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Emerging Biomimetic Applications of DNA Nanotechnology

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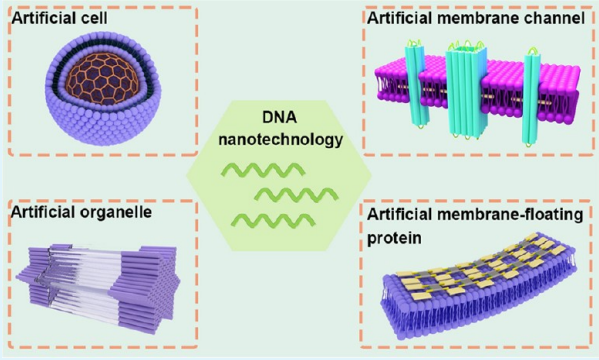
ABSTRACT: Re-engineering cellular components and biological processes has received great interest and promised compelling advantages in applications ranging from basic cell biology to biomedicine. With the advent of DNA nanotechnology, the programmable self-assembly ability makes DNA an appealing candidate for rational design of artificial components with different structures and functions. This Forum Article summarizes recent developments of DNA nanotechnology in mimicking the structures and functions of existing cellular components. We highlight key successes in the achievements of DNA-based biomimetic membrane proteins and discuss the assembly behavior of these artificial proteins. Then, we focus on the construction of higher-order structures by DNA nanotechnology to recreate cell-like structures. Finally, we explore the current challenges and speculate on future directions of DNA nanotechnology in biomimetics.



KEYWORDS: *DNA nanotechnology, self-assembly, DNA origami, membrane protein, artificial cells*

INTRODUCTION

Cell constitutes the basic functional and structural unit of life.[1] It can manage numerous biological processes, such as signal transduction, energy conversion, and intercellular communication, to name a few.[2] In recent years, re-engineering the structures and functions of cell and controlling over these biological processes exactly at micro−nanometer scale have elicited great interest.[3] Replication of these cellular processes can not only deepen our understanding on the molecular basis of life activities and further promote the applications of these biological mechanisms in areas such as artificial intelligence but also provide a simple model to unravel the mechanisms under disease occurrence/development and pave the way for medical diagnosis/treatment.[4,5] It is, therefore, imperative to develop biomimetic systems to mimic cellular components and biological processes.

DNA, known as carriers of genetic information, is an easily accessible macromolecules.[6−8] Taking advantage of the programmable self-assembly ability, DNA is considered as a powerful building material for the creation of nanostructures with specific shape and function.[9−11] The development of DNA origami technology has further revolutionized the application of DNA nanotechnology.[12−14] DNA origami enables folding of a long, single-stranded DNA into custom-shaped structure by a large number of short "staple" strands. Moreover, each strand used in the construction of DNA nanostructure can be independently functionalized with various chemical tags and biomolecules, making it possible to place tailored functionalities into the three-dimensional structure with defined orientation and precision.[15,16] Dynamic DNA nanotechnology, in which stimuli-responsive DNA machines are constructed, could be an alternative to illustrate dynamic behaviors at micro/nano scale.[17−19] Most importantly, because of the high biological compatibility, DNA molecules can be used safely in natural biological process.[20−22] By exploiting these interesting properties, DNA nanotechnology represents a unique tool for mimicking cellular components and processes.

Indeed, in recent years, a number of DNA nanostructures with different structures and functions have been reported for re-engineering of natural systems.[23,24] A typical example is the artificial membrane channel constructed by DNA origami technology.[25,26] This biomimetic channel is analogous to natural membrane-spanning channel manipulated by membrane proteins. Moreover, the polymerization of DNA origami blocks on lipid bilayer also opens up a new opportunity to study the assembly behavior of membrane-associated proteins.[27] For the purpose of studying more complicated cellular functions, the full design scope offered by DNA nanotechnology can be exploited to create higher-order structures. Inspired by natural compartmentalization, such as cellular organelles, scientists have constructed a series of DNA origami-based nanocontainers to conduct enzyme catalytic reactions. Moreover, scaffolds constructed by DNA origami technology can serve as rigid cytoskeletons to re-engineer cell-like structure. Here, the aim of this Forum Article is to summarize the recent progresses of DNA nanotechnology in biomimetic applications. We will highlight

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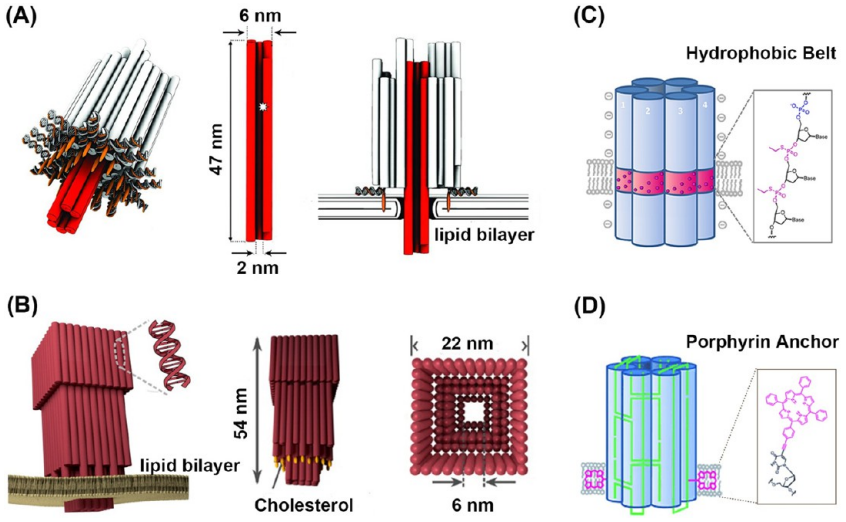

Figure 1. DNA-based membrane channels. (A) Schematics illustration of the synthetic DNA membrane channel. Red part denotes the transmembrane stem channel surrounded by a barrel-liked cap with 26 cholesterol moieties. Reproduced with permission from ref 25. Copyright 2012 The American Association for the Advancement of Science. (B) Structures and sizes of the large funnel-shaped DNA porin. Cholesterols were introduced to form membrane porin. Reproduced with permission from ref 43. Copyright 2016 American Chemical Society. (C) Schematic representation of the DNA channel features a charge-neutral hydrophobic belt. Reproduced with permission from ref 44. Copyright 2013 American Chemical Society. (D) DNA nanopore with two porphyrin-based lipid anchors. Reproduced with permission from ref 45. Copyright 2013 John Wiley and Sons.

important examples of DNA-based artificial membrane proteins, artificial organelles, and artificial cells and further speculate on the future directions in DNA-based biomimetics.

DNA NANOSTRUCTURE-BASED ARTIFICIAL MEMBRANE CHANNEL

Diverse arrays of biological processes are performed by proteins.[28] Among these proteins, membrane-spanning proteins play an important role in many fundamental pathways, such as ions or molecules transport, signal transduction, and cellular communication.[29,30] Re-engineering these channel proteins and their operation processes is vital for understanding the structure−function relationships and translating these processes into biomedical applications.[31,32] However, because of the high complexity of cellular environment and the sensitivity of channel proteins, it is quite difficult to access these processes directly.[33,34] Intriguingly, the development of DNA nanotechnology has made great progress toward the construction of biomimetic channels to expound the mechanisms of membrane proteins.[35] On the basis of the classic Watson−Crick base-pairing principle and DNA origami technology, a number of DNA-based nanopores with different sizes and lengths can be obtained de novo just by the simple programmable self-assembly.[36−38] These artificial membrane nanopores have shown significant similarity with natural membrane channels when inserted into lipid bilayers or the membrane of natural cells.

