MINI-REVIEW

Swimming nanorobots for opening a cell membrane mechanically

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Abstract
Swimming nanorobots performing efficient self-propulsion in various biofluids have drawn tremendous attention over 15 years due to their application including active drug delivery, precise cell manipulation, noninvasive surgery, rapid biosensor, and mobile in vivo imaging in the field of biomedicine. However, there are still many challenges in using swimming nanorobots in practice for active drug delivery and therapy, such as biocompatibility of chemical fuels or externally physical fields, biodegradation of synthetic materials, biofouling in bodily fluids, in vivo imaging of swimming nanorobots, and self-navigation for active targeting. In this review, we highlight the mechanical drilling of cell membranes by swimming nanorobots and discuss the issues, because the cell membranes are one of the key barriers for intracellular drug delivery and drug delivery efficiency of swimming nanorobots. We will summarize the recent advances in swimming nanorobots with different propulsion mechanism and introduce the fundamental issues of interaction between swimming nanorobot and cell membrane. Then, the process, mechanism, and optimization of mechanically opening a cell membrane by swimming nanorobots are discussed and the perspective on the challenge and solution is also included. Such swimming nanorobots capable of mechanically opening a cell membrane could help to better understand the biophysical property of cells and pave the development of precision medicine.

KEYWORDS
active delivery, cell membrane, self-propulsion, swimming nanorobot

1 | INTRODUCTION

Since 1959, R. P. Feynman gave a prospect of nanotechnology with his famous talk, “There is Plenty of Room at the Bottom”, abundant research about active drug delivery and therapy have been executed to pave the way for Fantastic Voyage. In recent 15 years, the emerging research interest in micro-/nanorobots-based medicine—a promising approach harnessing micro-/nanoscale robots to transport diagnostic and therapeutic cargos toward the hard-to-reach issues. Learning from motile living organisms, a significant number of synthetic swimming nanorobot
capable of converting surrounding chemical or physical energy into their mechanical movement have been developed.1

According to the driving power source, swimming nanorobots could be classified by chemical fuel (such as hydrogen peroxide and acid), ultrasound, light, magnetic field, electric field, and heat.2–10 Recent advances have demonstrated their potential in biomedical applications, including active drug delivery, precise cell manipulation, noninvasive surgery, biosensor, and imaging in vivo.11–19 However, biomedical swimming nanorobots have still many challenges including in practice chemical fuel toxicity or incomplete fuel degradation, biocompatibility of externally physical fields, biodegradation of synthetic material, biofouling in bodily fluid, in vivo imaging of swimming nanorobot, self-navigation for active targeting, and so on (Figure 1). For instance, the most used chemical fuel, hydrogen peroxide, is toxic, which hinders their application in biomedicine. Thus, various swimming nanorobots propelled by biocompatible fuels (eg, glucose and urea) or fuel-free nanorobots were further requested.12,20,21 The swimming nanorobots fabricated by noble metals or synthesized polymers usually result in bad biodegradability. By introducing “bottom-up” chemical self-assembly, recent research illustrated that it is versatile to build up multifunctional swimming nanorobots with good biodegradability and biocompatibility.22–25 For the clinical application, before reaching the defined sites of the body, the swimming nanorobots were also experienced with the problem of the biofouling and accompanying immune elimination.26–28 To actively search the areas of interest in human body, the in vivo imaging and corresponding self-navigation of swimming nanorobots were also limited by intravascular flow, biocompatibility, and penetration depth.29–31 The abovementioned challenges and solutions have been discussed in recent reviews.3,13,18,20,32–34 More particularly, biological barriers, including intravascular flow, cell membrane, blood-brain, mucus, and vitreous humor, of swimming nanorobots for in vivo biomedical applications were highly focused, because the biological barriers lead to the significant decrease of therapeutic efficiency. In early stereotypes of swimming nanorobots, owing to the ability of their motion and self-navigation and precision in single cell resolution, the swimming nanorobots seem to be efficient for the intracellular drug delivery, associating with potential application on cell-based therapies, cellular surgery, genome editing, and guiding cell fate.35–39 However, the cell membranes hindered the pathway of intracellular delivery and the swimming nanorobots were hard to mechanically open cell membranes in a short time due to insufficient driving force.40

