Systemic Delivery of Nucleic Acids for Prostate Cancer Therapy

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Background

Nucleic acids are emerging as a novel class of therapeutics for cancer treatment. For example, RNA interference (RNAi)-based gene silencing has been widely used for identification and validation of putative cancer targets, and several RNAi nanotherapeutics are now under clinical trials in cancer patients. Messenger RNA (mRNA) has also shown unique advantages for the development of cancer vaccine and gene therapy. Nevertheless, the safe and effective delivery of nucleic acids to target cells still remains a major hurdle for their widespread clinical applications.

Methods

We have developed several unique self-assembled nanoparticle platforms to tackle the challenges associated with the systemic delivery of nucleic acids to tumor cells, such as enzymatic degradation, rapid elimination by renal excretion or by the mononuclear phagocyte system, and insufficient cellular uptake and endosomal escape.

Results

Through a robust self-assembly strategy, we have rationally developed a new generation lipid-polymer hybrid nanoparticles composed of a solid polymer/cationic lipid core and a lipid-PEG shell. The hybrid nanoparticles are small and uniform, can efficiently encapsulate nucleic acids (e.g., siRNA and mRNA) and control their sustained release, and exhibit long blood circulation, high tumor accumulation and minimal *in vivo* side effects. In a recent effort, these nanoparticles have been successfully used for the delivery of PTEN mRNA to *PTEN*-null prostate cancer (PCa) cells *in vitro* and *in vivo*. Results demonstrate that the restoration of PTEN function by mRNA nanoparticles is efficient for inhibiting the growth of *PTEN*-null PCa tumor. In addition, we have generated a targeted sharp pH-responsive and membrane-penetrating polymeric nanoparticle platform for systemic PHB1 siRNA delivery to PCa tumor cells. These nanoparticles show high selectivity to PSMA-expressing PCa cells, efficient PHB1 silencing, and significant inhibition of tumor growth, offering a new potential strategy for PCa therapy.

Conclusions

Nanotechnology has shown promising features for the systemic delivery of siRNA and mRNA. It is expected that our nanoparticle platforms could become a versatile toolkit for both fundamental research and the development of new nucleic acid therapeutics in the PCa field.

Conflict of Interest and Funding Acknowledgements

This work is supported by PCF Young Investigator Award, Movember-PCF Challenge Award, and NIH grants R00CA160350 and CA200900. The author has no conflict of interest.