学位論文抄録
Abstract of Thesis

Polymer-conjugated glucosamine complexed with boric acid shows tumor-selective accumulation and simultaneous inhibition of glycolysis
(ホウ酸と複合体を形成したポリマー結合型グルコサミンは、腫瘍選択的な蓄積と解糖の同時阻害を示す)

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Background and Purpose:

The clinical application of boron neutron capture therapy (BNCT) is still limited due to lack of selective accumulation of ^{10}boron in tumor tissue and adverse effect of existing borono-drugs. To address the drawback of BNCT, we have developed a polymer drug namely styrene-co-maleic acid copolymer conjugated glucosamine and boric acid (SGB-complex) which accumulated in the tumor more selectively based on enhanced permeability and retention (EPR) effect.

Methods:

After synthesis of SGB-complex, the physicochemical properties of SGB-complex were analyzed by infra-red, circular dichroism, NMR spectroscopy, electron microscopy and dynamic light scattering (DLS). In vitro study was performed by using HeLa, colon carcinoma C26 and human oral squamous carcinoma cells in both mild-hypoxia (pO_2 5-10%) and normoxic state. In vivo application was conducted in mouse sarcoma S180, colon C26 and human squamous cell carcinoma tumor bearing mice.

Results:

SGB-complex showed a diameter of 10-15 nm as measured by electron microscopy and DLS. Intravenously injected SGB-complex bound to albumin during circulation, with a half-life of about 8 h in mouse plasma, and accumulated to tumor tissues about 5-10 times more than normal tissues. Primarily SGB-complex was developed for the BNCT, but surprisingly we discovered that it can inhibit cancer cell growth effectively in mild hypoxic condition and also in vivo even without neutron irradiation. As a possible mechanism, our data suggested that SGB-complex inhibits the glycolysis of cancer cells. We also confirmed the anticancer effect of this nanomicelle after neutron irradiation in vitro and in vivo. One hallmark event we observe that, SGB-complex did not affect the skin of the mice that was seen in boronophenylalanine plus neutron irradiation.

Conclusions:

SGB-complex will be able to control cancer by multiple mechanisms and thus, it strongly suggests a new modality for the successful treatment of BNCT in a clinic.