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Perspective

Emerging Trends in DNA Nanotechnology-Enabled Cell Surface Engineering

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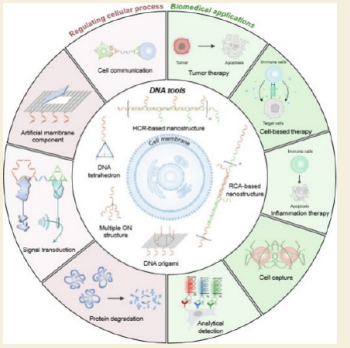
ABSTRACT: Cell surface engineering is a rapidly advancing field, pivotal for understanding cellular physiology and driving innovations in biomedical applications. In this regard, DNA nanotechnology offers unprecedented potential for precisely manipulating and functionalizing cell surfaces by virtue of its inherent programmability and versatile functionalities. Herein, this Perspective provides a comprehensive overview of emerging trends in DNA nanotechnology for cell surface engineering, focusing on key DNA nanostructure-based tools, their roles in regulating cellular physiological processes, and their biomedical applications. We first discuss the strategies for integrating DNA molecules onto cell surfaces, including the attachment of oligonucleotides and the higher-order DNA nanostructure. Second, we summarize the impact of DNA-based surface engineering on various cellular processes, such as membrane protein degradation, signaling transduction, intercellular communication, and the construction of artificial cell membrane components. Third, we highlight the biomedical applications of DNA-engineered cell surfaces, including targeted therapies for cancer and inflammation, as well as applications in cell capture/protection and diagnostic detection. Finally, we address the challenges and future directions in DNA nanotechnology-based cell surface engineering. This Perspective aims to provide valuable insights for the rational design of DNA nanotechnology in cell surface engineering, contributing to the development of precise and personalized medicine.



KEYWORDS: *cell surface engineering, DNA nanotechnology, targeted protein degradation, cell communication, cell-based therapy*

1. INTRODUCTION

As the fundamental unit of life, cells orchestrate a series of biological processes and play a vital role in medical treatment. Therefore, regulating and manipulating cellular behavior will promote our understanding of biological systems and for developing novel therapeutic strategies.[1−5] While manipulating intracellular components is important, regulating components on the cell surface is more direct and efficient, as cell surface serves as the interface between cell and its external environment.[6] As for cell membrane, it functions as both a selective barrier and a platform for key processes, including signal transduction, molecular transport, and intercellular communication.[7,8] Hence, precise modification and functionalization of cell surface will profoundly influence cellular physiology and hold significant promise for applications across biotechnology and medicine.

In recent years, DNA nanotechnology has become a promising and versatile tool for cell surface engineering.[9−13] DNA, beyond its traditional role as a carrier of genetic information, is increasingly utilized as a programmable material to construct nanostructures with remarkable precision and functionality.[14−19] This ability arises from the highly predictable base-pairing rules of DNA, which enable the design of sophisticated and customizable structures ranging from simple oligonucleotide sequences to complex three-dimensional architectures. In addition to the structural design, DNA also possesses functional properties, such as aptamers with specific binding abilities and DNAzymes with enzyme-like catalytic activities.[20−22] These characteristics make DNA an exceptionally powerful tool for engineering cell surfaces,[23−26] modulating cellular processes,[27−29] enhancing therapeutic performance,[30−32] and enabling novel diagnostic applications.[33,34]

Herein, this perspective aims to provide a comprehensive overview of the emerging trends in DNA nanotechnology-enabled cell surface engineering, focusing on DNA nanostructures-based tools, their role in regulation of cellular physiological processes, and their biomedical applications (Figure 1). By summarizing the current state of this field and highlighting recent advancements, we seek to illustrate the

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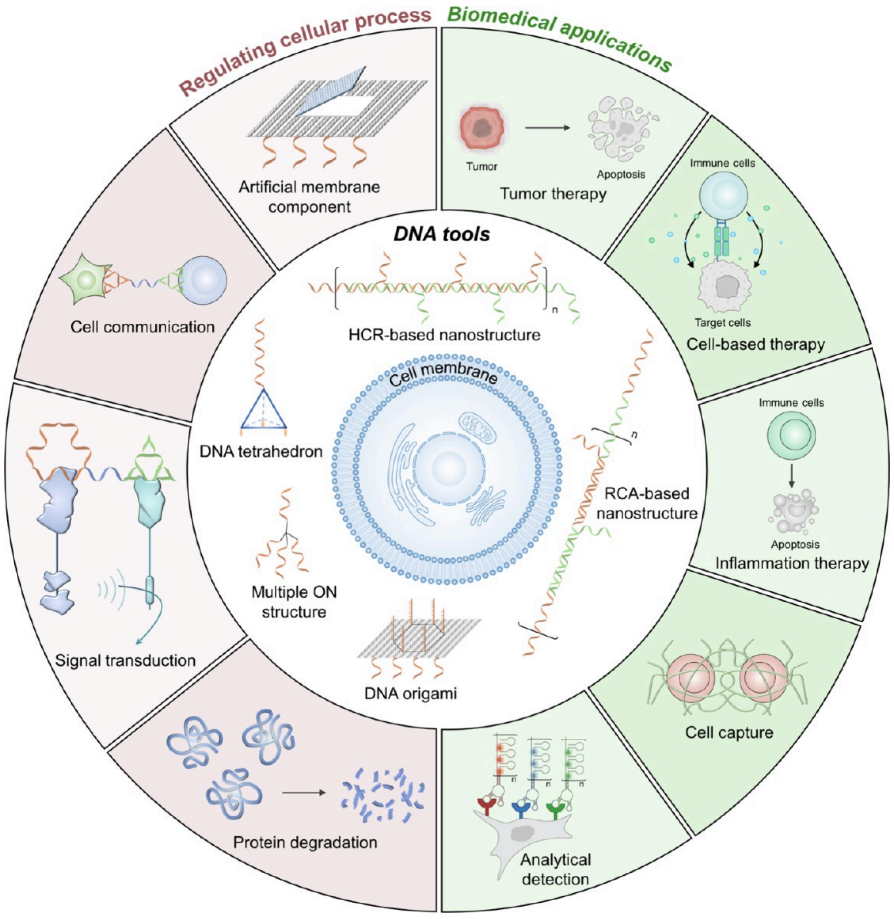

Figure 1. Overall schematic illustration of DNA nanotechnology-enabled cell surface engineering for cell regulation and biomedical applications. ON: oligonucleotide.

versatility and potential of DNA nanotechnology as a powerful tool for next-generation cellular engineering strategies. While several reviews also summarized the concept of surface DNA engineering of cells,[35−38] our perspective delves deeper into the chemistry underlying surface DNA engineering. We also offer a detailed analysis of the latest advancement of surface DNA-engineered cells in biomedical applications, especially in combination with emerging biotechnologies. Additionally, we highlight the challenges and future opportunities within this rapidly evolving research area.

2. DNA NANOTECHNOLOGY IN CELL SURFACE ENGINEERING

DNA nanotechnology has emerged as a groundbreaking approach for engineering cell surfaces, offering innovative solutions for controlling and modifying cellular functions in various biomedical contexts.[11,39−41] By integrating DNA-based elements onto cell surfaces, researchers have unlocked new opportunities in cell regulation, tumor therapies, and other biomedical applications. This section delves into the strategies for attaching oligonucleotides to cell surfaces and constructing high-order DNA nanostructure on cell surfaces.

2.1. Attachment of Oligonucleotides onto Cell Surfaces

The attachment of oligonucleotides onto cell surfaces is a critical prerequisite for surface DNA engineering. Once attached, these oligonucleotides can serve not only as functional units but also as connectors that initiate the formation of higher-order DNA nanostructures, further enabling advanced possibilities. However, the hydrophilic and negatively charged nature of DNA makes its interaction with cell membranes challenging. The following several strategies have been developed for oligonucleotide attachment onto cell surface (Figure 2).

2.1.1. Direct Chemical Conjugation. Direct chemical conjugation involves the formation of covalent bonds between oligonucleotides and cell surface proteins. Elegant phosphoramidite chemistry enables the introduction of various reactive groups to oligonucleotides, such as amino (−NH_2), carboxyl (−COOH), azide (-N_3), alkynyl (-C ≡ H), and dibenzocyclooctyne (-DBCO). Among these, "click" chemistry, which won the 2022 Nobel Prize in Chemistry,[42,43] has demonstrated superior conjugation efficiency and biorthogonality compared with traditional amide reactions between -NH_2 and −COOH.

One promising method for introducing azide (-N_3) groups onto cell surface is metabolic labeling using N-azidoacetylmannosamine (Ac_4ManNAz) (Figure 2A).[31,44] This approach ensures robust conjugation, as the labeled groups are intrinsically (in comparison to the hereafter-mentioned attaching strategies) arranged on cell surface, minimizing the possibility of dissociation from cell surface after oligonucleotide attachment. The stability of this attachment is crucial for downstream designs and applications. However, metabolic labeling is generally time-intensive (requiring preculture with cells of interest) and may induce cytotoxicity, potentially limiting its practical utility in certain applications.

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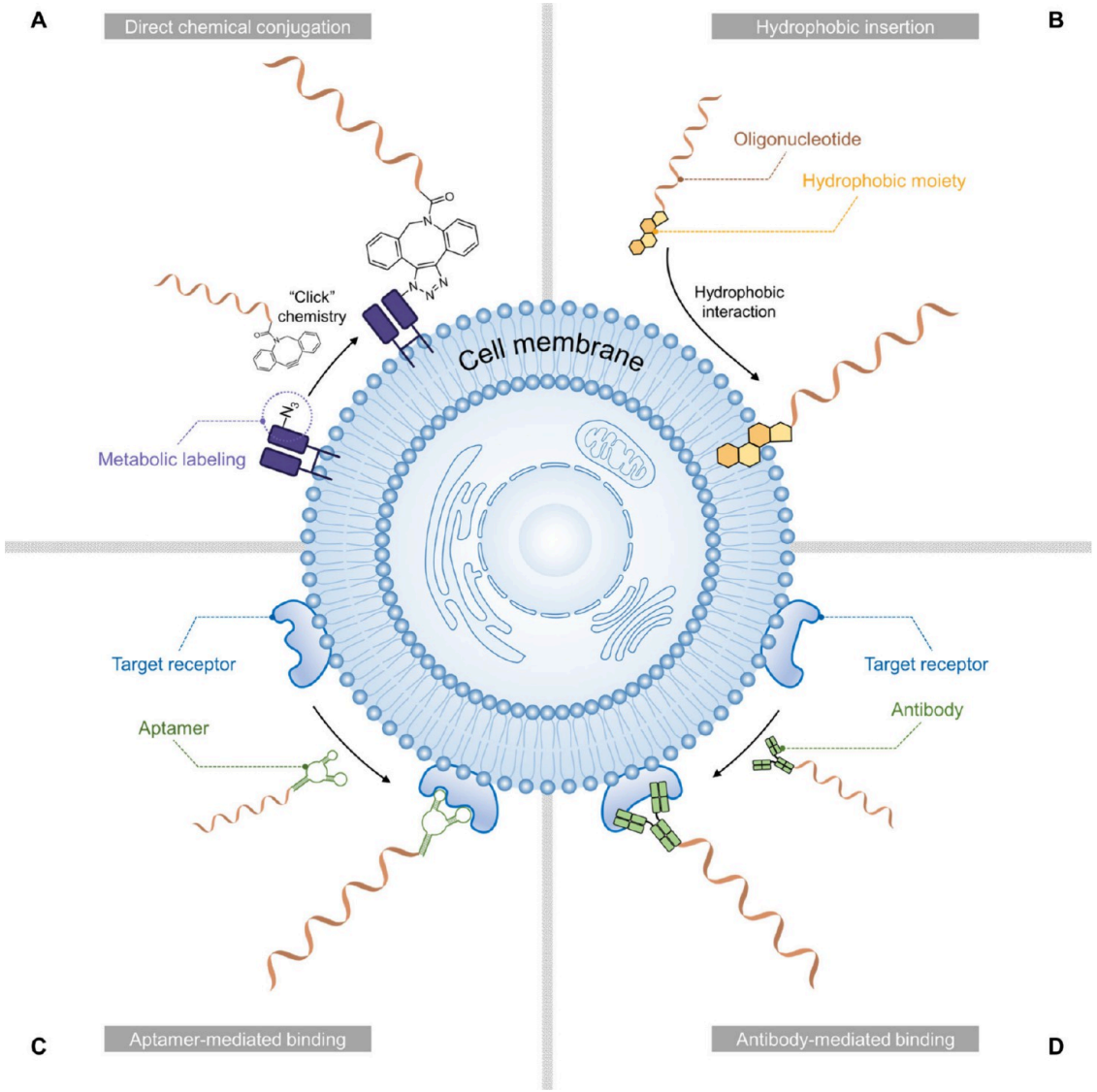

Figure 2. Strategies for attaching oligonucleotides onto the cell surface. (A) Direct chemical conjugation via "click" chemistry. (B) Hydrophobic insertion into the cell membrane using amphiphilic oligonucleotides. (C) Aptamer-mediated binding through the interaction between aptamer and cell surface receptors. (D) Antibody-mediated binding via the combination of antibodies and cell surface receptors.

