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Computational approach to design of aptamers to the receptor binding domain of SARS-CoV-2

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The aim of the research. In this work, in silico selection of DNA-aptamers to the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein was performed using molecular modeling methods.

Material and methods. A new computational approach to aptamer in silico selection is based on a cycle of simulations, including the stages of molecular modeling, molecular docking, molecular dynamic simulations, and quantum chemical calculations. To verify the obtained calculated results flow cytometry, fluorescence polarization, and small-angle X-ray scattering methods were applied.

Results. An initial library consisted of 256 16-mer oligonucleotides was modeled. Based on molecular docking results, the only one aptamer (Apt16) was selected from the library as a starting aptamer to the RBD protein. For Apt16/RBD complex, molecular dynamic and quantum chemical calculations revealed the pairs of nucleotides and amino acids whose contribution to the binding between aptamer and RBD is the largest. Taking into account these data, Apt16 was subjected to the structure modifications in order to increase the binding with the RBD. Thus, a new aptamer Apt25 was designed. The procedure of 1) aptamer structure modeling/modification, 2) molecular docking, 3) molecular dynamic simulations, 4) quantum chemical calculations was performed several times. As a result, four aptamers (Apt16, Apt25, Apt27, Apt31) to the RBD were designed in silico without any preliminary experimental data. Binding of the each modeled aptamer to the RBD was studied in terms of interactions between residues in protein and nucleotides in the aptamers. Based on the simulation results, the strongest binding with the RBD was predicted for two Apt27 and Apt31aptamers. The calculated results are in good agreement with experimental data obtained by flow cytometry, fluorescence polarization, and small-angle X-ray scattering methods.

Conclusion. The proposed computational approach to selection and refinement of aptamers is universal and can be used for wide range of molecular ligands and targets.

Key words: selection, aptamer, receptor-binding domain, SARS-CoV-2.

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest associated with the publication of this article.

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Selection of DNA-aptamers to the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein was performed using a novel approach based on the computational molecular modeling. At first stage of *in silico* aptamer selection, the initial library of the aptamer candidates was designed. A 16-mer hairpin loop was chosen as the starting structure of the aptamer. The double helix 5'-GGAATT-loop-AATTCC-3' was proposed as the constant stem part of the aptamers. The variable loop part was formed by four "NNNN" nucleotides. Taking into account all possible combinations of the DNA nucleotides, 256 structures was obtained as initial aptamer library.

At second stage, the molecular docking for all 256 models was performed using HDOCK webserver [1]. As a potential binding site, the concave upper region of the RBD protein was considered. Based on docking results, the aptamer candidate, which was predicted to bind with the upper part of the RBD, was selected. That 16mer with AGTC nucleotides in the loop part (Apt16) was chosen as the starting sequence for further structure modifications

in order to improve the binding affinity to the RBD. Next, the Apt16/RBD complex was subjected to the detailed analysis using molecular dynamic (MD) and quantum chemical simulations. MD simulations were conducted by using GROMACS 2019.8 software [2]. After MD the Apt16/RBD complex structure was optimized with FMO-DFTB/PCM [3, 4]. For the optimized structures, FMO fragmentation approach was used to obtain the interaction energies, which were evaluated with non-empirical RI-MP2/6-31G (d,p) method [5]. The total interaction energy E_{total} between RBD and aptamer (Table) and the partial contribution to the binding energy from single nucleotide in the aptamer were estimated using these computational methods.

Table

Total interaction energy E_{total} (kcal mol^{-1}) and the number of hydrogen bonds N_{HB} between aptamers and RBD

Aptamer*	N_{HB}	E_{total}	Aptamer*	N_{HB}	E_{total}
Apt16	12	-153.0	Apt27	17	-217.4
Apt25	12	-162.7	Apt31	13	-221.6

Based on the obtained calculated results, the structure of the Apt16 was modified in order to improve the affinity and specificity of the aptamer binding to the RBD protein. Thus, a new aptamer Apt25 5'-CCTAG-GAATT-TGTCT-AATTCCTAGG-3' was modeled. The same computational simulations described above for Apt16 was performed for Apt25. Comparison of the calculation results for RBD/Apt16 and RBD/Apt25 complexes confirmed that the aptamer structure modifications improve binding. The *in silico* selection scheme, which include aptamer structure modeling (modification), molecular docking, MD, and quantum chemical calculations, was applied a several times. As a result, two new aptamers were created: Apt27 5'-CGGATGGAAT-TTG TCTG-AT-TCCATCCG-3' and Apt31 5'-CGGATGGAAT-ACTT TGTC TGTC-ATTCCATCCG -3'. The results of simulations for all aptamers, Apt16, Apt25, Apt27, and Apt31, are shown in Table 1. The binding of the theoretically modeled aptamers to the RBD protein was confirmed experimentally by flow cytometry, fluorescence polarization, and small-angle X-ray scattering methods. The proposed scheme of *in silico* aptamer selection can be applied to a wide range of ligands and protein targets.

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