Peptide-mediated targeted delivery system towards triple negative breast cancer treatment

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Abstract

About 2.1 million new diagnosed breast cancer cases among women were estimated for 2018. Triple negative breast cancer (TNBC), characterized by the absence of hormone receptors (estrogen and progesterone), lack of expression of epidermal growth factor receptor-2 and poor prognosis, represents 10-20% of all breast cancers. Hence, the identification of novel biomarkers for this type of breast cancer is highly relevant for an early diagnosis. Additionally, TNBC peptide ligands can be used to design powerful drug delivery systems that specifically target this type of breast cancer. Therefore, the following study aimed to select and characterize novel peptides for a triple negative breast cancer murine mammary carcinoma cell line– 4T1. Using phage display, 7 and 12 amino acid random peptide libraries were screened against the 4T1 cell line. A total of four rounds, plus a counter-selection round using the 3T3 murine fibroblast cell line, was performed. The enriched selective peptides were characterized and their binding capacity towards 4T1 tissue samples was confirmed by immunofluorescence and flow cytometry analysis. The selected peptides (4T1pep1 – CPTASNTSC and 4T1pep2— EVQSSKFPAHVS) were enriched over few rounds of selection and exhibited specific binding to the 4T1 cell line.

Exosomes derived from BJ cells were isolated by differential centrifugation and further characterized by nanoparticle tracking analysis, transmission electron microscopy (TEM), flow cytometry and western blot. Cell-derived exosomes were efficiently uptake by different TNBC cell lines (MDA-MB-231, MDA-MB-453, MDA-MB-157 and Hs 578T). Moreover, in vivo circulation times and biodistribuition experiments were accomplished to assess performance. The ultimate goal is to develop multifunctional exosomes decorated with the previously selected peptides to achieve a drug delivery system with increased affinity/selectivity for triple negative breast cancer cells. Targeted exosomes have led to a completely new paradigm for the therapeutic delivery of drug molecules to specific targets, opening the door for new treatments of diseases caused by aberrant gene expression as cancer.