

Evaluation of Adenovirus Serotype 35 Vectors Using Genetically Modified Animals and Nonhuman Primates for Clinical Application

Fuminori Sakurai (National Institute of Biomedical Innovation)

Recombinant adenovirus (Ad) vectors are highly promising as gene transfer vectors and widely used in preclinical and clinical gene therapy. The commonly used Ad vectors are based on Ad serotype 5 (Ad5), which belongs to subgroup C. Ad5 requires coxsackievirus-adenovirus receptor (CAR) on cells as a primary receptor for infection. Therefore, Ad5 vector-mediated gene transfer to cells lacking sufficient CAR expression is inefficient. Unfortunately, the expression levels of CAR are often low in some of the important target cells for gene therapy, including primary cancer cells and dendritic cells. In addition, the high prevalence of adult humans (>50%) that produce neutralizing antibodies to Ad5 has been reported. Preexisting neutralizing antibodies prevent Ad vectors from transducing cells in vivo. To overcome these drawbacks, we have developed an Ad vector composed of human Ad serotype 35 (Ad35), which belongs to subgroup B. Ad35 vectors have several attractive features as gene delivery vehicles as follows; first, anti-Ad5 antibodies do not inhibit Ad35 vector-mediated transduction. Second, Ad35 is a serotype least neutralized by serum from healthy human blood donors. Third, Ad35 recognizes human CD46 as a cellular receptor, leading to a tropism different from Ad5. Whereas CD46 is ubiquitously expressed in primates, expression of mouse CD46 is limited to the testes. In addition, mouse and human CD46s are only 46% similar. These differences indicate that the conventional mouse is not a suitable small animal model for characterization of Ad35 vector-mediated transduction. Therefore, in the present study, we examined the transduction properties of Ad35 vectors using human CD46 transgenic mice and nonhuman primates, which ubiquitously express CD46 in all organs like human.