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Replication-Defective and Competent Adenovirus Recombinants as Vaccine Vectors

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ADENOVIRUS BIOLOGY AND VECTOR DEVELOPMENT FOR GENE DELIVERY AND VACCINES

Adenoviruses (Ads) have a long history of use as vectors for gene delivery, in part due to their ability to infect nondividing as well as dividing cells and to express transgenes at high levels. Ads can be grown to very high titers, making them suitable for large-scale manufacturing and clinical development. Their promise for gene therapy applications provided an impetus for a detailed understanding of the virology and molecular biology of the virus, particularly Ad serotypes 2 and 5. The use of Ad vectors as vaccines has been more recent: studies in animal models and humans have shown promise and are reviewed in this chapter. Recombinant Ad (rAd) vectors have been designed to deliver a myriad of vaccine antigens, including gene inserts encoding proteins of DNA viruses, such as Epstein-Barr virus (1), Herpes simplex virus type 1 (2), pseudorabies virus (3), and hepatitis B virus (4), and double- and single-stranded RNA viruses, such as rotavirus (5), vesicular stomatitis virus (6), rabies (7,8), measles (9), respiratory syncytial virus (10), parainfluenza virus (11), tick-borne encephalitis virus (12), Ebola (13), and Marburg (14) viruses. They have also been exploited for delivery of HIV and SIV antigens (15–17) and currently represent one of the most promising strategies for AIDS vaccine development. To understand why this is so, one needs to understand the biology of the virus and key characteristics (Fig. 1).

Ads are double-stranded DNA viruses with high genetic stability, exhibiting no mutations or insert deletions after multiple rounds of replication in vitro. Further, they do not integrate into the genome of the infected host, and consequently present less of a safety concern for gene delivery, as there is little risk of insertional mutagenesis and expression of potentially toxic or deleterious gene products is finite. Because they are nonenveloped, they are physically stable and can withstand lyophilization, suggesting a convenient means for storage, transport, and vaccine formulation relevant to global distribution. The primary targets of Ad infection are epithelial cells that line the respiratory tract and gut, key mucosal inductive sites. Ad displays the ability to induce mucosal immune responses, believed critical for mediating protective efficacy against infectious agents such as HIV, whose prime infection route is across the rectal and genital mucosa. In addition, many Ad serotypes readily infect dendritic cells (DCs), whose specialized ability to synthesize and present antigens is likely responsible for their potent immunogenicity. Ads, in fact, have been termed ''nature's adjuvants'' (18) because of their ability to upregulate costimulatory molecules and elicit cytokine and chemokine responses following target cell infection.

These attractive features have pushed Ad vectors to the forefront as vehicles for vaccine delivery. However, a significant concern in all rAd vaccine approaches is whether prior immunity to the vector, or anti-vector immunity induced as a result of immunization, will minimize the effectiveness of Ad vaccination. This concern arose principally as a result of gene therapy studies in which rAds were administered repeatedly at high dosages to maintain persistent expression of the therapeutic transgene. The result was development of vector immunity, which ultimately precluded continuous effective treatment (19,20). The extent to which such vector immunity will impact the utility of Ad-recombinant vaccines is currently not known and depends in part on the number and dosages of immunizations necessary to elicit the desired level of adaptive immunity. In principle, vaccination regimens should require lower doses of immunogen, administered infrequently to elicit immune memory responses. Nevertheless, several approaches have been exploited to circumvent this potential problem and will be discussed in this chapter. These alternatives include the use of alternate serotypes, Ad vectors of nonhuman origin, and chimeric Ad vectors in which neutralizing epitopes on the virion surface have been substituted with epitopes representing rare Ad serotypes.