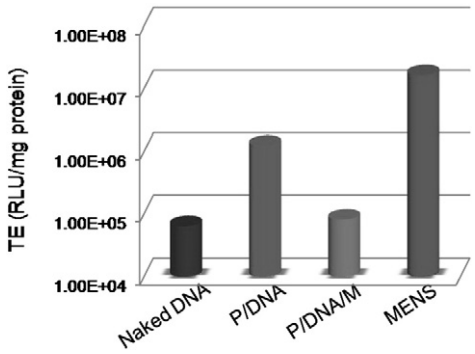

Fig. 3. Transfection activity of MENS compared to those of P/DNA, P/DNA/M and naked DNA.

Conclusions

We have used a novel programmed packaging strategy to develop a multicomponent envelope-type nanoparticle system (MENS) that is expected to overcome intracellular membrane barriers via step-wise membrane fusions. Preliminary TE measurements showed that MENS is a promising transfection candidate.

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siRNA transfection by dendritic core–shell nanocarriers

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Abstract summary

New targets for RNAi-based cancer therapy are constantly emerging from the increasing knowledge on the key molecular pathways that are paramount for carcinogenesis. Nevertheless, in vivo delivery of siRNA remains a crucial challenge for its therapeutic success. siRNAs on their own are not taken-up by most mammalian cells in a way that preserves their activity. Moreover, when applied in vivo, siRNA-based approaches are all limited by poor penetration into the target tissue and low silencing efficiency.

Introduction

Double stranded RNA (dsRNA) induces sequence-specific post-transcriptional gene silencing by a process known as RNA interference (RNAi). The mediators of RNAi are small interference RNA (siRNA) segments of 21–25 base pairs in length [1]. To achieve successful gene therapy, development of proper gene delivery systems is the main obstacle. For the uptake of DNA/siRNA various systematic and cellular barriers have to be circumvented [2].

Result and discussion

In order to circumvent these limitations, we have developed a series of pH-responsive core–shell architectures based around a dendritic polyglycerol (PG) core [3]. These nanoparticles have an approximate MW of 20 kDa and are thus sufficiently large to both passively accumulate in damaged tissues by the "enhanced permeation and retention effect" and endocytose across cell membranes. In vitro tests revealed that such architectures were able to efficiently transfect various types of siRNA leading to gene silencing in numerous cell lines. Activities were comparable to the benchmark in vitro transfection reagent HiPerFect™ and also comparable to polyamines such as polyethylene imine. Due to the benign PG core, our constructs showed favorable biocompatibility compared to purely polyamine systems.

When extended to in vivo systems, our carriers showed excellent siRNA delivery to tumour tissues in mice as measured by a luciferase silencing assay. Furthermore, no significant toxicity in cell proliferation assays was observed at concentrations required for efficient gene silencing. We believe that our core–shell materials are ideal for delivering growth gene silencing siRNA selectively to tumour tissues, thus impeding cancer cell proliferation.

Conclusion

Several pH-responsive core–shell architectures based on polyglycerol with a star-like oligoamine shell have been prepared by a simple two step protocol. These novel compounds carry charges at physiological pH on their shell, whereas the core is comprised of a highly biocompatible non-charged aliphatic polyether. By finetuning the nitrogen containing shell, better transfection/toxicity ratios in vitro were obtained. Our findings indicated that siRNA complexed with our systems can be systemically delivered to tumors and that our dendritic nanocarrier-siRNA system can efficiently inhibit expression of a specific gene in tumor cells.

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Design of solid lipid nanoparticles for gene delivery into prostate cancer

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Abstract summary

Prostate adenocarcinoma is the most common cancer occurring in male. The insufficient advances attained so far in cancer treatment