However, one of the central challenges in re-engineering of DNA-based membrane channels is to overcome the unfavorable interaction between the hydrophilic, negatively charged DNA nanostructures and the hydrophobic membrane environment. To overcome this obstacle, some strategies have been developed to insert DNA nanostructures into the hydrophobic center of lipid bilayer.[39−41] Simmel and co-workers constructed a synthetic membrane channel by means of DNA nanotechnology (Figure 1A).[25] The channel structure was inspired by natural membrane channel protein α-hemolysin. This DNA nanopore was consisted of two modules. A tube-liked stem with a length of 47 nm and an inner diameter of 2 nm was constructed by six DNA duplexes. This stem could serve as the transmembrane channel to penetrate lipid bilayers. A barrel-like cap with 26 cholesterol moieties was around the stem and could adsorb to the surface of lipid membrane. Transmission electron microscopy showed that this artificial DNA channel could bind to lipid vesicles in the desired manner. Single-channel electrophysiological measurement also indicated similar responsive features with natural protein channel, such as current gating and conductance. In general, the size and shape of synthetic DNA nanopore could be regulated simply by changing the numbers of DNA strands.[42] Following this route, a funnel-liked DNA-based porin was obtained to expand the space of nanopore (Figure 1B).[43] M13mp18 scaffold and 179 DNA staples were used to construct this DNA porin and 19 cholesterol anchors were introduced to facilitate the forming of membrane channel. The diameter of the cross section is 6 nm, which is wider than previous reported synthetic channels and comparable to the nuclear pore complex. These works demonstrate that DNA nanopores with different sizes and shapes can be constructed with various scaffolds and cholesterol-assisted membrane anchoring is a feasible method for recreating DNA-based membrane channel.

Another strategy for the construction of DNA-lipid assemblies is inspired by the amphiphilic nature of membrane proteins. Hydrophobic residues were well patterned around the membrane channel protein, which was coordinated with the nonpolar environment of lipid membrane. In this way, a hydrophobic belt was introduced to the outer surface of DNA backbone to construct artificial membrane channel. Howorka group reported a hollow channel that is enclosed by six DNA double-helixes (Figure 1C).[44] Then, a charge-neutral and hydrophobic belt of alkylphosphorothioates (PPT) with an ethyl moiety was introduced to the DNA strands, thereby masking the negative charge of the phosphate backbone. This strategy could overcome the inherent energetic mismatch between the negative charged DNA and the hydrophobic membrane environment. Obviously, most strategies for creating

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of DNA-based membrane channels need a large number of anchors.[25,43,44] With the purpose to simplify design strategies, Howorka and co-workers further reported a membrane-spanning channel with two porphyrin-based hydrophobic tags (Figure 1D).[45] According to their studies, solely two porphyrin derivative tags could meet the criterion of strong hydrophobicity to facilitate the anchoring of highly negatively charged DNA into the lipid membrane. Moreover, the fluorescent feature of the porphyrin tags allowed the visualization of the artificial membrane channel. This research for simplification of chemical anchors will increase flexibility in DNA-based nanostructures and promote many other applications such as biosensing and biomedical research.

The above-mentioned DNA nanostructures-based artificial membrane channels feature hollow channels with open ends. It is highly desired to develop artificial membrane channels with stimuli-responsive opening or closing property.[46] To advance the field of biomimetic channels, stimuli-responsive DNA nanotechnology have been exploited to extend the intelligence of artificial membrane channels.[47] On the basis of their previous work, Howorka et al. reported a ligand-controlled DNA channel to transport charged cargo across the biological membrane (Figure 2A).[48] The membrane-spanning channel was designed

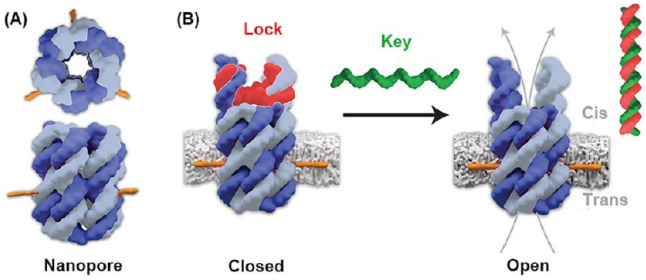

Figure 2. A rationally designed ligand controlled DNA channel. (A) Structural model of the synthetic nanopore. (B) Schematic illustration of the operating mechanism of the ligand-controlled membrane channel with lock strand (red) and key strand (green). Reproduced with permission from ref 48. Copyright 2016 Springer Nature.

with three steps. First, an opening barrel structure was formed by six concatenated DNA strands. A height of 9 nm was designed to match the thickness of the lipid bilayer. Then, a molecular gate was introduced to the entrance of the barrel. In brief, two duplex staves extended on the end of the barrel served as the docking sites and were able to hybridize with a simple "lock" strand by complementary pairing to close the channel. Importantly, the "lock" could be reopened upon binding with a "key" strand and released from the channel. As a final step, the channel was equipped with hydrophobic cholesterol moieties and further anchored into the lipid bilayer (Figure 2B). This obtained membrane-spanning channel can selectively transport small organic molecules across the lipid membrane.

Liu et al. reported a switchable DNA origami channel with a shutter at one end to control channel dimension.[49] This channel could be reversibly switched by DNA chain exchange reaction. In brief, a rectangle origami block with a row of DNA staple strands at one end of the concave side was rolled up to form the DNA nanochannel. After that, the staple strands could serve as the shutter of the channel. By adding the lock strands, which were complementary to the shutter strands, the pore was locked because of the forming rigid DNA duplexes. Moreover, by synthesizing the lock strands with a reasonable mismatch, locks could only be displaced from the shutter with their fully complementary sequences, and thus reopen the channel in a user-defined manner (Figure 3). The feasibility of this strategy

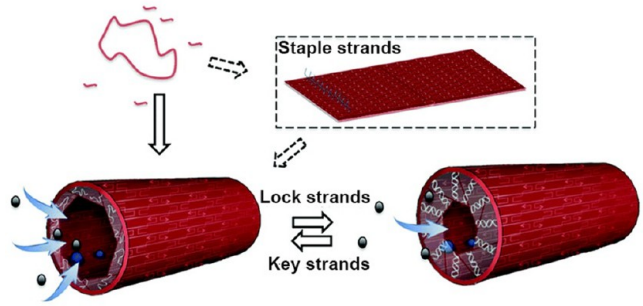

Figure 3. Schematic illustration of the switchable opening and closing of the synthetic DNA origami channel. Reproduced with permission from ref 49. Copyright 2016 Royal Society of Chemistry.

was confirmed by an enzyme cascade catalytic reaction. The responsive channel constructed in this study provides not only a simply strategy for recreating artificial membrane channels with more complex functions but also a powerful platform for investigating the operational mechanisms of natural membrane channels.

The works summarized in this section suggest that recreating membrane channel with DNA nanotechnology is an appealing field to understand questions concerning how channel proteins work. Future research interest in this field is to explore more flexible DNA pore architectures with various morphology and function. How to combine DNA-based channels with natural proteins and other components is another task to construct multifunctional membrane channel that rivals natural ones. With further progress in DNA nanotechnology, it is anticipated that a range of membrane channel events can be simulated by DNA-based nanopores.

DNA NANOSTRUCTURE-BASED MEMBRANE-FLOATING PROTEINS

In addition to biomimetic membrane-spanning proteins, cell membrane also contains a lot of membrane-floating proteins that play crucial roles in life activities.[3,50] Generally, many of the cellular functions such as cell adhesion, compartmentalization, and immune responses are mediated by the dynamic multistate assembly of membrane-floating proteins.[51] For example, clathrin is able to assemble into complexes upon receptor activation, which plays an important role in the formation of transport vesicles during endocytosis.[52] Moreover, the assembly behaviors of membrane proteins can dynamically change the morphology and function of cell membrane.[53] Thus, it is of great importance to illuminate the assembly behavior of membrane-floating proteins.

