Shape affects the interactions of nanoparticles with pulmonary surfactant

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The interactions with the pulmonary surfactant, the initial biological barrier of respiratory pathway, determine the potential therapeutic applications and toxicological effects of inhaled nanoparticles (NPs). Although much attention has been paid to optimize the physicochemical properties of NPs for improved delivery and targeting, shape effects of the inhaled NPs on their interactions with the pulmonary surfactant are still far from clear. Here, we studied the shape effects of NPs on their penetration abilities and structural disruptions to the dipalmitoylphosphatidylcholine (DPPC) monolayer (being model pulmonary surfactant film) using coarse-grained molecular dynamics simulations. It is found that during the inspiration process (i.e., surfactant film expansion), shape effects are negligible. However, during the expiration process (i.e., surfactant film compression), NPs of different shapes show various penetration abilities and degrees of structural disruptions to the DPPC monolayer. We found that rod-like NPs showed the highest degree of penetration and the smallest side-effects to the DPPC monolayer. Our results may provide a useful insight into the design of NPs for respiratory therapeutics.

INTRODUCTION

Nowadays, nanoparticles (NPs) have been widely used in biomedical applications. Much attention has been given to the design of diagnostic and therapeutic nanomedicines. These nanomedicines promote precise drug delivery for the treatment, prevention and diagnosis of diseases [1–8]. One of the popular applications is NP-mediated respiratory therapeutics [9–12]. Due to the large surface area, thin epithelial barrier, abundant underlying vasculature, low proteolytic activity, low acidity and thin mucus layer of the human lungs, using inhaled NPs as a drug carrier to the respiratory system shows great promises for treating lung diseases in lieu of systemic administration. However, after inhalation, the NPs may interact with the lung structures at all levels and possibly disrupt the functions of the related structures, thus causing potential pulmonary nanotoxicity [13]. Hence, in order to facilitate the applications of NPs in

respiratory therapeutics, balances between their ability to deeply penetrate lung structures and the potential side-effects of NPs need to be fully studied.

As we all know, much attention has been paid to study the interactions between NPs and cellular interfaces [14–21]. Different physicochemical properties of NPs such as size, shape, surface chemistry, roughness and surface coatings have been widely considered. Among these properties, the shape has attracted much attention for its roles in NP adhesion [22–24], cell penetration [25–30], drug delivery [31,32] and preferential targeting [33,34]. The shape of NPs may promote or impair their applications in respiratory therapeutics [35]. Hence, it is of great importance to study the pulmonary interactions with NPs of different shapes.

In this paper, we focus on the interactions between NPs of different shapes and the pulmonary surfactant (PS), which lines the entire alveolar surface and serves as the first biological barrier for particle translocation after inhalation. The PS maintains normal respiratory mechanics by reducing alveolar surface tension at the air-liquid interface and thus prevents the lung from collapsing at the end of expiration [30]. The PS consists of approximately 10% proteins and 90% lipids, with dipalmitoylphosphatidylcholine (DPPC) being the most abundant single lipid component for most mammalian species. Being the primary surface active component in the PS, the DPPC monolayer at the air-water interface has been widely used as a model PS system both in *in-vitro* experiments [30–39] and in molecular dynamics simulations [40–46].

Hence, we performed coarse-grained molecular dynamics simulations to study the interactions between NPs of different shapes and a DPPC monolayer at the air-water interface during the compression and expansion processes that simulate a respiration cycle. Three NP shapes were studied. For the purpose of comparison, all three shapes were approximated from a model cylinder with varying aspect ratios (length/diameter, l/d): rod ($l/d > 1$), barrel ($l/d = 1$) and disk ($l/d < 1$). For each shape, we studied two sizes

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(Here the larger value of l or d determines the size), 3 and 5 nm, making them comparable to the sizes of G3 and G5 polyamidoamine dendrimers [38], respectively. We name HL- X nm for hydrophilic NP with the size X nm and HB- X nm for hydrophobic NP with the size X nm. We found that the NP shape plays an important role in regulating hydrophilic/hydrophobic NPs' penetration abilities and degrees of structural disruptions to the DPPC monolayer, especially during film compression, i.e., the simulated exhalation process.

