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Immunity, Host Physiology, and Behaviour in Infected Vectors

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Abstract

When infection alters host behaviour such that the pathogen benefits, the behaviour is termed a manipulation. There are several examples of this fascinating phenomenon in many different systems. Vector-borne diseases are no exception. In some instances, as the term implies, pathogens directly interfere with host processes to control behaviour. However, host response to infection and host physiology are likely to play important roles in these phenotypes. We highlight the importance of considering host response and physiology from recent work on altered host-seeking in malaria parasite-infected mosquitoes and argue that this general approach will provide useful insights across vector-borne disease systems.

Introduction

Across taxa and transmission routes, there have been many documented cases of host behaviours that change with infection [1,2]. Currently, any change in host behaviour associated with infection that benefits the pathogen (here used as a general term for an

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infectious agent) is broadly categorized as manipulation. This categorization is currently applied regardless of the mechanisms that lead to that change, the role of the host in these behaviours, or how the change in behaviour affects the fitness of the infected host. Thus, even if a change in behaviour is a consequence of host adaptive response or pathology, it can be classified as manipulation [3,4]. The argument underpinning this broad definition is that any change in host behaviour elicited by the pathogen (even if this behaviour is the result of an adaptive host response) will be selected for if it enhances transmission.

This definition can be problematic if it is misinterpreted to mean that all host behavioural changes are the result of active and direct action on the part of the pathogen. Indeed, the word manipulation casts the pathogen in the role of puppet master, dynamically pulling on the host's strings. In some instances, evidence supports this narrative. Pathogens can alter behaviour directly by interacting with the host tissues [3,5], secreting substances that act directly on the host nervous system [5], or high jacking host cells and tissues to express these modulators [6–9]. For example, evidence suggests that the parasite *Toxoplasma gondii* increases dopaminergic activity by directly producing an enzyme required for the synthesis of L-DOPA (a dopamine precursor) in its mouse host [10]. Increased dopamine levels have been associated with changes in fear perception, resulting in a reduced anti-predatory behaviour, which is thought to increase parasite transmission success in this tropically transmitted parasite [Reviewed by [11]]. These types of neuropharmacological manipulations produce many of the dramatic and novel behavioural phenotypes most commonly associated with manipulation [2].

However, the host can also play a large role in these changes, and more recent work has demonstrated that pathogens may indirectly alter behaviour by interacting with host tissues [5]. Some of these include psychoneuroimmunological changes in host behaviour, which derive from ancient bidirectional connections between the immune and nervous systems [9]. For example, it has been proposed that neuro-inflammation in response to infection, rather than direct pathogen interference, is responsible for altered behaviours in infected crustaceans [12]. The behavioural phenotypes that derive from perturbations in these networks are often difficult to separate from generalized sickness behaviours [5].

Manipulation and vector feeding behaviour

Unlike classic manipulations leading to completely novel behaviours, such as those observed in *Cordyceps*-infected ants [13] or crickets carrying hairworms [14], changes in infected vector behaviour are for the most part changes in the degree and timing of normal behaviours. Notably, many behavioural changes in vectors are associated with feeding related behaviours (Table 1). For the purposes of this review we are focusing on changes in vector behaviour and not changes in the attractiveness of hosts [15–18]. These feeding events are both a point of contact between infectious vectors and susceptible hosts and intimately intertwined with major vector life history events such as reproduction.

Clarifying mechanisms of altered phenotypes is particularly important for vector-borne diseases (VBDs). Even minimal changes in vector behaviour in the small proportion of the population responsible for transmission can have large implications for pathogen

transmission and human health [19]. Further, identification of the mechanisms responsible for behavioural change may lead to novel methods for targeting infected individuals and developing tools for manipulating vector behaviour to decrease transmission.