In this review, we aim at giving a general view of swimming nanorobot for mechanically opening a cell membrane. By summarizing the physical and chemical characteristics of cell membrane and the propulsion of swimming nanorobot, we discuss the interaction between swimming nanorobot and cell membrane, a critical condition of swimming nanorobot for mechanically opening a cell membrane. Associating with recent advances in swimming nanorobots capable of opening the cell membrane, we discuss strategies of swimming nanorobot for mechanically opening a cell membrane, including structure design, permeabilization of cell membrane, and promoting applied force on cell membrane.

2 | BASICS OF SWIMMING NANOROBOT AND CELL MEMBRANE

2.1 | Swimming nanorobot

The first self-electrophoretic swimming nanorobot was reported in 2004, and since then, various swimming nanorobots driven by magnetic field, electrical field, bubble, light, and ultrasound were subsequently designed and fabricated (Figure 2A).20,32,41–44 Swimming nanorobots could convert chemical or externally physical energy into their mechanical movement in fluids and promise carrying out biomedical application.45,46 Thus, the movement abilities of swimming nanorobots rely on the type of energy sources. Figure 2B lists a brief catalog of swimming nanorobots classified with the driving energy source.
**FIGURE 2** Basics of swimming nanorobot and cell membrane. (A) Timeline of the development of swimming nanorobot. Self-electrophoresis nanorobot. Reproduced with permission. Copyright 2017 American Chemical Society. Magnetic nanorobot. Reproduced with

| Nanorobot                  | Driving     | Size            | Force  |
|----------------------------|-------------|-----------------|--------|
| (PANI)/Zn tube             | Chemical    | $2 \times 2 \times 10 \ \mu m^3$ | 5 pN$^{54}$ |
| Roll-up tube               | Chemical    | $0.8 \times 0.8 \times 10 \ \mu m^3$ | 60 pN$^{55}$ |
| (CHI/ALG)$_{18}$ tube      | Chemical    | $0.6 \times 0.6 \times 10 \ \mu m^3$ | 2 pN$^{56}$ |
| (PSS/PAH)$_5$ capsule      | Chemical    | $8 \times 8 \times 8 \ \mu m^3$ | 75 pN$^{57}$ |
| Fe coated helix            | Magnetic    | $0.25 \times 0.25 \times 2.4 \ \mu m^3$ | 0.02 pN$^{58}$ |
| Si/Ni/Au nanospear         | Magnetic    | $1 \times 1 \times 5 \ \mu m^3$ | 0.14 pN$^{59}$ |
| Ag/Ni/Ag nanowires         | Electric    | $0.3 \times 0.3 \times 6 \ \mu m^3$ | 1.2 pN$^{60}$ |
| Janus sphere               | Thermo-phoresis | $1 \times 1 \times 1 \ \mu m^3$ | 0.18 pN$^{53}$ |
| Polymer rocket             | Thermo-phoresis | $5 \times 5 \times 10 \ \mu m^3$ | 22 pN$^{60}$ |
| Bimetallic nanorod         | Ultrasound  | $0.3 \times 0.3 \times 2 \ \mu m^3$ | 1 pN$^{61}$ |
The driving force \( F_{\text{driving}} \) of swimming nanorobots can be roughly estimated by applying the Stokes’s drag equation:\(^{17-49}\)

\[
F_{\text{driving}} = \frac{2\pi \eta VL}{\ln \left( \frac{L}{R} \right) - 0.72},
\]

where \( \eta \) is the fluid dynamic viscosity, \( L \) is the length of the nanorobot, \( V \) is the velocity, and \( R \) is the radius of the nanorobot.

Therefore, a larger swimming nanorobot illustrated a larger driving force at the same speed. When the average diameter of swimming nanorobots is smaller than 1 \( \mu \)m, the majority of driving force from swimming nanorobots are limited to around 10 pN (apparent velocity is smaller than 100 \( \mu \)m/s), as shown in Figure 2B.

