Polymeric nanoparticles for hypoxia-triggered drug delivery

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Statement of Purpose: Hypoxia is an important characteristic of cancer as it contributes to chemoresistance, radioresistance, angiogenesis, invasiveness, and metastasis (1). Remarkably, hypoxic conditions are rarely seen in normal tissue, making it as a primary target in the development of diagnostic agents and therapeutic drugs. For hypoxia imaging, many nitroaromatic or quinone derivatives with hypoxia-responsive moieties have been employed in the molecular design of diagnostic agents. Of the derivatives investigated to date, 2-nitroimidazoles (NIs) have been most widely utilized in the development of imaging agents and bio-reductive prodrugs because of their high sensitivity to hypoxia (2). It has been demonstrated that, under hypoxic conditions, NIs are converted to hydrophilic 2-aminoimidazoles via a series of selective bioreductions, which are highly reactive to macromolecules in hypoxic tissues (3). Herein, we prepared the hypoxia-sensitive nanoparticles as a new platform for drug delivery systems.

Methods: The NI derivative was conjugated to the backbone of carboxymethyl dextran in the presence of EDC and NHS. The in vitro cytotoxicity was carried out using SCC-7 cell line by the MTT assay. In vivo biodistribution and therapeutic efficacy were evaluated using the SCC-7 tumor-bearing mice after systemic administration of doxorubicin-loaded nanoparticles.

Results: A series of polymer conjugates were synthesized, and the degree of substitution (DS) of the NI derivative was calculated using H1NMR. The conjugates were self-assembled into nanoparticles, in which the size was dependent on the DS. Hypoxia responsiveness was analyzed by UV-Vis spectroscopy, as the nitroimidazole group converters to aminoimidazole showing a characteristic peak at 280 nm. Doxorubicin was loaded into the nanoparticles with the loading efficiency of ~76%. The nanoparticles showed rapid release of the drug when they were incubated in the hypoxic condition. The in vitro cytotoxicity results implied that the nanoparticles kill more cancer cells in the hypoxic condition than in the normoxic condition. Furthermore, after systemic administration into the tumor-bearing mice, the nanoparticles showed significant accumulation in tumor than other major organs like liver and spleen. The ex vivo hypoxia staining demonstrated that the nanoparticles were evenly distributed in the hypoxic region of the tumor. The DOX-loaded nanoparticles could effectively reduce the tumor growth, compared to free doxorubicin.

Conclusions: We investigated the potential of hypoxia-responsive nanoparticles as drug carriers. These carriers were stable in physiological conditions and capable of selectively releasing the hydrophobic drug under hypoxic conditions. Doxorubicin-loaded nanoparticles showed higher toxicity to hypoxic cells than to normoxic cells. In addition, live animal imaging demonstrated that nanoparticles could effectively accumulate at the tumor site. As a consequence, Doxorubicin-loaded nanoparticles exhibited enhanced antitumor efficacy, compared to free doxorubicin. Overall, the results indicated that hypoxia-responsive nanoparticles are promising drug carriers for selective delivery of hydrophobic drugs into hypoxic cells.

References: