Development of Targeted Hydrogel Nanoparticles as Delivery Vehicles for Cancer Therapy and Imaging

by

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To my parents

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Abstract

Nanotechnology can provide powerful delivery carriers for cancer therapy. This dissertation addressed some key challenges for the development of nano-drug carriers: targeted therapy, multidrug resistance (MDR) and codelivery of multiple kinds of drugs. A variety of novel hydrogel nanoplatforms were developed for cancer therapy and imaging.

Two kinds of methylene blue-conjugated polyacrylamide (PAA) nanoparticles (NPs) were developed for targeted photodynamic therapy, where methylene blue (MB) was the photosensitizer. The conjugation of MB onto NPs improved the MB loading, prevented any leaching of MB and avoided MB degradation due to the effects of enzymes. After decoration with a tumor-targeting F3 peptide, the MB-PAA NPs showed a selective cell killing ability towards MDA-MB-435 melanoma cells *in vitro*, under illumination.

A highly engineerable hydrogel NP was developed for the optimal codelivery of a chemodrug, doxorubicin (Dox) and a chemosensitizer, verapamil (Vera), aiming at alleviating tumor MDR. The NP was based on the copolymer of acrylamide (AA) and 2-carboxyethyl acrylate (CEA). Dox and Vera were post-loaded into the respective co(CEA-AA) NPs. We delivered both Dox-NPs and Vera-NPs into the Dox-resistant NCI/ADR-RES cells. This codelivery increased the intracellular accumulation of Dox,

and significantly enhanced the cell killing ability of Dox with respect to NCI/ADR-RES cells *in vitro*.

For the targeted delivery of Dox, the co(CEA-AA) NP was further conjugated with F3 peptides via a “click reaction”. The F3 peptide targeting moieties dramatically improved the uptake of the NPs by the nucleolin-overexpressing glioma cell line 9L as well as by the drug-resistant cell line NCI/ADR-RES, correlating with nucleolin-mediated endocytosis. *In vitro* cytotoxicity results show that the Dox-F3-NPs have a stronger cell killing ability, towards both 9L and NCI/ADR-RES cells, than the nontargeted Dox-NPs.

Finally, a tumor-targeted, intensely blue colored, tumor contrast agent was introduced, based on targeted, Coomassie Blue (CB)-linked, PAA NPs. With high loading of CB (7 wt %), the NPs can clearly stain the tumor area, with a tolerable NP concentration. Again, the F3-targeted CB-PAA NPs demonstrated a better contrast delineation effect, as well as a longer retention time in the tumor area, in 9L-glioma bearing rats, compared to nontargeted CB-PAA NPs.