

The virus-immunity ecosystem

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Summary. The ecology of pathogenic viruses can be considered both in the context of survival in the macro-environments of nature, the theme pursued generally by epidemiologists, and in the micro-environments of the infected host. The long-lived, complex, higher vertebrates have evolved specialized, adaptive immune systems designed to minimise the consequences of such parasitism. Through evolutionary time, the differential selective pressures exerted variously by the need for virus and host survival have shaped both the “one-host” viruses and vertebrate immunity. With the development of vaccines to protect us from many of our most familiar parasites, the most dangerous pathogens threatening us now tend to be those “emerging”, or adventitious, infectious agents that sporadically enter human populations from avian or other wild-life reservoirs. Such incursions must, of course, have been happening through the millenia, and are likely to have led to the extraordinary diversity of recognition molecules, the breadth in effector functions, and the persistent memory that distinguishes the vertebrate, adaptive immune system from the innate response mechanisms that operate more widely through animal biology. Both are important to contemporary humans and, particularly in the period immediately following infection, we still rely heavily on an immediate response capacity, elements of which are shared with much simpler, and more primitive organisms. Perhaps we will now move forward to develop useful therapies that exploit, or mimic, such responses. At this stage, however, most of our hopes for minimizing the threat posed by viruses still focus on the manipulation of the more precisely targeted, adaptive immune system.

Introduction

Vertebrates are large, complex multi-cellular, multi-organ systems. In nature, each of us functions as sets of ecological niches for the support of simpler life forms. Our most intimate passengers are the viruses, which only replicate in living cells. Many commensal organisms live in balance on skin and mucosal surfaces. Some

of these apparently innocuous companions are clearly held in check by specific host response mechanisms, as they will invade and cause disease and death when the capacity to mount an effective T cell response is compromised by, for example, HIV/AIDS. This is also true for highly adapted pathogens like Epstein Barr virus (EBV), which may cause infectious mononucleosis following initial exposure, then persists as a substantially latent infection that can drive oncogenesis subsequent to loss of immune control [83]. Clearly, EBV has developed molecular strategies through evolutionary time that facilitate both spread and long-term carriage [69].

It is, in fact, reasonable to think that the current character of the human immune system has been partly shaped by the continuing relationship with EBV and the other herpesviruses that persist in our lymphoid cells and neurons. There can be little doubt that the evolution of adaptive immunity, which first appears with the jawed fishes about 350×10^6 years ago [93], has been driven by the need to deal with infection [34, 68]. The molecular mimics of, for instance, cytokine and chemokine receptors that are found in the large, complex, DNA viruses indicates that the reverse may also be true for many one-host pathogens [94, 116]. Such stable parasitism reflects reciprocal relationships developed through the long march of phylogeny.

Emergence and persistence in macro and micro environments

Pathogens that grow in a variety of hosts are less likely to have achieved a long-term interaction with us and can thus be very dangerous when encountered for the first time. Much of Bob Shope's research career [109, 110] focused on arboviruses that are maintained in wildlife reservoirs and cause only incidental infection of humans. Many totally new viruses were discovered as a consequence of, for example, the Rockefeller Foundation-funded programs of 1950–1970. Some, like Ross River virus [41] were only found to be causative agents of human disease by retrospective analysis of stored serum samples. The arbovirology community of this era included many who were as at home in tropical rain forests as in the laboratory.

Unlike the human herpesviruses, the mosquito-borne viruses that are normally maintained in (for example) birds have been under no selective pressure to accommodate to human immune response mechanisms. The same may be true for many of the "emerging" pathogens that impact on humans and domestic animals suddenly, or sporadically, as a consequence of changes in culture, behaviour and/or environment. The need to deal effectively with this enormous spectrum of novel infectious agents is likely to have been one factor driving the extreme diversity of both the B cell (immunoglobulin) and T cell receptor (TCR) families [1, 7, 42]. Another may be the rapid variation associated with the error-prone copying mechanisms of some RNA viruses. Furthermore, as the T cells focus on complexes (epitopes) formed by the binding of processed viral peptides to major histocompatibility complex (MHC) molecules [131], the extreme polymorphism of the MHC [34, 92] can also be considered to reflect the evolutionary need to attach previously un-encountered spectra of peptides to one or another MHC glycoprotein.

