Why do adaptive immune responses cross-react?
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Abstract

Antigen specificity of adaptive immune responses is often in the host’s best interests, but with important and as yet unpredictable exceptions. For example, antibodies that bind to multiple flaviviral or malarial species can provide hosts with simultaneous protection against many parasite genotypes. Vaccinology often aims to harness such imprecision, because cross-reactive antibodies might provide broad-spectrum protection in the face of antigenic variation by parasites. However, the causes of cross-reactivity among immune responses are not always known, and here, we explore potential proximate and evolutionary explanations for cross-reactivity. We particularly consider whether cross-reactivity is the result of constraints on the ability of the immune system to process information about the world of antigens, or whether an intermediate level of cross-reactivity may instead represent an evolutionary optimum. We conclude with a series of open questions for future interdisciplinary research, including the suggestion that the evolutionary ecology of information processing might benefit from close examination of immunological data.

Introduction

One of the most startling and impressive features of the vertebrate adaptive immune system is its ability to recognize and bind diverse parasite antigens. As part of this process, the immune system is able to generate extraordinary specificity of antibodies to particular antigens. This specificity is an axiomatic feature of the adaptive immune system, but it is also an incomplete picture. Cross-reactivity of lymphocyte receptors and antibodies to parasite antigens is common, with important consequences for both host and parasite, in terms of host health (e.g., Fesel et al. 2005; Urbani et al. 2005), antigenic variation (Lipsitch and O’Hagan 2007), parasite strain structure (e.g., Recker and Gupta 2005; Koelle et al. 2006a), and epidemiological dynamics (e.g., Adams et al. 2006; Koelle et al. 2006b; Wearing and Rohani 2006). However, the extent to which we should expect to see cross-reactivity of adaptive immune responses has not been fully explored, especially for antibodies.

In this perspective, we consider whether cross-reactivity is an evolved trait of the immune system, driven by conflicting costs and benefits of antigen specificity, or whether it is an inescapable side-effect of the problem of recognizing and binding to an enormous range of putative antigens. Throughout, we will use ‘parasite’ in a general sense, to include all infectious disease agents, and we define ‘specificity’ as the ability of the immune system to discriminate among antigens and ‘cross-reactivity’ as the absence of discrimination, in accordance with general (Janeway et al. 2001) as well as evolutionary (Frank 2002) immunological usage. Cross-reactivity is also known as ‘heterologous immunity’ (Page et al. 2006) or, in some contexts, by the more colorful term ‘original antigenic sin’ (e.g., Liu et al. 2006). Here we use ‘cross-reactivity’ to cover all cases. We would also stress that specificity and cross-reactivity should be considered endpoints of a spectrum rather than strict alternatives, and we would hope that our approach encourages thinking about quantitative predictions for the level of cross-reactivity we might expect lymphocytes or antibodies to exhibit.

To address whether cross-reactivity of adaptive immune responses is an evolved trait or a side-effect of biological or chemical constraints, we explore the...
The immune system as an information gatherer and processor

Precise phenotypic adaptation to environmental conditions requires that organisms process information about their surroundings in order to make appropriate context-dependent decisions (Dall et al. 2005). Optimal foraging decisions, for example, depend upon the ability of a forager correctly to perceive the relative resource value of different patches of food, in light of associated costs of foraging such as threats of predation (Stephens et al. 2007). Optimal offspring sex ratios for a given intensity of local mate competition require that female parasitoid wasps accurately perceive the number of other females laying eggs on a patch (Shuker and West 2004; Burton-Chellew et al. 2008). The mammalian immune system must similarly tailor action to context by processing information about the world of antigens: in the face of unpredictable exposure to diverse parasites, a host must perceive infections, identify parasites, and then mobilize the appropriate mechanisms to kill those parasites. In each of these examples of phenotypic adaptation, understanding the mechanisms by which information is gathered and translated to action – i.e., information processing – can help to explain why organisms may fail to be perfectly adapted to their environments (West and Sheldon 2002; Shuker and West 2004; Dall et al. 2005).