The successful construction of membrane-spanning DNA nanopores also urges researchers to imitate membrane-related events by DNA nanostructures, such as the assembly behavior of membrane-floating proteins. DNA origami technology allows building of various blocks with arbitrary shapes, including squares, rectangles, stars, and so forth. These highly modular blocks are capable of assembling into large-scale structures in a programmable manner.[54−56] With rational design, DNA nanostructures with the same length scale as membrane-floating proteins can be obtained. To mimic the assembly behavior of

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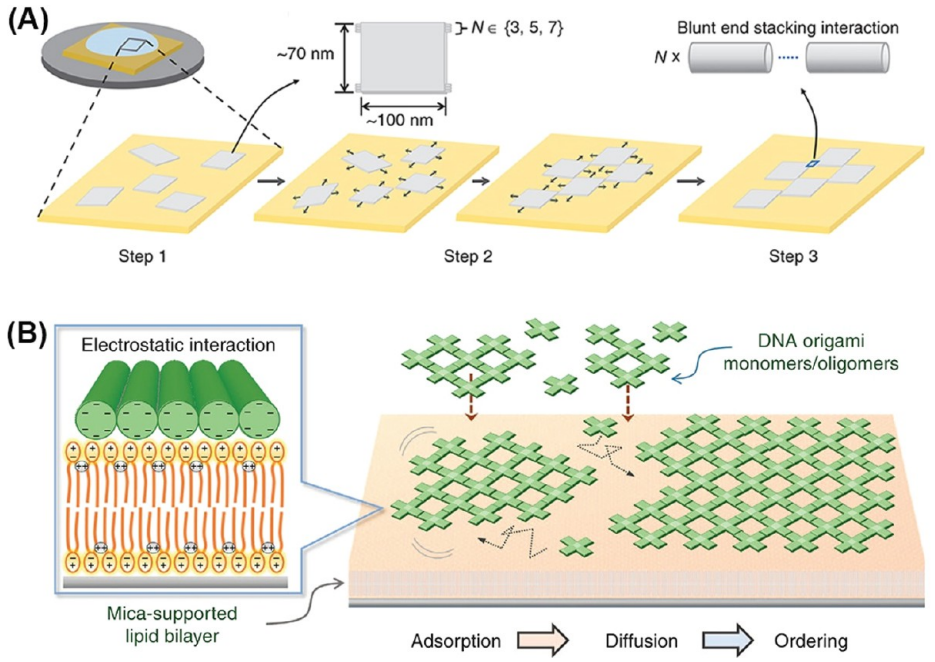

Figure 4. Schematic representation of the surface-assisted self-assembly behavior of unmodified DNA origami blocks in the presence of divalent cations. (A) Assembly of rectangular origami on the mica surface. Reproduced with permission from ref 61. Copyright 2014 Springer Nature. (B) DNA origami assembly on a mica-supported lipid bilayer. Reproduced with permission from ref 62. Copyright 2015 Springer Nature.

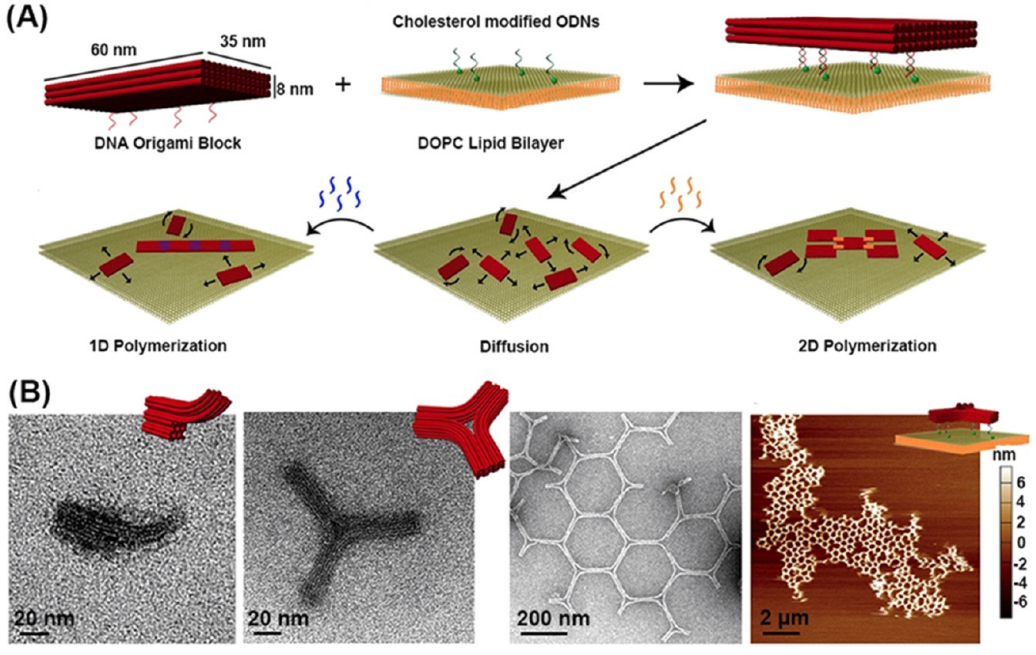

Figure 5. Self-assembly of cholesterol modified DNA origami blocks on lipid membrane. (A) Schematic representation of the construction and self-assembly of three-layered rectangular on DOPC lipid bilayer. (B) TEM and AFM images of DNA origami structures. From left to right: Y-shaped DNA origami block, a DNA triskelion assembled from three Y-shaped blocks, hexagonal lattices polymerized from DNA triskelions. Reproduced with permission from ref 27. Copyright 2015 American Chemical Society.

membrane-floating proteins by DNA nanotechnology, the system should satisfy two conflicting conditions: tethering DNA nanostructures onto the surface of substrate membrane and, concurrently, ensuring the mobility of these blocks for assembly.[57] For this purpose, the successful building of DNA-based assemblies on supported membrane has been achieved via various approaches.[58]

Unmodified DNA duplexes and DNA nanostructures can be electrostatically attached to the zwitterionic lipid membrane surface in the presence of divalent cations.[59] In this way, Simmel et al. studied the surface-assisted assembly of 2D DNA origami structure via the monovalent cations-controlled electrostatic binding.[60] Similarly, Rothemund and co-workers also demonstrated the successful self-assembly of DNA origami structure into two-dimensional checkerboard by rationally controlled

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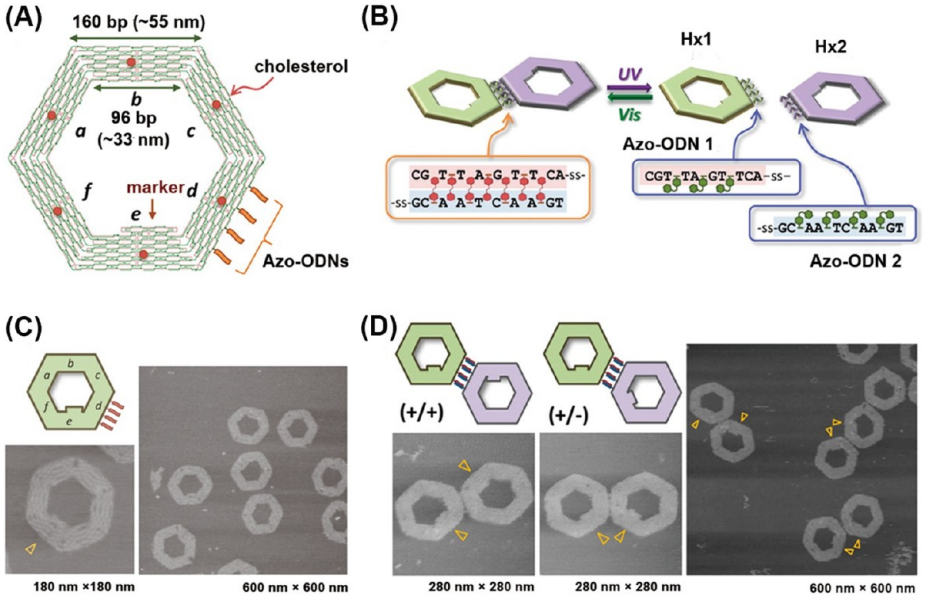

Figure 6. Photoresponsive reversible assembly of DNA origami structure. (A) Schematic representation of the hexagonal block. (B) Reversible assembly/disassembly of the origami dimer under UV/vis irradiation. AFM images of hexagonal monomer (C) and assembled dimers (D). Reproduced with permission from ref 64. Copyright 2014 American Chemical Society.

cations concentrations (Figure 4A).[61] However, as the high ions concentrations used in these techniques are far from the suitable conditions for DNA folding, Sugiyama and co-workers used a mica-supported zwitterionic lipid 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC) as the supported substance, and demonstrated that DNA origami could be adsorbed to the substance membrane and self-assembled into high-order lattices under the optimized condition (Figure 4B).[62]

DNA nanostructures can also be modified with anchors and further immobilized on the lipid membrane to study the in situ self-assembly behavior.[3] In 2015, Liedl et al. reported two DNA origami structures to mimic the assembly of membrane-floating proteins (Figure 5).[27] One is a three-layered rectangular with dimensions of 60 nm × 35 nm × 8 nm. Four staple oligonucleotides were extended from the bottom of the rectangular. The anchoring of origami blocks onto the lipid membrane was achieved by hybridization with the cholesterol-TEG-labeled oligonucleotides which were prelocated into the DOPC lipid bilayer. In their design, the rectangular would transform into different assemblies (end-to-end polymerization for one-dimension and corner-to-corner connection for two-dimension) by adding different sticky ends. The assembly could be demonstrated by transmission electron microscopy (TEM). The other reported DNA origami structure was inspired by the natural clathrin protein, which would assemble into polyhedral networks during membrane budding. This DNA architecture was nearly Y-shaped and one of the arms was truncated. The remained arms formed a 60° angle and the tip of the arm could be connected to the truncated arm. Therefore, three Y-shaped blocks could assemble into a triskelion structure. Moreover, the triskelion could be transformed into high-order hexagonal arrays with the same strategy. The successful assembly of such bioinspired structures demonstrate the potential of DNA nanotechnology in mimicking cellular self-assembly behaviors.

