

PERSPECTIVE

Principles of ecological immunology

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Abstract

Defending self against nonself is a major problem in a world in which individuals are under constant pressure from parasites that gain fitness benefits at a cost to their host. Defences that have evolved are diverse, and range from behavioural adaptations to physiochemical barriers. The immune defence is a final line of protection and is therefore of great importance. Given this importance, variability in immune defence would seem counterintuitive, yet that is what is observed. Ecological immunology attempts to explain this variation by invoking costs and trade-offs, and in turn proposing that the optimal immune defence will vary over environments. Studies in this field have been highly successful in establishing an evolutionary ecology framework around immunology. However, in order to enrich our understanding of this area, it is perhaps time to broaden the focus to include parasites as more than simply elicitors of immune responses. In essence, to view immunity as produced by the host, the environment, and the active involvement of parasites.

Introduction

Studies of immune mechanisms and immune function are widespread in modern biology. Furthermore, studies of the immune system have been central to the fields of health and medicine for over a century (Silverstein 1989). As a result, the immune system of vertebrates and in particular that of model organisms, such as mice, has been described in great detail (for an introductory yet comprehensive overview see Delves et al. 2006). These studies have tended to be with lab-based models in controlled conditions. While extremely useful, an understanding of immunity in the context of natural environments was lacking, until in the mid-1990s the field of ecological immunology emerged (Sheldon and Verhulst 1996). Ecological immunology went beyond outlining the physiological or molecular basis of immune responses, by placing them in the context of ecology and adaptation. In fact, despite the obvious benefits of fending off parasites (throughout this article parasite is used in its evolutionary sense, including viruses, bacteria, fungi, protozoa and metazoan parasites), hosts remain susceptible and immune responses vary widely across species and situations. Thus, a principal aim of ecological immunology is

to understand variation in parasite resistance and immune responses. In the years following its inception, ecological immunology has expanded rapidly and now boasts a huge number of studies investigating topics such as costs associated with immunity and the optimal use of immune defence. While the initial ideas that sparked the field were relevant for vertebrates, and in particular birds (Folstad and Karter 1992; Sheldon and Verhulst 1996; Norris and Evans 2000), subsequent work has been carried out on a broad range of taxa, with invertebrate ecological immunology being a particularly fruitful area (Rolff and Siva-Jothy 2003).

The ideas and concepts at the base of ecological immunology are of great importance for the areas of health and medicine. They allow us, for example, to understand variability in immune responses between populations, to relate the outbreak of diseases to the evolutionary history and ecology of populations in humans and economically important animals, and to analyze vectors of human and livestock diseases (for example mosquitoes and malaria, Tripet et al. 2008). In addition, there are a great number of other studies where results cannot be directly applied to health and disease in humans or domestic animals, but where the general concepts that they address are

Box 1. Important concepts of ecological immunology.

Cost of immune defence: the cost of an immune defence in terms of a loss in other fitness components.

Evolutionary costs of defence: the loss of performance in another fitness-relevant function of the organism as a consequence of a more powerful immune system.

Usage costs of defence: the cost of an immune defence in terms of a loss in other fitness components due to either maintenance or activation of the immune system.

Immunocompetence: an ill-defined term that generally describes the potential of an immune system to respond.

Auto-reactivity, auto-immunity: a cost of immune defence that is realized when using the immune system results in damage to own tissue.

Optimal immune defence: a theoretically expected combination of different immune defence components and/or the strength of the response that yields the highest fitness to its carriers. This includes the consideration of costs and benefits.

Plastic immune response: an immune response that varies according to environment; also includes the environment of parents when they can transfer their experience to offspring.

Immune evasion: a process by which parasites manipulate, subvert, impede or mislead the immune system of the host.

transferable. Here, we discuss such studies that address the major principles of ecological immunology. This article therefore presents some of the key concepts of ecological immunology (Box 1), discussing their basis, evidence and development. Towards the end of the article, future avenues of research are addressed. Ecological immunology of the late 20th and early 21st century has been essentially host-focused. The inclusion of parasite traits, such as immune evasion, will now expand the framework to better understand the ecological and evolutionary pressures that have shaped immune systems and their functioning.

Putting a price on immunity

If traits were cost free in terms of Darwinian fitness, then an organism with a perfect set of life histories would be able to evolve. However, fitness costs are assumed to be ubiquitous and are central to many concepts in both ecological and evolutionary theory. For example, while it is clear by their classification that parasites will harm their hosts, immune responses of hosts used to combat these parasites may also come at a cost to the host. The presence of these costs is one explanation for the variability that we observe between immune responses of different individuals and populations. Therefore, one of the main principles behind ecological immunology is that immune systems are not cost free and will carry different costs on different levels.

