Enhanced Chemotherapy for Brain Glioma by Transferrin-modified Magnetic Mesoporous PLGA Nanoparticles with Core-and-Shell Loading of Doxorubicin and Paclitaxel

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ABSTRACT SUMMARY

Transferrin-modified magnetic mesoporous PLGA nanoparticles (MNP-MSN-PLGA-Tf NPs) with the range of 40 ~ 60 nm in size were synthesized. Magnetic mesoporous silica was used as the core to load doxorubicin (DOX). In contrast, PLGA was used as the shell to load paclitaxel (PTX). Tf as targeting ligand was modified on the surface of MNP-MSN-PLGA NPs to enhance the efficacy of transporting across blood-brain barrier (BBB) and penetration of blood tumor barrier (BTB) of drug-loaded NPs. These drug-loaded NPs exhibited stronger anti-glioma activity and better chemotherapy for brain glioma.

INTRODUCTION

Due to the presence of BBB and BTB, drugs can be prevented from penetrating into central nervous system and tumor interior, respectively. The poor transport efficiency across these two barriers could cause the serious toxicity to normal tissues and then reduce the overall chemotherapeutic efficiency. Henceforth, brain glioma with the survival time of 12 ~ 15 months and a 5-year survival rate of less than 5% is still a malignant cancer¹.

Transferrin² (Tf) is effective to transport across BBB for drug-loaded NPs by binding with transferrin receptors (TfR), which are overexpressed in the brain cells and cancer cells. Mesoporous silica nanoparticles with high pore volume, large specific surface area and nontoxic properties are good candidates for use as carriers for loading drugs. Magnetic nanoparticles are used to drive drug-loaded NPs to the specific tumor location under the applied magnetic field. PLGA has been used widely in drug delivery because of its biodegradability and biocompatibility. In this study, we take full advantage of the properties of transferrin, mesoporous silica nanoparticles, magnetic nanoparticles and PLGA to design dual-drug-loaded system in order to improve the chemotherapeutic efficiency in the treatment of brain glioma.

EXPERIMENTAL METHODS

Transferrin-modified magnetic mesoporous PLGA NPs loading DOX and PTX were synthesized³,⁴ as follows, (i) Preparation of DOX-loaded magnetic mesoporous silica nanoparticles; Magnetic mesoporous silica NPs (10 mg) were dissolved into the DOX solution (5 mL), stirred for 24 h under light-sealed condition. (ii) Synthesis of DOX- and PTX-loaded MNP-MSN-PLGA NPs by double emulsification solid-in-oil-in-water solvent evaporation method; PLGA (100 mg) and PTX (20 mg) were dissolved into DCM (2 mL) and mixed for 2 min. DOX-loaded MNP-MSN NPs were added into the above mixture and emulsified for 1 min. Then, PVA (2 mL, 2%) was added and emulsified again for 1.5 min. The mixture were slowly poured into PVA solution (20 mL, 2%) and stirred for 4 h to evaporate the organic solvent. (iii) Modification of Tf on the surface of MNP-MSN-PLGA NPs by a two-step EDC/NHS activation method. Next, the structure property, in vitro drug release rate, cellular uptake amount, and cellular viability of the above drug-loaded NPs were characterized. After finishing the in vitro experiments, the chemotherapeutic efficacy in brain glioma was studied in vivo.

U-87 MG-luc2 cells (3 × 10⁶ cells / 10 µL) were injected into BALB/c mice on the left brain at 2.5 mm depth when mice were anesthetized via i.p. injection of Ketamine (50 mg·kg⁻¹) and Diazepam (5 mg·kg⁻¹). Then, the
non-invasive bio-luminescence imaging (BLI) was performed using IVIS® animal imaging system to measure tumor size every five days. Twenty days after inoculation, the brain glioma bearing mice were treated via injection of drug-loaded NPs at a dose of 50 mg/kg body weight every three days with four doses via tail vein.

RESULTS AND DISCUSSION

Representative TEM images of MNP-MSN-PLGA-Tf nanoparticles with the size between 40 and 60 nm were shown in Fig. 1, displaying the spherical shape. The black cores were magnetic nanoparticles. After coating with PLGA and Tf, the mesoporous structure of silica was not obvious.

![Fig. 1 TEM images of Tf-modified magnetic mesoporous PLGA nanoparticles.](image)

Cytotoxicities of blank NPs and drug-loaded NPs were evaluated at different concentrations by the MTT assay after incubation of 48 h with U-87 cells (Fig. 2). Antiproliferative effect of Tf-modified drug-loaded NPs was much higher (10 times) than that of NPs without Tf modification, suggesting that conjugation of Tf could improve anti-tumor growth efficacy.

![Fig. 2 Cell viability of U-87 cells incubated with NPs and drug-loaded NPs for 48 h.](image)

In vivo chemotherapeutic efficacy after treatment with saline, DOX-PTX-NPs, DOX-NPs-Tf, PTX-NPs-Tf, and DOX-PTX-NPs-Tf was studied (Fig. 3). Due to the different initial tumor sizes, the bio-luminescence signal intensity at each time point was normalized against the initial value before treatment (Day 0). The results indicated that DOX-PTX-NPs-Tf was the most efficacious to inhibit the tumor growth among all the formulations.

![Fig. 3 Normalized bio-luminescence intensity in in vivo intracranial U-87 MG-luc2 model as a functional time after treatment.](image)

CONCLUSION

Transferrin-modified magnetic mesoporous PLGA nanoparticles loading doxorubicin and paclitaxel had been successfully prepared with promising chemotherapeutic efficacy for treatment of brain glioma.

REFERENCES


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