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Resource conflict and cooperation between human host and gut microbiota: implications for nutrition and health

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Diet has been known to play an important role in human health since at least the time period of the ancient Greek physician Hippocrates. In the last decade, research has revealed that microorganisms inhabiting the digestive tract, known as the gut microbiota, are critical factors in human health. This paper draws on concepts of cooperation and conflict from ecology and evolutionary biology to make predictions about host–microbiota interactions involving nutrients. To optimally extract energy from some resources (e.g., fiber), hosts require cooperation from microbes. Other nutrients can be utilized by both hosts and microbes (e.g., simple sugars, iron) in their ingested form, which may lead to greater conflict over these resources. This framework predicts that some negative health effects of foods are driven by the direct effects of these foods on human physiology and by indirect effects resulting from microbiome–host competition and conflict (e.g., increased invasiveness and inflammation). Similarly, beneficial effects of some foods on host health may be enhanced by resource sharing and other cooperative behaviors between host and microbes that may downregulate inflammation and virulence. Given that some foods cultivate cooperation between hosts and microbes while others agitate conflict, host–microbe interactions may be novel targets for interventions aimed at improving nutrition and human health.

Keywords: microbiome; evolution; microbial ecology; cooperation; conflict; Western diet

Introduction

Conflict and cooperation are pervasive throughout the biological world, affecting interactions among family members, relationships between unrelated individuals, and interactions between hosts and their microbial inhabitants.[1] In the human body, conflict and cooperation between genetically different cells can profoundly affect human health by contributing to cancer—in the case of mutations leading to heterogeneous cell populations that exploit the host[2]—and to diseases during pregnancy, as in the case of maternal–fetal conflict underlying preeclampsia.[3] These diseases result from genetic conflict within the host, driven by cells with different genomes that have divergent fitness interests. In some cases, the divergent fitness interests lead to the evolution of complex adaptations for both manipulation and resisting manipulation, as has been proposed for placental invasion of the uterine arteries during pregnancy.[3]

Interactions between the host and its microbiota range from mutualistic (mutually beneficial) to parasitic (harmful to the host and beneficial to the parasite). Microbes benefit their hosts by producing energy and vitamins and excluding pathogens; hosts contribute to this cooperative relationship by providing resources for microbes and maintaining microbial habitat.[4–6] Yet, the gut microbiota also contributes to malnutrition, infectious disease, and chronic inflammatory, metabolic, and cardiovascular diseases.[7,8] The nature of these relationships between host and microbes can vary dramatically even within a single specific microbial species or strain and is also dependent on the local conditions within the host.[9] Genetic conflict exists between hosts and resident microbes because they typically do not share genes (or common fate) that could

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function to align fitness interests.[10] As is often the case with unresolved conflict, escalation of responses and counterstrategies often exacerbates conflict, resulting in negative outcomes for the parties involved.

A foundational principle of ecology is that access to resources (food, habitat) shapes the nature of interactions between organisms. Competition for access to limited resources is a potent selective pressure. In the ecology literature, antagonistic encounters with direct competition for access are described as exploitation (also known as scramble), while indirect competition is referred to as interference competition (also known as contest).[11] Interference competition involves the use of limited resources without other harm, while exploitation competition does entail inflicting additional harm to the competitor. Within the body ecosystem, microbial populations engage in both exploitation and interference competition with one another over access to preferred habitat as well as nutrients.[12] However, these interactions are not only characterized by resource competition but also by interspecies resource sharing in the form of metabolic cross-feeding, in which the end product of metabolism for one species is used by a different species.[13] In addition, resource exchange between multicellular species and bacteria is well documented for some taxa, including insect species.[14] These relationships have coevolved tight associations of mutual dependence: symbiotic bacteria are an integral part of the host phenotype and are required for normal development, and in some bacteria, the capacity to live outside the host ceases; such species are known as obligate symbionts.[14]

