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ACCEPTED MANUSCRIPT

Microvesicle- and exosome-mediated drug delivery enhances the cytotoxicity of paclitaxel in autologous prostate cancer cells

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Abstract

Background
Extracellular vesicles (EVs) are naturally occurring membrane particles that mediate intercellular communication by delivering molecular information between cells. In this study, we investigated the effectiveness of two different populations of EVs (microvesicle- and exosome-enriched) as carriers of Paclitaxel to autologous prostate cancer cells.
Methods
EVs were isolated from LNCaP- and PC-3 prostate cancer cell cultures using differential centrifugation and characterized by electron microscopy, nanoparticle tracking analysis, and western blot. The uptake of microvesicles and exosomes by the autologous prostate cancer cells was assessed by flow cytometry and confocal microscopy. The EVs were loaded with Paclitaxel and the effectiveness of EV-mediated drug delivery was assessed with viability assays. The distribution of EVs and EV-delivered Paclitaxel in cells was inspected by confocal microscopy.
Results
Our main finding was that the loading of Paclitaxel to autologous prostate cancer cell-derived EVs increasedits cytotoxic effect. This capacity was independent of the EV population and the cell line tested. Although the EVs without the drug increased cancer cell viability, the net effect of enhanced cytotoxicity remained. Both EV populations deliveredPaclitaxel to the recipient cells through endocytosis, leading to the release of the drug from within the cells. The removal of EV surface proteins did not affect exosomes, while the drug delivery mediated by microvesicles was partially inhibited.
Conclusions
Cancer cell-derived EVs can be used as effective carriers of Paclitaxel to their parental cells, bringing the drug into the cells through an endocytic pathway and increasing its cytotoxicity. However,due to the increased cell viability, theuseof cancer cell-derived EVs must be further investigated before any clinical applications can be designed.

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