In silico study of peptidic dendrimers as transfection agents in DNA/RNA vaccines

Filipe E. P. Rodrigues[1], Tamis Darbre[2], Miguel Machuqueiro[1]
[1]*BioISI: Biosystems and Integrative Sciences Institute,*
Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal
[2]*Department of Chemistry, Biochemistry and Pharmacy, Bern University, 3012 Bern, Switzerland*
email: ferodrigues@ciencias.ulisboa.pt

Peptide dendrimers are compounds related to dendrimers by virtue of their branched and polymeric structure, and to peptides and proteins because only amino acids are present in the dendrimer branches. In the past years peptide dendrimers with two or three amino acids in the branches have been reported to interact with biological molecules and cell membranes leading to good activity as antimicrobial agents, pathogenic biofilm inhibitors and superior vectors for DNA, siRNA and small oligonucleotides [1].

Recently, the use of such structures as vector molecules for mRNA and siRNA vaccines has been explored [2] , which resulted in some promising peptidic dendrimers, namely MH13 and MH18, which are solely constituted by lysines and leucines, and contain two palmitoyl chains or a leucine tetrapeptide as hydrophobic cores, respectively. Furthermore, some mutations in MH18 from *L*- to *D*-amino acids, results in improved transfection and delivery efficiencies, as well as improved resistance to proteolytic degradation [2]. Despite these promising results in penetrating the target cells, being resistant to degradation, protecting and delivering their cargo (DNA and RNA), and not triggering a significant cytotoxic or immunogenic reaction, it is remarkable how little we know about the molecular mechanisms of their actions [3].

In this work, we will present our preliminary findings regarding the pH-dependent conformational space of MH18 and its variants composed of a different number (and position) of D-amino acids. We will present a specific protocol to build our dendrimers without bias, coupled to a robust initialization/equilibration scheme that prepares the peptidic dendrimers to be used in our state-of-the-art CpHMD simulations. We will present the pH titration behavior and perform several conformational characterizations, including the radius of gyration and the root mean square deviation (RMSD). These results are pivotal to help us choose the next steps of the project, where the interactions with lipid membranes and DNA/RNA are planned, to help experimentalists interpret their data, and to design new and improved peptidic dendrimers.

References

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