MOLECULAR ECOLOGY

Molecular Ecology (2011) doi: 10.1111/j.1365-294X.2010.04938.x

OPINION

Wild immunology

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Abstract

In wild populations, individuals are regularly exposed to a wide range of pathogens. In this context, organisms must elicit and regulate effective immune responses to protect their health while avoiding immunopathology. However, most of our knowledge about the function and dynamics of immune responses comes from laboratory studies performed on inbred mice in highly controlled environments with limited exposure to infection. Natural populations, on the other hand, exhibit wide genetic and environmental diversity. We argue that now is the time for immunology to be taken into the wild. The goal of 'wild immunology' is to link immune phenotype with host fitness in natural environments. To achieve this requires relevant measures of immune responsiveness that are both applicable to the host–parasite interaction under study and robustly associated with measures of host and parasite fitness. Bringing immunology to nonmodel organisms and linking that knowledge host fitness, and ultimately population dynamics, will face difficult challenges, both technical (lack of reagents and annotated genomes) and statistical (variation among individuals and populations). However, the affordability of new genomic technologies will help immunologists, ecologists and evolutionary biologists work together to translate and test our current knowledge of immune mechanisms in natural systems. From this approach, ecologists will gain new insight into mechanisms relevant to host health and fitness, while immunologists will be given a measure of the real-world health impacts of the immune factors they study. Thus, wild immunology can be the missing link between laboratory-based immunology and human, wildlife and domesticated animal health.

Keywords: disease ecology, eco-immunology, ecological immunology, parasitology, wild mammals

Received 4 August 2010; revision received 15 October 2010; accepted 18 October 2010

Introduction

The advances in molecular biology of the last few years, especially with the advent of full genome sequencing, promised to 'decode all life' and in the process offer previously unforeseen solutions to disease and human health (Butler 2010). However, if we are to translate the exponential growth of molecular data into real-world benefits, much work is needed to disentangle the many sources of variation between genes, phenotypes and the environment (Weinberg 2010). Similarly, immunologists are continuously enhancing our mechanistic understanding of immune processes, yet little has been tested in the context of natural populations, including humans. In the few cases in which laboratory techniques have been applied in the wild, such natural variation has led to unforeseen outcomes for disease spread and vaccination success (Cooper *et al.* 1998; Harris *et al.* 2009; Ezenwa *et al.* 2010; Wammes *et al.* 2010). We assert that now more than ever, a two-way feedback between laboratory and field studies will deliver tangible advances in the well-being of humans, wildlife and domesticated animals. We propose that recent progress in genomic and postgenomic techniques and their ever-greater affordability at last allow us to take immunology into the wild and study how variation in genes and environment affect the key processes that maintain health.

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Understanding how natural populations are affected by their interactions with pathogens (e.g. viruses, bacteria, protozoans, helminths, etc.), commensal organisms and environmental heterogeneity is crucial. However, very little is known about how health and immunity are shaped by co-infection when both the environment and the host and pathogen genotypes vary. The field of ecological immunology ('eco-immunology') has begun to address the complexity of immune responses in an ecological and evolutionary context. The primary goals of this field have been to understand variation in immune function across individuals, with a focus on determining the fitness consequences of such variation (Norris & Evans 2000; Rolff & Siva-Jothy 2003; Schmid-Hempel 2003). This has led to some exciting discoveries and an increase in the crosstalk between ecology and immunology, which have previously been mostly disparate fields (Viney *et al.* 2005; Martin *et al.* 2006; Salvante 2006; Bradley & Jackson 2008; Graham *et al.* 2011; Hawley & Altizer 2011).

This crosstalk is helpful as immunologists and ecologists often speak and think differently about infections and the immune response. However, an important challenge remains to use state-of-the-art tools from each discipline to test and expand their respective outstanding questions. Immunologists know much about the immune responses of very few strains of mice, but very little about their relevance to mammalian (human or other) immune responses in the wild. On the other hand, ecologists have the tools to study complex interactions and variability, but typically have very little grasp on their mechanistic underpinnings because of a lack of relevant techniques. We need to build a bridge between these fields within an evolutionary framework that will allow us to test the relevance of mechanisms identified in laboratory models to the health of individuals in natural populations and, in return, to bring variation into the laboratory to better understand the immune system. Here, we aim to highlight how wild immunology can create synergistic benefits for our understanding of immunology, ecology, evolution and health.

