Diversity of adenoviruses in humans and in non-human primates
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Summary
The diversity of adenoviral serotypes provides an opportunity to improve the outlook for adenoviral vectors. In populations where the antibody prevalence against a particular serotype (e.g., HAdV-5) is high, it may be possible to construct vectors based on other rare serotypes. One of the hurdles which need to be overcome in order to make this possible is to select the appropriate rare serotypes of adenovirus. It is reasonable to assume that antibodies that cross-react with non-human adenoviruses would be rare in human populations and these adenoviruses would therefore be good candidates to use for vector construction. The second important hurdle is to be able to manufacture the novel vectors to high titer. Thus there would be a considerable benefit if these novel adenoviral vectors could be propagated in existing cell lines. Therefore the genetic proximity of ape adenoviruses to human adenoviruses was explored. This is described in chapter 3, where new adenoviruses were isolated from chimpanzees, bonobos and gorillas and the complete sequencing and genetic analysis of 30 new ape adenoviruses was done. These adenoviruses were isolated from the stools of healthy animals. The description of the genomes of four other chimpanzee adenoviruses is provided in chapter 4.

Because of the finding that normal apes shed adenoviruses in stools, it was postulated that adenoviruses may colonize the gut of other normal primates, including humans. Whether this is in fact the case is important with respect to expanding our understanding of normal human physiology, i.e., whether adenoviruses form part of the normal gut flora in the same way that gut bacteria do. This would have further implications toward our understanding of the response of the primate immune system to adenoviral vectors. Because humans, unlike apes, do not usually shed adenovirus in their stools, the presence of adenoviruses in the gut mucosa of humans was tested (chapter 2). Adenoviral DNA was found to be highly prevalent in the lymphocytes that can be isolated from human intestinal mucosa. As had been observed in apes, a wide variety of adenoviral sequences could be isolated; most of the sequences that were present belonged to adenoviral species B, C, and E.

Monkeys such as rhesus macaques are very commonly used as test subjects for the evaluation of the safety and efficacy of vaccines, including adenoviral vaccines. Because of this, the same considerations that underlie the importance of understanding the natural history of adenoviral colonization of the human gut also apply to monkeys. In chapter 5, the observation that adenoviruses are present in the lower gastro-intestinal tract of humans and apes was extended to rhesus macaques. Nine new adenoviruses were isolated and sequenced. Three additional adenoviruses that were available from the American Type Culture Collection (ATCC) were also sequenced. These new adenoviruses appear to cluster into a distinct clade within monkey adenoviruses for which a new species is proposed – SAdV-B. The clade SAdV-B members were found to have distinct properties with respect to the fiber and the E3 genes.

As discussed above, one of the principal incentives for the discovery of non-human primate adenoviruses was to expand the serotype repertoire for vector construction. The creation of replication-incompetent vectors based on ape adenoviruses is described in chapter 6, chapter 7 and chapter 8. It was found that ape adenoviruses were indeed good candidates for vector construction that afforded the possibility of
evading pre-existing immunity to adenoviruses in human populations. Additionally, it was found that it was possible to propagate these vectors in human cell lines.

It was also possible to create an E1-deleted vector based on a macaque adenovirus (SAdV-7) that, like ape adenovirus vectors, could be propagated in human E1-complementing cell lines. Complete sequencing of a SAdV-7 isolate revealed an unusual truncated E1 region. Vectors based on SAdV-7 are described in chapter 9.

The construction of chimpanzee adenovirus vectors based on different serotypes provided the means to experimentally dissect the particular adenoviral capsid proteins that serve as important antigenic determinants. This was done by creating vectors where hexon and fiber genes were interchanged; experiments using these chimeric vectors are described in chapter 10. These experiments confirmed that following administration of vectors to experimental animals such as rabbits and mice, the capsid component that elicited the most potent antibody response was the hexon and that anti-fiber antibodies were also capable of reducing vector infectivity.

The effectiveness of the chimpanzee adenoviral vectors as vaccines was tested in experiments using mouse challenge models for Ebola virus and influenza virus. A single administration of a SAdV-21-based vaccine expressing the Ebola glycoprotein was able to protect mice from a lethal challenge of Ebola virus (chapter 11). The influenza virus nucleoprotein is a good candidate as a component of a future universal influenza vaccine because it is subject to much less sequence variation than the surface proteins hemagglutinin and neuraminidase. Moreover T-cell responses against influenza nucleoprotein are also known to be protective against influenza. Because adenoviral vectors elicit a strong T-cell response to the encoded transgenes, the ability of a chimpanzee adenoviral vector (based on SAdV-24) expressing the nucleoprotein of H1N1 influenza (strain A/PR8/34) to protect against challenges with heterologous highly pathogenic H5N1 strains of influenza was tested and shown to be practicable (chapter 12).

In this thesis, the diversity of adenoviruses that are present in the gastro-intestinal tract of primates was explored. This diversity was utilized to construct adenoviral vectors that may be used for human applications. The practicality of using such vectors as vaccines was tested in mouse models.