The characteristics of viral emergence and persistence can thus be considered in two independent, though not necessarily unrelated, contexts. The first is in the broad environmental sense that considers such factors as climate, rainfall, forest management, vector and reservoir distribution, changing demographic profiles and so forth. The second concerns the environment within, whether “within” be infected cells and organs in arthropods, vertebrates or humans. Some determining factors are virus growth characteristics, virus escape mechanisms, immune receptor (antibody or TCR) specificity and diversity, immune selective pressure, antigen presentation characteristics, lymphocyte proliferation rates and the quality of immune effector function, both at the cell and the molecular level. When it comes to the practical consideration of developing protective vaccines, it is also necessary to think about the nature and durability of immune memory [21, 40, 115].

This brief discussion concentrates on adaptive immunity, the spectrum of precisely targeted host response mechanisms that maintain the functional integrity of the environment “within” subsequent to virus challenge. It ignores the innate immune system, which may be of great importance in the early stage of infection with some viruses, particularly the herpesviruses [71], but is neither conventionally antigen specific nor capable of generating the long-term memory that is the basis of immunization. Of course, both aspects of immunity work together. The themes of cytotoxic effector function [30] and localized cytokine production [95, 103], particularly γ -interferon (IFN- γ) and tumor necrosis factor- α (TNF- α), are shared by the cells of the innate and adaptive systems.

Plasma cells, B lymphocytes and antibodies

Antibody has been the traditional focus of virologists interested in the immediately practical concern of making effective vaccines. Techniques for generating strong serum antibody response to pathogens, or their products, were known through much of the 20th century, and provided our first opportunity to exploit immunotherapy with products like antitoxins and antivenenes. Many of the first immunologists were, in fact, called serologists. Early pioneering work on the immune system, including the discovery of the role of the plasma cell in antibody production [44] by Astrid Fagraeus (1913–1993), was done, for example, at the State Serum Institute in Copenhagen.

Measurement of serum neutralizing antibody is still the best correlate of vaccine-induced immunity for many viruses. In the main, the protective, virus-specific immunoglobulin (Ig) molecules are targeted to tertiary, conformed determinants of glycoproteins expressed on the surface of the virion [76]. Such pre-existing Ig may not completely block infection at (for example) mucosal surfaces [99], but it does prevent the systemic spread of blood-borne virus to distal sites of potential pathology such as the large motor neurons in poliomyelitis. One of the challenges for immunologists is to develop strategies for maintaining high levels of mucosal antibody [72]. Can we hope to vaccinate against HIV if the virus cannot be stopped at the initial site of entry?

Antibody-mediated selection pressure drives the diversification of the influenza A viruses manifested as antigenic drift in the broader ecological context [46, 127], while the continuing emergence of antibody escape variants within an infected individual is a depressingly familiar characteristic [54, 63] of pathogens like HIV and hepatitis C virus (HCV). Recent strategies for developing neutralizing antibody response to (for example) the M2 channel protein that is expressed on the surface of the influenza A viruses [84] suggest that it may be possible to generate protective antibodies directed at conserved determinants expressed on molecular structures that have little, if any, capacity to vary. This would, of course, be the “holy grail” for HIV research [23].

Serum antibody is often detected indefinitely after vaccination or primary infection. Recent experiments have shown that B lymphocytes specific for vaccinia virus may be circulating in peripheral blood for as long as 50 years after exposure to the DryVax vaccine [31]. Vaccinia virus is not present in the normal human environment, and it is unlikely that (at least) most urban dwellers will have encountered even a distantly related poxvirus that infects, for example, domestic animals. Memory in the B cell/plasma cell compartment can apparently be maintained in the very long term without further challenge by the inducing antigen.

Antibody production is a property of plasma cells, the terminally-differentiated stage of the B cell lineage. During the acute phase of an infectious process, activated B cells/plasmablasts circulate in the blood and localize to various distal sites. In the viral encephalitides, for instance, B cells/plasmablasts can be seen to transit [32] from the blood to the central nervous system (CNS), where they become plasma cells and continue local antibody production in the long term [52, 98]. Persistent infection with a defective variant of measles virus in subacute sclerosing panencephalitis is characterized by massive, long-term local antibody production [114]. Subclinical infection of the CNS with an encephalitic virus can also lead to the sustained presence of neutralizing Ig in cerebrospinal fluid (CSF) at titers that are clearly discordant with levels in serum, providing a clear indication of local Ig synthesis in the brain [98].

