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Viral vectors as vaccine platforms: from immunogenicity to impact

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Viral vectors are the vaccine platform of choice for many pathogens that have thwarted efforts towards control using conventional vaccine approaches. Although the STEP trial encumbered development of recombinant human adenovirus vectors only a few years ago, replication-deficient simian adenoviruses have since emerged as a crucial component of clinically effective prime–boost regimens. The vectors discussed here elicit functionally relevant cellular and humoral immune responses, at extremes of age and in diverse populations. The recent Ebola virus outbreak highlighted the utility of viral vectored vaccines in facilitating a rapid response to public health emergencies. Meanwhile, technological advances in manufacturing to support scale-up of viral vectored vaccines have helped to consolidate their position as a leading approach to tackling 'old' and emerging infections.

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Introduction

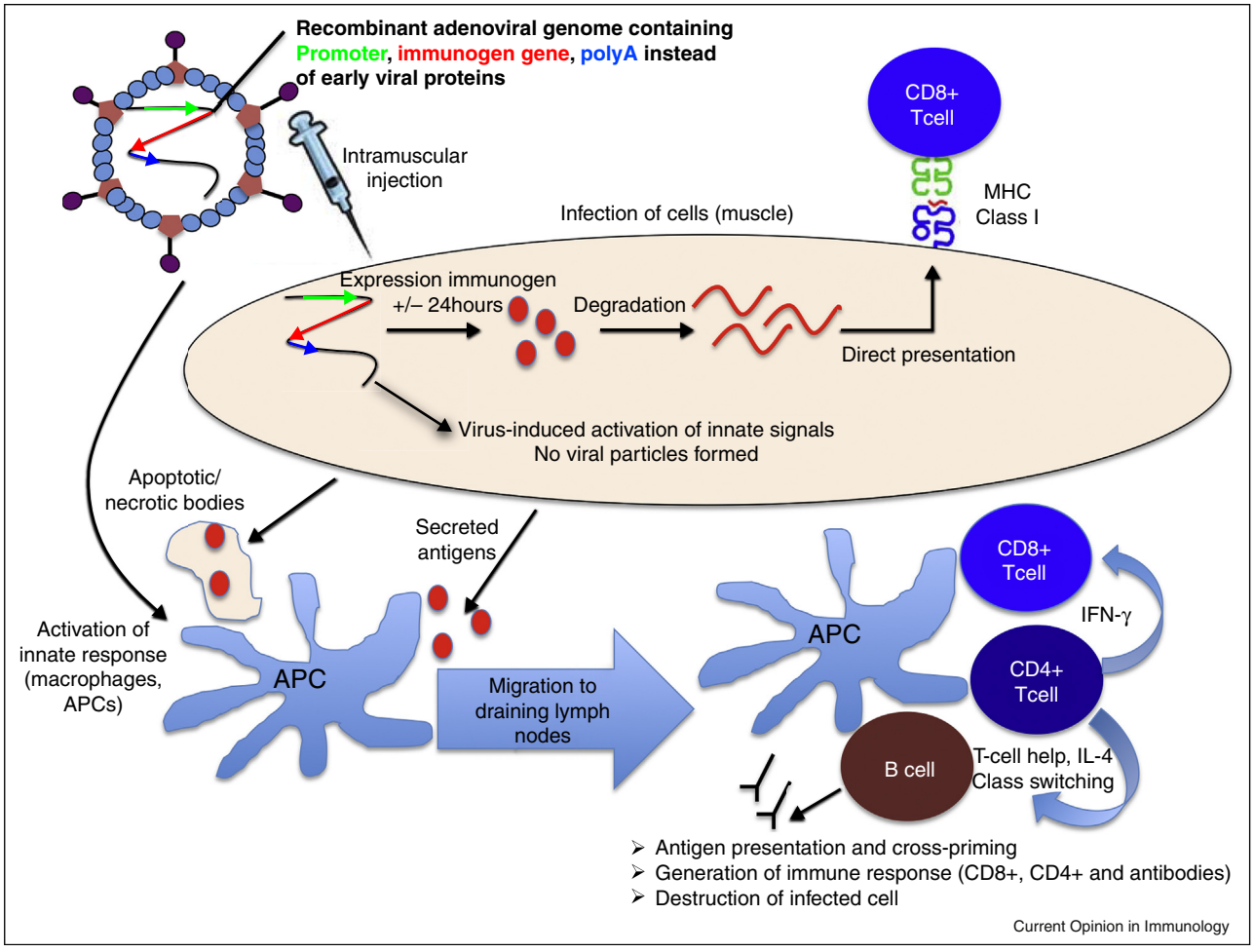
Recombinant viral vectors are a powerful technology for delivering heterologous antigens that combine the best features of other vaccine modalities, with minimal disadvantages. Their capacity to infect cells and express encoded antigens that may be shed into the extracellular milieu or directed to host intracellular processing pathways ensures highly efficient induction of both humoral and cytotoxic (CD8+) T cell responses (Figure 1). This provides a key advantage over subunit vaccines, since CD8+ T cells are critical for the elimination of intracellular pathogens. Viral vectors have intrinsic adjuvant properties, as they express diverse pathogen-associated molecular patterns which activate innate immunity. Targeted gene deletion is a widely used strategy to reduce or eliminate the replicative capacity of viral vectors, which ensures safety for human use without loss of potency. However, some replication-competent viral vectors can also be given safely and may provide equivalent potency at lower doses. The main drawback of viral vector vaccines is that the transgene-specific response may be dampened by pre-existing or *de novo* adaptive immune responses to antigenic targets within the vector itself. Strategies to overcome this include the use of higher doses, tolerability permitting, and heterologous prime–boost vaccine regimens.

