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THE IMMUNE SYSTEM AS AN INDUCIBLE DEFENSE

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Running head: ‘‘Immune System’’

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Abstract

Many parasites induce powerful immune defense mechanisms when they infect a vertebrate host. The vertebrate immune response can be roughly divided into nonspecific immunity, which can recognize relatively few parasites but can respond rapidly, and specific immunity, which can recognize many parasites but is slower to respond. The inverse relationship between the speed and the specificity of the response arises from the way in which the receptors used to recognize parasites are arranged in an immune cell population. Different effector mechanisms are induced against different parasites. The way in which nonspecific and specific immunity 'decide' on which effectors to use also differs as a consequence of the different arrangement of receptors on nonspecific and specific cells. The combined use of nonspecific and specific immunity provides the 'best of both worlds' in terms of mounting rapid, powerful, appropriate responses to many parasites.

Inducibility of the immune response may be important in reducing energy costs and immunopathology, but may be more important in allowing the magnitude of the immune response to change depending on the size of the parasite population. If the immune system can also discriminate between different parasites, then inducibility also allows the immune system to fine tune effector mechanisms to each type of parasite. The ability of the immune system to respond to the size and type of parasite on a timescale similar to the turnover of parasites is central to the ability of vertebrates to overcome parasites despite potentially rapid parasite replication and evolution.

The specificity of recognition of parasites by the immune system, which is central to the speed and type of response induced by different parasites, varies tremendously between host species. Whilst the energetic costs involved in expanding individual clones of specific immune cells may be important in limiting specificity, the need to have a functional immune repertoire early in life and/or the need to mount rapid responses when a

parasite infects may be more important, due to the inverse relationship between speed and specificity.

Introduction

Immune responses share with other inducible defenses the characteristics of being inducible, amplifiable, sometimes possessing a memory component, and a varying degree of specificity. The **vertebrate immune response** is a good example of how an inducible defense can track a complex, changing biotic environment. This chapter will focus mainly on the vertebrate immune response which probably arose only once (in the ancestors of jawed fishes), rather than attempting to review invertebrate internal defense systems which are likely to be of polyphyletic origin (Sima and Vetvicka 1990, Hoffman et al. 1994).

The first part of this chapter describes how the immune system responds to infection by parasites, focussing on the inducibility and specificity of the response. For further background in immunobiology and an excellent source of references, I refer the reader to Janeway and Travers (1994). There is an inverse relationship between the speed and the specificity of the response that arises as a consequence of the way in which receptors are arranged in an immune cell population. Vertebrate immunity achieves a high level of specificity by possessing many receptor variants arranged in clones of immune cells. This means that before an antigen is encountered, only a few cells will react to the antigen. Launching a specific immune response involves a delay while these rare clones of cells are expanded and selected. Higher vertebrates have reduced this delay by keeping specific cells in high concentrations in specialized lymphoid tissues which offer a microenvironment well suited for bringing together immune cells and antigen, with subsequent clonal expansion and selection. However, there is still a delay in inducing a specific response as it takes time for antigen to be transported to these tissues and for the immune cells to reach the site of infection. Different, often appropriate, effector mechanisms are induced by different types of parasite. I describe what information the immune system may use to 'decide' on an appropriate response. The nonspecific immune response, which recognises antigenic 'patterns' indicative of many parasites, is very important in instructing specific immune responses,

which lack the innate ability to discriminate between parasites and self.

In the second part of the chapter, I ask what selective pressures favour an inducible immune response over a constitutive one. I focus on (1) a strong, variable parasite selection pressure, (2) reliable recognition, (3) an effective response, and (4) a cost to defense (Harvell 1990*a*, *b*). The amplifiability of an inducible response allows the magnitude of the immune response to be fine tuned to the size of the parasite population. Specificity allows an inducible response to employ different effector mechanisms against different parasites. These advantages may be more important in favoring an inducible defense over a constitutive one than the reduction of energetic or immunopathological costs.

In the third part of the chapter, I ask what selective pressures favour a more specific response over a less specific one. Specificity of responses varies greatly between species, with vertebrates but not invertebrates possessing specific immunity, and higher vertebrates having a more specific immune response than lower vertebrates. The need to have a functional immune repertoire early in life and to mount rapid immune responses upon infection may be more important in limiting the specificity of immune responses than the hurdle of evolving a mechanism of generating receptor diversity and the high energetic costs involved in a highly specific immune system.

How is the vertebrate immune response induced?

The vertebrate immune system can recognize and launch a response to many parasites whilst generally avoiding launching a response which may be unnecessary, e.g. to food, or even injurious, e.g. to self-encoded antigens. This inducibility not only reduces costs associated with an immune response, but also allows the magnitude of response to react to the size of the parasite population, and if the immune system is specific

enough, to allow the type of response to be fine tuned to the type of parasite. Here 'parasite' is defined as an obligatory symbiosis ('living together') where the parasite benefits at the expense at the host (Cheng 1991). It should be noted that the degree of symbiosis and the net effect on the host are continuous variables, and hence the minimal reliance on and minimal damage to the host above which an organism is considered a parasite are somewhat arbitrary (Toft 1991). Defining what is meant by 'self' is problematical: I follow Matzinger (1994) in defining self as any part of the body, and nonself as everything else, noting that not all 'self' is seen by the immune system and not all 'nonself' elicits an immune response. Antigens are defined as molecules that react with antibodies (although despite what their name suggests, they may not have the ability by themselves to GENerate ANTIbodies).

