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PEGylation of the GALA peptide enhances the lung-targeting activity of nanocarriers that contain encapsulated siRNA

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Abstract

A α-helical GALA peptide (WEAALAEALAEALAEHLAEALAEALEALAA) has been found to possess dual functions: a pH-dependent inducer of endosomal escape, and a ligand that targets lung endothelium. In the present study, the flexibility of GALA was improved by modifying the edge with polyethylene glycol linker, to increase lung-targeting activity. We first investigated the uptake of the GALA-modified liposomes in which GALA was directly conjugated to the lipid (Cholesterol: GALA/Chol) or the phospholipid-PEG (GALA/PEG_{2000}). The liposomes that were modified with GALA/PEG_{2000} (GALA/PEG_{2000}-LPs) were taken up at a higher level by human lung endothelial cells (HMVEC-L), in comparison with particles that were modified with GALA/Chol (GALA/Chol-LPs). siRNA-encapsulating liposomal-based nanocarriers (multifunctional envelope-type nano device: MEND) that were formulated with a vitamin E-scaffold SS-cleavable pH-activated lipid-like material, namely GALA/PEG_{2000}-$MEND_{ssPalmE}$ were also modified with GALA/PEG_{2000}. Gene silencing activity in the lung endothelium was then evaluated against an endothelial marker; CD31. In comparison with the unmodified $MEND_{ssPalmE}$, GALA/PEG_{2000}-$MEND_{ssPalmE}$ exhibited a higher silencing activity in the lung. Optimization of GALA/PEG_{2000}-$MEND_{ssPalmE}$ resulted in silencing activity in the lung with an ED_{50}