METHODS

Coarse-grained model

The entire system was simulated using Martini force field, which is a very popular coarse-grained (CG) model for biomolecular simulations and allows molecular simulations at a larger length-scale and longer time-scale than the all-atom model [47,48]. Martini CG model is based on a four-to-one mapping, i.e., on average four heavy atoms are represented by a single interaction center. There are four main types of interaction sites: polar (P), nonpolar (N), apolar (C), and charged (Q). Each particle type has a number of subtypes, which allow a more accurate representation of the chemical nature of the underlying atomic structure. Within each main type, subtypes are either distinguished by a letter denoting the hydrogen-bonding capabilities (d: donor, a: acceptor, da: both, 0: none), or by a number indicating the degree of polarity (from 1, low polarity, to 5, high polarity). A shifted Lennard-Jones (LJ) 12–6 potential energy function and a shifted Coulombic potential energy function are used to describe the non-bonded interactions. A weak harmonic potential is applied for the bonded interactions.

The CG DPPC and water force field parameters were given in detail by Marrink *et al.* [48] and downloaded from <http://md.chem.rug.nl/cgmartini/>. For the CG NPs, we used *Nda*-type beads for hydrophilic NP and *C1*-type beads for hydrophobic NP (*Nda* and *C1* are parameters in Martini force field [48]). Rod, barrel, and disk NPs were all stacked by beads that were evenly spaced on the concentric surfaces. Beads within 1 nm were constrained by a spring to confirm rigid NPs as reported in our previous work [49]. Hence, three different kinds of NPs were constructed: rod NP ($l = 3$ or 5 nm and $d = 1$ nm), barrel NP ($l = d = 3$ or 5 nm), and disk NP ($d = 3$ or 5 nm and $l = 1$ nm).

Simulation details

A bi-monolayer system, which has been validated by many researches [40–46], was used to probe the interactions between the inhaled NPs and the DPPC monolayer. The air space was represented by vacuum. Our bi-monolayer sys-

tem consisted of $2 \times 1,024$ DPPC molecules and 82,944 CG water molecules. The normal of these two monolayers was set as the z -axis of the simulation system. After performing compression and expansion simulations, we extracted two frames from the resulting trajectories: one (averaged area per lipid $A_{av} = 0.64$ nm², liquid-expanded (LE) phase [50], box: 25.58 nm $\times$ 25.58 nm $\times$ 40 nm) as the initial conformation of the compression simulations for NP-DPPC monolayer systems; the other ($A_{av} = 0.47$ nm², liquid-condensed (LC) phase [50], box: 22.01 nm $\times$ 22.01 nm $\times$ 40 nm) as the initial conformation of the expansion simulations. The NPs were placed in the vacuum of these two frames near the DPPC monolayer to mimic the state of NP deposition onto the DPPC monolayer, followed by the compression and expansion simulations. Each of these simulations was performed with a time scale as long as 2.0 μ s.

For all simulations, a cutoff of 1.2 nm was used for van der Waals (vdW) interactions, and the LJ potential was smoothly shifted to zero between 0.9 and 1.2 nm to reduce the cutoff noise. For electrostatic interactions, the Coulombic potential, with a cutoff of 1.2 nm, was smoothly shifted to zero from 0 to 1.2 nm. The relative dielectric constant was 15, which was the default value of the force field [48]. Lipids, water and the NPs were coupled separately to Berendsen heat baths at $T = 310$ K [51], with a coupling constant $\tau = 1$ ps. The monolayer compression was simulated using semi-isotropic pressure coupling (Berendsen coupling scheme [51], coupling constant of 4 ps, compressibility in the lateral direction of 5×10^{-5} bar⁻¹ and in the normal direction of zero). Each of the simulations was performed for 2.0 μ s with a time step of 20 fs. The neighbor list for non-bonded interactions was updated every 10 steps. Snapshots of the simulation system in this paper were all rendered by VMD [52]. All simulations were performed with the GROMACS simulation package [53].

