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Review Article

Viral Vaccines and CTL Response

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Immune induction by successful vaccine formulations seems to involve stimulation of both humoral and cellular arms of immunity. Nevertheless, CD8+ CTLs are of critical relevance in the context of intracellular infection and tumor for many reasons. The task of exerting antipathogen activity by CD8+ T cells, which principally function to control and eradicate intracellular pathogens, is enabled by constitutive expression of MHC class-I molecules on all tissue types. CTL induction offers hope for vaccines against pathogens that are resistant to neutralizing activity. This review discusses the mechanism of immune induction by some successful vaccines and based on the accrued evidence suggests ideas for improved design of CTL-inducing vaccines.

1. Introduction

One of medicine's greatest triumphs has been the control of many infectious diseases with prophylactic vaccines. Successful vaccine formulation was confirmed with smallpox eradication and a similar outcome is expected with polio. Measles also has been eliminated as a pathogen in most developed countries. Highly effective vaccines also exist for mumps, varicella in children, yellow fever, hepatitis viruses A and B, rubella, and rabies, despite the fact that large numbers of people in the developing world fail to use them due to cost factor and logistics. This is particularly a tragedy with measles which is an extremely effective vaccine when used correctly in children. With many individuals remaining unvaccinated, unnecessary mortality and complications occur from measles infection.

However, several viruses are controlled by vaccines that still need improvement, notably the vaccines for influenza. The currently used inactivated vaccines have debatable efficacy. But the newly available attenuated vaccine, when administered mucosally, could be more effective due to an enhanced induction of a mucosal immune response. Even highly effective vaccines, such as the yellow fever vaccine, lack perfection because of complications in some aged individuals [1]. Many virus infections could be controlled by appropriately designed vaccines, yet the existence of multiple serotypes, sporadic nature, and economic realities may prevent this from being achieved.

Vaccines are also under advanced stages of development, or available for Dengue Virus, West Nile Fever (WNF), and Rift Valley fever. Of particular interest is the vaccine developed using reverse genetics to express recombinant proteins in the vector and the 17D attenuated Yellow Fever virus that are proving to be excellent vaccines for Dengue and WNF [2–5]. The Yellow Fever vaccine has been established to induce protection against the virus itself for at least 10 years. Such successes are encouraging for additional viruses that could be controlled by vaccines, but for many reasons vaccines may not be available any time soon.

2. Factors That Favor or Hinder Vaccine Success

In spite of great intellectual effort and big investments, we have failed to produce effective vaccines against Human immunodeficiency virus (HIV), hepatitis C virus (HCV), respiratory syncytial virus (RSV), and all herpes viruses (HSV) except for chicken pox (Varicella). The most difficult case of all is HIV which seems almost designed to outwit immunologists.

Some of the factors that contribute to vaccine failure may be common to certain pathogens (Table 1). These factors are dynamic with evolving pathogens that negatively influence

Table 1: Factors that makes control by vaccines problematic [6–9].

(i)	Antigenic plasticity—all RNA viruses
(ii)	Possession of immune evasion maneuvers, for example, targeting antigen-presenting cells and lymphocytes
(iii)	Persistence and latency
(iv)	Entrance and major replication at mucosal surfaces
(v)	Poor or retarded immune induction
(vi)	Resistance to neutralization by antibody
(vii)	Immunity solely dependent on T cells

Table 2: Factors that favor control by vaccines [10].

(i) Stable antigenic nature
(ii) Single host
(iii) Systemic infection
(iv) Immunity mediated by neutralizing antibody
(v) Virus removed by immune system
(vi) Agent induces long-term T and B cell memory

host competition for survival. In the case of all RNA viruses, antigenic plasticity seems to be the key issue. Additionally, viruses possess many tools in their armamentarium to evade host immune response. Viruses may target the tissue they initially infect, the sentinel cells that convey the information to specific lymphocytes, or directly the specific T/B cells. Pathogens may also choose to conceal themselves in cells that are inaccessible to the immune system or, ideally, the cells that constitute the immune system. These pathogens collectively cause chronic, persistent, or latent infection. The best examples are found in the virus family listed earlier (HIV, HSV, and HCV). These pathogens are generally resistant to neutralization by antibodies (Abs); therefore, immunity is dependent primarily on T cells.

