Biocompatible Nanoparticles as a Platform for Enhancing Antitumor Efficacy of Cisplatin-Tetradrine Combination

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Abstract

Combination therapy has been a standard strategy in the clinical tumor treatment. We have demonstrated that combination of Tetradrine (Tet) and Cisplatin (CDDP) presented a marked synergistic anticancer activity, but inevitable side effects limit their therapeutic concentration. Considering the different physicochemical and pharmacokinetic properties of the two drugs, we loaded them into a nanovehicle together by the improved double emulsion method. The nanoparticles (NPs) were prepared from the mixture of poly(ethylene glycol)-polycaprolactone (PEG-PCL) and polycaprolactone (HO-PCL), so CDDP and Tet can be located into the NPs simultaneously, resulting in low interfering effect and high stability. Images from fluorescence microscope revealed the cellular uptake of both hydrophilic and hydrophobic agents delivered by the NPs. In vitro studies on different tumor cell lines and tumor tissue revealed increased tumor inhibition and apoptosis rates. As to the in vivo studies, superior antitumor efficacy and reduced side effects were observed in the NPs group. Furthermore, 18 FDG-PET/CT imaging demonstrated that NPs reduced metabolic activities of tumors more prominently. Our results suggest that PEG-PCL block copolymeric NPs could be a promising carrier for combined chemotherapy with solid efficacy and minor side effects.

Full Text

Due to technical limitations, full-text HTML conversion of this manuscript could not be completed. However, the manuscript can be downloaded and accessed as a PDF.

Figures
Figure 1

The scheme of COOP-101 NPs preparation
Figure 2

Photos of Logo cells after 2 hours of staining with NPs loaded with rhodamme B and coumarm-6 (2DT, bar 50 um) a. cell morphology order the light microscopy b. cell morphology under fluorescence meroscope(PI fluorescence tunnel) c. cell morphology under fluorescence meroscope(FITC fluorescence tunnel) d. cell morphology under fluorescence meroscope(PI/PRC dual fluorescence tunnel)

Figure 3
In vitro cytotoxicity of the nanoparticles a. Cell viability of MKN28 after being co-cultured with drugs for 48 hours. The concentration of Tet was 24 times as much as the concentration of CDDP. b. Photos of MKN28 cells under the light microscopy (203a) after being co-cultured with drugs for 48 hours.

**Figure 4**

In vitro apoptosis lys by flow cytometry a Free CDDP b Free Tet c Free COOP+ Tet d CDDP-Tet NPs
Figure 5

Histoculture Drug Response Assay
Figure 6

Tumor volume of established H22 xenografts in ICR mice during therapy under different treatments. Mice were treated with different strategies on day 0 as shown in the figure: 3mg/kg of free COOP, free CDDP together with Tet (COOP 3mg/kg + Tet 7.2mg/kg). COOP-Tet-loaded hiPs (COOP 3mg/kg +Tet Zing/kg) respectively. Mean TS0 (n = 6) of each group was measured.
Figure 7

Apoptotic cells were detected by a TUNEL assay (green) and co-stained by nuclear Awning OAPI (blue)
Figure 8

Side effects evaluation a Body weights of established H22 xencrafts in ICR mice during therapy under different treatments b river specimens Wooled HE were on login microscopic observation (400X)
Figure 9

Male ICR mice bearing a subcutaneous Ho (marine hepatoma cell line) tumor at the left axillaw (arrows) Cr PET and fused PET/CT images are arranged in the figure from left to right. Tumor metabolic rate in free CDDP plus Tet group (blue arrow) was significantly higher than NPs group (yellow arrow).

 Supplementary Files

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- FigS3a.tiff
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