effect of the gut metagenome. Among other processes, the gut metagenome influences the dietary energy intake [43], and allows metabolizing of otherwise indigestible carbohydrates of fiber-rich food [60].
 - 2. **Toxicity resistance:** specific gut microbial arrangements can provide hosts with the capacity to feed on toxic food [33].
 - 3. **Energy metabolism:** the gut metagenome influences energy homeostasis during external temperature and metabolic rate variations by inducing thermogenesis, increasing insulin sensitivity, and incrementing caloric intake [24,27].
 - 4. **Morphology:** external morphological characters are poorly influenced by gut microorganisms, but the gut metagenome can promote considerable changes on gut morphology [24].
 - 5. **Behavior:** gut metagenotypes adapted to high-fat diets disrupt exploratory and cognitive behaviors of hosts [11].
- The study of the impact of the gut metagenome in host phenotype is in its initial stage. Hence, the scenario depicted in this box might be modified and expanded in the future.

Glossary

Acclimation capacity: the ability of an individual to adjust its phenotype to new environmental conditions to maintain fitness or moderate its loss.

Adaptation capacity: the ability of a population or species to adjust biologically so as to accommodate environmental variation by modifying the range of variability that it can cope with.

Gut metagenome: the complete set of DNA of symbiotic microorganisms residing in the animal's gut.

Gut metagenotype: the genetic constitution of the specific arrangement of symbiotic microorganisms residing in the animal's gut in a given moment and under certain environmental conditions.

Gut microbiota: community of microorganisms residing in the animal's gut.

Hologenome: the complete set of DNA of an organism and its symbiotic microorganisms (host genome + symbiotic organisms' metagenome).

Host genome: the complete set of nuclear and organellar DNA of the host organism.

Host genotype: the specific genetic constitution of the genome of the host organism.

Metagenomic plasticity: the capacity of the gut microorganism community to change its composition (including addition or loss of microbial members and their genes, as well as changes in their relative abundances) or gene-expression pattern in response to the host's physiological changes and variations of the external environment.

-ome/-type disambiguation: while all vertebrates have a genome, a gut metagenome and a phenotype, each organism has its own genotype and exhibits different metagenotypes and phenotypes depending on genetic, developmental, and environmental conditions.

-omic/-typic disambiguation: the elements undergoing variation are the metagenome (changing from one metagenotype to another) and the phenotype (changing from one phenotype to another). Therefore, we used the terms metagenomic plasticity and phenomic plasticity, rather than metagenotypic plasticity and phenotypic plasticity.

In light of these facts, we hypothesize that the capacity of the gut microorganism community to change its composition or gene-expression pattern in response to the host's physiological changes and variations of the external environment—hereafter referred as **metagenomic plasticity**—is likely an essential factor that facilitates host acclimation and adaptation to environmental change. The microbial community's plasticity might provide the host with an even higher and more rapid phenomic plasticity than would otherwise be available either through the genome or through a static gut microorganism community alone (Figure 2). We believe this boost of plasticity might play an essential role in increasing a host's **acclimation capacity** (individual property within a single generation) and **adaptation capacity** (population or species property over multiple generations) to rapid environmental variation scenarios. Our hypothesis is grounded in a number of studies we mention in this article, which have provided glimpses of the importance of metagenomic plasticity on vertebrate adaptation. However, no study has tested the hypothesis we propose and assessed its biological relevance in an eco-evolutionary framework. As there is still a long way to go to prove that metagenomic plasticity expedites host acclimation and adaptation to environmental change, we propose three major questions that could be addressed in future studies to shed light on the likely causal relation between metagenomic plasticity and acclimation and adaptation capacity of vertebrates (see Outstanding Questions). For each of those questions, we present relevant knowledge produced to date, highlight the main limitations of hitherto employed approaches, and discuss the experimental designs and methodological approaches that could be applied to address them (summarized in Table 1).

Is Metagenomic Plasticity a Major Driver of Host Phenomic Plasticity?

It is well known that organisms exhibit different phenotypes depending on environmental conditions. Environmental factors can produce irreversible variability during development within a single genotype, and organisms can also undergo reversible phenomic variations responding to environmental conditions [28]. The study of the molecular mechanisms of phenomic plasticity has so far focused on the **host genome**, where differential gene-expression and post-transcriptional processes mediated by multiple environment-responsive hormonal and epigenomic mechanisms have been identified as key processes [29–31]. However, recent studies have identified a causal connection between different gut microbiota profiles (**gut metagenotypes**) and host phenomic variation (Figure 3), and specific microbial species have been identified as key elements in shaping host phenotypes. For example, Sommer *et al.* [27] showed that summer (active) and winter (hibernating) brown bear (*Ursus arctos*) gut metagenotypes affect the host's capacity to accumulate fat, and Chevalier *et al.* [24] reported that under cold environmental conditions, the decrease of the mucin-degrading bacterium *Akkermansia muciniphila* produces a physiological phenotype with an increased intestinal absorptive capacity. These discoveries suggest that compositional and functional variation of the gut microbiota might account for a significant part of vertebrate phenomic plasticity.

