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A DNA aptamer targeting the PA endonuclease domain provided cross-protection against infections of different subtypes of influenza A virus

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Amino acid residues in the N-terminal of the PA subunit (PA_N) of the Influenza A polymerase play critical roles in endonuclease activity, protein stability and vRNA promoter binding. In addition, PA_N is highly conserved among different subtypes of the influenza virus, which suggests PA_N to be a desirable target for the development of anti-influenza agents. We selected DNA aptamers targeting the intact PA protein or the PA_N domain of an H5N1 virus strain using systematic evolution of ligands by exponential enrichment (SELEX). Binding affinities of selected aptamers were measured, followed by evaluation of in vitro endonuclease inhibitory activity. Next, antiviral effects of enriched aptamers against influenza A virus infections were further examined. A total of three aptamers targeting PA and six aptamers targeting PA_N were selected. Our data demonstrated that all three PA-selected aptamers neither inhibited endonuclease activity nor exhibited antiviral efficacy, whereas four of the six PA_N-selected aptamers inhibited both endonuclease activity and H5N1 virus infection. These results suggested that PA_N functional domain might be a better target than the intact PA protein for the screening of antiviral agents. Among the four effective aptamers, one exhibited cross-protection against infections of H1N1, H5N1, H7N7 and H7N9 influenza viruses with 50% inhibitory concentration (IC50) around 10 nM. Notably, this aptamer was identified at the 5th round but disappeared after the 10th round of the selection, suggesting that the identification and evaluation of aptamers at early rounds of the selection may be highly helpful for screening effective aptamers. Overall, our study provides novel insights for screening and developing effective aptamers as anti-influenza drugs.

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