A mitochondrial targeted paclitaxel loaded self-assembled nanocarrier reduces the multidrug resistance of breast cancer

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ABSTRACT SUMMARY

Multidrug resistance (MDR) is one of the major challenges for successful chemotherapy. Herein, we attempted to develop a mitochondria targeted paclitaxel (PTX) loaded self-assembled nanocarrier (PSN) to reduce the MDR of breast cancer. The IC_{50} of PTX in resistant MCF-7/ADR cells was greatly reduced from 101.45µg/mL to 5.39µg/mL by nanometer-sized PSN. The reversal of MDR by PSN could attribute to the mitochondria targeted delivery of PTX and enhanced apoptosis, other than reduction of overexpressed P-gp efflux transporter. After intravenous administration, PSN could induce a higher accumulation of PTX in tumor site. Moreover, the in vivo antitumor results indicated the tumor volume and weight in resistant MCF7/ADR cell induced xenograft model treated with PSN was only 9.62% and 13.75% of that treated with PTX solution, which effectively verified the validity of PSN in reversal of MDR. Thereby, the mitochondria targeted PSN represented great potential in reducing the PTX resistance in breast cancer.

INTRODUCTION

Paclitaxel (PTX) is one of the effective chemotherapeutic agents, which presents great potency in the treatment of a broad spectrum of solid tumors, including breast cancer, refractory ovarian cancer and non-small cell lung carcinoma, etc [1]. However, multidrug resistance (MDR) is usually developed in the clinical trials using PTX alone or in combination with other antineoplastic agents, which is one of the major challenges of successful chemotherapy. Moreover, MDR of PTX remains in more than 70% of patients at the d lime of initial diagnosis and almost in all patients upon relapse. Thereby, it’s greatly needed to reduce MDR of PTX in clinical application.

Mitochondria play a crucial role in regulating the intrinsic pathway of apoptosis, and are implicated in multiple aspects of tumorigenesis and tumor progression. However, mitochondria are commonly associated with the multidrug resistance of anticancer drugs in chemotherapy. Recently, we have come to realize that mitochondria are emerging target of anticancer drugs. Moreover, anticancer drugs can be selectively delivered to the mitochondria to improve the antitumor activities. Herein, we tried to develop a mitochondria targeted PTX loaded self-assembled nanocarrier (PSN) to reduce the MDR paclitaxel in breast cancer. The efficacy of overcoming the MDR was determined by in vitro and in vivo evaluations, and the possible mechanism was investigated.

EXPERIMENTAL METHODS

PSN was prepared by a self-assembled technique and the in vitro physicochemical properties of PSN were characterized. The reversal of MDR was measured in resistant MCF-7/ADR cells. Then, the cell cycles, P-gp expression, cellular uptake of PTX and intracellular localization in resistant MCF-7/ADR cells treated with PSN was respectively investigated to clarify the possible mechanism. Moreover, the in vivo distribution and in vivo efficacy of reversal of MDR was performed in MCF-7/ADR cells induced xenograft model.

RESULTS AND DISCUSSION

PSN were nanometer-sized spherical particles with the mean diameter of 25.12 ± 0.85 nm (PDI =0.125±0.022). The in vitro cytotoxicity results indicated that the IC_{50} value of PSN in MCF-7/ADR cells was 5.39µg/mL, which was comparable with that of PTX solution in sensitive MCF-7 cells and was only about 5.3% of that of PTX solution in MCF-7/ADR cells. Then, the possible mechanism of reversal of MDR was investigated. The LCSM images indicated that PSN was mainly localized in mitochondria. The mitochondrial potential values were greatly reduced to 30% of the negative control and the cell apoptosis was significantly enhanced 7.66-fold over the PTX solution. However, the cell cycle and P-gp expression in MCF-7/ADR cells treated with PSN was not significantly changed. The reversal of MDR by PSN could mainly result from the mitochondria targeted delivery of PSN other than the inhibition of overexpressed P-gp efflux pumps.
eflux pumps. After intravenous administration, PSN could induce a higher accumulation of PTX in tumor tissue and improve the anti-tumor activities of PTX in resistant MCF7/ADR cell induced xenograft model. Thereby, PSN demonstrated great potential in reducing MDR of breast cancer.

REFERENCES

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