Bio

New molecular technologies for stabilization and activation of nucleic acid drugs

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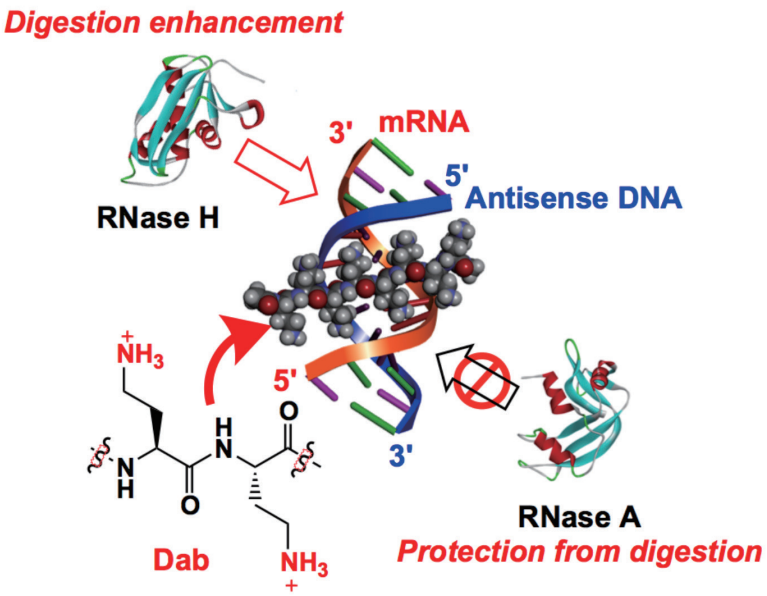
Purpose of Research

Recently, there has been an increase in the research and development of nucleic acid drugs such as antisense nucleic acid, ribonucleic acid interference (RNAi) medicine, and aptamers. Problems that must be solved before nucleic acid drugs can be put into actual use include improvement in the in vivo stability of nucleic acid molecules and the establishment of a delivery technology. As one methodology to solve these problems, this research focuses on the development of artificial cationic molecules that specifically bind to nucleic acid drugs with double-stranded nucleic acid, such as short interfering RNA (siRNA) and deoxyribonucleic acid (DNA)/RNA heteroduplex oligonucleotide (HDO), and not only protect these molecules from degradation enzymes in vivo but also improve the physiological activity itself.

Summary of Research



Novel artificial cationic oligosaccharide and artificial cationic peptide

Points

- Binds to double-stranded nucleic acid drugs and significantly improved thermodynamic stability and nuclease resistance of the double strand
- Improves activity of RNase H, which digests target mRNA

Conventionally, cationic carrier molecules used as drug delivery systems (DDS) for nucleic acid drugs require excessive administration. The ratio between the number of cationic functional groups and the number of anionic functional groups in a complex is expressed as the N/P ratio, but normally, an N/P of 2 or above is required to ensure sufficient in vivo stability of nucleic acids. We are developing molecules that specifically recognize and strongly bind to nucleic acid molecules with a defined higher-order structure in this research. In particular, anticipating application to double-stranded nucleic acid drugs such as siRNA and DNA/RNA heteroduplex oligonucleotide and we developed artificial cationic molecules (artificial cationic oligosaccharides and artificial cationic peptides) that recognize the specific higher-order structure of such double-stranded nucleic acids and specifically bind to them.

It was found that cationic peptides that recognize defined structures of double-stranded nucleic acids and selectively bind to them can selectively inhibit the activity of nucleic acid-degrading enzymes such as RNase A, and conversely, have the ability to improve specific nuclease activity such as RNase H. Using the cationic peptides developed in this research, it is anticipated that an effective methodology for the stabilization and high activity of nucleic acid drugs can be developed.

Future Developments

Nuclease resistance, RNase H activity, intracellular introducing efficiency, and the gene-expression suppression effect of artificial cationic molecule and double-stranded nucleic acid drug complexes have been evaluated in vitro.

In the future, we plan to conduct in vivo functionality evaluation, synthesize conjugates with ligand molecules, and evaluate organ-specific delivery and gene-expression inhibition.

■ Associated System: JST-CREST
Establishment of Molecular Technology towards the Creation of New Functions

*This research is in collaboration with Professor Takanori Yokota at Tokyo Medical and Dental University