Apart from the autonomous motion, the movement of swimming nanorobots can be operated toward specific cell in vitro conveniently by regulating the externally physical signal, including light gradient, acoustic frequency, and magnetic direction.\(^{39,40,50}\) As shown in Figure 2C, swimming nanorobots could be autonomously navigated to target the cell membrane. For further rapid intracellular delivery, the swimming nanorobot should open the cell membrane in a short time, and thus the properties of cell membrane should be investigated.

### 2.2 Cell membrane

Cell membrane, or plasma membrane, is known as the boundary of a living cell. Given that cell membrane segregates the inside and outside of a cell, cell membrane maintains cell in relatively stable condition with controllable composition.\(^{36}\) Phospholipid bilayer is the essential structure of cell membrane. Briefly, owing to the hydrophilic head and hydrophobic fatty acyl chains of phospholipid, phospholipid molecules parallel with lateral molecules and face their hydrophilic head to the water phase. Bilayers of phospholipid with hydrophobic interaction stabilize the structure in aqueous condition. The final thickness of the cell membrane ranges from 5 to 10 nm.\(^{35}\) The structure of cell membrane also combines elasticity and fluidity. Noting that cell membrane contains hundreds of different lipid species, cholesterol and protein also embed on the membrane structure. Therefore, the characteristic of cell membrane is complex, depending on cell type and surrounding condition.\(^{36}\)

For mechanically opening a cell membrane, the properties of disruption, strain, fluidity, permeabilization, and repair should be considered. A typical mechanical disruption of cell membrane by tensile strain was measured to be 3\%.\(^{65,66}\) For method of solid contact, the contact area is important for mechanically opening a cell membrane. Small contact area leads to a smaller critical condition and strain rate. Permeabilization of cell membrane is also important for intracellular drug delivery. Typically, the leakage of cell occurs at 42\(^{\circ}\)C. Even the rapid exchange of small molecular weight molecules could happen when the temperature is higher than 55\(^{\circ}\)C.\(^{67}\) The small hole that led to passing of molecular through cell membrane was generated by thermal phase transition of phospholipid on the cell membrane. By locally heating cell membrane, such as gold nanoparticles irradiated with NIR, extracellular molecular and nanoparticles could percolate into the cell.\(^{68}\) After opening the cell membrane, the cells spontaneously want to repair. Despite the method of opening a cell membrane, including mechanical force, electric field, thermal field, and so on, the influx of calcium ion gradient was first served to the repair process.\(^{69}\) The small holes that are usually smaller than 100 nm could be repaired by the following endocytosis and exocytosis. Larger holes were riskier and repaired by intracellular vesicles. It is important to note that different damage size, losing of cytoplasm, temperature, and cell type all result in different repair effect.\(^{35}\)
Theoretical and experimental investigations have been executed to illustrate the mechanical force for rupture and pore formation of membrane. The modulus of cell membrane was evaluated by AFM. The first peak of force related to displacement was the critical force (the product of modulus and contact area) for mechanically opening the cell membrane, as shown in Figure 2D. The modulus of cell membrane is also dependent on cell types and variability; to the best of our knowledge, the reported minimum critical stress ($\sigma$) is $0.6 \times 10^4$ N/m.\textsuperscript{62,71} Accounting swimming nanorobot with the characteristic size of $\sim 1 \mu m$, for mechanically opening a cell membrane, the applied force of swimming nanorobot on the cell membrane is estimated to be 6000 pN. In other words, the velocity of the swimming nanorobots comparable to 1 cm/s enables the opening of cell membrane. Therefore, the early works of intracellular drug delivery by swimming nanorobot were usually achieved by internalization.

