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S-nitrosated human serum albumin dimer with superior antitumor activity, long blood retention and excellent EPR effect

Recombinant human serum albumin dimer (HSA-dimer) was produced by the yeast *Pichia pastoris*. HSA-dimer has a longer circulation, compared with HSA-monomer. Thus, HSA-dimer is expected to have an enhanced accumulation in solid tumor via the EPR mechanism due to its large molecular weight (130 kDa). In this conference, we will present a novel DDS system of NO, potential anticancer therapeutic, using HSA-dimer as a carrier, namely, SNO-HSA-dimer. SNO-HSA-dimer treatment induced apoptosis of C26 tumor cells *in vitro*, depending on the concentration of NO. In in vivo experiments, SNO-HSA-dimer was found to specifically deliver large amounts of cytotoxic NO into tumor tissue but not into normal organs in C26 tumor-bearing mice. Interestingly, SNO-HSA-dimer caused a much higher concentration of NOx in the tumor than SNO-HSA-monomer. Moreover, especially, SNO-HSA-dimer has a high level of blood retention. The accumulation of SNO-HSA-dimer in tumor tissue is significantly high compared with SNO-HSA-monomer, suggesting that S-nitrosation of SNO-HSA-dimer further enhanced its EPR effect. Next, we examined whether SNO-HSA-dimer can enhance the activity of other macromolecular antitumor drugs via the augmented EPR effects. As antitumor drugs, we selected N-(2-hydroxypropyl) methacrylamide (HPMA)-zinc protoporphyrin (ZnPP) and doxil. HPMA-ZnPP (mean particle size: 80 nm) forms micelles and doxil has liposomal structure (mean particle size: 90 nm). The tumor growth was significantly inhibited when the two compounds were given simultaneously. The combination of SNO-HSA-dimer inhibited the tumor growth, compared with doxil or SNO-HSA-dimer alone. Furthermore, the combination of doxil and SNO-HSA-dimer significantly reduce the number of lung metastasis. Finally, possible side effects of SNO-HSA-dimer administration were evaluated by measuring blood pressure, heart rate and biochemical parameters. Fortunately, none of these above parameters were significantly affected by repeated administration of SNO-HSA-dimer. Thus, SNO-HSA-dimer strategy is a safe and effective therapeutic approach for improving the antitumor effects of macromolecular drugs.

Biography

Masaki Otagiri is currently a Professor and Dean of Faculty of Pharmaceutical Sciences, Sojo University. He completed his Graduation at Nagoya City University with a PhD degree in 1975. In 1980, he joined Pharmaceutics department, Faculty of Pharmaceutical Sciences, Kumamoto University as an Associate Professor and then promoted to Professor of Bio-pharmaceutics department, Kumamoto University in 1983. After his retirement from Kumamoto University in 2009, he appointed as Professor of Faculty of Pharmaceutical Sciences and Director of DDS Research Institute, Sojo University, Kumamoto.

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