



Cover Story

Multi-functional peptide-modified liposomes for treatment of glioma



Cancer is one of the top two fatal diseases in the United States, and its treatment is still rudimentary despite tremendous advances made in chemotherapy and immunotherapy in the last decade. The frustrating limitations of chemotherapy are due to a number of factors, including random distribution of drugs in the body, ineffective concentration of drugs at the tumor site, poor drug permeability into the tumor cells, inadequate understanding of the tumor microenvironment, and smart self-protection mechanisms evolved by the tumor cells. Numerous targeted drug delivery systems have been developed and tested in a hope to improve therapeutic efficacy of existing drugs and new drug candidates. Unfortunately, the clinical efficacy of such targeted drug delivery systems has been unsatisfactory. Glioma is known to progress rapidly with poor prognosis. Glioma chemotherapy is especially challenging due to intrinsic obstacles of the blood-brain barrier (BBB) and the blood-brain tumor barrier (BBTB). Other critical factors to consider for successful treatment include understanding drug transport into glioma cells, and inhibiting anti-apoptosis and chemoresistance of the glioma cells. In the work featured on the cover of this issue, Professor Gang Wei of Fudan University and his collaborator Dr. Yao-Zhong Lin from Celtek Bioscience have integrated the above concerns into multi-functional liposomes by surface modification with a cell-permeable nuclear factor- κ B (NF- κ B) inhibitor, named CB5005, for treatment of gliomas [1].

CB5005 is a rationally designed peptide, which can be divided into two cascaded segments: a cell membrane-permeable sequence and a nuclear localization sequence. Differing from many traditional cell-penetrating peptides, CB5005 possesses weak electro-positivity due to only two basic lysine residues in the membrane-permeable sequence. The nuclear localization sequence of CB5005 is derived from the p50 subunit of NF- κ B, which can competitively prevent the translocation of activated NF- κ B into the nucleus [2]. NF- κ B is found to be constitutively activated in most malignant cells and in the tumor microenvironment. Thus, blocking the NF- κ B pathway can inhibit tumor growth and enhance the sensitivity of tumor cells to chemotherapeutic drugs [3]. The authors have previously demonstrated that when applied with doxorubicin (DOX), CB5005 showed a synergistically antagonistic effect on gliomas [4].

In the work by the Wei-Lin team, CB5005 was employed to modify PEGylated liposomes loaded with DOX for penetrating the BBB and targeting gliomas. The authors demonstrated that CB5005 modification significantly increased *in vitro* cellular, and even nuclear, uptake of the liposomes by glioma cells, and substantially enhanced the cytotoxicity of DOX liposomes to glioma cells. *In vivo* imaging displayed that the CB5005-modified liposomes distributed in the brain and accumulated at a xenograft and intracranial glioblastoma after intravenous administration. As a result, CB5005-modified liposomes significantly

prolonged the survival time of the animal bearing intracranial glioblastoma. They are unique as compared with other multi-functional liposomes in that the CB5005 peptide has dual functions of cell membrane penetration and NF- κ B inhibition. This is better than grafting two different molecules to the liposome surface for two different functions. Thus, the CB5005-modified liposome delivery system is expected to improve the efficacy of those antineoplastic agents acting in the cell nuclei, and to be appropriate for those tumors associated with high NF- κ B activity.

Although the formulation is based on traditional liposomes, the safety and immunogenicity of the CB5005-modified phospholipid need to be tested. Like any other formulation, CB5005-modified liposomes require more information on the interactions between liposome and endogenous proteins, better insights into the *in vivo* distribution of the formulation and pharmacokinetics of the loaded drug. Since the results of xenograft mouse models have shown to be a poor predictor for clinical efficacy, other animal models and/or *in vitro* models need to be tested to validate the efficacy of the formulation before translating the formulation to the clinic. It is commendable for the Wei-Lin team to describe their formulations as “CB5005-modified liposomes” instead of using generic terms like “nanocarrier” or “nanomedicine”. Regardless of how we call the drug delivery systems, the experimental results will be the same. The inconsiderate abuse of the “nano-” prefix has not made drug delivery any better, but simply increased the undue expectation of an otherwise same formulation.

References

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