Editorial overview: Evolutionary ecology of insect immunity

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Why are some individuals better at defending themselves against disease compared with others? Research centering on why there is immunological variation between individuals, populations, and species, came to the fore in the mid-90s when researchers started considering immunological questions within an evolutionary ecology framework: This became known as the field of ecological immunology [1]. Physiological and behavioural immune defences towards parasites [see 2 for a comprehensive definition of the term parasite] are not uniform; their quantity and quality will be determined by a multitude of factors such as the host’s genotype, life-history stage, environmental conditions, nutritional status, and previous evolutionary experience with the parasite [3]. Ecological immunology tries to understand the importance of these factors in shaping disease defences and the resulting consequences of immunological heterogeneity on both host and parasite populations [4, 5]. The framework can be used to help guide public health, wildlife and agricultural decisions [3, 6], but also to inform parasite epidemiology and disease emergence [7, 8] by connecting the within- and between-host infection processes.

A central cornerstone of ecological immunology is the idea that immune defences can be costly, and as such they can be traded-off with other life history traits [9, 10], for example, longevity [11]. Costs can be due to the evolution, maintenance or deployment of immune defences, which can act at a physiological or genetic level [9]. Individuals will experience costs of varying intensity, and these costs will determine the shape of immune responses based on an individual´s current ecological setting (resource allocation trade-offs), and they will affect the evolution of defences over a longer timescale (evolutionary trade-offs) [4, 12]. The ecological immunology field has advanced considerably over the years; it has helped to explain the causes of natural variation in immune phenotypes, including the role of immunity in shaping animal life histories. Moreover, by including the concept of costs, ecological immunology has highlighted important differences in how we think about host defence strategies against disease, for example resistance and tolerance, which both have considerably different outcomes for parasite populations and their evolution [13, 14].

Although evolutionary ecology principles can be applied to defences across taxa [5, 15], insects have proven to be particularly valuable models for ecological immunology studies [5, 16]. Studies on insects have provided insight into a multitude of factors that can affect immune defences, parasite infectivity, transmission and host health; e.g., the influence of nutrition on infection outcome [17, 18], immunological priming and specificity of immune responses [19, 20], the harm done by the immune system and the necessity to protect against immunopathology [21, 22], or the influence of host defensive behaviour on pathogen communities and competition outcomes [23]. Nevertheless, as the articles in this issue address, there are still many open questions and ample room for the field to expand and integrate even further with other disciplines.

**Recent advances in the evolutionary ecology of insect immunity**

This issue of *Current Opinion in Insect Science* aims to provide an up-to-date overview and a look to the future for nine themes on the evolutionary ecology of insect immunity, which we have identified as some of the key current or emerging topics in the field. Here, we introduce the topics presented in this issue within a temporal and spatial framework, with respect to steps in the infection process, immunological responses, and outcomes, together with the ecological and evolutionary processes that affect this framework.

Evading infection in the first place will likely be a cost-effective strategy for a host. Behavioural modifications in response to disease cues mean that a host can limit or completely circumvent the negative impact of an infection [24, 25]. Notably, parasite “smell” and the recognition of these disease cues could be under strong selection. Behavioural responses to disease have been described in multiple insect taxa [25-28], yet little is known about disease cues that trigger such responses. **Barbara Milutinović** and **Thomas Schmitt** [29] review known chemical cues emitted by parasites, diseased, or dead conspecifics that can modulate not only insect behaviour, but also their physiology: recent research has shown that insects utilise this information to prophylactically ramp up their immune systems in anticipation of parasite attack. The authors emphasise the immunomodulatory role of disease cues as an emerging research area that calls for closer collaboration between ecological immunologists and chemical ecologists.

Despite the behavioural options that can be employed to avoid infections of self or other conspecifics, parasites often manage to infect their hosts. Once a parasite has entered the host, the early infection dynamics, including the time to control the infection load and the rate of proliferation seem to be crucial parameters determining the outcome of infection. **David Duneau** and **Jean-Baptiste Ferdy’s** [30] contribution addresses these parameters, as well as pathogen load upon death and the set-point pathogen load, in the context of bacterial and viral infections. By closely following the pathogen load during early infection phases and upon death, these parameters can provide insight into disease outcome [30]. Duneau & Ferdy’s review is highly complementary to the review by **Ann Tate** and **Nora Schulz** [16], who use within-host and between-host ecology of insects and their parasites as a case study to exemplify the benefits of integrating experiments and theory, particularly when trying to get a handle on complex phenomena such as these. Mathematical models are essential predictive tools that can generate exciting new hypotheses to be tested in insects, but which could receive more attention amongst experimentalists.

