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VIRUSES – FROM PATHOGENS TO VACCINE CARRIERS

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Summary

Vaccination is mankind's greatest public health success story. By now vaccines to many of the viruses that once caused fatal childhood diseases are routinely used throughout the world. Traditional methods of vaccine development through inactivation or attenuation of viruses have failed for some of the most deadly human pathogens, necessitating new approaches. Genetic modification of viruses not only allows for their attenuation but also for incorporation of sequences from other viruses, turning one pathogen into a vaccine carrier for another. Recombinant viruses have pros and cons as vaccine carriers, as discussed below using vectors based on adeno-, herpes-, flavi-, and rhabdoviruses as examples.

Introduction

About 200 different viruses can infect humans and, on average, two new species of virus are discovered and added to this list each year. However, vaccines are currently only available for 15 of those 200. Today's successful vaccines are mainly based on attenuated or inactivated virions that elicit neutralizing antibodies, which in turn prevent infections. Vaccines for the remaining 180 or so viruses have not been successfully developed. Vaccines for viruses that cause no or only minor disease, such as adeno-associated viruses or rhinoviruses are not needed. Some viruses, such as human papilloma viruses, cannot be grown in vitro and, thus, can neither be attenuated nor inactivated. Others, such as HIV-1, express only a few copies of the envelope protein on their surface and are hence poor inducers of neutralizing antibodies. Certain viruses, such as HIV-1 or hepatitis C virus, mutate so rapidly that a single vaccine may not induce a broad enough antibody response to neutralize all circulating subtypes. In some cases, antibodies can even exacerbate disease, as exemplified by dengue virus, which in the presence of antibodies to a different yet cross-reactive strain can cause hemorrhagic fever.

There are other issues with traditional vaccines. Vaccines based on inactivated viruses are generally safe but protection is commonly fleeting or not that impressive, as exemplified by Flu vaccines administered to the elderly [1]. Attenuated vaccines perform better, but they are also more reactogenic and, in extreme cases, such as the live attenuated vaccine to poliovirus, may convert back to virulence. Furthermore, speed of vaccine development can be an issue. As opposed to 100 years ago, humans in the 21st century crisscross the globe

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rapidly and viruses travel with them. For instance, the 2009 pandemic influenza strain was first detected in March of that year and by June had spread to every continent. A vaccine for the pandemic strain did not become available to the general population until October. While the strategy for generating influenza virus vaccines are well established, generating a new vaccine to an emerging virus would take disproportionately longer – about 10 years or more.

Advances in molecular virology have enabled the genetic manipulation of viruses, which has opened new opportunities for vaccine development. Not only can viruses be attenuated far more rapidly by modifying parts of their genome but they can also be harnessed into vaccine carriers that express bits and pieces of another virus. Poxviruses, which have large DNA genomes, were first to be genetically altered [2] and one of which, a recombinant vaccinia virus that expresses the rabies virus glycoprotein, has been used for nearly two decades for immunization of wildlife animals [3]. Vectors based on other double-stranded DNA viruses, such as adenoviruses [4] or herpesviruses [5], were next to be developed, followed by vectors based on single, negative- or positive-stranded RNA viruses, such as myxoviruses [6], rhabdoviruses [7], or flaviviruses [8]. By now techniques are available to genetically modify just about any virus that is out there.

Recombinant viral vector vaccines have several advantages. First, they can be developed rapidly. They induce a full spectrum of immune responses including antibodies and $CD8^+$ T cells. Additionally, the vaccine carrier rather than the pathogen against which the vaccine is meant to protect will determine the flavor of the immune response through induction of the initial inflammatory response and thereby largely dictate reactogenicity, furthermore, once a prototype vector has been tested extensively, safety trials may be sped up. While some vaccine carriers are very safe, such as vectors based on E1-deleted, and hence replication defective, adenoviruses (Ad) or highly attenuated poxviruses, such as Modified Vaccinia Ankara, others are currently viewed as potentially too risky for use in humans, such as those based on lentiviruses that may integrate, or those based on replicating herpesviruses that may persist at high levels.

The plethora of recombinant viruses that are undergoing preclinical testing precludes doing justice to all of them in a single review. We will therefore focus on a few examples: recombinant adenovirus and herpesvirus vectors for DNA virus-based vaccine carriers, flaviviruses for positive-sense single-stranded RNA and rhabdoviruses for negative-sense single-stranded RNA recombinants.

