**Effects of the Structure of Lipid-based Agents in their Complexation with a Single Stranded mRNA fragment: a Computational Study**

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**ABSTRACT**

Complexation of a lipid-based ionizable cationic molecule (referred to as DML) with RNA in an aqueous media, was examined in detail by means of fully atomistic molecular dynamics simulations.1 The different stages of the DML-RNA association process were explored, while the structural characteristics of the final complex were described. The self-assembly process of the DML molecules was examined in the absence and in the presence of nucleotide sequences of different length. The formed DML clusters were described in detail in terms of their size and composition and were found to share common features in all the examined systems. Different timescales related to their self-assembly and their association with RNA were identified. It was found that beyond a time period of a few tens of ns, a conformationally stable DML-RNA complex was formed, characterized by DML clusters covering the entire contour of RNA. In a system with a 642-nucleotide sequence, the average size of the complex in the longest dimension was found to be close to 40nm. The DML clusters were characterized by a rather low surface charge, while a propensity for the formation of larger in size clusters close to RNA, was noted. Apart from hydrophobic and electrostatic interactions, hydrogen bonding was found to play a key-role in the DML-DML and in the DML-RNA association.

In the following we examined two groups of lipid-based complexation agents, differing in the degree of hydrophobicity and in the overall charge.2 The first group was comprised of cationic ionizable agents while the second included electrically neutral amphoteric phosphatidylcholine lipids. It was found that the overall charge of the complexation agents played the most decisive role in the energetics of the lipid/RNA association, while their degree of hydrophobicity affected their self-assembly and their complexation kinetics.

The information obtained regarding the structural features of the final complex, the timescales and the driving forces associated with the complexation and the self-assembly processes, provide new insight towards a rational design of optimized lipid-based ionizable cationic gene delivery vectors.

**KEYWORDS:** RNA; lipid-based complexation agents; self-assembly; Molecular Dynamics Simulations

**REFERENCES**

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