The costs of immunity can be broken down into two main categories, representing the stage on which they act. These are the evolutionary costs involved in evolving an efficient immune system, and secondly, costs of maintaining and using this immune system to successfully combat parasites and pathogens that pose a significant threat to the integrity of self.

Evolutionary costs

The different traits of an organism are frequently not independent of one another. In many organisms there is,

for example, an intimate link between the immune system and other compartments and life-processes, and immunity is not able to evolve independently. Genetic correlations, arising from linkage or pleiotropy between the genes involved, will influence the evolution of the associated traits. Negative genetic correlations indicate evolutionary trade-offs. Negative correlations have been demonstrated between fecundity and bacterial resistance in the fruit fly *Drosophila* (McKean et al. 2008), and sperm viability and immune lysozyme activity in crickets (Simmons and Roberts 2005). Such correlations will constrain the evolution of immunity due to its ties with other fitness related traits.

Further evidence for evolutionary trade-offs involving immunity comes from experimental evolution experiments. For example, lines of *Drosophila melanogaster* were selected for increased encapsulation ability of a parasitoid (Kraaijeveld and Godfray 1997). The selection regime achieved its desired effect, with a later study showing that the lines had increased twofold the number of immune cells used in encapsulation (Kraaijeveld et al. 2001). However, larvae of these lines were poorer competitors under conditions of scarce resources. In the reverse situation, selection on a non-immune trait can lead to a decrease in immunity (Hosken 2001; Koella and Boete 2002), again demonstrating that immunity is in an evolutionary trade-off with other traits.

Evolutionary costs may also materialize from negative correlations between immune traits. For example, work on the lepidopteran, *Spodoptera littoralis*, demonstrated a negative genetic correlation between antibacterial lysozyme activity and immune cell density (Cotter et al. 2004); but see (Lambrechts et al. 2004). These traits are still determined by separate loci, but at the extreme of the spectrum we can also have an evolutionary trade-off between immune traits at a single locus when there is specificity within the system. In some cases, it has been shown that resistance against one type of parasite does not influence resistance against another (Webster and Woolhouse 1998).

However, when one allele confers specific resistance against one parasite type, while a different allele at the same locus confers specific resistance against another with no cross-reactivity, there will be an evolutionary trade-off between the resistances against each of the parasite types.

Maintaining and using the immune system

The immune system needs to be prepared at all times, ready to repel parasites. This will incur costs on other fitness traits that are referred to as maintenance costs. When infection actually takes place the response should be rapid and effective. This will incur costs known as costs of use or deployment.

These costs involved in maintaining and using the immune system will mean that investment into immunity must be traded-off with investment that is devoted to other relevant fitness traits. Indirect evidence that immune function is costly comes from the common observation that poor nutrition is associated with disease (Sheldon and Verhulst 1996). Furthermore, reduced nutrition has been shown to result in a lower immune response in mealworm beetles, *Tenebrio molitor* (Siva-Jothy and Thompson 2002). Trade-offs between immunity and life-history traits can be mediated in a wide variety of ways, from hormones (Rolff and Siva-Jothy 2002), to caretonoids (Lozano 1994), or simply by energy (Sheldon and Verhulst 1996). Evidence for energetic trade-offs has been demonstrated in bumblebees (König and Schmid-Hempel 1995) and birds (Hasselquist et al. 2001), but see Nilsson et al. (2006) for arguments of why energy cannot form the basis of a trade-off. The literature covering costs of immune activation is vast and shows the occurrence of costs on a number of fitness related traits in both invertebrates and vertebrates. Fitness costs in terms of survival on responding to an immune challenge have been shown for survival on starvation in bumblebees (Moret and Schmid-Hempel 2000) and lifetime survival in mealworm beetles (Armitage et al. 2003). Further costs have been shown for reproductive output (Ilmonen et al. 2000; Schwartz and Koella 2004), secondary sexual signalling (Faivre et al. 2003; Jacot et al. 2005a), growth (Brommer 2004), learning (Mallon et al. 2003), and antipredator defence (Rigby and Jokela 2000), to name only a small selection.