Most assembly behavior of protein is reversible in nature.[63] It is thus of great importance to control the assembly of DNA nanostructure in a switchable manner. Sugiyama and co-workers demonstrated that the reversibility could be achieved by a light-inducible hexagonal origami structure. In their works, the d-edge of each origami monomer was functionalized with four oligodeoxynucleotides (ODNs) which carries *trans*-form azobenzene (Azo) molecules (Figure 6A).[64] To verify feasibility of this method, two hexagonal monomers with pseudocomplementary Azo-ODNs, named Hx1 and Hx2 respectively, were used as models in this study. Hx1 and Hx2 would assemble into dimers under vis-irradiation due to the hybridization of the ODNs. Correspondingly, disassembly of the dimers was induced by UV irradiation because of the configuration change of azobenzene molecules. Hence, the reversible assembly behavior of DNA origami monomers could be governed by photo irradiation (Figure 6B). Furthermore, when cholesterol-TEG anchors were modified at the bottom face of the hexagonal origami, the reversible assembly/disassembly could be observed at the sphingomyelin-enriched phase-separated bilayer with atomic force microscopy (AFM) and transmission electron microscopy (Figure 6C, 6D). Moreover, in one of their another work, they also demonstrated that DNA origami blocks could assembly into predesigned multiorientational patterns with the same strategy.[65]

During the assembly of DNA-based blocks on the lipid membrane, an interesting phenomenon was discovered that the formation of DNA assemblies may also deform the morphology of vesicles.[27] This is similar to a class of membrane-sculpting proteins such as Bin-Amphiphysin-Rvs (BAR) domain superfamily that is important for membrane transformation and organization of numerous cellular processes.[66,67]

Petra Schwille and co-workers have published several works about mimicking the membrane deforming. In 2012, they reported an amphipathic DNA nanorod and assessed their switchable liquid-ordered/liquid-disordered behavior on free-standing phospholipid membranes.[68] Taking this off-the-shelf amphipathic DNA nanostructure as the membrane-scaffolding tools, they re-engineered the membrane-sculpting events by the oligomerization of these origami blocks. They synthesized a bulk 3D origami platform with a bottom flat face and a smaller top face (Figure 7A).[69] After that, several cholesterol-TEG anchors

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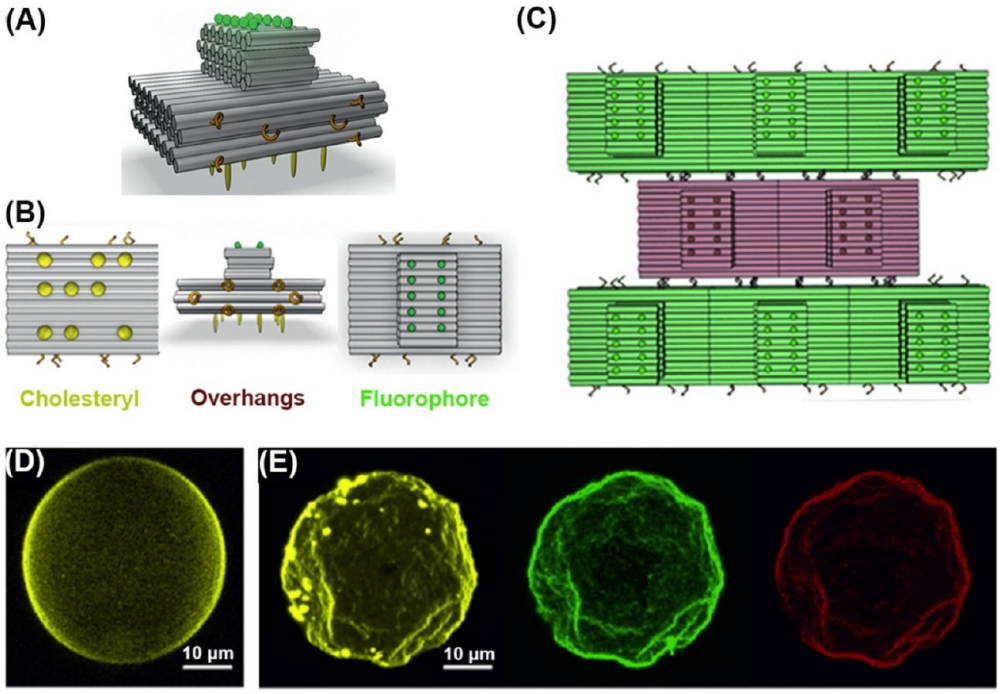

Figure 7. (A) Schematic illustrations of the constructed bulk 3D origami platform. (B) Diagrammatic sketch of the 3D origami with cholesterol-TEG anchors (yellow), sticky overhangs (orange), and fluorescent molecules (green) at different sites. (C) Formation of assemblies after mixing Construct A (green) and construct B (red). (D) 3D reconstruction of the free vesicle. (E) 3D morphology of vesicle bearing constructs A and B with sticky overhangs. Reproduced with permission from ref 69. Copyright 2015 John Wiley and Sons.

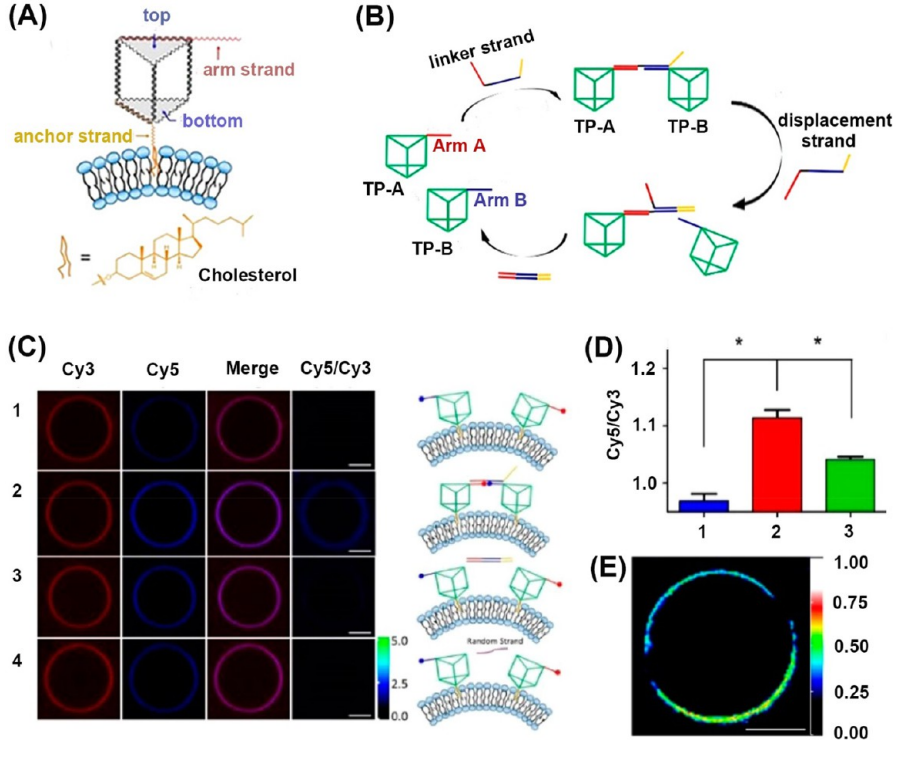

Figure 8. Schematic representation of the 3D DNA nanoprism. (A) Insertion of DNA triangular nanoprism on cell-derived vesicles. (B) Reversible assembly/disassembly of TP-A and TP-B by linker strand and displacement strand. (C) Confocal imaging of manipulation of DNA nanoprism on cell-derived vesicles. Each condition was illustrated at the right of the photos. (D) Normalized fluorescence intensity measurements. (E) Acceptor bleaching experiment to study FRET efficiency on an individual vesicle. Scale bar: 5 μm. Reproduced with permission from ref 78. Copyright 2017 American Chemical Society.