The most revealing evidence perhaps derives from gut microbiota transplants, where the gut microbiota of hosts exposed to different conditions are inoculated into receptors (usually germ-free mice), allowing measurement of the effect of the gut microorganisms on host phenomes. This is exactly how Chevalier *et al.* [24] and Sommer *et al.* [27] demonstrated that the gut metagenotype affects the energy metabolism of the host, and Bruce-Keller *et al.* [11] showed that the gut metagenotype of obese organisms disrupts the exploratory and cognitive behavior of hosts.

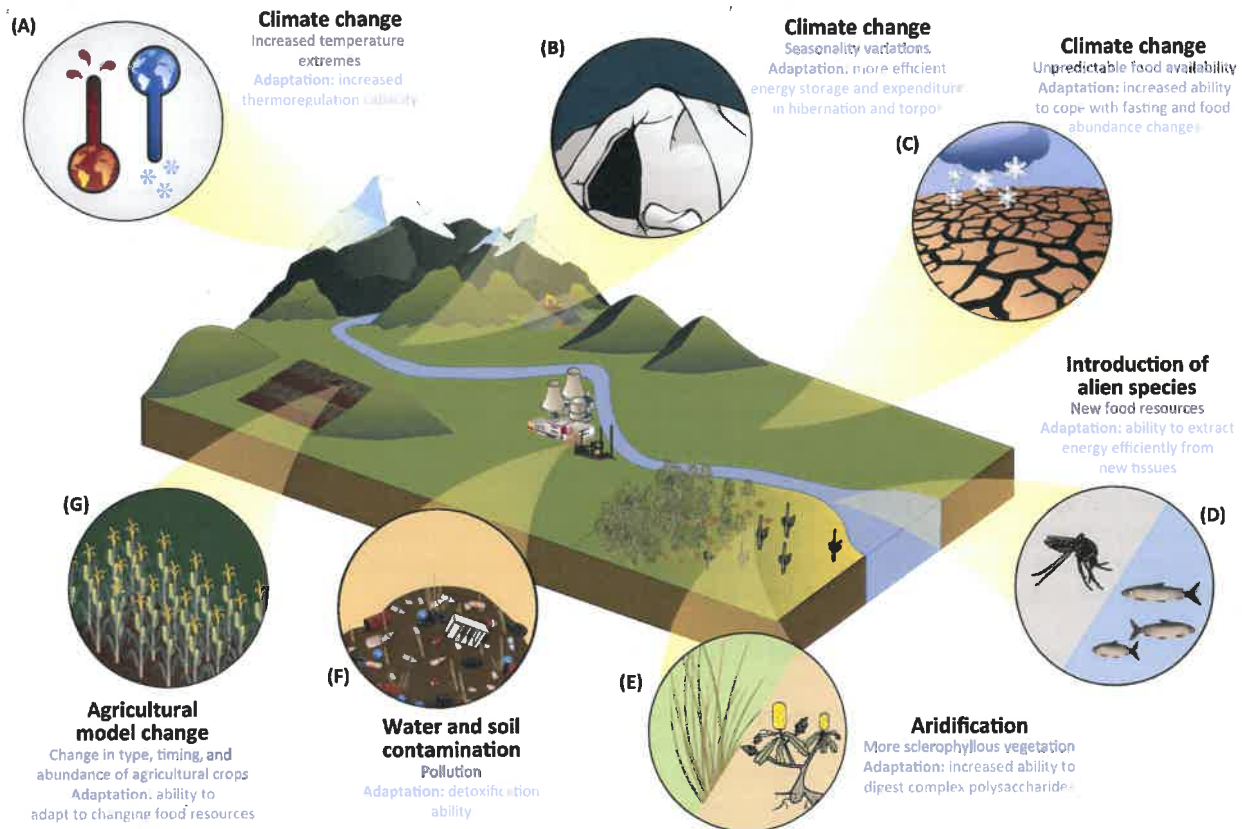
Microbiota transplants can demonstrate the effect of gut microorganisms on host phenomes, but they provide little information about mechanisms underlying phenomic variation, unless they are combined with metagenomics and other meta-omics approaches mentioned later in this paper [24]. While the broadly used metabarcoding approach provides presence-absence information about the taxonomic composition of the gut microbiota, metagenomics captures

Phenome: the complete collection of observable or measurable physical, biochemical, or behavioral characteristics of organisms, as determined by genomic, metagenomics, and environmental influences.

