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Photodynamic therapy and imaging based on tumor-targeted nanoprobe, pHPMA-conjugated zinc protoporphyrin, and its augmentation

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We previously reported the antitumor effect of heme oxygenase-1 (HO-1) inhibitor zinc protoporphyrin (ZnP), as well as its application for photodynamic therapy (PDT). Along this line, we synthesized a highly tumor targeting ZnPP micelle by conjugate HPMA polymer (pHPMA) to ZnP, which becomes highly water soluble and behaves as nano micelles in aqueous solution due to the hydrophobic interaction of ZnP, exhibiting mean hydrodynamic particle sizes of 82.8 nm. Accordingly, it exhibited significantly prolonged plasma half-life (t1/2>12h) and selective tumor accumulation by taking advantage of the enhanced permeability and retention (EPR) effect. pHPMA-ZnP alone did not show apparent cytotoxic effect, perhaps due to its slower intracellular uptake and thus lower HO-1 inhibition activity. However, a significant antitumor effect was found both *in vitro* and *in vivo* upon light irradiation, in different tumor models including autochthonous cancer. One dose of pHPMA-ZnP at 20 mg/kg (ZnP equivalent) administered I.V. followed by 2-3 times of light irradiation at an intensity of ≥20 J/cm2 caused necrosis and disappearance of most tumors (>70%) in all tumor models. We also confirmed pHPMA-ZnP-based tumor imaging in autochthonous breast tumor in rat and mouse colon cancer models. The light dependent cytotoxicity was attributed to the generation of singlet oxygen. These findings warrant further development of pHPMA-ZnPP as an agent for PDT, and more important, as a fluorescent probe for tumor imaging due to its high tumor targeting property. The tumor distribution of pHPMA-ZnP micelles could be increased by concomitant application of vascular modulator like nitroglycerin.

Biography

Jun Fang has completed his PhD at Kumamoto University Medical School in 2003 and 2-year Post-doctoral studies from Duke University Medical Center. He is the Associate Professor of DDS Research Institute/Faculty of Pharmaceutical Science at Sojo University, Japan. His major research topic is development of innovative strategies to target solid tumor for therapy and imaging, based on EPR effect and nanotechnology; particularly focusing on the important molecule heme oxygenase-1 (HO-1) and its active product carbon monoxide (CO). He has published more than 60 papers in reputed journals and has been selected as a Thomson Reuters Highly Cited Researcher 2014, 2015.

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