The factors that favor success for a vaccine against a pathogen are the stable nature of antigens, systemic infection involving a single host, immunity that is mediated by neutralizing antibodies, pathogens inducing long-term high-efficiency T and B cell memory if the host survives the infection, and finally sterilizing immunity that clears the pathogen (Table 2). The scenario which makes for highly effective control by vaccines is perhaps best illustrated by the first agent that was successfully controlled, smallpox. However, the actual mechanisms involved in recovery from infection and resistance to challenge have only recently been identified. Such studies were done in the mouse model of Vaccinia since work with Variola in humans is, of course, not possible. Intriguingly, immunity to smallpox is exceedingly durable [11, 12]. Edward Jenner, on the basis of inoculation studies with smallpox material, demonstrated that a patient that had natural cowpox 53 years earlier was resistant to challenge (reviewed in [13]). Not so long ago, the laboratories of Mark Slifka and Rafi Ahmed have shown that all forms of immunity and particularly neutralizing antibody can be detected in Vaccinia vaccines for at least 30 years and in some instances 75 years [14–16]. Indeed Slifka's group estimated the half-life of humoral immunity to be about 80 years and T cell responses between 8–15 years [16]. How Abs persist so long is perplexing. It is not explained by persistent viruses or by exposure to other cross-reacting microbes since no cross-reactivities with Vaccinia are known. One expects the explanation to lie with the persistence of memory B cells in the bone marrow.

3. Lessons from B Cell and Role of T Cells

Studies done by the Berzofsky and Bevan groups in mice with Vaccinia have revealed several clues about mechanisms of immunity [17, 18]. These studies serve to emphasize the conclusion that neutralizing Abs play the predominant role in both curtailing infection and certainly in preventing disease following reinfection. However, the desirable Ab is a high-affinity IgG, which requires appropriate helper T cell co-stimulation for its induction. In Vaccinia infection, the viral immunologist's favorite cell type—the CD8+ T cell—appears to play a minor and possibly dispensable role. This raises the issue of whether or not immunity to reinfection is ever solely dependent on one or another subset of immune T cells.

The case for CD8+ T cells in recovery from infection and resistance to challenge was made most strongly by studies in mice of the noncytopathic arenavirus and lymphocytic choriomeningitis virus (LCMV) which is a cousin of Lassa Fever Virus [19]. In this model, resolution of infection and long-term immunity to reinfection primarily involve CD8+ T cells [20]. Recently, exciting studies on the nature and function of antiviral memory in LCMV have provided clues to understand memory that may have application to novel CTL vaccine design [21].

4. Acute versus Chronic Infection Scenario

Acute infection with LCMV results in a prompt and vigorous CD8+ T cell response that mediates rapid viral clearance. Most of the antigen-specific T cell effectors die rapidly of apoptosis with approximately 10%–20% persisting at stable levels indefinitely [24]. These cells turn over homeostatically, an event driven by cytokines such as IL-15 [25]. In this system, memory sustenance is an antigen-independent event as it seems to be the case for Vaccinia in the human system. Nonetheless, others believe that memory changes with time as a consequence of exposure to cross-reacting or perhaps bystander influences [26]. Fascinating studies by several groups have revealed that the establishment of the long-term CD8+ T cell memory response actually requires coinduction of CD4 helper T cells or replacement of their function with certain costimulants or cell type [27–29]. Curiously, memory CD8+ T cells that are induced in the absence of help respond poorly to restimulation by antigens. Upon restimulation, "helpless" memory CD8+ T cells are eliminated in a TNF-related apoptosis-inducing ligand- (TRAIL-) dependent mechanisms [30].

Perhaps of even more interest are the studies on the nature of CD8+ T cell in memory situations in which the

Table 3: Immunity to Hepatitis C Virus—A Flavivirus with no vaccine [9, 22].

(i)	60%–80% of patients remain chronically infected and suffer consequences
(ii)	Patients who do recover develop multiepitope-specific CD8+ and type 1 CD4+ T cells
(iii)	Neutralizing Ab production takes 6–8 months and highest titers occur in chronics. Recovered patients may test negative
(iv)	Abs always gone by 10–20 y, but specific T cells persist for life in liver (in chimps)
(v)	Chimps without CD4+ or CD8+ T cells fail to control infection
(vi)	Escape mutants for Ab and T cells occur readily

Table 4: Hepatitis C Immune Escape Tricks [8, 9, 23].