Why study immunology in the wild?

Why would immunologists want to work on wild systems? Moving from highly controlled laboratory settings with a constant supply of food and water, limited genetic diversity, controlled infection and trusted immune markers to the wild, with high genetic diversity, multiple infections, variable nutrition and difficulty in recapturing animals seems to be an unattractive proposition. However, only under natural conditions is one likely to measure the effects of immune phenotypes on host health and fitness. Crucially, wild immunology will help link mouse and human immunology, because humans are a lot more like a wild mammal than a caged laboratory mouse; we live in variable environments, are genetically diverse, and suffer multiple simultaneous and sequential infections as do wild mammals (Ezenwa *et al.* 2010, Telfer *et al.* 2010). In addition, wild immunology should inform therapeutic intervention strategies, because the range of natural conditions that wild animals face better reflect the challenges faced by human treatment programmes. While controlled laboratory settings are good for reproducibility of results, immunologists have long appreciated that the genetic background has a major effect on immune responses and susceptibility to pathogens (Reiner & Locksley 1995). It is indeed clear for both ecologists and immunologists that immune responses, and ultimately health, are the result of many contributing factors: (i) genetic variability (e.g. MHC alleles), (ii) history of infection (immune memory, current infections), (iii) physiological condition (e.g. sex, age, reproductive state and history), (iv) resource availability (e.g. diet), (v) abiotic conditions (e.g. seasonality and temperature) and (vi) co-evolutionary history between host and pathogen.

Life in the wild is tough. Individuals face both biotic and abiotic pressures that will affect their survival and reproduction. Many of these pressures may also affect immune function and the costs associated with mounting a response. Factors that will affect host fitness and will likely affect the immune response are pathogen interactions, resource limitation, competition, predation, seasonality and sex differences, etc. (Martin *et al.* 2008; Lazzaro & Little 2009). Recent studies on wild populations of field voles (Telfer *et al.* 2010) and African buffalo (Ezenwa *et al.* 2010) have shown the importance and complexity of parasite–parasite interactions for determining disease prevalence and the invasion of novel infectious diseases. These studies have the potential to change our overly narrow approach to modelling and treating infectious diseases one at a time (Fenton *et al.* 2008; Lafferty 2010).

In addition, we know that wild populations are outbred and therefore have a high degree of genetic variation that likely affect the components that make an immune response protective (Abolins *et al.* 2011). It is also becoming clear that the gut microbiota communities of wild mammals affect both the development of the immune system (Chung & Kasper 2010; Round & Mazmanian 2010) and the establishment and transmission of co-infecting parasites (Hayes *et al.* 2010). Currently, the importance of such diversity for host health is unknown. However, given these early findings from laboratory systems, there is great potential for both of these factors to structure the immune system and its interactions with parasites and thus to affect the

outcome of therapeutic interventions. Given this knowledge and the increasing availability and affordability of genetic tools, it is time to reevaluate the costs and benefits of studying mammalian immunology in wild populations. To date, laboratory immunology has mostly focused on a few strains of mice, and only some studies look at comparative responses across these strains, which often differ substantially (Butler 2010). For example, pathogenesis of *Leishmania* infection differs greatly between BALB/c mice, which develop a more pronounced anti-macroparasitic Th2 response when infected and C57BL/6 mice, which develop a classically anti-microparasitic Th1 response (Reiner & Locksley 1995). Likewise, while BALB/c mice allow the filarial nematode *Litomosoides sigmodontis* to release transmissible offspring, C57BL/6 mice are resistant to this parasite, and this protective immune phenotype requires IL-4, a major component of the Th2 response (Le Goff *et al.* 2002; Babayan *et al.* 2003). In addition, studies from human populations suggest that ethnicity, age and sex can affect rates of re-infection with *Schistosoma mansoni* after drug treatment (Pinot de Moira *et al.* 2010). Thus, it should be clear that the mixture of genotypes in natural populations, in concert with the biotic and abiotic pressures that affect fitness, will alter the landscape of disease occurrence and resistance throughout the population as well as responses to intervention. Therefore, to truly understand how the immune system functions, protects the host from disease or causes immunopathology, it is crucial to bring our impressive immunological toolbox into wild populations to measure immune phenotypes.

