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Competitive Coexistence in Antiviral Immunity

RAMY A. ARNAOUT*† AND MARTIN A. NOWAK‡

*William B. Castle Society, Harvard Medical School, Boston, MA 02115, U.S.A.
‡Institute for Advanced Study, Princeton, NJ 08540, U.S.A.

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Adaptive immunity to viruses in vertebrates is mediated by two distinct but complementary branches of the immune system: the cellular response, which eliminates infected cells, and the humoral response, which eliminates infectious virus. This leads to an interesting contest, since the two responses compete, albeit indirectly, for proliferative stimuli. How can a host mount a coordinated antiviral campaign? Here we show that competition may lead to a state of "competitive coexistence" in which, counterintuitively, each branch complements the other, with clinical benefit to the host. The principle is similar to free-market economics, in which firms compete, but the consumer benefits. Experimental evidence suggests this is a useful paradigm in antiviral immunity.

Introduction

A host can fight viral infection in two ways: by eliminating infected cells or neutralizing the infectious virus. Vertebrates do both. In the cellular immune response, antigen-specific T cells recognize specially processed viral antigens, develop cytotoxic activity, proliferate and destroy the infected cells from which the antigens were derived. In the humoral immune response, antigen-specific B cells recognize intact viral antigens, mature, proliferate and secrete antibodies that complete the circle by neutralizing intact virus. Despite some simplification, this is the essence of adaptive immunity (Paul, 1998).

But this system presents a seeming paradox. An effective cellular response will eliminate infected cells and stem virus production, but less virus means less B cell stimulation, less antibody, and hence less virus neutralization. Similarly, an effective humoral response will eliminate infectious virus and thereby slow the rate of infection of new cells, but fewer infected cells means fewer cytotoxic T lymphocytes (CTL) to clear cells already infected. One branch seems to succeed at the expense of the other. How can a host mount a concerted, effective response amid such infighting?

Here we address this question mathematically. We show that competition between the cellular and humoral responses may benefit the host by leading to a state of "competitive coexistence" in which each branch actually complements the other. Whether this happens or not depends on the cytopathic and replicative characteristics of the virus as well as on the strength of the cellular and humoral responses. We explore this concept in the context of various clinical and experimental observations, and conclude by speculating about the evolutionary origins of immune mechanisms that seem to blunt competition's effects.

† Author to whom correspondence should be addressed.
E-mail: ramy_arnaout@student.hms.harvard.edu

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The Model

We begin with a simple model by considering a population of virus and the cells it infects. The humoral response depends on the virus encountering antigen-specific B cells in the context of specific $CD4^+$ T cell help. Meanwhile, the cellular response depends either on dendritic cells, which present antigen from infected cells to antigen-specific $CD8^+$ T cells, driving their differentiation to CTL, or possibly on infected hematopoietic cells, which may be able to elicit this response directly (Sigal *et al.*, 1999). We capture these essentials as follows (Fig. 1):

$$\dot{y} = \beta v - ay - pyz, \tag{1}$$

$$\dot{v} = ky - uv - jvw, \tag{2}$$

$$\dot{z} = cyz - bz, \tag{3}$$

$$\dot{w} = fvw - gw. \tag{4}$$

The variables y and v denote infected cells and free virions, respectively, while z denotes the cellular and w the humoral immune responses. Including uninfected cells in the model yields qualitatively similar results (not shown), so for simplicity we consider them no further here. The dots mark time derivatives. In the absence of both responses, the infected cell pool grows without bound proportional to the infectivity of the virus, β, and the per capita death rate of infected cells, a (the average lifespan of an infected cell in the absence of the cellular immune response is then given by $1/a$). Note that a is a measure of viral cytotoxicity; it is large for cytotoxic viruses and small for relatively non-cytotoxic ones. In this scenario viral load also grows without bound, faster for larger k, the rate at which virus is produced from infected cells, and slower for larger u, the per virion decay rate of free virus.

The cellular response limits the size of the infected cell pool by cell-mediated lysis (by perforin, Fas–Fas–ligand interaction, or local interferon release; $CD8^+$ or $CD4^+$ T cells). This is captured in the $-pyz$ term, where p is the rate of killing. Similarly, the humoral response limits viral load by antibody-mediated neutralization, captured in the $-hvw$ term; h is the rate of antibody-mediated clearance. Both the cellular and humoral responses are generated by clonal expansion proportional to the amount of infected cells or virus, respectively; hence the constants c and f, respectively, denote cellular and humoral responsiveness, which are roughly measures of the quickness with which the host elaborates these responses. The constants b and g are the respective per capita natural decay rates of the cellular and humoral responses.

