WATERLOO INSTITUTE FOR NANOTECHNOLOGY

distinguished lecture series

Self-assembled Nanodevices from Smart Block Copolymers for Gene and Drug Delivery

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Drug vehicles have gained attention as versatile nanomedicine platforms with enhanced efficacy and reduced side effects in cancer treatment. Particularly, nanodevices for intracellular drug delivery are an emerging concept to maximize the selectivity and efficacy of the potent antitumor agents. We developed novel supramolecular nanodevices, polymeric micelles that release the platinum antitumor agent, DachPt, with different rates responding to changes in pH and chloride ion concentration following the internalization into tumor cells. Processes can be monitored by *in vivo* fluorescent imaging using rapid-scanning confocal microscopy. The polymeric micelles circumvent the drug detoxification systems in the cytoplasm and enhance the efficiency of drug delivery to the nucleus, thereby displaying remarkably enhanced *in vivo* antitumor activity even against the oxaliplatin-resistant cancer cells. Furthermore, by incorporating clinically approved Gd-based MRI contrast agents into the DachPt-loaded polymeric micelles, simultaneous imaging and therapy of an orthotopic animal model of human pancreatic tumor were successfully done without serious toxicity. The strong tumor contrast enhancement achieved by the micelles correlated with a 24 times increase of r_1 relaxivity of Gd-chelates. From the micro-synchrotron radiation-X-ray fluorescence spectrometry (μ-SR-XRF) scanning of the lesions, we confirmed both Gd-chelates and platinum drugs delivered by the micelles selectively co-localized in the tumor interior.

As for the anti-angiogenic gene therapy of the subcutaneous pancreatic tumor model, the polyplex micelle loaded with plasmid DNA (pDNA) encoding the soluble form of vascular endothelial growth factor (VEGF) receptor-1 (sFlt-1) was developed. Significant gene expression was detected selectively in tumor tissue by intravenous administration of the micelles, and a strong anti-tumor efficacy was confirmed by tumor growth suppression as well as by decreased vascular density inside the tumor. Therefore, the polyplex micelle loading sFlt-1 pDNA has great potential for anti-angiogenic cancer therapy by systemic application.

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