A typical human immune response can be divided into three phases; an immediate phase (0-4 hours after infection), an early induced phase (4-96 hours) and a late phase (after 96 hours) (Gibbons 1992). Table 6.1 summarizes how recognition and effector components of the immune response depend upon the phase of the immune response and the type of parasite. There are two main points to note. Firstly, during the course of an immune response, the recognition mechanisms change but are similar for different kinds of parasite. Secondly, the effector mechanisms launched depend upon the type of parasite (see also Table 6.2) but are remarkably similar during the different phases of the immune response. These two points are now discussed in more detail, and both are related to the way in which parasites are recognised by various components of the immune system.

The different recognition mechanisms used during different phases of infection arise from the inverse relationship between speed of induction and specificity

The vertebrate immune response can be roughly divided into nonspecific immunity and specific immunity,

which have different dynamics and are induced in different ways.

Nonspecific immunity is launched against many conserved parasite antigens. It is rapidly induced but wanes after the parasite has been cleared with second-set responses to a particular antigen being identical to the first response. Nonspecific cells possess several, genetically encoded receptors, each of which can recognize a different parasite antigen, the function (and hence structure) of which has to be conserved. This simple 'pattern recognition' allows nonspecific immune cells to reliably recognize many parasites whilst not reacting to self (Janeway 1992, 1994).

Specific immunity on the other hand can potentially recognize a vast number of antigens but takes longer to mount than nonspecific immunity. After the parasite is cleared, effector mechanisms wane but unlike nonspecific immunity, second-set responses are induced more rapidly, are more specific, and employ effector mechanisms which are better at clearing the particular parasite – the phenomenon of immune memory. Each specific immune cell possesses only one receptor that is used to recognize antigens. The ability of specific immunity to recognize many parasites arises from the diversity of receptors across the population of specific immune cells, with huge amounts of receptor diversity (10^7-10^9 different specificities in birds and mammals; Du Pasquier 1982) being generated by somatic gene rearrangement. Different specific cells recognize different antigens in different ways. B cells, which are important in patrolling the body cavity, possess receptors that recognize conformations on whole antigens, which can be carbohydrates, proteins or simple chemical groups. T cells, which are important in monitoring cellular changes in solid tissues, can only recognize peptide antigens in association with cell surface molecules called major histocompatibility complex (MHC) molecules (Matzinger and Zamoyska 1982). There are two classes of MHC; class I tends to be associated with antigens produced within the cell and class II tends to be associated with antigens taken up from outside the cell. Killer T cells recognize antigen associated with MHC class I, allowing these cells to detect

intracellular parasites such as viruses. Antigen presenting cells take up antigen from outside the cell and present it in association with MHC class II to helper T cells, allowing these cells to detect extracellular parasites.

Natural killer (NK) cells, which are normally included in the nonspecific immune response, can nonspecifically lyse virally infected and cancerous cells. They are induced by virus much sooner than specific antiviral immunity (e.g. killer T cells) and they control virus replication until killer T cells are produced which can eliminate the virus. Unlike other nonspecific cells, NK cells have clonally arranged receptors, similar to specific cells, although of much more limited diversity, leading to the suggestion that they are related to specific T cells (Versteeg 1992). The rapid speed of induction (like nonspecific immunity) to many kinds of virus (like specific immunity) has been hypothesised to arise from the way in which they discriminate infected from infected cells (Raulet and Held 1995). NK cells have two types of surface receptor; one that recognizes carbohydrate on self, which triggers NK cells to kill; the second recognises certain cell surface molecules (MHC class I) which inhibits the killing signal from the first receptor. Some viruses, e.g. herpes viruses, downregulate expression of MHC class I molecules (which are used by specific immunity to recognise infected cells) to avoid specific immunity but will be killed by NK cells.

The timecourse of a typical immune response is now described, and the inverse relationship between the speed and specificity of nonspecific and specific recognition of antigen is related to the different way in which nonspecific and specific immunity recognize antigen.

Immediate responses (0-4 hours after infection) are a result of nonspecific recognition

Pre-formed nonspecific effector cells already at the site of infection rapidly (0-4 hours after infection) recognize parasites and help to remove the infectious agent. The rapidity of response is due to each

nonspecific cell being 'hard-wired' to recognise parasites. There is often a large number of nonspecific immune cells at potential sites of infection, such as at the skin and epithelia, allowing rapid clearance of parasites.

Some subsets of so-called specific immune cells are more similar in their speed of response to nonspecific cells than to truly specific B and T cells, and are characterised by low receptor diversity and high frequency at potential sites of infection. One subset of T cells, γδ T cells, is found in surface epithelia, with essentially homogenous receptors in any one epithelium and may act by killing infected epithelial cells to prevent further spread of the parasite. One subset of B cells, CD5+ B cells, is found at high frequency in the body cavity, which offers an ideal environment for the growth of extracellular parasites, and appears to recognise common bacterial polysaccharides. These 'first lines' of defense may constitute the most evolutionary ancient form of specific immune cells (Stewart 1994).

