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Control of Intracellular Delivery of Oligonucleotides by Conjugation with Signal Peptides

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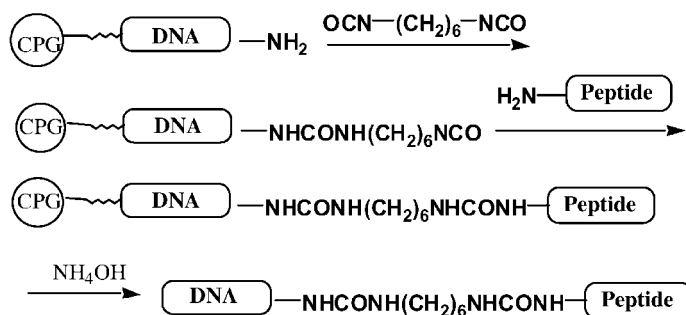
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INTRODUCTION

It has been shown that intracellular localization of proteins are controlled by the interaction between signal domains in proteins to transport and proteins to be transported.^[1] Taira and his colleagues have reported that efficiency of ribozymes largely depended on the intracellular localization of it.^[2] In the present paper, rational control of intracellular delivery and localization of oligonucleotides by oligonucleotide-signal peptide conjugates was studied.

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Scheme 1. Synthesis of DNA-peptide conjugates by solid phase fragment condensation (SPFC).

RESULTS AND DISCUSSIONS

Conjugation of oligonucleotides and a variety of signal peptides was successfully achieved by solid phase fragment condensation (SPFC) and chemical and biological properties of the conjugates were characterized.^[3] (Sch. 1).

As a consequence, cellular uptake was largely accelerated by conjugation with lipophilic peptides derived from membrane fusion domain of proteins or designed amphipathic peptides with cationic character. Oligonucleotide conjugates with nuclear localizing signal (NLS) peptides were successfully delivered into nucleus but have insufficient membrane permeability. Improvement was accomplished by the combination of fusion peptides and NLSs. It is to be noted that oligonucleotides conjugated with both of them have been effectively taken up into cytoplasm and also

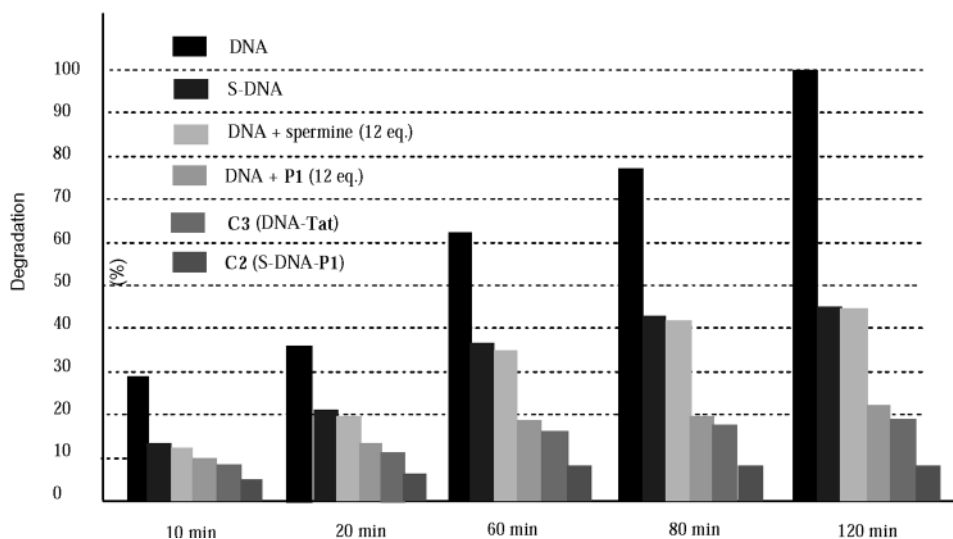


Figure 1. Production of DNA from DNase 1 digestion by amphiphilic peptides.

delivered into nucleus. On the other hand, localization of oligonucleotides in cytoplasm was also successfully established by conjugation with fusion peptides and nuclear export signal (NES) peptides. Additional effects of conjugation of oligonucleotides with a variety of peptides were that oligonucleotides have increased stability against nuclease digestion (Fig. 1) and that complimentary hybrid duplexes of RNA-DNA conjugate and hybrid triplexes of dsDNA-DNA conjugate were formed with a higher affinity than those which consist of native oligonucleotides.

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