Medical & heathcare, Drug discovery, Cancer therapy

Development of a novel oncolytic adenovirus that can overcome the problems of a conventional oncolytic adenovirus

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Abstract

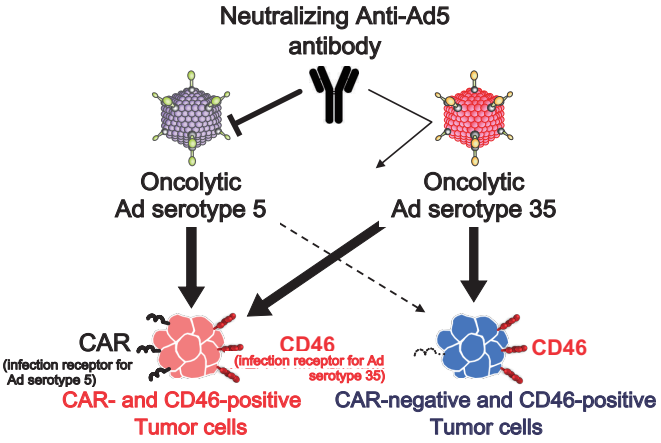
Oncolytic adenoviruses (OAds) are among the most promising oncolytic viruses. Almost all oncolytic adenoviruses are composed of human adenovirus serotype 5 (Ad5) (OAd5). However, expression of the primary infection receptor for Ad5, coxsackievirus-adenovirus receptor (CAR), often declines on malignant tumor cells. In addition, at least 80% of adults have neutralizing antibodies against Ad5. In order to overcome these problems, we developed a novel OAd fully composed of human adenovirus serotype 35 (OAd35). OAd35 recognizes CD46, which is ubiquitously expressed on almost all human cells and is often upregulated on malignant tumor cells, as an infection receptor. Moreover, 20% or fewer adults have neutralizing antibodies against Ad35. OAd35 mediated efficient cell lysis activities in various types of tumor cells. Anti-Ad5 serum did not inhibit OAd35-mediated *in vitro* tumor cell lysis. OAd35 significantly suppressed growth of the subcutaneous CAR-positive and CAR-negative tumors following intratumoral administration. These results indicated that OAd35 is a promising alternative oncolytic virus for OAd5.

Background & Results

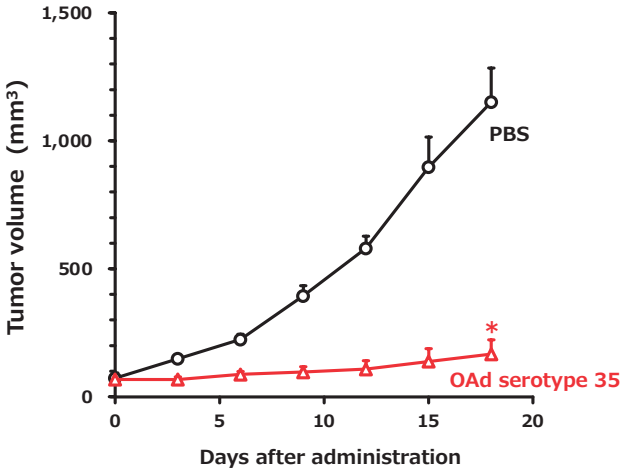
Oncolytic viruses, which can specifically replicate in and kill tumor cells without apparent toxicity to normal cells, are attracting much attention as a novel cancer therapeutic agent. Among various types of oncolytic viruses, the oncolytic adenoviruses (OAds) are one of the most promising. Almost all OAds are composed of human adenovirus (Ad) serotype 5 (Ad5), which belongs to species C. However, the OAd composed of Ad5 (OAd5) has two major drawbacks. OAd5 recognizes coxsackievirus-adenovirus receptor (CAR) as an infection receptor. CAR expression is often reduced on malignant tumor cells, leading to inefficient infection with OAd5. In addition, more than 80% of adults have neutralizing antibodies against Ad5 due to natural infection with Ad5 during childhood. In order to overcome these drawbacks, we developed a novel OAd fully composed of human Ad serotype 35 (Ad35) (OAd35), which belongs to species B2. Ad35 recognizes human CD46 as an infection receptor. CD46, which is a complement regulatory protein, is ubiquitously expressed on all human cells except erythrocytes. Moreover, CD46 is often upregulated on malignant tumor cells. In addition, 20% or fewer adults have neutralizing antibodies against Ad35. OAd35 efficiently killed not only CAR-positive but also CAR-negative tumor cells. Anti-Ad5 serum did not inhibit the OAd35-mediated tumor cell killing. Intratumoral administration of OAd35 resulted in significant growth suppression of the subcutaneous CAR-positive and CAR-negative tumors.

Significance of the research and Future perspective

OAd35 can become a promising alternative oncolytic virus, especially for tumors resistant to a conventional oncolytic Ad.



Advantages of oncolytic adenovirus serotype 35



Tumor volumes following intratumoral administration of oncolytic Ad serotype 35 in tumor-bearing mice

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