Early induced responses are a result of nonspecific and specific recognition

An immediate response may not be sufficient to clear the parasite. This could be due to insufficient nonspecific effectors being present at the site of infection. In such a case, an early induced response is seen (4-96 hours) where nonspecific effectors are recruited to the site of infection by nonspecific effectors already at the site. In addition, nonspecific immunity passes on information to specific immune cells and begins the induction of specific immunity (Fearon and Locksley 1996). This is important as specific cells do not possess the innate ability to determine what is a parasite and what is not. Specific cells not only require antigen to be activated, but a second signal. Nonspecific cells such as macrophages can provide this second signal to specific cells when they detect parasites. The nonspecific immune response is very important in alerting specific immunity to the presence of the many parasites that display conserved antigenic patterns, allowing specific immunity to

discriminate between ‘infectious’ and ‘noninfectious’ (Janeway 1992, 1994)

However, many parasites may avoid the ‘pattern recognition’ of specific immunity, although once they grow to a certain population size, it is unlikely that they will avoid signalling their presence to the immune system by causing damage to surrounding tissue. It has been proposed that detection of ‘danger’, for example by the detection of heat shock proteins, which are produced by cells of many organisms in response to almost any kind of stress, may trigger specific immunity (Matzinger 1994). Activation of antigen presenting cells, which pick up and process antigen, and transport it to lymphoid tissues to present it to specific immune cells, may respond to signs of damage, allowing the immune system to discriminate between ‘safe’ and ‘dangerous’.

Late immune responses (>96 hours after infection) are a result of mainly specific recognition

During the early induced phase of an immune response, although specific recognition occurs, specific effector mechanisms are not yet mounted. This is a consequence of two processes. As individual specific cells possess only one variant of their antigen receptor, efficient functioning of the specific immune response depends on expansion of individual clones of specific immune cells in response to antigen and subsequent selection amongst clones, causing a delay in induction of specific immune effector mechanisms. Higher vertebrates have evolved specialised lymphoid tissues where immune cells are concentrated which provide a microenvironment well suited to this expansion and selection, reducing this delay. However, a further delay is involved to transport antigen to the lymphoid tissues and for effector cells to migrate to the site of infection. Consequently, specific immune responses are seen later than nonspecific responses, after about 96 hours.

During an immune response, the specific immune system becomes better at recognizing the parasite. This is due to two processes, the clonal expansion of B and T cells which possess receptors which bind strongly to parasite antigens, and somatic hypermutation of B cell receptors, with further selection of B cell

clones which bind more strongly to the parasite. There is also a shift in the type of antibody produced during responses against extracellular parasites, a process called isotype switching. IgM, which by forming polymers binds strongly to repetitive epitopes (e.g. bacterial cell wall polysaccharides), dominates early primary responses with IgG, IgA and IgE dominating secondary and subsequent responses. These changes facilitate antigen uptake and presentation, allowing specific responses at lower doses of antigen rather than qualitatively changing the immune response.

Reinfection

If there is reinfection, recognition and effector mechanisms are launched much more rapidly than during the primary response. Depending on the gap between primary infection and reinfection, this so-called 'protective immunity' consists of pre-formed immune reactants and immunological memory. Pre-formed immune reactants offer rapid, but often short term defense against reinfection. Specific memory against localised mucosal infections caused by viruses such as rotavirus, rhinovirus and respiratory syncytial virus is usually very short. In these cases, protective immunity may be afforded only by preexisting effectors (Ahmed and Gray 1996). After a parasite has been cleared, effector mechanisms wane, presumably due to the cost of maintaining these responses. Possible costs include the energy required to maintain a response, the possible immunopathology an effector may cause, and the diminishing of responses to other pathogens while the immune system is concerned with pathogens that it has already cleared. However, parasite specific clones of 'memory' cells remain expanded, although in a resting state, allowing more rapid induction and a more powerful effector response on reinfection. For example, the primary antibody response consists of low affinity antibodies from a large number of cells whereas the secondary antibody response comes from far fewer, high affinity precursors that have undergone clonal expansion (a four to ten fold increase) and extensive somatic

mutation. Over time, specific immunity becomes 'hard-wired' to recognize the parasites which have attacked the host during its lifetime (and hence may attack in the future).

In summary, generally there is an inverse relationship between the speed of recognition and the specificity of recognition. Nonspecific cells and certain subsets of B and T cells with low receptor diversity at potential sites of infection recognize parasites early in infection. Specific cells with high receptor diversity in lymphoid tissues recognize parasites later in infection.

Effector mechanisms induced by parasites are often appropriate for their removal and remain relatively unchanged during the three phases of infection

Over the timecourse of an immune response, specific immune responses are added to the already powerful nonspecific immune responses. Functionally effector responses are similar throughout the infection but different mechanisms are launched against different parasites (see Tables 6.1 and 6.2) e.g. during the early stages of viral infection, NK cells nonspecifically lyse infected cells whereas later specific killer T cells lyse cells. In this section, the ways in which nonspecific and specific immunity 'decide' on which effector mechanisms to employ are described.

Nonspecific immune cells are hard-wired to launch appropriate responses against particular parasites

The 'hard-wiring' of each nonspecific immune cell to recognize different kinds of parasite also allows the 'hard-wiring' of effector responses to different kinds of parasite. For example, when mannan, a constituent of the cell walls of many bacteria, is detected, macrophages produce interleukin 6 (IL-6), which induces the liver to produce molecules such as mannose binding protein, involved in triggering the activation of complement, a mechanism to punch holes in bacterial cell walls. Macrophages also possess receptors that recognize β-1,3

glucans, a common constituent of fungal cell walls.

Specific immune cell populations become hard-wired to launch appropriate responses against particular parasites over the course of primary infection and any subsequent reinfection

During the initial response naïve CD4+ T cells, which help orchestrate the specific immune response, differentiate into either inflammatory T cells (T_H1) or helper T cells (T_H2) (Mosmann et al. 1986, Mosmann and Sad 1996). T cell responses against intracellular parasites tend to be dominated by inflammatory cells, which stimulate effectors that attack intracellular parasites such as killer T cells. T cell responses against extracellular parasites tend to be dominated by helper T cells, which help B cells to produce antibodies, an important defense against extracellular parasites. The real situation is far more complex, with multiple overlapping effector mechanisms (see Allen and Maizels (1997) for a recent critique), probably reflecting parasite escape from host defenses and host evolution to clear parasites. However, this simple division of specific responses into 'type 1' (against intracellular parasites) and 'type 2' (against extracellular parasites) can help illustrate how the specific immune system 'decides' on an appropriate response.