The history of association between the human host and its microbiota predates not only humans but also all vertebrates.[15] This long history of symbiosis between microbes and multicellular organisms is evidenced by the phylogenetic divergence of gut-dwelling microbes in vertebrates and invertebrates from those that colonize gut-similar habitats outside the body.[15] Gut microbes exhibit tremendous diversity at strain- or species-level divisions, with markedly lower diversity at the division level compared to free-living microbes in similar habitats. Such patterns of taxonomic distribution suggest that gut niches were colonized by relatively few pioneer organisms whose descendants have diverged within the gut niche to a vast array of closely related gut-dwelling strains.[16] The extent to which human and microbiome relationships can be characterized as mutualistic or even coevolved remains unresolved,[17] yet useful predictions can be made about the nature of current interactions on the basis of the payoff structure of the "games" that hosts and microbes are playing[1] when they consume certain foods. In particular, when hosts and microbes consume foods that can be utilized by either the host or microbes, which we term *conflict foods*, this can lead to a zero–sum interaction characterized primarily by conflict over resource utilization. In contrast, other foods can be best utilized if they are cooperatively processed, leading to nonzero-sum interactions between host and microbes.

Hosts provision and tolerate gut microbes in exchange for energy and protection

The assembly of the complex ecosystem in the gut of each human host begins at birth. In vaginal births, this process is initiated by vertical transmission, through ingestion of microorganisms as the neonate passes through the birth canal.[18] The establishment of pioneer species is aided by provisioning of the infant microbiome by human mothers. Breastfeeding provides maternal milk carbohydrates that have been naturally selected to feed mutualist microbes in the infant's microbiota.[19] As a source of nutrition and microbes, breastfeeding is also credited with reducing infant mortality and limiting the risk of chronic diseases later in life.[20] Breastfed infants have a Bifidobacteria-dominated microbiota that induces a tolerogenic immune response in the gut, while reducing the risk of pathogen colonization, infection, and gut inflammation.[19,20]

The growth of these protective Bifidobacteria in the infant gut is fueled by human milk oligosaccharides (HMOs), which comprise 5–10% of the energy content of milk and are the second most abundant milk carbohydrate after lactose.[21] HMOs cannot be digested by humans and require microbial fermentation to produce absorbable energy in short-chain fatty acids (SCFAs). In addition, sialylated oligosaccharides in breast milk prevent pathogen adhesion to the epithelial cells, thereby preventing infection.[22] The lipid fraction of breast milk also contributes to its antipathogen properties. Milk triglycerides are converted to antimicrobial fatty acids and monoglycerides by infant lipases that directly kill viral, bacterial, and protozoan pathogens, discouraging the growth of harmful microbes. These

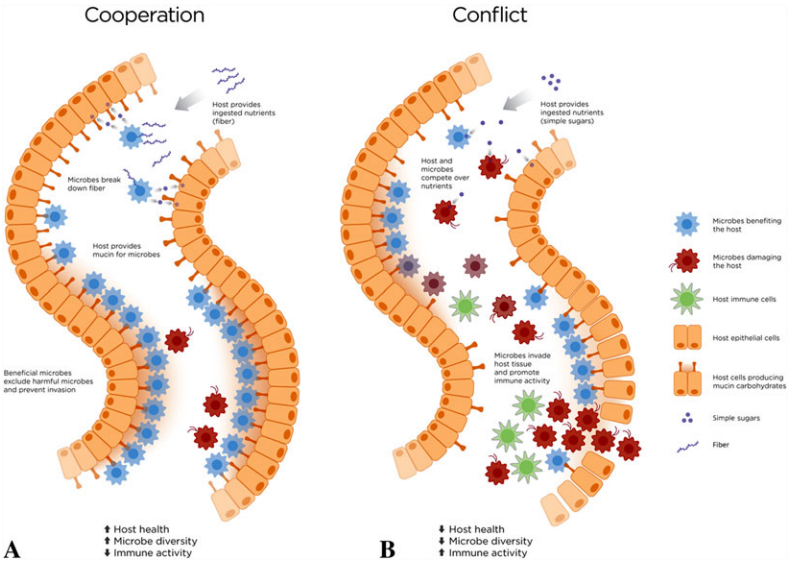

Figure 1. (A) Cooperation in nutrition occurs with reciprocal feeding of microbes with dietary fiber, yielding short-chain fatty acids that are absorbed by intestinal cells as energy. Cooperative feeding also occurs when intestinal epithelial cells secrete mucus that supports the growth of mucus foragers. The presence of mucus foragers and a healthy mucus barrier reduces pathogen attachment to epithelial cells, a precursor to invasion of host tissues. (B) Conflict can be expected when different genetic entities have access to resources that they compete over. Simple carbohydrates, unlike fiber, can be utilized by both host and microbiome, resulting in conflict over these resources. Conflict also occurs when foods interfere with cooperative feeding of microbes at the mucus barrier. These conflicts generate host inflammation and adverse changes in microbes that occur when mucus is thinned by diets high in simple sugars, fat, and emulsifiers in processed food.

pathogenic microbes are thus excluded from the beneficial nutrients in the milk, making those nutrients available for the host and to fitness-enhancing microbes.

