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Design and development of a series of recombinant fusion vectors for targeted cancer gene delivery

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Background and Aims: In this study a new series of recombinant vectors was designed and genetically synthesized for targeted gene delivery to ZR-75-1 cancer cells. The vector structure contained multiple domains including: 1) two tandem repeating units of histone H1 to condense pDNA, 2) a targeting motif from phage display library for ZR-75-1 breast cancer cells, 3) a pH-responsive fusogenic peptide, KALA, to destabilize endosomal membrane, and 4) a nuclear localization signal from HIV to translocate pDNA towards the nucleus.
Methods: The vectors were cloned and expressed in E.coli BL21 (DE3) followed by purification with Ni-NTA affinity chromatography. The vectors were characterized using physicochemical and biological methods such as gel retardation assay, particle serum stability, size, zeta potential, hemolysis assay, cell transfection, cytotoxicity and etc. to evaluate the gene delivery efficiency and vector multifunctioanlity.
Results: The results of biological analyses demonstrated that the vector bearing all four functional motifs (FS3) had the highest rate of gene transfection efficiency as compared to the vectors which lacked one or more functional motifs (FS1 and FS2). Beside the ability to target, the developed vector was able to disrupt endosomal membranes, reach cell nucleus by utilizing microtubules and transfect efficiently while showing no detectable toxicity. FS3 at N/P ratios above 6 have equal or higher transfection efficiency than the PEI 25 kDa positive control ($p<0.001$).
Conclusions: The most valuable finding to emerge from this study is that incorporating of different domains from various sources could improve gene delivery efficacy without affecting their functionality.

Keywords: Gene therapy; Gene delivery; Non-viral vector; Breast cancer; Recombinant DNA technology