Systematic DNA aptamer design with amino acid-nucleic acid hybrids (ANHs) for thrombin inhibition

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Chemical modifications on innate DNA/RNA aptamers can significantly improve their functions. Previously, we have established a systematic modular strategy to incorporate amino acid residue into DNA oligonucleotides via an acyclic D-threoninol backbone for chemical modification of oligonucleotides.1,2 Herein, we introduce our modular strategy using amino acid-nucleic acid hybrids (ANHs) to modify a thrombin binding DNA aptamer to increase its inhibitory activity and binding affinity. (Figure 1) We chose a structurally and functionally well-defined TBA sequence (TBA15) as the basis for developing ANH-based TBA sets. A variety of ANH building blocks were incorporated instead of thymines on the loop through solid-phase DNA synthesis. All devised TBAs form antiparallel G-quadruplex structures regardless of incorporated amino acid residue. ANH-aptamers with amino acids (Phe, Met, and Trp) to replace T3 of loop region (T3F) afforded remarkably enhanced thrombin inhibition property, involving hydrophobic interaction of amino acid of modified TBA to binding site in thrombin. Moreover, surface plasmon resonance assay and molecular modeling results supports the significant difference in anticoagulation activity.

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Figure 1. ANHs-modified TBA15 library and the evaluation of TB inhibition