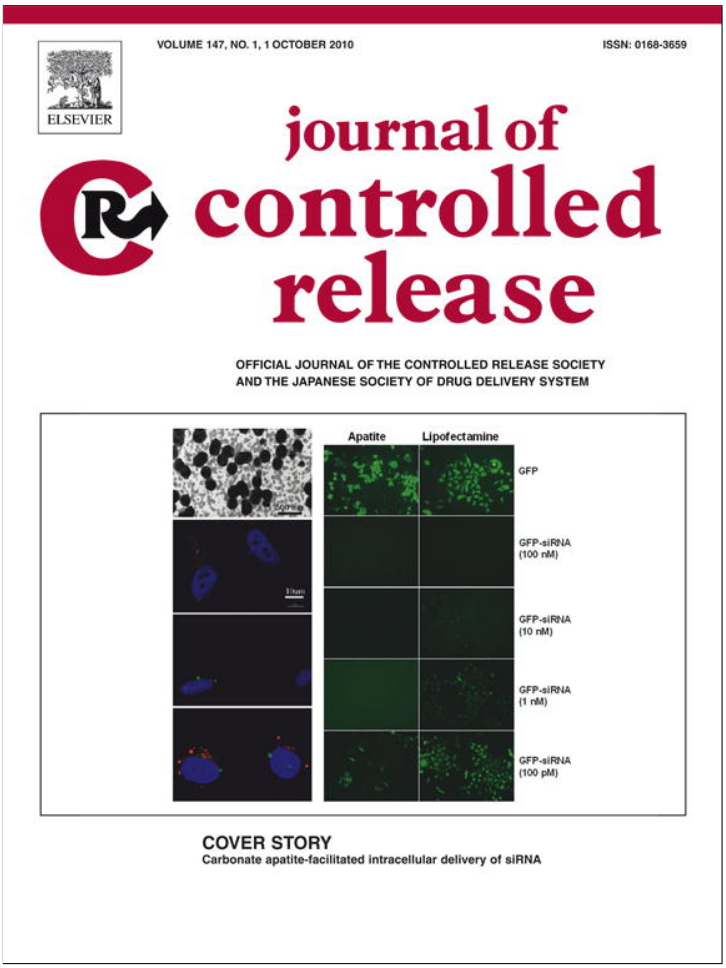

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Cover story

Carbonate apatite-facilitated intracellular delivery of siRNA

Gene therapy through intracellular delivery of a functional gene or a gene-silencing element is a promising approach to treat various critical diseases. Elucidation of the genetic basis of human diseases with complete sequencing of human genome has revealed many vital genes as possible targets in the gene therapy programs. RNA interference is a powerful tool in functional genomics to selectively silence messenger RNA (mRNA) expression, and it can be harnessed to rapidly develop novel drugs against diverse disease targets. The approach of using small interfering RNA (siRNA), however, has been hindered by the lack of suitable delivery systems for systemic and intracellular targeting. Even if siRNA is delivered to the target tissues and cells, the naked siRNA is unable to passively diffuse through cell membranes. Delivery of siRNA into intracellular target sites remains as one of the major hurdles for full exploitation of the potential of the siRNA technology. For this reason, a large number of scientists have been developing efficient siRNA delivery systems for treating a variety of diseases, especially cancer. The major obstacle for siRNA delivery using non-viral delivery systems is degradation of a significant portion of the internalized siRNA by lysosomal nucleases. Thus, the endosomal escape of siRNA is a crucial step in successful gene silencing.

In an article published in this issue of Journal of Controlled Release Professor Toshihiro Akaike and his group report on the development of pH-sensitive carbonate apatite to efficiently deliver siRNA into the mammalian cells [1]. Carbonate apatite has high affinity interactions with siRNA, and the size of the resulting siRNA/apatite complex is highly desirable for effective cellular uptake through endocytosis. Another desirable property of the siRNA/apatite complexes is its ability to release siRNA following cellular internalization. The release of siRNA from the apatite carrier is essential for binding with specific mRNA in the cytoplasm for efficacy. The approach taken by Professor Akaike is to rapidly dissolve the particles in the endosomal acidic pH condition so that the associated siRNA can be released into the cytoplasm. Their study showed that the siRNA/apatite complexes, following endocytosis, were almost completely dissolved in the condition below pH 7.0 very quickly. This might have contributed to the destabilization of endosomes, resulting in the release of siRNA to the cytoplasm. The siRNA/apatite complexes were more effective in silencing reporter genes at relatively lower doses than commercially available Lipofectamine™. Knockdown of cyclin B1 gene with only 10 nM of siRNA delivered by carbonate apatite resulted in the significant death of cancer cells, suggesting that the new method of siRNA delivery reported by Professor Akaike is highly promising.

The difficulty of delivering siRNA into the cytoplasm after endocytosis is not limited to RNA, but it is a common problem for delivering various biomacromolecules, including peptides and proteins. The approach described by Professor Akaike and his group in this issue presents a highly useful alternative to existing methods of cytosolic delivery of biomacromolecules for pre-clinical and clinical cancer therapy as well as vaccine deliveries for HIV and other diseases.

Reference

[1] S. Hossain, A. Stanislaus, M. Jang Chua, S. Tada, Y. Tagawa, E.H. Chowdhury, T. Akaike, Carbonate apatite-facilitated intracellularly delivered siRNA for efficient knockdown of functional genes, J. Control. Release 147 (2010) 101–108.

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