The nonspecific immune system can help determine whether a response is type 1 or type 2 by the production of chemical messengers called cytokines (Romagnani 1992, Fearon and Locksley 1996). Macrophages and NK cells produce interleukin-12 and gamma interferon, two cytokines which stimulate type 1 immunity, in response to viruses and some intracellular bacteria such as Listeria. Mast cells produce interleukin-4, which stimulates type 2 immunity. Another source of IL-4 comes from a subset of 'natural' CD4+ T cells that, unlike other CD4+ T cells, possess a nearly invariant T cell receptor (Bendelac et al. 1995), although the nature of antigen recognised by these (nonspecific-like) T cells is unclear. However, even when parasites escape providing antigenic clues as to their identity, we often see specific effector mechanisms 'fine

tuned' to particular kinds of parasite.

Antigenic dose, and how it is presented, can shape the specific immune response. Type 2 immune responses are induced by low levels of antigen on antigen presenting cells whereas type 1 immune responses are induced by higher levels of antigen. This may be due to the need to respond more rapidly against extracellular parasites than intracellular ones. Extracellular parasites often proliferate rapidly whereas intracellular parasites initially infect a small number of cells, proliferate slowly and cause little damage early in infection. However, at very high levels of stimulation, type 2 immunity is induced (Bluestone 1995). The role of this high dose effect in parasite defense is not clear and it may simply be a mechanism of reducing the immunopathology caused by an overly aggressive type 1 response.

Lee Segel (personal communication) has suggested that a 'parasite destruction feedback' mechanism could allow the specific immune system to choose the most effective response in the absence of any specific cues from the nonspecific immune system. Dead, dying or doomed parasites are hypothesised to provide positive feedback to the effectors most responsible for their death and/or negative feedback to the effectors least responsible. This requires that a range of effector mechanisms are 'tried' in tiny simulations within lymphoid tissue, with spatial compartmentalisation ensuring that the most effective responses receive the most positive (or least negative) feedback on parasite destruction. The production of heat shock proteins, which are produced by many organisms in response to almost any kind of stress, either directly (by the parasite) or indirectly (e.g. by infected cells) could provide such a positive feedback signal. Such a mechanism, if it really exists, would be an extremely powerful way to choose an appropriate response as the most effective responses available would always be chosen.

In summary, the nonspecific immune system is extremely important in providing information about the type of parasite to the specific immune cells, which lack the 'hard-wired' ability to detect certain kinds of

parasite. Dose effects do appear to be important in determining the type of specific response, although the role of these effects in host defense is not clear. It is possible that during an infection, the population of specific immune cells become hard-wired to employ the most effective effectors via a positive feedback mechanism.

Why is vertebrate immunity inducible rather than constitutive?

When should a defense be inducible rather than constitutive? Harvell (1990a, b) has pointed out several factors which may be important in the selection of inducible responses which, in the context of immune systems and parasites are; (1) parasites often exert a strong, variable, selection pressure; (2) parasites often provide reliable, non-lethal cues; (3) the immune system constitutes an effective defense and (4) mounting an immune response is often costly. The importance of these factors in maintaining the inducibility of both the nonspecific and specific components of the immune response are discussed, as well as parasite counteradaptations to overcome the inducible nature of the immune response.

(1) PARASITES OFTEN EXERT A STRONG, VARIABLE SELECTION PRESSURE

What is the evidence to show that parasite selection pressure on hosts has been important?

Parasitism, by definition, is associated with morbidity and mortality of the host. There are many theoretical studies suggesting that parasites may be involved in the regulation of host abundance and the maintenance of host genetic diversity via the effects of infection on fecundity and mortality (Anderson and May 1978, May and Anderson 1978, Hamilton 1982, Gulland 1995, Lively and Apanius 1995, Read et al. 1995). However, empirical evidence of regulation and maintenance of genetic diversity by parasites is sparse, especially in wild animal populations. Evidence that parasites can regulate host abundance in a free-living species comes from data on the interaction between Trichostrongylus tenuis in red grouse, Lagopus lagopus (Hudson et al. 1985,

Hudson and Dobson 1995). Correlational (but not causal) evidence for parasites exerting a strong selection pressure on human populations comes from studies of MHC polymorphism (see Kelsoe and Schulze, 1987 for background on how MHC evolves). As T cells can only recognize peptide antigens in association with MHC molecules, the structure of the MHC is very important in determining how well specific immunity recognizes parasites. Several hypotheses have been advanced to account for the extreme polymorphism of MHC (Nei and Hughes 1991), all of which rely at least in part on diversification due to parasite selection pressure (Potts and Wakeland 1990, Hughes and Nei 1988, 1989, Jones et al. 1990, Ohta 1991). For example, in individuals from West Africa where malaria is endemic, the allele HLA-B53, which is associated with recovery from a lethal form of malaria, is very common (Hill et al. 1992). The pattern of MHC alleles across North American Indian populations shows evidence of selection suggested to be caused by parasite selection pressure (Parham and Ohta 1996). Evidence for parasite selection pressure in a non-human population comes from a study of Soay sheep on the island of St. Kilda, Scotland, where a high frequency of heterozygotes for adenosine deaminase (deficiency of which is associated with defective T and B cell production) appears to be maintained by a gastointestinal nematode worm (Gulland et al. 1993).