The development of viral vectors as vaccine platforms has continued unabated, in response to the need for new or improved vaccines against known and emerging pathogens. Two viral vectored vaccines are now licensed for human use and others are likely to follow, as the utility of this technology for a rapid response to global health threats is now clearly recognised. We highlight here the most significant progress in the development of viral vectored vaccines in the past five years and the steps taken to address obstacles to their deployment, together with important insights into mechanisms of protective immunity gained from clinical trials.

Pushing the boundaries: immunogenicity across diverse infectious diseases, populations and age groups

Proof of concept for heterologous prime–boost vaccinations was first demonstrated over a decade ago, with experimental vaccines for malaria using DNA and Modified Vaccinia Virus Ankara (MVA) vectors [1,2]. These early promising results have since been eclipsed by the success of regimens incorporating recombinant adenoviruses as the priming vaccine, thanks to their vastly superior capacity to induce potent cellular and humoral responses. Pre-existing vector-specific immunity, the main drawback of human adenoviruses, has been effectively circumvented by substitution with replication-deficient (E1-deleted) chimpanzee adenoviruses (ChAds). ChAd63, the first simian adenovirus vector to enter clinical trials, has now been tested in ~1500 individuals [3] (Table 1). A critical result was the finding that prime–boost immunisations with ChAd63-vectored and MVA-vectored *Plasmodium falciparum* malaria vaccines targeting

Figure 1



Mechanism of induction of transgene-specific cellular and antibody responses by replication-defective viral vector vaccines. Administration of a recombinant adenovirus vaccine by intramuscular injection results in infection of muscle cells (non-productive in the case of replication-defective viral vectors) followed by expression of the transgene within 24 hours, together with triggering of innate immune responses via interactions between viral nucleic acids and pathogen recognition receptors. Expressed proteins undergo proteasomal degradation and presentation to CD8+ T cells in association with MHC class I molecules or may be secreted and taken up by professional antigen presenting cells (APC). APC may also acquire vaccine antigens as apoptotic or necrotic bodies or may be directly activated by interaction with the viral vector. Antigen-loaded APC migrate to draining lymph nodes where they are able to prime CD8+, CD4+ T cells and B cells.

the pre-erythrocytic stage conferred significant protection against both controlled human malaria infection in naïve volunteers and natural infection in malaria-exposed adults. Protection was correlated with high frequencies of antigen-specific CD8+ T cells [4,5•]. Following this, spectacular immunogenicity of other ChAd (ChAd63, ChAd3, PanAd3, ChAdOx1) prime/MVA boost regimens in humans has been demonstrated for HIV-1, hepatitis C virus (HCV), influenza and respiratory syncytial virus (RSV) immunogens [6–9] (Table 1).

These studies have been conducted largely in healthy young adults to minimise risk in early stage trials. Encouragingly, a recombinant MVA vaccine was shown to induce comparable cellular immune responses to influenza antigens in adults aged >65 years, a target group in which poor immunogenicity is frequently observed [10]. This is an important finding, as alternative approaches have included higher doses or potent adjuvants, both of which carry the risk of unacceptable reactogenicity [11,12]. Indeed, MVA may provide sufficient intrinsic adjuvant effect, as humoral and cellular responses to licensed (split virion) vaccines were enhanced when co-administered with the MVA-NP + M1 vaccine [13].

Promising results have also emerged from studies in children <5 years, a key population for which malaria and tuberculosis vaccines are urgently needed. In the past