A COMPARATIVE STUDY ON THE BINDING OF CELL PENETRATING PEPTIDES TO siRNA USING MOLECULAR DOCKING

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Though successful gene therapy techniques have been developed recently, their application is limited by the lack of efficient delivery systems. An appealing approach to deliver such molecules involves non-covalent complexation with cell-penetrating peptides (CPPs) that are able to penetrate cell membranes of mammals. Although a large group of natural and synthetic CPPs have been discovered, studies on their complexation and translocation are as yet, insufficient. In this study, computational techniques are used to investigate the complexation of CPPs onto siRNA. Specifically, seventeen CPPs were chosen in three different categories: cationic, amphipathic and hydrophobic. The stability of siRNA in aqueous medium was studied through a molecular dynamics simulation using the CHARMM force field and NAMD code. The simulation was carried out with explicit solvent model with 19378 water molecules at physiological temperature (310 K) for 24 ns. Docking calculations were performed by ClusPro online server (Fast Fourier Transform-based rigid docking program) with default configurations, up to 1:30 siRNA to CPP ratio. Binding scores from docking simulations show highest binding affinity for amphipathic peptides over cationic and hydrophobic peptides. Furthermore, results indicate that initial complexation of peptides occur along the major groove of the siRNA, driven by electrostatic interactions between negatively charged siRNA and positively charged residues on CPPs. Subsequent CPPs bind to the minor groove and later on tend to bind in a random manner, either to siRNA or previously bound CPPs through hydrophobic and van der Waals interactions. In addition, hydrophobic CPPs do not show a distinct binding pattern unlike the other two categories. Ultimately binding yields a positively charged complex capable of non-invasive cellular translocation of siRNA.