Other B cells/plasmablasts find their home in the bone marrow (BM), a process that is clearly independent of antigen [60, 111] localization to that site. Long term Ig production seems, in fact, to be a function of the BM compartment [112]. The mammalian BM functions to provide continuous replacements for cells in the hemopoietic lineages, including naïve B cell precursors. Perhaps the spectrum of growth and differentiation factors that are required for this purpose also act to sustain the antibody-producing plasma cells [26].

Though we have been studying antibodies for a very long time, there are still big gaps in our understanding of topics like virus neutralization. The traditional neutralization assay done in tissue culture does not, for example, take account of the possible role of complement activation [132], or of opsonization and destruction by macrophages, mechanisms that are likely to be operational in the *in vivo* situation. The possible role of enhancing antibodies as a mechanism for promoting virus growth and damage in macrophages and epithelial cells has been

a major focus for those interested in hemorrhagic dengue [55]. Similar questions have been raised for HIV, though more in the context of promoting virus growth and persistence [80]. The structural basis of antibody neutralization is clearly an important focus [8]. More research is being done on antibody neutralization, particularly as attempts are made to develop immunization strategies to limit the ravages of the AIDS pandemic [23, 70].

Helper and effector CD4⁺ T cells

No long-term, protective antibody response is generated in the absence of CD4⁺ helper T cell function. Viruses can promote some IgM production, but even the generation of substantial IgM titers depends on the involvement of helper T cells [104]. In general, the requirement is for “cognate help”: the two categories of lymphocytes must interact directly via TCR-mediated CD4⁺ T cell recognition of viral peptide in the binding site of the appropriate MHC class II glycoprotein on the surface of the B cell. Early IgA production may break this rule [105], but there is still an absolute requirement for the concurrent stimulation of CD4⁺ T cells by other antigen presenting cells, particularly dendritic cells (DCs). The possible mechanism is that the T cells promote IgA production by B cells that have bound viral components via surface Ig and are in sufficient proximity to be stimulated by secreted lymphokines and cytokines. However, this is likely to be an exceptional situation.

Though a concurrent CD4⁺ T cell response does not seem to be required for the development of an effective CD8⁺ T cell response [14], it is clear that both the qualitative and quantitative character of virus-specific CD8⁺ T cell memory may be compromised in the absence of concurrent CD4⁺ T help [13]. This applies to both the generation and the recall of memory CD8⁺ T cells. Unlike the B cell/antibody response, CD4⁺ T help for the CD8⁺ responders is thought to operate via the DCs, with the role of the CD4⁺ T cells being to activate the DCs to be more effective antigen presenting cells [15, 100]. High-level virus persistence in the absence of CD4⁺ T help is also associated with a progressive loss of functional capacity by CD8⁺ T cell effectors [79, 82, 133]. This “immune exhaustion” effect is seen most clearly with LCMV, and is less apparent for persistent infections that are characterized by less fulminant antigen production [75, 117].

Activated CD4⁺ T cells play a very important role as direct mediators of immune control in the host response to intracellular bacteria [67] and herpesviruses [81]. In general, a primary requirement for these CD4⁺ T cell effectors [28] is the production of IFN- γ . Mice that are CD4⁺ T cell deficient as a consequence of disruption of the H2I-A^b gene can only partially limit the lytic phase of murine γ herpesvirus 68 (γ HV68) infection, and succumb after about 100 days with a late-onset, wasting disease [25]. Experiments with the influenza A viruses suggest that CD4⁺ T cells promote recovery by providing help for the antibody response [121], though there is other evidence that they can function directly in the site of pathology [136]. Selective priming of CD4⁺ T cell memory can lead to a more rapid antibody response to Sendai virus, to greater localization of CD4⁺ T cells to

the infected lung and to more rapid virus clearance [136]. Recent evidence with the mouse hepatitis coronavirus neurological disease model suggests that CD4⁺ T cells can mediate virus clearance in the absence of antibody, but with substantially delayed kinetics (S. Perlman, personal communication).

Cytokine production by CD4⁺ T cells can also have profound deleterious effects. Mice that lack CD8⁺ T cells as a consequence of disruption of the β 2-microglobulin (β 2-m) light chain of the MHC class I glycoprotein fail to clear lymphocytic choriomeningitis virus (LCMV) and develop a chronic, wasting disease [37]. This was shown to reflect the persistent stimulation of CD4⁺ T cells by the otherwise non-pathogenic LCMV. Also, if mice acutely infected with LCMV (or with an influenza A virus) are dosed with a “superantigen” (staphylococcal enterotoxin B), the resultant, massive, cytokine “dump” by highly activated, virus-specific CD4⁺ T cells can lead to death from TNF α -mediated shock [106, 134]. It is also possible that cross-reactive CD4⁺ memory T cell stimulation [77] and the resultant cytokine release could be a factor in the hemorrhagic syndrome that can follow secondary infection with heterologous dengue viruses [87].

