Polyethyleneglycol Conjugation Enhances the Apoptotic Effect of Alpha-tocopheryl Succinate in Cancer Cells

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α-Tocopheryl succinate (TOS), a vitamin E analog, is a promising anticancer agent due to its abilities to inhibit proliferation and to induce apoptosis in a variety of human malignant cell lines, while being relatively less active toward normal cells. In our previous study, we demonstrated that, while TOS can induce apoptosis ROS-dependently or –independently according to the differences in cell types, the ROS generation upon treatment with TOS seems to be an important factor determining the susceptibility of cells to TOS-induced apoptotic cell death. Moreover, we reported that TOS-triggered ROS generation is involved in caspase-independent cell death in cancer cells.

In this study, we sought to investigate whether polyethylene glycol conjugation of TOS, which increases its water-solubility, affect its apoptotic effect in cancer cells (Fig. 1). At first, we compared the growth suppressive effect of TOS and PEG-TOS on human lung carcinoma xenograft models in nude mice. Intraperitoneal administration of PEG-TOS more potently suppressed the growth of tumor compared with that of TOS (Fig. 2), suggesting the enhanced anticancer efficacy of PEG-TOS. Our *in vitro* study using cell culture showed that PEG-TOS also more potently inhibited the proliferation of cancer cells. The enhanced antiproliferative effect of PEG-TOS was correlated with increased caspase activation, ROS generation and apoptosis induction compared with TOS (Fig. 3). Finally, our data show that the enhanced apoptotic effect of PEG-TOS might be, at least partially, due to its more rapid uptake into cells. Our data justifies further studies to investigate the potential usefulness of PEG-conjugated TOS in cancer prevention and treatment.

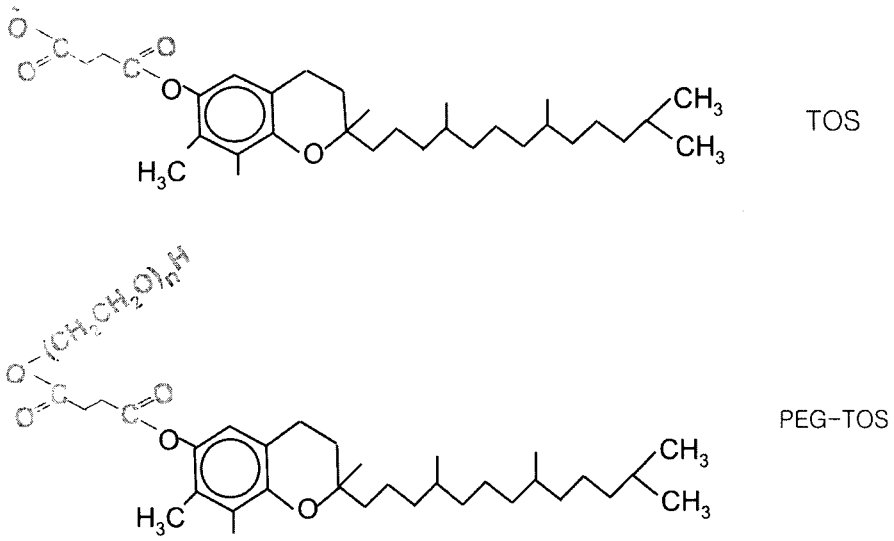

Fig. 1. Schematic diagram showing the chemical structure of TOS and PEG-TOS

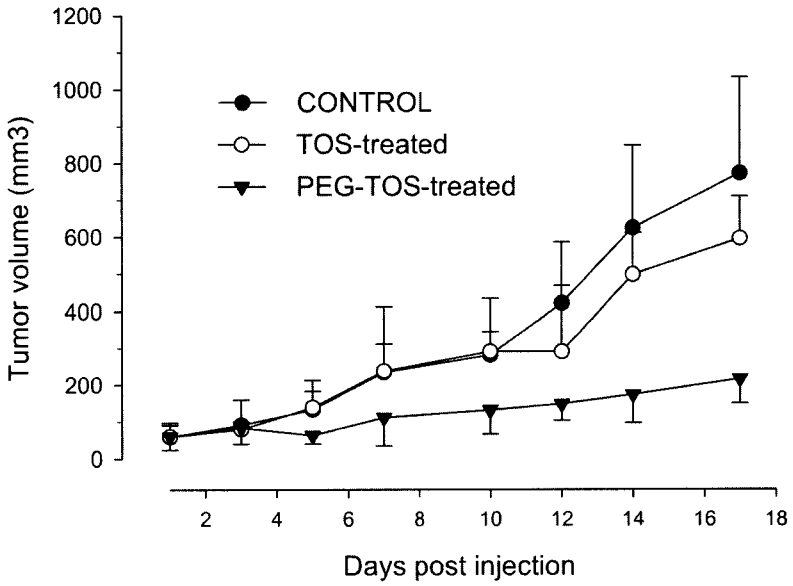

Fig. 2. Intraperitoneal administration of PEG-TOS more potently suppressed the growth of human lung carcinoma xenograft in nude mice compared with that of TOS **PEG-TOS.**

