

DNAi-peptide nanohybrid smart particles target BCL-2 oncogene and induce apoptosis in breast cancer cells

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Abstract

Genomic DNA sequences provide unique target sites, with high druggability value, for treatment of genetically-linked diseases like cancer. B-cell lymphoma protein-2 (BCL-2) prevents Bcl-2-associated X protein (BAX) and Bcl-2 antagonist killer 1 (BAK) oligomerization, which would otherwise lead to the release of several apoptogenic molecules from the mitochondrion. It is also known that BCL-2 binds to and inactivates BAX and other pro-apoptotic proteins, thereby inhibiting apoptosis. BCL-2 protein family, through its role in regulation of apoptotic pathways, is possibly related to chemo-resistance in almost half of all cancer types including breast cancer. Here for the first time, we have developed a nanohybrid using a peptide-based carrier and a Deoxyribonucleic acid inhibitor (DNAi) against BCL-2 oncogene to induce apoptosis in breast cancer cells. The genetically designed nanocarrier was functionalized with an internalizing RGD (iRGD) targeting motif and successfully produced by recombinant DNA technology. Gel retardation assay demonstrated that the peptide-based carrier binds single-stranded DNAi upon simple mixing. Dynamic light scattering (DLS) and transmission electron microscopy (TEM) analyses further revealed the formation of nanohybrid particles with a size of 30 nm and a slightly positive charge. This hemocompatible nanohybrid efficiently delivered its contents into cancer cells using iRGD targeting moiety. Gene expression analysis demonstrated that the nanohybrids, which contained DNAi against BCL-2 proficiently suppressed the expression of this oncogene in a sequence specific manner. In addition, the nanohybrid, triggered release of cytochrome c (cyt c) and caspase3/7 activation with high efficiency. Although the DNAi and free nanocarrier were separately unable to affect the cell viability, the nanohybrid of 20 nM of DNAi showed outstanding antineoplastic potential, which was adjusted by the ratio of the MiRGD nanocarrier to DNAi. It should be noted that, the designed nanohybrid showed a suitable specificity profile and did not affect the viability of normal cells. The results suggest that this nanohybrid may be useful for robust breast cancer treatment through targeting the BCL-2 oncogene without any side effects.

Keywords: Nanohybrid, BCL-2 DNAi, Breast cancer, Apoptosis, Peptide-based carrier