3 | ENHANCED INTERNALIZATION OF SWIMMING NANOROBOTS

As discussed above, although the swimming nanorobots are available to be navigated toward the targeted cells, penetration of cell membrane is difficult because the driving force of swimming nanorobots is insufficient to mechanically open the cell membrane. In the early stage of the study, the swimming nanorobots or loading cargos were internalized into the cell through endocytosis. The difference between opening a cell membrane and endocytosis leads to different drug delivery time and efficiency. The endocytosis was the route of cellular uptake with limited particle size less than 100 nm. Also, the endocytosis often results in low cytosolic release (the amount of release is usually smaller than 10%) and long endocytosis time (usually hours and relying on cellular type, temperature, and media condition).\textsuperscript{38} Even though the swimming nanorobot promises the active delivery in various biomedium, the efficiency of swimming nanorobot drug delivery is limited by the biological barriers of cell membrane.

3.1 | Internalization of loading cargo

The precision targeting drug delivery was usually achieved by magnetically propelled swimming nanorobot (Figure 3A). The Au/Ni/Si nanorobot with a length of $\sim 5 \mu m$ and a tip diameter of $\sim 50$ nm was manipulated to actively target the cell by utilizing a magnet.\textsuperscript{59} Loaded with green fluorescent protein (eGFP) expression plasmids, the swimming nanorobots approach to the adherent U87 glioblastoma cells with magnetic navigation, and the fluorescence in eGFP channel from the glioblastoma cells verified the internalization of eGFP into the cell after incubation for 24 h. Despite the efforts attempt to reduce the contacting area with the cell membrane and elevate the velocity to 5 $\mu m/s$, the force applied by the swimming nanorobot was still insufficient to open cell membrane mechanically.

Electric field could also be utilized to navigate the swimming nanorobots. Two pairs of parallel electrodes with typical voltages (called as electric tweezers) control nanowire orientation and movement in cell media (Figure 3B).\textsuperscript{6} The electric field with typical voltages did not affect the viability of the most cells in swimming nanorobot navigation. Once navigated with tumor-necrosis factor-alpha cytokine (TNF-$\alpha$; which worked by inducing nuclear factor-kappaB in cells) coated gold nanowire to the targeted cell, the swimming nanorobots do not penetrate the cell membrane directly, but stimulated the cells expressing fluorescence. The fluorescence change illustrated the translocation of nuclear factor-kappaB by immunocytochemical staining of p65, suggesting the internalized delivery of TNF-$\alpha$.

3.2 | Enhanced internalization by acoustically driven motion

As another nondestructive technology, acoustic field (ultrasound) provides a route to power the swimming nanorobots for the intracellular delivery. In the acoustic chamber, swimming nanorobot would move to the suspending levitation plane and then move toward the pressure node due to the acoustic standing wave.\textsuperscript{73} By frequency regulation, swimming nanorobot could be controlled and move toward the target cell. The swimming nanorobots based on various metals (such as gold, copper and galium) could behave significantly active motion than pure polymer particles under exposure of acoustic field, suggesting that the fabrication materials play a critical role in acoustically propelled motion.\textsuperscript{74} A rod-like liquid metal swimming nanorobot was driven by acoustic field and navigated toward cancer cells in Figure 3C. The liquid metal swimming nanorobot was fabricated by pressure-filter-template technology with length of 5.5 $\mu m$ and diameter of $\sim 400$ nm. The velocity of the swimming nanorobot was $\sim 23 \mu m/s$ under exposure of acoustic field. The internalization of the liquid metal swimming nanorobot was also accomplished by incubation swimming nanorobot and cells with 24 h. Another acoustically propelled single-stranded DNA (ssDNA)/graphene oxide-coated gold swimming nanorobot performed similar active targeting and internalization process, as schematic in Figure 3D. The acoustically propelled gold nanowire illustrated an internalization time of 20 min after contacting the cell. The internalization time is much shorter
than the previous report of swimming nanorobot. So, the acoustic field enhances the internalization process and decrease internalization time, suggesting that acoustic field may increase the probability of contacts between swimming nanorobot and cell membrane.

