BINDING DYNAMICS OF SIRNA WITH SELECTED LIPOPEPTIDES: A COMPUTER-AIDED STUDY OF THE EFFECT OF LIPOPEPTIDES' FUNCTIONAL GROUPS AND STEREOISOMERISM

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ABSTRACT

We present recently published results [1] on modeling lipopeptide molecules binding small fragments of genetic material, i.e. small interfering RNA molecules (siRNA), aiming at the elucidation of structure-function relationships of potent nanoparticle platforms for the delivery of genetic material in cells. The engineering issues pertaining to nanoparticle systems toward targeted gene therapies and the development of gene vaccines have not been fully probed. Recent experiments have identified specific structural characteristics of a novel class of lipopeptides (LP) that may lead to potent nanocarriers intended as RNAi therapeutics, albeit the molecular mechanism that underlies their performance remains unexplored. For this, we conducted molecular dynamics simulations coupled with free energy computations to study the dynamics and thermodynamics of an acrylate- and an epoxide-derived LP, members of the aforesaid class, upon their binding to siRNA in aqueous solution aiming at examining structure-potency relations. We found that the entropic part of the free energy of binding predominates; moreover, the first LP class tends to disrupt the Watson−Crick base pairing of siRNA, whereas the latter leaves the double helix intact. Yet, the identified tug-of-war effect between LP−water and LP−siRNA hydrogen bonding in the supramolecular complex can underpin synthesis routes toward tuning the association dynamics. Our simulations on two diastereomers of the epoxide-derived LP showed significant structural and energetics differences upon binding, as a result of steric effects imposed by the different absolute configurations at their chiral centers. These findings may serve as crucial design parameters toward modulating the interplay between complex stability and ease of releasing the nucleic acid drug into the cell.

KEYWORDS: gene therapy, gene vaccines, nanoparticles, lipopeptides, computer simulation

REFERENCES

[1] Pantatosaki, E., Papadopoulos, G. K. (2020). *J. Chem. Theory Comput.* 16 (6): 3842−3855.