2.1.2. Hydrophobic Insertion. The phospholipid bilayer of cell membrane features a hydrophobic interlayer, which provides a possibility for hydrophobic interaction-mediated insertion. Oligonucleotides can be conjugated with hydrophobic moieties, such as cholesterol,[24,45−47] tocopherol,[45,46] or long aliphatic chains,[46,48] which facilitate their integration into the lipid bilayer through hydrophobic interactions (Figure 2B). This strategy is relatively straightforward, as it does not require complex chemical linkers and enables rapid DNA engineering on cell surfaces. However, hydrophobic insertion presents several limitations. For instance, it may destabilize cell membrane, disrupting the native structure and functionality of cell membrane. Nonspecific interactions with serum proteins and inefficient insertion (forming into nano assembly from amphiphilic oligonucleotides rather than proper insertion into cell membrane) also pose challenges. Moreover, the insertion process lacks predictability in terms of the localization and density of the inserted DNA molecules, which may hinder reproducibility and effectiveness for certain applications. In addition to conventional hydrophobic insertion, the Xing group has utilized membrane fusion technology to enable DNA engineering on the inner face of cell membranes (most of the hydrophobic insertions are outside the cell membrane.),[23] further broadening the scope of this approach.

2.1.3. Aptamer-Mediated Binding. Aptamers, often referred to as "chemical antibodies", are short single-stranded oligonucleotides folding into specific three-dimensional structures that bind target molecules with high affinity.[49,50] This unique property makes aptamer-mediated binding a powerful tool for attaching DNA to cell surfaces. By directly extending DNA sequences from the 3 or 5′ ends of the aptamers, virtually any DNA molecule can be anchored onto cell surfaces (Figure 2C). This approach is particularly attractive due to the versatility of aptamers, which can be designed to bind to a wide variety of cell surface markers, including cancer biomarkers,[12,51] and immune checkpoint proteins.[30,40] Such specificity offers unparalleled precision in targeted cellular manipulation. Despite these advantages, aptamer-mediated binding is highly susceptible to environmental factors, such as ionic strength and temperature, which

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may impact aptamer stability and binding efficiency. Moreover, the selection and synthesis of aptamers with high binding affinity and minimal off-target effects are labor-intensive and require extensive screening.

2.1.4. Antibody-Mediated Binding. Antibody-mediated binding is another highly specific strategy for introducing oligonucleotides onto cell surfaces. Antibodies exhibit highly specific and high-affinity interactions with their corresponding antigens, making them ideal candidates for precise targeting.[52,53] This method typically involves conjugating oligonucleotides to antibodies, which subsequently bind to their target epitopes on the cell surface (Figure 2D). The high specificity of antibody−antigen interactions allows for the selective targeting of specific cell types or subpopulations within a heterogeneous environment, such as cancer cells expressing unique surface markers.[54−56] This precision minimizes off-target effects and ensures accurate localization of DNA nanostructures on the cell surface. However, high-quality primary antibodies are often expensive and require stringent quality control. Additionally, the conjugation of antibodies with oligonucleotides is technically demanding, requiring sophisticated protocols and expertise, which may complicate downstream applications.

Table 1 exhibits the summary of the approach of attaching oligonucleotides onto cell surfaces.

2.2. High-Order DNA Nanostructure on Cell Surfaces

Single-stranded oligonucleotides can be attached to cell surfaces; however, they often exhibit limitations such as instability on the cell membrane, or relatively weak affinities.[57] In this aspect, high-order DNA nanostructures offer a promising solution to these challenges. Moreover, these nanostructures provide superior programmability for regulating cells with more patterns. This section highlights several types of high-order DNA nanostructures currently employed in cell surface engineering (Figure 3), including multiple oligonucleotide structures, DNA tetrahedrons, hybridization chain reaction (HCR)-based structures, rolling circle amplification (RCA)-based structures, and DNA origami.

2.2.1. Multiple Oligonucleotide Structures. Multiple oligonucleotide structures refer to the structure formed by several oligonucleotide strands, such as clusters of oligonucleotides[58] or assemblies of multiple aptamers.[12,59] These designs allow DNA nanostructures to bind to multiple receptor sites[12] or special receptors (e.g., scavenger receptors[58]) on cell surface, enabling more complex interactions than single-strand oligonucleotides. For example, dendritic DNA structures composed of four strands of oligonucleotides have been reported to specifically bind to scavenger receptors on cell surfaces (Figure 3A).[58] These structures can target a broad range of receptors, and the density of oligonucleotides can be precisely controlled to optimize their functional performance. However, synthesizing multiple oligonucleotide structures may be time-consuming and technically demanding and may require concern for the undesired interaction with serum proteins.[60,61]

2.2.2. DNA Tetrahedron. DNA tetrahedrons are highly stable, three-dimensional nanostructures self-assembled from single-stranded DNA oligonucleotides. These structures, characterized by their four triangular faces, are widely explored in various biomedical applications, including drug delivery,[62,63] detection,[64,65] and imaging.[66] Additionally, DNA tetrahedrons are easily functionalized with other DNA sequences or

Table 1. Summary of the Approach of Attaching Oligonucleotides onto Cell Surfaces

approach	mechanism	advantages	disadvantages	reference
direct chemical conjugation	covalent conjugation between oligonucleotides with sugar moieties	robust conjugation; minimizes dissociation from cell surface	time-intensive; potential cytotoxicity	31, 44
hydrophobic insertion	hydrophobic interaction between lipophilic moieties-conjugated oligonucleotides	quick and straightforward	may destabilize cell membrane; nonspecific interactions with serum proteins; inefficient insertion; imprecise the localization and density of the inserted DNA molecules	24, 45−48
aptamer-mediated binding	molecular binding between aptamer-linked oligonucleotides and ligands on cell surface	versatile; precise targeting of cell surface markers	sensitive to environmental factors; labor-intensive aptamer screening.	12, 51
antibody-mediated binding	molecular binding between antibody-linked oligonucleotides and ligands on cell surface	high specificity; accurate localization of DNA nanostructures on the cell surface	expensive; complex conjugation between antibodies with oligonucleotides; requires stringent quality control	54−56

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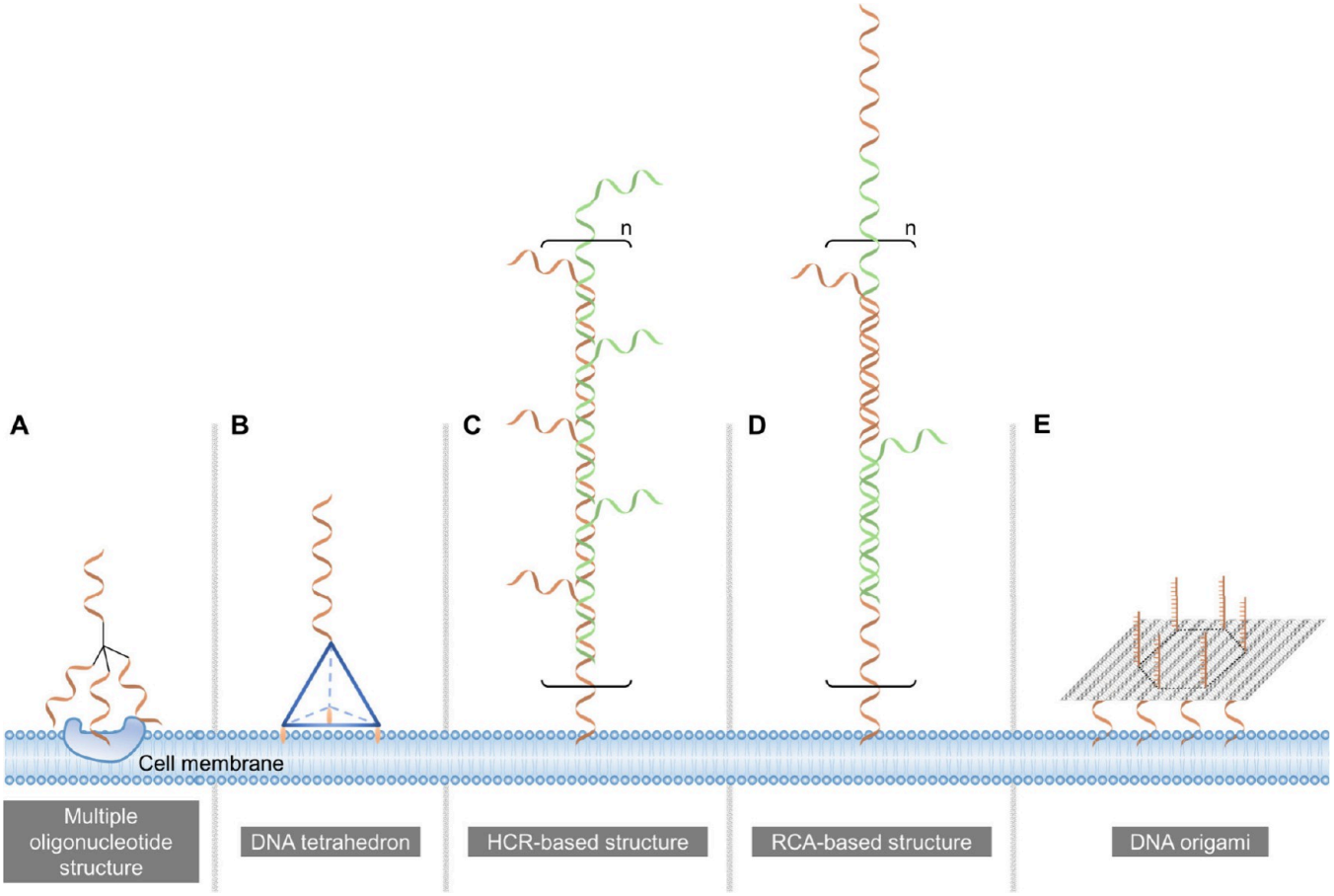

Figure 3. Representative high-order DNA nanostructures on the cell surface. (A) Multiple oligonucleotide structures. (B) DNA tetrahedron. (C) HCR-based structure. (D) RCA-based structure. (E) DNA origami.

biomolecules, such as aptamers, to extend their utility and enhance their biological interactions.