Why might parasite selection pressure be variable?

During its lifetime, the vertebrate host encounters many different types of parasites with varying levels of exposure. Varying parasite selection pressure may arise for several reasons. For example, host-parasite systems, in a similar fashion to predator-prey or host-parasitoid systems, show a propensity to oscillate. Spatial and stochastic effects can also contribute to the variability of parasite selection pressure. A large difference in the generation time, as is common between microparasites and their hosts, provides a large window of time within which parasite selection pressure can be variable. A high level of host motility may

increase the risk of parasite encounters and a high level of complexity of the host may permit a high level of parasite diversity (due to the higher number of 'niches' within the host).

(2) PARASITES OFTEN GIVE RELIABLE, NONLETHAL CUES

The nonspecific immune response is induced by common microbial constituents which provide a reliable cue of certain parasites. Many parasites express more than one of these constituents, the function (and hence structure) of which have to be conserved. The specific immune system can be triggered by the nonspecific response, and provide better recognition of these parasites. Parasites may not be able to avoid providing more general signals of 'danger' which may be important in inducing an immune response (Matzinger 1994), but this view is not universally accepted.

Parasites often provide cues before the host dies. Infecting doses of parasites are often low (although quantitative data on exact numbers are scant), and hence there is often a window of time before appreciable damage to the host can accumulate. This is especially true for intracellular parasites, which rely upon replication within the host to reach high densities and initially infect only a small number of cells. In addition, many parasites (such as directly transmitted parasites) require the host to live (at least for a short time) in order to transmit to another host, and so may evolve to a level of virulence which does not result in the rapid death of the host (although how parasite virulence evolves is a controversial topic; Frank 1996).

Parasite evasion of recognition

Some parasites may avoid nonspecific 'pattern recognition' if they do not exhibit conserved antigens. Trypanosomes and some bacteria are covered in a coat that hides conserved antigens from nonspecific immunity. Specific immunity can recognize these antigens due to the immense diversity of the clonal receptors,

but needs to be alerted of the presence of a parasite. Some parasites have evolved to mimic host antigens and exploit the hosts need to remain tolerant of its own tissues. Many DNA viruses (vaccinia, Epstein Barr virus, cytomegalovirus in humans) and RNA viruses (feline and murine sarcoma viruses) mimic host defense proteins. Host defense proteins, e.g. interleukins and interferons, are much more diverse than other proteins not involved in defense, and molecular mimicry by parasites could have selected for this high diversity (Murphy 1993). Parasites may also evolve to escape recognition by particular MHC molecules - if parasite antigens cannot be presented by MHC, T cells cannot 'see' them. In South East China and Papua New Guinea, where about 60% of the population carry the HLA-A11 allele, many isolates of Epstein-Barr virus have mutated to no longer bind to MHC. Virally infected cells often downregulate MHC expression, effectively making them 'invisible' to T cells. Natural killer cells may have evolved to complement the activity of T cells, as they nonspecifically lyse cells with low MHC class I expression. Some parasites may avoid providing reliable cues by hiding in immunologically privileged sites or by existing at levels too low to be detected. Herpes simplex and herpes zoster viruses both have a latent stage where they infect nerves, to be reactivated later, usually by some stress or alteration in immune status. Mycobacterium tuberculosis, an etiological agent of tuberculosis, may enter a dormant stage which would aid persistence until the immune response weakens.

In summary, the combined use of nonspecific and specific immune responses make it very difficult for the parasite to entirely escape detection. However, recognition is only one component of the immune response; the rapid deployment of effectors is just as important. The ability of the immune system to 'choose' an appropriate immune response, and to mount the response rapidly, together with parasite counteradaptations to the effector component, is now discussed.

(3) THE DEFENSE IS EFFECTIVE

For an inducible response to be effective, it should be mounted rapidly after detection of the threat. The combination of nonspecific and specific components provides the best of both worlds in terms of rapid response kinetics and an ability to recognize a large number of antigenically diverse parasites. The response should also be appropriate to clear the parasite. As already discussed, the immune system can translate information on the parasite (such as the site of entry, the size of the parasite population, whether parasites are extracellular or intracellular) into an appropriate response.

Effectiveness of the nonspecific immune response

The nonspecific immune system can respond rapidly after infection to a large number of parasites, due to the nonclonal nature of its receptors that can recognize a variety of invariant parasite antigens. The tight coupling of rapid nonspecific recognition to nonspecific effectors allows rapid responses to many parasites, buying time for the induction of a specific response, which is more powerful but takes longer to mount. The nonspecific immune system was probably a very important prerequisite for the evolution of specific immunity as specific immunity alone would involve time lags so long as to be ineffectual. The nonspecific immune response is also 'hard-wired' to recognize different kinds of parasite, and hence can launch appropriate nonspecific effector mechanisms. The nonspecific immune response also relays this information to the specific response. However, not all antigens can be recognized by nonspecific immunity.

Many parasites may be cleared extremely quickly without triggering an early induced response which we can detect, making it difficult to quantify exactly how effective nonspecific immunity is. Some data illustrating the effectiveness of nonspecific immunity come from individuals with genetic defects of nonspecific immunity. There are many genetic defects which lead to phagocyte and complement deficiencies, associated with a susceptibility to bacterial infections (Colten and Rosen 1993, Rotrosin and Gallin 1987). A defect of

natural killer cells is associated with a susceptibility to herpes viruses, which can evade specific recognition by downregulation of MHC class I.