were modified at the bottom of the origami to attach to the membrane. Complementary single-stranded overhangs were introduced at the two opposing sites for the oligomerization of the origami blocks. Then, different fluorophores were placed to

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the top face for visualized detection (Figure 7B). In this way, they created two monomers, named construct A (with green fluorophore) and construct B (with red fluorophore), to observe the interactions between each blocks (Figure 7C). According to the results of fluorescence detection, free vesicles appeared well-defined spherical in shape and similar results were found by attaching constructs without overhangs to the vesicles surface (Figure 7D). In contrast, in the presence of intact constructs A and B, these blocks would assemble into large-scale scaffold and further drive the membrane transformation (Figure 7E). This work provides a new insight into the oligomerization mechanism of membrane-floating proteins and the transformation of living cell membrane during various physiological processes.

Many of the reported models for studying the dynamic assembly behaviors of DNA mimetic membrane-floating proteins are performed on artificial lipid membranes.[39,70,71] However, the natural biological membrane is more complex and has a significant difference with lipid bilayers. The physicochemical properties of membrane have a significance influence on the DNA-based dynamic assembly behaviors.[72,73] In recent years, vesicles derived from living cells have attracted great attentions.[74,75] Cell-derived vesicles sustain similar structure and physicochemical properties with biological membrane, and they possess superiority in mimicking the membrane-related behaviors.[76,77] Tan group took these giant membrane vesicles as the supporting membrane models and observed the in situ assembly/disassembly behavior of synthetic 3D DNA architecture.[78,79] In their work, a box-like triangular prism (TP) folded by three single-stranded DNAs was selected to construct the 3D model. One single-stranded DNA with specific sequence elongated from the top face was serving as the arm strand for assembly. Simultaneously, a cholesterol-labeled nucleotide sequence was elongated from the bottom side and served as the anchor strand to immobilize the DNA structure onto the giant membrane vesicles (Figure 8A).[78] After successfully construction of this 3D model, the assembly and disassembly behavior was investigated by rational design of different prisms. Two monomer triangular prisms TP-A and TP-B were created simply by decorating the top face of triangular prisms with alternative arm strands. TP-A and TP-B could assemble into dimeric nanoprism after hybridizing with linker strand and disassemble by adding a displacement strand (Figure 8B). The anchoring of DNA nanoprisms on cell derived vesicles was observed by multicolor fluorescence colocalization. Two fluorophores labeled DNA prisms, named TP-Cy3 and TP-Cy5 respectively, were used to study the assembly/disassembly process on membrane surface (Figure 8C and 8D). The assembly of two triangular prisms could be achieved by hybridizing with excess linker strands at 4 °C and a strong FRET efficiency was observed between two fluorescent dyes. In order to monitor the disassembly, 2-fold excess displacement strands were added and a decreased FRET efficiency was observed by confocal laser scanning microscopy imaging. Interestingly, the acceptor bleaching experiment showed a heterogeneous FRET efficacy around the vesicle, which demonstrated the heterogeneity of the cellular membrane (Figure 8E). These studies suggest the potential of cell-derived vesicles for re-engineering artificial cellular components and investigating the cellular behaviors.

In nature, the interactions between homologous/heterogeneous membrane-related proteins can dynamically influence the structure and function of cellular membranes. Works summarized in this section mainly focus on the dynamic assembly behaviors of DNA-mimicked membrane proteins and the ability of DNA assembly to change the morphology of vesicles. At this stage, the reversible assembly and disassembly should be more flexible and performed in a user-control manner. Additionally, the dynamics of these assembly reactions should be speeded up to meet practical applications, such as drug delivery and signal transduction.

DNA NANOSTRUCTURE-BASED ARTIFICIAL ORGANELLES

In nature, living cells always adapt a strategy called compartmentalization to perform multiple specific cellular reactions.[80] Among these compartments, organelles with specific structures and functions are essential to life and provide different optimal conditions for cellular reactions. Creating artificial organelles has triggered intensive interest as it offers a new sight to treat cellular dysfunctions and even in favor of the design of artificial cells.[81] Nowadays, the concept of artificial organelles is meanly focused on the liposome or polymersome structures.[82−84] However, several characteristics should be satisfied when creating artificial organelles. First, an inner chamber is needed to fully encapsulate guest molecules and support specific reactions. Second, structural integrity should be maintained in situ to protect activity of inner components. Third, the constructed structure should be suitable for cell-uptake.

DNA origami technology allows construction of nanoscale containers with multiple configurations and can serve as a promising approach to create artificial organelles.[85,86] The solid wall and internal cavity of nanocontainer make it possible to enclose cargo molecules.[87] Moreover, DNA nanocontainers with dynamic mechanisms have been realized to control the opening and closing states in a user-controlled manner.[88,89] Furthermore, both sides of the wall can be functionalized with various molecules, such as recognition motifs, gate sequences and even lipid molecules.[90,91] These characteristics described above hold many similarities with living organelles.

Scientists have demonstrated that DNA cages could be used to encapsulate biological molecules.[92−94] A rigid DNA tetrahedral cage has been reported to encapsulate several guest molecules such as Cytochrome C,[95] peptide,[96] transcription factor[97] and oligonucleotides[98−100] in a covalent or noncovalent manner. Knudsen and co-workers reported a DNA nanocage to encapsulate and release enzyme horseradish peroxidase in a temperature-controlled pattern (Figure 9).[101] In brief, edges of the DNA cage were covalently closed by 12 double-stranded B-DNA helices,[102] and then cage corners were obtained by interrupting double stranded helices with short thymidine linkers. To allow for temperature-controlled configuration change, one of the corners was replaced by a sequence that capable of folding into a hairpin structure. The dimension of the

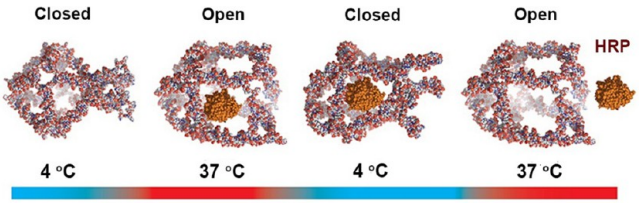

Figure 9. Temperature-controlled encapsulation and release of HRP in DNA cage. Reproduced with permission from ref 101. Copyright 2013 American Chemical Society.

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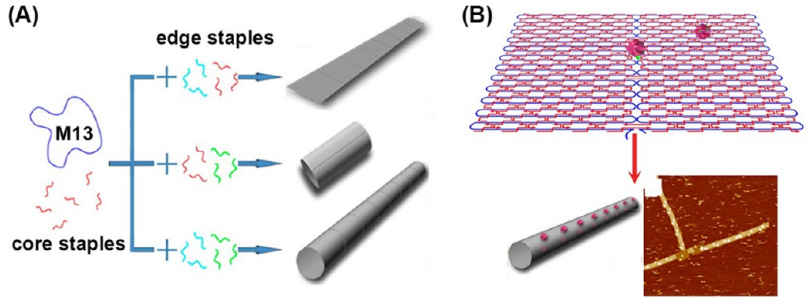

Figure 10. Design principles of DNA origami and protein array. (A) One-pot creation of DNA origami structures. (B) Schematic illustration of the streptavidin array on DNA nanotubes. Reproduced with permission from ref 108. Copyright 2013 American Chemical Society.