Details of the mechanisms by which pathogens alter vector behaviour are scarce. Changes in feeding efficiency have been linked to parasites physically blocking or inhibiting vector host functions to accomplish manipulation. For example, *Leishmania* parasites secrete a gel that blocks the feeding apparatus of sand flies [20]. Similarly, plague bacilli form a biofilm that blocks a portion of the flea midgut, resulting in repeated attempts at feeding and increased pathogen transmission [21]. Less, however, is known about the mechanisms driving the changes in host seeking patterns and persistence. Recent work in the malaria-mosquito system has highlighted the potential importance of host physiology in changes to vector feeding behaviour. We propose that changes in host physiology with infection are likely to play an important role in VBD systems and should be a priority for investigating the underpinning mechanisms of behavioural change associated with infection.

Case study: Malaria as a manipulator, but not as we know it?

A variety of changes in the behaviour of malaria parasite-infected mosquitoes have been reported [18–20]. Generally, during parasite development host seeking propensity and sensitivity to host odours seem to be depressed, while feeding efficiency is elevated (Table 1). Once the parasite reaches the infectious stage, a behavioural switch occurs in which infectious females are more likely to feed and less efficient when they do so. These changes in behaviour are predicted to increase transmission in two ways. First, feeding and reproduction are relatively risky activities and decreased feeding during parasite development theoretically could increase transmission by increasing the number of females that survive the extrinsic incubation period of the parasite [19]. Second, decreased feeding efficiency associated with infectious parasites improves the likelihood that females will transmit parasites to hosts and bite multiple hosts in attempting to engorge successfully.

Given that these changes in vector behaviour should benefit the parasite, they are termed a manipulation. Until recently, mechanisms explaining observed changes in host-seeking, probing, and host feeding were limited. As in other systems, changes in feeding efficiency and probing behaviour associated with infection have been linked with decreased apyrase activity in the salivary glands in some mosquito-malaria parasite combinations [23]. For example, it may be that parasites inhibit production of apyrase directly, or mechanically damage the salivary gland and its secretion machinery during invasion of this tissue [24].

Until very recently, it was unclear by what mechanism infection was altering host-seeking of infected mosquitoes. There are documented changes in the vector head proteome during sporozoite infection, but it remains unclear if and how these changes in protein expression and enzyme activity are caused by parasites [23]. Our work and the work of others demonstrated that changes in the sensitivity of the mosquito peripheral nervous system to host odours underlie changes in host-seeking [25,26]. The host response to non-specific immune challenge may also play an important role in regulating these “manipulated” host-seeking phenotypes. Specifically, when female mosquitoes were challenged with heat-killed

Escherichia coli, we observed changes in behaviour magnitude, pattern, and timing [26] that were similar to those observed during infection with malaria parasites. Hence, our observations indicated that changes in host-seeking were not specific to infection with malaria parasites or to infection. Rather, the magnitude of the change in feeding was correlated with the dose of heat-killed *E. coli*, the magnitude of the resulting immune response, and the timing of the immune challenge relative to the blood meal [27]. In this context, pre-existing infection-induced trade-offs among digestion, immunity, reproduction and vector behaviour may benefit parasite development.

Functional trade-offs have been proposed to drive other infection associated behaviours in non-vector systems. For example, down regulation of feeding during infection or illness-induced anorexia resulting from immune and neural connections [28,29] may be adaptive by increasing host survival during infection [30,31] and reducing trade-offs between energy-consuming digestion and immunity [29,31,32]. The timing of infection is intimately linked with several important life history traits for the female mosquito. Life history traits affect the basic survival and reproductive schedules of organisms (e.g., age-specific birth rates, growth rates, age-specific death rates, size at birth, quantity of offspring produced, etc.)[33]. Further, life history theory assumes that organismal investment into one trait for example, reproduction is a zero-sum game that decreases potential investment in other traits such as survival, growth, or future reproduction. Organisms that are most successful, in turn, maximize lifetime fitness by optimizing differential investment across a suite of life history demands [33]. Thus, a female mosquito must optimally allocate resources toward somatic effort (e.g. self-maintenance nutritive reserves and immunity) and reproductive effort (e.g. egg production quantity and quality of eggs) after taking an infectious blood meal. We hypothesized that functional trade-offs between reproduction and digestion or between reproduction and immunity could, therefore, drive the altered feeding phenotypes of malaria parasite infected mosquitoes.

