Cell interaction with elastic nanoparticles

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Mechanical properties play critical roles in the cell uptake of nanomaterials. Here we perform a theoretical study on the kinetics of receptor-mediated endocytosis of elastic nanoparticles, focusing on how the uptake rate depends on the nanoparticle stiffness and size. It is shown that the wrapping of the spherical soft nanoparticles is kinetically faster than that of the stiff nanoparticles. This study provides insight into the elasticity effects on cell uptake and may serve as design guidelines for the controlled endocytosis and diagnostics delivery.

1. Introduction

Cell uptake of nanoparticles is of fundamental to the understanding of biological functions and a broad range of applications including drug delivery, virology and nanoparticle hazard prevention. There are studies on the stiffness effect on the cell uptake rate of nanoparticles with different sizes and material compositions (Beningo & Wang, 2002; Yue & Zhang, 2013; Anselmo et al., 2015). However, there exist apparent inconsistencies in the literature. For example, phagocytosis of stiff microparticles by bone-marrow-derived macrophages exhibits higher efficiency than soft ones (Beningo & Wang, 2002). In contrast, stiffer hydrogel nanoparticles of radius 100 nm exhibit an enhanced integrated rate of membrane binding and uptake in their interaction with macrophages, epithelial and endothelial cells (Anselmo et al., 2015). Recent molecular dynamics simulations demonstrate that soft vesicular nanoparticles undergo a faster membrane wrapping process than rigid ones (Yue & Zhang, 2013). Although it is clear that the stiffness of nanoparticles has pronounced influences on their interaction with cells, the results from different experiments and simulation studies are not all consistent and the underlying mechanisms are far from clear. This calls for further investigations at a fundamental level.

Receptor-mediated endocytosis is one of the most important and best characterized cellular uptake pathways. Here we present a theoretical model on the kinetics of receptor-mediated endocytosis of elastic nanoparticles, focusing on how the rate of uptake depends on the nanoparticle stiffness and size, membrane tension and binding strength between membrane receptors and ligands grafted on the nanoparticle surface. The analysis presented here is based on our recent study (Yi & Gao, 2017).

2. Model and methods

Consider an initially flat cell membrane wrapping around an elastic spherical nanoparticle coated with compatible ligands (Fig. 1). The ligands on the nanoparticle surface are immobile and uniformly distributed at a density of ξ_L, whereas the receptors on the cell membrane are mobile, and can diffuse in the membrane until they bind specifically with the ligands on the nanoparticle. Before the nanoparticle contacts the cell membrane, the receptors are assumed to be uniformly distributed at density ξ_0. Once the contact starts, each ligand within the contact region is assumed to bind with a receptor. The receptor-ligand binding lowers the free energy of interaction, and causes the membrane to wrap around the nanoparticle. The membrane wrapping is characterized by the wrapping degree *f* which is defined as the ratio between the contact area and the total area

of the nanoparticle. The wrapping time t is counted from the moment of contact (t=0) until the state of full wrapping (t=t_w), with t_w defined as the total wrapping time.

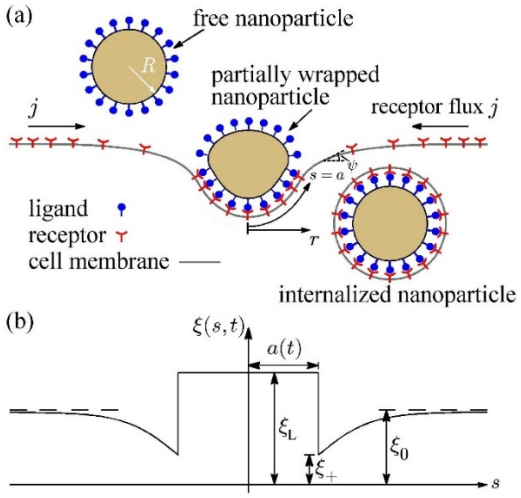

Fig. 1. (a) Schematic of receptor-mediated endocytosis of a spherical elastic nanoparticle of an initial radius R. (b) During the wrapping process, the receptor density distribution in the membrane is nonuniform, with receptor density ξ depleted in the vicinity of the binding region, which in turn induces global receptor diffusion toward the contact edge. The horizontal axis s represents the arclength of the cell membrane. Axisymmetric configurations are assumed throughout the analysis.

During the wrapping process, the elastic deformation energy of the nanoparticle and cell membrane can be expressed in terms of the Canham-Helfrich functional and their mechanical properties are characterized by the bending stiffnesses κ_p and κ_m, respectively. Subscripts 'p' and 'm' are used to identify quantities associated with the nanoparticle and cell membrane, respectively. The kinetics of receptor diffusion occurring in the cell membrane is characterized by the evolution of receptor density $\xi(s,t)$ and could be determined by solving a deterministic moving boundary problem. With the help of tonservation of the total number of receptors, continuity equation and Fick's first law, we can determine the governing equation for receptor diffusion along the deformed outer free membrane. Following a power balance between elastic deformation and receptor diffusion, we can proceed to determine the wrapping rate df/dt. The total wrapping time is then obtained as $t_w = \int_0^1 (df/dt)^{-1} df$.

3. Results

A typical set of parameter values used in our calculations is summarized in Table 1. Taking theses typical parameter values, the wrapping degree f is determined and shown in Fig. 2(Left) as a function of the normalized time $t\xi_L D$ for different κ_p/κ_m at $\bar{\sigma}=0.5$, $\bar{\xi}=0.025$ and $R=200$ nm. Here $\bar{\sigma}=2\sigma R^2/\kappa_m$ is the normalized membrane tension, D is the diffusivity of receptors in the cell membrane. As wrapping proceeds, the wrapping rate df/dt decreases.

Table 1. Physical constants adopted in our calculations

κ_m (k_BT)	D (μm^2/s)	e_{RL}	ξ_L (1/μm^2)	$\bar{\xi}=\xi_0/\xi_L$
20	0.1	15	5×10^3	0.025

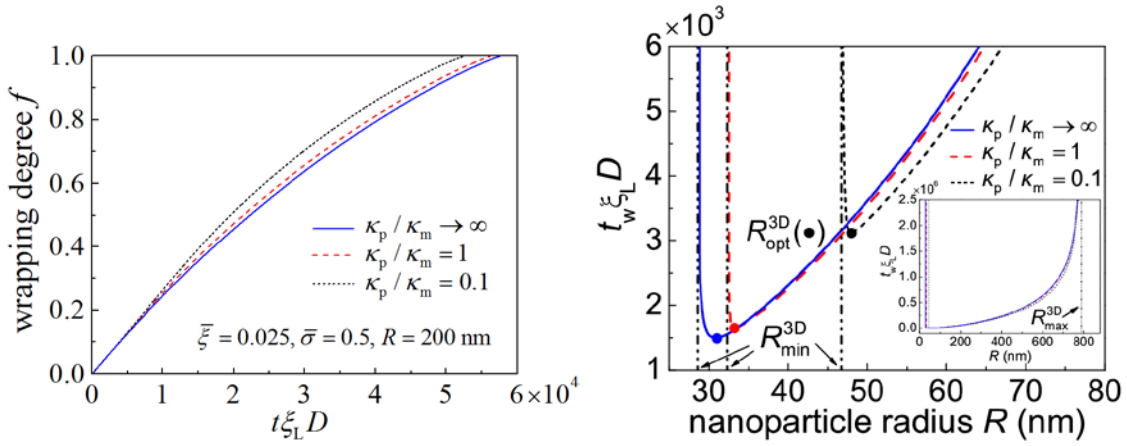

Fig. 2. (Left) Wrapping degree f as a function of the normalized time $t\xi_L D$ for different values of the nanoparticle-membrane stiffness ratio κ_p/κ_m at $\bar{\sigma} = 0.5$, $\bar{\xi} = 0.025$ and $R = 200$ nm. (Right) The normalized total wrapping time $t_w \xi_L D$ as a function of the nanoparticle radius R for different values of the particle-membrane stiffness ratio κ_p/κ_m at $\bar{\sigma} = 0.5$ and $\bar{\xi} = 0.025$. R^{3D}_{min} and R^{3D}_{max} (inset) represent the minimum and maximum radii of a particle that can be wrapped, respectively. R^{3D}_{opt}, marked by solid circles, denotes the optimal wrapping radius at minimum wrapping time. R^{3D}_{max} is determined by the number of receptors.

Fig. 2(Right) shows the normalized total wrapping time $t_w \xi_L D$ as a function of the nanoparticle radius R for different values of the particle-membrane stiffness ratio κ_p/κ_m. As κ_p/κ_m decreases, so does t_w. The ratio of t_w between a soft particle with $\kappa_p/\kappa_m = 0.1$ and a rigid one is about 0.9. Further numerical analysis indicates that the time ratio decreases as $\bar{\xi}$ increases.

Conclusions

A theoretical model of receptor-mediated endocytosis limited by receptor diffusion has been developed to describe the kinetic process of the membrane of a cell wrapping around an elastic nanoparticle via diffusional aggregation of receptors in the membrane to the cell-particle binding site. It was shown that the higher uptake rate of a softer nanoparticle results from enhanced receptor diffusion as a result of larger contact area between the membrane and particle at the early- and mid-stages of the wrapping process. There is an optimal particle size corresponding to the shortest wrapping time. The minimum particle radius required for full internalization increases as the particle stiffness decreases; while the maximum particle radius that still allows full wrapping is insensitive to particle stiffness.

References

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