Note that while dendritic cells and $CD4^+$ T-helper cells do not appear explicitly in the model, their contribution is felt through c and f. For

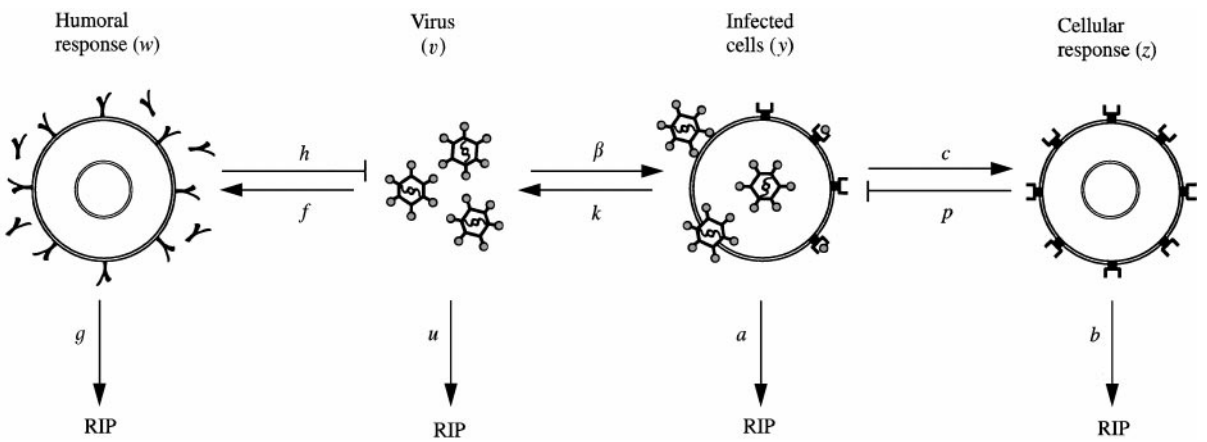

FIG. 1. Immune interactions considered in the model. Virus (v) maintains and is maintained by a population of infected cells (y). This may induce both humoral (w) and cellular (z) immune responses as shown, which control infection by neutralizing free virions and infected cells respectively. These interactions can be described mathematically by the differential equations (1)–(4) in the text (see text for details).

example, inefficient antigen capture by dendritic cells might result in an impaired cellular immune response (Sigal *et al*., 1999); we would express this impairment in terms of decreased cellular responsiveness by making c small. Also, we might imagine c and f are linked in some way, since $CD4^+$ T cell help is necessary not only for maturation of the humoral response but also for the maintenance of the cellular response; hence a defect in $CD4^+$ T cell help would lower both c and f. For simplicity, we ignore the effect of other antiviral mechanisms, such as antibody-dependent cell-mediated cytotoxicity. Finally, this model assumes that infectible cells are in excess, but the arguments that follow also hold for models that consider target-cell limitation (not shown).

Outcomes of Infection

The system converges to one of four stable equilibria, depending on whether neither, one, or both sides of the following condition hold:

$$\frac{k}{u} > \frac{cg}{bf} > \frac{a}{\beta}. \tag{5}$$

These equilibria correspond to three qualitatively different possible outcomes of infection: viral clearance independent of the immune response, persistence controlled by a single response, and persistence controlled by both responses (Fig. 2). Interestingly, the condition in eqn (5) depends only on the relative rates of generation and decay of free virus (k/u), the cellular response (c/b), the humoral response (g/f), and infected cells (a/β), and not on the rates of cell-mediated killing (p) or antibody-mediated clearance (h); these remain the principal determinants in models where immune responses are described by other mathematical forms (not shown). We will return to this point as we discuss each case in turn.