How to study wild immunology?

Many ecological studies use the term 'immune function', but do not properly define it, which is problematic as it can be overly general and have many different meanings for different disciplines. Often immune function is used as a catch-all phrase to describe the complete immune response, the immune system, or the specific components of an immune response that are elicited against a specific pathogen infection. Following the terminology proposed by Bradley & Jackson (2008), we define 'immune phenotype' as the multivariate, context-dependent state of the immune system at any given time. Thus, we could go out into a natural population to sample an animal and measure its immune phenotype (antibodies, cytokines, cellular responses, etc.). Consequently, the 'protective immune phenotype' is defined as the subset of the immune phenotype that protects an organism from disease (both pathogens and immunopathology). A protective immune phenotype will be defined by the commonalities across individuals infected with a specific pathogen that either clear the infection, or tolerate it and survive with little harm. A protective immune phenotype can not always be measured by looking at one immune factor or by measuring the magnitude of a specific immune response i.e. antibody titres, proliferative response to mitogen, T-cell proliferation or activation), as it is most probably the result of multiple factors acting in concert. Traditionally, ecological immunology studies in wild populations have focused on measuring a single or very few general measures of immunocompetence i.e. phytohemagglutinin (PHA) assays, leucocyte counts, L:H ratio, bacterial killing assays, phagocytosis (Norris & Evans 2000; Lee & Klasing 2004), but it is indeed unlikely that there is a single measure of immune function that will predict the outcome of infection or host health. More realistically, a protective immune phenotype will be multi-dimensional, dependent on the taxonomic class of the pathogen (i.e. virus, helminth, bacteria, etc.), the pathogen's immune evasion strategies and the history of exposure (i.e. primary vs. secondary immune response), such that aiming for a single immunocompetence measure is not a realistic benchmark for wild immunology (Viney *et al.* 2005; Lemus *et al.* 2010).

The immune phenotype is thus purely descriptive and broad, while the protective immune phenotype is the subset of that immune phenotype that enhances host fitness. More formally, identifying the protective immune phenotype requires determining the direction of the causal relationships between variation in host health and variation in immune phenotype and can only be measured through longitudinal sampling or experimental manipulations. Furthermore, both are context-dependant (i.e. dependent on host genotype, pathogen infection and co-infection, history of infection and exposure, and the biotic and abiotic environment). For example, a protective immune phenotype that would likely be effective against helminth infections will require an active Th2 response (CD4 + T cells, IgE, eosinophils) (Anthony *et al.* 2007). In contrast, a protective immune phenotype of a host infected with a virus would have an activated Th1 response (type 1 interferons, type 1 antibody, CD8+ cytotoxic T cells) (Pamer 2009; Welsh *et al.* 2010). Measuring and identifying a protective immune phenotype in wild populations will be difficult and will certainly require broad preliminary descriptive measures (of our 'immune phenotype'), we would therefore suggest measuring as many factors that have been identified from laboratory-based immunological studies as possible.

Similar ideas are being presented in human immunology, and there is a call to move away from a mouse model of human health, to instead develop noninvasive sampling 'metrics' that can distinguish a healthy