Effectiveness of the specific immune response

The clonal nature of specific receptors allows many antigens to be recognized, but as initially a particular clone of specific cells may be rare, specific responses take some time to mount. To compensate for this, there is strong positive feedback during the immune response that increases the rate of induction. Activated antigen presenting cells activate T helper cells, which in turn activate antigen presenting cells, and so on. After the primary response, the initially small clone of antigen specific cells has expanded, and can respond more strongly and rapidly to the next antigenic challenge; the phenomenon of immune memory. Isotype switching and affinity maturation during the primary response to an antigen also help the secondary response to be faster and stronger. By clonal selection, the immune system can generate powerful, hard-wired responses to parasites over the timescale of the host lifetime, rather than over an evolutionary timescale.

Data showing the effectiveness of the specific response come from individuals with genetic defects of the specific immune response and those suffering from immunodeficiency due to cancer, certain radiotherapy and chemotherapy patients or infection with human immunodeficiency virus. A lack of B or T cells results in general susceptibility to many parasites. MHC class I deficiency, which results in a lack of killer T cells results in a susceptibility to viruses. A defective antibody response, such as a lack of B cells or no isotype switching, is associated with increased susceptibility to extracellular bacteria. IgA deficiency is associated with an increased susceptibility to respiratory infections. The destruction of CD4+ T cells in HIV infection results in defects in both cellular and humoral immunity, resulting in an increased susceptibility to many parasites e.g. cytomegalovirus, Pneumocystis carinii (a fungal parasite causing pneumonia), and Mycobacterium avium

intracellulare. Many of these parasites are 'opportunistic', being controlled in healthy individuals by robust T cell responses.

Parasite counterstrategies to immune effector mechanisms

The delay in mounting a response allows the parasite a period of relatively unrestricted growth during which it can establish itself. If this delay is too long, then too much irreversible damage may have been done, and constitutive defenses may be favoured over inducible ones. Measles and influenza viruses adopt a strategy of replicating rapidly during the primary response, relying upon a high transmission rate between hosts to perpetuate.

The threshold of activation and the magnitude of the immune response is under tight control. If the threshold of activation of an immune response is too low, then the risk of launching an immune response in the absence of a parasite is high. Some parasites may exploit this by growing only very slowly. Whilst not achieving high levels of parasitaemia, such parasites may avoid aggressive immune responses, allowing persistence at low levels (McLean and Kirkwood 1990). Mycobacterium tuberculosis may adopt such a strategy (Antia et al. 1996). Once induced, a very aggressive immune response may cause more damage to the host than the parasite, and so at high levels of stimulation, the immune response is inhibited. Some parasites have evolved to overstimulate the immune response using so-called 'superantigens' that stimulate 2-20% of all T cells, resulting not in an efficient parasite defense, but the pathological overproduction of cytokines and concomitant reduction in adaptive immunity.

A major benefit of inducibility coupled with specificity is the ability to fine tune effector mechanisms to different kinds of parasite. However, many parasites have evolved the ability to divert immune responses into launching inappropriate effectors. HIV and tuberculosis are effectively cleared by type 1 responses, but type

2 responses are often induced during infection, allowing persistence of the parasites (Mosmann and Sad 1996). The complex nature of vertebrate immunity, with multiple, overlapping mechanisms, may reflect selection pressure by parasites to manipulate effector mechanisms.

To summarize, the combination of nonspecific and specific effector mechanisms which are tightly coupled to nonspecific and specific recognition mechanisms allow the vertebrate immune response to respond reliably, rapidly and appropriately to many (but not all) parasites, overcoming two important constraints for a response to be inducible. The benefits of an inducible defense compared to a constitutive one are now discussed.

(4) THERE ARE COSTS TO DEFENSE

The immune response may be costly in terms of energy and immunopathology

Benefits of inducibility are often discussed in relation to cutting **costs** associated with the defense (e.g. see Lively and Apanius 1995). Every aspect of an immune response requires energy, yet little data is available on energetic cost. Chickens undergoing induced immune responses have retarded growth rates (Klasing et al. 1987). The induction of fever, which can help clear parasites directly (due to higher mortality of parasites) and indirectly (through faster immune responses at higher temperatures) is energetically costly. A **fever** of 3 degrees Celsius above baseline in birds and mammals is associated with an increase of 20% in metabolic rate above baseline (Kluger 1979). However, after an immune response and during chronic stress, the immune response is downregulated, a process which itself requires energy, suggesting that energy may not be the only cost associated with an immune response (Sapolsky 1994). An immune response is often a 'two-edged sword' resulting in damage to the host as well as the parasite, and this is an important cause of pathology in infections such as HIV and tuberculosis. A classic example of this is infection of mice with lymphocytic

choriomeningitis virus (LCMV) where the immune response causes all the damage – immunosuppressed mice are completely healthy (Zinkernagel et al. 1986). However, it remains unclear whether the reduction of costs of an immune response is sufficient to select for inducibility.

A very important benefit of inducibility is the flexibility it confers on the response. An inducible specific system, such as vertebrate immunity, can fine tune its response to the size and type of the infecting parasite population. The ability of the immune response to be stronger when stimulated by a larger parasite population allows it to deliver a 'short sharp shock' to the parasite population, which may be more effective in clearing parasites than a constant, constitutive defense and may also slow the evolution of escape from host defenses. By responding to parasites as they infect the host, a specific system can choose particular effectors to efficiently clear the parasite. The need to respond sufficiently and appropriately to a diverse parasite population may be a very important advantage of inducibility over constitutiveness. Due to their short generation time, parasites can potentially evolve very rapidly. An inducible defense allows the host to respond to these evolutionary changes in the parasite on a timescale equivalent to that of the turnover of the parasite, and this may be an important reason why parasites may not have necessarily 'won' the 'arms race' exemplified by host-parasite coevolution.

