Exploration of Advanced Photosensitizers for Switchable Photodynamic and Photothermal Therapy

用於可切換光動力和光熱治療的先進光敏劑的探索

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Photodynamic therapy (PDT) against tumor hypoxia is an important and challenging topic that has received much current attention. We utilized Cu^{2+} ions to promote the self-assembly of a GSH-responsive carboxy ZnPc-based photosensitizer, both in the absence and presence of the anticancer drug **SN38** to form the nanosystems **ZnPc*/Cu@NP** and **ZnPc*/Cu/SN38@NP**, respectively. These nanoparticles were found to be highly stable in physiological conditions. In an acidic environment (pH 5.5), **ZnPc*/Cu/SN38@NP** disassembled gradually probably through protonation of the carboxylate moieties and disruption of the complexation with Cu^{2+} ions. Its photosensitizing property could be largely restored upon the action of glutathione (GSH). More importantly, the encapsulated Cu^{2+} ions could also effectively promote the conversion of H_2O_2 to oxygen via a Fenton-like reaction, rendering these nanosystems possessing an oxygen-replenishing property. The disassembly process, GSH-responsive property, and oxygen-replenishing ability of these nanosystems were also demonstrated in vitro using HT29 cells through a series of experiments under both normoxic and hypoxic conditions. Studies of their dark- and photocytotoxicities clearly showed the PDT effect of **ZnPc*** and the chemotherapeutic effect of **SN38**, which worked in a synergistic manner. By using the Annexin V and 7-aminoactinomycin D costaining and immunofluorescence caspase-3 staining methods, it was found that the cell death was mainly through apoptosis. Finally, the biodistribution and PDT efficacy of the nanosystems were also investigated using HT29 tumor-bearing nude mice, focusing on their antitumor efficacy and hypoxia-relieving ability. The results showed that **ZnPc*/Cu/SN38@NP** was particularly potent due to the dual antitumor effects. It could also effectively down-regulate the hypoxia-inducible factor-1□ level and relieve the hypoxic condition in the solid tumor of nude mice. *(Paper to be submitted)*