Costs of using the immune system may also result from damage to self, or autoreactivity. The best-known cases of costs of this kind are autoimmune diseases that are found in humans and other vertebrates (Sarvetnick and Ohashi 2003). In addition, the effects observed in many severe pathogen-related diseases also stem from this immune mediated self-harm (Graham et al. 2005). Further, it has also been demonstrated that innate immune effectors of

insects employing general cytotoxic cascades can also have autoreactive consequences (Sadd and Siva-Jothy 2006). The presence of these autoreactive costs could explain why some studies of the costs of immune elicitation only uncover effects under stressful conditions (e.g. Ilmonen et al. 2000; Moret and Schmid-Hempel 2000). Stressed animals may have a lower capacity to repair damage resulting from an immune response (Read and Allen 2000). Following this logic, protection against un-repairable damage could explain why immunity is often found to be reduced under stressful conditions (Dabbert et al. 1997; Siva-Jothy and Thompson 2002; Martin et al. 2008a). In other words, the immune response may be constrained by the organism's capacity to repair the autoreactive damage that the immune response causes.

Questioning costs

Not all studies aiming to investigate the occurrence of immune-related costs have found them (Schmid-Hempel 2003). Male mosquitoes of lines selected to be refractory to the rodent malaria *Plasmodium yoelii nigeriensis* show higher levels of melanization against beads introduced into the body cavity than susceptible lines, but no consequential decrease in reproductive success (Voordouw et al. 2008). Challenging female crickets repeatedly with an immune elicitor did not result in reduced reproductive output (Shoemaker and Adamo 2007). Additionally, the presence of costly immunity is not the only idea relating to the maintenance of genetic diversity in immune defence (See Box 2). This has led to scepticism in some circles about the universal presence of costs of immunity and their evolutionary significance (Rigby et al. 2002). Furthermore, it has been argued that costs will be negated by evolution of compensatory mechanisms, as is the case with costs of antibiotic resistance in bacteria (Coustau et al. 2000). However, this is most plausible to occur when the situation remains static, yet interactions involving the immune system are likely to be more dynamic. This is especially probable under a unified model of defence (Box 2), which marries the dynamics of specific interactions between hosts and parasites and the costs of defence.

Most notably, the taxonomically widespread demonstrations of immune system costs and their estimated sizes (Lochmiller and Deerenberg 2000) suggest that they are not simply the product of a particular set of parameters in a special system. Nevertheless, when searching for costs of immunity it should always be kept in mind that the exact nature of these costs is likely to vary. Exact trade-offs and energetic costs will depend on the species in question, the immune challenges employed, and importantly the background environmental conditions.

Box 2. Specificity versus costs.

Evolutionary ecology has advanced two principle explanations for the maintenance of variation in immune defence and resistance (Schmid-Hempel 2003). These are firstly that immune defence is a costly trait and is therefore traded-off with other life-history traits, and secondly the idea of specificity in host–parasite interactions. The presence of specific interactions within a host–parasite system (for examples see Carius et al. 2001; Schmid-Hempel 2001) is likely to lead to dynamics of antagonistic coevolution (Hamilton 1980, 1982). In this case, negative frequency dependent selection driven by coevolving parasites will maintain genetic variability for defence.

While these two ideas could naively be seen as competing, there is no reason to assume that they are mutually exclusive. In fact, the explanation of specificity can be nested within costs of immune defence. The maintenance of variation through specific interactions can be viewed as a trade-off between different immune traits. In other words, a form of an evolutionary cost of immune defence. Conversely, specificity may be seen as limiting immune defence costs by partitioning resources into a particular defence component, while reducing allocation to others (Frank 2000).

It seems reasonable to expect that specific host–parasite interactions and costly immunity both play a role shaping immune defences. However, a unification of the two has only received limited attention (Frank 2000; Jokela et al. 2000). Given that these unified models of defence merge two key and well-supported ideas of evolutionary ecology, they deserve further investigation.

Optimality in immunity

Maximum defence is not necessarily the optimal defence, especially when this would come at substantial costs for other fitness relevant traits. Due to the presence of costs in immunity, and variation between environments of the adaptive value of a particular immune response, the optimal immune defence will vary both temporally and spatially. Environments will differ in the threats they pose: the risk of exposure to parasites will vary, as will the virulence of those parasites. This landscape will shape selective pressures acting upon the immune system. This local optimization of immunity will lead to differences in the immune responses of different populations that have experienced diverse environments.

