Design and Construction of Hypoxically Activated Drug Release System

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Statement of Purpose: Hypoxia is a feature of solid tumors and tumor hypoxia is well known to promote mutagenesis, invasiveness and to be associated with a worse prognosis. Recently, cancer stem cells are reported to present in the hypoxia area of tumors, accordingly, the treatment of tumor in the hypoxic region is highly demanded. Several hypoxically activated prodrugs have been introduced into clinical trials, however, there is no approved drug.

To develop the hypoxia-specific antitumor agents, prodrug which is inactivated under normoxia condition but activated under hypoxic region is useful because this system reduces the cytotoxicity to normal tissues which are generally present under normoxia condition, resulting in the reduction in the adverse effect. Recently, we have developed a novel system in which antitumor agent is inactivated by the modification with the functional group but activated under hypoxic condition (Figure 1).

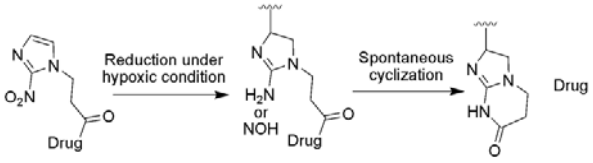

Figure 1. Design of hypoxically activated prodrug

Methods: A series of hypoxically activated prodrugs have been synthesized and confirmed by NMR and MS. Drug release and anti-tumor activities were evaluated with human pancreatic cartinoma (MIA PaCa 2). The experiences on the anticancer activity in vivo were carried out using BALB/c (4 weeks old, male, approximately 24 g). Tumor- bearing mice were randomly divided into three groups (5 mice/group). Animals treated with vehicle (50 % PEG(400) solution), doxorubicin (Dox) and doxorubicin prodrug (pro-Dox). Dox (4 mg/kg) was administered intraperitoneally on day 0 and pro-Dox (16 mg/kg) was administered intraperitoneally on day 0, 2, 4, 6 and 8.

Results: Structures of the newly synthesized hypoxically activated doxorubicin and gemcitabine were described in Figure 2. To demonstrate selective drug release under hypoxic condition, gemcitabine prodrug was incubated with MIA PaCa-2 and released amounts of gemcitabine were analyzed by LC/MS. As clearly shown in Figure 3a, the release of gemcitabine was enhanced under hypoxic condition, indicating spontaneous cyclization reaction occurred inside cells under hypoxic condition. Antitumor activities of designed prodrugs were evaluated in vitro. Figure 3b shows enhanced antitumor activity of gemcitabine prodrug under the hypoxic condition. These results support the enhanced drug release under the hypoxic condition as we anticipated.

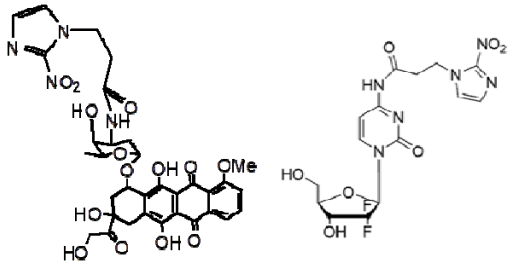

Figure 2. Structure of hypoxically activated doxorubicin prodrug (left) and gemcitabine prodrug (right).

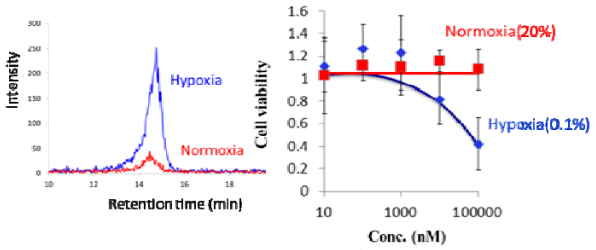

Figure 3. Enhanced drug release (left) and antitumor activity (right) of gemcitabine prodrug under hypoxic condition.

Antitumor activity of doxorubicin prodrug was evaluated using tumor bearing mice. Significant anti-tumor effect of prodrug was observed when pro-Dox (16 mg/kg) was administered on every two days. Importantly, administration of prodrug did not show any apparent adverse effect such as body weight loss and improved survival rate of mice drastically. These results indicate our strategy contributes the developments of hypoxically activated prodrugs which reduce adverse effects of conventional anticancer drugs

Conclusions: In this study, we developed a novel molecular system which enables drug release at tumor hypoxia by spontaneous cyclization reaction. Significant anti-cancer activity of developed prodrug was confirmed in vivo and body weight loss caused by adverse effect of anti-cancer drug was drastically suppressed.