VIRAL CLEARANCE

Consider the case where $k/u < a/\beta$, which upon rearrangement yields $k\beta/au < 1$. This means that even before the effects of the immune response are factored in, fewer infected cells and virions are produced than are destroyed at equilibrium (Anderson & May, 1991; Nowak & Bangham, 1996). It is easy to see that this will result in clearance. This is the case for poorly adapted cytotoxic viruses, which kill infected cells before they can produce sufficient amounts of viral progeny, with the result that the infection burns itself out. This is also the case for highly attenuated viruses, for which a combination of low infectivity, low burst size or virion instability results in infection never taking hold. Infection with either type of virus will be self-limiting. Consequently, neither spreads beyond its initial

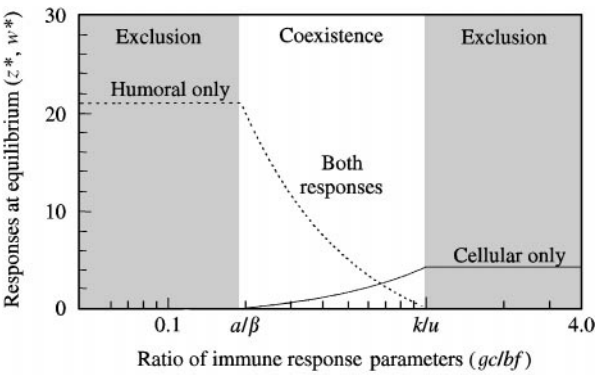

FIG. 2. Outcomes of infection. The model predicts four possible outcomes of infection, corresponding to the four stable equilibria of the system described by eqns (1)–(4). One of these is viral clearance without persistence of immune responses; this is the case when $a/\beta > k/u$. The other three, in which one or both immune responses persist, are represented here as a graphical version of eqn (5) for the case $a/\beta < k/u$. Which immune responses persist depends on whether or not the ratio of immune response parameters, gc/bf (x-axis), lies between a/β and k/u. Briefly, if $gc/bf < a/\beta$, either the virus is too cytotoxic (high a) or not infectious enough (low β) to maintain a cellular response, or else the cellular response is not generated quickly enough (low c) relative to its rate of decay (b) and the rates of generation (f) and decay (g) of the humoral response, for the cellular response to persist; hence only the humoral response will persist. On the other hand, if $gc/bf > k/u$, either the virion production rate (k) is too low (or the virion clearance rate, u, too high) or the humoral response is not generated quickly enough (low f) relative to its decay rate (g) and to the rates of generation (c) and decay (b) of the cellular response for the humoral response to persist; hence only the cellular response will persist. We note that these are limiting cases that best correspond to situations *in vivo* where the cellular or humoral responses are very low but not necessarily entirely absent. Most infections likely correspond to the middle region, where $k/u > gc/bf > a/\beta$ and both responses persist, and where the model predicts an inverse relationship between the strength of cellular and humoral responses at equilibrium. Parameters were $a = u = 1.0\ \text{day}^{-1}$, $k = 1.0$ virions infected $\text{cell}^{-1}\ \text{day}^{-1}$, $p = 1.0$ unit cellular $\text{response}^{-1}\ \text{day}^{-1}$, $h = 0.2$ unit humoral $\text{response}^{-1}\ \text{day}^{-1}$, and $b = 5.2\ \text{day}^{-1}$; gc/bf was varied as a single quantity.

innoculum, and it is highly unlikely that either can cause disease. It is therefore not surprising that in this case neither cellular nor humoral response persists. This could account for the failure of some live attenuated virus vaccines to elicit protection (Johnson & Desrosiers, 1998).

Note that in the model this case depends exclusively on viral characteristics—infectivity, cytotoxicity, viral production rate and viral decay rate—and is independent of the kinetics of either immune response. It is also interesting to note what happens near the boundary condition, where $k\beta/au = 1$. At this boundary, each virion gives rise on average to just one new virion, and each infected cell gives rise on average to just one new infected cell. As a result infection still cannot spread beyond the initial innoculum size, but virus can persist indefinitely at very low levels without generating a lasting immune response. This may be the case for certain localized, chronic, but minor infections of the skin or mucosa. In general, however, we suggest that true viral clearance of this sort is a rare event restricted to poorly adapted or highly attenuated viruses, and fails to elicit lasting immunity.

PERSISTENCE WITH A SINGLE IMMUNE RESPONSE: COMPETITIVE EXCLUSION

Consider now the case for a virus that satisfies the condition $k/u > a/\beta$, such that infection can spread unless controlled by the immune response. Whether or not responses persist now depends not only on viral characteristics but also on immune kinetics: specifically, on the ratio of immune responsiveness to rate of decay for each population of immune cells.