immune response from an unhealthy one (Davis 2008; Leslie 2010). Following from this, if we define a protective immune phenotype as the effective or optimal strategy, we also need to understand that more, or a stronger immune response, is not always better (Viney *et al.* 2005; Graham *et al.* 2011). In addition, a protective immune phenotype that responds effectively to a parasite infection, by controlling or eliminating the parasite and increasing host fitness, may not be correlated with a host's protective immune phenotype to a different pathogen. These trade-offs in the immune response to different pathogens have the potential to be important for host health and pathogen transmission in cases of co-infection (Fenton *et al.* 2008). For example, studies from human populations have shown that helminth infections, which are often associated with a strong Th2 response, may impair immune responses to concurrent co-infections or vaccination. Specifically, helminth infection can influence immune regulation (T regulatory cells (Treg) and IL-10), which can impair the efficacy of immunization, by suppressing immune responses to BCG (tuberculosis), *Plasmodium falciparum*-parasitized red blood cells (Wammes *et al.* 2010) and to tetanus vaccination (Cooper *et al.* 1998). Given that a higher immune response (e.g. higher antibody titres, increased inflammation) does not always maximize host fitness or eliminate that pathogen, the definition of a protective immune phenotype allows a nonlinear relationship between the immune phenotype and host fitness. To identify and measure this protective immune phenotype, we need to measure functional aspects of the immune response, parasite/pathogen fitness and host fitness through experimental or longitudinal studies (Viney *et al.* 2005; Graham *et al.* 2011).

While the aim of wild immunology is to develop tools that can be used in many wild animals, it may be most advantageous to start with systems that are phylogenetically related to immunologically well-studied animals and amenable to experimentation with large sample sizes. In particular, we suggest developing wild rodent systems. These will allow us to adapt the vast genetic and immunological resources that have been developed with the laboratory mouse model of mammalian immunology to wild mice and voles (e.g. Jackson *et al.* 2009, 2011; Abolins *et al.* 2011). For example, Abolins *et al.* (2011) in this issue compare wild house mice (*Mus musculus* C57BL/6 strain) to laboratory mice (*M. musculus* C57BL/6 strain) to assess the quantitative and qualitative nature of immune function in wild populations. They find that wild mice tend to have higher and more variable immune responses (both more avid antigen-specific responses and greater standing concentrations of IgG and IgE antibodies) than a relatively immuno-responsive laboratory strain (C57BL/6).

Techniques and approaches for wild immunology

There are many new and existing technologies that can be employed for the study of wild immunology, both by utilizing immunological tools developed for model systems and through new molecular approaches. Using techniques and tools from laboratory systems is a necessary first step, but because a protective immune phenotype in a laboratory system may differ from what is protective in a wild animal, we suggest a three-stage programme to develop new model systems for wild immunology. The first phase of establishing such a model would involve deep sampling of a limited number of individuals in a wild population for immune variables, host demography and parasitology to collect extensive information about host–parasite interactions and the immune phenotypes of individuals. As a first pass, wild immunologists would test the full arsenal of techniques and tools that have been optimized for phylogenetically closely related species, and where possible, optimize them for the wild species. Second, from this wealth of information, the goal would be to identify representative markers that can be reliably measured and that capture the diverse arms of the immune system. These may be a set of individual immune factors (i.e. quantitative PCR assays that measure cytokines, cell identification, antibody concentrations), or a multivariate component of these factors (such as a principal component analysis of several individual immune factors) that captures as much of the immune phenotype as possible for a given host–pathogen combination. The ultimate aim is to develop noninvasive markers to allow longitudinal sampling, which will be crucial for inferring causation and identifying the protective elements of an immune phenotype. Third, one would set up a longitudinal field study or experimental manipulation, to measure the immune phenotype in combination with host demography and parasitology. From here, we can make connections between immune phenotypes that increase fitness for specific pathogen pressures (i.e. the protective immune phenotype), and with this knowledge, we can begin to address the fundamental and interesting questions about how life in the wild may affect the development and expression of a protective immune phenotype.

