Polymeric nanoparticles for hypoxia-triggered drug delivery

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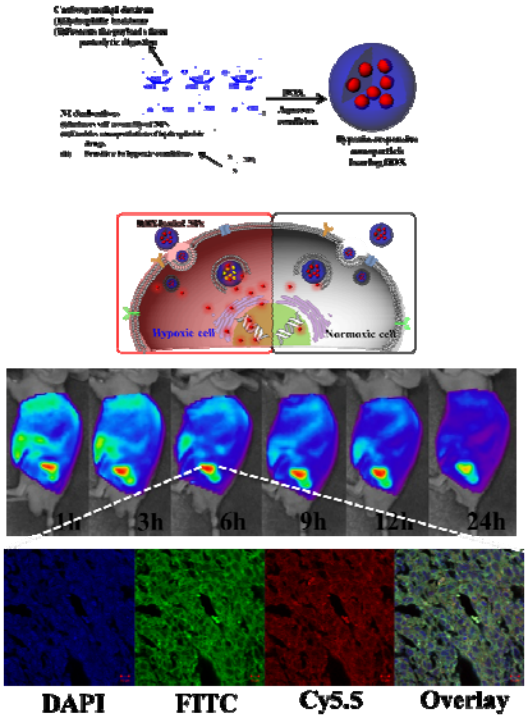
Statement of Purpose: Hypoxia is an important characteristic of cancer as it contributes to chemoresistance, radioresistance, angiogenesis, invasiveness, and metastasis (1). Remarkably, hypoxic conditions are rarely seen in normal tissue, making it as a primary target in the development of diagnostic 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. I*n vivo* biodistrubution and therapeutic efficacy were evaluated using the SCC-7 tumor-baring 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 H^1NMR. 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 naonparticles 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:

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2. Kiyose K. J Am Chem Soc. 2010;132:15846-15848.
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