Development of a synthetic high density lipoprotein based drug delivery system for chemotherapy in glioma treatment.

Glioblastoma multiformes (GBM) is the most aggressive primary tumor within the central nervous system. Chemotherapy is a commonly used clinical treatment for GBM. However, the low solubility, short half-life, nonspecific cytotoxicity, and low permeability through blood brain barrier (BBB) limit the efficacy and application of chemotherapeutic agents. Nanoparticles (NPs) have been shown the ability to meet the need for targeted delivery of therapeutics and imaging agents. High density lipoprotein (HDL) is a naturally occurring NP that, unlike many engineered NPs, circulates in plasma for long periods of time (t1/2 ~ 3-4 days) and has a major role in cholesterol transport and other molecules. Several synthetic ApoA-I peptide-based HDL products, which are more cost-effective and easier to produce on a large scale, have been administered safely to humans in Phase I/II studies. Scavenger receptor class B-1 (SR-B1) has been reported to be overexpressed on brain capillary endothelial cells and several glioma cancer cell lines. HDLs are able to interact with SR-B1 receptor to facilitate the uptake of loaded cargo from HDL-like NPs to the cytosol via a non-endocytic pathway—thus preventing lysosomal degradation of the HDL-like NP payload. Therefore, HDL was considered to be a suitable drug-delivery carrier for GBM therapy, capable of overcoming the current challenges within traditional chemotherapy, owing to their structural features, biocompatibility and intrinsic targeting ability via receptor-mediated mechanisms. In this study, synthetic HDL (sHDL) NPs were developed to effectively deliver chemotherapeutic agents to GBM cells in preclinical models. We assessed experimentally whether sHDL NPs would target GBM in vitro and in vivo, and if sHDL loaded with chemotherapeutic agents could induce GBM tumor regression and improve the therapeutic effect on tumor-bearing animals. Several GBM cell lines expressing SR-B1 were compared and used for evaluation. We also incorporated near-infrared fluorescent dyes as payloads into sHDL, enabling molecular imaging of invasive GBM cells and targeted drug delivery. Tumor-bearing animal model was established to evaluate the therapeutic effect of the drug delivery system.