In summary, the immune system in its interaction with parasites fits the requirements for the evolution of inducibility; parasites exert a strong, variable selection pressure; the immune system can recognize parasites reliably; the immune system can rapidly mount sufficient, appropriate responses; and there are costs to defense, not only in terms of energy and immunopathology, but also the potential cost of responding insufficiently and/or inappropriately to a parasite threat. Consequently, attempts to quantify the cost of an immune response will have to be measured in the context of parasite infection. Inducibility allows the immune response to be flexible in the face of a diverse, potentially rapidly evolving parasite population. Note that successful antibiotic therapy

often bears similarities to a healthy immune response; rapid, correct diagnosis (especially of any preexisting drug resistance) and the rapid administration of several appropriate complementary antibiotics with different effects.

The specificity of the immune response underlies the speed at which the response is induced, and when coupled with inducibility, allows effectors to be fine tuned to different parasites. In order to fully understand the inducible nature of immunity, we must understand what factors determine the specificity of the immune response. The next section speculates what these factors may be.

What determines the specificity of the immune response?

The specificity of immune responses varies tremendously between animals. With the exception of the jawless fishes, all vertebrates but no invertebrate studied so far possess specific immunity. The most specific (in terms of discriminating self from nonself) 'immune systems' are found in marine colonial sponges where the 'immune response' appears to function to maintain genetic integrity rather than to defend against parasites, and discrimination between different types of nonself is poor. Even within vertebrates, there is considerable variation in the specificity of the immune response. Lower vertebrate immune systems have a much smaller number of specificities than birds and mammals (less than 500 000 compared to between 10^7 and 10^9, Du Pasquier 1982).

Parasite selection pressure and the need to remain tolerant to ones own tissues may make high levels of specificity selectively advantageous. An animal may require many specificities as it may encounter a very varied parasite population over its lifetime. This could arise for many reasons. A higher level of antigenic complexity may offer more 'niches' for different kinds of parasite. A long lifespan and high levels of motility may also increase the diversity of parasites to which the animal is exposed. However, relatively few

specificities are required to recognize all parasites. De Boer and Perelson (1993) have suggested that in organisms which are more antigenically complex, more specificities are required to ensure that many parasites are recognised whilst remaining tolerant to self.

There are several costs of specificity that may limit the number of antigens recognised by the immune system. If lymphocytes are energetically expensive to produce, the expansion and selection of a few clones of cells, with destruction of many cells in the process, may make the generation of high levels of diversity too energetically costly. The number of MHC alleles found in a given population may be limited by the need to tolerise many T cells to each variant of MHC. There is also a cost of the delay in setting up a diverse immune repertoire early in life and the cost of the delay in launching a specific response. If the animal is exposed to many pathogens early in life, there may not be enough time to generate high levels of diversity before infection occurs, so the immune system must rely more on germ line encoded receptors and any mutants among them. If the delay in inducing a response is long, as is the case for a highly specific response, launching a late response may confer little benefit.

There are several barriers to the production of high levels of diversity. Firstly, a mechanism for generating diversity has to evolve. Janeway (1994) suggested that the complex mechanism of somatic gene rearrangement used to produce specific receptors may have evolved originally to regulate gene expression rather than to generate diversity *per se*. Even if such a mechanism were present, if cells cannot proliferate rapidly, if the number of lymphocyte generations are small compared to the lifetime of an individual or if lymphocyte populations are small, somatic recombination will generate little diversity and so the animal would have to rely more on its germ line cells and any mutants among them.

In order to understand the relative importance of the benefits, costs and contraints of generating a given level of specificity, more quantitative data is needed. Understanding why invertebrates do not possess

specific immunity, and why specific immunity in vertebrates is so much higher than in lower vertebrates requires a more detailed knowledge of (a) the timecourse of infection, (b) the time lags involved in setting up a fully functional repertoire and (c) the delay in inducing a specific response after infection.

Conclusions

The vertebrate immune response provides us with an excellent example of an inducible defense tracking a complex biotic agent. In keeping with other inducible defenses, there is evidence to show that the selection pressures maintaining the inducibility of the immune response are (1) that parasites exert a strong, variable selection pressure, (2) parasites often provide reliable cues, (3) the immune response is usually effective at clearing parasites, and (4) that there are costs in mounting an immune response, although the data needed to quantify these factors are sparse.

Benefits of inducibility are often discussed in terms of saving costs of energy and immunopathology, although it is unclear whether these costs are high enough to select for inducibility. A very important benefit of inducibility is the flexibility it confers. Immune responses are amplifiable i.e. responses are stronger when parasite loads are higher (generally), and the delivery of a 'short sharp shock' may be more effective at parasite clearance than a constitutive defense. The ability to recognize many different parasites allows (through mechanisms that are currently unclear) the immune system to 'choose' which effectors will be most effective. The ability to mount sufficient, appropriate responses without error to a changing parasite population may be an important advantage of inducibility over constitutiveness. Whilst parasites may rapidly evolve mechanisms to escape host immunity due to their short generation time, hosts can respond rapidly to these changes due to the inducible nature of immunity. The ability of the immune system to respond on a timescale similar to the turnover of parasites is central to the ability of vertebrates to overcome parasites

despite potentially rapid parasite evolution.