When hydrophobic moieties (e.g., cholesterol or tocopherol) are conjugated to DNA tetrahedron strands, amphiphilic DNA tetrahedrons are formed, enabling their stable anchoring onto cell membranes through hydrophobic interactions (Figure 3B).[9,57,67] These anchored nanostructures provide enhanced stability on the cell surface and reduce the risk of exfoliation. Despite these advantages, the rigid geometry of DNA tetrahedrons may limit their adaptability in the highly dynamic and complex environment of cell membranes, potentially restricting their functionality in certain applications.

2.2.3. HCR-Based Structures. The Hybridization Chain Reaction (HCR) is a DNA amplification process that facilitates the construction of dynamic and complex DNA nanostructures. The HCR involves the hybridization of DNA hairpins, which undergo conformational changes and polymerization in the presence of specific DNA triggers.[68,69] This self-assembling process enables the construction of large, branched DNA nanostructures that can be anchored onto cell surfaces (Figure 3C).[24,26] Therefore, multiple functional units can be incorporated into HCR-based structures, such as aptamers and stimuli-responsive sequences.[26] Additionally, the branched DNA networks formed by HCR can protect encapsulated cells, offering potential applications in tissue engineering and cell delivery. However, challenges remain in achieving precise control over the reaction kinetics to ensure consistent assembly and functionality. Furthermore, the stability of HCR-assembled structures in physiological conditions remains a concern, particularly for long-term in vivo applications.

2.2.4. RCA-Based Structures. Rolling Circle Amplification (RCA) technology provides the capability of generating ultralong single-strand DNA with repeated sequence units, which allows the carrying of more functional units, such as therapeutic agents,[70,71] or molecular sensors.[72] The polyvalence effect of multiple functional units enhances the output performance of functional units on cell surface (Figure 3D). In addition, RCA-formed DNA networks can protect cells or cargo, making them useful for cell capture and delivery.[73−75] However, while RCA offers significant advantages, one limitation of RCA is the risk of misalignment during hybridization due to the large number of repeated sequences. This can result in undesired interactions, potentially affecting the precision and effectiveness of applications.

2.2.5. DNA Origami. DNA origami is a well-known and highly versatile approach for folding long strands of DNA into predefined shapes. The technique relies on a scaffold strand that is folded into a specific shape with the help of hundreds or even thousands of short "staple" strands.[76] This results in highly organized nanostructures that can be functionalized with various biomolecules to interact with the cell surface (Figure 3E).[77] For instance, DNA origami structures have been employed to construct scaffolds for receptor clustering, which can modulate cellular responses, such as signal transduction or immune activation, either by promoting or inhibiting these processes.[40] Despite the advantages, the synthesis of DNA

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origami structures requires the use of long, high-purity DNA strands, which are currently expensive and labor-intensive to produce. Furthermore, the relatively large size and rigidity of these structures may hinder their ability to efficiently interact with cell membranes, limiting their effectiveness in certain applications.

Table 2 exhibits the summary of the high-order DNA nanostructure on cell surfaces.

3. REGULATING CELLULAR PHYSIOLOGICAL PROCESSES THROUGH SURFACE DNA

Cells, as the basic units of life, are responsible for carrying out essential physiological processes. In this section, we summarize recent advancements in this field, focusing on key areas including targeted degradation of membrane-associated proteins, regulating cell signaling, constructing artificial cell components, and controlling cell communication.

3.1. Targeted Degradation of Membrane-Associated Proteins

Targeted protein degradation has emerged as a promising therapeutic strategy to eliminate dysfunctional proteins implicated in various diseases.[78] In theory, this approach holds the potential to degrade any protein of interest (POI). A prominent example is proteolysis-targeting chimeras (PROTACs), which primarily target and degrade cytosolic proteins. However, PROTACs are typically limited in degrading membrane-associated proteins. To address this limitation, lysosome-targeting chimeras (LYTACs) have been developed, directing the membrane-associated protein to the lysosome for degradation.[80] The engineered DNA molecules can be applied to LYTACSs technology, typically designed as aptamers that simultaneously bind to lysosome-trafficking receptors (LTRs) and the POI, thereby facilitating the transport of the POI into the lysosome for degradation. Recent reports in DNA-based LYTACs have demonstrated significant advancements.[12,30,40,51,58,59,79,81−84]

In a significant advancement, the Han group introduced bispecific aptamer-based chimeras, wherein one aptamer binds to an LTRs, cation-independent mannose-6-phosphate receptor (CI-M6PR), on the cell membrane, while the other aptamer specifically binds to the POI on the membrane (Figure 4A).[51] This dual-aptamer system effectively "hijacks" the target protein, transporting it into the lysosome for degradation. However, a limitation of this approach is that the binding between the aptamer and the POI is noncovalent, which increases the possibility of off-target effects.

To overcome this challenge, the Liu group developed a covalent LYTAC strategy (Figure 4B).[30] In this system, an aptamer is designed to specifically bind PD-L1 (programmed death ligand-1), while simultaneously undergoing a click reaction to form a covalent bond with the PD-L1 protein. A second aptamer, which binds to CI-M6PR, facilitates the trafficking of the PD-L1-aptamer complex into the lysosome for degradation. The covalent linkage between the PD-L1 aptamer and PD-L1 enhances the on-target degradation efficiency and improves the specificity of the degradation process.

Given that CI-M6PR expression levels vary widely across different cell types, there is a need for the development of more universal LTRs capable of degrading a broader range of disease-related proteins. The Tan group developed a biaptamer-based LYTAC in which one aptamer binds to

Table 2. Summary of the High-Order DNA Nanostructures on Cell Surfaces

DNA nanostructure	constructing approach	advantages	disadvantages	reference
multiple oligonucleotide structures	covalent conjugation	allows multiple receptor bindings or binding special receptors (e.g., scavenger receptors)	time-consuming; technically demanding; undesired interaction with serum proteins	58, 60, 61
DNA tetrahedron	strand assembly via complementary base pairing	enhanced stability on the surface; reduced exfoliation risk	rigid geometry structure may limit their adaptability in dynamic cell membranes	9, 57, 67
HCR-based structures	cascade reaction using multiple DNA hairpins	integrating multiple functional units (aptamers, stimuli-responsive sequences); protecting encapsulated cells; useful in tissue engineering and cell delivery	difficult to control reaction kinetics; unstable in physiological conditions	24, 26
RCA-based structures	enzymatic amplification of circular DNA template	carrying multiple functional units (therapeutics, sensors); polyvalence effect of multiple functional units; protecting cells or cargo	risk of misalignment during hybridization due to repeated sequence	73−75
DNA origami	folding long DNA strands into nanoscale shapes	highly organized nanostructures with precise control	expensive and labor-intensive to produce high-purity long DNA strands; large and rigid structures may hinder their interaction with cell membranes	40, 77

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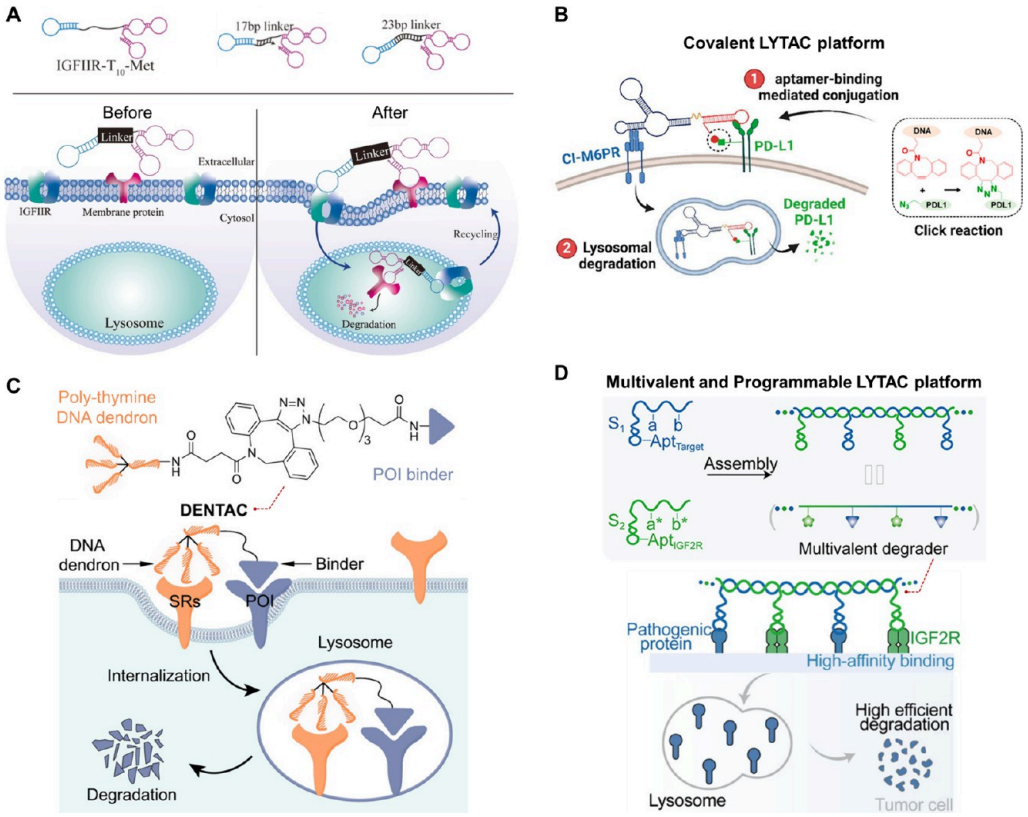

Figure 4. (A) Biaptamer chimeras for targeted protein degradation on the cell membrane. IGFIIR: cation-independent mannose-6-phosphate receptor, also abbreviated as CI-M6PR. Reproduced with permission from ref 51. Copyright 2021 Wiley-VCH GmbH. (B) Aptamer-binding-mediated covalent conjugation reduces the off-target rate of LYTAC and enhances its on-target efficacy. Reproduced with permission from ref 30. Copyright 2023 American Chemical Society. (C) An alternative LYTAC platform targeting lysosome receptors: scavenger receptors (which mediate the endocytosis of polyanions). Reproduced with permission from ref 58. Copyright 2023 Wiley-VCH GmbH. (D) A multivalent, programmable DNA-based LYTAC platform with enhanced selectivities. IGF2R: insulin-like growth factor 2 receptor, a lysosome-targeting receptor. Reproduced with permission from ref 79. Copyright 2024 American Chemical Society.

integrin $\alpha 3\beta 1$ (ITGA3B1), a type of LTRs that is widely involved in the physiological and pathological processes of various cells, and the other aptamer targets the POI. They demonstrated the high efficacy of these integrin-facilitated bispecific aptamer chimeras in degrading POIs across multiple cell lines.[82]

In addition to integrin-based LYTACs, other DNA-chimeric systems have been developed. For instance, dendritic DNA chimeras and trivalent N-acetylgalactosamine (GalNAc)-aptamer chimeras target scavenger receptors (SRs) (Figure 4C)[58] and asialoglycoprotein receptors (ASGPR),[83] respectively, both of which are typical LTRs. Furthermore, the development of multivalent aptamer-based LYTACs has enabled the simultaneous degradation of multiple target proteins (Figure 4D),[79] offering a potential for more comprehensive therapeutic interventions.[12,40,59,79,84]