RESULTS

NP-DPPC monolayer interactions during the compression process

We first simulated the particle translocation through the DPPC monolayer during the compression process (Fig. 1). NPs of three different aspect ratios initially contact the DPPC monolayer at the LE phase from the air phase to mimic the cases of inhaled NPs. We found that all hydrophobic NPs can tightly immerse in the hydrophobic region of the DPPC monolayer during the whole compression process. However, rod NPs seldom disrupt the DPPC monolayer, while barrel NPs and disk NPs induce large structural disruptions of the DPPC monolayer. Generally, hydrophilic NPs tend to penetrate the DPPC monolayer. However, different shapes bring about different transmem-

Figure 1 Snapshots for the interactions of NPs of different shapes with the DPPC monolayer during the compression process. The NPs are placed in the gas phase near the DPPC monolayer. Here, we consider two different phases of the DPPC monolayer at the initial state (LE phase and LC-LE co-existence phase). The phase differences of the DPPC monolayer at the initial state do affect the interactions between the NPs and the DPPC monolayer, especially for barrel-like and disk-like NPs.

brane dynamics. Rod NPs still adsorb onto the hydrophilic head-groups of the DPPC monolayer after translocation across the lipid monolayer. Small disk NPs and barrel NPs could penetrate and separate from the DPPC monolayer. However, larger disk NPs and barrel NPs encounter increased difficulties in crossing the DPPC monolayer, and they may even disrupt the structure of the DPPC monolayer.

We also consider the case that NPs adsorb onto the DPPC monolayer at a different stage of compression process (LC-LE phase, a more condensed state compared with the LE phase shown in Fig. S1). We use these two compression processes to simulate the interactions of NPs with the pulmonary surfactant at different stages of the exhalation process. During the LC-LE→LC compression process, almost all NPs cannot penetrate across the DPPC monolayer. This may be ascribed to the fact that the monolayer becomes too condensed to penetrate before the NPs rotate properly. The NPs' behaviors between these two processes are quite different. The NPs rotate themselves to have the maximum contact area with the DPPC monolayer. When the NPs adsorb onto the DPPC monolayer, they will change the local properties of lipids [49], which may initiate the structural disruption of the lipid monolayer. The contact area and how fast NPs rotate to get the maximum contact area both affect the disruption degree. Barrel NPs have the largest contact area and can quickly reach the maximum contact area, because they are closest to the isotropic. Rod NPs have the smallest contact area, and disk NPs are something in between. This may explain why the degrees of disturbance to the DPPC monolayer structure are in order: barrel NP > disk NP > rod NP.

Both *in-vitro* experiments [35–39] and computer simulations [40–46] have confirmed that the phospholipids of PS undergo surface phase transition during the compression-expansion cycles. During film compression, phospholipid monolayers undergo surface phase transitions from a “fluid-like” LE phase to a “solid-like” LC phase, which is opposite to the direction of phase transition during film expansion. Phospholipid phase transition and separation have been proven to play an important role in regulating the biophysical function of PS film [36,38]. Hence, we monitored the changes of order parameters of the interfacial DPPC molecules at the air-water interface during the compression processes (LE→LC and LC-LE→LC). Without NPs, the pure DPPC monolayer becomes more condensed during the compression process, and order parameter of the interfacial DPPC tails increases (Green line in Fig. 2), which is defined as normal phase transition during the compression process. As shown in Fig. 2, the increasing trends of the order parameter are inhibited in many cases, in which NPs all cause large structural disruption to the

lipid monolayer. In other words, the large structural disruptions of the DPPC monolayer caused by NPs are always accompanied by normal phase transition of the interfacial DPPC molecules.