The idea of optimal immune defence varying in relation to the surrounding environment is one that is at the very heart of ecological immunology. Despite this, the question is not an easy one and researchers have often struggled to link host ecology and immune traits or resistance. A particular problem is that neither the environments in which hosts live, nor the host's immune system are simple. It is, for example, hard to categorize immunity as a single trait. It should be seen rather as a multi-faceted defence system. Furthermore, it is even harder to categorize host environments, especially the biotic environments, by a single or a few variables. It is likely that in even the best-studied natural systems there is not a complete list of parasites and pathogens for a particular host species, let alone a secured knowledge on the most critical host life-history stages that are affected by them. This incomplete picture makes it difficult to predict what the optimal investment in immune defences of a particular population should be. However, some studies have convincingly overcome these difficulties and have successfully linked host ecology and investment into immune defences. One example is a recent study of *Drosophila* antibacterial immunity that has shown an

association between the historical environment experienced by a host population and the contemporary levels of defence (Corby-Harris and Promislow 2008). Further, comparative studies related to group living have also demonstrated that particular ecological situations can be correlated with immunity. Social life and cooperative breeding are both predicted to have an increased risk of parasitism due to the communal living of closely related individuals. This would have an impact on the selection of optimal immune investment, with those species or individuals living in groups being selected to have a greater immune capacity. Support for this idea has come from the measurement of immune traits in cooperatively breeding and non-cooperatively breeding birds (Spottiswoode 2008), and in bees of different levels of sociality (Stow et al. 2007).

Plasticity in immunity as a response to a variable environment

We have previously talked about differences in immune investment in populations exposed to varied pressures in terms of genetic differences (see Corby-Harris and Promislow 2008). However, it is also possible that differences come about through phenotypic plasticity, where individuals respond to the prevailing environment and the perceived future risk. The ability to adjust facultatively investment into immunity depending upon the prevailing need will have a clear evolutionary benefit when immunity is costly, yet necessary to varying degrees across environments.

There are clear predictions and evidence suggesting that the threat of disease is related to the density of host individuals (Brown and Brown 1986; Daily and Ehrlich 1996). In line with this, it has been shown that organisms are able to assimilate information relating to density and adjust their investment into immunity accordingly (Barnes and Siva-Jothy 2000; Wilson et al. 2002). This

phenomenon, known as density-dependent prophylaxis, means individuals experiencing higher densities, where the risk of parasite exposure is generally thought to be greater, will invest into immunity at a higher level.

While it is possible for individuals to adjust investment into certain immune traits depending on the perceived risk (e.g. density-dependent prophylaxis), it is also clear that it would be beneficial to take into account the encountered threats to the integrity of self. Immune memory in vertebrates can be seen to function in this way (Delves et al. 2006), with future secondary responses being greater and offering more protection. Functionally, similar outcomes have been found in invertebrates, where the increase in immunity and protection can be long-lasting (Jacot et al. 2005b), independent of the relationship between first and second immune challenges (Moret and Siva-Jothy 2003), or show specificity (Sadd and Schmid-Hempel 2006). Adjustment of immunity dependent on prior immune experiences not only occurs within individuals, but can also span across generations in the case of trans-generational immunity in both vertebrates (Grindstaff et al. 2003, 2006) and invertebrates (Moret and Schmid-Hempel 2001; Little et al. 2003; Sadd et al. 2005; Moret 2006; Sadd and Schmid-Hempel 2007), and between individuals within social groups (Traniello et al. 2002).

It is easy to see from the examples above that immune responses vary across individuals and are not solely determined by the genetics of an individual. A particular immune response will certainly be genetically encoded to some degree, but will also be a product of such things as diet (Siva-Jothy and Thompson 2002; Martin et al. 2008b), gender (Kurtz et al. 2000; Rolff 2002; Joop et al. 2006), age (Doums et al. 2002; DeVeale et al. 2004), and past or ongoing biotic interactions, be they with conspecifics (Wilson et al. 2002) or heterospecifics, including parasites (Sadd and Schmid-Hempel 2006).

Considerations of future avenues

As discussed previously in this article, the evidence in favour of costly immunity is now abundant. Those working within the field of ecological immunology should therefore be careful about treading in the same footsteps, in doing so perhaps adding another study species to the list, but essentially adding nothing new to the picture. Researchers should rather expand their horizons and in doing so engage new challenges. While there are many fruitful research directions that deserve further attention, these cannot all be addressed here. Subsequently, this article will focus on the phenomenon of immune evasion and its broad ranging importance.

Immune evasion and manipulation

Up until this point the focus has been principally on the influence of the host and the host's environment in determining immune investment and responses against infection. However, the other side of an infection, the parasite or pathogen, can also have a large impact on the response. Parasites need time in a host to develop, reproduce and ultimately ensure transmission into a new host. However, during this time parasites are faced with a relentless barrage from the host's immune system. It is therefore not surprising that parasites have evolved counter measures, with evasion and manipulation of host immunity a widespread practice seen in both vertebrate and invertebrate hosts (Schmid-Hempel 2008). The strategies employed by parasites fall into two main categories: (i) avoidance of the immune response, and (ii) manipulation of immunity to favour establishment and maintenance of infection.

