Structure, Dynamics and Stability of Pure and Chemically Modified Nucleic acids Studied via Molecular Dynamics Simulations

by

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in

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Introduction

- Chemical modifications in nucleic acids play a prominent role in gene therapy.
- Because of the poor stability and low resistance to nuclease cleavage of pure DNA and RNA strands, a suitable chemical modification is required to stabilize against nucleases.
- The modified nucleic acids (AOs) will block the passage of genetic information at translation level by forming stable nucleic acid duplex with mRNA.

The AOs are susceptible to RNase H activity which cleaves the RNA strands in the heterogeneous duplexes.

These novel molecules have been shown to be potential therapeutic agents in antisense therapy.

Objective

- To understand the structure-function relationship and the impact of chemical modifications on the structure, dynamics and stability of DNA-RNA hybrids.

Computational details

- Explicit MD simulations were performed using CHARMM27 and CHARMM36 all atom nucleic acid force fields with CHARMM and NAMD simulation packages at various time scales and using different computational techniques such as traditional and replica exchange molecular dynamics simulations.
- Initial structures were collected from PDB or modeled with SYBYL software from ideal A and B duplexes.
- Neutralization and minimization of all these structures were done in TIP3P water box.
- All the simulations were done in NPT ensemble at room temperature and 1 atm pressure.
- The REMD simulations were performed on nucleosides of five bases with modifications using 12 replicas in the temperature range 300-360K in an exponential scale.

Conclusions

- The hybrid properties mainly depend on their deoxyribose content and ATGC ratio.
- The inability of RNase H enzyme to cleave the DNA-RNA hybrid with 100% dPy content mainly due to it's close behavior with pure RNA duplex.
- The introduced LNA modifications slowly turn the hybrid conformation towards ideal A-form and this effect highly depend on the number, position and gap between modifications.
- The LNA duplexes have different helical conformation than ideal A and B-forms with elongated pitch and small twist angles.

Chemically Modified Nucleic acid duplexes

References

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