Host glycan provisioning to microbes does not stop when breastfeeding ends, because glycans produced by intestinal epithelial cells share structural homology with HMOs, and gut microbes utilize similar pathways to digest them.[23] The intestinal epithelium is covered with a gel mucus, consisting of a protein core covered with mostly O-glycosylated carbohydrate chains.[24] In humans, O-glycosylated mucins have been proposed to feed specific commensal bacteria.[25] In return, commensal bacteria produce SCFAs, which allow the host to recover some of the energy spent on mucin manufacture.[26] Hosts also benefit from this mutualistic relationship when commensal bacteria occupy glycan-binding sites in mucus and prevent pathogens from penetrating the mucus layer.[24]

Microbes provide fiber digestion services

A mutually beneficial relationship between the human host and its microbiota has been well described for the digestion of dietary polysaccharides (fiber), which contain energy that is inaccessible to the host without fermentation by the fibrolytic (fiber-degrading) microbial community (Fig. 1A). Plant polysaccharides are converted to SCFAs by colonic fermenters, including acetate, propionate, and butyrate. SCFA absorption in the colon is estimated to provide between 5% and 10% of daily energy requirements in humans.[5] These species have been argued to allow dietary flexibility in human hosts by releasing them from genetic accommodation for the digestion of new plant foods.[27,28] The benefit of fibrolytic species is not limited to additional energy extraction. Some of these microbes also constrain the growth and invasiveness of pathogenic microbes by occupying ecological niches in the gut or even producing factors that control pathogenic microbes,[6] thereby reducing the costs to the host of engaging a strong immune response.

Low overlap in resource use has been argued to be an important factor in the development of mutualisms.[29] Since humans lack the capacity to degrade complex dietary fiber without microbial

assistance, competition with microbes over this resource is minimal. In mammalian evolution, fiber-degrading microbes are thought to be a prerequisite for the transition to herbivory,[15] suggesting that low resource competition may have characterized this initial association. The emergence of resource provisioning in the absence of genetic kinship may have been initiated incidentally, as a byproduct benefit for the host from the typical metabolism of the microbe.[30] Ongoing association between partners can select for adaptations that reinforce mutualism. Vertical transmission can reinforce mutualistic associations if symbionts lose the capacity to survive outside the host ("symbiont capture").[31] Although fibrolytic species are not "captured," their capacity to colonize additional hosts is somewhat limited by adaptation for the relatively stable gut-specific environment.[15] An obligately anaerobic lifestyle and a lack of spore-forming capacity maintain mutualism by reducing horizontal transmission opportunities.[32] Hosts may also evolve mechanisms that restrict the transmission opportunities for these beneficial symbionts.[33] Vertical transmission dependency reinforces mutualism by coupling the fitness interests of the host with its microbiota: colonization of new hosts is dependent upon the fitness of the current host, in the same way that opportunities for horizontal transmission permit the evolution of virulence and pathogenesis.[34]

Microbes and hosts compete to utilize and sequester iron

Competition for nutrients can favor strategies to limit competitor access, including sequestration and monopolization. These strategies are targeted toward growth-limiting substrates used by pathogens as well as hosts. For example, free iron is sequestered by the host by the iron-binding proteins transferrin and lactoferrin. In bacterial pathogens, such as *Neisseria meningitidis and Haemophilus influenzae*, a microbial protein involved in iron theft, called bacterial transferrin-binding protein A (TbpA), competes with human transferrin for access to this nutrient.[35] Natural selection during primate evolution has produced human-specific variation and functional adaptations in the iron-binding protein transferrin that prevent iron piracy by bacterial iron-scavenging proteins. Genomic, proteomic, and functional analyses of TbpA and transferrin are consistent with intense, ongoing selection.[35]