For the immune system, is the apparent imperfection in discrimination of parasite antigens (manifested as cross-reactivity) a deliberate strategy to fight parasites across antigenic space with cross-reactive antibodies, or merely an information constraint imposed by the task faced by the immune system?

The antigen recognition task of the adaptive immune system is not easy: it must distinguish self from nonself, and one parasite from the next, in a sea of molecules. The innate immune system drives the process of sifting through this antigenic information (Janeway and Medzhitov 2002), but it is the adaptive immune system, via T and B cells, that possesses the remarkable machinery necessary for posing ‘search terms’ over antigenic space, and for recognizing matches to those terms (Fig. 1). We thus consider that the immune system gathers information by binding to parasite antigens, with a failure to obtain that information (a failure to recognize and bind to a parasite antigen) posing a serious risk to the organism’s health (and we also note that avoiding being observed by immune systems is a legitimate and not uncommon strategy of parasites (Maizels et al. 2004; Tortorella et al. 2000)). The capacity of lymphocyte receptors to recognize antigen is in theory infinite (Pancer and Cooper 2006). However, this initial searching of antigenic space is only the first step taken by the immune system (Fig. 1). Via somatic hypermutation, B cells generate more specific receptors for a given antigen, which can be construed as a form of ‘local searching’ of antigenic space, or gaining very specific information about the antigen to inform further action, which in this case is the generation of antibodies by plasma cells (Fig. 1). B cells may provide a more focused information-gathering capacity, as they provide very fine-grained information about a certain part of antigenic space.

Despite this sophistication, antibodies often do cross-react with, and take action against, antigens displayed by parasite strains or species other than the one that induced the initial response. Is this cross-reactivity a deliberate feature of the overall strategy of the immune system, or an unselected constraint posed by the realities of antigenic variation? To address this, we first turn our attention to the initial searching problem faced by T and B cells.

How should the immune system search antigenic space?

Given the huge range of possible antigens that an immune system might have to recognize, how best should the immune system cover, or search, antigenic space? In particular, in terms of the adaptive immune system, how specific should the T and B cell repertoire be?

Energetic and other constraints affect many aspects of immunological function (Viney et al. 2005; Martin et al. 2007), and the degree of antigen specificity is probably no exception. Hosts may be constrained by lymphocyte numbers as well as the need to avoid self-damaging responses in their search of antigenic space. For example, the lymphocyte pool of each person bears millions of different T-cell receptors and billions of different B-cell receptors, but every mammalian cell may display $10^{12}$ potential
protein antigens on its surface (Sun et al. 2005), and parasites of mammals span a huge range of biological (and probably antigenic) diversity – from archaea (Lepp et al. 2004) to metazoa (Maizels et al. 2004). Given these constraints, attempts have been made to predict the information-gathering potential of lymphocytes. Empirically grounded theoretical work suggests that, prior to exposure to antigen, a certain degree of cross-reactivity in the lymphocyte search algorithm is essential (Langman and Cohn 1999). Indeed, hosts may ensure recognition of a large parasite set, or a rapidly evolving parasite set of any size, by coarse-graining antigen recognition (Oprea and Forrest 1998), enabling production of antibody libraries that are strategically placed to generalize over antigenic space (Oprea and Forrest 1999). Moreover, the optimal level of cross-reactivity increases with decreases in repertoire size – i.e., fewer lymphocyte receptors must cross-react more, to cover antigenic space – but that strategy risks autoimmunity (Borghans et al. 1999). To balance these factors for the size range of the human repertoire, a low degree of cross-reactivity is optimal for both T (van den Berg et al. 2001; Borghans and De Boer 2002) and B cells (Louzoun et al. 2003).

Theory further suggests that a receptor’s cross-reactivity should be adapted to the portion of antigenic space in which it binds (Fig. 2). By this logic, receptors very unlikely to bind self antigens should have wide circles of reactivity. In studies comparing fixed low cross-reactivity
with plastic cross-reactivity set by proximity to self antigens, both strategies eliminated self-reactivity but the latter achieved greater coverage of antigenic space, including the space near self peptides (van den Berg and Rand 2004; Scherer et al. 2004). If cross-reactivity is good for the information gathering phase of an immune response, what about the next phase?