The great majority of autoimmune disease that are thought to be T cell mediated have been associated with CD4⁺ [16] rather than CD8⁺ T cell response, though this perception may be changing [73]. Such syndromes may, of course, reflect the breaking of self-tolerance by exposure to molecular mimics of self-components expressed by invading viruses or bacteria [88, 108]. The broad alternative is that this apparent autoimmunity is directed at persistent, but as yet uncharacterised, viruses [114].

CD8⁺ effector T cells

The CD8⁺ T cell is the primary mediator of virus clearance in the acute phase of most infections, and can act in the absence of CD4⁺ T help and antibody production to deal with at least some lytic viruses that lack a persistent phenotype [39, 126]. Though activated, virus-specific CD8⁺ T cells are potent producers of cytokines [113], particularly IFN- γ and TNF- α , the principal effector mechanism in many infectious processes is thought to be cell-mediated cytotoxicity. Activated CD8⁺ cytotoxic T lymphocytes (CTL) contain large intracytoplasmic granules that express the pore-forming protein, perforin, and a range of serine esterases, or granzymes [62, 74]. These discharge their contents at the “immunological synapse” that forms at the interface between the “killer” lymphocyte, and the infected cell, with the perforin and granzymes then acting synergistically to trigger the classical apoptosis pathway [45].

Apoptotic elimination can, if the perforin/granzyme pathway is disrupted, also be induced via the interaction of Fas ligand on the CTL with Fas expressed on the infected cell [120]. The latter mechanism may, however, be less precisely constrained by TCR/epitope recognition, and thus more likely to induce bystander killing of other cells that happened to have increased Fas expression [122]. Even in the absence of such “promiscuous” lysis, some immunopathology is an inevitable

consequence of any virus-specific CTL response [33, 90, 128]. The simultaneous elimination of large numbers of infected cells in (particularly) sensitive sites like the CNS can lead to massive functional impairment and even death.

The nature of the infectious process can determine the relative significance of different CD8⁺ T cell effector mechanisms. While IFN- γ seems to play (at most) an ancillary role in the control of influenza pneumonia [50, 96], local production of IFN- γ by CD8⁺ T cells is clearly important for the clearance of respiratory syncytial virus from the lung [90]. Another situation where IFN- γ produced by the CD8⁺ T cell is the primary mediator of virus control is in the transgenic mouse, human hepatitis model studied by F. Chisari and colleagues [53]. Production of IFN- γ by CD8⁺ T cells is also central to the limitation of alphavirus [18, 19] and enterovirus infections [101] in the central nervous system. Though inflammation may alter the normal profile [24, 97], neurons do not generally express MHC class I glycoproteins [124]. Any T cell-mediated control of neuronal infection is thus likely to work via locally secreted factors rather than by the precisely targeted, direct T cell/target contact that is required for cytotoxic elimination.

What we learned through the 1990's from experiments with genetically disrupted, "knockout" mice is that disabling molecular mechanisms that are thought to constitute the primary mode of virus control often serves simply to reveal the existence of potent, alternative, effector functions [36]. In the phylogenetic sense, it is easy to see the reason for this divergence. The large DNA viruses, such as the herpesviruses [49] and poxviruses [86], have evolved a number of strategies for defeating cell-mediated immunity. It is important, both for the survival of the host and the parasite in the evolutionary sense, that there should always be an alternative means of control, at least to the level that allows for some persistent virus production, or reactivation from latency.

T cell memory and the recall response

The development of FACS staining approaches utilizing tetrameric complexes [2] of MHC class I glycoprotein + peptide (tetramers) has greatly facilitated the analysis of both the effector and memory phases of virus-specific CD8⁺ T cell responses [20, 40]. This technology has moved more slowly for the CD4⁺ T cell subset [5, 6, 58], partly because the comparable MHC class II + peptide reagents are more difficult to produce [129], and partly because CD4⁺ T cell responses can tend to be both more diverse and smaller in magnitude.

