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A computational study on the nature of DNA G-quadruplex structure

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Summary

DNA G-quadruplexes are higher-order structures self-assembled from guanine-rich oligonucleotides. These DNA structures are composed of stacked planar G-quartets, a cyclic Hoogsteen hydrogen bonding arrangement of four guanine bases, that are stabilized in the presence of monovalent cations. The identification of G-quadruplex structures in the human genome, particularly telomeres and oncogene-promoter regions offer unique avenues to selectively target these structures for anticancer drug development. In addition, G-quadruplex structures have attracted considerable attention for their regulatory roles in cellular processes including DNA replication, transcription, and translation. Apart from the therapeutics and biology, the unique structure of the G-quadruplex makes it an interesting building blocks for the development of nanodevices. The aim of this thesis is to investigate different aspects of G-quadruplex based systems for these applications with the aid of computational techniques. The details about G-quadruplex applications and theoretical approach are discussed in **Chapter 1** and **Chapter 2**.

Chapter 3 presents the G-quadruplex application in cancer therapy. MD simulations were performed to investigate the binding interactions between quinazolone derivatives as stabilizing ligands and G-quadruplex in the oncogenic promoter region like c-KIT. The results revealed that the arrangement of amido bond in quinazolone derivatives improves binding affinity toward G-quadruplex and the terminal amino substituents play a crucial role in hydrogen bond formation and electrostatic interactions with the phosphate backbone of the G-quadruplex. We also proposed a new derivative of quinazolone with a terminal amino substituent instead of a 3-phenyl group, which stabilizes the c-KIT G-quadruplex much better than other derivatives.

Chapter 4, following the results obtained from MD simulations of G-quadruplex-quinazolone complexes, we provide detailed insight into the nature of interactions between other quinazolone derivatives and c-KIT G-quadruplex. We demonstrate that the key interactions in G-quadruplex-ligand complexes are $\pi - \pi$ stacking and hydrogen bond interactions. However, neither of these two interactions alone determines the stability of the G-quadruplex-ligand complexes; rather, it is the result of an intricate interplay between the two. In addition, a free energy decomposition analysis at the residue level demon-

strated the crucial roles of two hot spot residues for the binding of ligands to G-quadruplex and highlighted the importance of the planar aromatic moiety of ligands in G-quadruplex stabilization via $\pi - \pi$ stacking interactions.

Chapter 5, present the application of G-quadruplex in nanodevices. We carried out a series of simulations to investigate the effect of the size and substitution pattern of three azobenzene derivatives on the photoisomerization mechanism as well as their spectroscopic properties within the smallest G-quadruplex structure. We demonstrated that the size and the substitution pattern do not affect significantly the cis-trans photoisomerization mechanism of the azobenzene derivatives in the gas phase. In addition, molecular dynamics simulations revealed that the G-quadruplex with para-para substitution pattern undergoes larger structural changes compared to the other two which can facilitate photoisomerzation reaction between a stacked G-quadruplex and an unstructured state after trans-cis isomerization occurring in a longer time dynamic, in agreement with the experimental finding. Finally, the QM/MM simulations of the absorption spectra indicated that the thermal fluctuation plays a more crucial role on the main absorption band of the azobenzene derivatives than the inclusion of the G-quadruplex, implying that the influence of the G-quadruplex environment is minimal. We propose that the latter is attributed to the position of the azobenzene linkers in the G-quadruplexes, i.e. the edgewise loops containing the azobenzene moieties that are located above the G-quartets, not being fully embedded inside or involved in the stacked structure.

Lastly, in **Chapter 6**, we performed a series of simulations using different force fields to investigate the binding interactions between RHAU proteins and two different G-quadruplex structures. Our results from atomistic and Martini 2.2 simulations showed the conformational variations of the G-quadruplex loop during RHAU binding at the 5′-end side of the parallel G-quadruplex. However, in Martini 3.0 simulation, we observed that RHAU20 is able to bind onto both 5′- and 3′-end sites of the G-quadruplex. In addition, Martini 3.0 simulations for nonparallel G-quadruplex and RHAU20 revealed that there is no preferred recognition site in the G-quadruplex for RHAU20 which is consistent with experimental data. The simulation performed with Martini 3.0 for parallel G-quadruplex-RHAU20M complex showed that there are some close residual contacts between RHAU20M and G-quadruplex, indicating the electrostatic interactions between positively charged residues and the phosphate backbone of the G-quadruplex which is inline with experimental findings. Consequently, the results obtained from the Martini simulations should be interpreted with great care and further optimizations are needed.