Yu-Ting Huang et al., J Material Sci Eng 2018, Volume 7
DOI: 10.4172/2169-0022-C7-111

Controlled release of CPT-11 and shRNA from graphene oxide-entrapped thermosensitive chitosan hydrogel for glioma treatment

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The purpose of this study is to develop an intra-tumoral drug delivery system for delivery of chemical (CPT-11) and gene drugs (SLP2 shRNA) for glioma treatment. The pH-sensitive Graphene Oxide (GO) nanocarrier was produced by Hummer's method, followed by modification with biocompatible polymer (DSPE-PEG-NH2) and monoclonal antibody (cetuximab, CET) that could be identified by the Epidermal Growth Factor Receptors (EGFR) highly expressed on cancer cell surface. The anticancer drug (irinotecan, CPT-11) was first loaded to GO-CET-CPT-11 by π-π stacking interactions. GO-CET-CPT11 was further entrapped with SLP2 shRNA in thermo-sensitive hydrogel (chitosan-g-poly(N-isopropylacrylamide), CPN). GO-CET-CPT-11 was characterized by DLS, zeta potential, TEM, FT-IR, Raman and XRD. CPN@GO-CET-CPT-11@shRNA was characterized by zeta potential, DSC, FT-IR, TGA and rheometer. The CPT-11 loading analysis showed that 0.5 mg/ml GO-CET can absorb 1.8 mg/ml CPT-11. The CPT-11 release analysis showed that drug release at pH 5 was three times higher than that at pH 7.4, which is beneficial for control release in the intracellular acidic environment. The CPT-11 and shRNA release analysis of CPN@GO-CET-CPT-11@shRNA showed that CPT-11 and shRNA was slowly released from CPN due to the degradation of CPN *in vitro*. *In vitro* cell culture analysis with U87 glioma cells showed that GO modified with CET will enhance intracellular uptake through interactions of highly expressed EGFR on cell surface. The IC50 of CPT-11, GO-CPT-11 and GO-CPT-11-CET are 94.86, 32.50 and 6.21 μg/ml, respectively, due to enhanced cytotoxicity of GO-CPT11-CET U87. The transfection efficiency and gel electrophoresis analysis showed that degraded chitosan from CPN will complex with shRNA to facilitate the transfection efficacy of U87. The Western blot and flow cytometry analysis showed that CPT-11 would lead to cancer cell apoptosis and SLP2 shRNA would knockdown the expression of SLP2 gene by U87. An in vivo model using xenograft of U87 carrying luciferase gene was established in nude mice to evaluate the efficacy of intra-tumoral delivery of CPN@GO-CET-CPT-11@shRNA and compared with intra-tumoral delivery of CPT-11+shRNA. The results were analyzed through tumor size and IVIS analysis. After treatment for 28 days, the tumor size of CPN@GO-CET-CPT-11@shRNAgroup was significant different from those of control, CPN@GO-CET and CPT-11+shRNA groups. H and E staining and IHC staining of the tumor tissue confirmed that CPN@GO-CET-CPT-11@shRNA can effectively inhibit the growth of U87 for glioma treatment.

Biography

Yu Ting Huang work at the Yu-Jen, Lu Physician Laboratory at Chang Gung University (2017~). her research focus on establishing of patient-derived xenograft for tumor model, especially in orthotropic brain tumor model. In addition, she is also interested in targeting nanoparticles design, including grapheme oxide and liposomes with multifunctional for cancer therapy..

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