Standard laboratory immunology approaches

Unfortunately, the study of immunology in nonmodel species suffers from a lack of reagents needed to measure immune phenotypes (Bradley & Jackson 2008). However, a representative subset of specific immunological reagents (such as monoclonal antibodies) could

be developed for new species that could complement other measures. In a few cases, it may be possible to use laboratory reagents created for humans, laboratory mice, poultry, or domestic animals that work effectively in nonmodel organisms (Lee & Klasing 2004; Martin *et al.* 2007; Ezenwa *et al.* 2010; Graham *et al.* 2010). For example, Jackson *et al.* (2009) used reagents developed for laboratory mice to measure splenocyte proliferation and toll-like receptor expression in wild wood mice (*Apodemus sylvaticus*) and found negative associations with some parasite infections and innate immunity activation. In addition, Abolins *et al.* (2011) have used several techniques developed for laboratory mice (e.g. in vivo immunization and in vitro splenocyte stimulation with keyhole limpet haemocynanin (KLH) to measure IFNγ, IgG and IgE, and FACS analysis of T helper and regulatory cells) in wild house mouse populations, and it is possible that some of these mouse-specific reagents will work in related wild rodents. In addition, ELISA for detecting IgG antibodies to KLH has been used in laboratory populations of more than six species of *Peromyscus* mice to measure variation in standing and elicited responses (Martin *et al.* 2007). Following on, several bird studies have successfully used techniques and tools developed for the poultry industry, but adapted to work in wild birds (Lee & Klasing 2004; Salvante 2006), for example circulating CD4 and CD8 cells were measured in wild caught kestrels using flow cytometry and mouse antiavian monoclonal antibodies originally designed for poultry (Lemus *et al.* 2010). In addition, tools and techniques developed for livestock have been successfully adapted to wild ungulate systems (Jolles *et al.* 2008; Ezenwa *et al.* 2010; Graham *et al.* 2010). Recently, Ezenwa *et al.* (2010) measured both baseline and antigen-stimulated interferon γ (IFNγ; as a measure of Th1 immune function) using reagents designed for cattle.

Many of the standard immunological assays that have been commonly used in ecological immunology (i.e. white blood cell counts from smears, PHA assays, bacteria killing assays, etc.) may, in some cases, be useful for measuring an immune phenotype. However, to assess parasite-specific immune phenotypes, more detailed measurements of immune components are needed beyond the classical eco-immunology tool set. Recent evidence from an experimental study that monitored the immune response after parasite infection and vaccination demonstrated that many standard measures (WBC counts and PHA assay) did not reveal the important changes in circulating lymphocytes detected through flow cytometry (Lemus *et al.* 2010).

Classical immunological tools and techniques may be useful in closely related species, but will probably not have much applicability for distantly related mammals. In cases where these tools cannot be readily adapted, newly available molecular approaches should provide a useful alternative for nonmodel organisms, and collaborative efforts across research groups to develop classical immunological reagents for new model organisms (i.e. a zebra finch immunology consortium) could create standard tools available for new groups of wild species. For instance, it would be highly desirable to produce monoclonal antibodies specific for major cytokines and antibody isotypes, markers of cell type and activation state as is standard for laboratory mice. However, such standard immunological techniques used in laboratory immunology are often invasive and may only be useful in some aspects of wild immunological studies. We suggest that developing and investigating both standard invasive and noninvasive techniques during the first phase of investigation will be useful for characterizing the multi-dimensional immune phenotype. For example, invasive (terminal) sampling of the spleen, lymphoid organs and blood samples can be used to measure both local and systemic immune responses. Identifying strong correlations between invasive and noninvasive data would then allow later studies (phase 3 of our suggested research programme) to use only the most informative noninvasive sampling methods that are amenable to ecological approaches and longitudinal sampling.

Genomic approaches

The progress of relatively inexpensive high-throughput sequencing technology has opened the path for immune studies on nonmodel animals, and it is now in principle feasible to reach a significant coverage of the genome of any species. In addition, the extensive knowledge of the *M. musculus* genome provides the basis for accurate identification of many genes of other rodent species, which can then serve as a reference for comparative transcriptomic studies of immune (or other relevant) gene transcription profiles (Waterston *et al.* 2002). This will facilitate the design of more accurate primers for immune genes than the currently used degenerate primers, for example to quantify the mRNA production of known immune genes in wild mice based on knowledge of the immunology of *M. musculus* in the laboratory (Jackson *et al.* 2011). Linking this kind of study with experimental manipulations in the field or within longitudinal studies that measure both co-infection and host fitness is a goal of wild immunology. Further, deep sequencing can be expected to allow mapping multiple genes to complex immune phenotypes. In addition, the recently published zebra finch genome (Warren *et al.* 2010), and the rapidly decreasing costs of genome sequencing, may provide templates for developing

immunological markers, both genomic and protein-based, for birds.