Phenomic character: a specific observable or measurable physical, biochemical, or behavioral characteristic (e.g., ear length, blood type, foraging range).

Phenomic domain: a set of phenomic characters related to a given biological or methodological framework (e.g., behavior, nutrition, morphology, energy metabolism).

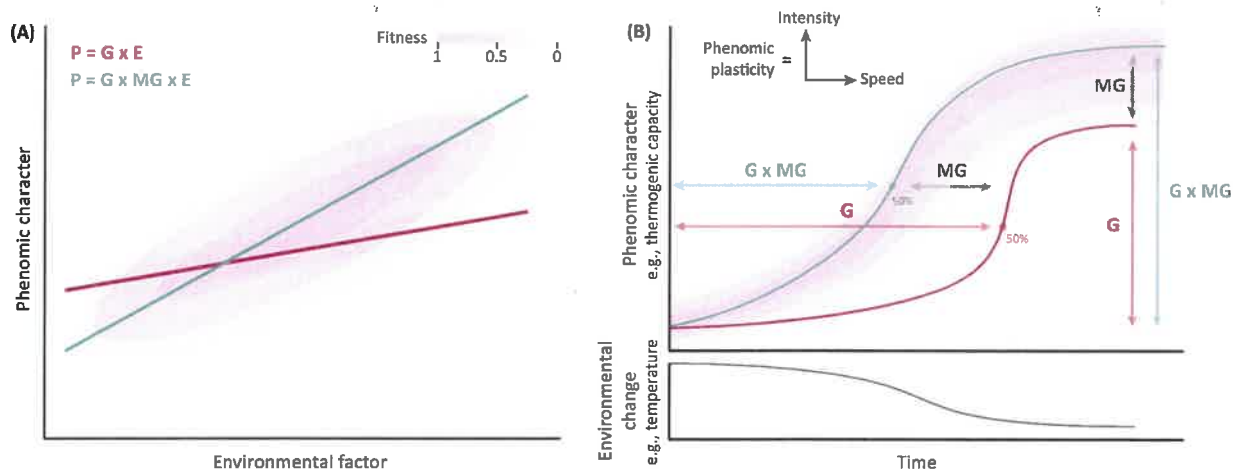
Phenotype: a specific phenome an organism exhibits in a given moment and under certain environmental conditions.



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Figure 1. Example Environmental Changes that Vertebrates Face Due to Global Climate Change, and Potential Metagenome-related Adaptations They Might Need to Develop in Order to Survive. (A) In many areas, extreme atmospheric temperatures are expected to increase. Hence, vertebrates will need to enhance their thermoregulation capacity. (B) Changes in season lengths will force vertebrates to adapt their annual biological cycles, which in case of heterothermic animals such as bears, marmots, and bats will imply modifying energy storage and expenditure dynamics. (C) Weather will become more unpredictable in many areas, modifying food availability patterns. Consequently, vertebrates might have to face longer fasting periods. (D) Because of direct human translocations or geographic shifts as a response to environmental change, many animal and plant species will colonize new areas. Consequently, native species might encounter new dietary sources that might require different digestion capacities to efficiently extract energy from the food. (E) Many areas are expected to get drier, and thereby sclerophyllous plants will be benefited. Because sclerophyllous plants contain more fibers and aromatic compounds than more tender plant species, vertebrates will need to adapt to efficiently utilize them as a food source. (F) Human activities pollute the environment. This forces vertebrates to increase their capacity to metabolize and excrete toxic compounds. (G) Many vertebrate populations rely broadly on agricultural crops for feeding. Changes in type, timing, and abundance of crops will thus force vertebrates to modify their foraging behavior. Some of the elements in this figure have been obtained and modified from the Integration and Application Network, University of Maryland Center for Environmental Science (<http://ian.umces.edu/symbols/>).