The most useful techniques for analysing CD4⁺ T cell memory depend on the measurement of IFN- γ production by peptide-stimulated lymphocytes, measured either in a flow cytometric assay or by ELISpot analysis after 24–48 hours of *in vitro* culture [66]. Persistent CD4⁺ T cell memory is, for example, found for adenoviruses in healthy humans [89]. Lack of progression to AIDS has been correlated with the continued presence of more HIV-specific IFN- γ than IL-10-producing CD4⁺T cells in the peripheral circulation [91]. Priming CD4⁺ T cell memory to a prominent Sendai virus epitope led to a more rapid antibody

response and enhanced virus clearance [136]. Low-level γ HV68 persistence induced continuing $CD4^+$ and $CD8^+$ T cell responses that substantially prevented the establishment of further lytic, but not latent, infection following respiratory challenge of antibody-negative, μ MT mice with the same virus [4]. Immune $CD4^+$ and $CD8^+$ T cells contributed to this protective effect in an additive way. Though adoptively-transferred $CD4^+$ and $CD8^+$ T cells promoted the recovery of μ MT mice from influenza virus infection, the $CD8^+$ set was clearly more effective in this regard [51]. In general, we understand less about $CD4^+$ than $CD8^+$ T cell memory.

Persistent $CD8^+$ T cell memory can be demonstrated in both mice and humans following a single exposure to an inducing virus [38, 56, 61, 65, 78]. These long-lived T cells and their progeny express high levels of telomerase activity [57] though, under conditions of continuing antigen stimulation, telomere length may be shortened to the extent that clonal survival is impaired [102, 125]. The maintenance of $CD8^+$ T cell memory reflects the survival of clonotypes expanded during the initial, antigen driven phase of the host response [123], but does not seem to require either the persistence of the inducing epitope or even the continued presence of MHC class I glycoprotein [59, 85]. What does seem to be important is exposure to the cytokines IL-7 and IL-15, both during the acute response phase and in the long term. [17, 64, 107, 119, 135].

The recall of $CD8^+$ T cell memory can certainly provide a measure of protection against virus challenge [27], a possibility that is particularly attractive for viruses that vary their surface glycoproteins as a consequence of antibody-mediated selection pressure. Virus-specific $CD8^+$ T cell responses tend to be directed at peptides derived from conserved, internal proteins [12, 130], a situation that may be quite different from that found with $CD4^+$ T cell responses [22]. This cross-reactivity is, for instance, a good reason for thinking about the use of live influenza vaccines, combined with other mechanisms for boosting CTL memory [29, 43].

The problem with relying on the recall of $CD8^+$ T cell memory for protection is that, though the injection of peptide-pulsed cells is generally associated with rapid elimination [9], the recall of effective $CD8^+$ T cell memory to a distal site of virus growth is substantially delayed [35, 47]. When memory T cell numbers are at what might be thought of as physiological levels, there is a clear necessity for further proliferation in the lymphoid tissue, followed by emigration into the blood and localization to the target organ [48]. Even when memory T cell numbers are very high in, for example, the lung, a rapidly growing influenza A virus will still become fully established before $CD8^+$ T cell effectors operate to eliminate the infected cells and control the growth of the pathogen [29].

Thus, though vaccines directed at promoting $CD8^+$ T cell memory can limit the damage done by lytic viruses that do not have a capacity for persistence, they seem unable to prevent the establishment of persistent infections [4, 118]. This has been clearly demonstrated for monkeys primed with candidate HIV vaccines [3, 10]. The T cells function for a time to limit the extent of virus replication, but escape variants eventually emerge [11].

Conclusions

Some virus infections may be controlled by either an effective CD8⁺ T cell response, or by a high quality B cell/antibody response that depends on CD4⁺ T help. In general, however, the host response is optimally mediated by all three categories of immune lymphocyte operating together. This is clearly the case for the large DNA viruses, particularly the herpesviruses, which also require the involvement of cytokine-producing CD4⁺ effector T cells [28]. Most of our successful vaccines to date depend on the capacity of a persistent neutralizing antibody response to limit systemic spread to distal sites of virus growth. Memory CD8⁺ T cells may not prevent the establishment of an infectious process, though the more rapid recall of CTL effector function is likely to ameliorate the severity of pathology and consequent clinical impairment by speeding virus clearance [29]. Again, with viruses that have the capacity to persist, the available evidence suggests that an optimal vaccine will prime all the components of adaptive immunity [3].

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