

Generating re-targeted adenoviral vectors with altered tropism

SUMMARY

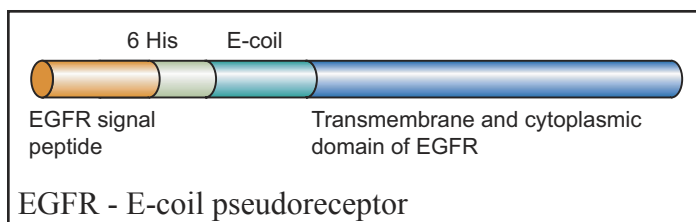
Adenovirus gene delivery vectors (AdVs) are useful in many gene therapy applications but their broad tropism means that they cannot be directed to a specific target cell. In addition, some cells are infected by the AdVs with difficulty. Therefore, a process has been developed whereby the ablation of native tropism and the introduction of new tropism for target cells is made possible using two de novo peptides (K-coil and E-coil) by creating a new cell entry pathway. This technology is useful to increase the efficacy of AdVs by augmenting its ability to infect cells using ligands that specifically bind to the surface of targeted cells. It is also useful to improve the safety of AdVs by preventing infection of other cell types. This technology could be applied in the gene therapy research sector, forecast to grow to \$US 5.7 billion by 2011.

APPLICATIONS

- Gene therapy.
- Treatment of tumor cells or proliferating cells.
- Reagent kit.
- Treatment or prevention of genetic, tumor, autoimmune or infectious diseases.

CONCEPT

Two de novo-designed peptides (E-coil and K-coil) have been constructed to establish a new receptor-ligand system. A pseudoreceptor is constructed using E-coil fused to a cell surface protein (EGFR). A new cell line (293E) is also constructed to express this



pseudoreceptor, which allows the propagation of AdV lacking the natural tropism (CAR-ablated). In addition, the AdV contains the complementary K-coil motif incorporated into the fiber protein. Virus entry is mediated in a CAR-independent pathway via E-coil/K-coil interaction of the pseudoreceptor and fiber protein. Therefore, the 293E packaging cell line and K-coil-AdV constitute a useful platform for the generation of AdVs with modified tropism. The AdVs can be re-targeted at will by conjugating it to a ligand having a strong affinity to a specific cell type (cancer cells, muscle cells, brain cells, etc). The conjugation can be performed using the E-coil/K-coil interaction by incubating the AdV with the ligand fused to the E-coil. Alternatively, the ligand can be directly inserted into the sequence of the AdV fiber protein.

FEATURES AND BENEFITS

Improved efficacy and specificity

The transduction level of the tropism modified-virus will be increased toward the targeted cells by using the optimized ligand. This will reduce the dose of AdV required for therapeutic treatment and will permit delivery of AdV using a systemic route of administration (essential for treatment of metastases).

Improved safety

The ablation of native tropism will prevent infection of non-targeted tissues. Thus, AdV expressing suicide or apoptotic gene for cancer therapy will spare healthy cells.

PROTECTION STATUS

Ligand-pseudoreceptor system for generation of adenoviral vectors with altered tropism (NRC no. 11498).

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