As per the above-discussed driving method, the delivery of cargos by magnetically, acoustically, and electrically propelled swimming nanorobot most relied on the internalization process. Even for the swimming nanorobots with a tip diameter of 50 nm, a longer internalization time is requested. Therefore, swimming nanorobots could not mechanically open the cell membrane due to insufficient driving force without special strategies of opening a cell membrane.

4 | MECHANICALLY OPENING A CELL MEMBRANE

Suffering from low efficiency and long period during the internalization process, the active opening of a cell membrane was carried out. However, based on the data in Figure 2B, we can qualitatively obtain the limitation of swimming nanorobots’ driving force. Thus, the strategies of increasing driving force, decreasing contact area, and permeabilization were explored.

4.1 | Microdrilling

The driving force of microrobot was usually larger than that of swimming nanorobot. Therefore, with comparable contact area, it was easier for microrobot to mechanically open cell membrane. As shown in Figure 4A, the microrobot enabled precise opening of cell membrane through their magnetically powered rotation. The microrobot was extracted from Dracaena sp. with tip of ~1 μm, width of 2.5 μm, and length of 60 μm (Figure 4B). In rotating magnetic field, the microrobot illustrated vertical drilling at 800-1600 rpm. Thus, after navigating the microrobot onto the cell by regulating magnetic field, the microrobot could serve a tangential force to the cell membrane. The
FIGURE 4 Microrobot for mechanically opening a cell membrane. Reproduced with permission. Copyright 2015 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (A) Schematic of the microrobot drilling on the cell membrane. (B) Microscope image of the microbotubes. (C) Brightfield and fluorescence images of microrobot drilling on the cell membrane and opening the cell membrane.

The cell illustrated red fluorescence after microrobot drilling process, suggesting that the cell membrane was opened by the microrobot and the extracellular propidium iodide entered into the cell. Although the microrobot drilled hole on the cell membrane with magnetic rotation, the further in vivo application was also obstructed due to the microscale.

4.2 Permeabilization of cell membrane

For further biomedical application, smaller swimming nanorobot should be utilized to open cell membrane. Even the contact area becomes smaller, the driving force of smaller size swimming nanorobot also decreased with the size, so the applied pressure on the cell membrane could not reach the critical pressure to open the cell membrane. Therefore, the permeabilization that makes the cell transiently permeable to swimming nanorobot with increasing fluidity and nanopores is considered.

As shown in Figure 5A, we consider the four steps of opening the cell membranes and assume that the velocity and acceleration of swimming nanorobot are zero at maximum deformation of cell membrane to predict force for mechanically opening the cell membrane, because the whole propulsion force of swimming nanorobot contributes to the applied force on the cell membrane in this assumption. In the example of the Janus mesoporous silica nanorobot in Figure 5B, the near-infrared (NIR) light-powered Janus mesoporous silica swimming nanorobot moved toward the target cell via photothermal effect caused by self-thermophoretic force. The diameter of sphere swimming nanorobot is 70 nm (transmission electron microscopy (TEM) image in Figure 5C). The estimated pressure on the cell membrane is 1.7 N/m,
4.3 Photomechanically opening

