Targeted Therapeutic Evaluation on Inhibition of Fatty Acid Synthase in a Human Prostate Carcinoma LNCaP/tk-luc Bearing Animal Model with Molecular Imaging

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Abstract

Fatty acid synthase (FAS), with ability of de novo fatty acid synthesis, is highly expressed in most human cancers, including prostate carcinoma. FAS is overexpressed at both mRNA and protein levels in prostate carcinoma associated with a 4-fold risk of disease recurrence and higher stage. As a novel potential therapeutic target, inhibition of FAS could arrest cell cycle and trigger apoptosis rapidly, implying the reliance of cancer cell survival on FAS activity. In this study, we used the FAS inhibitor, C75, to manifest the inhibition effect of endogenous fatty acid metabolism in a human prostate carcinoma LNCaP/tk-luc cells both in vitro and in vivo. Multimodalities of molecular imaging were used to demonstrate the inhibition effects of FAS in a LNCaP/tk-luc bearing mouse model, which constitutively expresses herpes simplex virus type-1 thymidine kinase (HSV1-tk) and luciferase (luc) genes. Bioluminescent imaging (BLI) and nuclear imaging (gamma scintigraphy and PET) were used to monitor tumor progression and metastatic spreading. LNCaP/tk-luc cells were implanted subcutaneously into NOD/SCID mice. Animals were i.p. injected with high-dose C75 (total 120 mg/kg, i.e. 30 mg/kg once a wk for 4 weeks). The results showed that the intensity levels of BLI from in vivo and ex vivo post treatments were well correlated to the tumor growth inhibition, and were further confirmed by immunohistochemistry. [I-131]FIAU was also used to evaluate the tk expression in the tumor. In conclusion, the targeted therapy using enzyme inhibitor, such as C75, for specific enzyme could be explored using reporter genes combined with multimodalities of molecular imaging.

Introduction

Fatty acid synthase (FAS), the sole enzyme responsible for the de novo synthesis of fatty acids from carbohydrate, is highly expressed in common human tumors. In the androgen-dependent prostate cancer cell line LNCaP, androgens have been shown to stimulate coordinate expression of FAS and enzymes involved in cholesterol synthesis, which may be mediated through sterol regulatory elements. Fatty acid synthase inhibition by C75 leads to apoptotic cell death.

Results

Cell viability and cell cycle analysis after FAS inhibitor, C75 treatment

Therapeutic evaluation with FAS inhibitor, C75

Molecular-Imaging Approach

Conclusions

We demonstrate that the inhibition of FAS using C75 could induce apoptosis in LNCaP prostate cancer cells in vitro. Interestingly, the LNCaP/tk-luc bearing animal model was also shown with tumor growth delay after C75 treatment.