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Review

Prime-boost vaccine strategy against viral infections: Mechanisms and benefits

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ABSTRACT

The essential goal of vaccination is to generate potent and long-term protection against diseases. Among different vaccine modalities, prime-boost vaccine strategies could enhance cellular and also humoral immunity in several animal models. These strategies have been applied for the development of vaccines against important infectious diseases such as HIV, SIV, HCV, HSV, and HBV indicating promising results even in clinical trials. Several factors including selection of antigen, type of vector, delivery route, dose, adjuvant, boosting regimen, the order of vector injection, and the intervals between different vaccinations influence the outcome of prime-boost immunization approaches. The reported data suggest that the prime-boost strategy as a combination of vaccines (*i.e.*, heterologous prime-boost) may be better than a single vaccine for protection against infectious diseases. Indeed, in many cases, heterologous prime-boost can be more immunogenic than homologous prime-boost strategy. This review discusses the recent advances in prime-boost immunization strategies as well as their benefits and mechanisms of action.

1. Introduction

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At present, human vaccines are used in the prevention of more than thirty infectious diseases [1,2]. Traditional vaccine formulations include live attenuated microorganisms and inactivated microorganisms. The problems of traditional vaccines such as the lack of safety, adverse host reactions, and difficult culture of the pathogenic microorganisms have led to the design of subunit vaccines [3,4]. Subunit vaccines are based on peptides, proteins or polysaccharides containing protective epitopes [4]. However, the recombinant subunit vaccines are poorly immunogenic and require some additional components to increase the potency of protective immunity. Therefore, the use of adjuvants and also repeated boost immunizations are suggested to enhance the efficiency of subunit vaccines [3]. Recently, heterologous prime-boost immunization protocols using different gene expression systems have proven to be successful approaches for protection against different diseases in preclinical and even clinical trials. The main reason for using this approach is to develop the ability of expression cassettes to prime or boost the immune system in different ways during vaccination [5]. In this review, we describe various homologous or heterologous prime-boost strategies as an efficient approach for enhancing the potency of subunit vaccines.

2. Prime-boost vaccination: heterologous or homologous approaches

The prime-boost regimens have been shown to be an effective approach to induce both humoral and cellular immune responses [6]. Homologous prime-boost strategy contains the same formulation used in both the prime and boost regimens. On the other hand, heterologous prime-boost approaches involve different formulations used in more than one injection [7]. Some studies indicated that heterologous prime-boost is more effective than the homologous prime-boost approach [8]. The advantage of heterologous prime-boost immunization is the induction of both humoral and cellular immunity against a specific antigen using each delivery system individually. For instance, subunit vaccines usually elicit a predominant humoral immune response, while recombinant live vector vaccines and DNA vaccines are effective delivery vectors for inducing the cell-mediated immunity (CMI) [7]. The studies demonstrated that in comparison with homologous prime-boost approach with the same DNA vaccine, boosting a primary response with a heterologous vector leads to 4- to 10-fold higher T cell responses [9]. Heterologous prime-boost regimens mostly use a viral or a DNA vector for priming, followed by a boost with a protein-based vaccine. This immunization strategy results in the induction

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of a strong cellular immune response and is associated with a higher and more specific antibody response against the vaccine target compared to homologous immunization and can overcome the issue of anti-vector immunity [10].

Recently, the prime-boost strategy has been studied where both prime and boost immunizations were injected systemically. For many pathogens, immunity at mucosal surfaces was also important to evaluate the effects of prime-boost strategies and limit infections. These types of administrations were safe and more immunogenic at different ages as compared to intramuscularly (*i.m.*) administered vaccines [11,12]. Some studies showed that homologous protein-based immunization is very effective for generating humoral immune responses, but it is generally inefficient for eliciting cell-mediated immunity important for protection against intracellular pathogens [13,14]. Also, the effective prime-boost strategies often involve priming with a DNA vaccine followed by boosting with recombinant viral vectors or proteins. For example, the use of a heterologous prime-boost immunization for HIV-1 vaccine development was based on some data such as: (a) the recombinant envelope (Env) glycoproteins eliciting specific neutralizing antibody responses were unable to induce CTL responses, and (b) the recombinant *vaccinia* expressing HIV-1 antigens could mainly induce T-cell responses but not high levels of protective antibodies. Thus, the combined immunization containing both of them may be more effective than either immunogen alone [2,8].

3. Different methods of prime-boost vaccine strategies

The studies showed that the heterologous prime-boost approach can induce superior immune responses, especially T cell responses, compared to the repeated doses of the same vaccine in several animal models and clinical trials I–III [15]. Generally, there are various preventive or therapeutic modalities for prime-boost immunizations as follows.

