糖部 2',5'-デュアル修飾型ヌクレオチドを含むオリゴヌクレオチドの合成と機能評価

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Synthesis and characterization of oligonucleotide containing 2', 5'-dual modified nucleosides.

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The use of chemically modified artificial nucleic acids is one of the most effective tools for the practical use of nucleic acid drugs. In our laboratory, modified nucleic acids with aminoalkyl groups introduced at the 4',5'-positions of the sugar moiety were synthesized in combination with 2'-OMe modification, both of which have extremely high nuclease resistance compared to natural oligonucleotides. In addition, the 5'-functional group has less steric hindrance with the 2'-functional group compared with the combination of the 4'- and 2'-modifications. The later one has a higher binding affinity with the complementary RNA strand and show strong nuclease resistance. Therefore, in this study, we newly synthesized 2'-MOE (methoxyethyl), which is expected to have higher affinity for RNA and nuclease resistance than 2'-OMe modification, and 2'-OAE (aminoethyl) modification, which is expected to have cell membrane permeability due to positive charge, combination with the 5'-aminopropyl modification, and evaluated their properties.

Keywords : anitisense, oligonucleotide therapeutics, aminoalkyl,

核酸医薬の実用化に向けて、化学修飾された人工核酸の利用は最も有効な手段の一つである。当研究室では糖部 4',5'位のアミノアルキル基修飾と組み合わせて 2'-OMe 修飾を導入した修飾核酸を合成し、いずれも天然のオリゴヌクレオチドと比較して非常に高いヌクレアーゼ耐性を有することを明らかにしている [1]。また、4'位修飾と 2'位修飾を組み合わせた場合と比較して、5'位の修飾基は 2'位の修飾基との立体的な反発が小さく、高い相補 RNA 鎖との結合親和性、ヌクレアーゼ耐性を示すことを見出してきた [1]。そこで本研究では 2'位の修飾基として、2'-OMe 修飾よりも高い RNA 親和性、ヌクレアーゼ耐性が期待される 2'-MOE (メトキシエチル)、正電荷による細胞膜透過性が期待される 2'-OAE (アミノエチル) 修飾を 5'位アミノプロピル修飾と組み合わせた人工核酸 (Fig. 1) を合成し、その性質評価を行った。

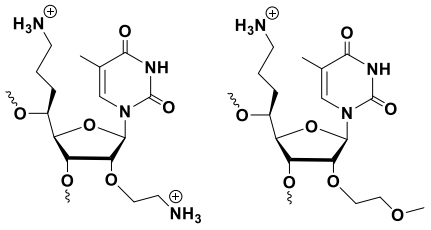

Fig. 1. Structure of 5′-aminoalkyl-modified-nucleosides.

(1) R. Kajino, Y. Ueno, *et. al, J. Org. Chem.* 2019, 84, 6, 3388–3404.