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CD44 antibody-targeted liposomal nanoparticles for molecular imaging and therapy of hepatocellular carcinoma

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ABSTRACT

Most hepatocellular carcinoma (HCC) therapies fail to target cancer stem cells (CSCs) and monitor cancer progression or regression. The purpose of this study was to evaluate the possibility of cancer imaging and simultaneously monitoring targeted therapy in a single animal by anti-CD44 antibody-mediated liposomal nanoparticle. In this study, an *in situ* liver tumor model was applied for therapy by injecting 1.0×10^6 HepG2 cells carrying a reporter system encoding a double fusion (DF) reporter gene consisting of firefly luciferase (Fluc) and green fluorescent protein (GFP) into the liver of NOD/SCID mice. A strategy was developed which specifically targeted HCC via anti-CD44 antibody-mediated liposomal nanoparticle delivery, loaded of either doxorubicin (Dox) or a triple fusion (TF) gene containing the herpes simplex virus truncated thymidine kinase (HSV-ttk) and renilla luciferase (Rluc) and red fluorescent protein (RFP). The NOD/SCID mice were subsequently treated with ganciclovir (GCV) and the growth status of tumor was monitored by optical bioluminescence imaging (BLI) of Fluc and specific targeting of the liposomal nanoparticle was tracked by Rluc imaging. CD44 antibody-mediated liposomal nanoparticle, loaded of TF plasmids, were shown to be useful for monitoring and evaluating targeting efficacy and gene therapy by non-invasive molecular imaging. Here, we demonstrate the time intensive preclinical steps involved in molecular target identification, validation, and characterization by dual molecular imaging. This targeted and traceable therapeutic strategy has potential advantages to overcome the problems of conventional tumor therapy and may open a new application for the treatment of HCC by targeting CSCs.

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third leading cause of cancer death [1]. Over 80% of the world's cases occur in developing countries, with 44% in China alone [1,2]. Advances in treatment, imaging, surgical techniques and liver transplantation have resulted in considerable improvements in therapy of HCC. However, most of these fail to consider the differences in drug sensitivities of cancer stem cells (CSCs) compared to their non-tumorigenic progeny. Chemotherapy and radiotherapy target rapidly proliferating non-tumorigenic cells and spare the relatively quiescent cancer stem cells. Moreover, surgery is directed at reducing the bulk of tumor mass, but cannot sufficiently clear tumorigenic/metastatic cells. Consequently, such treatments are often followed by recurrence of tumor and relapse of diseases in the majority of cases [3].

By contrast, if therapies can directly target against tumorigenic CSCs, even without shrinking tumors, this may render the tumors unable to maintain themselves or grow, thus eventually leading to cures [4]. To date, a number of putative markers for liver CSCs have been reported, including CD133, CD90, CD44, OV6, epithelial cell adhesion molecule (EpCAM) and CD13 [5–8]. It has been shown that activating anti-CD44 monoclonal antibody markedly reduced leukemic repopulation [9] and inhibited proliferation and stimulated apoptosis [10]. Therefore, CD44 is potentially an attractive therapeutic target especially in tumors overexpressing CD44.

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