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Recombinant human serum albumin dimer: Preclinical study and possible future therapeutic applications

Objective: Albumin dimers have great potential and advantages for clinical applications as both a plasma expander and a drug carrier. In this conference, we present information on the design, physicochemical/biological properties, toxicological studies, pharmacokinetics, medical and pharmaceutical applications of rHSA-dimers. Experimental: A recombinant human albumin dimer (rHSA-dimer) was produced by the yeast Pichia pastoris. The CD spectrum of the rHSA-dimer was nearly identical to that of the rHSA monomer.

Results and Discussion: Acute toxicity tests showed no differences between the rHSA-dimer and the rHSA-monomer. The pharmacokinetics of the 125I-labeled rHSA monomer and the rHSA-dimer were, however, clearly different: the rHSA-dimer showed a longer blood retention time. Interestingly, this tendency was more clear in experiments using carrageenan-air-pouch rats. These results suggest that the rHSA-dimer has the potential for use as a new plasma volume expander. In addition, its use would allow a reduction in multiple administrations that are needed in in the case of conventional HSA preparations. Moreover, experimental results using tumor rats indicated that the level of tumor accumulation for the rHSA-dimer was significantly higher compared with that for the rHSA-monomer. On the basis of these findings, we developed an S-nitrosated rHSA-dimer (SNO-dimer) and examined its potential for use as an anticancer therapy. The accumulation of the SNO-dimer in tumor tissue was substantially higher compared with that of rHSA-dimer. Furthermore, the SNO-dimer exhibited an excellent EPR effect, as shown in the extravasation of Evans blue dye in the tumor tissue by an iv treatment with SNO-dimer. These findings suggest that the use of a combination of the SNO-dimer with anticancer agents may be a novel therapeutic strategy for cancer treatment. In fact, we obtained positive results when a combination the SNO-dimer and some anticancer drugs, including doxil, were used.

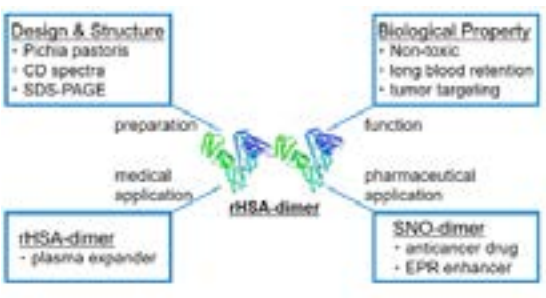

Fig. 1 Possible therapeutics of rHSA-dimer and SNO-dimer

Recent Publications

1. Taguchi K et al (2010) Superior plasma retention of a cross-linked human serum albumin dimer in nephrotic rats as a new type of plasma expander. Drug Metab Disps 38:2124-2129
2. Taguchi K et al (2012) Pharmaceutical aspects of the recombinant human serum albumin dimer: Structural characteristics, biological properties, and medical application. J Pharm Sci 101:3033-3046
3. Ishima Y et al (2015) S—nitrosated human serum albumin dimer as novel nano-EPR enhancer applied to macromoleular antitumor drugs such as micelles and liposomes. J Control Release 217:1-9
4. Otagiri M and Victor TG Chuang (eds) (2016) Albumin in medicine: Pathological and clinical applications. Springer
5. Kinoshita R et al (2017) Improved anticancer effects of albumin -bound paclitaxel nanoparticle via augmentation of EPR effect and albumin-protein interactions using S-nitrosated human serum albumindimer. Biomaterials 140:162-169

Biography

Masaki Otagiri is currently a Professor in the Faculty of Pharmaceutical Sciences and DDS Research Institute, Sojo University. He graduated from Nagoya City University with a PhD degree in 1975. In 1983, he was promoted to the rank of Professor of Biopharmaceutics Department, Kumamoto University. After his retirement from Kumamoto University in 2009, he was appointed as a Professor in the Faculty of Pharmaceutical Sciences, Sojo University, Kumamoto, Japan. He has published more than 600 original research papers.

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