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A New System for Targeted Delivery of Doxorubicin into Tumor Cells

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ABSTRACT

The use of vector molecules for the targeted delivery of antitumor drugs provides their selectivity for cancer cells. The recombinant receptor-binding fragment of alpha-fetoprotein (rAFP3D) was used as a vector molecule. The specific receptor of alpha-fetoprotein is a universal tumor marker, being expressed on the surface of many tumor cells, but not in normal human tissues. And rAFP3D includes the receptor binding cite of AFP. A three-component delivery system including vector protein rAFP3D, PAMAM G2 dendrimer and antitumor antibiotic doxorubicin (Dox) was synthesized. The attachment of two dendrimer molecules to the vector protein did not affect the effectiveness of rAFP3D binding to AFP receptor on the surface of tumor cells nor the effectiveness of receptor-mediated endocytosis. Dox was conjugated with G2 via cis-aconitic anhydride (acid labile linker). The *in vitro* Dox release study showed that the conjugate was stable at neutral pH but was labile at pH < 6. The Dox release was correlated with the intracellular distribution of conjugate in tumor cells. The rAFP3D-G2-Dox conjugate demonstrated a high cytotoxic activity against human ovarian adenocarcinoma cell lines: Dox-sensitive SKOV3 cells and Dox-resistant SKVLB cells and was low-toxic against human peripheral blood lymphocytes. Based on our findings, we may conclude that it is possible to significantly increase the effectiveness of Dox delivery to tumor cells by using the targeted delivery system comprising the recombinant third domain rAFP3D as a vector molecule.

1. Introduction

The insufficient effectiveness of conventional anticancer chemotherapy is explained mainly by low selectivity of antitumor drugs and the risk of development of multidrug resistance (MDR) in tumor cells.

Targeting of drugs via specially designed delivery systems is a good alternative to improve the therapeutic effectiveness and reduce the systemic toxicity of antitumor agents. The most