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Opinion

Bacteria–Bacteriophage Coevolution in the Human Gut: Implications for Microbial Diversity and Functionality

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Antagonistic coevolution (AC) between bacteria and bacteriophages plays a key role in driving and maintaining microbial diversity. Consequently, AC is predicted to affect all levels of biological organisation, from the individual to ecosystem scales. Nonetheless, we know nothing about bacteria–bacteriophage AC in perhaps the most important and clinically relevant microbial ecosystem known to humankind – the human gut microbiome. In this opinion piece I review current research on bacteria–phage AC in *in vitro* and natural populations of microbes. I then examine the evidence and discuss the potential role of AC in driving observed patterns of intra- and interindividual variation in the gut microbiome together with detailing the potential functional consequences of such AC-driven microbial variation for human health and disease.

Towards an Understanding of the Factors Driving Microbial Diversity In the Human Gut Microbiome

The human gut is host to a diverse and complex microbial ecosystem that plays a fundamental role in health and disease [1]. Recent advances in sequencing technologies that have enabled high-resolution investigations of microbial diversity have also highlighted considerable intra- and interindividual strain variation within the human gut microbiome [2–5]. This is best exemplified by comparative analysis of individual strains of the same species of bacteria and by strain reconstruction and temporal analysis of shotgun sequence data generated from whole communities of microbes [2–4,6,7]. However, given the strain-specific nature of bacterial functionality [5,8], a better understanding of what factors drive bacterial diversification in the gut and how diversity at the strain level impacts on host health and disease is required [5,9,10]. Although several studies have considered the effects of different factors – such as diet, age, geography, antibiotic administration, and host genetics – on compositional variation of the gut microbiome [1,11–13], the effects of eco-evolutionary processes have not received much research attention. Consequently, we have little knowledge of how potentially important processes such as bacteria–bacteriophage **antagonistic coevolution (AC)** (see Glossary) could impact on the diversification and consequent functionality of the gut microbiota.

AC between bacteria and phages is defined as the reciprocal evolution of bacterial resistance and phage infectivity [14]. During coevolution, initially isogenic populations can rapidly diversify into a range of host and parasite resistance and infectivity phenotypes, respectively, with the specific type of coevolutionary interaction between bacteria and phage playing a key role in the observed outcomes of AC, including population-level diversity [14–16] (Box 1). However, in more complex scenarios (such as natural ecosystems like the gut microbiome), where multiple

Trends

Genomic studies demonstrate the importance of bacteria–phage antagonistic coevolution as a key driver of molecular evolution.

Although research into bacteria–phage AC in naturally occurring ecosystems is in its infancy it has been demonstrated in soil, marine, and arboreal environments and is likely to be a ubiquitous process.

A large proportion of variation in gut bacterial strain diversity is linked to genes associated with phage resistance evolution.

Temporal analysis of metagenomic sequence data highlights a dynamic and rapidly evolving human gut microbiome (both bacteria and phages).

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Box 1. The Dynamics of Bacteria–Phage Antagonistic Coevolution (AC)

AC interactions are typically dynamic and complex but are broadly considered as following either an **arms race dynamic (ARD)** or **fluctuating selection dynamic (FSD)** [54]. Crucially, the specific type of coevolutionary interaction between bacteria and phage plays a key role in the observed outcomes of AC, including population-level diversity [14–16]. ARDs are directional and typified by escalating defence and counter defence resulting in increasing bacterial resistance and phage infectivity ranges through time. This type of interaction can, in principle, purge a population of genetic diversity as it selects for increasingly generalist resistance and infectivity alleles that can potentially sweep through a population [55]. ARDs are constrained, however, by the costs associated with the evolution of generalism together with potential constraints on mutation supply [56]. FSDs are characterized by the continuous fluctuation of phage and bacterial genotypes with different infectivity and resistance profiles, respectively. A key feature of fluctuating selection is negative frequency-dependent selection whereby phages evolve to infect common bacterial genotypes thereby giving a selective advantage to rare bacterial resistance alleles which, in turn, rise in frequency.