3.2. Regulating the Cell Signaling Pathway

Cell signaling and behavior are fundamental for maintaining cellular homeostasis and orchestrating complex physiological processes. These signaling pathways govern cellular functions, including growth, differentiation, apoptosis, migration, and immune responses.[85] Disruptions in these signaling networks are closely associated with various diseases, such as cancer, autoimmune disorders, and neurodegenerative conditions. Understanding and modulating these pathways has become a central focus in both basic and applied biomedical research.[86] In this aspect, the precise spatial manipulation of DNA nanotechnology and affinities of functional nucleic acid offer a powerful tool for modulating cell surface signaling molecules, thus enabling the regulation of cell signaling and behavior.[13,45,87−93]

Cell membranes exhibit high complexity in terms of lipids and proteins, which are dynamically distributed into distinct domains that coordinate various cellular functions. The Qiu group developed two sets of amphiphilic DNA tetrahedrons, with hydrophobic moieties consisting of cholesterols or tocopherols respectively, that selectively target lipid-order (Lo) and lipid-disorder (Ld) domains on live cell membranes (Figure 5A).[45] This enables dynamic protein translocation without genetic modification. By incorporating protein-recognition aptamers, these DNA nanodevices can regulate the translocation of target proteins between these two membrane domains. The group demonstrated that the localization of PTK7 (protein tyrosine kinase 7) to the Lo domains promotes tumor cell migration, while sequestering PTK7 in the Ld domains suppresses this movement. This strategy was also applied to manipulate CD45, a transmembrane protein tyrosine phosphatase on T cells, where it enhanced T cell activation by CD45 translocation. The Li group developed a DNA origami-based nanoheater system that controls local lipid temperature using near-infrared laser illumination.[94] This temperature change altered the membrane's thermodynamic properties, affecting integrin-mediated cell migration. This method offers a powerful way to

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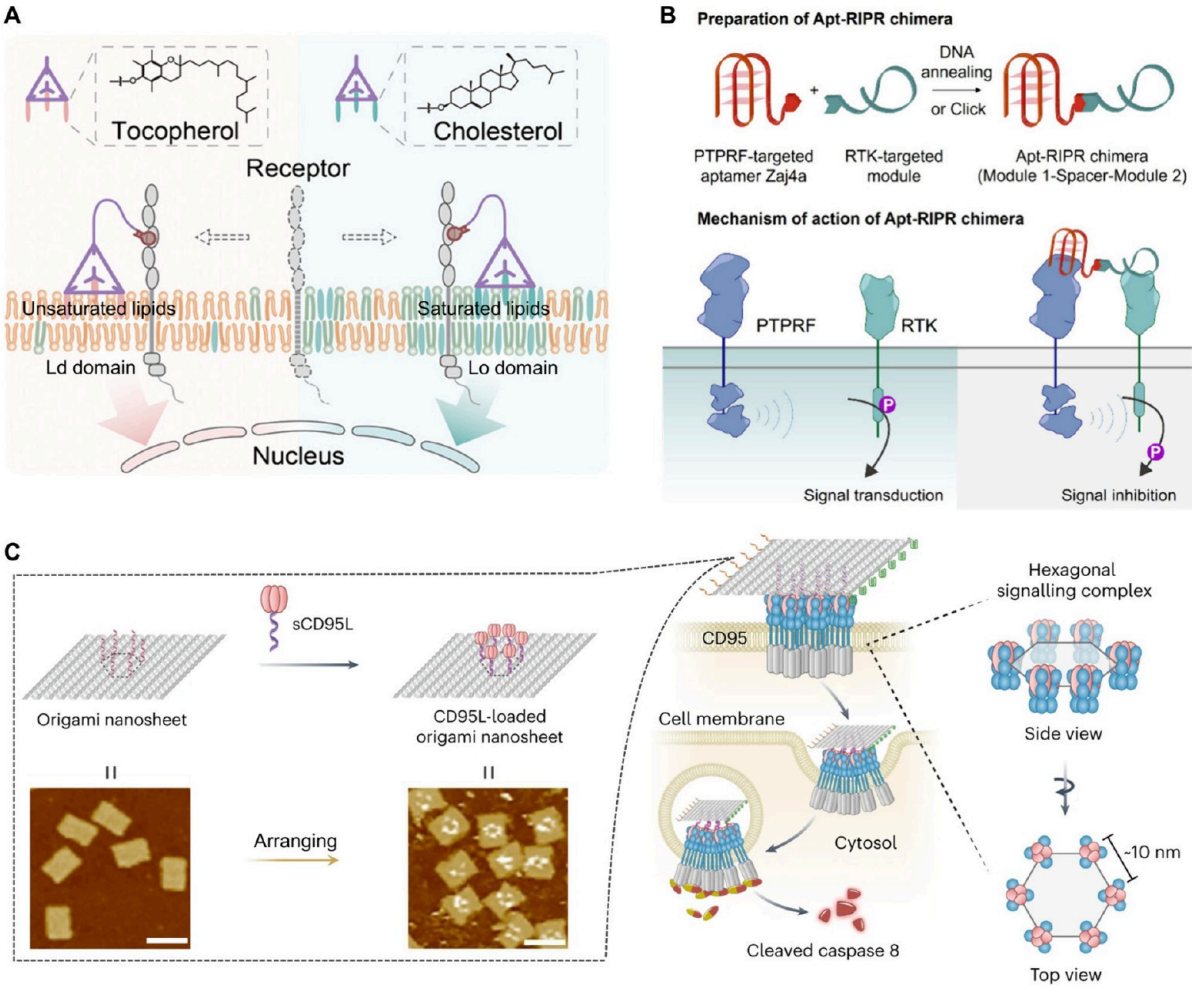

Figure 5. (A) Control of signal molecule translocation across membrane domains using amphiphilic DNA tetrahedra, thereby regulating cellular signaling pathways. Reproduced with permission from ref 45. Copyright 2024 American Chemical Society. (B) Inhibition of RTK phosphorylation by forced recruitment of PTPRF using aptamer-based chimeras. RIPR: receptor inhibition by phosphatase recruitment. Reproduced with permission from ref 13. Copyright 2024 American Chemical Society. (C) Programmable DNA origami for the hexagonal arrangement of CD95/CD95L signaling molecules, efficiently triggering CD95-mediated cell death. Reproduced with permission from ref 10. Copyright 2024 Springer Nature.

manipulate membrane heterogeneity and explore cellular functions by altering plasma membrane biophysical properties. In another study, a DNA nanodevice was used to induce clustering of lipid rafts, disrupting the interaction between adhesion receptors and the extracellular matrix, which resulted in reduced cell migration.[95]

Regulating the phosphorylation of receptor tyrosine kinases (RTKs) represents a promising strategy for tumor therapy. The Tan group reports aptamer-based chimeras that selectively inhibit RTK phosphorylation, including c-Met (hepatocyte growth factor receptor) and EGFR (epidermal growth factor receptor), by forcibly recruiting the protein tyrosine phosphatase receptor type F (PTPRF) (Figure 5B).[13] These chimeras effectively suppress RTK phosphorylation, induced by growth factors or autodimerization, across various cell lines, thereby modulating cell behaviors.

The precise spatial control of signaling molecules is crucial for determining their biological effect. The Chen group developed a reconfigurable, two-dimensional DNA origami that displays geometrically patterned CD95 (an apoptotic molecule) ligands, mimicking the natural hexagonal arrangement of CD95 receptors on immune cells (Figure 5C).[10,41] This spatially controlled arrangement of CD95 ligands effectively triggered CD95-mediated cell death in activated immune cells within inflamed tissues, leading to the promoted release of TGF-β, a canonical anti-inflammatory cytokine. This approach provides a promising therapeutic strategy for diseases characterized by excessive immune responses.

Taken together, the regulation of cell signal transduction is often influenced by the spatial positioning of signaling molecules on the cell membrane. Mechanisms such as distance shortening,[13,88] dimerization,[89−93,96−98] hexamerization,[10] and translocation between membrane domains[45,99] are key to modulating cellular signaling. These positional changes in the positions of signal molecules can be precisely controlled using DNA molecules, which offer unique advantages in regulating cellular signals and behaviors.

3.3. Controlling Cell Communication

Cell communication is fundamental to cellular processes, enabling the exchange of information and coordination of activities. It plays a crucial role in maintaining tissue homeostasis, immune responses, and development. By controlling cellular communication, cellular behaviors could be artificially manipulated, which is a promising strategy for

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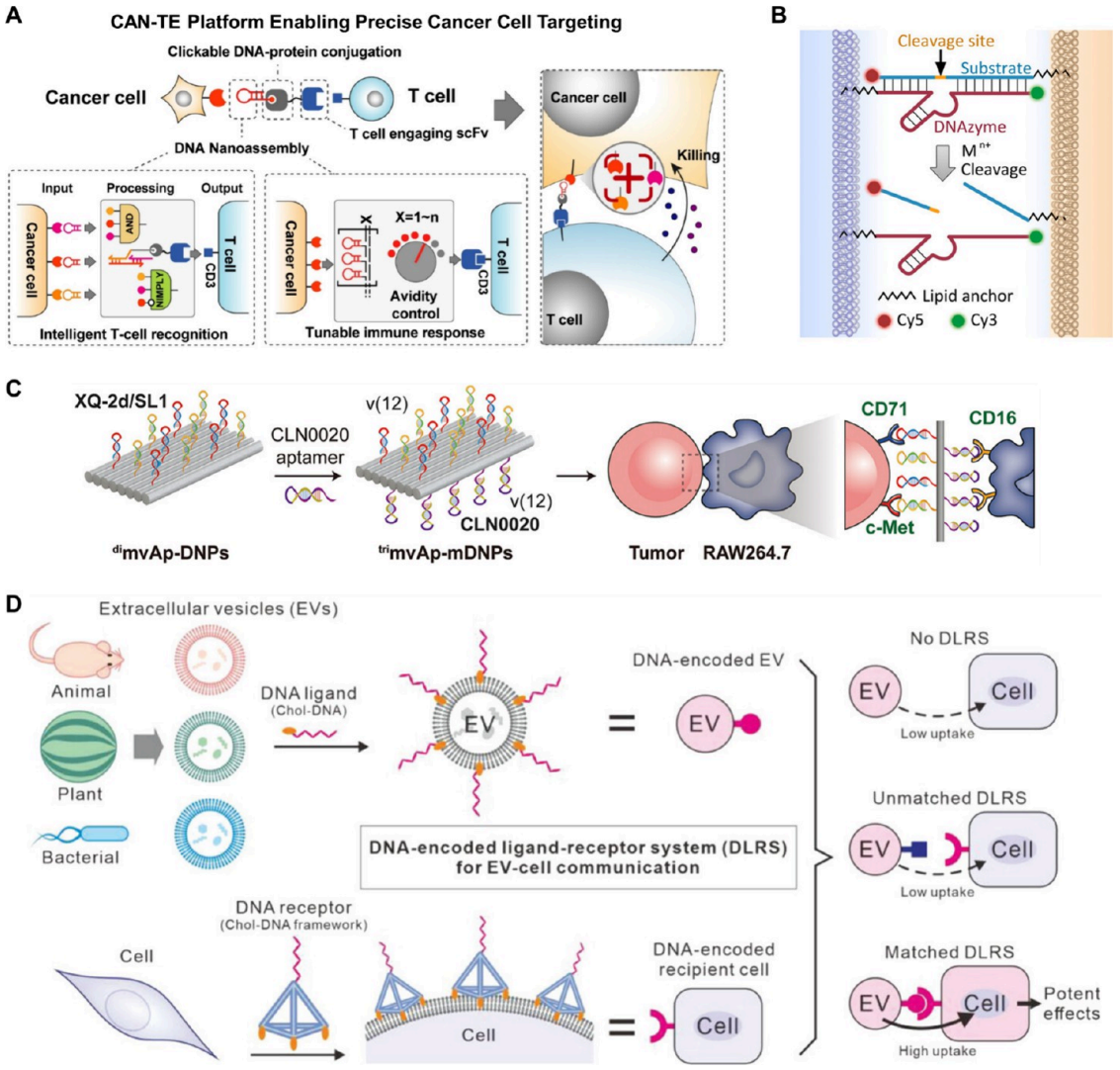

