

OPINION

Harnessing the Power of Defensive Microbes: Evolutionary Implications in Nature and Disease Control

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Microbes are vital to the functioning of multicellular organisms. This realisation has fuelled great interest in the effects of microbes on the health of plant [1–3] and animal hosts [4–6] and has revealed that microbe-mediated protection against infectious disease is a widespread phenomenon (Table 1) [7–11]. Defensive microbes can protect hosts from infection by parasites (including pathogens and parasitoids) by direct or host-mediated means (Box 1). Such protective traits have made these microbes attractive candidates for disease control. In fact, defensive microbes are already being applied in phage therapy and bacteriotherapy for humans, as well as to control vector-borne and agricultural diseases (Table 2).

Despite the impact defensive microbes can have on host and parasite fitness, our current perspective of host–parasite evolution is largely based upon pairwise species interactions [12]. By combining knowledge of defensive microbe–parasite interactions at the mechanistic level with evolutionary theory, we can predict how defensive microbes might alter the evolution of host and parasite traits, such as resistance and virulence. This will not only shape how we understand patterns of host–parasite coevolution in nature but will inform our decisions in utilising defensive microbes as disease control agents. We propose three potential evolutionary implications of defensive microbes on host–parasite interactions.

Defensive Microbe–Parasite Coevolution

Microbes can be an evolvable component of host defence (Box 2). Given that they can have short generation times, high mutation rates, and large within-host population sizes, defensive microbes might adapt to parasites much faster than their longer-lived eukaryotic hosts are able [11]. Consequently, coevolution between defensive microbes and parasites could provide “real-time” disease control, whereby evolutionary changes in parasites are met by rapid reciprocal evolution in defensive microbes. For defensive microbes utilising direct mechanisms of interaction with parasites (Box 1), coevolution is likely to depend upon the population size, generation time, and gene flow of the defensive microbe population. For defensive microbes utilising host-mediated mechanisms of interaction with parasites (Box 1), coevolution is more likely to be limited by the rate of host evolution, since those mechanisms employ host-encoded traits. Exploring the potential for defensive microbe–parasite coevolution will be fundamental for predicting the long-term efficacy of microbe-mediated defence in the face of parasite evolution.

There are a variety of methods, traditionally used to study host–parasite interactions, that can be extended to look for evidence of defensive microbe–parasite coevolution. These include: (1) testing for signals of selection at the molecular level [13], (2) identifying coevolutionary



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Box 1. Mechanisms of Defensive Microbes

Direct

Hyperparasitism or predation: Microbes can parasitise or predate upon the parasite [39].

Interference competition: Microbes can produce toxic compounds, such as antibiotics or bacteriocins, that may either kill the parasite or reduce its growth rate [40–42].

Resource competition: Microbes can compete with parasites for host resources [10,42], usually via the rate of resource acquisition [40,41].

Host-mediated

Host immune-mediation: Microbes can elicit a host immune response to which the parasite is not resistant [40,42].

Host tolerance-mediation: Microbes can increase the fitness of their host during infection without reducing the fitness of the parasite by enhancing host tolerance (e.g., via tissue damage prevention and/or repair) [43,44].

Box 2. Evolution of Defensive Microbes

Microbe-mediated defence is hypothesised to evolve from two sources of selection [11]. Firstly, microbe-mediated defence can be directly favoured when microbial fitness depends strongly on host fitness [45], such as when microbes are vertically transmitted (e.g., *Wolbachia* in Table 1) or when the host exercises “partner choice” or “host sanctions” and selectively cultures defensive microbes [8, 9, 11]. It is thought that beewolf wasps selectively acquire protective *Streptomyces* bacteria to ensure continued defence [46]. Alternatively, microbe-mediated defence might be selected as a byproduct of intra-specific and interspecific microbial interactions [11,47] (e.g., via competition over resources) or hyperparasitism (e.g., hyperparasitic viruses parasitise fungal pathogens of plants in Table 1). Hosts may also impose partner choice by exploiting microbial competition, termed “competition-based screening” [48].

Ultimately, defensive traits may differ in their efficacy over evolutionary time [11]. It is likely that defensive traits that evolve via partner choice or maternal inheritance are more evolutionarily persistent than those that evolve as a byproduct of microbial interactions. This difference is because host defence is a directly selected trait in microbes in the former but a byproduct of another interaction in the latter. Above all, evolutionary persistence will depend upon the presence of parasites [49,50]. From the defensive microbe’s perspective, high parasite prevalence can select for their persistence in the host population [50,51]. However, parasites are not always highly prevalent and can have a natural periodicity (e.g., seasonality) or be spatially variable [15,52]. How this variation alters the intensity of selection for and maintenance of defensive microbes has been explored theoretically [53] and in field patterns [54] but has rarely been tested directly [4].