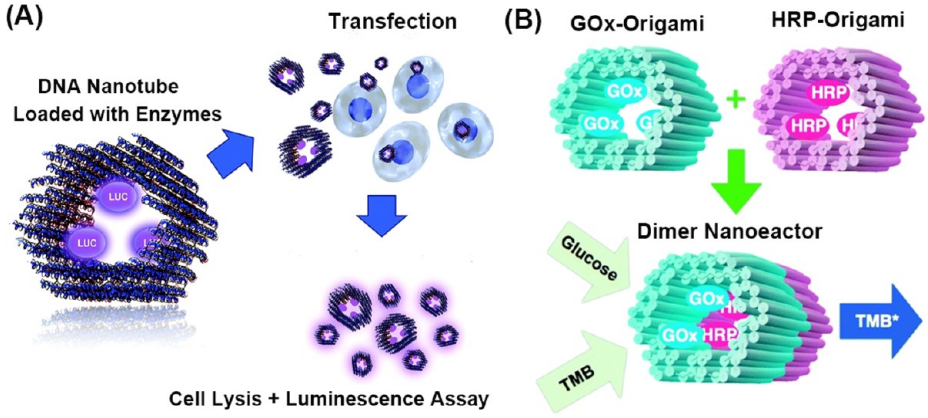

Figure 11. Tubular DNA origami-based enzyme nanoreactor. (A) Schematic representation of enzymes-loaded DNA origami tube is transiently transported into cells. Reproduced with permission from ref 109. Copyright 2016 Royal Society of Chemistry. (B) Working principle of the nanoreactor to control the enzyme cascade reaction of GOx/HRP pair. Reproduced with permission from ref 110. Copyright 2015 Royal Society of Chemistry.

cage adopted was able to accommodate enzyme HRP. Taking advantage of the annealing temperature of the hairpin structure (22 °C), the cage was expected to appear an open conformation at 37 °C and allowed the entrance or release of enzyme cargo. At a constant temperature of 4 °C, the cage transformed into a fully closed state to encapsulate HRP in the inner cavity.

As we all know, organelles possess a myriad of enzyme essential to life and are widely used to gate numerous complex reactions including multistep enzymes catalytsis.[82] Using this strategy, the local concentration of enzyme is elevated to enhance reaction efficiency. Simultaneously, the intermediates are shielded, thereby reducing competing cross-reactions and cell toxicity.[103,104] Taking inspiration from natural cellular organelles, various DNA origami container structures have been developed as artificial organelles to manage enzyme catalytic reactions.[105−107]

One of the simplest models of DNA-based nanoreactors is DNA nanotube. These tubular structures are capable of confining various biological molecules such as enzymes into a semiclosed interval, just as many natural cellular organelles do. Moreover, many cellular activities are also conducted in microtubules. Fan group reported a single-step method to synthesize DNA-based nanoreactors.[108] In this study, DNA nanoreactors could be fastly constructed by mixing scaffold strand (M13), core staple, and various edge staple strands in one-pot (Figure 10A). Meanwhile, streptavidin molecules could be anchored at different sites (upside and downside) of the origami monomer. After folding, one of the streptavidin molecules was inside of the obtained nanotube and the other was outside. These results suggested that the as-prepared DNA nanotubes could serve as addressable array for protein patterning (Figure 10B). Linko and co-workers also reported a tubular-like DNA origami container which was further loaded with active enzymes by avidin−biotin linking technology (Figure 11A).[109] Furthermore, this designed enzyme nanoreactor could be transported into cell as an artificial organelle. With the similar approach, Kostiainen and co-workers proposed an appropriate example to arrange enzyme cascade reactions by the modular nanoreactor.[110] Different enzymes could be placed into the internal cavity of each DNA nanotube. Then these nanotubes with desired functions were assembled together via DNA base pairing in a preprogrammed order. GOx and HRP were modified inside of the nanoreactors separately to illustrate the feasibility of this concept. Dimer nanoreactor was formed by mixing GOx-contained nanotube and HRP-contained nanotube. After that, glucose and 3,3′,5,5′-tetramethylbenzidine (TMB) were added to study enzyme cascades reaction (Figure 11B). The results demonstrated that the enzyme pair in assembled nanoreactor has a higher catalytic activity than free enzyme pair in bulk solution.

In addition to dimeric nanotubes, DNA origami nanocage was also used as artificial organelle to encapsulate enzyme pair. Yan group reported a DNA-based nanocage to conduct enzymes reaction.[111] Individual enzyme was attached into an open half-cage by cross-linking the lysine residue of enzyme to the thiol-modified oligonucleotide. Then two kinds of half-cage were mixed, followed by adding short bridge strands to form a full-DNA nanocage with an inner cavity dimensions of 20 nm × 20 nm × 17 nm. Moreover, several small holds with 2.5 nm in diameter were distributed at both surfaces of the nanocage to

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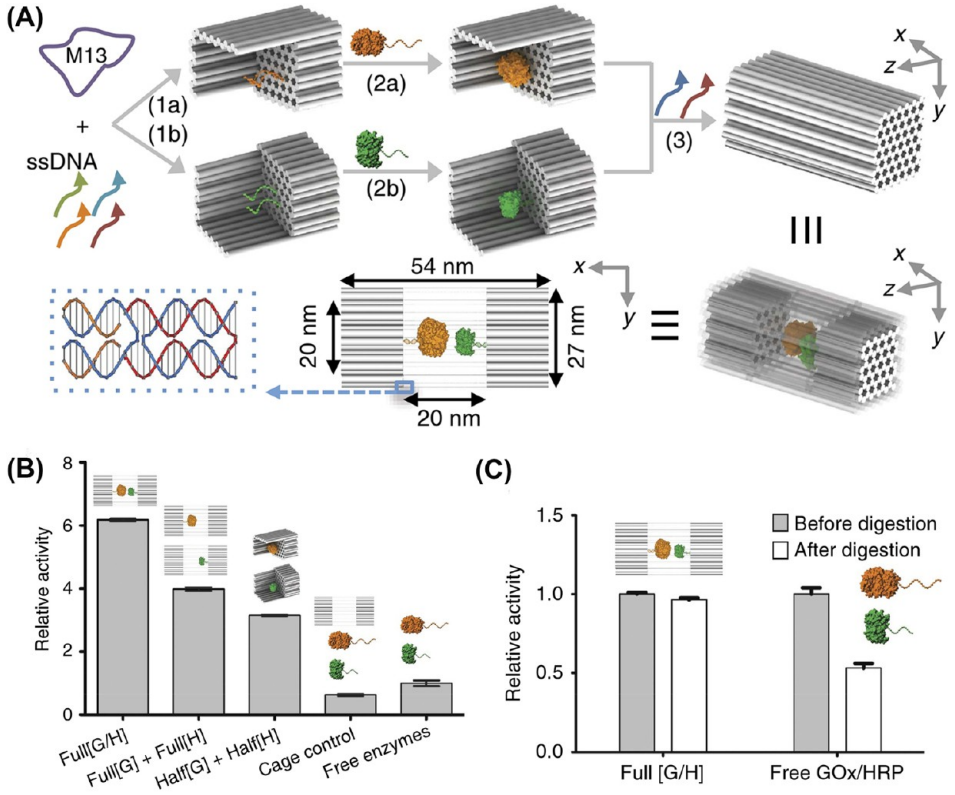

Figure 12. (A) Schematic illustrations of the encapsulation of individual enzymes and the assembly of two halves into a full DNA nanocage. (B) Normalized cascade activities of GOx/HRP pair at different assay conditions. (C) Relative catalytic activity of encapsulated enzyme pair and free GOx/HRP pair before and after protease-mediated degradation. Reproduced with permission from ref 111. Copyright 2016 Springer Nature.