the complete gut metagenome, allowing functional profiling. The identification of specific genes can allow for uncovering metabolic pathways where the gut microorganisms are involved with a direct effect on the host phenotype [32]. For instance, Kohl *et al.* [33] showed that Mojave Desert woodrats (*Neotoma lepida*) have an increased capacity to ingest toxic plants compared with their conspecifics from the Great Basin Desert, because they have developed a gut metagenome that harbors many genes associated with the metabolism of aromatic compounds, which appear responsible for enabling them to digest plant toxins. Although gene abundance is extensively used as a proxy for the importance of such genes in the metabolic processes carried out by the gut microbiota, microbial gene abundance does not necessarily mirror gene expression [34]. Furthermore, environmental variation might lead to changes in microbial gene-expression levels without altering the taxonomic composition of the gut microbiota, a



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Figure 2. Graphical Representations of the Hypothetical Scenario Where the Combined Effect of the Host's Genome and the Gut Metagenome Confers Higher Phenomic Plasticity Than the Host's Genome on Its Own. E = environment; G = host genome; MG = gut metagenome; P = phenome. Fitness is represented with the pink background. (A) Phenomic plasticity represented as a simple reaction norm, where the slope of the line indicates the degree of plasticity. The steeper slope of the $G \times MG \times E$ model allows higher fitness across a given environmental gradient. (B) Graphical representation where two components of phenomic plasticity, namely, intensity (vertical axis) and speed (horizontal axis), are considered. Here, the joint effect of the genome and the gut metagenome allows reaching a higher fitness state as a relatively quick response to the environmental change, while the sole effect of the genome confers a slower adaptation and only reaches a lower fitness state. The horizontal axis highlights the importance of speed of phenotypic change under fast environmental variation. The joint effect of the genome and the gut metagenome allows a faster phenomic change, while the slow pace of phenomic change achieved through the genome alone drives the phenomic change outside the minimum fitness values, which implies death or extinction. Note that this figure represents one of the multiple possible scenarios. The relations between the gut metagenome, phenotypic plasticity, and fitness could be different, including neutral or negative effects.

phenomenon that is undetectable with DNA-based approaches [35]. Thus, metagenomics should ideally be complemented by meta-omics approaches such as metatranscriptomics (sequencing and analysis of RNA transcripts), metaproteomics (analysis of peptides), and metametabolomics (study of metabolites) [36]. These state-of-the-art approaches are still relatively expensive and require complex bioinformatics pipelines, but they render it possible to measure the activity of functional networks between the gut microbiota and the host. Thereby, they might facilitate uncovering the functional variation of the gut microbiota that metagenomics studies are not able to measure.

Does Metagenomic Plasticity Increase Host Acclimation Capacity?

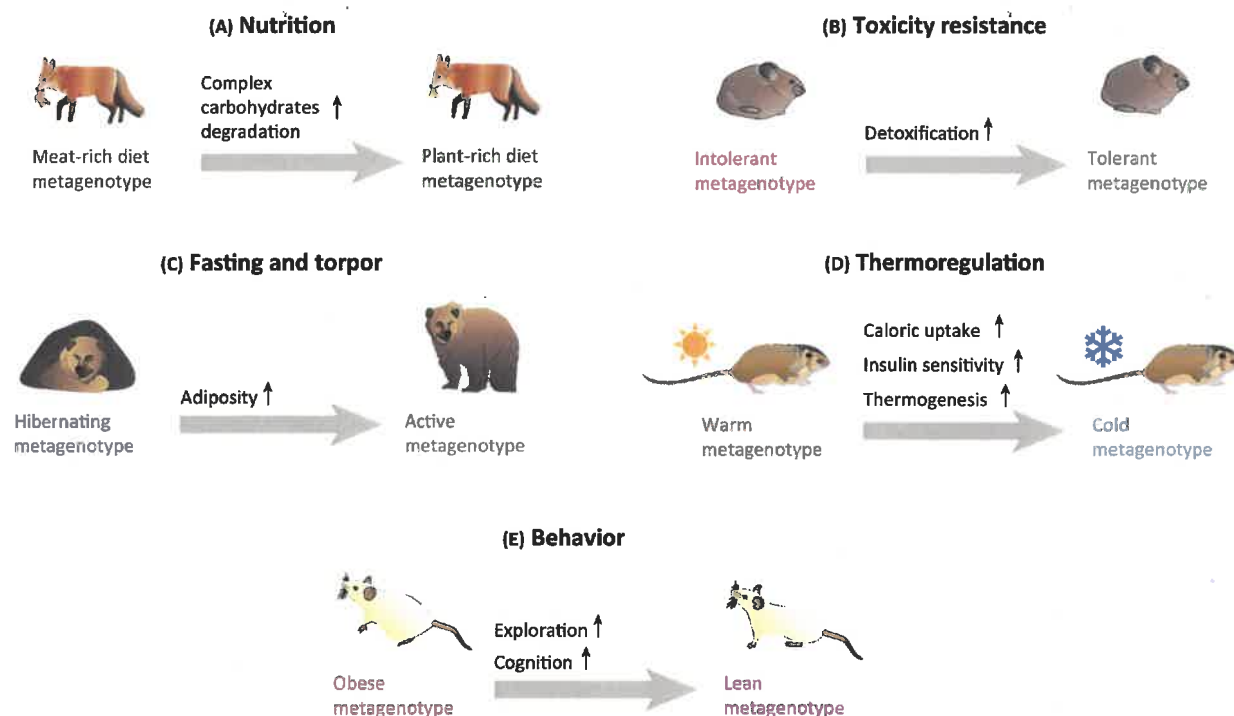
Global change has increased the incidence of fast environmental change events that can occur within the timescale of a single generation, such as habitat variation or extreme climatic events [37]. Given that the capacity of organisms to acclimate to novel conditions basically depends on their phenomic plasticity, we hypothesize that metagenomic plasticity might increase their acclimation capacity under such scenarios (Figure 4, Key Figure). *Prima facie*, a plastic gut microbiota might seem deleterious as recent research has shown that the gut microbiota community of healthy humans tends to remain stable in the long term [38]. However, metagenomic plasticity should not be understood as the result of a continuously fluctuating uncontrolled gut microbiota, but as the capacity of a gut microorganism community to change in response to stimuli from the host and the external environment. Research has demonstrated that the gut microbiota can be quickly and profoundly altered when the external environment changes [39,40].

