Co-Silencing of PKM-2 and MDR-1 Sensitizes Multidrug Resistant Ovarian Cancer Cells to Paclitaxel in a Murine Model of Ovarian Cancer

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ABSTRACT

**Purpose:** The aim of our study was to evaluate the effectiveness of combination therapy with siMDR-1 and siPKM-2 in SKOV-3WT and SKOV-3TR human ovarian adenocarcinoma cell lines and xenograft models. Using hyaluronic acid (HA)-based self-assembling nanoparticles targeted for the epidermal growth factor receptor (EGFR) on the surface. We aimed to investigate whether co-silencing of PKM-2 and MDR-1 could enhance the efficacy of paclitaxel (PTX) against MDR ovarian cancer.

**Experimental Methods:** The nanoparticles with the siRNA were characterized for morphology, size, charge, encapsulation efficiency and transfection efficiency. In vivo studies included biodistribution, assessment, gene knockdown confirmation, therapeutic efficacy, and safety analysis.

**Results:** The self-assembling nanoparticles showed a spherical morphology in TEM with particles in size range of 106-125 nm and surface charge ranging from -125 to -328 mV. Fluorescence confocal microscopy studies showed higher permeability efficiency in EGFR targeted system. Down-regulation of MDR-1 gene expression (60-80%) was confirmed by transfection studies. A decrease in IC50 was detected from combination therapy compared with single siMDR-1 therapy using cytotoxic assay. In vivo knockdown studies showed the targeted nanoparticles provided down-regulation MDR-1 (65%) and PKM-2 (65-70%) in SKOV-3 tumor bearing mice. Combination therapy showed improved tumor growth inhibition (TGI) and tumor volume doubling (TVD) time for all treatment groups compared to PTX alone.

**Conclusions:** This study showed the encapsulation and delivery of siMDR-1 and siPKM-2 in HA-PEI based self-assembling nanoparticles improved the efficacy and cytotoxic effect of PTX in cancer cells. Plus, these agents can provide synergistic activity for cancer therapy.

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