Improvement of inhibitory activity of SNA-based anti-miRNA-21 by introduction of pseudocomplementary bases

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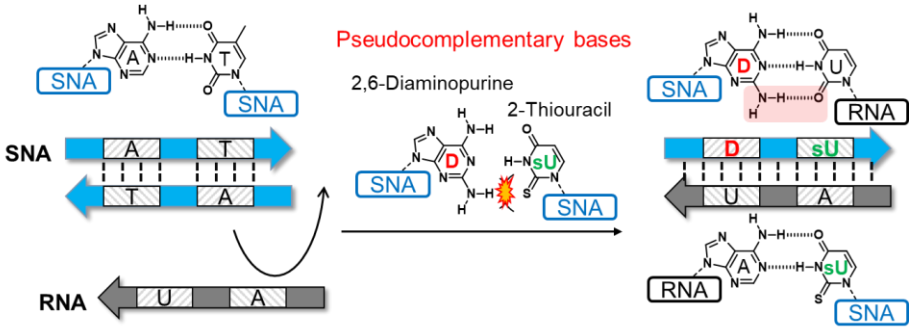
Artificial nucleic acids that have high nuclease resistance and affinity to natural oligonucleotides are promising for use in nucleic acid drugs. We have developed an acyclic artificial nucleic acid, SNA that can stably hybridize with natural oligonucleotides and have remarkably high nuclease resistance. Using SNA we have attempted to develop anti-miRNA oligonucleotides (SNA-AMOs) for inhibition of disease-related miRNA. Previously we reported improvement of the antisense activity of SNA-AMO against miR-21 by replacing of adenines with 2,6-diaminopurines (D).[2] However we also found that multiple introductions of D promote self-association of SNA-AMO, resulting in reduction of its anti-miRNA activity. To solve this issue, we focused on D and 2-thiouracil (sU) known as "Pseudocomplementary bases".[3] The sulfur atom on sU causes steric hindrance that prevents pairing with D, whereas D can recognize uracil much stronger than adenine through three hydrogen bonds. Therefore, we introduced multiple sU residues at the base-pairing position of D residue in the complementary region of SNA-AMO. We conducted T_m measurements and Native-PAGE analyses to investigate effect of D-sU incorporations into SNA-AMOs on SNA-SNA or SNA-RNA interactions. We succeeded in decrease of SNA-SNA interaction and increase of affinity to miR-21 simultaneously upon substitution with D-sU pairs. Significant improvement of the antisense activity against miR-21 by introducing of D-sU pairs into SNA-AMO was also clearly demonstrated.



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