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Molecular dynamics simulation of non-covalent single-walled carbon nanotube functionalization with surfactant peptides

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ABSTRACT

Non-covalent functionalized single-walled carbon nanotubes (SWCNTs) with improved solubility and biocompatibility can successfully transfer drugs, DNA, RNA, and proteins into the target cells. Theoretical studies such as molecular docking and molecular dynamics simulations in fully atomistic scale were used to investigate the hydrophobic and aromatic π–π-stacking interaction of designing four novel surfactant peptides for non-covalent functionalization of SWCNTs. The results indicated that the designed peptides have binding affinity towards SWCNT with constant interactions during MD simulation times, and it can even be improved by increasing the number of tryptophan residues. The aromatic content of the peptides plays a significant role in their adsorption in SWCNT wall. The data suggest that π–π stacking interaction between the aromatic rings of tryptophan and π electrons of SWCNTs is more important than hydrophobic effects for dispersing carbon nanotubes; nevertheless SWCNTs are strongly hydrophobic in front of smooth surfaces. The usage of aromatic content of peptides for forming SWCNT/peptide complex was proved successfully, providing new insight into peptide design strategies for future nano-biomedical applications.

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1. Introduction

Single-walled carbon nanotubes (SWCNTs) are cylinders designed by rolling a single graphite sheet with diameters ranging from 0.5 to 5 nm. They are characterized by a pair of integers (*n*, *m*) called the chiral vector which is the graphene sheet translation vector defining the axial direction of the nanotube [1]. Many reports have shown the importance of SWCNTs for a variety of biomedical applications, such as drug delivery, cancer treatment, tissue engineering, bioterrorism prevention, biosensing and diagnostics [2–5]. Due to SWCNT's high surface area which is capable of conjugating with diverse therapeutic and diagnostic agents, they have been successfully applied in pharmacy and medicine, as a novel tool for the delivery of therapeutic molecules [5,6]. The easy immobilization of their outer surface with biocompatible materials makes SWCNTs superior nanomaterials for drug delivery in nanomedicine. However, the pure SWCNTs have smooth surfaces without any substitution groups, which make them chemically inert and insoluble, not only in protic solvents but also in most apolar solvents [5,6]. Hence, incompatibility of SWCNTs with various solvents is one of the major disadvantages for their biomedical applications [7]. There are two main strategies to increase the solubility of SWCNTs, leading to the reduction of cell toxicity [5]; (I) covalent functionalization, where SWCNTs are covalently modified with functional groups on the surface; (II) non-covalent functionalization approach, which involves physical adsorption of molecules onto the surface of SWCNTs through hydrophobic interactions or π–π interactions. The large aromatic (π-electrons) and hydrophobic surface of SWCNTs makes them ideal partners for non-covalent interactions with suitable complementary molecules. This refers to physical adsorption or wrapping of molecules or polymers onto the surface of SWCNTs without any chemical bonding. Non-covalent functionalization not only improves the solubility of SWCNTs but also preserve the unique geometric, mechanic and electronic properties of nanotubes in way that they can be effectively used in nano-medicine [8–10]. Three main approaches for non-covalent functionalization of SWCNTs are schematically indicated in Fig. 1. (A) Wrapping biomolecules like DNA, RNA, peptides and proteins around the SWCNT walls. (B) π–π stacking interaction between aromatic rings of the loaded material and π electrons of SWCNTs. (C) Hydrophobic interaction between hydrophobic

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material such as surfactants with hydrophobic surfaces of SWCNTs. Peptides can bind to the surfaces of SWCNTs by means of their hydrophobic/aromatic segments and solubilize SWCNTs [11,12]. The previous studies showed that average hydrophobicity, aromatic amino acids contents and α-helical conformation are important factors for binding of peptides to the surfaces of SWCNTs [11–16]. Dieckmann et al. have studied amphiphilic-helical conformation of peptides in order to examine the interaction affinity into SWCNTs [14]. It has been approved that the SWCNTs are efficiently dispersed by the peptides in biological media [14,15,17]. Molecular dynamics (MD) simulations are widely used to investigate the details of peptides interaction with SWCNTs. MD simulations provide an opportunity to characterize atomic-level biomolecular processes, such as the conformational transitions associated with receptor/ligand non-covalent interactions [13,18].

To achieve non-covalent functionalization of SWCNTs with biologically compatible molecules, and also atomic-level characterization of peptides/SWCNTs interactions, we designed four surfactant peptides and their SWCNTs surface conjugation capabilities have been followed using MD simulations approaches.