For example, if the left-hand side of condition (5) fails, we have $k/u \leq cg/bf$. In this case, both virus and the cellular immune response will persist, but the humoral response, after transient activity, will decay to zero. This can happen if either humoral responsiveness or the viral production rate is very low; but counterintuitively, it can also happen if cellular responsiveness is very high. In the latter case, the cellular response controls infection very effectively, drives infected cell titers down to very low levels, and leaves viral load too low to maintain a long-term humoral response. From an ecological perspective, this is a case of competitive exclusion: the cellular response outcompetes the humoral response for viral stimulation and drives it to extinction.

The reverse may also occur. If the right-hand side of condition (5) fails, we have $cg/bf \leq a/\beta$, and the cellular response, following a period of transient activity, will decay to zero, while the humoral response will persist and keep the virus in check. Analogous to the previous case, this may happen if either infectivity or cellular responsiveness is very low, or if humoral responsiveness is very high. This may also happen if cytotoxicity is very high, in which case extensive cytopathology lowers the equilibrium frequency of infected cells until it is too low to support a long-lived cellular response. Whatever the reason, the net effect again is competitive exclusion, this time by the humoral response. Note, however, that this is not the same as CTL exhaustion, seen in experimental murine lymphocytic choriomeningitis virus (LCMV) infection (Moskophidis *et al*., 1993), which occurs even in B-cell-deficient animals (Thomsen *et al*., 1996); evidence suggests that this exhaustion results most directly from overinduction (Zajac *et al*., 1998) not understimulation or outcompetition (but see below).

PERSISTENCE WITH BOTH RESPONSES: COMPETITIVE COEXISTENCE

Finally, consider the case where both sides of condition (5) hold. Now infection induces both cellular and humoral responses, but neither fully outcompetes the other (Fig. 3). Ecologically, this situation is known as competitive coexistence (Holt, 1977); its stability in this model depends on the fact that the two branches are in only indirect competition for proliferative stimuli. Note that, importantly, coexistence does not imply a peace of equals: it is likely that one response will emerge as dominant and will be responsible for most of the antiviral activity at equilibrium. Which one prevails depends on both viral characteristics and response kinetics—although, as noted earlier, not on rates of cellular killing or antibody-mediated neutralization.

For example, the model predicts that a non-cytotoxic virus will elicit a strong cellular response, but a relatively weaker humoral response.