Parasites have evolved a number of strategies for avoiding the immune response of a host. Anatomical seclusion from the immune response is employed by the eye flukes *Diplostomum* spp. of fish that develop within the immune-privileged eye (Wegner et al. 2007), and in the larvae of braconid parasitoids that are protected from the immune response of their insect hosts by a serosal membrane (Grimaldi et al. 2006). Molecular mimicry is also widespread, where parasites produce host-like proteins to disguise themselves from the immune system (Salzet et al. 2000). Perhaps one of the most famous strategies for avoiding the host's immune response is that of antigenic variation employed by, among others, African trypanosomes. Trypanosomes keep a step ahead of the adaptive immune system and establish chronic infections by periodically switching the make-up of the 'variant surface glycoproteins' found on their cell surface (Stockdale et al. 2008).

Beyond merely hiding, parasites can avoid the full effects of an immune response by manipulating the host's immune system. Immune manipulation as an immune evasion strategy is used against recognition, signalling and effector arms of an immune response. Several viruses are known to downregulate the expression of MHC class I, and in doing so can circumvent immune recognition (Tortorella et al. 2000; Seet et al. 2003). Signalling pathways are a frequent target of manipulation by parasites (Schmid-Hempel 2008). *Toxoplasma gondii* hijacks immune regulation mechanisms of its vertebrate host (Luder and Gross 2005). In uninfected individuals, expression of a molecule known as FasL keeps sensitive areas such as the vertebrate eye immune-privileged by inducing apoptosis of immune cells. *Toxoplasma gondii* utilizes this pathway to cause the apoptosis of immune cells outside of these immune-privileged areas, thus lessening the immune

response against it. Effector molecules of the host response can also be nullified by parasites. *Staphylococcus aureus* uses a metalloproteinase to cleave and therefore inactivate a human antimicrobial peptide (Sieprawska-Lupa et al. 2004). The examples here only give a faint taste of the multitude of strategies that are employed by parasites across the taxonomic spectrum (Hornef et al. 2002; Sacks and Sher 2002; Seet et al. 2003). Furthermore, within one parasite many strategies may be employed in unison, as is the case in African trypanosomes (Donelson et al. 1998).

Very few studies in the area of ecological immunology consider parasites other than as factors that elicit an immune response. In many ways, this approach has been successful, with the use of benign immune elicitors or inactivated parasites enabling control over the level of immune activation without confounding virulence effects. Most of the studies referred to earlier in this article that address fundamental questions in ecological immunology used inactivated parasites or components of parasites. However, incorporating parasites as active players into studies of ecological immunology, and in doing so accepting that immune systems will additionally have been selected for resilience against parasite sabotage strategies, is likely to be a fruitful avenue for understanding variability in immune defence. Moreover, there is a high likelihood that the genetic underpinnings of immune evasion will also be variable. For example, the *var* genes involved in immune evasion by *Plasmodium falciparum* show high degrees of polymorphism and also a level of geographic structuring (Barry et al. 2008). Additionally, the expression of these immune evasion traits may also depend on the environment experienced by the parasite. Acquired immunity to the rodent malaria *P. yoelii* leads to transcriptional changes in the expression of putative immune evasion factors (Cunningham et al. 2005). Given the last two points concerning polymorphism and environmental dependence, together with what is already well characterized concerning immunity and the environment, it is clear that a multitude of interactions are possible. A significant challenge for the future will be getting a grasp of these interactions through thoroughly and thoughtfully designed experiments, followed by subsequent piecing together of their relevance. For example, an optimal immune response may no longer be the one that is energetically most efficient, but one that is safest against subversion and manipulation by parasites (Bergstrom and Antia 2006).

Conclusion

The essential points to take from the findings of the field of ecological immunology are: (i) immune defences do vary in nature, (ii) immune defences can be costly, (iii)

optimality of immunity will rarely be achieved and only transiently, and (iv) observed immune defences will depend on both historical and contemporary factors within an individual's environment. Combining these concepts with a thorough understanding of the mechanistic details of immunity will enable predictions concerning the use and strength of particular immune components. For example, it can be helpful to consider major issues such as immunopathology in this way (Graham et al. 2005). Furthermore, including an in-depth knowledge of relevant parasites into this framework will enable health and disease prevention programmes that are targeted and specific to the situation at hand.

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