Figure 6. (A) A DNA-antibody chimera enabling programmable DNA nanostructure assembly to enhance T cell activation and immune response. CAN-TE: chimeric antibody-nucleic acid T-cell engager. Reproduced with permission from ref 106. Copyright 2022 Wiley-VCH GmbH. (B) Control of metal-ion-mediated cell communication using DNAzymes. Reproduced with permission from ref 111. Copyright 2021 American Chemical Society. (C) Regulation of macrophage-tumor immune interactions using a DNA nanosheet. XQ-2d: an aptamer binding to transferrin receptor (CD71). SL1: an aptamer binding to mesenchymal-epithelial transition (c-Met). Reproduced with permission from ref 39. Copyright 2024 American Chemical Society. (D) Mediation of interkingdom EV-cell communication using DNA tetrahedra. Reproduced with permission from ref 9. Copyright 2023 Wiley-VCH GmbH.

therapeutic applications such as targeted drug delivery, cancer treatment, and tissue regeneration.[100] In this aspect, DNA nanotechnology offers a potent tool for engineering cell surfaces, with advantages including high specificity, programmability, and minimal invasiveness. A representative example of DNA-mediated intercellular communication is the interaction between immune cells and tumor cells,[67] such as T cells,[32,57,101−108] macrophages,[39] and natural killer (NK) cells.[31,109,110] DNA molecules on the cell surface can reduce the spatial distance between cells, thereby facilitating enhanced communication. Furthermore, the programmability of DNA enables diverse intercellular signaling, such as promoting multivalent interactions that strengthen cell−cell communication.

For instance, the Wei group developed a DNA-antibody conjugate platform to engineer T-cell recognition, selectively activating immune responses against cancer cells (Figure 6A).[106] Using programmable DNA nanoassemblies, they achieved precise modulation of T-cell engagement. By integrating multiple aptamers for combinatorial tumor antigen recognition, the system performed higher-order logic operations to selectively activate T-cells. Additionally, the valence of antigen-binding aptamers was tuned to optimize avidity, thus enhancing the efficacy of tumor elimination both in vitro and in vivo. Similar polyvalent effects of multiple aptamers in boosting intracellular communication have also been reported.[103,104,110] Besides aptamer-mediated recognition, metal-mediated DNAzymes were employed to control T-cell-tumor interactions (Figure 6B).[111]

Macrophages also play a pivotal role in immune responses by phagocytosing pathogens, including tumor cells, significantly influencing antitumor immunity and immune regulation. The Zhang group designed various DNA nanostructures displaying aptamers to improve tumor cell recognition. They employed optimized sheet-like DNA nanostructures to mediate interactions between macrophages (RAW264.7 cells)

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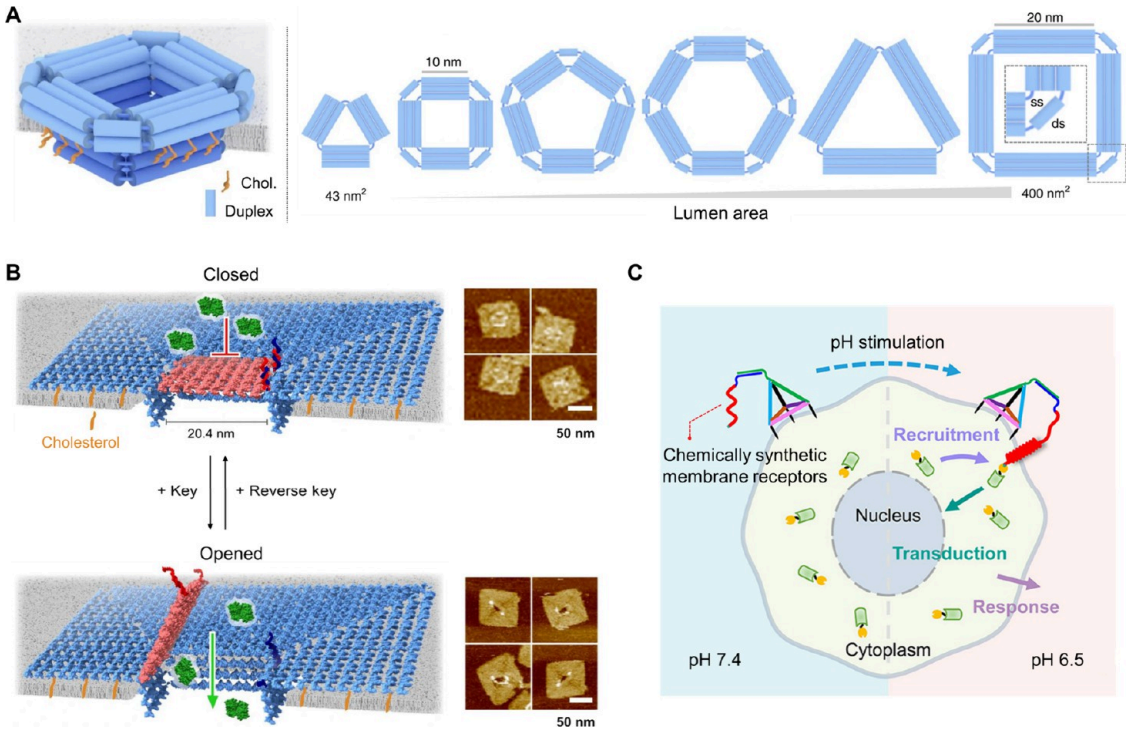

Figure 7. (A) An artificial membrane channel constructed using DNA nanotechnology exhibits high tunability in both shape and size. Reproduced with permission from ref 118. Copyright 2022 Springer Nature. (B) A DNA-based membrane channel designed for protein transport, featuring a reversibly gated mechanism. Reproduced with permission from ref 119. Copyright 2022 Springer Nature. (C) A chemically synthetic receptor constructed from amphiphilic DNA tetrahedra, capable of responding to pH stimuli and triggering downstream signaling pathways. Reproduced with permission from ref 121. Copyright 2023 American Chemical Society.

and tumor cells (Figure 6C),[39] which promoted the secretion of tumor necrosis factor-α (TNF-α) and enhanced the tumor cell-killing effect.

Unlike T cells, NK cells can directly recognize and attack abnormal cells without prior antigen processing. They kill tumor cells by releasing perforin and granzymes. The Yang group equipped NK cells with aptamers that specifically recognize tumor cells and block checkpoints to enhance their specific cytotoxicity against hepatocellular carcinoma.[31] Furthermore, the Wang group utilized HCR (hybridization chain reaction) to in situ generate multivalent, recognition-specific aptamers, which enhanced the killing effect of NK cells on tumor cells.[110]

Additionally, the Wu group reported an innovative approach for engineering interspecies extracellular vesicle (EV)-cell communication using DNA to encode interfaces between EVs and cells (Figure 6D).[9] By utilizing cholesterol-modified DNA strands and tetrahedral DNA frameworks as artificial ligands and receptors, they successfully facilitated efficient, specific EV-cell interactions without the need for covalent or genetic modifications. This DNA-programmed system allows for the manipulation of EVs to interact with human cells from diverse species, including mice, watermelon, and *E. coli*, highlighting the potential for orthogonal EV-cell communication in complex environments.

3.4. Constructing the Artificial Cell Membrane Component

Constructing artificial cell membrane components facilitates the understanding of the fundamental functions of cell membranes and holds significant importance for improving membrane functionality in a controllable manner. Among various construction methods, DNA nanotechnology offers unparalleled structural precision and tunability, making it an ideal tool for engineering membrane components. As early as 2012, the Simmel group utilized DNA nanostructures to construct artificial lipid membrane channels,[112] marking a significant milestone in this field. Since then, the associated research on constructing artificial cell membrane components using DNA nanotechnology has progressed rapidly.[11,113−121]

The Howorka group has leveraged DNA molecules to construct membrane nanopores that are highly tunable in both shape and size (Figure 7A).[118] By bundling DNA duplexes into modular pore subunits, the design enabled the construction of nanopores with adjustable shapes and lumen widths of up to 10 nm. This tunability allows for the accommodation of various molecular sizes and types, significantly enhancing the flexibility of these nanopores. Furthermore, the incorporation of functional units for recognition or signaling could further extend the versatility of these pore structures, broadening their potential applications.

To achieve intelligent, responsive membrane channels, the Yan group developed a synthetic DNA-based channel that enables the controlled, stimulus-responsive transport of functional proteins across lipid bilayers (Figure 7B).[119] The channel design features a programmable nanomechanical lid that opens and closes via a lock-and-key mechanism, mimicking natural transport systems. In another example, a triangular DNA nanopore with a stimulus-responsive, lumen-tunable feature was designed.[11] The nanopore underwent dynamic size changes between expanded and contracted states without altering its stable triangular shape, demonstrating a high degree of structural stability and responsiveness. Additionally, a DNA nanomachine capable of responding to membrane tension was also developed,[120] further expanding

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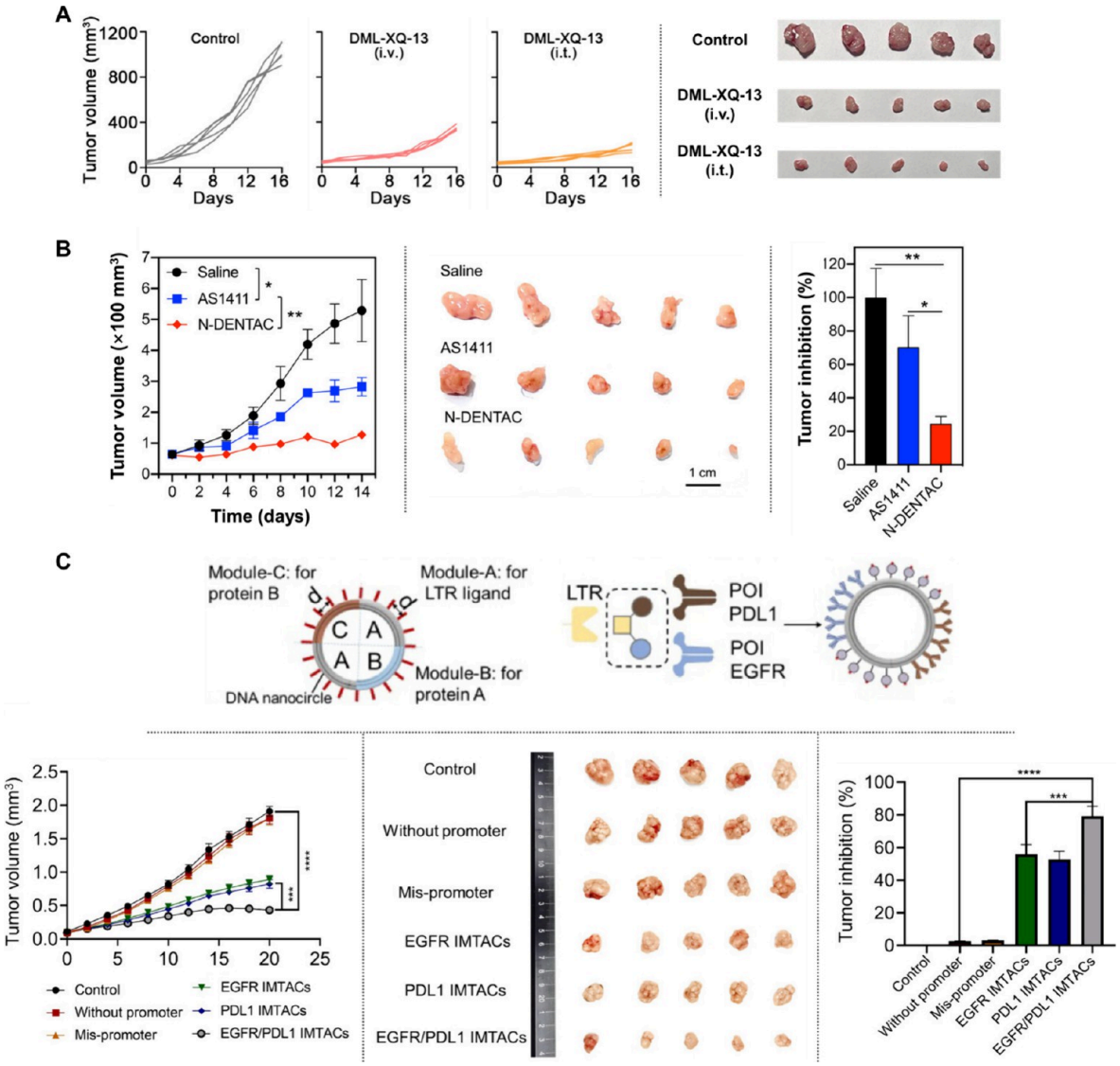