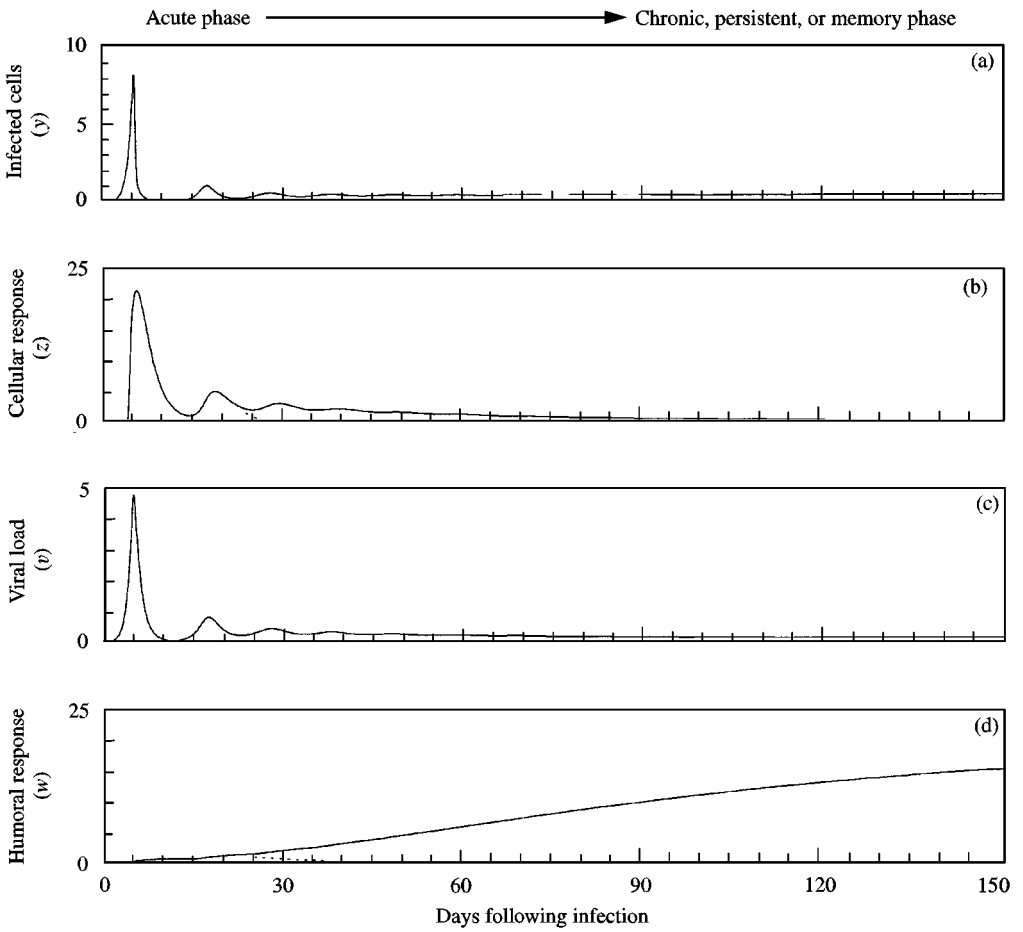

FIG. 3. Dynamic equilibrium among virus, infected cells, and the cellular and humoral responses: immune control as a consequence of interbranch competition. System shown approaching equilibrium via damped oscillations. Note that the cellular response is maintained at low levels by a small population of infected cells; the elevated humoral response similarly depends on the maintenance of virus. Parameters were $a = u = 1.0\ \text{day}^{-1}$, $c = p = 1.0$ unit cellular response^{-1} day^{-1}, $k =$ virions infected cell^{-1} day^{-1}, $f = h = 0.2$ unit humoral response^{-1} day^{-1}, $g = 0.02\ \text{day}^{-1}$, $b = 0.5\ \text{day}^{-1}$, $\beta = 5.2$ infected cells virion^{-1} day^{-1}, $y_o = 0$, $v_o = 0.01$, $z_o = 0.01$, $w_o = 0.1$. Dashed lines show schematically the results of competitive exclusion on the cellular or humoral responses.

By contrast, all other things being equal, a more cytotoxic virus will shift the balance in favor of the humoral response. If the goal is to control infection, these strategies can be readily explained. A non-cytotoxic virus will persist in infected cells unless the cellular response can remove them, and so in this first example the host devotes its resources to the cellular response at the expense of the humoral response. In the second example, because virus-mediated lysis aids in the elimination of infected cells, the cellular response need not be as strong, and so the host may devote more resources to the humoral response. Other factors can similarly be shown to favor one branch or the other (Table 1); the sum of these

TABLE 1
*Factors that influence the host response**

Factor	High-value favors
Viral production rate (k)	Humoral
Viral clearance rate (u)	Cellular
Viral infectivity (β)	Cellular
Viral cytotoxicity (a)	Humoral
Cellular responsiveness (c)	Cellular
Cellular response decay rate (b)	Humoral
Humoral responsiveness (f)	Humoral
Humoral response decay rate (g)	Cellular

*See text for details and discussion.

effects will determine which response plays the more important role in a given infection.

These examples illustrate a key point: interbranch competition serves a regulatory role, allowing automatic allocation of antiviral resources. Counterintuitively, then, competition allows each branch to respond as needed to the demands of a particular viral infection, resulting in a complementary and coordinated immune response.

Persistence and Disease

Note that even when both cellular and humoral responses are maintained, virus persists. However, it is important to note that this need not cause disease. In fact, persistence at low levels provides the antigenic drive necessary to maintain immune responses past the acute phase, and in this capacity may be essential for protecting the host from reinfection (Zinkernagel *et al.*, 1996). By contrast, high viral load or infected cell frequency during chronic infection are common disease indicators, as is a runaway cellular response in infection with non-cytotoxic viruses. Whether persistence leads to protection or disease depends on the equilibrium expressions for the cases described above; we now examine these in turn.