The host-associated costs of harbouring defensive microbes can affect the potential for such microbes to evolve and, as such, their position on the mutualism–parasitism continuum [55]. In many cases, defensive microbes have been found to be physiologically and ecologically costly to their hosts [4,56–58]. Nevertheless, if the benefit of

protection to the host outweighs any costs, then the evolution of defensive microbes will be favoured [59]. Alternatively, a host–parasite interaction would arise if defensive microbes become more costly than beneficial [59]. For example, a microbe that protects a host as a byproduct of competing for resources with a parasite could itself evolve increased host exploitation, and so virulence, by means of competition. If the cost (virulence) of this microbe now outweighs its benefit (defence), this defensive microbe is now a parasite.

Table 1. Defensive microbes in nature. Defensive microbes are listed with their host(s), the parasite(s) they protect against, their mechanism(s) of defence, their impact on parasite fitness, and their mode of transmission.

Host Group	Host(s)	Defensive microbe (s)	Parasite(s)	Mechanism(s)	Impact on parasite fitness	Transmission mode	Ref(s).
Crustacea	American Lobster	gram-negative bacterium	Fungi	Interference competition	Negative	Unknown	[80]
	Shrimp	<i>Alteromonas</i> bacteria	Fungi	Interference competition	Not measured	Unknown	[81]
Insects	Aphids	<i>Hamiltonella defensa</i> ; <i>Regiella</i>	Parasitoids	Interference competition	Negative	Vertical	[82,83]
	Aphids	<i>Regiella</i> ; <i>Rickettsia</i> ; <i>Rickettsiella</i> ; <i>Spiroplasma</i>	Fungi	Unknown	Negative	Vertical	[84–86]
	Beewolf wasp; Subterranean termite	<i>Streptomyces</i> bacteria	Fungi	Interference competition	Negative	Vertical and Horizontal	[87,88]
	Bumble bees	<i>Gilliamella</i>	Protozoa	Unknown	Negative	Horizontal	[16]
	Dampwood termite	Undefined microbiome	Fungi	Interference competition	Negative	Unknown	[89]
	Fruit flies	<i>Spiroplasma</i>	Parasitoids Nematodes	Interference competition	Negative	Vertical	[54,90,91]
	Fruit flies; Mosquitoes	<i>Wolbachia</i> sp.	Arboviruses Protozoans Fungi	Resource competition Immune mediation	Negative None	Vertical	[92–95]
	Invasive Whitefly	<i>Rickettsia</i>	Fungi	Unknown	Negative	Vertical	[96]
	Leaf cutting ants	<i>Actinomyces</i> bacteria	Fungi	Interference competition	Negative	Vertical and Horizontal	[97,98]
Leaf-rolling Weevil	<i>Penicillium herquei</i>	Unknown microbes	Interference competition	Negative	Unknown	[99]	
Plants	Cacao Tree	Foliar Endophytic fungi; Arbuscular Mycorrhizal fungi	Fungi Oomycetes	Resource and Interference competition Immune mediation	Negative	Horizontal	[100–103]
	Chestnut trees	Virus	Fungi	Hyperparasitism	Negative	Horizontal	[104]
	Plant species	Mycoparasitic fungi	Fungi	Hyperparasitism	Negative	Horizontal	[3,39]
Vertebrates	Hoopoe birds	<i>Enterococcus faecalis</i>	Bacteria	Interference competition	Negative	Unknown	[105,106]
	Humans	Undefined microbiome in breast milk	Bacteria	Unknown	Negative	Unknown	[107]
	Metazoan hosts (incl. humans)	Bacteriophage	Bacteria	Hyperparasitism	Negative	Unknown	[108]
	Metazoan hosts (incl. humans)	<i>Bdellovibrio bacteriovorus</i>	Bacteria	Predation	Negative	Horizontal	[109,110]
North American Bullfrog	Undefined skin microbiome	Fungi	Interference competition	Negative	Unknown	[5]	

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dynamics via translocation or time-shift experiments [4,12,14,15], and 3) detecting specificity in defensive microbe–parasite interactions [16–21]. Although tests 2 and 3 cannot be performed in human hosts, it is possible for defensive microbes and parasites of humans to be studied in model organisms, e.g., mice [22] or *Caenorhabditis elegans* [23], in which such studies could be carried out. To date, research has found that defensive microbes often interact specifically with parasites, suggesting defensive microbe–parasite coevolution [16–21]. In the case of aphid protection against parasitoids by *Hamiltonella defensa*, the specificity of microbe-mediated defence [17,19] is associated with a high diversity of toxin genes within the locus responsible for parasitoid resistance [24], indicative of rapid gene turnover due to coevolution [25]. Consistent with these data, mathematical models have revealed conditions under which defensive microbes coevolve with parasites to the point that the host becomes irrelevant [26].

