Development of PEGylated adenovirus vector for cancer gene therapy

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Adenovirus vectors (Ad) have been frequently used for cancer gene therapy research because of their high gene transduction efficiency. However, systemic administration of conventional Ad can lead to the acute accumulation of virus particles and transgene expression in the liver, which may cause severe hepatotoxicity. For these reasons, clinical application of Ad for systemic administration has been limited, although intratumor administration of Ad has shown marked antitumor effects. Therefore, to promote the application of Ad in systemic cancer gene therapy, especially against the distant metastatic cancer, a novel Ad with marked accumulation in tumors and minimal hepatic distribution is needed. From this perspective, bioconjugation with polyethylene glycol (PEGylation) to Ad surface is a promising strategy, and we are trying to develop cancer targeted Ad by PEGylation approach. Through our study, we particularly clarified that PEGylated Ad (PEG-Ad) with optimized PEG modification ratio exhibited the enhanced distribution and gene expression in tumor tissue via systemic injection, which was based on the enhanced permeability and retention (EPR) effect. Moreover, PEG-Ad encoding therapeutic gene demonstrated not only stronger tumor-suppressive activity but also fewer hepatotoxic side effects compared with conventional Ad. In addition, we further attempted the active targeting using targeting ligand on the tip of PEG. We revealed that PEG-Ad with transferrin as a tumor targeting ligand could transduce more efficiently into tumor cells, which express transferrin receptor, compared with conventional PEG-Ad. In this symposium, I will present our approach for development of cancer targeted Ad by PEGylation.