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Cover story

RNA interference (RNAi), a recently discovered gene silencing process, has considerable potential for the development of a new class of nucleic acid based therapeutics. Synthetic small interfering RNA (siRNA) consisting of 21–23 nucleotide double strand RNA duplexes has shown efficient RNAi-mediated sequence-specific gene suppression with much reduced doses. However, delivery systems for siRNA therapeutics have been recognized as a major hurdle for clinical applications. A variety of cationic lipid and polymer materials have been used for the generation of nano-sized siRNA complexes for facile cellular uptake and gene silencing. More recently, siRNA bioconjugates have been introduced for systemic delivery to treat various diseases including cancer. As several siRNA therapeutic candidates are currently under clinical trials, systemic delivery vehicles with good safety and targeted gene silencing efficiency are highly demanded.

In the article published in this issue by our group [1], vascular endothelial growth factor (VEGF) siRNA was conjugated with poly (ethylene glycol) (PEG), and complexed with a cationic polymer to form core/shell type, stable, nano-sized polyelectrolyte complex (PEC) micelles. In a tumor animal model, we showed impressive anti-tumor effects by inhibiting VEGF expression for both local and systemic administration. The systemically delivered PEC micelles were also accumulated at the tumor site. The *in vivo* results were substantiated by comprehensive biochemical and imaging analysis, demonstrating that siRNA–PEG conjugate complex micelles could have highly promising potentials for systemic siRNA delivery. Previously, cationic lipid and polymers were PEGylated for condensing siRNA to confer superior complex stability in the blood stream. The current study, however, exploited a unique PEGylated siRNA strategy to produce nano-complexes with polyethylenimine (PEI). Many other cationic core-forming species other than cytototoxic lipids and polymers could also be used for the micelle formulation. For instance, less cytotoxic cationic peptides, proteins, micro-emulsion droplets, and even inorganic nano-crystals can be alternatively used without PEGylation for condensing siRNA–PEG conjugates for systemic and local delivery.

Our study [1] proposes a novel formulation of siRNA therapeutics for systemic administration. We expect to see more exciting *in vivo* results for treating other disease models based on the PEG conjugated siRNA in the near future.

Reference

[1] S.H. Kim, J.H. Jeong, S.H. Lee, S.W. Kim, T.G. Park, Local and systemic delivery of VEGF siRNA using polyelectrolyte complex micelles for effective treatment of cancer, J. Control. Release 129 (2008) 107–116, doi:10.1016/j.jconrel.2008.03.008. (this issue).

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