Two main premises have to be fulfilled if metagenomic plasticity is to increase host's acclimation capacity. First, the effect of the new microbiota arrangement occurring in response to novel environmental conditions must benefit the host, since microbial community variations could also

Table 1. Summary of the Hitherto Produced Evidence and the Methodological Approaches Suggested to Answer the Proposed Questions.

Questions	Experimental evidence	Methodological approach
Is metagenomic plasticity a major driver of host phenomic plasticity?	<ul style="list-style-type: none"> ✓ Different gut metagenotypes yield different host phenotypes. × The relative influence of gut metagenomes on phenomic variations is not evaluated. 	<ul style="list-style-type: none"> • Measurement of phenomic variation after transplants of gut microbiotas acclimated to specific environmental conditions • Identification of molecular pathways involved in the phenomic variations using meta-omics approaches
Does metagenomic plasticity increase host acclimation capacity?	<ul style="list-style-type: none"> ✓ Several studies suggest a positive answer. × No studies directly designed to test the hypothesis have been so far published. 	<ul style="list-style-type: none"> • Environmental stress experiments followed by microbiota transplants • Physiological measurements after microbiota transplants • Survival and fitness measurements after microbiota transplants
Can microbiota rearrangements be beneficial for the host?	<ul style="list-style-type: none"> ✓ Certain microbial arrangements provide benefits to their hosts. × The actual biological transcendence (fitness and survival) of the physiological processes triggered by gut microorganisms is broadly unknown. 	
Do microbiota rearrangements occur fast enough so as to counteract the speed of environmental change?	<ul style="list-style-type: none"> ✓ Gut microbiota profiles can change in few hours or days. × Whether the intensity and speed of gut microbiota variations are enough to counteract rapid environmental change is unknown. 	
Does metagenomic plasticity increase host adaptation capacity?	<ul style="list-style-type: none"> ✓ A few examples suggest so. × No studies specifically designed to test the hypothesis have been so far published. 	<ul style="list-style-type: none"> • Comparative longitudinal studies between closely related organisms that live in different environments, ideally covering multiple generations
Is metagenomic plasticity principally determined by host's heritable phenomic characters?	<ul style="list-style-type: none"> ✓ Gut microbiota composition is partially driven by host's heritable phenomic characters. × The extent to which heritable phenomic characters drive metagenomic plasticity is unknown. 	
Does metagenomic plasticity vary across individuals, populations, or species?	<ul style="list-style-type: none"> ✓ Gut metagenomic composition varies across individuals, populations, or species, thus the same could be expected to occur with metagenomic plasticity. × Actual evidence of metagenomic plasticity variations is restricted to a few studies. 	
Is metagenomic plasticity a major evolutionary strategy?	<ul style="list-style-type: none"> ✓ Organisms adapted to heterogeneous environments tend to exhibit higher phenomic plasticity. × No comparative studies of metagenomic plasticity have been hitherto published. 	