The balancing act of immune regulation, i.e., activation and shutdown kinetics, is addressed by **Brian Lazzaro** and **Ann Tate** [31]. To maximise fitness in the face of pathogens, the immune system must “decide” how and to what degree to respond, and then deactivate the response in a timely manner. It is a delicate navigational act: the path is strewn with potential costs associated with using the immune system and immunopathology, whilst the consequence of not responding appropriately will mean that the pathogen could get the upper hand. The review also points out the potential for genetic variation in immune regulation to influence pathogen virulence evolution and host infection tolerance, highlighting again that together, theory and empirical studies will increase our understanding of the evolution of immunity.

The pathways and molecules involved in canonical insect immune defences are well described [32]. However, an emerging topic over the last few years is the role of epigenetics in insect defence, and this is the focus of the review by **Krishnendu Mukherjee** and **Ulrich Dobrindt** [33]. They show that regulation of insect immune defences against parasites is indeed often regulated by epigenetic changes, such as transcriptional reprogramming of immunity genes by DNA methylation, histone acetylation and microRNAs, which can also be trans-generationally inherited.

**Paul Schmid-Hempel** [34] then elaborates on defence mechanisms in the context of disease space [35], connecting this immunological take on defences, with the functional evolutionary ecology concept of the defence chart [36]. In this novel framework, which is broadly applicable across taxa from insects to vertebrates, the concepts explained can together help us to understand what the fitness costs and benefits of a particular defence are, and how the defence can be optimised for a given environment. As mentioned in our introduction, the principle that immune defences are costly is a fundamental cornerstone of the ecological immunology field: because of trade-offs with other life history traits, costs are one reason why we see variation in immune responses across individuals and populations. These costs feed into Schmid-Hempel’s [34] framework by affecting the fitness landscapes.

The last three articles highlight the importance of external factors, i.e., diet and microbiota, in influencing variation in immunity and the outcome of infection. **Sheena Cotter** and **Ekhlas Al Shareefi** [2] review the myriad of ways in which dietary components can influence parasitism, be it via efficacy of the immune response, direct toxicity, modifications of the host’s physiological environment, or via the diets’ effect on gut microbiota. They point out that although we have made good progress in our understanding of diet as a mediator of the outcome of infection, the identification of generalisable patterns will require deeper knowledge about the mechanisms by which these effects take place.

The topic of microbiota is then picked up in the review by **Eric Caragata** and **Sarah Short** [37] where they focus on fungus/bacteria microbiota interactions with a range of vertebrate pathogen taxa inside their arthropod hosts. They highlight that studies on many host-parasite systems show that susceptibility of arthropod vectors to pathogen infection can be affected by perturbation of microbiota or influenced by the presence or absence of specific microbes. The mechanistic underpinnings of the interactions are beginning to be characterised in some systems: for example, immune signalling or alterations of mosquito physiology by the microbiota can affect susceptibility to infection. The influence of microbiota on pathogens opens the possibility to manipulate these relationships to control or prevent transmission, a point which is also discussed in the review. Lastly, **Sophie Armitage** and colleagues [38] consider the interplay between host immunity, bacterial microbiota, and pathogens, and how this interplay can affect pathogen virulence evolution. They review the competitive interactions between the three partners, and the non-competitive effects such as immunopathology, immunosuppression, and microbiota-mediated tolerance. The authors argue that to understand the evolution of pathogen virulence, a combination of competitive and non-competitive effects should be taken into consideration.

**Future directions**

Host-parasite interactions are complex: there are at least two quite different species interacting with each other in a dynamic system within ecological space and at physiological and evolutionary time scales. As a result, the evolutionary ecology of insect immunity involves different areas of research that look at immunological variation and its consequences from multiple angles. Some of these areas were not included in this issue because they have been recently addressed elsewhere in reviews that include insects. For example, social defences against parasites [39], disease tolerance [14, 40], immune priming/memory [41, 42], the evolutionary genetics of insect immunity [43], and the influence of circadian rhythms [44] and reproduction [45] on immunity and infection outcome. Although ecological immunology is and has been an integrative discipline, this issue has highlighted important gaps that could be considered in future research.

One recurring theme to emerge from the collected articles is that integrating experimental work with theoretical/mathematical models [e.g., 16, 31, 38], will be necessary to aid understanding of such complex systems. Mathematical models can be utilised to fill the gaps in empirical data that often arise due to difficulty in collecting biological samples, but also as essential predictive tools, including for empirical study design, making such collaborative approaches invaluable for development of the field. Likewise, there is scope for even more integration with researchers from other disciplines, such as immunologists, microbiologists, parasitologists, and chemical ecologists, from which we can borrow established methods and approaches and use them to answer novel questions.

A second point to emerge is that mechanistic details of the observed phenotypes and integration of physiological processes are essential for understanding the causes of immunological variation and what predictions can be drawn from it [15], yet they are often still lacking. A better understanding of mechanisms, e.g., immune regulation [31], will also allow comparative approaches and help gain insights into how generalizable the patterns we observe across insects are [e.g., 2, 29, 37], and it will enable us to evaluate the adaptive function of defences [34]. One way to do this is to also take full advantage of technological advances that have received less attention, such as epigenetic regulation in infectious disease management [33].

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