The true costs of inducibility may be the need to recognize parasites reliably, the need for a threshold of activation and the time lags involved in launching an appropriate response. The specificity of the response lies at the heart of these constraints. Vertebrate specific immunity can recognize many parasites but is slow to mount. It is unlikely that specific immunity could have evolved in the absence of nonspecific immunity, which provides rapid defense against many parasites and provides important information to the specific immune system about the type of parasite. The different levels of specificity generated in different host species may reflect the balance between the need to recognize many parasites and the need to respond rapidly to parasites on infection. The phenomenon of immune memory results in a shift in this balance towards faster responses over the lifetime of an individual, with relatively little cost in reduced recognition of other parasites due to the focus on parasites which have attacked in the past, and hence are likely to attack in the future. Quantifying costs so intimately linked to the dynamics of an immune response is likely to be extremely difficult.

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Table legends

Table 6.1. The components of the three phases of the immune response involved in defense against three major classes of parasite. Adapted from Janeway and Travers (1994). [1]Neutralisation is where antibodies bind to intracellular parasites to prevent entry into cells. [2]Opsonisation is where antibodies bind to bacteria to allow better nonspecific recognition.

Table 6.2. Different kinds of parasites induce different effector mechanisms that are appropriate for parasite clearance. Adapted from Janeway and Travers (1994).

Phase of the immune response	Immediate (0-4 hours)		Early induced (4-96 hours)		Late induced (>96 hours)	
Recognition mechanisms	Nonspecific Innate No memory No specific T cells		Nonspecific and specific Inducible No memory No specific T cells		Specific Inducible Memory Specific T cells	
Barrier functions	Mechanical	*Tight junctions between cells and flow of air or liquid across epithelia*	Local inflammation	*Recruits immune cells to site of infection*	IgA antibody in luminal spaces	*Neutralisation*[1]
	Chemical	*Lysozyme in saliva, sweat and tears. Pepsin in gut. Low pH in stomach. Antibacterial peptides in intestine.*	Local TNF-α	*Activates macrophages and induces nitric oxide production*	IgE antibody on mast cells	*Sensitises mast cells to recruit effector cells and increases transport of antigen to lymphoid tissues*
	Microbiological	*Normal flora compete for nutrients and attachment*				
Response to extracellular pathogens	Phagocytes	*Engulf parasites*	Mannose binding protein	*Binds to mannose on bacteria, activating complement and opsonising*[2] *them*	IgG antibody and Fc receptor-bearing cells	*Neutralises*[1] *bacterial toxins and viruses*
	Alternative complement pathway	*Punches holes in parasite cell walls, recruits phagocytes, opsonises*[2] *parasites, aiding their removal by phagocytes*	C-reactive protein	*Binds to phosphorycholine on bacteria, activating complement to opsonise*[2] *them*	IgG, IgM antibody and classical component pathway	*Complement punches holes in parasite cell walls, recruits phagocytes, opsonises*[2] *parasites, aiding their removal by phagocytes*
			T-cell independent B-cell antibody plus complement	*Coat bacteria and promote ingestion by phagocytes*		
Response to intracellular bacteria	Macrophages	*Activated macrophages lyse bacteria in phagosomes and produce nitric oxide, which is a potent bacteriocide.*	T-cell independent macrophage activation	*Activated macrophages lyse bacteria in phagosomes and produce NO*	T-cell activation of macrophages by IFN-γ	*Activated macrophages lyse bacteria in phagosomes and produce NO*
			IL-1, IL-6, TNF-α	*Stimulates liver to produce acute phase proteins (C-reactive and mannose-binding), mobilises neutrophils which phagocytose bacteria, increase body temperature and activate the immune system to decrease parasite replication, increase antigen processing and increase specific immune response*		
			IL-12	*Stimulates type1, cellular immunity*		
Response to virus-infected cells	Natural killer cells	*Nonspecifically lyses virally infected cells with low expression of certain MHC class I molecules*	IFN-α and IFN-β	*Inhibition of viral replication in uninfected cells and enhances ability of virus infected cells to present antigen to specific killer T cells*	Killer T cells	*Specifically lyses virally infected cells*
			IL-12 activated NK cells	*Stimulates type 1, cellular immunity*	IFN-γ	*Upregulates expression of MHC class I and II, allowing more powerful specific recognition*

Site of infection	Intracellular		Extracellular	
	Cytoplasmic	Vesicular	Interstitial spaces, blood, lymph	Epithelial surfaces
Parasites	Viruses *Chlamydia* spp. (one species is sexually transmitted and can cause sterility in women) *Rickettsia* spp. (e.g. typhus, Rocky Mountain spotted fever) *Listeria monocytogenes (bacteria)* Protozoa	Mycobacteria *Salmonella typhimurium* (food poisoning) *Leishmania* (leishmaniasis) *Listeria* spp. (food poisoning) *Trypanosoma* spp. (e.g. sleeping sickness (*T. brucei brucei*) and Chagas disease (*T. cruzi*)) *Legionella pneumophila* (Legionnaire's disease) *Cryptococcus neoformans* (fungal opportunistic parasite) *Histoplasma* (fungal opportunistic parasite) *Yersinia pestis* (plague)	Viruses Bacteria Protozoa Fungi Worms	*Neisseria gonorrhoeae* (gonorrhoea) Worms *Streptococcus pneumoniae* (otitis media, pneumonia, bacteremia, or meningitis) *Vibrio cholerae* (cholera) *Escherischia coli* (can cause food poisoning) *Candida albicans* (thrush) *Helicobacter pylori* (can cause ulcers)
Effectors	Killer T cells Antibody dependent cell-mediated cytotoxicity Natural killer cells	T-cell dependent macrophage activation	Antibodies Complement Phagocytosis Neutralisation	Antibodies, especially IgA Inflammatory cells