POLY-S-NITROSYLATED HUMAN SERUM ALBUMIN REVERTS THE RESISTANCE TO DOXORUBICIN IN HUMAN MYELOGENOUS LEUKEMIC CELLS

Marie Hara¹, Yu Ishima¹, Ayaka Suenaga¹, Masaki Otagiri¹,2 and Toru Maruyama¹,3
¹Graduate School of Pharmaceutical Sciences, Kumamoto University, 5-1, Oe-honmachi, Kumamoto, 862-0973, Japan, ²Faculty of Pharmaceutical Sciences, Sojo University, 4-22-1 Ikeda, Kumamoto, 860-0082, Japan, ³Center for Clinical Pharmaceutical Sciences, School of Pharmacy, Kumamoto University, 5-1, Oe-honmachi, Kumamoto, 862-0973, Japan.

[Purpose] Human serum albumin (HSA) is the most abundant circulating protein and its S-nitrosylated form serves as a reservoir of nitric oxide (NO). Previously, we prepared poly-S-nitrosylated HSA (SNO-HSA) and evaluated its possible utility as a novel anticancer agent through apoptosis involving the caspase-3 pathway. Recently, NO donors such as nitroglycerin were reported to revert the resistance to anticancer agents. Therefore, we evaluated the effect of SNO-HSA on the resistance to doxorubicin in human myelogenous leukemic cells (K562 cells).

[Methods] The expression of P-glycoprotein (P-gp) on cellular surface was evaluated by Western blotting. The intracellular accumulation of doxorubicin was evaluated by flow cytometry. The cell viability was determined using WST-8.

[Results and Discussion] Compared with parent K562 cells, the higher expression of P-gp and lower accumulation of doxorubicin were shown in doxorubicin-resistant K562 cells (K562/dox cells). The expression of P-gp was decreased and the doxorubicin accumulation was increased in K562/dox cells by the treatment with SNO-HSA. In addition, SNO-HSA decreased the viability of K562 cells and K562/dox cells equally. Furthermore, co-treatment of SNO-HSA enhanced anticancer effect of doxorubicin in K562/dox cells. Isobologram analysis clearly showed that this effect was a synergistic fashion.

[Conclusions] SNO-HSA reverted doxorubicin resistance in K562/dox cells via the decreasing of P-gp expression.

IMPROVED THERAPEUTIC EFFECT OF THIOREDOXIN BY FUSION TO HUMAN SERUM ALBUMIN AGAINST BLEOMYCIN-INDUCED PULMONARY FIBROSIS

Ryota Tanaka¹, Masato Furukawa¹, Yu Ishima¹, Ken-ichiro Tanaka¹, Toru Mizushima¹, Hiroshi Watanabe¹,2, Masaki Otagiri³ and Toru Maruyama²,3
¹Graduate School of Pharmaceutical Sciences, Kumamoto University, 5-1, Oe-honmachi, Kumamoto, 862-0973, Japan, ²Center for Clinical Pharmaceutical Sciences, School of Pharmacy, Kumamoto University, 5-1, Oe-honmachi, Kumamoto, 862-0973, Japan, ³Faculty of Pharmaceutical Sciences, Sojo University, 4-22-1 Ikeda, Kumamoto, 860-0082, Japan.

[Purpose] Thioredoxin 1 (Trx 1) is a redox-active protein ubiquitously present in a human body. Recently, it was reported that an administration of human Trx 1 (Trx 1) was effective in animal models with severe lung diseases. However, the half-life (t½) of rhTrx 1 in plasma is very short (≏1 hr) in mice after iv administration of rhTrx 1. To overcome this limitation, we design the longer-acting Trx 1 that is the recombinant human serum albumin-Trx 1 fusion protein (HSA-Trx) and examine the impact of HSA-Trx on bleomycin (BLM)-induced pulmonary fibrosis. [Methods] HSA-Trx was prepared in yeast expression system. Mice were administrated by intratracheal injection of bleomycin (5mg/kg) in PBS (1 ml/kg). 3.5 nmol/mouse of HSA-Trx was administrated intravenously just before the BLM administration. On days 3 and 14, the therapeutic effect of HSA-Trx in BLM-induced mice was evaluated. [Results and Discussion] HSA-Trx significantly decreased the bronchoalveolar lavage (BAL) total cells, alveolar macrophages, neutrophils and lymphocytes number in BLM administrated mice on days 3. HSA-Trx also suppressed BLM-induced pulmonary fibrosis by histopathological analysis and measurement of pulmonary hydroxyproline levels on 14 days. BLM treatment markedly induced oxidative stress in lung and it was significantly inhibited by HSA-Trx. [Conclusions] HSA-Trx improved therapeutic effect against BLM-induced pulmonary fibrosis via its antioxidative action.