PD42-01
ENHANCED INTRACELLULAR DELIVERY OF BCG CELL WALL SKELETON INTO BLADDER CANCER CELLS USING LIPOSOMES FUNCTIONALIZED WITH FOLIC ACID AND PEP-1 PEPTIDE
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INTRODUCTION AND OBJECTIVE: Although bacillus Calmette–Guerin cell wall skeleton (BCG-CWS) might function as a potential substitute for live BCG, its use in the treatment of bladder cancer remains limited owing to issues such as insolubility and micrometer-size following exposure to an aqueous environment.

METHODS: To develop a novel nanoparticulate system for efficient BCG-CWS delivery, liposomal encapsulation was carried out using a modified emulsification-solvent evaporation method (targets: Size, <200 nm; encapsulation efficiency, ≥60%). Further, the liposomal surface was functionalized with specific ligands, folic acid (FA), and Pep-1 peptide (Pep1), as targeting and cell-penetrating moieties, respectively.

RESULTS: Functionalized liposomes greatly increased the intracellular uptake of BCG-CWS in the bladder cancer cell lines, 5637 and MBT2. The immunoactivity was verified through elevated cytokine production and a THP-1 migration assay. In vivo antitumor efficacy revealed that the BCG-CWS-loaded liposomes effectively inhibited tumor growth in mice bearing MBT2 tumors. Dual ligand-functionalized liposome was also superior to single ligand-functionalized liposomes. Immunohistochemistry supported the enhanced antitumor effect of BCG-CWS, with IL-6 production and CD4 infiltration.

CONCLUSIONS: We conclude that FA- and Pep1-modified liposomes encapsulating BCG-CWS might be a good candidate for bladder cancer treatment with high target selectivity.

PD42-02
THE EFFECTS OF RECOMBINANT BACILLUS CALMETTE-GUERIN RESISTANT TO ANTIMICROBIAL PEPTIDES ON ORTHOTOPIC BLADDER CANCER MOUSE MODEL
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INTRODUCTION AND OBJECTIVE: Although Mycobacterium bovis Bacillus Calmette-Guerin (BCG) is the most widely used bladder cancer immunotherapy, innate immune responses involving antimicrobial peptides (AMPs) cause BCG failure. Here, we developed genetically modified recombinant BCG (rBCG) strains which escape AMPs and evaluate the efficacy and effects of rBCG.

METHODS: We constructed rBCG strains expressing Streptococcal inhibitor of complement (Sic), which confers resistance to human α-defensin-1 and cathelicidin, and d-alanyl carrier protein ligase (dltA), which confers resistance to cationic AMPs. Sic and dltA were separately cloned into the pMV306 plasmid and introduced into BCG via electroporation. The efficacy of the Sic and dltA gene electroporation into BCG was evaluated by quantitative real-time polymerase chain reaction (qRT-PCR). The internalization rates and anti-cancer effects of the rBCG strains containing Sic (rBCG-Sic) and dltA (rBCG-dltA) was evaluated by the orthotopic bladder cancer mouse model.

RESULTS: The cycle quantification (Cq) values of rBCG-Sic (y = -4.8823x + 13.645, R² = 0.9996) and rBCG-dltA (y = -5.438x + 11.641, R² = 0.9995) were inverse correlations to the amount of Sic and dltA genes dose dependently. The mean introduction proportions of Sic and dltA genes into BCG by electroporation were 22.2%, 27.5% and 29.8%, 34.8% and showed constant efficacy. In the orthotopic bladder cancer mouse model, the relative internalization number of rBCG-Sic, and rBCG-dltA into bladder cell in mouse bladder were higher than that of BCG and the tumor volume at rBCG-Sic were lower than at BCG and rBCG-dltA at 11, 14 m and 18 days.

CONCLUSIONS: Our results showed that constructed rBCG-Sic and rBCG-dltA by electroporation and the rBCG-Sic and rBCG-dltA can effectively escape BCG-stimulated AMPs, and significantly improved immunotherapeutic tools to treat bladder cancer in orthotopic bladder cancer mouse model.

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