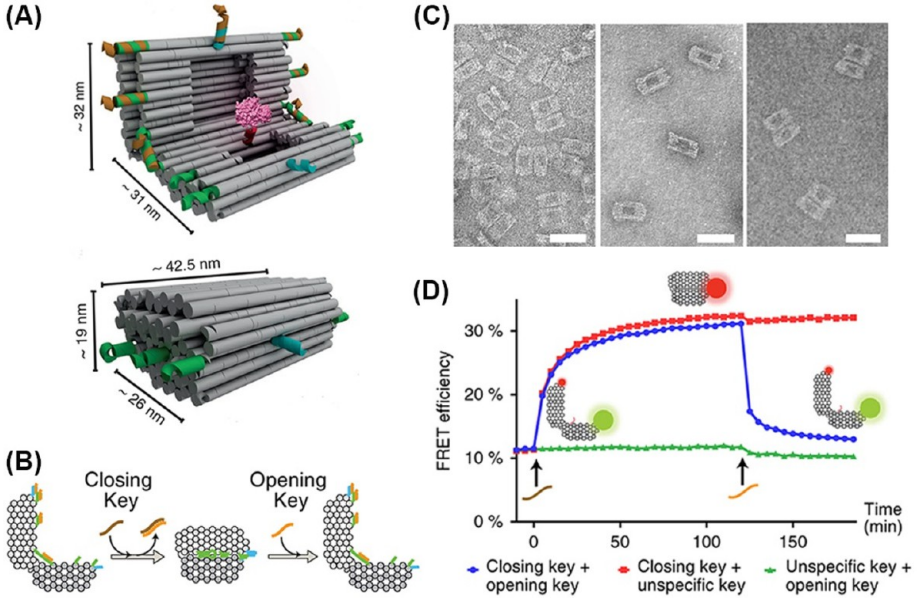

Figure 13. Structure and working principle of the DNA vault. (A) 3D schematic sketch of the DNA vault in the open (top) and closed (bottom) states. (B) Schematic of the opening-closing mechanism of DNA vault. (C) TEM images of DNA vaults in both open and closed states. Scale bar: 50 nm. (D) FRET efficiency of DNA vault at different conditions. Reproduced with permission from ref 113. Copyright 2017 Springer Nature.

promote the diffusion of enzyme substrates (Figure 12A). The successful encapsulation of GOx and HRP was verified by transmission electron microscopy. Glucose and 2,2′-azino-bis(3-ethylbenzthiazoline 6-sulfonic acid) (ABTS) were used to evaluate the catalytic activity of the encapsulated GOx/HRP pair. According to their results, catalytic efficiency of the encapsulated GOx/HRP pair was observably elevated than free enzyme pair (Figure 12B). They further showed that after incubation with trypsin for 24 h, more than 95% of the initial activity of the encapsulated GOx/HRP pair was retained while only 50% left for free GOx/HRP (Figure 12C). This result is consistent with the fact that DNA origami nanostructures is

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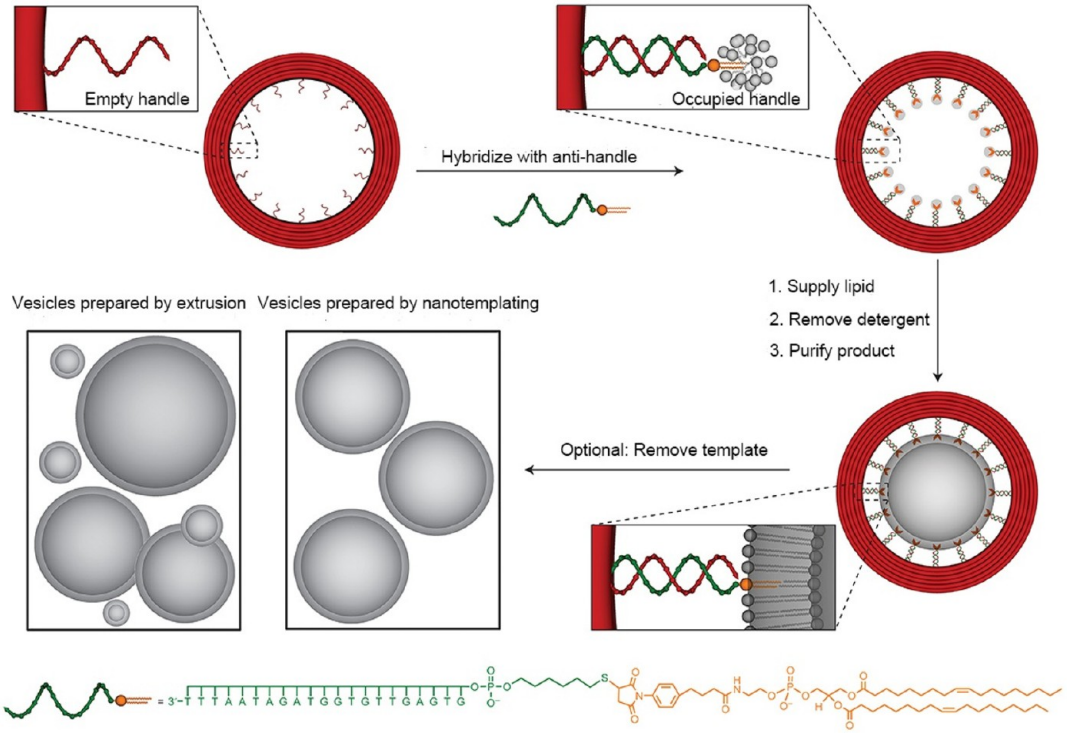

Figure 14. Scheme for generating size-controlled vesicles by DNA mimetic external cytoskeleton template. Reproduced with permission from ref 124. Copyright 2016 Springer Nature.

more stable than free DNA strand molecules and can keep inner cargoes from digestion.

In addition to these DNA-based nanoreactors, scientists also constructed many DNA nanocages feature dynamic behaviors. For example, Kjems et al. reported an addressable lid-functionalized DNA box with a big inner cavity that was capable of enclosing cargoes.[112] The lid was modified with a dual lock-key system and could be opened by adding specific key oligonucleotides in a user-control manner. Komiyama et al. also constructed a box-shaped 3D DNA origami motif which was able to fold into a closed form.[105] The structure can be fully controlled and hold great promise for the encapsulation of other molecules. Both of these examples feature controllable opening and closing characteristics for cargo encapsulation and release. Andersen and co-workers designed a dynamic 3D DNA nanovault with reversible opening/closing features to fully encapsulate enzymes and further separate such enzyme from corresponding substrate (Figure 13A).[113] Two halves of this nanovault were connected by a hinge and formed an inner cavity. A single-stranded DNA modified in the cavity was serving as the activity site for enzyme anchoring. Then a flexible hinge was introduced to create a reversibly lock. By adding the closing key, the nanovault could be closed and kept the inner protease away from external substrate molecules, inhibiting the enzymatic reaction. On the contrary, when an opening key was added, the reopen of the nanovault could expose the enzyme to the substrate and trigger the catalytic reaction (Figure 13B). The open and close of this DNA nanovault at different conditions was characterized by TEM and Förster resonance energy transfer (FRET) efficiency (Figure 13C, 13D). This work represents a general method to control enzymatic reactions by DNA-based compartmentalization. With further research, more locking system can be developed to respond to various signals, such as proteins, small molecules, and metal ion, as well as temperature, pH, and even pressure.

In this section, we mainly discussed the recent development of DNA nanotechnology in artificial organelles. Taking these strategies in hand, it seems very likely that different DNA-based artificial compartmental systems can be constructed to mimic the natural compartment, such as mitochondria, endoplasmic reticulum, lysosomes, and other organelles.