Evolution of Host Dependence on Defensive Microbes

Given that defensive microbes protect hosts from parasite-induced fitness costs, they could reduce selection for costly immune-based or behavioural-based host defence mechanisms [10]. Unless defensive microbes employ host-encoded traits (e.g., host immune or tolerance mediation), selection favouring host defences could wane, making hosts dependent on microbe-mediated protection over evolutionary time. It has been speculated that the loss of immune genes in pea aphids and honeybees that possess defensive microbes are a result of the evolution of host dependence [10,27,28]; however, further research is required to test this hypothesis. Ultimately, a dependence on microbes for defence could increase host susceptibility to infection, making defensive microbe perturbation or loss (e.g., via antibiotics or diet changes) dangerous for the host [29,30].

Phylogenetic comparisons can be used to test the hypothesis that defensive microbes remove selection for host-based defences. Here, the innate resistance of host populations that harbour defensive microbes can be compared with those that do not. We can predict that host populations associating with defensive microbes should have a lower innate resistance to parasites. In support of this prediction, natural *Trachymyrmex* ant populations that harbour protective antibiotic-producing bacteria exhibit significantly reduced cleaning behaviour than populations without the bacteria [31]. The innate resistance of host populations can be assessed by removing the defensive microbe and measuring resistance to parasitic infection and/or the activity level of a host-encoded resistance trait. Given that it is rare to find natural populations that differ only in their association with a defensive microbe, an experimental evolution approach could be used, whereby host populations are coevolved with parasites in the presence or absence of a defensive microbe. The use of lab-tractable host organisms with short generation times and well-studied innate immune systems, such as *C. elegans* [32] or *Drosophila melanogaster* [33], would facilitate such experimentation and allow us to determine whether particular immune system components have been lost or are expressed less over evolutionary time.

Defensive Microbes and Parasite Virulence Evolution

Parasite virulence is defined as the infection-induced decrease in host fitness [34] and is assumed to be an inevitable consequence of host exploitation and so parasite replication [35]. The evolution of virulence can be shaped by interactions between parasites and other microbes within a host; most research to date has focused on the effects of parasite coinfections on virulence evolution (for a full review, see [36]). Critically, as mechanisms of interaction that occur between coinfecting parasites (e.g., resource competition, interference competition, and immune mediation) are similar to those between a defensive microbe and a parasite (Box 1),

Box 3. Case Examples of the Application of Defensive Microbes

Wolbachia and vector-borne parasites

Wolbachia are bacteria that live within the cells of 60%–70% of insect species and can spread vertically via manipulating host reproduction [60,61]. Two *Wolbachia* strains isolated from *Drosophila*, *wMelPop* and *wMel*, have been found to reduce the infection load of a range of human parasites, including dengue virus, malaria, yellow fever, chikungunya, West Nile virus, and filarial nematodes, when introduced into the novel hosts *Aedes aegypti* and *Anopheles gambiae* [62–68]. Consequently, there is great interest in using *Wolbachia* to halt disease transmission [53,61]. It has been suggested that host immune mediation may be the protective mechanism of *Wolbachia* within mosquitoes [62,69–71]; however, more research is required to assess the role of other mechanisms (Box 1) across different host–*Wolbachia* combinations and over evolutionary time [72]. Trial introductions of *Wolbachia*-infected mosquitoes into natural populations have so far resulted in the successful spread of the *wMel* strain [73,74].

More information will be critical to predicting the long-term efficacy of *Wolbachia* as a disease control strategy [75]. Specifically, determining whether the intracellular existence and vertical transmission of *Wolbachia* could constrain its evolution will indicate the potential for *Wolbachia*–parasite coevolution and so persistent disease control. Secondly, identifying the mechanism of protection will be vital in predicting whether *Wolbachia* will drive the evolution of mosquito dependence on microbe-mediated defence; if protection is indeed dominated by host immune mediation, *Wolbachia* may not remove the selection pressure for mosquito defences. Finally, characterising the mechanism(s) of *Wolbachia*-mediated defence will be important in predicting whether *Wolbachia* will select for changes in parasite virulence [75].

