BR PP 1-5

Disruption Of Collagen Alignment By An MMP2-responsive Nanosystem To Enhance Penetration Of Chemotherapeutic Agents In Pancreatic Ductal Adenocarcinoma

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Background : Collagen is one of the most important stromal components of pancreatic ductal adenocarcinoma (PDAC), and studies have revealed its double-edged role in the progression of PDAC. On the one hand, collagen can physically limit the rapid growth of tumor cells. On the other hand, the linear arrangement of collagen promotes the differentiation of tumor cells and inhibits the infiltration of chemotherapy drugs. Therefore, disrupting the linear arrangement of collagen while preserving the limiting effect of collagen on tumor cell growth is of great significance for promoting the treatment of pancreatic cancer.

Methods : Second-harmonic generation (SHG) and Scanning electron microscope was used to analyze the architecture of collagen fibers. Immunohistochemistry was used to evaluate the expression of LOXL2 in PDAC tissues. DDR1 inhibitor was first incorporated into PEG-PLGA nanoparticles using a modified double emulsion method. And then the nanoparticles were encapsulated into liposomes with the LOXL2 inhibitor to construct the MMP2-responsive nanosystem LOXL2-DDR1@MLP. Transmission electron microscope (TEM) was used to observe the morphology and dynamic light scattering (DLS) was used to analyze the size distribution of LOXL2-DDR1@MLP. Orthotopic PDAC model characterized with abundant tumor stroma was used to evaluate the anticancer efficacy of the nanosystem combined with nab-paclitaxel (Nab-p) in vivo.

Results : We confirmed that collagen fibers in PDAC tissues showed a significant linearized arrangement, and the degree of collagen fiber alignment was positively associated with the expression level of LOXL2. The LOXL2-DDR1@MLP nanoparticles encapsulated LOXL2 and DDR1 inhibitors and responded to the MMP2 enzyme effectively. The LOXL2-DDR1@MLP successfully disrupted the alignment of collagen and maintained the stable content of collagen in vitro and in vivo. In orthotopic PDAC models, the nanosystem enhanced the treatment of nab-paclitaxel (Nab-p) significantly.

Conclusions : We have successfully devised an MMP2-responsive nanosystem for delivering LOXL2 and DDR inhibitors. The nanosystem disrupted collagen alignment and enhanced penetration of chemotherapeutic drugs effectively, which provided a new therapeutic strategy in desmoplastic pancreatic cancers.

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