BIOMEDICAL POLYMERIC MATERIALS-BASED DELIVERY SYSTEMS FOR siRNA

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siRNA is a powerful tool to control cellular processes at the post-transcriptional level. However, its therapeutic potential is limited because of low stability in biological fluids and the lack of simple and efficient delivery systems. To overcome these obstacles, different system for siRNA stabilization and delivery have been developed, including those based on the use of various polymeric materials.

The micelle-like nanoparticle (MNP), based on the combination of a covalent conjugate of phospholipid and polyethylenimine (PLPEI) with polyethylene glycol (PEG) and lipids were suggested for siRNA delivery. MNPs were prepared by condensing siRNA with PLPEI. The addition of a PEG/lipid coating to the PLPEI complexes generated particles with sizes of ca. 200 nm and a neutral surface charge compared with positively charged PLPEI polyplexes without the additional coating. MNPs protected the loaded siRNA against enzymatic digestion and enhanced the cellular uptake of the siRNA payload. MNPs carrying green fluorescent protein (GFP)-targeted siRNA effectively downregulated the gene in cells that stably express GFP. Low-molecular-weight polyethylenimine (DOPE-PEI) nanocarriers have also been suggested for intravenous delivery of anti-P-pg siRNA to tumors. Therapeutic efficacy and safety of DOPE-PEI/siRNA-mediated P-gp downregulation in combination with doxorubicin (Dox) chemotherapy in MCF-7/MDR xenografts was clearly demonstrated.

A triblock co-polymeric system, poly(amidoamine) dendrimer (generation 4)-poly(ethylene glycol)-1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (G(4)-D-PEG-(2K)-DOPE). G(4)-PAMAM dendrimer was also utilized as a cationic source for efficient siRNA condensation; DOPE provided optimum hydrophobicity and compatible cellular interaction for enhanced cell penetration; PEG rendered flexibility to the G(4)-D for easy accessibility of siRNA for condensation; PEG-DOPE system provided stable micellization in a mixed micellar system. The G(4)-D-PEG-(2K)-DOPE has the higher efficacy for siRNA delivery, whereas G(4)-D-PEG-(2K)-DOPE/PEG-(5K)-PE micelles appear to be a promising carrier for drug/siRNA co-delivery, especially useful for the treatment of multi-drug resistant cancers.

Stimuli-sensitive siRNA delivery systems were also suggested. Thus, siRNA was reversibly modified with a phosphothioethanol (PE) portion via the reducible disulfide bond and the resulting siRNA-S-S-PE conjugate was incorporated in nanosized PEG-PE micelles. In the mixed siRNA-S-S-PE/PEG-PE micelles obtained, siRNA was well-protected against degradation by nucleases and was released easily from these nanoparticles in free form in the presence of glutathione (GSH) at a concentration mimicking the intracellular levels. A redox-sensitive micellar nanopreparation based on a triple conjugate of polyethylene glycol, polyethyleneimine and phosphatidylethanolamine, PEG-SS-PEI-PE (PSSPD) was also prepared. This non-toxic system efficiently condenses siRNA and specifically downregulates target green fluorescent protein (GFP) only under reducing conditions via intracellular siRNA release after de-shielding of PEG due to increased glutathione (GSH) levels characteristic of cancer cells.

To prepare a hypoxia-responsive copolymer for siRNA delivery, a polyelectrolyte-lipid conjugate (polyethyleneimine 1.8 kDa-dioleyl-phosphatidylinositol, PEI-PE) and polyethylene glycol 2000 (PEG) were assembled via the hypoxia-sensitive azobenzene (Azo) unit to obtain the PEG-Azo-PEI-DOPE copolymer. This copolymer can condense siRNA and shows hypoxia-induced cellular internalization and reporter gene downregulation in vitro and tumor accumulation in vivo after parenteral administration The proposed nanoformulation represents a novel tumor-environment-responsive modality for cancer targeting and siRNA delivery.