have neutral or negative effects [41]. So far, very few studies have measured the actual benefit that gut microbiota rearrangements provide the host [24,27,42,43]. Instead, due to methodological difficulties, most studies still rely on correlative data and thus can only speculate about possible benefits [39,44]. To test the hypothesis, we propose that it is necessary to measure the



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Figure 3. Graphical Summaries of Phenomic Variations Produced by Changes in Gut Microbiota under Different Environmental Conditions. (A) The consumption of diets composed of animal or plant products alters the microbial community structure. The metagenotype acclimated to plant-rich diet provides improved capacity to degrade complex carbohydrates. This study was conducted on humans, but could be extended to other omnivorous organisms [22]. (B) Desert woodrats (*Neotoma lepida*) that have been in contact with toxic plants have developed a toxicity-tolerant metagenotype that provides them with enhanced detoxification capacities of toxic plant compounds [33]. (C) The summer and winter gut metagenotypes of brown bears (*Ursus arctos*) are different. The former fosters energy storage by promoting adiposity [27]. (D) Cold exposure produces compositional and functional variations in the gut microbiota, and the cold-acclimated metagenotype provides enhanced caloric uptake, insulin sensitivity, and thermogenesis compared with the warm-acclimated metagenotype [24]. (E) The metagenotypes of lean and obese mice affect the behavior of hosts. The obese metagenotype fosters more active behavior and enhances the cognitive abilities [11]. Some of the elements in this figure have been obtained and modified from the Integration and Application Network, University of Maryland Center for Environmental Science (<http://ian.umces.edu/symbols/>).

actual effect of observed molecular variations in host physiology and health in response to metagenomic variation. Global physiological measurements such as metabolic rate or body mass variation after microbiota transplants, or more detailed analyses of the production, assimilation, or excretion of certain metabolites are some of the approaches that can be used for this task. The ultimate goal would be to address whether metagenomic plasticity confers higher fitness on the host, which could be assessed by measuring fitness indicators such as survival or reproduction success [33].

The second issue is whether the microbiota changes occur fast enough. The gut microbiota is generally portrayed as a plastic element that can undergo rapid variation in the scale of days or weeks [25]. However, since the mere variation of the gut metagenome does not imply benefits to the host, we advocate replacing the descriptive question 'How plastic is the gut microbiota?' with the hypothesis-driven question 'Is the gut microbiota plastic enough for a certain goal?' In this case, the goal is the ecological acclimation of the host. While several examples of metagenomic changes that fulfill host's needs have been reported [24,33], to the best of our knowledge, no study designed to assess the speed of variation of the gut microbiota in response to environmental change has been published. Consequently, we do not know whether the time

Key Figure

Vertebrate Gut Microbiota and Their Potential Roles in Acclimation and Adaptation to Environmental Change

