Influence of nucleotide sequence on conformational flexibility of the RNA dangling ends in the complexes with DNA: molecular dynamics studies

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Development of the approaches for directed regulation of intracellular and extracellular processes is an actual task of molecular biology, biochemistry and fundamental medicine. In February 2017, WHO published a list of bacteria that pose a special threat for humanity. They are multidrug-resistant to various antibiotics, including carbapenems and third-generation cephalosporins. Thus, new substances that can effectively suppress these pathogens are required. Existing and approved antibiotics usually are a low-molecular weight compounds, which does not have the proper specificity and selectivity. Thus it affects not only on pathogenic, but also on symbiotic bacteria. The solution of the specify problem can be the usage of the antisense approach in combination with the ability of therapeutic compounds to cleave strictly defined phosphodiester bonds in the chosen target RNA in the catalytic regime. The fact that confirms that this approach is promising is the presence of already approved by FDA U.S. of four therapeutic drugs for antisense therapy based on nucleic acid derivatives. It was proposed to develop block systems containing oligonucleotides (natural, their analogs or derivatives) capable of strictly sequence specific bind to RNA target and peptide-like residues (artificial ribonuclease, aRNase). Such structures will be able to cleave in the catalytic regime strictly determined phosphodiester bonds in the target RNA molecule. These two facts ensure strict specificity of the developing aRNase. There are a number of important points in design of aRNase. One of them is conformational flexibility of the single stranded RNA in complex with DNA. In this work we have analyzed the influence of nucleotide sequence on conformational flexibility of the RNA dangling ends in the complexes with DNA. For this purpose the molecular dynamics methods were used because the application of the experimental techniques is a difficult. We designed complexes with two dangling ends at 3’ and 5’-end of RNA. All ten nearest-neighbour dinucleotide at different positions were analyzed at different temperatures. The probabilities of “in-line” conformation which is necessary for RNA cleavage were determined. First we found what the probabilities of the “in-line” conformation are extremely low at room temperature. Thus at the next stage the temperature replica exchange molecular dynamics simulation (T-REMD) were performed at temperature range 293 - 370 K with temperature step 7 K. Simulations were performed in explicit solvent shell (TIP3P water model, cuboid box d=14 Å). The analysis of the total 600 ns trajectory for each complex shows that the probability of “in-line” conformation is increases at higher temperature. The results analysis shows the statistically significant difference in conformational flexibility of 3’ and 5’-ends. More over the probability of “in-line” conformation strongly depends on the distance from the terminal base pair of DNA/RNA duplex. The ssRNA flexibility is sequence

dependent.

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