3.1. DNA prime/viral vector boost, viral vector prime/DNA boost, and different viral vectors

The DNA prime/viral vector boost approach focuses on the induction of T-cell immune responses. Viral vectors used as booster include *adenovirus*, *vaccinia*, *fowlpox* and *vesicular stomatitis virus* [9,16]. Vaccine strategies that involve primary vaccinations with a DNA vaccine followed by boosting with a recombinant *poxvirus* vector encoding the same immunogen have known as special approaches for eliciting protective CD8+ T cell responses against various diseases such as HIV, malaria, and cancer [17]. At present, there are many animal studies indicating the immunogenicity of DNA vaccines and attenuated viral vectors that some of them have developed to clinical trials. However, the levels of specific immunity induced by these vectors have been insufficient for protection against pathogens [18]. The studies indicated that heterologous prime-boost vaccination protocols using a recombinant *vaccinia* virus (rVV) and bacterial plasmids could be used for the development of *flavivirus* vaccines [5]. In addition, the combined use of DNA vaccines with viral vectors in a prime/boost regimen has been proven useful for enhancing response levels in clinical studies [19–22]. For instance, DNA prime/*adenovirus*-5 or MVA boost enhanced T-cell immunity against HIV [23]. Furthermore, a DNA prime/*poxvirus* boost (NYVAC) approach targeting HIV-1 was tested in a Phase I clinical trial and induced polyfunctional, durable T-cell responses to Env. The immune responses in heterologous DNA–NYVAC were higher than in homologous NYVAC–NYVAC regimens [23]. The reported data in clinical trials demonstrated that prime-boost vaccination with recombinant DNA and MVA vectors (*modified vaccinia virus Ankara*) can induce multifunctional HIV-1-specific T cells in the majority of vaccinees [24]. Indeed, HIV-DNA priming followed by two HIV-MVA boosts could induce potent antibody-dependent cellular cytotoxicity (ADCC)-mediating antibodies in a high proportion of Tanzanian vaccinees [25]. The use of different viral vectors has been proved as another efficient approach against HIV infection. For example, non-human primate data has supported the efficiency of *adenovirus* prime/*poxvirus* boost approach for vaccination against HIV [15].

On the other hand, different forms of prime-boost regimens were used to further enhance therapeutic human papillomavirus (HPV) DNA vaccine potency. Studies showed that priming with a HPV 16 E6/E7 DNA vaccine followed by boosting with recombinant *vaccinia*/*adenovirus* or with the HPV 16 E6/E7 expressing tumor cell-based vaccine can elicit antigen-specific CD8+ T cell immune responses in vaccinated mice higher than each regimen, individually [26]. A clinical trial using pNGVL4a/Sig/E7(detox)/HSP70 DNA prime followed by the *vaccinia*-based vector vaccine (TA-HPV) boost was also evaluated in patients with cervical intraepithelial neoplasia 2/3 (CIN 2/3) lesions, with or without the topical application of imiquimod [26].

This approach was also used to design a potent vaccine against hepatitis C virus (HCV), influenza, and *ebolavirus*, as well. For example, prime with a DNA vaccine expressing HCV genotype 1a NS3/4A proteins (ChronVac-C) and boost with a modified *vaccinia* virus Ankara vaccine expressing genotype 1b NS3/4/5B proteins (MVATG16643) was used to treat chronically infected HCV patients [22]. Also, a heterologous prime/boost of HCV core protein, using DNA vaccine priming followed by Lambda boost, induced highest level of CD8+ T cell responses, and shifting the immune response toward a Th1 pattern [27].

In another study, a heterologous DNA prime followed by inactivated influenza vaccine boost was shown to be more immunogenic than homologous prime-boost using either DNA or inactivated influenza vaccine alone in animal model [28]. In addition, the optimal prime-boost combination using DNA, porcine-derived adeno-associated virus serotype 6 (AAV-po6), and human *adenovirus* serotype 5 (Ad5) vector was studied for a short-term protection in mouse model of EBOV infection. The data showed that vaccination with DNA prime/Ad5 boost induces a higher cellular immune response and also the best protection. In contrast, priming with AAV-po6 (or Ad5) followed by DNA boost showed better protection correlated with a higher total glycoprotein-specific IgG titer [29]. Some studies demonstrated that the recombinant *vesicular stomatitis virus* (rVSV)-based vaccine vectors, which encode an EBOV glycoprotein instead of the VSV glycoprotein, have elicited 100% efficacy against homologous *Sudan ebolavirus* (SEBOV) or *Zaire ebolavirus* (ZEBOV) challenge in nonhuman primates (NHPs) [30]. Recently, several different strategies were evaluated against *Bundibugyo ebolavirus* (BEBOV) using rVSV-based vaccines such as a single injection of a homologous BEBOV vaccine, a single injection of a blended heterologous vaccine (SEBOV/ZEBOV), and a prime-boost using heterologous SEBOV and ZEBOV vectors. The results showed that cynomolgus macaques vaccinated with the homologous BEBOV vaccine or the prime-boost showed no overt signs of illness and survived against challenge as compared to animals vaccinated with the heterologous blended vaccine and unvaccinated controls. Indeed, the heterologous rVSV-based *filovirus* vaccine vectors used in the prime-boost approach could provide protection against BEBOV [30].

3.2. DNA prime/protein boost or DNA prime/peptide boost

Priming with DNA and boosting with protein (or peptide) is another promising approach that is able to develop both humoral and cell-mediated immune responses with a main focus on eliciting

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