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Cover Story

Enhanced antitumor effects of hTRAIL by binding to endogenous albumin

During the past few decades, recombinant human tumor necrosis factor-related apoptosis-inducing ligand (hTRAIL) has attracted great interest in cancer therapy. In vitro, hTRAIL induced apoptosis in various types of human tumor cells at nanomolar concentrations without affecting normal cells. In clinical trials, intravenously injected hTRAIL was well tolerated and showed activity in some patients with chondrosarcoma or colorectal cancer. The superior activities of hTRAIL observed in *in vitro* experiments, however, were not reproduced *in vivo*. The short half-life of hTRAIL, ranging from several minutes in rodents to 60 minutes in humans, was considered to be one of the reasons for the lack of *in vivo* efficacy. Thus, extending the blood circulation time of hTRAIL has been explored using nanoparticles, PEGylation, and albumin conjugation or fusion. Of these, albumin attracted great interest as a carrier. Albumin is the most abundant protein in plasma with a long half-life of about 3 weeks in humans and the capability to accumulate in solid tumors [1]. Genetic fusion and chemical conjugation to human serum albumin significantly prolonged the half-life of hTRAIL. The preparation of albumin-hTRAIL using the mammalian expression system, however, was limited by extremely low yield. Chemical conjugation of hTRAIL to plasma-derived exogenous albumin may be an alternative, but it has its own limitations.

The paper by Professor Xiaofeng Lu and his team in this issue provides an alternative way to endow hTRAIL with albumin-binding property by fusion of hTRAIL to a short albumin-binding domain (ABD) derived from a bacterial protein [2]. Several ABDs derived from streptococcal protein G have superior (pM to nM) affinities for albumin of many species. In this paper, the 46-amino acid ABD was genetically fused to the N-terminus of hTRAIL. ABD-fusion did not interfere with the recombinant expression of hTRAIL. The fusion protein, ABD-hTRAIL, was also expressed in *E. coli* as a soluble protein at the concentration of 20-30 mg/L. ABD-hTRAIL preserved the cytotoxicity of hTRAIL and the binding property of ABD to both human and mouse serum albumin. The half-life of hTRAIL was prolonged from several minutes to approximately 15 h in mice, resulting in the drastic (6-16 fold) increase of tumor uptake of ABD-hTRAIL. Accordingly, intravenous injection of ABD-hTRAIL induced long-lasting apoptosis in tumor grafts. Tumor suppression in a xenograft mouse model by ABD-hTRAIL was 3-4 times greater than that of hTRAIL alone.

ABD-hTRAIL was also evaluated for its ability to eliminate circulating tumor cells (CTC). ABD-hTRAIL was intravenously injected into mice followed by injection of tumor cells at different times. ABD-hTRAIL was able to kill CTCs for approximately 8 times longer than the native hTRAIL. Another paper in this issue also describes the usefulness of TRAIL. The paper by professor Michael R. King and his collaborators describes a Trojan-horse strategy to target and kill CTCs via genetic modification of platelets for expressing surface-bound TRAIL [3]. Platelets are produced from megakaryocytes derived from hematopoietic stem/progenitor cells in bone marrow. The King group utilized a lentiviral vector carrying the TRAIL gene under the control of a megakaryocyte-specific αIIβ integrin promoter for specific expression on the surface of megakaryocytes and platelet-like particles. They were effective in neutralizing CTCs and attenuating metastasis.

This study performed by the Lu group demonstrates that ABD-fusion significantly prolonged the half-life, thus increased the tumor uptake and enhanced the antitumor effect of hTRAIL in solid tumor models. Both ABD-hTRAIL and the TRAIL-expressing platelets were effective in neutralizing CTCs in blood circulation. To be clinically useful, however, they need to be prepared easily for scale-up production. ABD-hTRAIL was expressed in *E. coli* at a level that is significantly higher than that of albumin-hTRAIL produced in mammalian cells. The study performed by the Lu group provides a simple but reliable approach to producing long-acting hTRAIL. Additional studies on ABD-hTRAIL, however, need to be done to make sure that it is not immunogenic. Although most short peptides have a low immunogenicity, if any, the fact that PEGylated albumin and recombinant human serum albumin are immunogenic requires careful analysis of the potential immunogenicity of ABD-hTRAIL.

References

[1] B. Elsadek, F. Kratz, Impact of albumin on drug delivery-new applications on the horizon, J. Control. Release 157 (2012) 4–28.
[2] R. Li, H. Yang, D.L. Jia, Q.X. Nie, H.W. Cai, Q. Fan, L. Wan, L. Li, X.F. Lu, Fusion to an albumin-binding domain with a high affinity for albumin extends the circulatory half-life and enhances the in vivo antitumor effects of human TRAIL, J. Control. Release 228 (2016) 96–106.
[3] J. Li, C.C. Sharkey, B. Wun, J.L. Liesveld, M.R. King, Genetic engineering of platelets to neutralize circulating tumor cells, J. Control. Release 228 (2016) 38–47.

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