In the guts of breastfed infants, most iron is sequestered by the lactoferrin in breast milk. It has been suggested that this low iron environment helps establish beneficial *Lactobacillus* and Bifidobacteria that have iron-independent growth in the guts of breastfed infants.[36] *Escherichia coli* and many other Gram-negative pathogens, on the other hand, require iron for growth. In the gut, access to iron by pathogens and pathobionts results in increased pathogen growth, adhesion to intestinal epithelial cells, and invasiveness.[37–39] This suggests that early-life dietary supplementation of iron could be harmful in some cases, especially in a pathogen-rich environment. Some empirical evidence supports this prediction: in a human dietary supplementation study,[40] addition of dietary iron in Cote d'Ivoirian children resulted in a dysbiosis with decreased Bifidobacteria and increased enterobacteria, accompanied by increased intestinal markers of inflammation. Furthermore, Pakistani infants randomized for supplementation with iron along with zinc had an increase in bloody diarrhea that was attributed to an adverse effect of free iron on the microbiome.[41] Together, these results suggest that pathogen utilization of iron can lead to growth of these pathogens and subsequent inflammatory activity of the host. If the host is unable to sequester dietary iron quickly enough to prevent pathogen growth, it may become necessary for the host to mobilize an inflammatory response to keep these pathogenic microbes in check. Thus, a failure of the host to effectively compete with microbes over available iron may lead to a pathogen bloom and the subsequent escalation of conflict between host and microbiome. This suggests that excess resource availability does not necessarily reduce conflict between parties competing over it and, in fact, can escalate conflict when it provides pathogenic microbes with the ability to rapidly proliferate and pose a greater threat to the host.

Dietary fat and sugar can contribute to pathogen growth

Some fats and simple sugars are growth substrates that can be utilized by hosts as well as potentially harmful microbes. Fat in the form of exogenous long-chain saturated fatty acids can provide membrane substrates for pathogenic microbes, such as *E. coli*, reducing bacterial energy requirements.[42] Sugars are a primary carbon source that regulate growth and virulence in a variety of gut pathogens

and pathobionts.[43] For Western industrialized populations, the abundance of fats and sugars is often a greater health problem than scarcity, and overconsumption of these nutrients is associated with chronic inflammatory diseases.[44] The link between the Western diet and gut inflammation has been attributed to increased epithelial attachment of gut pathogens,[45] dietary alteration of mucosal glycosylation,[46] and modulation of regulatory T cells resulting from dysbiosis and microbial metabolism.[47] These mechanisms may explain why consumption of animal fat and simple sugars confer increased risk of inflammatory bowel disease.[48,49] Diabetes and prediabetes are also influenced by diet and microbiome. In a recent study, impaired glucose control after eating simple carbohydrates was shown to depend on the composition of the microbiota;[50] increases in Proteobacteria, the phylum that includes many important Gram-negative human pathogens, contributed to higher postprandial blood glucose levels.[50] Collectively, these results suggest that diets high in fats and refined sugar can (1) fuel harmful ecological change in the gut, and (2) escalate the intensity of host countermeasures in the form of inflammation and possibly altered glucose metabolism.

Habitat competition and coexistence

In adulthood, the human body is a habitat for approximately 2 kg of microbes, numbering approximately 30 trillion. These microbes are not evenly distributed in the body; instead, the majority of the human microbiota reside in the gut, mostly in the colon. Although the immune system generally tolerates a high density of microbes in the distal gut, a similar density in the small intestine (e.g., during a bowel obstruction) causes severe illness,[51] and a few milligrams entering the circulation can cause cardiovascular collapse and death. To the extent that a healthy microbiota is corralled by the human immune system,[52] competition for limited niches and nutrients may lead to selection for invasive microbes in some circumstances. This includes both microbes invading inappropriate habitats within the gastrointestinal tract and microbes breaching the barrier of the intestinal epithelium. Several anatomic and physiologic features prevent dense microbial colonization of the small intestine. These traits likely reduce resource competition in the small intestine, which is the site of most fat and carbohydrate absorption in humans. Retrograde movement of colonic microbes into the small intestine is prevented by peristalsis causing forward transit of intestinal contents and by the ileocecal valve. Secretory IgA preferentially targets microbes in the small intestine compared to in the large intestine.[53] Lower pH, especially in the proximal intestine, along with bile acids, antimicrobial fatty acids, and antimicrobial peptides, reduces the number of microbes in the small intestine.