Human microbiome

Research into the human microbiome has uncovered information regarding microbe-mediated host defence and has highlighted promising routes for disease control (Table 2). Treatments aimed at manipulating the human microbiome commonly rely on the introduction of defensive microbes that suppress parasites by various means (Box 1). Faecal transplantation [6,76] and the introduction of probiotics [77] are two ways to use microbes to restore an unhealthy gut microbiota back to a healthy state. These methods likely rely on microbial competition to eliminate infections. Phage therapy, on the other hand, is a technique that kills targeted bacteria with hyperparasitic lytic phage viruses [78] and is another promising route to manipulate the composition of our microbiota [79]. Importantly, these methods all involve applying defensive microbes that have great evolutionary potential and so could act as persistent disease control agents in the face of parasite evolution.

Despite growing interest in the manipulation of the human microbiome to prevent or cure infectious disease, the evolutionary implications have been largely overlooked. Recent theory has shown that microbiome engineering could lead to the evolution of increased parasite virulence [38]. This prediction is based on the assumption that parasite resistance traits are also virulence traits [38]. This may often be the case, e.g., when the parasite’s response to microbe-mediated defence is to elicit host inflammation or to produce a toxin against the defensive microbe that also harms the host. Such mechanisms might be common in the use of faecal transplantation and probiotics, as microbial

competition is likely dominant [38]. In direct contrast to this, studies of hyperparasite–parasite interactions have shown that bacteria become less virulent as they resist phage attack (for full review see [37]), suggesting that phage therapy in the human microbiome may select for decreased, rather than increased, virulence. Here, parasite resistance and virulence traits may instead trade off against each other. Further investigations of the generality of these predictions will be necessary to better understand how different approaches to manipulate the microbiome affect parasite virulence evolution.

Table 2. Applications of defensive microbes in infectious disease control. Defensive microbes are listed with their host(s), the parasite(s) they protect against, their mechanism(s) of defence, their impact on parasite fitness, and their mode of transmission.

Host(s)	Defensive microbe(s)	Parasite(s)	Mechanism(s)	Impact on parasite fitness	Transmission mode	Ref(s).
Fish	Probiotics (oral)	Bacteria	Multiple mechanisms	Negative	Horizontal	[111]
	Faecal transplant undefined microbiome	Bacteria	Multiple mechanisms	Negative	Horizontal	[6,76]
Mammals (inc. humans)	Phage	Bacteria	Hyperparasitism	Negative	Horizontal	[78,79,112]
	Probiotics (oral)	Bacteria Fungi	Multiple mechanisms	Negative	Horizontal	[77,113]
Mosquitoes	<i>Wolbachia sp.</i>	Arboviruses Protozoans	Resource competition Immune mediation	Negative	Vertical and Horizontal	[61,74]
Plants	Foliar Endophytic fungi; Arbuscular Mycorrhizal fungi	Fungi Oomycetes	Resource competition Interference competition Immune mediation	Negative	Horizontal	[2,3,103]

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predictions for virulence evolution based on coinfection might be applied to microbe-mediated defence. For example, it is predicted that if a parasite competes over resources under coinfection by evolving increased host exploitation, it will become more virulent [36]. Similarly, this prediction could be made for parasites resisting defensive microbes that function via resource competition. Consistent with this, recent theory on defensive microbes has hypothesised that if parasite resistance to microbe-mediated defence is correlated with parasite virulence, then defensive microbes will alter the evolution of parasite virulence [11,37,38]. It follows that the direction of this correlation will determine the direction of virulence evolution. For example, if parasite resistance measures are also virulent to the host, defensive microbes will select for increased virulence [38]. Alternatively, if parasite resistance and virulence traits trade off against each other, defensive microbes will select for decreased virulence.

The extent to which defensive microbes might affect parasite virulence evolution is of concern in the application of microbe-mediated disease control strategies (Box 3). If microbe-mediated defence via resource competition indeed selects for more virulent parasites, this potential outcome could influence the choice of the defensive microbe being applied (Table 2). This example thus illustrates the significance of linking the mechanism of microbial protection to parasite virulence evolution in the application of defensive microbes.

Conclusions

Defensive microbes are abundant in nature and have important fitness consequences for hosts and their parasites. By considering defensive microbes in the light of evolution, we can identify

traits that enable their coevolution with parasites and reveal their impacts on the evolution of host-based resistance and parasite virulence. Such information will help us to choose defensive microbes for optimal disease control. Ultimately, by combining our understanding of defensive microbes at the mechanistic level with current evolutionary theory, we will be better able to predict the role of defensive microbes in driving host and parasite evolution in nature and in the context of disease control.

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