When only the cellular response persists, respective equilibrium expressions for viral load, infected cell frequency, and the cellular response are given by $v^* = kb/uc$, $y^* = b/c$, and $z^* = (\beta k - au)/(pu)$. Note that both viral load and infected cell frequency vary inversely to cellular responsiveness; hence an effective cellular response is necessary to avoid disease induced by direct (i.e. virus-mediated) cytopathology (Table 2). Note also that an effective response need not be overwhelming. If T cells kill efficiently, relatively few will be necessary to control infection. Mathematically, this means p is large, and so z^* will be small and the cellular response will consist of relatively few cells, avoiding immunopathology (Matloubian *et al.*, 1999; Stepp *et al.*, 1999). However, because the expression for z^* varies negatively as a, the less cytotoxic the virus, the more likely immunopathology will be, and the more effective killing must be to prevent it. This is because a non-cytotoxic virus by definition will cause relatively little cytolysis on its own, leaving a bigger job to the cellular response. Also, the higher the virus production rate, the stronger the cellular response must be to control viral load.

TABLE 2
Factors that influence disease

Factor	Disease mechanism
Low cellular responsiveness (c) or humoral responsiveness (f)	Cytopathology
Low cellular killing rate (p), viral clearance rate (u), or viral cytotoxicity (a)	Immunopathology

Note: Control of virus prevents cytopathologic but not necessarily immunopathologic disease, which is more likely for less efficient killing and less cytotoxic or longer-lived viruses.

The scenario is similar when only the humoral response persists. In this case, $v^* = g/f$, $y^* = \beta g/af$, and $w^* = (\beta k - au)/ah$, where w^* is the equilibrium humoral response. In the absence of a long-lived cellular response, viral load and infected cell frequency are set by the kinetics of the humoral response. Analogous to the previous case, both viral load and infected cell frequency may be driven to arbitrarily low levels if humoral responsiveness is sufficiently high. Again, the response itself need not be overwhelming if antibody-mediated clearance is efficient and h is high, i.e. if the antibodies are strongly neutralizing *in vivo*. Note that, as before, the less cytotoxic the virus, the more effective the response must be to avoid immunopathology (Table 2); because infected cell frequency is inversely proportional to cytotoxicity, a less cytotoxic virus will also be able to maintain a larger infected cell frequency even if viral load is very low.

Finally, in the case where both immune responses persist, $v^* = g/f$, $y^* = b/c$, $z^* = (\beta gc - afb)/pfb$, and $w^* = (kfb - ugc)/hgc$. Now viral load is determined only by humoral response kinetics, while infected cell frequency is determined by only cellular response kinetics, irrespective of virus cytotoxicity or production rate (again, these remain the predominant, although not necessarily the sole, determinant of models with other

functions for the immune response). In the context of the model, this may be understood as follows. A cytotoxic virus eliminates more infected cells, resulting in less stimulation of the cellular response, and hence in less overall killing; by contrast, a non-cytotoxic virus eliminates fewer infected cells, resulting in more stimulation of the cellular response, proportionately more overall killing, but hence essentially the same equilibrium number of infected cells. The case is analogous for humoral control of viral load.

The cellular response is still stronger for less cytotoxic viruses, but now control of infected cells comes at a price: increased cellular responsiveness now results in a larger cellular response, threatening immunopathology. In the context of the model, the immune system has two options for avoiding this threat. One is that the cellular response be shorter lived; however, this would lead to a higher infected cell frequency, which is acceptable only if the virus is non-cytopathic. The other, interestingly, is to increase humoral responsiveness: this eliminates the competitive advantage of the cellular response, reducing its magnitude (and reducing viral load in the bargain). As noted above, coregulation at the level of antigen presentation and joint dependence on $CD4^+$ T cell help makes the latter possibility biologically plausible. (It should be noted that a third possibility not explicitly considered thus far is CTL exhaustion; we will return to it below.)

Overall, then, virus may persist without causing disease if the immune system is responsive, but the cellular response must also be efficient to avoid immunopathology (Table 2). These conditions keep viral load, infected cell frequency and the immune responses low. Hence, all other things being equal, viruses that interfere with either cellular or humoral responsiveness (e.g. through infection of these cells or other antigen-presenting cells) or with efficiency of killing (e.g. through downregulation of surface markers required for killing), are more likely to cause chronic systemic disease.

It is interesting to note that persistence in our model has the defining attributes of antigen-dependent immunological memory (Zinkernagel *et al*., 1996), although whether this will be protective from disease characterized by acute viremia or a runaway cellular response depends in the model on host and viral parameters (not shown). Dependence on routes of virus entry is for simplicity not considered.

Theory and Experiment

The branches of the immune system are usually seen as partners that work in concert; hence, it is both unconventional and counterintuitive to see them also as competitors that work at odds. Here we show that both views are valid: competition at the level of virus-derived resources results automatically in partnership at the level of the host. The principle is similar to free-market economics, in which firms compete but the consumer benefits.