Mucus is another feature that prevents dense colonization of the intestinal brush border, where nutrients are absorbed by the host. The physical barrier of mucus produced by intestinal goblet cells protects the intestinal epithelium from microbial colonization and pathogen invasion[24] (Fig. 1A). The importance of an intact mucus barrier is evident during intestinal obstruction, when commensal bacteria penetrate the mucus barrier, disrupt the brush border, and directly enter epithelial cells.[54] Disruption of the mucus layer by commensal and pathogen mucinases is also a key step in the persistent colonization of pathogenic *Helicobacter pylori*[55] and during infection by *Entamoeba histolytica*.[56]

The Western diet, high in fat and simple carbohydrates, has been shown to cause mucus layer thinning and increased bacterial density at the intestinal epithelium.[45] Mucus thinning may occur when microbes starved of dietary fiber turn instead to secreted glycans,[57] or when dietary heme, the iron pigment found in red meat, promotes microbial erosion of the mucus barrier and causes epithelial damage.[58] Emulsifiers in food can also cause mucus thinning and epithelial inflammation because of detergent effects on mucus[59] (Fig. 1B). By increasing microbial colonization and translocation into tissues, these food ingredients not only interfere with the normal absorptive function of epithelial microvilli, but also generate conflicts over microbial access to privileged host habitats that are contested by the host.

Escalating conflict with the microbiome can be damaging to the host

When pathogenic microbes proliferate, invade host tissues, and prey on host cells, hosts often respond in turn by targeting offending microbes. McFall-Ngai has proposed that an important functional innovation during the evolution of the vertebrate immune

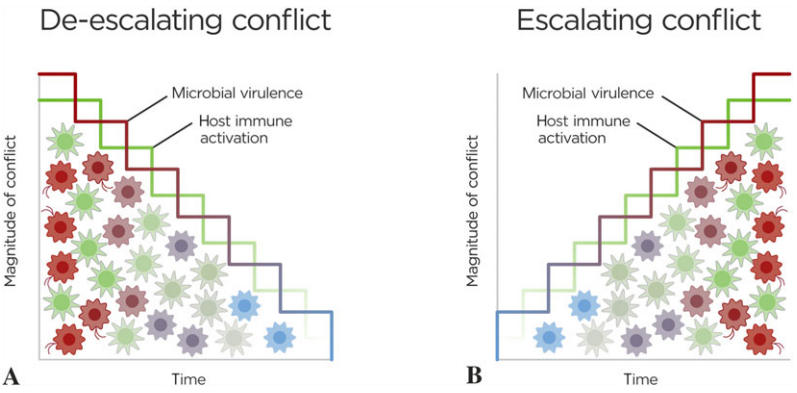

Figure 2. (A) De-escalation of conflict can reduce associated costs to both host and the microbiota. Host immune tolerance may have evolved as a strategy of managing conflict between host and microbiome, reducing costly host inflammation and microbial virulence. (B) Dangerous escalation may result from unresolved conflict between host and the microbiota, fueled by a competitive arms race between host and microbes. Immune resistance is triggered by microbial signals associated with invasion or other harm to the host. Inflammation, in turn, causes increased microbial virulence gene expression. Positive feedback perpetuating escalating conflict can result in increasing costs and a negative outcome for both partners.

system is the ability to control the microbiome.[60] The policing function of the immune system is performed by antigen-sampling dendritic cells and by Toll-like receptors (TLRs), such as TLR5, which detect flagellin, a protein involved in bacterial motility and virulence.[61] Activation of TLR5 initiates directed immunity against flagellin-expressing bacteria.[61] In the gut, secretory IgA in the intestine shows a pattern of preferential coating of potentially pathogenic Enterobacteriaceae as compared to noninvasive *Lactobacillus* in the gut.[62] This targeted immunity exerts a direct selective effect on microbial populations in the human gut, selecting against microbes and functions that are harmful to the host.