2. Computational methods

2.1. Construction and optimization of SWCNT structure

Initial structure of an armchair (6,6) SWCNT was constructed from a graphite sheet via TubeGen software 3.4 [19]. The (6,6) SWCNT was widely used in biomedicine applications [12,20].Therefore we applied the (6,6) SWCNT nanostructure, consisting of 252 carbon atoms, having a diameter of 8.1 Å, and the length of 25.8 Å. The geometry optimization was performed using density functional theory (DFT) method with Becke's three-parameter hybrid function (B3LYP) [21]. The optimization was carried out using 6-31G(d,p) basis set implemented in GAMESS-US [22] package. In order to confirm the accuracy and precision of SWCNT structure, the bond length was compared with known data. The nearest neighbor distance between carbon–carbon (C—C) bonds length was found to be 1.42 Å (which corresponds to a C=C bond).

2.2. Initial 3-D structure of peptides

Two parameters are important for non-covalent functionalization of SWCNTs using peptide biomolecules; a the hydrophobic effects (considering on the number of hydrophobic residues). b the aromaticity effects (focusing on the number of aromatic residues of tryptophan, tyrosine, phenylalanine). Zuo et al. showed that the SWCNT has interaction affinity with the hydrophobic segment of peptides by the help of MD simulations method [23]. Xie et al. reported the importance of aromaticity of peptide with high affinity for SWCNTs by applying optical spectroscopy methods. The ranking of binding affinity of aromatic residues in surfactant peptides into SWCNT surface proposed as tryptophan (Trp) > tyrosine (Tyr) > phenylalanine (Phe) [11,12]. We employed the reference sequence of the surfactant peptide with the sequence of Trp–Val–Val–Val–Val–Val–Lys–Lys. It was already shown that the sequence indicates strong affinity into SWCNT surface by experimental methods [11,12]. The π–π-stacking interaction between the aromatic compound of Trp and carbon nanotube surface provides effective binding of them and is often used in non-covalent functionalization of nanotube [11,12,14–16,24,25]. Consequently, we designed three surfactant peptides in which some residues in reference sequence were replaced by Trp residues. The designed surfactant octa-peptides were subjected to concomitant assessment of two important parameters for non-covalent functionalization of SWCNT including; hydrophobic effects and aromatic π–π-stacking interaction effects. Three

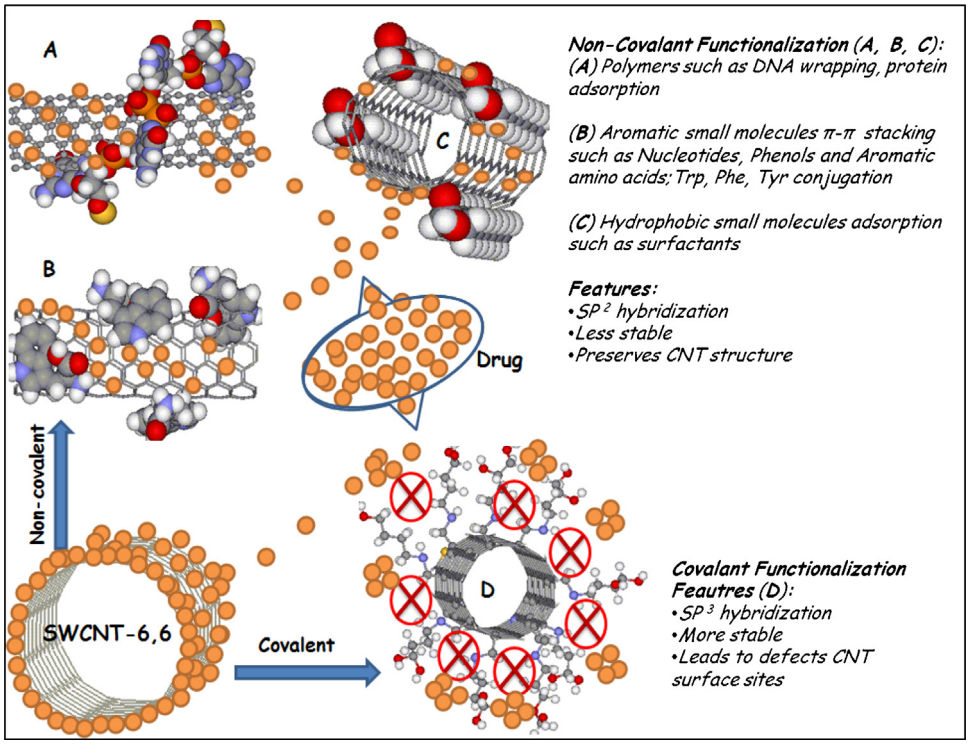

Fig. 1. Schematic representation of different ways for functionalization of single walled carbon nanotubes (SWCNTs) surfaces in order to improve their solubility and biocompatibility. SWCNTs have high potency to load and delivery of wide variety of drugs onto the surfaces due to have high surface area. Covalent functionalization of SWCNTs leads to lose this effectiveness mainly because of converting their surface SP^2 hybridization to SP^3. Non-covalent functionalization preserves the structure of SWCNTs to conjugate drugs with improving solubility for their application in nanomedicine.

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