Recombinant vaccines based on DNA viruses

DNA viruses in general have large genomes that accommodate insertion of one or more complete genes from a different virus. Poxvirus vectors have been used successfully as vaccine carriers for a number of pathogens. Although such vectors were found to be safe, their immunogenicity was limited, which possibly reflects competition between immune responses to the transgene and to the approximately 80 poxvirus proteins encoded by its 130–300 kilobasepair (kbp) genome. Herpesvirus' genomes are also large with a size of up to 235 kbp but they encode fewer proteins because they contain long repeat sequences. Ad viruses in comparison are small with a genome of 26–45 kbp.

Ad virus-based vaccines

Of the family of *adenoviridae*, the genus mastadenoviruses is further divided into species A–G, which contain the 54 human, as well as, the 7 simian Ad viruses. The Ad virus genome is divided into immediate early (E1A), early (E1B, E2–4), and later transcription units (L1–5) with the latter encoding the three major coat proteins hexon, fiber and penton and minor coat proteins, such as protein IX (pIX). In order to attach to cells, most Ad

viruses use the coxsackie adenovirus receptor, which is primarily expressed on epithelial cells [9], but those of species B1 bind to CD46, a more ubiquitously expressed complement component [10]. In general Ad vectors used as gene transfer vehicles are deleted in E1, which renders them replication-defective, and hence safe, and reduces transcription of the late genes, thus focusing immune responses onto the transgene product. Ad vectors are commonly also deleted in E3, which allows for insertion of foreign sequences of up to 8.5 kb [11]. Pre-existing immunity to Ad viruses is problematic for vectors based on common human serotypes, such as 5 or 26. Neutralizing antibodies, which depending on age and geographic region, can be found in up to 90% of human adults [12], prevent transduction and transgene product expression, which in turn reduces immune responses to the vaccine antigen. This can be circumvented by the use of Ad viruses isolated from different species such as chimpanzees [13]. Ad vectors induce potent inflammatory responses characterized by production of cytokines, most notably IL-6 and type 1 interferons [14]. Pathogen recognition receptors have not yet been conclusively identified for Ad viruses but studies suggest that they engage a multitude of different receptors, some of which signal through MyD88 or TRIF [15]. Ad vectors induce very potent $CD8^+$ T and B cell responses and modest Th1-like $CD4^+$ T cell responses [4,13]. One of the most remarkable features of Ad vector-induced immune responses is that they are very sustained with minimal contraction of responding T cells, which for months largely remain at the effector/effector memory stage [16]. This may reflect that Ad vectors, similar to wild-type viruses, persist mainly in T cells and remain transcriptionally active. Another attractive feature of Ad vectors is that foreign sequences can be incorporated into the capsid, which may facilitate induction of high affinity B cell responses to antigens that are displayed in a repetitive and orderly fashion. Small epitopes can be placed into the variable regions of hexon [17], the most abundant of the capsid protein and the target of most Ad virus neutralizing antibodies; larger proteins can be placed onto the C-terminus of the minor capsid pIX [18], which forms 4 trimers on each of the 20 faces of the isocahedral Ad capsid.

Currently several Ad vectors are in clinical trials as vaccines for various infectious agents and although efficacy has not yet been demonstrated, vectors have shown robust immunogenicity in humans [19].

Herpesvirus vectors

Herpesviruses of both the *alpha*- and *betaherpesvirenea* subfamilies have been vectored. For herpes simplex virus (HSV-1) recombinants, the DNA binding protein IPC8 was mutated or ICP4, 27, 22, and 47 were deleted [20]. Either alteration renders the virus replication-defective. For rhesus cytomegalovirus (rhCMV)-based vaccines, the transgene cassette was inserted into an intergenic region between rh213–214 [21]. These vectors remained replication-competent and established persistent infection in nonhuman primates. One would expect the immunogenicity of either type of vaccine to be affected in humans by pre-existing immunity to the wild-type virus [22,23]. The replication-defective HSV-1 vaccine expressing antigens of SIV induced a robust T cell response in monkeys that rapidly contracted into memory, while transgene product-specific B cell responses were modest. When combined with a DNA vaccine, the HSV-1 vaccine lowered viral loads upon a high dose challenge with SIV [24]. The rhCMV based vaccine in contrast induced a by far more potent and sustained effector/effector memory $CD8^+$ T cell response that provided partial protection to SIV acquisition given repeated at low doses to the rectum [21]. Although these results are very promising the use of replication-competent CMV vectors for mass vaccination has to be viewed with caution. In humans CMV causes birth defects [25], significant morbidity and mortality in immunocompromised individuals, and strong T cell responses to CMV have been associated with immunosenescence and decreased life expectancy [26].