Figure 8. (A) Antitumor therapeutic efficacy based on integrin-mediated DNA-LYTAC platform. Reproduced with permission from ref 82. Copyright 2024 American Chemical Society. (B) Antitumor therapeutic efficacy based on a scavenger receptor-mediated DNA-LYTAC platform. Reproduced with permission from ref 58. Copyright 2023 Wiley-VCH GmbH. (C) Antitumor therapeutic efficacy based on a multimodule dual-target DNA nanodevice LYTAC platform. Reproduced with permission from ref 40. Copyright 2024 American Chemical Society.

the range of possible applications for DNA-based membrane components.

Beyond mimicking membrane pore channels, the development of artificial, chemically synthetic receptors has also gained attention. The Qiu group, for instance, used amphiphilic DNA tetrahedra conjugated with pH (low) insertion peptides to create synthetic receptors capable of sensing and responding to external pH changes (Figure 7C).[121] Upon encountering a pH stimulus, the DNA receptor underwent a conformational change that facilitated the recruitment of membrane-proximal proteins, triggering downstream signaling events. The authors demonstrated the potential of this system in regulating PKCε (protein kinase C epsilon)-related signaling pathways and in activating T cells in response to pH changes. These advancements highlight the significant potential of DNA nanotechnology in constructing artificial membrane components, offering new avenues for synthetic biology, molecular sensing, and cell engineering.

4. BIOMEDICAL APPLICATIONS OF DNA ENGINEERING ON THE CELL SURFACE

DNA engineering offers unique advantages in regulating cellular physiological processes. These processes will influence the fate of the cells, including apoptosis, altered cellular signaling, and altered cellular secretion behaviors. Such physiological modifications have driven advancements in areas like tumor therapy, cell-based immunotherapy, and the treatment of metabolic diseases. Additionally, DNA engineering on cell surface boosts the progress in the isolation, protection, and culture of cells, as well as in imaging and detection applications.

4.1. Protein Degradation-Mediated Tumor Therapy

The strategy of lysosome-targeting chimeras (LYTACs) has shown considerable promise in tumor therapy, particularly when the targeted proteins are critical metabolic regulators in tumor cells. LYTACs efficiently mediate the degradation of such target proteins, offering a novel therapeutic approach.

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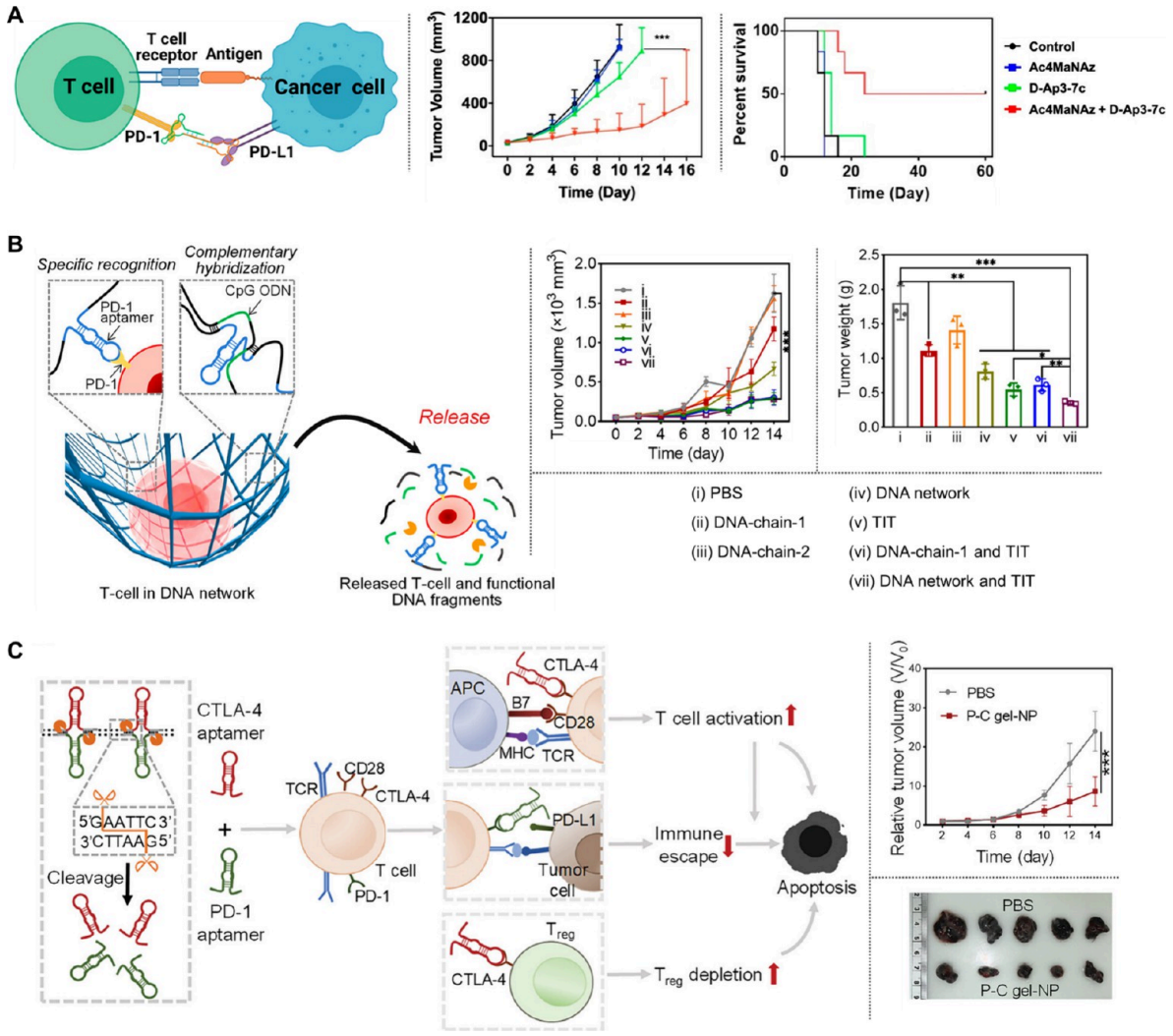

Figure 9. (A) The bispecific aptamer simultaneously binds to PD-1 and PD-L1, blocking the immune checkpoint and thereby enhancing the cytotoxic activity of T cells against tumor cells. D-Ap3-7c: a DBCO-labeled bispecific aptamer. Reproduced with permission from ref 107. Copyright 2022 American Chemical Society. (B) DNA network-captured and released surface-DNA-engineered T cells exhibit immune-mediated cytotoxicity against tumors. TIT: tumor-infiltrating T-cells. Reproduced with permission from ref 122. Copyright 2021 American Chemical Society. (C) Bispecific aptamer-engineered T cells enhance antitumor efficacy through the immune checkpoint blockade. Reproduced with permission from ref 123. Copyright 2024 Wiley-VCH GmbH.

These DNA-based LYTACs not only proved their efficacy in cells but also in the in vivo model.[40,58,81,82]

The Tan group developed a bispecific aptamer-based LYTAC platform for targeting and degrading pathological membrane proteins, such as CD71 (transferrin receptor) and PTK7 (tyrosine kinase-7).[82] By modulating the specificity of the aptamers, these LYTACs effectively inhibit tumor growth. Specifically, the reported DML-XQ-13—where DML is the aptamer targeting integrin $\alpha 3\beta 1$, XQ targets CD71, and "13" refers to the 13-base pair length of the linker—demonstrated an IC50 (half maximal inhibitory concentration) of 172.2 nM against DU145 cells (human prostate cancer cells). In a tumor-bearing mouse model, DML-XQ-13 exhibited substantial tumor suppression following either intratumoral or intravenous administration, with no significant off-target effects observed in vital organs (Figure 8A).

In addition to aptamers, the Li group presented a DNA dendron-based LYTAC (N-DENTAC) platform.[58] The DNA dendron bound to the scavenger receptor, which mediated the endocytosis of polyanions and also served as a lysosome trafficking receptor (LTR). The other end of the LYTAC was a binder, such as an antibody or an aptamer (e.g., AS1411, which binds to nucleolin), to target the protein of interest. Using this DNA dendron-AS1411 LYTACs, the Li group achieved an impressive 76% tumor inhibition in the A549 lung cancer mouse model (Figure 8B).

Targeting and degrading a single protein may not always yield optimal therapeutic outcomes. To address this, the Chao group developed a DNA origami nanocircle that incorporates three distinct modules:[40] Module A targets the LTR ligand, Module B binds the epidermal growth factor receptor (EGFR), and Module C targets programmed cell death ligand-1 (PDL1). EGFR plays a pivotal role in tumor growth, and its knockdown can inhibit cancer progression. PDL1 degradation, which is critical for immune checkpoint regulation, can enhance the effectiveness of immunotherapy. The combination of these two therapeutic targets resulted in a synergistic treatment effect, with a remarkable tumor inhibition rate of 80% (Figure 8C).