**Fine-grained information: the problem of discrimination**

If lymphocytes search antigenic space efficiently by being initially cross-reactive, then discriminating between closely related antigens is not a problem for them. However, the task assigned to antibodies in the immune response is one that may require discrimination, if antigen-specificity is advantageous. Discrimination is a key component of information processing theory (reviewed by Stephens 2007); also see Fig. 3. From this theory, we should expect the binding specificity of a given antibody to be a function of the difference between two antigens (i.e., the target and any nontarget antigens) and the relative costs and benefits of specificity versus cross-reactivity. First we will consider how easy or difficult it might be to discriminate between antigens using the concept of antigenic distance.

If we are going to predict when cross-reactivity will occur, when it will help or hinder the host, or to identify the optimal degree of cross-reactivity for a given context, we need to understand the antigenic distance between parasites: how different do different parasites appear from the perspective of the immune system? The analogy from behavioral ecology is working out what an animal can perceive, in order to make sense of behavioral responses to environmental change (Boomsma et al. 2003; Shuker and West 2004). The problem of antigenic distance is a difficult one, and not just for the immune system. In this era of whole-genome sequencing of parasites, it has become clear that antigenic distance can bear a decidedly nonlinear relationship to phylogenetic distance (Gog and Grenfell 2002), partly because the recognition of antigen can be as much about physical conformation as about amino acid sequence (e.g., Donermeyer et al. 2006), and partly because antigens can be conserved across taxa. For example, cross-reactivity can occur between antibodies induced by parasites with rather distant phylogenetic

![Figure 2](image-url) Contrasting degrees of cross-reactivity over two-dimensional antigenic space. Seven parasite antigens (P1–7) and five self antigens (S) are represented on a grid. The size of the filled circle represents the range of cross-reactivity of a given lymphocyte receptor or antibody. The host in (A) plays a more cross-reactive strategy than the host in (B). Both avoid self-reactivity and respond to all parasite antigens, but (A) covers more antigenic space with fewer lymphocyte lineages. Is that a good thing? The answer probably depends upon context. For example, imagine both hosts are sequentially exposed first to P3 and then P4. If P3 and P4 were different strains or species of malaria, the host using strategy (A) would likely benefit from cross-protection (e.g., Mota et al. 2001). If P3 and P4 were different serotypes of dengue virus, however, the strategy depicted in (A) could be lethal (e.g., Goncalvez et al. 2007). Figures are modified from Scherer et al. (2004), based on shape-space tools for immunological reactivity developed by Perelson and colleagues (e.g., Smith et al. 1997).

![Figure 3](image-url) Optimal discrimination among environmental cues, depending upon the perceived magnitude of the difference between cues, as well as the benefits of the ability to perceive the difference. For example, if the x-axis represents a cue that a forager can perceive regarding the food quality of a patch, then low versus high food quality may be more easily discriminated in (A) than in (B). Still, if there are great rewards for perceiving the difference in (B), then optimal discrimination may have the relatively high resolution depicted in (B).
relationships, such as helminths and malaria (Mwatha et al. 2003; Naus et al. 2003). Within parasite species, phylogenies may largely parallel antigenic distances over long genetic distances (Frank 2002), but a stepwise and nonlinear relationship between genetic and antigenic change may become evident when examined at higher resolution. In influenza, for example, silent mutations may move a parasite to new regions of antigenic space that are realized with the occurrence of one last mutation; such a mechanism can account for the way in which a single amino acid change can release a strain from immune pressure while the preceding 19 changes led to little antigenic change (Koelle et al. 2006a). The functional form of the relationship between genetic and antigenic change is likely to shape parasite strain structure (Adams and Sasaki 2007) and epidemiology (Gog and Grenfell 2002; Adams et al. 2006; Koelle et al. 2006b) as well as the efficacy of vaccines (Gupta et al. 2006) and memory responses (Deem and Lee 2003).