VIRAL PROPERTIES AND CORRELATES OF PROTECTION

The model makes several general predictions. For example, the relative strength of cellular and humoral responses should depend on viral properties, and these properties should also decide which branch is more important for control (although, as in the case of immunopathology, not necessarily which is more important in preventing disease; see Table 2). This idea has been explored previously with respect to viral cytotoxicity (Zinkernagel *et al*., 1996), and is borne out in a variety of experimental and clinical infections in which it appears that the more cytotoxic the virus *in vivo*, the more important the humoral response, and vice versa for less cytotoxic viruses and the cellular response (Table 3). The same trend should be seen in viruses with higher rates of virion production (k) or lower per virion rates of infection (β).

Interestingly, if, as more is learnt about the role of the humoral response in human immunodeficiency virus (HIV) infection, evidence continues to support the view that the cellular response is the more important for control (Harrer *et al*., 1996; Ogg *et al*., 1998; Schmitz *et al*., 1999), the model predicts that HIV *in vivo* is relatively non-cytotoxic (Klenerman & Zinkernagel, 1997; Zinkernagel & Hengartner, 1994). This runs contrary to conventional wisdom and may have important consequences for disease pathogenesis (Arnaout *et al*., 2000; Pantaleo & Fauci, 1996).

TABLE 3
Requirements for control of different viral infections

Virus	Cytotoxicity *in vivo*	Required for control	Model agrees?
VSV, Ebola	High	Humoral	Yes
LCMV, HBV	Low	Cellular	Yes
MHV-68	High	Humoral?	—
HIV	Low?	Cellular	—

Note: The model predicts that the humoral response will be more important for controlling cytotoxic viruses, while the cellular response will be more important for controlling non-cytotoxic viruses. This prediction has been confirmed for vesicular stomatitis virus (VSV) (Thomsen *et al*., 1997) LCMV (Homann *et al*., 1998; Zinkernagel *et al*., 1996), HBV (Chisari & Ferrari, 1995; Rehermann, 1996), and recently for Ebola virus (Baize *et al*., 1999), among others. Furthermore, it predicts that in the murine gamma herpesvirus MHV-68, which is cytotoxic during the lytic phase (Stevenson *et al*., 1999), the humoral response should be more important for control, and that HIV is relatively non-cytotoxic (Klenerman & Zinkernagel, 1997; Zinkernagel & Hengartner, 1994), consistent with the proven importance of the cellular response in this infection (Fauci, 1996; Harrer *et al*., 1996).

COMPETITIVE EXCLUSION

The model also predicts the possibility of competitive exclusion. This is a limiting case of the mathematics, and may best correspond to situations in which one or the other response is simply very weak. Even in the context of the model, exclusion will probably be unlikely or difficult to observe, for the following reason. Stable infection requires that the rates of spread (k, β) be greater than the rates of infected cell death (a) and viral clearance (u); this is the meaning of the condition $k\beta > au$. To assure persistence, clinically important viruses have likely evolved such that $k\beta$ is not just greater, but much greater, than au. Since exclusion requires $cg/bf > k/u$ or $< a/\beta$, this possibility seems unlikely for these viruses under natural conditions. However, experimental infections in which one or the other response is deliberately weakened may be free of such constraints. For example, in mice deficient for CD40 ligand (CD40L), a cell surface receptor required for strong antibody responses (Bachmann & Zinkernagel, 1997), infection with LCMV results in a transient antibody response that gradually declined to extremely low levels over time (Whitmire *et al*., 1996). In the model, CD40L deficiency would be reflected by low humoral responsiveness (f), a condition that can cause exclusion. It is possible that this is also the case *in vivo*.

In the more common case of coexistence, the model predicts an inverse correlation between the strength of cellular and humoral responses (Fig. 2), although the prominence of this correlation will be a consequence of viral and host factors, as well as other immune mechanisms (see below). While this has been observed (Stevenson *et al*., 1998, 1999; Thomsen *et al*., 1996; Zinkernagel *et al*., 1999) and remarked upon (Stevenson *et al*., 1998) in passing in studies that examined the effects of selective abrogation of T or B cell responses in mice, to the best of our knowledge this prediction has yet to be directly tested.