Incorporating this view of host physiology into our exploration of altered host-seeking behaviour led us to ask which cellular pathways might regulate life history trade-offs during parasite development in the mosquito host. Our studies pointed to the insulin/insulin like growth factor signalling (IIS) pathway and to action of endogenous mosquito insulin-like peptides (ILPs) in the midgut. In particular, ILP activation of IIS appears to connect midgut-specific control of parasite infection with changes in host-seeking behaviour. For example, similar patterns of *ILP3* and *ILP4* transcript expression were evident in the midgut following challenge with malaria parasites or with heat killed *E. coli,* with sequential under- and over-expression of these peptides coincident with temporal changes in feeding behaviour associated with “manipulation”. Further work has established that distinct ILP3- and ILP4-dependent biochemical shifts in intermediary metabolism and mitochondrial function regulate parasite infection and changes in mosquito blood feeding [34]. ILP3 induces an orexigenic response perhaps through increased synthesis of excitatory neurotransmitters, resulting in increased nutrient intake and a high energy, biosynthetic state that can reduce parasite infection. In contrast, ILP4 induces an energy deficient, low biosynthetic state that increases parasite infection. In response to ILP4, flight is reduced, fat deposits are mobilized for energy, and food intake is increased at the second blood meal to restore energy levels. Here, energy consuming-biosynthesis is associated with *increased* resistance to infection.

Further, both ILP3 and ILP4 reduce expression of known anti-parasite immune genes, indicating that ILP-specific effects on metabolism rather than host immunity per se explain the observed effects on parasite infection. ILP3-dependent biosynthesis clearly does not benefit parasite development, but to what extent ILP4-mediated energy deficiency degrades non-immune host defences to increase parasite infection is not yet clear. Collectively, these observations demonstrate how considering the role of the host in infection-associated behaviour can facilitate a broader understanding of the behaviour of malaria parasite-infected mosquitoes.

Taking this approach to malaria associated phenotypes could provide answers to other lingering questions about experimental evidence for altered feeding in infected mosquitoes. For example, in a recent study using field derived mosquito colonies and parasites there was no change in host-seeking response with infection [35]. Traditionally, it would be challenging to explain why some combinations (usually unnatural laboratory combinations) exhibit altered phenotypes, while coevolved natural mosquito-parasite combination do not. Approaching these phenotypes as shifts in host physiology provides potential explanations for this discrepancy. For example, different parasite-mosquito combinations may elicit different metabolic responses toward infection (e.g. rodent vs. human parasites) or different levels of response toward infection [36]. If altered phenotypes are in part a result of host functional trade-offs we would expect the altered phenotype to be sensitive to these parameters. Further, like other components of behaviour that influence vector life history, these phenotypes are likely to be highly dependent on the condition and environment of the vector instead of being fixed by a manipulator.

Suggestions for moving forward

Consideration of host physiology has been successfully integrated in the study of manipulation in other systems. We advocate incorporating this perspective as we start to dissect mechanisms in VBD systems. This approach will not only better inform our investigation of the mechanisms of manipulation, but will also provide useful insights into the regulation and coordination of multiple life history traits.

Instead of thinking of these changes in behaviour as fixed host or parasite traits, it is more appropriate to consider them an extension of vector and pathogen life history trade-offs. A pathogen maximizes its fitness in a host under immune challenge and a host maximizes its fitness while being challenged. These goals are not necessarily at odds and they may not require any “manipulations” from either party. The emergent phenotype, is the result of an interaction between pathogen and host physiology and could result in behavioural shifts that benefit the host as well as the pathogen [37]. This perspective is particularly important to keep in mind when approaching mechanisms of behavioural changes in VBD systems.