DNA NANOSTRUCTURE-BASED ARTIFICIAL CELLS

As the basic structural and functional unit of life, cells can response to external stimuli and manage numerous biological processes. Recreate these cell structures and mimic cellular functions can not only open up new opportunities to understand how cells works but also provide a simple platform to unravel the disease mechanisms and pave the way for medical diagnosis/treatment. A central task in engineering artificial cell structure is to form a dynamic boundary which is equals to the cell membrane.[114] Customized lipid membrane possess the ability to meet the prerequisites for recreating cell structure.[115−117] However, lipid membrane usually lacks defined shape and can be deformed or destroyed easily. In cells, cytoskeleton plays a crucial role in shaping and stabilizing cell membrane.[118,119] As cytoskeleton is a complex scaffold and made up of vast interlinked proteins, it is quite difficult to re-engineer this scaffold structure with predictable shape.[120,121]

Structural DNA nanostructures are capable of forming programmable nanostructures with arbitrary shape and outstanding stability. These properties make it an appealing analogue of cytoskeleton to help create cell-like architecture.[122,123] Furthermore, amphipathic anchors can be placed at arbitrary position of the DNA nanostructures, making it possible to guide the formation of desired liposomes. In this way, Lin group have achieved highly monodispersed lipid vesicles

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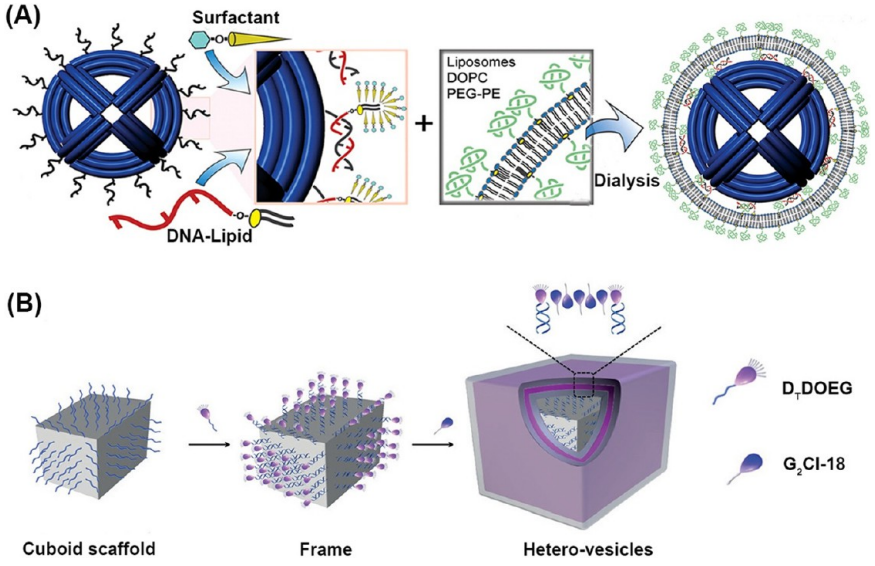

Figure 15. Schematic illustrations of the forming of cell-like structures with different shaped DNA-based internal cytoskeleton. (A) Octahedron DNA origami as the internal cytoskeleton. Reproduced with permission from ref 126. Copyright 2014 American Chemical Society. (B) Cuboid origami serves as the internal cytoskeleton. Reproduced with permission from ref 127. Copyright 2016 John Wiley and Sons.

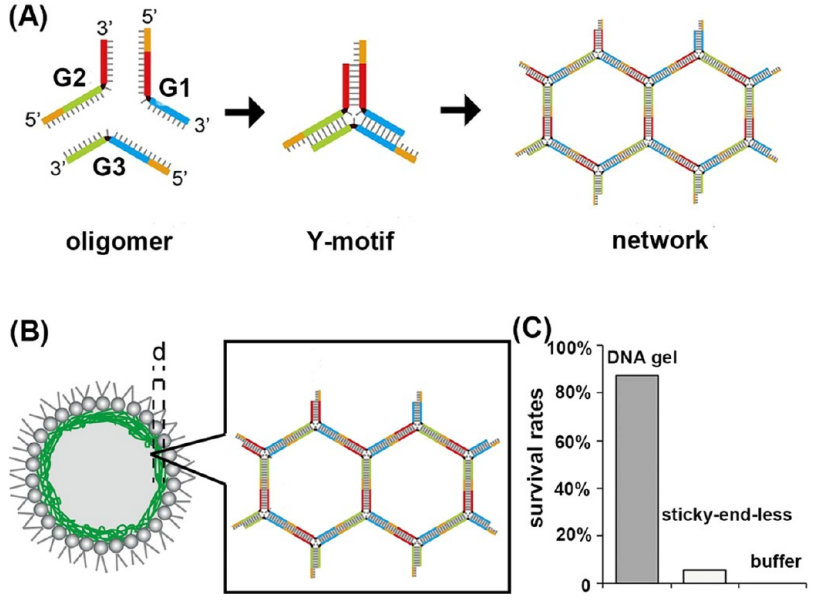

Figure 16. DNA gel as the internal cytoskeleton for stabilizing artificial cells. (A) Scheme of the formation of DNA network. (B) Schematic illustration of the DOTAP droplet with DNA gel network around the interior face. (C) Survival rates of liposomes after osmotic treatment. Reproduced with permission from ref 129. Copyright 2017 National Academy of Sciences.

using DNA origami as the external cytoskeleton template (Figure 14).[124] Scaffold strands and staple strands with preselected sequences were mixed in a certain molar ratio and further underwent thermal annealing to form a well-folded ring. It is worth noting that every ring featured 16 evenly spaced single-stranded inner handles and eight outer handles. Lipidated strands with complementary sequences were next introduced to hybrid with inner handles. After that, liposomes could be formed via self-assembly of added lipid. Notably, the size of liposomes was determined by DNA rings and obtained liposomes could be removed from the templates easily. In another work, similar DNA template was also used to control the size and numbers of functional groups of vesicles to study the membrane fusion process.[125]

In addition to guiding the self-assembly of liposomes inside the inner cavity, DNA template is also capable of serving as internal cytoskeleton. For this purpose, the anchors were modified at the outer face of the DNA origami with high precision. Shih et al. constructed an octahedron DNA origami and further encapsulated the origami within a lipid membrane to mimic the morphology and functions of virus particles (Figure 15A).[126] Liu group also described heterovesicles by employing cuboid and dumbbell-shaped DNA origami as template scaffolds (Figure 15B).[127] In general, this method is modular and capable of forming various dynamically membrane structures by simply adjusting the configurations of the DNA scaffolds and the distribution of attached amphipathic anchors.[128]

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DNA gels was also used as the internal cytoskeleton to stabilize lipid-based artificial cells.[129] In their work, Y-motif with sticky ends was hybridize with each other to form the gel-liked network (Figure 16A). Then, these hybridized DNA were encapsulated into a positively charged lipid 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP) droplets. Negatively charged DNA spontaneously accumulated near the interior surface of the droplet and formed a shell through electrostatic interaction (Figure 16B). Stability analysis of these obtained liposomes with DNA gel shell was evaluated by osmolyte stress study. Liposomes with sticky-end-less DNA or without DNA were performed as controls. Liposomes with DNA gel shell remained spherical shapes but most control groups appeared collapse after hypertonic treatment (Figure 16C). Therefore, DNA gel can serve as the internal cytoskeleton of artificial cells, which is similar to the cytoskeleton in live cells, to strengthen membrane structures. This reported lipid-DNA cytoskeletons can be considered as an ideal system to create artificial cells and understand how cells work.

Both the external and internal cytoskeleton template approaches provide an avenue to guide the formation and dynamic changes of lipid bilayer. Moreover, asymmetric and large membrane vesicles can also be constructed through rational design, which is important for recreating cell-liked structure. In a word, DNA scaffold is a powerful analogue of cytoskeleton to guide the formation of artificial cell structure.

CONCLUSIONS AND FUTURE PROSPECTS

This Forum Article primarily summarizes the recent achievements of DNA nanotechnology in biomimetics. The capability of DNA to fold into precisely defined architectures with different shape and function makes it a powerful tool to re-engineer certain cellular components and biological processes. Interestingly, DNA could be folded into pore-like nanostructures and served as the artificial membrane-spanning proteins. The self-assembly behavior of membrane-relate proteins could also be replicated by highly modular DNA origami blocks. Moreover, structural DNA nanotechnology has been shown to be suitable to serve as artificial cell structure.

Even though significance breakthroughs have been made in biomimetic field, existing investigations still suffer from several challenges. First, unlike natural proteins, DNA has a much simpler composition of only four similar nucleotide components of A, T, G, and C, which limits the structural and functional complexity of DNA nanotechnology.[130−132] Thus, artificial bases are highly desired to increase chemical diversity and versatility needed for design of various DNA-based biomimetic structures.[133,134] Second, lipid membrane are widely used to mimic the cellular components and processes. However, an obvious obstacle has been overlooked as the natural membrane features more complex physicochemical environment compared with lipid bilayer. Researchers have showed that this barrier can be overcome by cell-derived membrane vesicles. Currently, most of the present systems have provided a simplified and modular model and pave a way to understand natural ones. Future researches will explore more complex biological pathways with DNA nanotechnology and other biomimetic materials. This will help to answer questions concerning how life works and further shed light on the origin of diseases for biomedical applications.

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Notes

The authors declare no competing financial interest.

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