Oligonucleotides-Conjugated Poly(ethylene oxide)-Block-poly(ε-caprolactone) (PEG-*b*-PCL) Nanoparticles as Drug Carriers Targeting Scavenger Receptor Class A

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Purpose

Polymeric nanoparticles as drug carriers offer many attractive advantages including solubility and stability enhancement, improved safety profiles, etc. However, they often suffer from low cellular delivery efficiency due to a lack of active targeting. Oligonucleotides have high affinity towards scavenger receptors Class A (SR-A), which are abundant in a range of epithelial and endothelial cells. Herein, we reported the use of paclitaxel (PTX)-loaded oligonucleotides-conjugated polymeric nanoparticles for the inhibition of angiogenesis, which accounts for the pathogenesis of a number of major diseases such as cancer.

Methods

Oligonucleotides-conjugated PEG-*b*-PCL was prepared by a standard method reported in the literature with modifications through Michael addition reaction of oligonucleotides onto functionalised PEG-*b*-PCL. The drug-loaded polymeric nanoparticles were prepared by an anti-solvent method. The nanoparticles were characterised for particle size and polydispersity by dynamic light scattering and the drug loadings and encapsulation efficiency were determined by an UPLC-UV. C166, a mouse yolk sac derived endothelial cell line with positive expression of SR-A, was used in this study. A cellular uptake study was carried out using coumarin-6 loaded nanoparticles and the quantification of cellular uptake was based on the fluorescent intensity of coumarin-6. The efficacy against angiogenesis of each formulation was determined using *in vitro* proliferation and migration cell based assays.

Results

Oligonucleotides-conjugated PEG-*b*-PCL nanoparticles (ODN-Np) have a mean particle size of 58.1±0.5 nm with a polydispersity index of 0.156±0.022 and a zeta potential of -30.9±3.0 mV, which is comparable to non-conjugated PEG-*b*-PCL (PEG-Np) (57.7±0.4 nm, 0.137±0.012 and -11.5±1.1 mV respectively). The decrease in zeta potential is likely due to the presence of negatively charged ODN on the surface of Np. ODN-Np improved the solubility of PTX by 200x to 200 μg/mL with 99.5% encapsulation efficiency. ODN-Np has shown 3.94x improvement in cellular uptake compared with non-conjugated PEG-Np. Further investigation on the uptake mechanisms using endocytosis inhibitors (chlorpromazine, methyl-β-cyclodexrin and fucoidan) indicated that the uptake improvement is mainly attributable to CAV-1 and SR-A mediated endocytosis. In the proliferation assay, PTX-loaded ODN-Np showed improved efficacy compared to PTX-loaded PEG-Np (At 100 μg/mL PTX; ODN-Np = 32.0±3.4% proliferation vs PEG-Np = 48.5±6.8% proliferation). PTX-ODN-Np showed significant improvement in inhibiting cellular migration compared with PTX-PEG-Np and the control (no treatment) (12.5 μg/mL PTX; After 36 hours, ODN-Np = 44.9±1.5% inhibition, PEG-Np = 26.1±4.4% inhibition and control = 15.4±5.5% inhibition, respectively).

Conclusion

ODN-Np improved the solubility of PTX by 200x. Relative to non-conjugated PEG-Np, ODN-Np showed an enhanced cellular uptake and better efficacy in inhibiting cell proliferation and migration *in vitro*. The improvement is mainly attributable to the presence of ODN as a targeting ligand for SR-A receptors. Further investigations of this formulation using an *in vivo* model to determine its stability, biodistribution and efficacy are on-going.