NP-DPPC monolayer interactions during the expansion process

To study the interactions of NPs with model PS during inhalation (i.e., film expansion), we simulated NP translocation across the DPPC monolayer during the expansion process. The NPs were firstly placed near the DPPC tails in the air phase. As shown in Fig. 3, all NPs show little or no effects on the structure of the DPPC monolayer, except that hydrophobic barrel NPs cause slight disruptions to the DPPC monolayer. All hydrophobic NPs immerse themselves into the hydrophobic tails of DPPC molecules, while all hydrophilic NPs could penetrate the DPPC monolayer and adsorb onto the hydrophilic head-groups of DPPC molecules. By analyzing the corresponding order parameter of lipid tails (Fig. 4), we find that all NPs we considered show little or no influences on the normal phase transition of interfacial DPPC molecules during the expansion process (LC phase to LC-LE phase, to LE phase). We also considered NPs initially adsorb onto the DPPC monolayer of a different stage (LC-LE phase) during the expansion process (LC-LE phase to LE phase). Still, there are little or no difference on NP-DPPC monolayer interactions during this expansion process. This is quite different from the case of the compression process. During both expansion processes (LC→LE and LC-LE→LE), the systems become more and more sparse. It is this difference that makes NPs penetrate the DPPC monolayer easily without disrupting the monolayer much.

DISCUSSION

There are clear differences about NP-DPPC monolayer interactions during the compression (Figs 1 and 2) and the expansion (Figs 3 and 4) processes. During the expansion processes, all considered NPs show no or little influence on the structural properties and the normal phase transition of the interfacial DPPC molecules. Rather, hydrophobicity of the NPs determines their ability of penetrating the DPPC monolayer. It was found that the hydrophobic NPs immerse themselves in the hydrophobic tails of the interfacial DPPC molecules, while hydrophilic NPs adsorb onto the hydrophilic head-groups of the interfacial DPPC molecules. This finding is in good agreement with previous *in-vitro*, *in-vivo* and *in-silico* translocation results [39,46,54–58].

During the compression processes, the shape of NPs plays an important role in the structural disruptions to the DPPC monolayer (Fig. 5). The apparent structural disruptions can be classified into three types, which all inhibit the

Figure 2 The variation of order parameter for the systems of rod-shaped (a, b), barrel-shaped (c, d) and disk-shaped (e, f) NPs during the compression process. Phase transition inhibition of the interfacial DPPC molecules is always accompanied by the large structural disruption of the DPPC monolayer.

normal phase transition of the interfacial DPPC molecules during the compression process. Types ① and ② are the most common cases, while type ③ more probably happens to hydrophilic NPs (Probably because hydrophobic NPs do not prefer lipid tails). From our simulations, we find that

types ② and ③ are both evolved from type ①. Type ① may be considered as the first step that NPs induce structural disruptions to the DPPC monolayer. For hydrophobic NPs, the system could keep the type ① status or go further to type ② status; in some cases hydrophobic NPs (disk)

Figure 3 Snapshots for the interactions of NPs of different shapes with the DPPC monolayer during the expansion process. The NPs are placed in the gas phase near the DPPC monolayer. Here, we consider two different phases of the DPPC monolayer at the initial state (LC phase and LC-LE co-existence phase). The phase differences of the DPPC monolayer at the initial state seldom affect the interactions between NPs and the DPPC monolayer.

Figure 4 The variation of order parameter for the systems of rod-shaped (a, b), barrel-shaped (c, d) and disk-shaped (e, f) NPs during the expansion process. All NPs show little or no influence on the normal phase transition of the interfacial DPPC molecules.

will be pulled back to the interface to get the maximum contact area with lipid tails if they do not rotate properly in the type ① status. For hydrophilic NPs, they do not prefer the lipid tails; they either cross the monolayer to form the type ③ II status or move back to the interface to minimize the contact with the lipid tails and form the type ③ I status.