However, excessive microbiome-targeted immunity can backfire, causing harm to the host. In humans, increased flagellin-stimulated TLR5 signaling, associated with gut dysbiosis, was recently linked to adipose inflammation, obesity, and diabetes.[63] Some evidence also points to inflammation as a source of conflict escalation with microbial populations. For example, proinflammatory host molecules, such as norepinephrine and tumor necrosis factor-α, are known to stimulate the growth of bacterial pathogens.[38,64] Additionally, infection by certain pathogens can benefit from intestinal inflammation.[65] Escalating virulence and invasiveness (Fig. 2B) may be de-escalated in some circumstances by mechanisms of immune tolerance. Tolerance, in contrast to immune resistance aimed at eliminating pathogens, can be considered a damage-control strategy that has an attenuated effect on the biological fitness of microbes[66] (Fig. 2A). In the context of this cooperation and conflict framework, immune tolerance and reduced microbial virulence are a relatively cooperative détente in what could otherwise be a rapidly escalating conflict between host cells and an increasingly virulent microbiota.

From an ecological perspective, microorganisms that exploit hosts for their own benefit are considered parasites. This designation is not typically applied to facultative exploitation by commensal species inhabiting the gut, which are instead termed *pathobionts*. Yet, there are many parallels between host–parasite interactions and host–microbiome interactions, especially under conditions where there is competition over the utilization or sequestration of limiting resources in the gut. In parasite–host interactions, overlap in resource utilization is argued to predict the intensity of virulence,[67] consistent with the proposal that host–microbiome competition over simple sugars, fats, and iron contributes to poorer outcomes for host nutrition and health.

Mismatch between ancestral and modern diets disrupts host–microbe resource sharing

The Paleolithic diet hypothesis proposes that the negative health effects associated with modern Western diets result from an adaptive lag in genetic

accommodation for a novel food environment (i.e., a mismatch). This hypothesis proposes that modern humans are genetically adapted to consume the diet that was most prevalent from the advent of our genus, approximately 2.5 million years ago, to the development of agriculture, approximately 12,000 years ago.[68] In a recent meta-analysis of studies comparing the Paleolithic diet to control diets, including those advocated by the governments of two Scandinavian countries, metabolic syndrome symptoms were improved by adherence to the Paleolithic diet.[69] This diet is distinguished by avoidance of processed foods, added sugars, refined fats, and refined carbohydrates. Adoption of a Western diet was associated with negative changes to health among indigenous Australians, and readoption of the traditional diet resulted in improved health measures.[70]

The cooperation and conflict framework proposed here is consistent with some aspects of the Paleolithic diet hypothesis, as some host–microbiota conflict appears to result from dietary novelty, such as exposure to emulsifiers.[71] However, the framework that we propose is distinct from the Paleolithic diet hypothesis in that we suggest that many conflicts are not simply the result of dietary mismatch, but may be much more ancient, such as ongoing evolutionary arms races over access to micronutrients, such as iron.[35] Adverse health effects of other nutrients, such as simple sugars (monosaccharides), may reflect conflicts over access to growth-limiting nutrients, which may be substantially exacerbated by novel dramatic changes in availability of these nutrients, compared to what would have been available in ancestral foods. Thus, the modern Western diet may contribute to the escalation of conflict between hosts and gut microbes, sometimes leading to a greater degree of parasitism and inflammation. These changes likely contribute to the chronic inflammation and associated diseases linked with the Western diet.

Conclusion

A variety of diseases, from cancer to preeclampsia, result from genetic conflict within the host, because cells with different genomes can have divergent fitness interests. In this paper, we suggest that genetic conflict may also be a driver of metabolic disease and malnutrition, with divergent host and microbe fitness interests driving resource competition, virulence, and inflammation. However, cooperation also occurs between hosts and microbes despite the fact that host cells and microbial cells have different genomes. These cooperative interactions range from hosts and microbes sharing resources to microbes protecting hosts from pathogens. Cooperative behaviors among individuals who lack genetic kinship require other mechanisms to stabilize that cooperation, whether in the form of reciprocity[1] or other mechanisms that align fitness interests and promote fitness interdependence,[10] for example, through ensuring common fate. Future research on cooperative interactions between hosts and microbes should further investigate the mechanisms that promote and stabilize cooperation. These mechanisms may include conditional responses that both hosts and microbes are able to use in response to each other's behavior, which allow them to potentially play sophisticated multistep games[1] and commitment mechanisms that limit the outside options for each party, as occurs in the evolution of obligate symbiosis.[14,31] A better understanding of mechanisms underlying both cooperation and conflict between human hosts and microbes should facilitate the development of novel interventions with the potential to influence many important domains of human health.

Conflicts of interest

The authors declare no conflicts of interest.

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