Commentary

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Nucleic acid drugs and DNA-based delivery systems

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Summary **Nucleic acids are biologically active materials, and chemically modified nucleic acids are now being used in nucleic acid drugs. DNA, one of the two types of nucleic acids, can also be used as a material to construct DNA-based delivery systems, such as DNA hydrogel, for therapeutic compounds. Use of chemically modified nucleic acids would greatly increase the therapeutic potency of such DNA-based delivery systems. However, attention should be paid to the differences in the physicochemical properties of natural and chemically modified nucleic acids. Another, more important concern for chemically modified nucleic acids is the high cost of their synthesis. Reducing the cost of synthesizing oligonucleotides, and especially ones with chemically modified nucleic acids, is crucial to the expanded use of both nucleic acid drugs and DNA-based delivery systems.**

Keywords: Nucleic acid drug, DNA-based delivery system

Amplification of specific sequences of DNA is now widely performed in many laboratories all over the world. This polymerase chain reaction process requires pairs of primers, which are short DNA or oligodeoxynucleotides (ODNs). Therefore, huge amounts of ODNs are being commercially synthesized and used every single day. This large-scale synthesis of ODNs has greatly reduced the cost of this process. The cost of ODNs depends on oligo companies, but the most inexpensive ones are about ¥1,000 Japanese yen (about $10 US dollar) for each milligram of ODN of about 90 nucleotides or shorter. Oligoribonucleotides and oligonucleotides with chemical modifications are generally much more expensive than natural phosphodiester ODNs. The process of purifying oligonucleotides increases their quality but also their cost.

Nucleic acid drugs, including antisense oligonucleotides, aptamer, small interfering RNA, and immunomodulatory oligonucleotides, have attracted considerable attention over the past years. There are only a few clinically approved nucleic acid drugs worldwide, but numerous candidates are being developed. Mipomersen, an antisense oligonucleotide targeting human apolipoprotein B100 mRNA, is a 20-mer oligonucleotide (*1*). It is one of the "second-generation" antisense oligonucleotides, in which the nucleotides are linked with phosphorothioate linkages, and the sugar parts of the both ends are 2'-O-methoxyethyl-modified ribose. These chemical modifications are necessary for nucleic acid drugs because degradation by enzymes precludes them from displaying pharmacological activity *in vivo*. A pioneer study that systemically administered antisense oligonucleotides to mice found that ODNs with a few modifications were very quickly degraded and eliminated from the circulation (*2*). Chemical modification, however, will also significantly alter the physicochemical properties of nucleic acid drugs. A typical example of such alterations is the high protein binding capacity of phosphorothioate oligonucleotides, which greatly regulates their plasma protein binding and tissue distribution (*3*). Therefore, oligonucleotides with specific chemical modifications may have identical base sequences but they do, in fact, differ from one another.

The current authors have developed self-gelatinizable nucleic acid technology (*4*), by which injectable DNA hydrogels are obtained using two or more ODNs in a very simple process. This DNA hydrogel is a promising

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DNA-based delivery system for bioactive compounds. The current authors have shown that DNA hydrogel is useful for sustained delivery of doxorubicin (an anticancer agent), peptides, and proteins (*5,6*). The physicochemical and biological properties of this DNA hydrogel can be modulated through the use of chemically modified nucleotides, which would greatly increase its therapeutic potency and, inevitably, the cost of its synthesis. Therefore, reducing the cost of synthesizing oligonucleotides is crucial to the development and expanded use of both nucleic acid drugs and DNA-based delivery systems, such as DNA hydrogel.

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