And the detailed relationships between these three types of structural disruptions are summarized in Fig. 5a. The differences of the structural disruptions to the DPPC monolayer by NPs of various shapes together with their transmembrane dynamics can be ascribed to two points: (1) Particle shape influences the capillary forces acting on par-

Figure 5 (a) Three types of the large structural disruptions of the DPPC monolayer induced by NPs and their relationships, “pink” representing the inhibition of normal phase transition of the interfacial DPPC molecules. (b) Shape plays an important role in determining the occurrences of these structural disruptions. Rod-like NPs seldom disrupt the DPPC monolayer, while barrel-like NPs show the greatest probability in causing disruptions. (c) The monolayer penetration abilities of NPs of different shapes.

titles at the air-water interface, which is important for NP dynamics [23,24]. (2) Particle shape affects the rotation and orientation abilities of NPs on the membrane [25,26,29]. As summarized in Fig. 5, we could draw the following three conclusions. (1) Hydrophilic rod-like NPs show the high-

est penetration ability and the smallest side-effects to the DPPC monolayer. (2) Both the penetration ability and the side-effects of barrel-like NPs are notable. (3) Hydrophilic disk-like NPs have the lowest penetration ability together with the reduced side-effects. Hence, our simulations suggest that the rod-like NPs show the greatest potential in respiratory therapeutics without disturbing the functions of pulmonary surfactant films. Considering the decreasing aspect ratios (l/d) for rod-like NPs ($l/d > 1$), barrel-like NPs ($l/d = 1$) and disk-like NPs ($l/d < 1$), l/d could be used as an important factor to achieve the best design of NPs for respiratory therapeutics.

It should be noted that the respiratory translocation pathway for inhaled NPs also consists of the alveolar epithelium cells, extracellular basement membrane, and capillary endothelium cells. The PS film at the air-water interface of alveoli is only the initial barrier of this pathway. The roles of particle shape in affecting surfactant films may be different for the interactions of particles with other barriers during this pathway, which makes the actual translocation behavior of engineered NPs very complex. For example, Adriani *et al.* [34] found that disk-like particles showed better targeting efficiency to the diseased microvasculature compared with spheres and rods. Agarwal *et al.* [59] found that mammalian epithelial and immune cells preferentially internalize disc-shaped, negatively charged hydrophilic NPs of high aspect ratios compared with nanorods and lower aspect-ratio nanodiscs. The behavior of disk-like NPs in other barrier of this pathway is quite different from that in pulmonary surfactant reported in this work. Besides, there are also some consistent reports about shape effects on different lung structures. For instance, rod-like NPs appeared to adhere more effectively to the surface of endothelial cells of blood vessels and could be used for targeting the tumor vasculature [32,33]. This once again shows great promises for the applications of rod-like NPs to respiratory therapeutics.

CONCLUSION

With coarse-grained molecular dynamics simulations, we found that the length-to-diameter aspect ratio of cylindrical NPs could affect their penetration ability and structural disturbance on DPPC monolayers. Rod-like NPs show the highest penetration ability and the lowest side-effects to the DPPC monolayer. Furthermore, considering the advantages of rod NPs in targeting the tumor vasculature, rod NPs show great promises in respiratory therapeutics.

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Conflict of interest The authors declare that they have no conflict of interest.

Supplementary information Schematic diagram for normal phase transition is available in the online version of the paper.

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中文摘要 肺表面活性剂是纳米颗粒经呼吸途径进入人体的初始生物屏障, 纳米颗粒与肺表面活性剂的相互作用直接决定纳米颗粒潜在的诊疗应用和毒性。虽然已有很多研究致力于优化纳米颗粒的理化性质以提高其输运和靶向特性, 但是纳米颗粒的形状效应对其与肺表面活性剂相互作用的影响仍鲜有报道。本文运用粗粒度分子动力学的方法研究了纳米颗粒的形状效应对其与一种模型肺表面活性剂——DPPC磷脂单分子层膜的作用的影响。研究表明, 吸气过程中(磷脂单分子层膜扩张过程), 形状效应基本可以忽略; 呼气过程中(磷脂单分子层膜压缩过程), 不同形状的纳米颗粒表现出不同的跨膜能力对膜的结构扰动亦有所不同, 其中棒状纳米颗粒具有最强的跨膜能力, 同时对膜的结构扰动也最小。该研究结果对促进纳米颗粒的呼吸诊疗应用具有积极的作用。