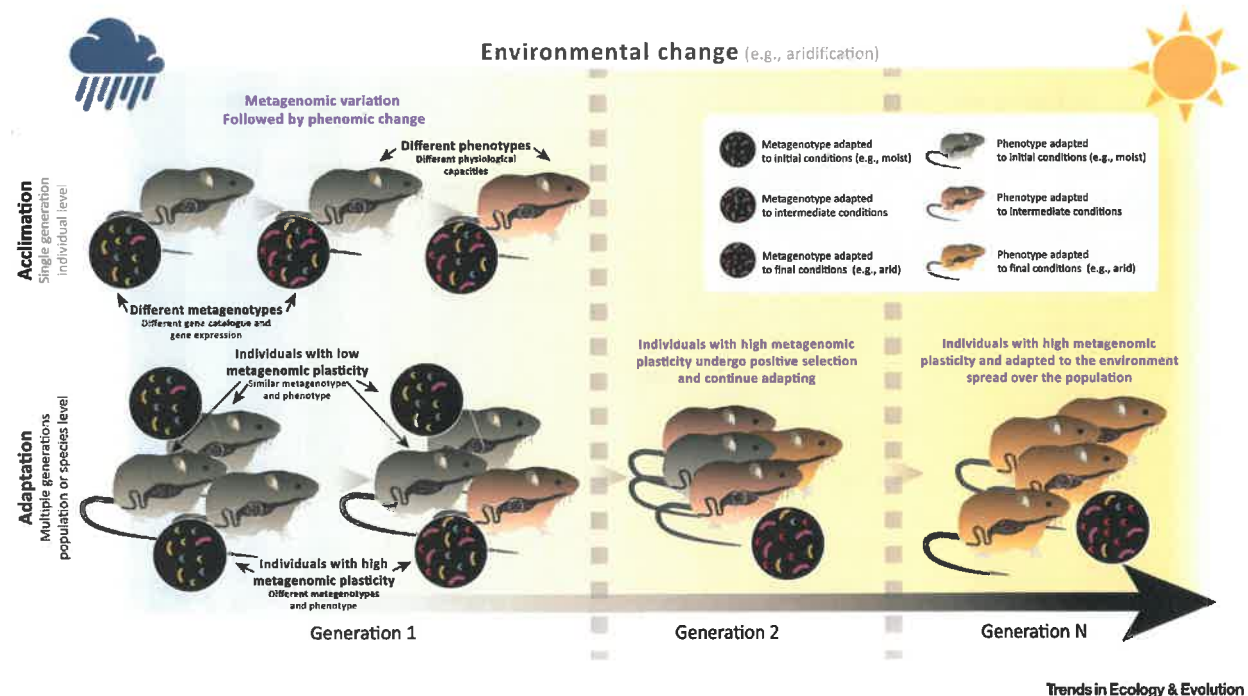


Figure 4. Acclimation is a phenomenon that occurs at the individual level within a single generation. We propose that environmental change might trigger gut metagenomic variation yielding a new host phenotype that is acclimated to the new environmental conditions. Adaptation is a population or species-level phenomenon that occurs across multiple generations. Our hypothesis posits that individuals with higher metagenomic plasticity might have enhanced capacity for developing a phenotype adapted to the new environmental conditions. Those individuals would undergo positive selection and continue to adapt. Eventually, individuals with high metagenomic plasticity that are adapted to the new environment would spread throughout the population.

needed to get the most beneficial microbial taxonomic and functional profiles might be fast enough to counteract the speed of environmental variation. For instance, if a vertebrate is forced to endure increased periods of fasting, the shortage of food might drive variation in the host gut metagenome due to the selective pressures that starvation induces on the gut microbiota [23]. However, those selective forces might be antagonistic to other pressures produced by the host or other gut microorganisms, which might delay or prevent the development of a gut metagenome that could eventually provide the host with enhanced ability to cope with food scarcity. We know that metagenomes fluctuate across seasons; for instance, the gut microbiota of giant pandas (*Ailuropoda melanoleuca*) undergoes large variations as environmental factors fluctuate [39], and the summer and winter microbiotas of hibernating bears (*U. arctos*) are different [27]. However, no study has yet required species to acclimate to completely new environmental conditions while measuring the contribution of the gut microbiota variations in the process. Environmental stress experiments coupled with microbiota transplants could be an appropriate approach to measure the intensity and the speed of the beneficial gut microbiota variations. Animals could be exposed to gradually changing environmental conditions (e.g., from tender to

sclerophyllous vegetation) at different speeds, and microbiotas developed at different points of the experiment transplanted to receptors kept at initial conditions. By comparing the performance (e.g., physical condition variations) of microbiota receptors with control individuals at certain conditions of the environmental gradient, the effect of gut microorganisms could be unveiled.

Does Metagenomic Plasticity Increase Host Adaptation Capacity?

The temporal scale of many environmental variation processes, such as climate warming or aridification of certain areas, spans multiple generations of vertebrate organisms. However, these processes also seem to occur too fast to allow genomic adaptation [3], and thus the role of phenomic plasticity is pivotal in these cases. Although plasticity has its limits and costs [45], theoretical models and experimental data show that changing environments generally drive positive selection on highly plastic phenomes [46], because they are more likely to develop the phenotype providing higher fitness under novel conditions than less flexible phenomes. The same could be applicable to metagenomic plasticity, with plastic gut microbiotas allowing new microbial arrangements that provide higher adaptation capacity under novel environmental conditions. Under scenarios where metagenomic plasticity provides net fitness gains rather than costs, it is reasonable to hypothesize that this plasticity might be favored by natural selection (Figure 4). The previously mentioned Mojave Desert woodrats have developed a gut metagenome that allows them to consume toxic plants. Metagenomic plasticity provided them with an enhanced adaptation capacity to the environment [33], since switching from intolerant to tolerant phenotypes would probably take much longer, or would not be possible, without metagenomic plasticity. Those individuals with a higher metagenomic plasticity that allowed the inclusion and proliferation of toxin-degrading bacteria in their gut microbiota were likely more successful than individuals with a lower plasticity.