Postgenomic approaches

Recent advances in deep sequencing technology promise unprecedented scope for the mechanistic understanding of health and immunity. Until now, only small numbers of genes, usually stemming from a candidate gene approach, could be studied. An example is the study by Jackson *et al.* (2011) who use quantitative PCR methods, developed from sequence data on laboratory mice and other rodent sequences to measure cytokine mRNA in natural populations of field voles. The authors used this qPCR approach in concert with standard laboratory immunological assays (i.e. mitogen stimulation of toll-like receptors and Th cell responsiveness in splenocyte culture) to measure immune expression and variation in a wild rodent population (Jackson *et al.* 2009, 2011). Through the deep sequencing of transcriptomes, large-scale identification of gene expression patterns can also provide longitudinal accounts of protective immune phenotypes and immune correlates of health. If combined with experimental manipulation in the wild, causal links between molecular patterns and individual infection and health status become possible. Postgenomic tools are commonly used in human immunology because of the constraints of noninvasive sampling techniques, and borrowing and adapting these tools and biomarkers to wild immunology systems will be very important. For example, measuring the peripheral-blood transcriptome (Mohr & Liew 2007), quantifying genome-wide expression through oligonucleotide arrays of peripheral leucocytes (Cobb *et al.* 2005), and identification and quantification of microRNAs in serum (Gilad *et al.* 2008) could all help measure host health, parasite infection or specific protective immune phenotypes. Building these postgenomic tools to test immune phenotypes across nonmodel organisms will allow us to look at comparisons of the immune phenotype and the functional evolution of the immune response across species and eventually to generalize immune processes across taxonomic boundaries (Martin *et al.* 2007).

Host demography and parasitology

Wild populations are a composite of individuals of different age, sex, sexual maturity, reproductive state (e.g. gravid, lactating) and are at different population densities and within communities of different species compositions. This variation at the individual and population scale will influence host susceptibility and exposure to parasites and therefore will affect immune priming and maintenance of immune memory and ultimately, host fitness (Martin *et al.* 2008; Lazzaro & Little 2009). In turn, host survival and reproduction will affect population density and future pathogen transmission. Thus, to truly understand a protective immune phenotype, measures of host demography and fitness and parasite transmission must also be included in the studies of wild immunology (Viney *et al.* 2005; Graham *et al.* 2011). In addition, both the history of infection and concurrent infections, both at the individual level and over evolutionary history, will be very important for giving context to a specific immune phenotype. Thus, studies that identify and measure the vast community of parasites and pathogens that can infect a natural population, not just a single pathogen species, will be crucial (Pedersen & Fenton 2007). As many methods of sampling for pathogens use visual identification and are difficult to scale up for large experimental studies, we suggest incorporating diagnostic tests (antibody-based or sequence-based) to facilitate the detection of multiple pathogens.

How do we link wild and laboratory immunology?

While it may be quite obvious how introducing immunological tools can inform the study of wild population health and dynamics, it may be less clear how wild immunology can contribute to laboratory immunology. We suggest that there are several reasons for immunologists to consider bringing their research questions, tools and expertise to the wild. First, wild immunology can help laboratory immunologists identify which aspects of the immune response are relevant for a protective immune phenotype in a natural setting. This is especially important considering that unexpected dynamics can emerge from interactions between parasite and host communities (Pedersen 2005; Telfer *et al.* 2010). Next, as immunologists gain an ever more detailed understanding of immune mechanisms from laboratory experiments, it becomes highly relevant to weigh these advances in the context of natural populations. Wild immunology studies that incorporate immunology, parasitology and demography will allow immunologists to understand how life in the wild may affect various aspects of an immune response, and to define how natural variation between individuals and over time affect the diversity of factors that contribute to an individuals protective immune responses. In addition, the study of wild immunology may bring us closer to understanding immunity in humans, and how best to improve health. For example, using a wild study system may inform strategies for how vaccines can be

designed to immunize hosts under environmental stressors or co-infection. It is also well documented that diet and nutrition (e.g. protein scarcity, extreme lipid contents) can affect immune responses and lead to different immune phenotypes (Koski *et al.* 1999; Ing *et al.* 2000). Thus, pairing the wild immunological approach with diet manipulations may better inform immunization and treatment strategies.