Recombinant vaccines based on RNA viruses

RNA viruses are in general small and less of their genome is devoted to evasion of immune responses. In turn, they do not accommodate lengthy foreign sequences unless they are from a related virus, and as such can replace an endogenous gene without loss of function. A multitude of both negative and positive stranded RNA viruses have been vectored as exemplified below for members of the *Flaviviridea* and *Rhabdoviridea* families, yellow fever virus and vesicular stomatitis virus (VSV), respectively.

Yellow Fever virus-based vaccines

Yellow fever virus is a mosquito-borne RNA virus causative for yellow fever. A live, attenuated vaccine based on the YF-17D strain is available and has proven to be one of the most successful vaccines developed to date. YF-17D induces a strong innate immune response by signaling through TLRs 2, 7, 8, and 9 [27]. Protection is primarily related to the induction of neutralizing antibodies, although the vaccine also induces $CD8^+$ T cells [28]. The viral genome is initially transcribed into a single polyprotein, which is then processed. The viral envelope genes, prM and E, can be replaced with those of other flaviviruses, such as Japanese encephalitis virus [8], dengue virus [29] or West Nile virus [30] resulting in fit viruses that induce neutralizing antibodies to the new membrane proteins. Ongoing clinical trials have shown both safety and immunogenicity for such recombinant vaccines [8].

VSV-based vaccines

VSV causes disease in livestock but no or only minor symptoms in humans. It has a single stranded RNA genome that encodes five viral proteins. The magnitude of transcription follows a gradient: genes at the 5’ end are expressed more abundantly than those at the 3’ end of the viral genome. Incorporation of a foreign glycoprotein-encoding gene leads to formation of mosaic virus particles that express both the endogenous and the foreign antigens [7]. VSVs are attractive as vaccine carriers because they can be grown to high titers, are generally stable upon insertion of foreign sequences, and can be applied through various routes due to their broad tropism. Neutralizing antibodies to VSV are rare in humans, although one would expect them to be induced upon vaccination with a VSV vector. Notwithstanding, alternative serotypes are available for booster immunizations. VSV vectors have shown preclinical efficacy for a number of viruses including SIV/HIV chimeras [31], influenza virus [32], and hepatitis B virus [33]. The first generation VSV vectors, which were replication competent and established persistent infection [34], were introduced into the central nervous system following intranasal inoculation. This necessitated further attenuation of VSV vectors, which was achieved either by truncation of the cytoplasmic domain of glycoprotein or by complete deletion of this gene [35]. These modifications render the virus replication-defective and, therefore, safe, but unfortunately affect the vectors’ growth parameters and reduce their immunogenicity.

Conclusion

The main disadvantage for all viral vector-based vaccines is pre-existing immunity and the induction of vector neutralizing antibodies upon their initial use, which impairs their ability to elicit potent primary or secondary responses, respectively. This can be overcome by the use of viruses that do not circulate in humans, such as viruses that preferentially infect other species, and by switching serotypes for booster immunizations. Alternatively, nanoparticles complemented to TLR agonists have been shown to induce T and B cell responses [36] that may equal in potency those of viral vectors as has to be further investigated. The main advantage of viral vector-based vaccines is their high versatility; almost any virus can be turned into a vaccine carrier. Each virus, through interactions with pattern recognition

receptors of the innate immune system, induces a signature inflammatory response, which in turn shapes the ensuing adaptive immune response to the vaccine antigen. In theory, for each virus, the most suitable viral vector to induce correlates of protection with minimal risk to the vaccine recipient could be selected. Once we further our knowledge of basic principles that govern induction of the exact immune responses that provide protection to specific viruses, theory may turn into practice.

Highlights

- Ad vectors are safe, easy to construct, and versatile. They persist at low-levels and induce potent and sustained immune responses.
- Safety of herpesvirus vectors has not been assessed. They induce sustained effector and effector memory CD8+ T cell responses.
- YF-based vaccines induce a potent innate immune response. They are both safe and immunogenic in the clinic.
- VSV-based vectors are versatile, and easily constructed. Modifications to enhance safety lead to reduced growth and immunogenicity.

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