ARDs have been observed in *in vitro* studies for a number of different host species and their lytic phages [14,16,17,28]. However, a single bacteria–phage combination can give rise to either dynamic whereby an ARD can give way to FSD due to costs incurred during the process, for example, host resistance range expansion [56]. The dynamic observed is also dependent on the time-scale of the time-shift experiments performed [54] and the specific bacteria–phage combination [15]. Ecological context is also of crucial importance to the dynamics and outcomes of host–parasite AC as interactions between bacteria and phage are not only contingent on ecology but the outcome of bacteria–phage AC can feed back into, and alter, the biotic and abiotic environment [18,23,26,27]. The importance of ecological context was demonstrated in a relatively recent study of *P. fluorescens* SBW25 and phi2 which were coevolved in soil microcosms [26]. Instead of the ARD normally observed during coevolution *in vitro* over similar time-frames, bacteria–phage interactions in soil microcosms were typical of FSDs.

Glossary

Antagonistic coevolution (AC): AC between a host and parasite is defined as the reciprocal evolution of host defence and parasite infectivity. AC in experimental and natural populations is typically assessed by monitoring temporal changes in host and parasite genotype frequencies and relative infection/resistance rates using time-shift assays.

Arms race dynamics (ARDs): ARDs are a form of directional selection that arise from recurrent selective sweeps for novel infectivity and resistance alleles resulting in increasing host and parasite resistance and infectivity ranges, respectively, through time.

Epistasis: the interaction between genes and their genetic background such that the effect of a mutation in a gene will depend on its genetic background. Epistasis results in mutations having different effects in combination than independently, resulting in nonadditive effects.

Fluctuating selection dynamics (FSDs): FSDs are driven by parasite-mediated selection against common host resistance alleles, whereby phages evolve to infect common bacterial genotypes, which gives a selective advantage to rare bacterial resistance alleles which, in turn, rise in frequency. This negative frequency-dependent selection leads to the continuous fluctuation of phage and bacterial genotypes with different infectivity and resistance profiles, respectively.

Pleiotropy: pleiotropy relates to the phenomenon of one gene being responsible for more than one phenotypic trait. Pleiotropic effects of resistance to phage therefore occur when a resistance mutation occurs in a gene that affects more than one phenotypic trait.

Second-order selection: second-order selection relates to selection acting on the processes that regulate genetic adaptation. Second-order selection thereby facilitates adaptation to novel environments by selecting for traits involved in enhancing mutation supply or mutational processes (e.g., recombination, mutator alleles).

populations of coevolving bacteria and phages can potentially coexist, AC will also ultimately impact on diversity at broader scales, that is, community-level diversity. Consequently, studies of bacteria–phage AC suggest that it is key to explaining many observed evolutionary and ecological phenomena at different levels of ecological organisation as well as higher order interactions within the ecosystems they inhabit [17–19]. Such phenomena include driving molecular evolution and between-population genetic and phenotypic diversification, mediating interspecific competition and cooperation, and determining niche specialization [17,18,20–22] (Boxes 1 and 2). Accordingly, the importance of AC to the ecology and evolution of microbes in natural habitats is receiving increasing research recognition [19,23].

To date, the role of phages in mediating the ecology and evolution of microbes is largely studied and reviewed from the perspective of horizontal gene transfer (HGT) [24,25]. Undoubtedly, HGT is likely to play a crucial role in microbial community diversity and function in the gut; however, this should not overshadow the exploration of a role for bacteria–phage AC in this regard. In this opinion piece I assess the evidence in support of my hypothesis that AC between bacteria and phages plays an important role in driving intra- and interindividual variation in microbial diversity in the gut microbiome. I then discuss the potentially profound consequences of bacteria–phage AC on the structure and function of the gut microbiome, including its likely impacts on host health.

Bacteria–Phage Antagonistic Coevolution in Semi-Natural Microcosms and Natural Microbial Populations

Although much of the research into bacteria–phage AC has been conducted *in vitro*, the recent extension of the *Pseudomonas fluorescens* SBW25-phi2 model system to the soil environment has provided a major step forward in moving away from the simplified *in vitro* experimental conditions that are typically employed [14,26,27]. Here, Gomez and Buckling inoculated microcosms containing soil with isogenic tagged *P. fluorescens* SBW25 and phi2 bacteriophage and periodically sampled and analysed the communities over 48 days. Bacteria–phage AC was explicitly demonstrated in these complex microbial communities [26]. Moreover, this study unequivocally showed that biotic interactions such as interspecific competition (competition between the focal host bacterium *P. fluorescens* SBW25 and other bacteria present in the