Unfortunately, there may be limits to how much information inbred strains and controlled laboratory settings can inform human, livestock and wildlife health studies, and therefore, a wild immunology approach that incorporates genetic variation and other ecological noise may be necessary to broaden our knowledge. We propose a link from laboratory studies to the wild, and from wild immunological studies back to the laboratory. This two-way approach may further enlighten the mechanisms driving the immune response, and how they are likely to affect host health and fitness in the wild. However, comparing results between laboratory and wild systems will not be straight-forward. For example, Abolins *et al.* (2011) in this issue attempt to do this with wild populations of house mice, but there are still questions about how many laboratory strains we need to test to make sure that the variability and degree of response is consistent with or different from what we find in wild mice. So it seems that one of the most important reasons to develop wild immunology (to understand the consequences of genetic diversity for immune response and host fitness) may also be our biggest hurdle.

Conclusions

To identify causal relationships between immune phenotypes and parasite prevalence (i.e. to define protective immune phenotypes), experimental manipulations in wild populations will be essential. These may be able to inform optimal treatment strategies that take into account the interactions between co-infecting pathogens. It may be, for instance, that the most effective strategy to reduce viral infections and increase health and fitness of a given population is to mass treat against helminths. Such counter-intuitive approaches can only be tested with manipulative studies on wild populations (Pedersen & Fenton 2007), at scales that are unwieldy for livestock, and difficult in humans for ethical reasons. We acknowledge that bringing the tools and techniques from laboratory immunology into wild populations will be a difficult task. However, given the pressing challenges for human, livestock and wildlife health (e.g. emerging pathogens, selection of drug-resistance, zoonotic diseases) and the recent expansion of genomic and post-genomic tools that are now available, we believe that now is the time for wild immunology. This can be accomplished if immunologists, ecologists, evolutionary biologists, disease biologists, parasitologists and others bring their expertise together to work on these complex and dynamic systems. Eventually, detailed studies across multiple wild systems may also allow phylogenetic comparative studies of immune strategies across populations and species. Here, we have tried to show why now is the time for wild immunology, what techniques and approaches can be used to develop non-model study systems and how immunologists and ecologists can bring their unique toolboxes together to answer shared questions about the role of the immune system in natural populations and give greater insight into how the host immune response, pathogens and environment interact in the wild.

Acknowledgements

We thank Steve Paterson, Dana Hawley, Andrea Graham, Karen Fairlie-Clarke, Tom Little, Andy Fenton, Judi Allen, Emily Griffiths, Vincent Straszewski and one anonymous reviewer for very helpful comments on the manuscript. ABP is supported by a Wellcome Trust Centre for Infection, Immunity and Evolution (CIIE) Advanced Fellowship and SAB is supported by a Wellcome Trust CIIE Junior Fellowship at the University of Edinburgh.

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A.B.P.'s research goal is to expand the one host – one parasite framework that dominates the study of disease ecology and evolution, specifically developing two major projects under this theme: (1) to evaluate the interactions that occur between co-infecting parasites within a host and their consequences for the immune response and host health and (2) to expand our knowledge of multi-host parasites, in particular to test the ecological factors that facilitate persistence of a recently emerged disease on a new host. S.B.'s research interests are to understand how parasites ensure their survival and transmission in the face of the host's immune responses. Specifically, parasitic nematodes employ immune-dependant phenotypic plasticity and immune manipulation to ensure they transmit; S.A.B. is interested in identifying the mechanisms that underlie these strategies in order to inform vaccine design against parasitic nematodes, and how host diversity in genetic, nutritional, and infectious backgrounds interacts with parasite life history and host immunity.