(i)	Viral sequence mutations allow escape of both Ab and T cell recognition (NB high replication rate)
(ii)	HCV core protein binds a complement protein that results in downregulation of IL-12 production and affects T cell induction
(iii)	Express a protease which interrupts induction of interferon a/b
(iv)	Incomplete differentiation of HCV-specific T cells may occur (like chronic memory cells)
(v)	Induction of IL-10-producing Treg cells
(vi)	Also an involvement of CD4+ CD25+ natural Tregs

virus remains as a chronic infection. Studies on chronic memory cells in the case of persisting LCMV clone 13 infection revealed major differences from acute memory cells. First, the chronic memory cells failed to overcome the initial acute infection. Secondly, when transferred to an antigen-free environment, the acute memory cells survived and maintained their numbers by turning over homeostatically, but the chronic memory cells failed to divide and ultimately disappeared [31]. Thus, chronic memory cells are dysfunctional when addicted by an antigen, resulting in upregulation of some inhibitory machinery [32, 33]. Other explanations include the induction of third-party regulatory cells possibly in response to antigen presentation by a subset of dendritic cells (DCs) [34, 35].

The outcomes of studies on LCMV in an animal model raise the question of relevance to human chronic virus infections. In this regard, the two most important human chronic viruses are Human immunodeficiency virus (HIV) and Hepatitis C virus (HCV). HCV has become a major human pathogen and, although controlled in some by antiviral drugs, is a major cause of chronic disease and mortality [36]. Currently, vaccines are unavailable, and prospects are dim to develop them soon. As summarized in Table 3, HCV infection induces an immune response that is usually noneffective and occurs late during infection. Unlike vaccine-controllable viruses such as Vaccinia and polio, neutralizing Abs seem to play an insignificant role in control of infection or the prevention of reinfection [37, 38]. Indeed, individuals who make the highest levels of neutralizing antibody subsequently develop chronic disease [39]. HCV appears to possess an abundance of strategies that serve to circumvent immune defenses; these include properties that avoid innate immunity as well as adaptive defenses (listed in Table 4). HCV, like HIV, is a moving target antigenically since sequence mutants are frequent [22]. Moreover, it seems that in some, perhaps the majority of patients, HCV stimulates a regulatory T cell response which actually counteracts the otherwise protective CD8 and CD4 IL-2-producing T cell responses [40, 41]. Making an effective vaccine against HCV will require identification of the components that induce protective T or antibody responses and deliver them in such a way that protective rather than regulatory responses are induced. Furthermore, there is the ever-more daunting challenge of attempting to change response in chronically infected individuals by changing their ineffective response pattern to one that provides protection using therapeutic vaccines.

5. Vaccine Design

HIV, HCV, and many parasitic infections represent microbes that urgently demand effective vaccines. Hopefully, this demand can be met, but progress will likely be slow and convoluted. The ideal solution might occur if scientists identify successful means of inducing neutralizing antibodies especially if they can be induced at the site of viral entrance. For instance, although a vaccine for RSV is unavailable, passive protection can be effected with a monoclonal Ab that recognizes the F protein [42]. In situations that mainly demand a durable neutralizing antibody response, the task should be feasible as long as sequences that encode neutralizing epitopes and helper T cell costimulation can be identified. Recombinant proteins administered with adjuvants work successfully for hepatitis B [43]. More recently, the capsule polysaccharide antigen of Hemophilus influenza coupled to a protein carrier given with alum adjuvant has been a strikingly successful vaccine (reviewed in [44]). As mentioned, the 17D yellow fever vector holds great promise to induce IgG antibody and may also be valuable to achieve CD8+ T cell induction [4].

