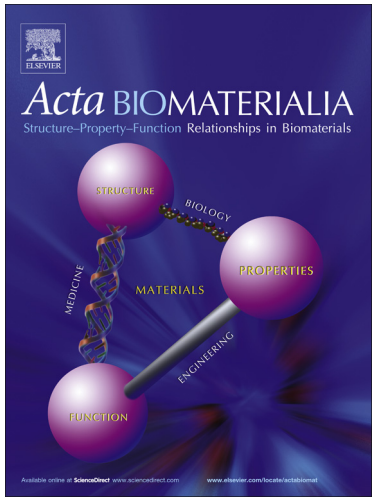

Full length article

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In situ Dual-crosslinked Nanoparticles for Tumor Targeting Gene Delivery

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Abstract

The instability of gene delivery systems and their "off-target" features are among the major hurdles in gene therapy. In this study, a facile fabrication platform is constructed to endow the gene delivery system with high stability in the circulation system and achieve targeted delivery of plasmid DNA (pDNA) into cancer cells. Aldehyde groups-bearing hyaluronic acid (HA-CHO) is initially synthesized through oxidation, and is then shielded on polyethylenimine/DNA (PEI/DNA) complex particles to form dual-crosslinked nanoparticles *in situ*. These nanoparticles simultaneously possess electrostatic and chemical crosslinks between outer layers and cores. The dual-crosslinking system further offers the following advantages when used for gene delivery. First, the two different *in situ* crosslinking routes strengthen nanoparticle stability. Second, targeting ligands on HA layers mediate specific recognition toward cancer cells. Cell and animal experiments demonstrate that the as-prepared complex particles exhibit enhanced stability in serum and excellent long circulation behavior *in vivo*. Third, the dual-crosslinked nanoparticles present good accumulation ability in tumors after intravenous injection into nude mice bearing HeLa tumors. Overall, the dual-crosslinking strategy is a promising solution for constructing an efficient gene delivery system.

Statement of Significance

This manuscript focused on the in situ dual-crosslinked nanoparticles for tumor targeting pDNA delivery. The novel system is prepared by in situ shielding HA-CHO on PEI/DNA complexes. The