If positive selection on metagenomic plasticity is to influence the evolutionary process, the following are also prerequisites: (i) metagenomic plasticity should principally be determined by the host's heritable phenomic characters, and (ii) these characters should vary across organisms. Knowledge about the heritability of the specific factors that determine metagenomic plasticity is limited, since most studies to date have focused on gut microbiota composition rather than its plasticity. However, we know metagenomic composition largely depends on phenomic characters encoded in the **host genotype** [47,48]. For instance, recent studies have shown that the presence or absence of certain gut proteins encoded by the host genotype modulates the composition, diversity, and function of the microbiota [49,50]. Hence, it seems reasonable to postulate that host genetics might also regulate metagenomic plasticity to a certain degree, via similar regulation mechanisms. The gut microbiota can also vary depending on behavioral characters of the host with a considerably more complex genetic background, among which dietary habits [51] and social behavior [52] play a major role, suggesting that behavior should also be accounted for as a likely determinant of the metagenomic plasticity. Nevertheless, metagenomic plasticity might also be conditioned by factors that are not directly related to the host's heritable phenomic characters. Experimental evidence shows that the previous contact with a given environmental condition is an important factor providing metagenomic plasticity [53]. In addition, the already established gut microbiota conditions the acquisition of new taxa and, besides, the relationships between different species can also condition the replication of others [54].

The second prerequisite when extrapolating the importance of the metagenomic plasticity to the evolutionary framework is whether metagenomic plasticity differs among individuals, populations, or species. If so, it would imply that certain organisms could be selected for at the detriment of others. Although empirical evidence of differential metagenomic plasticity is still scarce, sex-related [55], population-dependent [53], and interspecific [23] differences in

microbiota variations responding to external stimuli have been reported. This variation is also essential to identify the factors underlying metagenomic plasticity. To address both questions, cross-sectional studies (i.e., samples obtained from different populations at one specific point in time) should be replaced by comparative longitudinal experiments (i.e., repeated observations over long periods), where compositional and functional changes of the gut metagenome as a result of environmental variation could be measured in cohorts with different genetic, behavioral, or historical features.

The ultimate question is whether developing higher metagenomic plasticity is a major evolutionary strategy or not. If plastic metagenomes were beneficial under highly heterogeneous environments, we would expect vertebrates in variable environments to carry more dynamic gut microbiotas than animals in very stable ones (e.g., temperate vs. tropical environments). These predictions could be tested by analyzing the metagenomic plasticity of phylogenetically closely related species or populations living in areas with different environmental variabilities.

Concluding Remarks

In recent years, researchers have mainly focused on the co-evolutionary relations between hosts and their gut microbiota, while the role of the gut microbiota on host phenomic plasticity as well as acclimation and adaptation capacity has been largely unexplored. Recently produced preliminary evidence suggests that a causal link between the dynamism of gut microorganism communities and the adaptation capacity of hosts might exist. Thus, we firmly believe that research effort should be allocated to this topic to delineate the specific connections between the gut microbiota variations and the host's physiology and fitness. This would improve our understanding of the contribution of gut microorganisms in the acclimation and adaptation processes of vertebrates to fast environmental variation such as the ongoing global change. In addition, it is necessary to investigate the degree to which metagenomic plasticity is ruled by host genetics and behavior, gut microorganisms' interactions, and environmental factors. Finally, most studies have hitherto investigated model organisms such as humans and mice, but the overwhelming variation of natural processes lies outside the realm of the laboratory and model organisms. Thus, we believe that future studies need to include wild vertebrates, and should also embrace nonmammalian taxa to determine the relevance of metagenomic plasticity on the ecology and evolutionary biology of vertebrates.

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Outstanding Questions

We hypothesize that there is a direct relationship between the degree of plasticity of the vertebrate gut metagenome and the ability of the host to acclimate and adapt to some rapid environmental changes. To test this hypothesis, and assess its ecological and evolutionary transcendence, it will be necessary to answer the following questions:

Is metagenomic plasticity a major driver of the host's phenomic plasticity? Recent studies have shown that the genomic content of gut microorganisms (gut metagenome) contributes to the shaping of the phenome of vertebrates. However, the role of metagenomic plasticity in the phenomic plasticity is still not clear.

Many environmental variations occur within the timescale of a single vertebrate generation, meaning that organisms have to acclimate quickly in order to survive. In that regard, does metagenomic plasticity increase the host acclimation capacity? Given that phenomic plasticity is the main driver of acclimation, metagenomic plasticity might also contribute to enhance the capacity of organisms to acclimate to novel conditions.

The scale of other environmental variations spans multiple generations of vertebrate organisms. Under this scenario, does metagenomic plasticity play a considerable role in providing enhanced adaptation capacity to populations or species? And if so, is metagenomic plasticity favored by natural selection? Changing environments generally induce positive selection on plastic phenomes. Hence, metagenomic plasticity also represents a trait that could be under selection pressure.

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