Various methods can be used to quantify antigenic distance. Much of the work in this area has been on influenza, because annual attempts are made to match vaccine antigens with antigens of the strain that caused the preceding year’s outbreak. Hemagglutination inhibition assays, for example, measure the ability of ferret antibodies induced by one strain of influenza A to block agglutination of red blood cells by another strain; if strong cross-reactivity is evident, a small antigenic distance is inferred (Smith et al. 2004; Koelle et al. 2006a). Such measurements sometimes successfully predict the efficacy of vaccines, but predictions can be improved by knowledge of the antigenic distance between the dominant antibody binding sites rather than whole viruses (Gupta et al. 2006). Another way of assessing antigenic distance is to measure the dilution of serum at which cross-reactivity disappears (K. J. Fairlie-Clarke, T. J. Lamb, J. Langhorne, A. L. Graham, and J. E. Allen, unpublished data). If cross-reactivity persists at million-fold dilutions (and it can), then the antigenic distance is small.

Such methods can be used to compare antigens from different parasite lineages, as well as antigen samples from a single lineage over time, and are necessary if we are to understand whether cross-reactivity is something that cannot be escaped by antibodies – two antigens are just too alike to be separated, even if they are from very different strains (or kingdoms) of parasites – or whether cross-reactivity is a deliberate, selectively advantageous strategy. If antigenic distances were measured among a wide array of parasite taxa, the data would enable assessment of how fully or evenly occupied parasite antigenic space may be. The data might also clarify how many cases of apparent cross-reactivity are due to specific molecular recognition of antigens that are conserved across parasite taxa. Mapping antigenic space (sensu Smith et al. 2004), but applied across a much wider set of parasites) would therefore be extremely useful for understanding the causes of antibody cross-reactivity and host–parasite interactions more generally.

Differences among antigens might not be the only constraint on antibodies, however, because the mechanics of the immune system may also be important. For example, the persistence of cross-reactivity once antigenic information is available (i.e., after filter A of Fig. 1) may be explained by lymphocyte limitation in some contexts. The clonal lymphocyte lineage whose receptor best binds a given antigen replicates more rapidly than other clones (Janeway et al. 2001), such that the best-matched lymphocyte lineage wins by competitive exclusion (Scherer et al. 2006). This process tends to favor specificity, but when lymphocytes are limiting, cross-reactivity may result. For example, if B cells undergo fewer rounds of cell division and somatic hypermutation when a host is resource-limited, the antibodies produced may fall short of the maximal possible specificity. Furthermore, lymphocyte dynamics during memory responses may constrain the development of specific responses to new antigens. For example, cross-reactive antibodies are produced in preference to specific antibodies during secondary exposure to dengue because memory B cells are so rapidly activated and thus outcompete cells that are more specific to the new virus (Rothman 2004), a phenomenon observed in memory responses to various other viruses (e.g., Brehm et al. 2002; Liu et al. 2006). The mechanisms whereby the immune system permits recognition of all possible antigens with limited lymphocyte numbers may therefore constrain its ability to match antibody perfectly to antigen. Given these possible constraints, what are the possible costs and benefits of cross-reactive antibodies?

Is cross-reactivity of antibodies a deliberate strategy?

Models have suggested that cross-reactivity at the lymphocyte level is an effective strategy, but what about at the level of antibodies? For antibody cross-reactivity to be favored by natural selection, the costs of cross-reactivity need to be balanced by the benefits. The typical textbook view is that antibody specificity is a good thing, and indeed fine discrimination of parasite antigens can bring fitness benefits to hosts. When a host precisely targets antigen with specific antibodies, it is often rewarded with efficient clearance of infection. For example, antigen-specific antibodies, but not antigen-induced, cross-reactive antibodies, protect mice against parasites such as the intracellular bacteria *Nocardia brasiliensis* (Salinas-Carmona and Perez-Rivera 2004) or lymphocytic chorio-
malaria parasites, however, those same antibodies can actually promote parasite replication. These apparent failures of specificity can have health consequences. A classic case is the enhancement of dengue virus replication by cross-reactive antibodies, alluded to above. Antigen-specific antibodies provide long-lasting protection against reinfection with the same serotype (Sabin 1952, cited by Goncalvez et al. 2007), but cross-reactive antibodies are associated with dengue hemorrhagic fever during subsequent infection with a different serotype, and the severity of disease varies with the combination and order of appearance of serotypes (Endy et al. 2004; Rothman 2004). Unable to neutralize the virus, the cross-reactive antibodies instead facilitate viral uptake to cells (Goncalvez et al. 2007). The antibodies are specific enough to bind but not to kill parasites. Costs of cross-reactive responses are also observed across parasite species. For example, cross-reactive responses induced by influenza A exacerbate liver disease due to hepatitis C virus (Urbani et al. 2005).

