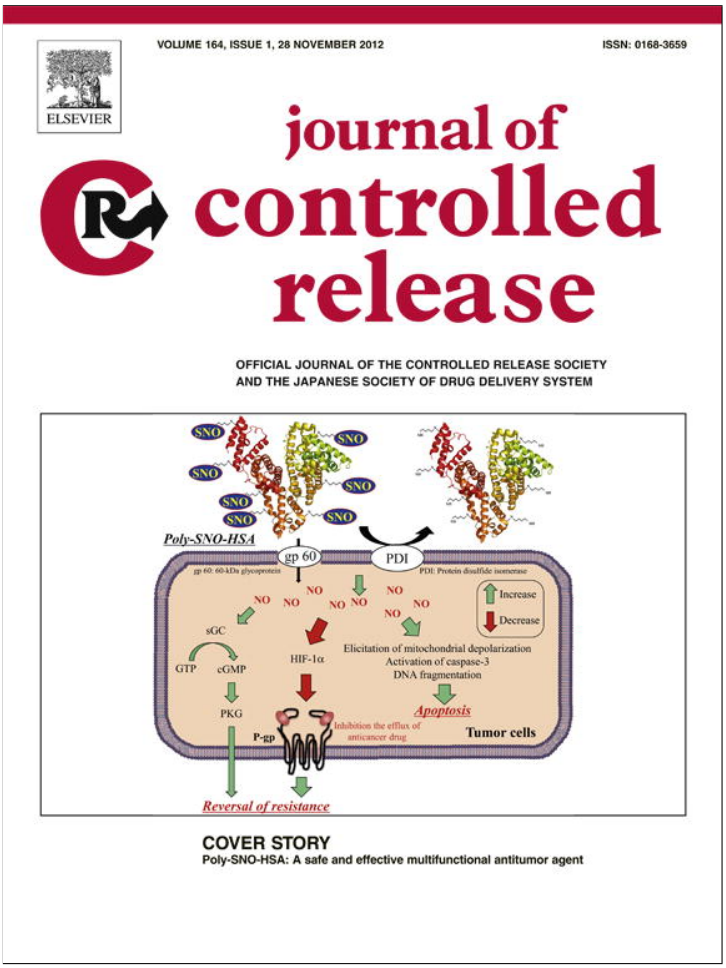

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Cover Story

Poly-SNO-HSA: A safe and effective multifunctional antitumor agent

Cancer treatment remains one of the most important clinical challenges. One difficulty in treating various cancers is the development of multidrug resistance (MDR) by cancer cells. Various approaches have been tested to overcome MDR using agents that inhibit P-glycoprotein (P-gp) directly or indirectly through altering the cell membrane and using targeted drug delivery. Most of the approaches have shown some success in small animal models but its clinical application has been limited. One of the compounds that have shown promises in treating cancer is nitric oxide (NO).

NO is a unique, diffusible molecular messenger that plays a central role in mammalian pathophysiology. The effects of NO are pleiotropic, including vascular smooth muscle relaxation, inhibition of platelet aggregation, and regulation of immune function. Under certain circumstances, however, NO can be cytotoxic. For example, high concentrations of NO can inhibit tumor cell growth and induce apoptosis. Recent studies have revealed that NO is associated with not only apoptosis of cancer cells, but also with cancer progression and metastasis, as well as cancer angiogenesis and microenvironment. It also functions as a modulator for chemo/radio/immuno-therapy. Despite highly useful properties, the use of NO has been impeded by the fact that its *in vivo* half-life is so short (~0.1 s) that NO itself cannot be used as a therapeutic agent. Such a short half-life can be overcome using continuous release of NO from a reservoir, such as the *S*-nitrosated form of human serum albumin (HSA).

The *S*-nitrosated HSA (SNO-HSA) as an NO donor has been investigated for its potential therapeutic applications. It has been shown that administration of SNO-HSA to animals with ischemia–reperfusion injury minimizes the tissue damage that occurs after reperfusion [1]. However, there are no reports describing the effects of SNO-HSA on cancer. The research group led by Maruyama and Otagiri has produced poly-*S*-nitrosated HSA (Poly-SNO-HSA) using a chemical linker, imminothiolane or N-succinimidyl S-acetylthioacetate, to find that this HSA form can induce apoptosis. The apoptosis occurs *via* activation of the intrinsic apoptosis pathway in murine colon 26 carcinoma cells and in the rat tumor cell line-LY-80 (a variant of Yoshida sarcoma) both *in vivo* and *in vitro* [2]. In this issue, the Maruyama and Otagiri team has further examined the underlying mechanisms of apoptosis and reversal of MDR. Their study has shown that Poly-SNO-HSA causes increased doxorubicin (dx) accumulation in dx-resistant K562 (K562/dx) cells by decreasing the expressions of P-gp and hypoxia-inducible factor (HIF)-1α. Other experiments with the guanylate cyclase inhibitor reveal that a cyclic guanosine monophosphate (cGMP) signaling pathway is also involved in the increase in dx accumulation induced by Poly-SNO-HSA. Furthermore, *in vivo* studies showed that co-treatment with Poly-SNO-HSA enhanced the anticancer effect of dx in K562/dx cells-bearing mice [3].

To clarify the mechanisms of Poly-SNO-HSA to overcome MDR, the Maruyama and Otagiri group evaluated the effect of Poly-SNO-HSA on two different intracellular pathways which have been demonstrated to contribute to the chemoresistance. First, they studied the effect of NO on the expression of P-gp representing the ABC efflux transporters. The data show that Poly-SNO-HSA inhibits the P-gp expression *via* down regulation of HIF-1α, and that P-gp inhibition results in an increased intracellular dx concentration in K562/dx cells. In addition, they found that Poly-SNO-HSA activated a cGMP dependent pathway in K562/dx cell. Previously, several antitumor NO-cGMP-dependent signaling pathways, such as protein kinase G, have been identified in cancer cells [4]. There is evidence that the activation of NO-cGMP-dependent signaling pathway by NO donors or cGMP analogs represents a novel approach to cancer therapy including the chemoresistance. Taken together, Poly-SNO-HSA reverts dx resistance in part through a cGMP dependent pathway. They have previously demonstrated that side effects of Poly-SNO-HSA, such as renal toxicity, liver toxicity and large fall in blood pressure, were absent in animal models.

The findings by the Maruyama and Otagiri team suggest that Poly-SNO-HSA can be developed as a safe and strong, multifunctional antitumor agent. This is especially true if the Poly-SNO-HSA can be formulated into suitable carriers targeted to tumors. One of the limitations of the current nanovehicles for targeted drug delivery is accumulation of the vehicles in non-target organs, causing serious side effect. Since NO is rather benign unless the concentration is too high, it presents a unique opportunity to achieve treating tumors without significant side effect. The current approach of nanotechnology-based drug delivery to tumors can benefit significantly through understanding of the underlying mechanisms of drug actions, *e.g.*, therapeutic mechanisms of NO as described in the paper in this issue [3].

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