Coarse-grained Modeling of Receptor-Mediated Endocytosis of Nanoparticles

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Summary We employ a recently developed coarse-grained membrane model to study receptor-mediated endocytosis of nanoparticles (NPs) with varying size, shape, and ligand density. Our simulations revealed that, for spherical NPs, there exists an optimal condition (in terms of size and ligand density) under which the NP endocytic time minimizes. For NPs of the same volume, spherical NPs enter faster than the spherocylindrical ones. Our simulation results provide useful guidance to the design of biomarkers and drug delivery bioagents for cancer diagnosis and therapy.

INTRODUCTION

In recent years, virus-inspired nanoparticles (NPs) have attracted much attention for their significant applications in targeted drug delivery and disease diagnosis. Coated with ligands and tagged with drug molecules on their surface or interior, these NPs target specifically the receptors on malignant cells, due to the ligand-receptor interaction and recognition, thereby mitigating the adverse side effects in conventional chemotherapy in cancer treatment [1]. Despite the potential applications, controlling factors for the receptor-mediated endocytosis are yet to be determined. Previous theoretical analyses have showed that for spherical NPs, NP size and ligand density interrelatedly govern the uptake properties. Experimental studies have demonstrated that NP shape also plays an important role in the cellular uptake. Yet the underlying mechanism for the regulative effects of NPs shape remains unknown [2-5]. In this article, we present a coarse-grained molecular model to study the effects of size, shape, and ligand density on the uptake kinetics.

THE COARSE-GRAINED MODEL

Our coarse-grained model is extended from the one-particle-thick fluid membrane model in which each particle represents a cluster of lipid molecules[6]. In the fluid membrane model, the interaction of lipid particles is described by an anisotropic pair potential. The inter-particle interaction strength depends on both particle distance and relative particle orientation. Each lipid particle in the model occupies an area of ~2nm^2, which enables the computational access to much larger systems. As an extension, we identify certain particles to carry a dual rule: a lipid particle that interacts with its neighboring ones and at the same time a receptor that may binds to ligands on the NPs. These particles in the extended model are hereafter known as receptor particles. In our simulations, the initial receptor density is set to be 400 μm^{-2}, consistent with the physiological condition.

Ligands are uniformly coated on the NP surface with varying density. The ligand-receptor interaction is described by the Lennard-Jones (0.8-1.6) potential, with a binding energy of 60 k_BT. During endocytosis, ligand-receptor binding depletes the receptors in the vicinity of the NP, creating a receptor density gradient that drives the diffusion of the receptors from the remote regions toward the NP. In our coarse-grained simulations, the membrane is sufficiently large such that the endocytosis is receptor diffusion-limiting. In addition, to maintain a roughly constant receptor density in the remote region, we add a new receptor to from the membrane boundary whenever a ligand-receptor binding event occurs. In our simulations, the system is thermostated at a temperature $k_BT = 0.2\varepsilon$, where ε is the interaction strength of a pair of lipid particles, and the membrane tension is set to be zero. The coarse-grained molecular dynamics (MD) simulations are thus carried out on a *NAT* ensembled.

SIMULATION RESULTS

Using the extended model, we aim to study the effects of NP size and ligand density on the endocytic time. Our simulation begins with a coarse-grained membrane of size 500nm×500nm (250×250 lipid particles). The NP size in our simulation is $\leq$ 37.5 nm in radius. Convergence studies showed that for the NPs of our consideration further increasing the membrane size does not affect the endocytic time of the NPs. Therefore, this size is used for all our simulations, as described below. Figure 1 shows 4 snapshots of the NP endocytosis from our simulations.

Figure 2 shows the size effect of the NPs on the endocytic time, where the ligand density is fixed at 0.026 nm^{-2}. For small radius (R = 15 nm), endocytosis does not occur due to the large membrane bending penalty in membrane wrapping. Membrane wrapping ceases after the NP is halfly wrapped. For NPs with radius of 22.5 nm, wrapping proceeded smoothly, and endocytosis occurred. Further increasing the NP size slows down the endocytosis. The

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longer endocytic time for larger NPs stems from the increasing diffusing time since more receptors are needed to pair the increased number of ligands on the NPs. Our simulations thus indicate that there exists an optimal size of about R=22.5 nm at which the endocytic time minimizes. We further simulate the endocytic time of NPs with varying ligand density but fixing the NP size at 22.5 nm, as shown in Fig. 3. At a ligand density of 0.021 nm^{-2} endocytosis does not occur because the total adhesion energy supplied by the ligand-receptor binding is insufficient to overcome the membrane bending penalty. At a ligand density of 0.026 nm^{-2}, endocytic time minimizes. Further increasing ligand density slows down the endocytosis. We further studied the NP shape effect and found that at the same volume, spherical NPs take less time to be endocytosed than the spherocylindrical NPs.

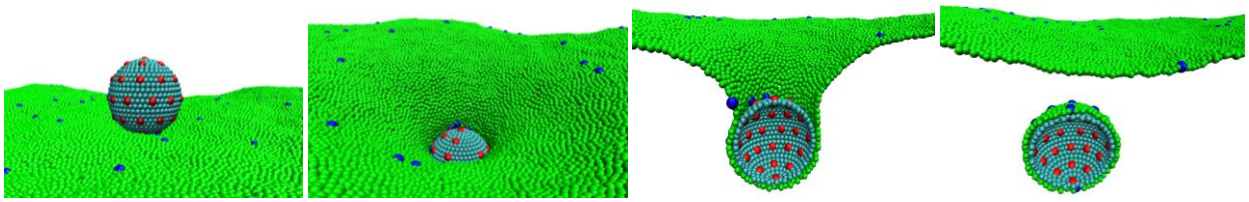

Fig. 1. Snapshots of NP endocytosis. (a) docking; (b) and (c) partially wrapped; (d) fully wrapped.

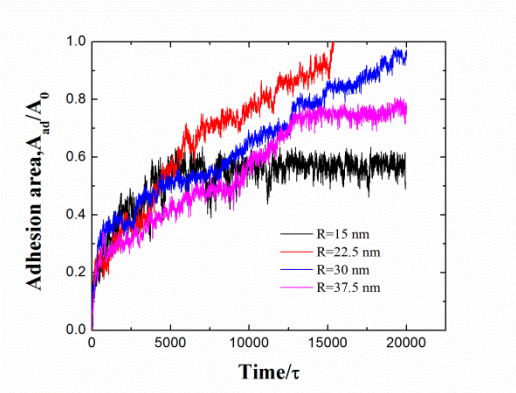

Fig. 2 The effect of NPs size on endocytosis

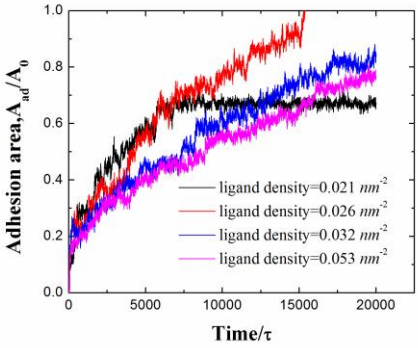

Fig. 3 The effect of ligand density on endocytoiss

CONCLUSION

We presented an extended coarse-grained model for the study of endocytosis of NPs with varying size, shape, and ligand density. Our simulations showed that there exist optimal NP size and ligand density at which the endocytic time minimizes; for NPs of the same volume, spherical NPs enter the cell faster than the spherocylindrical ones. Our simulation results shed light on the design of NP-based biomarkers and drug delivery agents for cancer diagnosis and therapy.

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