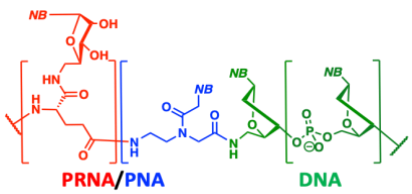
触媒的標的 RNA 切断機能を有する新規人工核酸の開発
－ 癌治療を志向したキメラ人工核酸の合成と機能評価 －

（東北大多元研 [1]・長崎大薬 [2]・東京医科歯科大学 [3]）○矢野 輝 [1]・稲垣 雅仁 [1]・山本 剛史 [2]・西嶋 政樹 [1]・荒木 保幸 [1]・山吉 麻子 [2]・石橋 哲 [3]・横田 隆徳 [3]・和田 健彦 [1]
Studies on Synthesis and Property of Chimeric Artificial Nucleic Acid Conjugated with DNA for Catalytic Target RNA Cleavage ([1]Institute of Multidisciplinary Research for Advanced Materials, Tohoku University, [2]Department of Chemistry of Biofunctional Molecules, School of Pharmaceutical Sciences, Nagasaki University, [3]Department of Neurology and Neurological Science, Tokyo Medical and Dental University) ○Akira Yano,[1] Masahito Inagaki,[1] Tsuyoshi Yamamoto,[2] Masaki Nishijima,[1] Yasuyuki Araki,[1] Asako Yamayoshi,[2] Satoru Ishibashi,[3] Takanori Yokota,[3] Takehiko Wada,[1]

Oligonucleotide therapeutics have been attracting attention as next-generation molecularly targeted drugs, but there is a need to improve the issues of low therapeutic effect mostly originated by extremely low intracellular concentrations of the compounds. In this study, we designed artificial nucleic acid for targeting Vasohibin 2, which mainly appeared in the cancer cell and contributed to angiogenesis. We have proposed and demonstrated the improved target RNA cleavage efficiency by the chimeric artificial nucleic acids consisted of PNA/PRNA conjugated with DNA with RNase H. In the strategy, we focused on the thermal stabilities of the hybrids before and after RNA cleavage. To improve the catalytic cleavage efficiency, drastic stability change of the hybrid down to physiological temperature after RNA cleaved should be a key factor, due to promoting the rapid dissociation of the RNA cleaved hybrid from RNase H complex. For this purpose, we have proposed the position selective cleavage of the target RNA by a non-sequence selective endonuclease, RNase H with the chimeric artificial nucleic acids. To realize the issue, we designed and synthesized the chimeric artificial nucleic acid, which consisted of DNA moiety to bind the positive channel of RNase H conjugated with PNA/PRNA moiety for improving the stability of the hybrid with the target RNA. In the presentation, we'll report the demonstration of the target RNA cleavage efficiency with UV/CD melting experimental and gel electrophoresis studies.
Keywords : Artificial Nucleic Acid, Catalytic Oligonucleotide Therapeutics, RNase H

現在注目されている核酸医薬は、細胞内極低濃度に起因する低治療力価問題さえ改善できれば、幅広い疾患への適用が期待されている。本研究では、主に癌細胞に発現し、血管新生に関与する Vasohibin 2[1)]を標的としたキメラ人工核酸を設計・合成し、治療力価向上に資する RNase H による標的 RNA の高効率触媒的切断を検討した。RNase H による標的 RNA の高効率切断を実現する為、切断後の DNA/RNA 複合体の迅速な解離を誘起し得る位置での RNase H による RNA 選択切断を発案した。標的 RNA の位置選択切断には、RNase H の塩基性チャネル [2)]への選択的結合可能な負電荷骨格 DNA と、電荷を有しないアミド骨格 PNA/PRNA[3)]を融合したキメラ人工核酸が有効であると仮説し、設計・合成、特性解析に取り組んだ。発表では、同配列を有する天然型 DNA、チオエステル修飾 S-oligo との機能比較も併せて発表する。



1) Sato, Y., *J. Biochem.* **2013**, *153*, 1, 5. 2) Yang, W. *et. al., Mol. Cell* **2007**, *28*, 2, 264. 3) Wada, T. *et al. J. Am. Chem. Soc.* **2000**, *122*, 29, 6900. (Selected reference)