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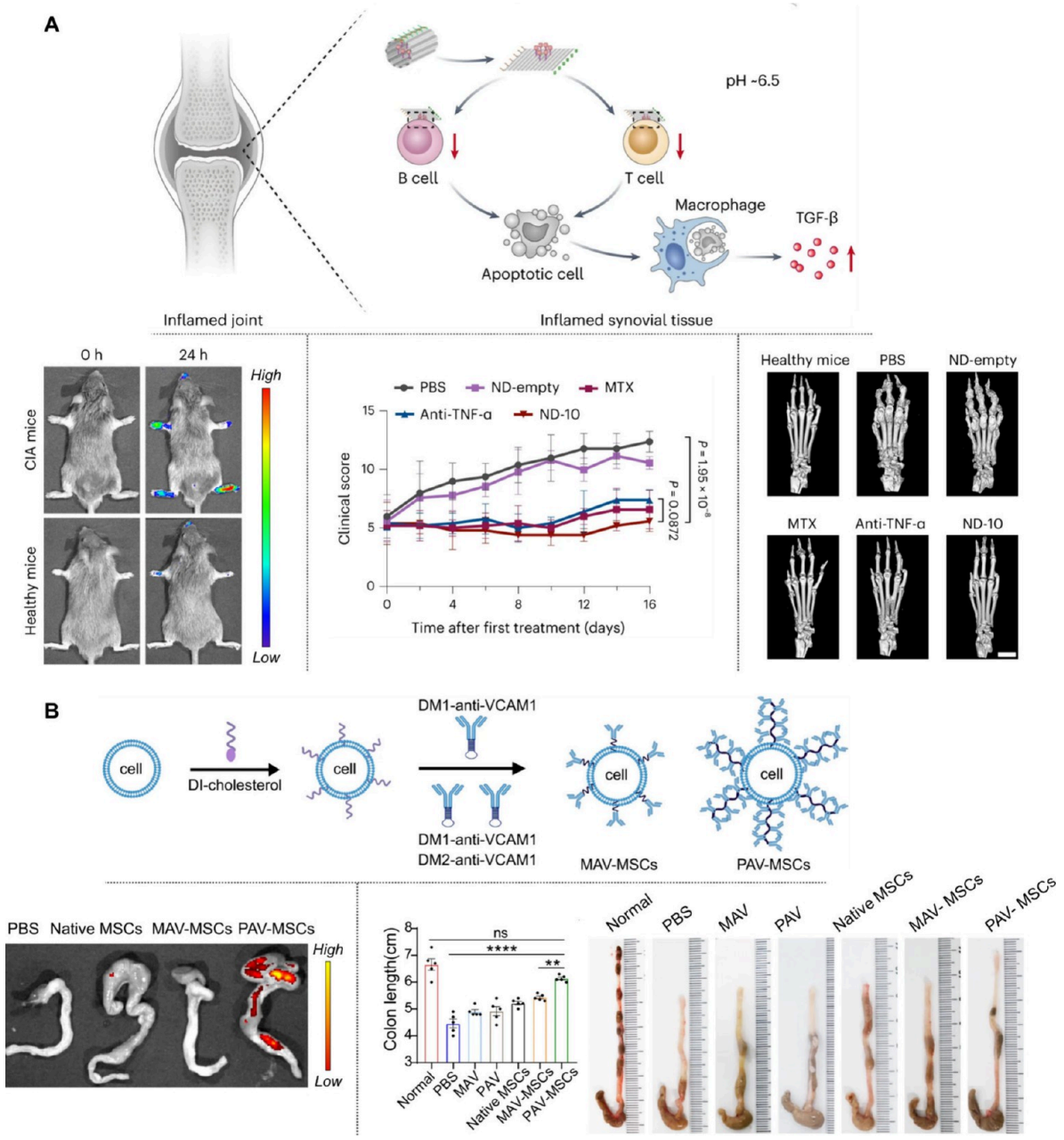

Figure 10. (A) DNA origami devices are used to spatially control the arrangement of CD95 signaling molecules, which in turn modulate the signaling pathway. This leads to the downregulation of immune cells, inducing immune tolerance near the site of osteoarthritis and alleviating its symptoms. MTX: methotrexate. ND: nanodevice. Reproduced with permission from ref 10. Copyright 2024 Springer Nature. (B) HCR-mediated engineering of multivalent antibodies on the surface of mesenchymal stem cells and their application in the treatment of colitis in mice. DM: DNA monomer for polymerization. Reproduced with permission from ref 124. Copyright 2023 Springer Nature.

4.2. Cell-Based Tumor Therapy

Cell-based tumor therapy generally refers to utilizing immune cells to activate or enhance immune system to specifically recognize and kill cancer cells. Representative cytotoxic immune cells include T cells and natural killer (NK) cells. Modifying the surface of immune cells or tumor cells with DNA can improve the efficacy of cell-based tumor therapies.

Significant progress has been achieved in enhancing T cell-based immunotherapy using a bispecific aptamer strategy. This strategy typically targets and blocks PD-L1 on surface of tumor cells and/or PD-1 on T cells.[30,32,103,105−108,122,123] For example, a bispecific aptamer that simultaneously blocked both PD-1 and PD-L1 has been demonstrated to enhance T cell-mediated cytotoxicity against tumor cells (Figure 9A).[107] This strategy also incorporated a "recognition-then-conjugation" approach, where covalent bonding further minimized off-target effects. In the B16F10 tumor model, 50% of mice treated with this strategy exhibited complete tumor ablation.

Our team has also made notable advances in engineering the surface of T cells. In 2021, we reported the development of a DNA network designed to specifically capture T cells via a PD-1 aptamer (Figure 9B).[122] Under inflammatory conditions, the T cells were released, while the PD-1 aptamer remained on the T cell surface, facilitating immune checkpoint blockade and enhancing the T cell cytotoxicity against tumor cells. This strategy demonstrated excellent antitumor efficacy in mouse

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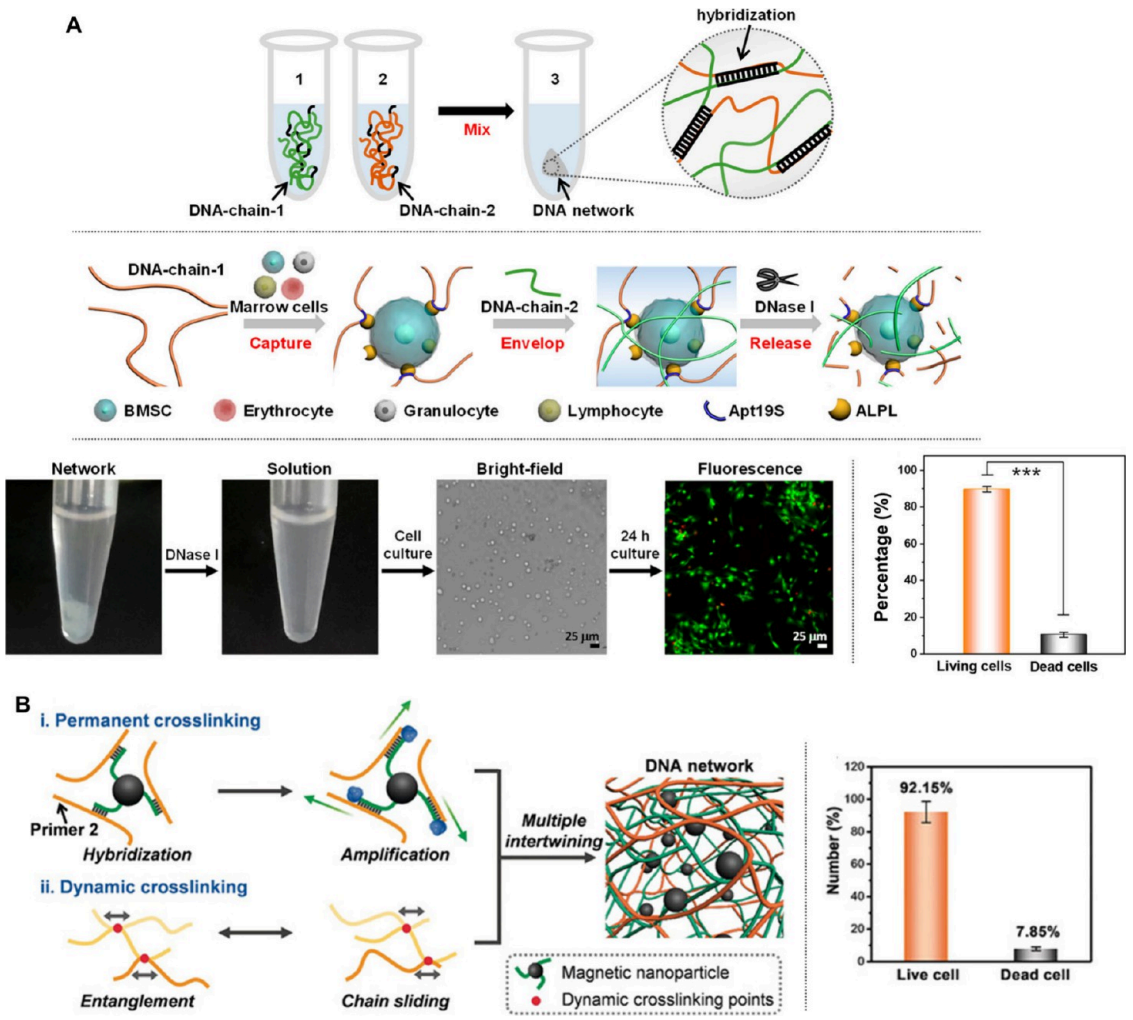

Figure 11. (A) DNA networks formed by dual ultralong single-stranded DNA for stem cell capture and release. Reproduced with permission from ref 75. Copyright 2020 American Chemical Society. (B) Supramolecular interactions between long single-stranded DNA and upconversion nanoparticles for cell protection and transport. Reproduced with permission from ref 74. Copyright 2020 Wiley-VCH GmbH.

tumor models. Furthermore, we recently developed a dual-targeted DNA hydrogel for immune checkpoint blockade therapy (Figure 9C).[123] This hydrogel contains two polyvalent aptamers, PD-1 and CTLA-4 aptamers, to promote T cell enrichment. The addition of restriction enzymes allowed the DNA hydrogel to be cleaved in response to the inflammatory tumor microenvironment, thus releasing T cells at the tumor sites. The PD-1 and CTLA-4 aptamers block immune checkpoints, activating T cells within the tumor. In a melanoma-bearing mouse model, this DNA hydrogel demonstrated significant antitumor effects, with tumor growth inhibition reaching approximately 65%. In addition to T cells, NK cells also possess potent cytotoxic activity. In one study, active targeting aptamers and PD-L1 aptamers were equipped onto the surface of NK cells, which were then adoptively transferred into recipient mice. This approach led to remarkable therapeutic effects in the HepG2 xenograft model.[31]

4.3. Treatment of Inflammation-Related Diseases

Inflammation is typically associated with abnormal immune responses, infections, and tissue damage. As a key immune response, inflammation is generally aimed at eliminating pathogens. However, in certain cases, excessive inflammation may lead to uncontrolled inflammation can lead to tissue damage. Modulating the key signaling pathways or immune cells involved in inflammation offers a promising strategy for alleviating inflammation-related diseases. In this regard, DNA surface engineering strategies present a novel and effective approach.

CD95/CD95 ligand signaling plays a critical role in the clearance of activated lymphocytes and the induction of immune tolerance to self-antigens. The Chen group utilized DNA origami to spatially control the geometry of the CD95 ligand, downregulating the B-cell and T-cell populations and inducing immune tolerance in rheumatoid arthritis (Figure 10A).[10] In a collagen-induced arthritis (CIA) mouse model, the DNA origami device exhibited significant accumulation at the inflammation sites, particularly in the mouse paws. Subsequent treatment of arthritis with this device significantly alleviated disease progression, and micro-CT imaging showed joint morphology similar to that of healthy mice.