We learned several lessons in our investigation of altered feeding patterns in malaria parasite-infected mosquitoes, which may be informative in pursuing mechanisms across VBDs. First, it is important to establish the role of infection versus exposure. Many studies on VBD manipulation do not confirm infections (Table 1). If changes in behaviour can be recapitulated without an actively replicating pathogen, this suggests that host physiology is

likely involved. Further, if exposure is adequate, then it is important to determine the specificity of response. A lack of specificity does not negate a role for the pathogen. However, when host pathways are generally triggered by infection it suggests that the vectors response is a product of evolutionary pressure from general immune challenge not just the pathogen.

Finally, few studies simultaneously assess the effect of modified behaviours on host and pathogen fitness simultaneously. In the malaria example, if we had not considered vector fitness in a broader context and the potential mechanisms within vector mediating life history trade-offs, we would have missed the potential role of the IIS. Moving forward, we need more unbiased approaches to understanding how host-pathogen interactions influence multiple physiological systems (stress, immunity, reproduction, digestion, etc.) to produce the behavioural changes associated with VBD parasite infection.

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Highlights

- There is evidence that infection alters the behaviour of disease vectors and the majority of these changes in behaviour have been interpreted as manipulation.
- Recent work in malaria has highlighted the potential importance of vector physiology and in particular the role of the vector immune response in infection behaviours.
- We discuss this recent work and highlight the importance of host physiology in understanding infection associated behaviours in vector--borne diseases.

Table 1

Examples of vectors that exhibit altered feeding behaviours when infected with pathogens they transmit

There are many ways that pathogens alter vector physiology. Here we specifically focus on changes in host feeding behaviour as opposed to other behavioural changes (e.g., dispersal), host physiological processes (e.g., immunity) or host life history traits (e.g., survival). These behaviours have been grouped into feeding efficiency (probing, regurgitation, ingestion, engorgement), host-seeking (response to host stimuli), and host-attack persistence (the probability that a vector attempts to bite multiple hosts or a single host multiple times). In some examples, direct mechanisms have been identified (yes or "Y"). In others, while the mechanisms have not been identified ("N"), they are known to be specific to infection with a particular pathogen as opposed to a general response to immune challenge. In still other cases, the response has been found to be non-specific and to involve host physiology. In these cases it is unclear whether indirect manipulation or simply a host response is responsible for altered behaviour. In a surprising number of cases, including economically and medically important pathogens, the specificity or role of the host in infection associated changes in feeding behaviour has not been investigated (indicated as "?").

Study	Vector/Pathogen	Feeding Behaviours Altered By Infection	Potential Direct Mechanism Identified?	Specific to Infection with VB Pathogen?	Role of vector physiology?
[21]	Fleas/Plague	Feeding Efficiency	Y	Y	N
[20,38,39]	Sandflies/*Leishmania*	Feeding Efficiency	Y	Y	N
[40,41]	Tsetse Flies/ *Trypanosoma*	Feeding Efficiency and Host-attack Persistence	Y	Y	N
[29–32]	Mosquitoes/Malaria Parasites	Feeding Efficiency	Y	Y	N
[46]	Mosquitoes/Malaria Parasites	Host-attack Persistence and Feeding Efficiency	N	N	?
[25–27]	Mosquitoes/Malaria Parasites	Host-seeking (however see [35])	N	N	Y
[47]	Mosquitoes/Malaria Parasites	Host-attack Persistence	N	Y	?
[48]	Mosquitoes/Filarial Parasites	Host-seeking	N	N	?
[49]	Mosquitoes/Dengue Virus	Feeding Efficiency	N	?	?
[50]	Mosquitoes/Dengue Virus	Host-seeking	N	?	?
[50]	Mosquitoes/Dengue Virus	Host-attack Persistence	N	?	?
[51]	Mosquitoes/LaCrosse Virus	Feeding Efficiency	N	?	?
[52]	Midges/Vesicular Stomatitis Virus	Feeding Efficiency	N	?	?
[53]	Aphids/Barley Yellow Dwarf Virus	Host reference	N	?	?
[54]	Thrips/Tomato Spotted Wilt Virus	Feeding Efficiency	N	?	?
[55]	White Flies/Tomato Spotted Wilt Virus	Feeding Efficiency	N	?	?