IMPLICATIONS FOR CTL EXHAUSTION

Interestingly, however, this prediction is consistent with findings regarding CTL exhaustion (Moskophidis *et al*., 1993) or induction of unresponsiveness (Zajac *et al*., 1998) in LCMV infection. It has been observed that (i) CD4 + T cell-deficient (Battegay *et al*., 1994; Thomsen *et al*., 1996) and B-cell-deficient (Thomsen *et al*., 1996) transgenic mice are more susceptible to exhaustion; (ii) this is more likely for infection with faster-replicating strains (DOCILE) than slower-replicating ones (WE) (Battegay *et al*., 1994); and (iii) addition of neutralizing antibodies render mice infected with faster-replicating strains (DOCILE) selectively more susceptible to CTL-mediated immunopathological disease (Battegay *et al*., 1993; Zinkernagel *et al*., 1996).

These observations are explained in the model as consequences of interbranch competition. The key is that, in normal mice, the humoral response exerts competitive pressure on the cellular response (Thomsen *et al*., 1996; Zinkernagel *et al*., 1996). B cells thereby limit CTL expansion, overinduction and eventual exhaustion. Hence, absent B cells ($f = 0$), CTL expand more vigorously and are more prone to exhaustion or anergy. Since CD4 + T cells are necessary for B cell maintenance, the same is seen in CD4 + T cell-deficient mice. That exhaustion is more likely in faster-replicating strains in this situation is also

explained by competition. Faster replication favors the humoral response (Table 1), so abrogation of this response results in a relatively stronger induction of CTL for such strains than it would for slower-replicating strains, again favoring exhaustion or anergy. Finally, this bias toward the humoral response also explains why neutralizing antibodies should be harmful in infection with faster-replicating strains. In the context of the model, competition by neutralizing antibodies hinders CTL expansion and exhaustion, resulting in CTL maintenance, but also thereby in immunopathology (Thomsen *et al*., 1996; Zinkernagel *et al*., 1996). Overall, the close agreement of model and experiment suggests that competition is a useful concept for understanding disease pathogenesis, perhaps not just in LCMV but in clinical diseases as well (Pantaleo *et al*., 1997).

EVOLUTION OF "PROTECTIONISM"

For purposes of simplification, the model assumes that cellular and humoral responses depend on the presence of replication-competent virus; this feature provides for strong interbranch competition. However, antigen depositing on follicular dendritic cells provides a dedicated mechanism for antigen retention that does not require persistence of infectious virus (Banchereau & Steinman, 1998; Tew *et al*., 1990; Zinkernagel *et al*., 1996, 1999). The consequence is the maintenance of a humoral response that is protected from interbranch competition. Why should such "protectionism" exist?

One possibility is that it is just an accidental feature of the machinery of B cell affinity maturation (Bachmann, 1998; McHeyzer-Williams & Ahmed, 1999). However, it is also conceivable that antigen depositing more directly reflects the importance of life-long humoral persistence. This may suggest an evolutionary role for non-cytotoxic viruses, since (i) competitive exclusion of the humoral response, which might lead to recrudescence by an antibody-escape variant, is more a danger in non-cytotoxic than in cytotoxic virus infections; (ii) antigen persistence disfavors CTL exhaustion, which is more likely in non-cytotoxic virus infections, perhaps especially if the virus is lymphotropic (Wodarz *et al*., 1998); and (iii) if depositing is on a large scale, downward humoral pressure will discourage immunopathology.

Concluding Remarks

Despite recent experimental observations (Battegay *et al*., 1993, 1994; Thomsen *et al*., 1996, 1997, 1998; Zinkernagel *et al*., 1996), cellular and humoral responses are almost always considered separately in clinical infections (Chisari & Ferrari, 1995; Pantaleo & Fauci, 1996). The present study suggests that much may be gained by considering them together as possible competitors. This should not be a foreign concept. Immunodominance, for example, is readily explained by competition among CTL clones (Nowak *et al*., 1995); B cell maintenance (Cyster *et al*., 1994), Th1/Th2 cell cross regulation (Fishman & Perelson, 1994), and renewal of the T cell repertoire (De Boer & Perelson, 1997) have also been explained as competitive processes. We argue that the principles of competitive coexistence and interbranch competition may apply quite broadly in the immune system, for example, between antibodies and the natural killer (NK) cell component of the cellular response (Brundler *et al*., 1996); this may be fruitful ground for future investigation. It would not be surprising to find that we all benefit from a little competition.

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