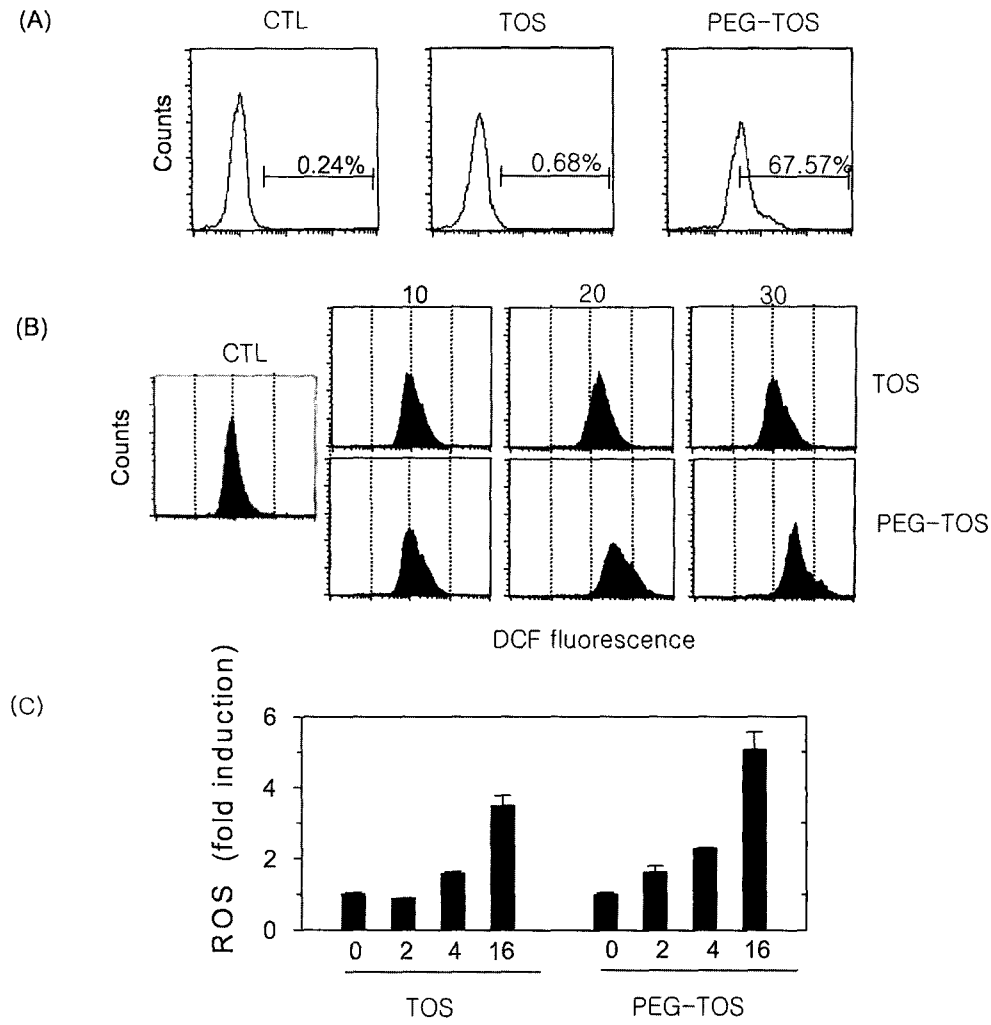

Fig. 3. The enhanced antiproliferative effect of PEG-TOS was correlated with increased ROS generation (B, C) and apoptosis induction (A) compared with TOS. A549 (A) and H460 (B and C) cells were treated with TOS or PEG-TOS, respectively. After overnight incubation, cells were ubjected to ROS analysis or TUNEL assay for apoptosis analysis. ROS data are expressed as the fold increase in mean channel fluorescence of treated cells over vehicle-treated cells.