Considered the drive force is not enough to open the cell membrane, recent efforts attempt to realize the swimming nanorobot to perforate cell membrane through addition of extra forces. The swimming nanorobot achieved mechanical opening of cell membrane with the assistance of NIR light irradiation. The gold nanoshell-functionalized polymer tubular swimming nanorobot with a length of 10 μm possesses asymmetric geometry along the long axis (big opening of ~800 nm, and small opening of ~200 nm). The big opening functionalized by gold nanoshells led to small opening leading orientation and benefits the acoustically propelled motion. By regulating the frequency of acoustic field, the swimming nanorobot moved toward the targeted cell (Figure 6A). A small amount of swimming nanorobots with big opening leading orientation were bounced off once it touched the cell. The swimming nanorobots with small opening leading orientation could attach the cell membrane but could not open cell membrane due to insufficient applied force on cell membrane (Figure 6B). With the assistance of NIR light on the big opening, instantaneous photothermal force vertical to the long axis was generated, which was theoretically sufficient (~10^{-9} to ~10^{-8} N) to open cell membrane. This photothermal force was also utilized to propel swimming nanorobot in previous reports, which illustrated a superfast NIR-driven microrobot with velocity of 160 μm/s. Given that the velocity was recorded using a camera with equalization, the practical instantaneous velocity and acceleration would be larger. After NIR irradiation, the swimming nanorobot was inserted into the cell membrane and confirmed by position-dependent fluorescence change in nucleus, CLSM rebuilding image, and SEM image (Figure 6C). The mechanical opening of cell membrane by the tubular swimming nanorobot relied on the force perpendicular to the cell membrane, illustrated as mechanical injection. In contrast, the microrobot in Figure 4 applied a tangential force on the cell membrane, illustrated as microdrilling. In contrast to the permeabilization of heat-mechanical swimming nanorobot, the cell perforating process of the swimming nanorobot in Figure 6...
Mechanically open cell membrane with swimming nanorobot. Reproduced with permission. Copyright 2019 American Chemical Society. (A) Schematic of the acoustically propelled swimming nanorobot opening a cell membrane with assistance of near-infrared (NIR) light. (B) Time-lapse images illustrating the nonattachment of a big opening leading swimming nanorobot and end-on attachment of a small opening leading swimming nanorobot. (C) Time-lapse image, fluorescence image, confocal laser scanning microscopy (CLSM) image, and scanning electron microscopy (SEM) image of the swimming nanorobot opening a cell membrane and inserting into the cell.

The roughness of swimming nanorobots for clinical transformation.

4.4 Simulation of opening the cell membranes

For further understanding the mechanical process of opening a cell membrane, the numerical calculations have also been established. The swimming nanorobot was studied as a particle moving with a constant driving force, and the cell membrane was composed of particles that have dipolar, steric, and elastic interactions with each other (Figure 7A). With insufficient driving force, the swimming nanorobot would be trapped by the cell membrane, illustrated as blue square in Figure 7B. The numerical calculation also reveals that larger driving force benefited the further repair process of the cell membrane, and the increase in mem-

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brane elasticity decreased the penetration ratio, which agreed with the experimental results. The theory verified that the opening of cell membrane occurs when the driving force was larger than the restoring forces of membrane, smaller swimming nanorobot would benefit the repair process (Figure 7C), and higher velocity increased the penetration ratio (Figure 7D). Even though the theory gave a simplified view of opening a cell membrane and particle system of cell membrane, the analytical theory also revealed the optimal direction of opening a cell membrane by swimming nanorobot: driving force, initial velocity, size, contact area, and the properties of cell membrane.

5 | CONCLUSION AND OUTLOOK

In this review, we give a briefly theory of mechanically opening a cell membrane by swimming nanorobot. By summarizing the factors that influence the driving force of swimming nanorobot and the properties of cell membrane, we discuss the critical condition of swimming nanorobot for mechanically opening a cell membrane. However, to the best of our knowledge, the mechanically opening a cell membrane by swimming nanorobot still needs improvement. The mentioned methods in Section 4 have different disadvantages, including too large size, heating effect, and complex propulsion process. The undesired death of cell also indicates that opening process should be optimized, which means the waste of propulsion. Nevertheless, the micro-/nanorobot-based perforation of cell membrane still holds promises for the further application, including precise intracellular delivery, precise cell surgery, genome editing, and physical therapy, distinguishing from the traditional method for opening a cell membrane method including electroporation, thermal poration, optoporation, nanowire, and microinjection. The mechanical opening of cell membrane by swimming nanorobot could also be further optimized, including more powerful biocompati-
ble driving mechanism, higher energy exchange efficiency, materials, shape, and less contact area. The permanent damage that influences repairing process after opening a cell membrane should also avert. Even though the design of the swimming nanorobot is limited, the properties of cell membrane, such as permeabilization, could also be utilized and explored to benefit cell membrane opening process. In the future, such swimming nanorobot capable of mechanically opening a cell membrane could help to better understand the biophysical characteristics of cells and pave the way to precision medicine.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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