Synthesis and cross-link properties of 2-amino-6-vinyl-7-deazapurine-deoxyriboside for anti-miRNA therapy

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MicroRNAs (miRNAs) endogenously regulate gene expression through RNA interference process. Inhibition of miRNAs using anti-miRNA oligonucleotides (AMOs) have gained attention for treatment of diseases associated with aberrant expression of certain miRNAs. To enhance anti-miRNA effect using AMOs, we have been developing cross-linkable 2-amino-6-vinylpurine (AVP) nucleosides. The AMOs incorporating AVP derivatives were expected to induce stronger inhibition of the miRNA function through covalent bond formation.[1]

Recently, we have designed a cross-link forming oligonucleotide (CFO) consisted of 2'-OMe-RNA strand incorporating 2-amino-7-deaza-7-propynyl-6-vinylpurine-riboside, ADpVP (Fig. 1a).[2] The propynyl group at the 7-position significantly enhanced the kinetics of the cross-link formation toward uridine by orienting the 6-vinyl group into the s-*cis* conformation. Despite its promising cross-linking ability, the synthesis of ADpVP proved to be an arduous process. To overcome this hurdle, in this study, we designed deoxyribo-type of ADpVP termed dADpVP (Fig. 1a), which can be simply synthesized. We expected that the change of sugar moiety at a single site of 2'-OMe CFO would not affect the cross-linking efficiency. The phosphoramidite of vinyl-protected dADpVP was chemically synthesized and incorporated into 2'-OMe CFO using an automated DNA synthesizer. The cross-linking reaction was conducted using the FAM-labeled complementary RNA strand, and the reactions were analyzed by denaturing PAGE. We found that dADpVP exhibited the uridine selective cross-link formation with a comparable reaction rate to the previously reported ADpVP (Fig. 1b). The details of the synthesis and cross-link reactions will be reported in the presentation.

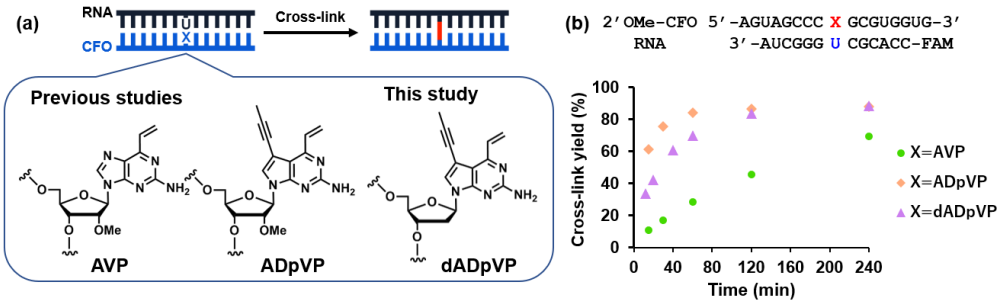

Fig. 1 (a) Structures of cross-linking AVP derivatives. (b) The cross-link properties of each AVP derivative.

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