Balanced against these benefits of specificity and costs of cross-reactivity, it is apparent that cross-reactive immune responses can, in some contexts, simultaneously protect hosts against a wide array of parasites, a possibility that has not been lost on vaccinologists (Nagy et al. 2008). Indeed, cross-reactive antibodies induced by infection or immunization can protect hosts against other infections. For example, mice experimentally infected with a single malaria clone make cross-reactive antibodies that can bind to antigens of other parasite clones (displayed on the surface of infected red blood cells) and lead to their phagocytosis by macrophages in vitro (Mota et al. 2001). Similarly, cross-reactive antibodies from a person infected with Plasmodium vivax can inhibit the growth of Plasmodium falciparum in vitro (Nagao et al. 2008). More importantly, cross-reactive antibodies benefit human hosts living in areas of multi-strain or multi-species malaria transmission in nature (Fesel et al. 2005; Haghdoost and Alexander 2007). Benefits of cross-reactive antibodies are also observed amongst flaviviruses: St. Louis encephalitis virus and Japanese encephalitis (JE) vaccine both induce cross-reactive antibodies to West Nile virus that ameliorate the disease in hamsters (Tesh et al. 2002). The induction of cross-reactive antibodies to West Nile by JE vaccine was corroborated in humans (Yamshchikov et al. 2005), though whether the antibodies are protective remains to be seen. In the case of influenza, cross-reactive responses induced by immunization with one virus can protect hosts against other viral genotypes (Sandbulte et al. 2007; Levie et al. 2008; Quan et al. 2008). Cross-reactive antibodies have also been implicated in protection against fungal infection (Casadevall and Pirofski 2007).

Imprecision of antibody responses can therefore benefit the host in some contexts. Ideally, the degree of cross-reactivity would match the infections at hand (see Fig. 2; Scherer et al. 2004; van den Berg and Rand 2007). Variation in the activation thresholds of individual cells (van den Berg and Rand 2007) or tuning mechanisms such as the immunomodulatory molecules employed by regulatory T cells (Carneiro et al. 2005) should allow precise targeting when needed and cross-reactivity when needed. Recognizing need, however, would require lymphocytes to gather information on the relatedness of parasite antigens – e.g., during co-infections, or comparing remembered to current antigens – to generate the optimal imprecision for a given context. The likelihood of such additional information processing ability is unclear, but even if the immune system could not manage by itself, biomedicine could potentially promote cross-reactive responses (i.e., help the immune system to see two parasites as related), if the context were right. Predicting when imprecisely targeted immune responses will occur, and when they will be to the detriment or benefit of hosts, is therefore of clear biomedical relevance, for vaccination programs and other medical interventions.

**Outlook**

Why, then, do adaptive immune responses cross-react? While we cannot give a definitive answer to this question, we suggest that the answer is likely to depend on context. In some cases, the true antigenic distance between phylogenetically distant parasites may be very small, such that specificity becomes a biochemical impossibility (and the ‘information’ cannot be discerned by the immune system). In other cases, strict constraints such as the physical limits of binding strengths or physiological constraints such as lymphocyte limitation may operate. We do not currently know how common these constraints on the immune system actually are. However, we also do not yet know exactly how natural selection operates on the specificity of adaptive immune responses, though we do know that the effects of cross-reactive antibodies on host fitness are context-dependent. Would natural selection always favor greater specificity, but constraints intervene? Or might variability in exposure to parasites over space and time, for example, impose fluctuating selection on the specificity of immune responses? We do at least know that the genetic variation that selection could act upon to effect
evolutionary change is present in the immune system (Frank 2002). For example, thresholds for B-cell activation or the number of rounds of somatic hypermutation, and thus the timing of plasma cell differentiation, may be polymorphic (Fig. 1). Hosts are known to be heterogeneous in the specificity of the antibodies that they make to a given antigen (e.g., Lyashchenko et al. 1998; Sato et al. 2004). What remains to be done is to measure the selective consequences of variation in cross-reactivity in the different components of the immune system.