Several approaches can be used to successfully induce $CD8^+$ T cell responses, which are needed particularly for protection against HIV and HCV. With regard to HIV, a large number of different live vectors given alone or in combination with a priming dose of DNA or protein vaccine have been evaluated in primate test systems [45, 46]. Although many model exposure systems have yielded encouraging results, attempts to translate them to the human situation have so far proven disappointing [47]. In the past, the best vaccines have been attenuated mutants, but this approach may not be acceptable, at least with HIV, likely for safety reasons. Even so, such attenuated mutants appear superior to protect nonhuman primates against a lentivirus challenge [48].

6. Need for CD8+ CTL Induction

The importance of CD8+ CTLs in the context of intracellular infection and tumor is well established. Immune induction by successful vaccine formulations seems to involve stimulation of both humoral and cellular arms of immunity. Nevertheless, in some diseases scenario CD8+ CTLs are of critical relevance for the following reasons: (a) task of exerting antipathogen activity (lysis of infected cell or purging of infectious material by cytokine production), (b) enabled by constitutive expression of MHC class-I molecules on all tissue types, (c) principally function to control and eradicate intracellular pathogens, and (d) finally offering hope for vaccine against pathogens that are resistant to neutralizing activity.

The three main factors that determine the success of a CTL-inducing vaccine are its ability to induce high frequency of virus-specific CD8+ T cells, polyfunctional CD8+ T cells, and proximity to the site of initial infection. In other words, the quantity, quality, and location of the memory CD8+ T cells response as discussed recently in the context of HIV/SIV infection [49] may hold true for many other viral infections.

An important variable is the differentiation status of CD8+ T cell that is to be activated. Naive CD8+ T cells are the ones that reside normally in the lymphoid tissues and have not been exposed to antigen after emergence from thymus. First exposure to antigens presented on MHC-I results in primary response and is called priming. On the other hand, memory CD8+ T cells are generated by priming and persist long after the original priming event has terminated. Memory CD8+ T cells reside in lymphoid tissue and extravascular sites and respond quickly and vigorously to reexposure. Most of the vaccine design has been targeted to priming a response and less on memory reactivation or rescue of defective priming.

7. Turning on CD8+ T Cells

Progress in the induction of protective T cell-mediated immunity is expected to come by using antigens given along with the appropriate choice of adjuvants and co-stimulators to direct and maximize immune responses. This topic has received extensive reviews including attempts to achieve optimal mucosal immunity [50–54]. One clue for success may be to exploit the well-accepted notion that antigen delivered by an appropriate subset of dendritic cells represents an approach to tailor the nature and magnitude of the immune response [55]. Thus antigens loaded ex vivo into DCs of various types are expected to be useful as therapeutic vaccines in certain cancers [56–58]. However, a more practical approach would be to find ways of delivering antigen in vivo selectively to appropriate types of DCs or perhaps other antigen-presenting cells [55, 59]. Cytokine such as GM-CSF and IL-12 as adjuvants along with antigen-loaded DC has proven to be effective in priming high-quality CD8+ T cells in some animal models. Homeostatic cytokines that belong to γ-chain family (IL-2, IL-7, IL-15 and IL-21) may prove useful during recall responses or serve as effective partner (adjuvant) for therapeutic vaccine candidates [60–64].

Perhaps of particular interest are the results of the von Andrian group which showed the apparent imprinting effect of DCs on the homing fate of antigen-specific T cells [65]. For instance, if Ag was administered into the skin, DC transported antigen to the draining LN and the specific T cells induced mainly homed back to cutaneous sites. In contrast, antigen arriving via the gut resulted in the induction of gut-mucosa seeking T cells [65]. Since controlling infections requires prompt recruitment of effectors to sites of entrance, vaccination schemes that prime for T cells that home quickly to infected sites might tip the balance in favor of the host and stop the infection from spreading. It will be exciting to see whether such strategy worked for vaccine delivery.

Prophylactic vaccines have been able to do a reasonable job in priming adequate CD8+ T cell response, yet the need for a therapeutic vaccine to induce CD8+ T cell is more pertinent in the context of certain chronic infections and cancer. As suggested by Ahlers and Belyakov in a recent review, new vaccine strategies that elicit high-avidity CD8+ T cell effector/memory responses, which are capable of clearing virus-infected cells at entry sites, are required to curtail disease manifestation. Judging at the pace of research and the recent technological advances, effective CTL-inducing vaccines are achievable in the near future.

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