In a different approach, the Shi group developed a strategy using DNA to engineer polyvalent antibodies (PAV) on the surface of mesenchymal stem cells (MSCs), enhancing the therapeutic efficacy for inflammatory bowel disease (Figure 10B).[124] The engineering of polyvalent antibodies on the MSC surface increased their accumulation at the inflammatory site in

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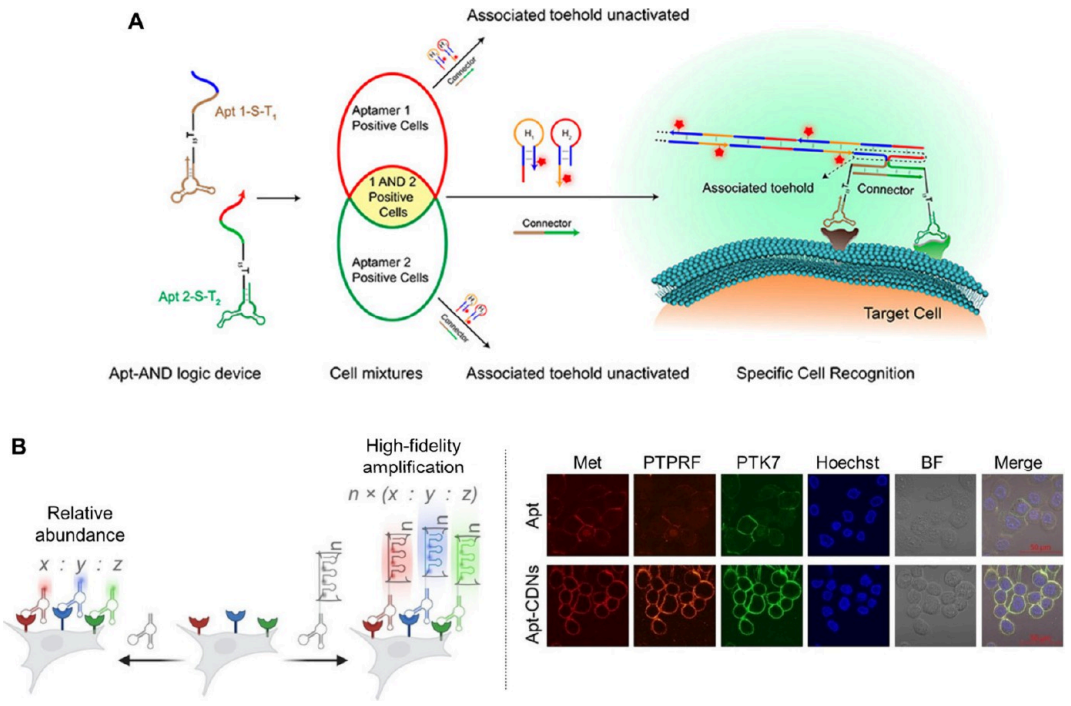

Figure 12. (A) Amplified imaging of cell membrane proteins activated by DNA logic-based scaffolds. Reproduced with permission from ref 125. Copyright 2020 American Chemical Society. (B) DNA-encoded amplification reactions enabling the imaging of live cell membrane proteins with enhanced signal. Reproduced with permission from ref 126. Copyright 2024 Wiley-VCH GmbH.

the intestine. Specifically, compared with MSCs engineered with monovalent antibodies (MAV), the polyvalent antibody-engineered MSCs accumulated 3.5 times more at the site of inflammation. Furthermore, in a dextran sulfate sodium (DSS)-induced colitis model, polyvalent antibody-engineered MSCs demonstrated excellent therapeutic effects by efficiently promoting the repair of damaged intestinal tissues.

4.4. Capture and Protection of Cells

Functional cells play a critical role in various biomedical fields, particularly in tissue engineering, regenerative medicine, and immunotherapy. Efficient capture of these functional cells specifically enables targeted delivery and localized treatment. However, a major challenge in this field is maintaining cell viability and functionality while minimizing the impact during the capture process. In this regard, DNA hydrogels provide a powerful tool.

Our team developed a dual-RCA approach to create a double-stranded single-chain DNA network for stem cell capture (Figure 11A).[75] One DNA strand contains aptamers that specifically bind to stem cells, allowing for targeted cell capture. The other strand partially hybridizes with the first DNA strand to form cross-linking points, thereby resulting in a DNA network. After the capture process, DNase I can be employed to degrade the DNA network and release the captured cells. Our results demonstrated that this strategy offers excellent protection for the cells during capture, with only ∼10% cell death observed.

In another study, we utilized DNA-modified magnetic nanoparticles and ultralong single-stranded DNA generated via RCA to form a magnetic DNA hydrogel (Figure 11B).[74] This hydrogel was highly soft and superelastic, capable of recovering its original shape even after experiencing up to 3000% deformation. Leveraging these unique properties, we used the hydrogel for cell encapsulation and transportation, achieving a cell survival rate of 92.15%. Additionally, we developed a flash-synthesis method for DNA hydrogels through supramolecular interactions between DNA strands and upconversion nanoparticles, allowing for hydrogel formation in just one second.[73] This resulting hydrogel was also employed for cell capture and protection, achieving an 88.7% cell survival rate, demonstrating the potential of DNA hydrogels in cell protection.

4.5. Analytical Detection

The direct application of cell surface-engineered DNA is the analysis and detection of cell membrane-associated substances. Significant progress has been achieved in this field in recent years, with DNA emerging as a powerful tool for molecular detection, particularly through molecular beacons, which have seen remarkable success in biological analysis.[46,125−131]

The Jian group recently reported the development of a dynamic DNA nanomachine that was anchored to the cell surface and underwent pH-responsive triplex−duplex conformational switching. This system enables tunable sensing and imaging of extracellular pH.[130] However, single molecular beacons typically suffer from low sensitivity. To address this limitation, several higher-order DNA structures for signal amplification have been developed, such as RCA,[128,131] and HCR.[125,127] For example, the Wang group presented a DNA logic gate driven by membrane proteins and extracellular pH heterogeneity, which combined the superior signal amplification of HCR with the precision of logic operations.[127] In this strategy, the DNA logic gate was activated only when two heterotypic biomarkers were present simultaneously. In a 200 μL buffer, the gate was able to detect 70 cells and could accurately distinguish target cancer cells from complex cell mixtures.

In another approach, the Tan group utilized a combination of aptamers with recognition capabilities and DNA scaffold

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Table 3. Summary of DNA Nanotechnology-Enabled Cell Surface Engineering and Related Biomedical Applications

biomedical application	biological mechanism	approach of attaching oligonucleotides	type of surface DNA nanotechnology	reference
protein degradation-mediated tumor therapy	degradation of key proteins	aptamer-mediated binding	dual/polyaptamer strategy	82
			circle DNA origami	40
		cluster effect binding with cell surface receptor	dendronized DNA	58
cell-based tumor therapy	blocks immune checkpoint	aptamer-mediated binding	dual/polyaptamer strategy	30, 32, 107, 108, 122
	regulating signal pathway	chemical conjugation	HCR-based structure	103
		aptamer-mediated binding	HCR-based structure	105
		aptamer-mediated binding	DNA circuit	106
treatment of inflammation-related diseases	regulating signal pathway	ligand−receptor molecular recognition	DNA origami	10
		antibody-receptor molecular recognition	HCR-based structure	124
capture and protection of cells	molecular recognition or physical encapsulation	aptamer mediated binding	RCA-based structure	74, 75
analytical detection	molecular beacons	aptamer mediated binding	HCR-based structure	125, 127
	molecular beacons	biomacromelcular recognition	RCA-based structure	128, 131

sequences for signal integration and amplification, using these as two molecular "keys" to construct a DNA nanodevice anchored onto the cell surface (Figure 12A).[125] This device performed "AND" Boolean logic analysis for multiple biomarkers, allowing for the precise identification of target cell subtypes from a large population of similar cells based on the presence or absence of specific biomarkers.

More recently, the Han group developed a novel signal amplification strategy, distinct from RCA and HCR, known as the Template Adhesion Reaction (TAR) method (Figure 12B).[126] TAR involved the assembly of amplifiable DNA sequences with different affinity ligands, such as aptamers or antibodies, to achieve high-fidelity quantitative amplification and multiplexed imaging of live cell membrane proteins. The TAR strategy allows for precise control over signal amplification by adjusting the concentration ratio of hairpin template and primers, enabling the proportionate amplification of membrane protein targets with variable abundances. This method provided enhanced signal-to-noise ratio (SNR) without disturbing the original ratios of membrane proteins, making it ideal for sensitive and accurate visualization of multiple membrane proteins.

Table 3 exhibits summary of DNA nanotechnology-enabled cell surface engineering and related biomedical applications.

5. CONCLUSION AND FUTURE PERSPECTIVE

In summary, this review provides an overview of DNA nanotechnology in cell surface engineering and its promising biomedical applications, particularly in regulating cellular physiology as well as advancing disease therapy and detection. We first discussed various strategies for attaching oligonucleotides to cell membranes, such as direct chemical conjugation, hydrophobic insertion, and aptamer- or antibody-mediated binding. Furthermore, we have highlighted the high-order DNA nanostructures on cell surfaces, like DNA origami, tetrahedra, and structures based on RCA and HCR, which offer a versatile platform for manipulating cellular behavior with unprecedented precision.

Subsequently, we summarized and discussed the emerging progress of engineering DNA nanostructures on the cell surface for modulating cellular physiological processes, including targeted degradation of membrane-associated proteins, regulation of cell signaling pathways, construction of artificial membrane components, and control of cell communication. These advances have been translated into a broad spectrum of biomedical applications, particularly in cancer therapy, cell-based therapies, inflammation treatment, capture and protection of cells, and analytical detection. DNA nanodevices capable of targeting specific diseased cells or tissues offer novel opportunities for precision medicine, with the potential for tailored therapies and advanced diagnostic platforms. This positions DNA-engineered cell surfaces not only as valuable tools for fundamental research but also as promising strategies for future therapeutic interventions. By leveraging DNA nanotechnology that possesses incomparable precision and almost infinite functionalities, novel opportunities for precision medicine with the potential for tailored therapies and advanced diagnostic platforms will be explored.

Despite the significant progress made in DNA nanotechnology for cell surface engineering, several challenges remain. We outline these challenges and future directions as follows:

(1) Stability of engineered DNA nanostructures. One of the major concerns is the stability of engineered DNA nanostructures on cell surfaces, particularly regarding their susceptibility to endocytosis, degradation, and shedding from the membrane. These issues are particularly critical for in vivo applications.

(2) Biosafety considerations. The long-term biosafety of surface-engineered DNA nanostructures must be carefully evaluated, as potential immune responses to these constructs could limit their clinical applicability.

(3) *In vivo* DNA engineering on cell surface. Currently, surface DNA engineering is typically performed *in vitro* before being transferred into *in vivo* systems. This process is time-consuming and labor-intensive. Developing transformative methods for engineering DNA nanostructures directly on specific cell surfaces *in vivo* will be a crucial research direction.

(4) Complex logic operations. Developing advanced DNA nanodevices capable of executing complex logic operations directly on cell surfaces will represent an exciting and promising research direction.

(5) Integration with emerging technologies. Integrating DNA nanotechnology with cutting-edge technologies

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such as CRISPR-based gene editing will provide powerful tools for the precise modification of cellular functions.

Overall, DNA nanotechnology offers a versatile tool for cell surface engineering, though presenting several challenges. Foreseeing ahead, as those challenges are addressed and the field continues to advance, DNA nanotechnology-based cell surface engineering will play a pivotal role in advancing personalized therapies, particularly in cancer immunotherapy, autoimmune diseases, and regenerative medicine.

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Author Contributions

Conceptualization: D.Y.; original draft writing: F.X., X.S., W.T.; review and editing: D.Y. All authors have read and agreed to the published version of the manuscript. CRediT: **Fan Xiao** conceptualization, funding acquisition, writing - original draft, writing - review & editing; **Xinghong Shen** writing - original draft, writing - review & editing; **Wenqi Tang** writing - original draft, writing - review & editing; **Dayong Yang** conceptualization, funding acquisition, supervision, writing - original draft, writing - review & editing.

Notes

The authors declare no competing financial interest.

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