One intriguing possibility, given the antigenic diversity of parasites as well as the uncertainty of exposure to those parasites, is that imprecision in antigen recognition might ultimately be to the benefit of hosts. Might cross-reactive antibodies represent an adaptation to an unpredictable wide world of antigenic exposures? It has been suggested that imprecision in the waggle dance of honeybees is an adaptation that spreads foragers over an optimal patch size: natural selection is proposed to have tuned the amount of error in the waggle dance, to balance the benefits of known nectar sources against benefits of wider searching (Weidenmuller and Seeley 1999; Gardner et al. 2007); but see Tanner and Visscher (2006). An alternative analogy from evolutionary ecology is that of ‘bet-hedging,’ whereby life history decisions (such as how much energy to invest in offspring, or where to lay eggs) are deliberately variable, to try to cater for uncertainty in the future environment (Seger and Brockman 1987). Bet-hedging has had its conceptual problems over the years (e.g., Grafen 1999, 2006), but it can be favored under a range of circumstances (e.g., King and Masel 2007), and it would be interesting to explore further the evolution of imprecise antibodies in this context.

We envision several further potential contributions that evolutionary ecologists could make towards understanding and controlling the antigen-specificity of immune responses. For example, evolutionary ecological analyses could aid identification of contexts in which hosts would do well to hedge their bets and make cross-reactive antibodies, or clinics would do well to administer gamma globulin shots. As epidemiologists are often able to characterize exposure risks on local geographical scales, we could combine such information with data on antigenic distances and the relative efficacy of antigen-specific responses to allow evolutionary optimization models to advise which specificity strategy best suits a given setting. Thus quantitative evolutionary ecology could enhance the potential for biomedicine to tailor treatments to epidemiological settings.

Another important issue for the attention of evolutionary ecologists is that biomedical success in generating cross-reactive immune responses with vaccines (Nagy et al. 2008) is likely to feed back on the structure of parasite populations (Restif and Grenfell 2007). Calculation of the co-evolutionary risks of altered antigen-specificity of immune responses is therefore essential; might cross-reactive vaccines impose strong selection for escape mutants to make larger antigenic, and perhaps more virulent, leaps than they do naturally? It will also be critical to identify the role of parasite strategies in promoting cross-reactivity of immune responses. The theory reviewed here (e.g., van den Berg and Rand 2004; Scherer et al. 2004) suggests that the closer the antigenic distance between self and parasite antigens, the less likely that infection will promote cross-reactive antibodies. Do parasites that mimic host molecules select for antigen-specific immunity? These questions are amenable to both theoretical and, more importantly, experimental study.

Finally, we suggest that evolutionary ecology might also gain tremendous insights from the immunological data itself. In particular, interactions between the mammalian immune system and parasites present a rare and useful combination of traits for studies of information processing and adaptation. For a start, the molecular details of the antigens and antibodies or receptors are either known or knowable (Boudinot et al. 2008). Thus the information-gathering system is likely to be better characterized than is usually possible in behavioral ecology systems. Such data might be powerfully combined with quantitative tools such as statistical decision theory, an increasingly important component of studies of information processing (Dal et al. 2005). Statistical decision theory is based on Bayesian approaches, and the parallels between an organism making decisions based on updated knowledge of the environment (formalized as ‘prior’ and ‘posterior’ distributions, before and after information acquisition) and the workings of the adaptive immune system, with its updatable immunological memory, are striking. Further, the functional consequences of changes in specificity of immunological recognition can often be measured in exquisite detail. Thus in the immune system, as perhaps in few others, one might be able to discover whether there are limits to the benefits of perfect knowledge of the environment.

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