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DNA hydrogels and their derivatives in biomedical engineering applications

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Abstract

Deoxyribonucleotide (DNA) is uniquely programmable and biocompatible, and exhibits unique appeal as a biomaterial as it can be precisely designed and programmed to construct arbitrary shapes. DNA hydrogels are polymer networks comprising cross-linked DNA strands. As DNA hydrogels present programmability, biocompatibility, and stimulus responsiveness, they are extensively explored in the field of biomedicine. In this study, we provide an overview of recent advancements in DNA hydrogel technology. We outline the different design philosophies and methods of DNA hydrogel preparation, discuss its special physicochemical characteristics, and highlight the various uses of DNA hydrogels in biomedical domains, such as drug delivery, biosensing, tissue engineering, and cell culture. Finally, we discuss the current difficulties facing DNA hydrogels and their potential future development.

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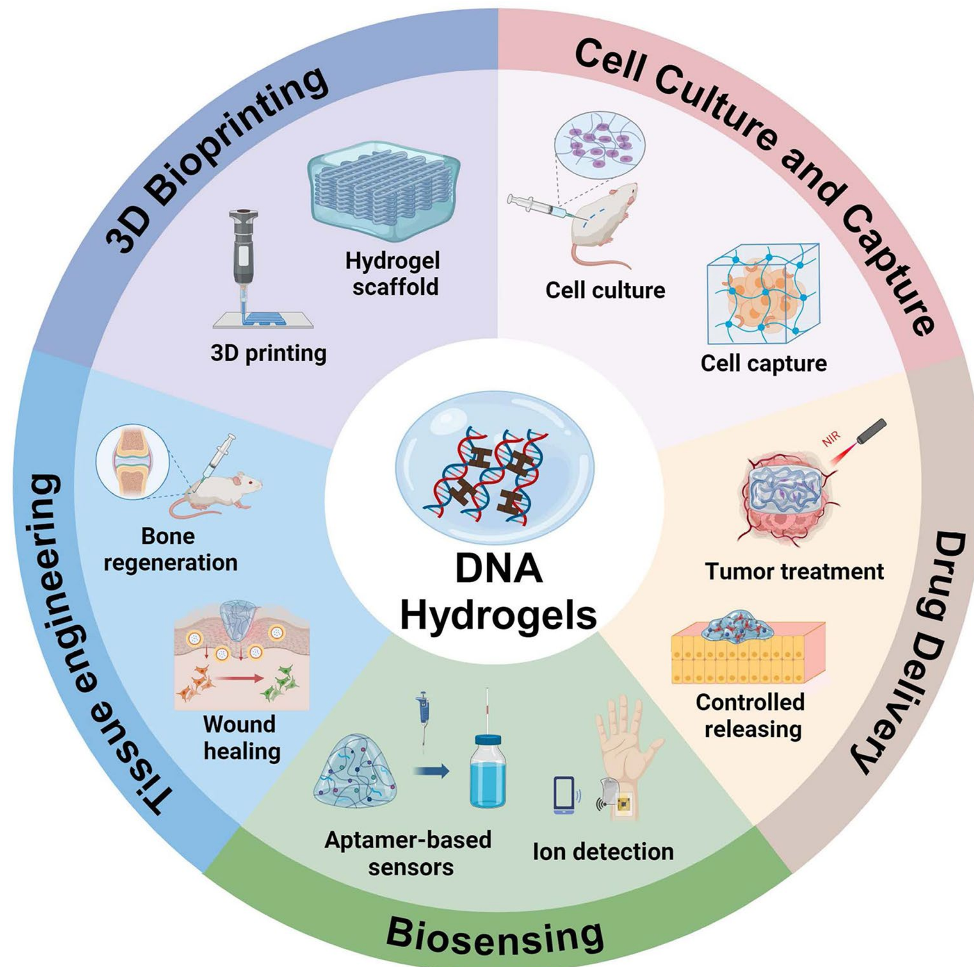
Graphical Abstract



Keywords DNA hydrogels, Self-assembly, Crosslinking, Mechanical-properties, Biomedical application

Introduction

Deoxyribonucleotide (DNA) is a natural biopolymer with controllable chemical structure and biological function, presenting substantial potential for development as a functional material [1]. As a natural biopolymer, DNA serves as the primary vehicle for encoding, storing, and transferring genetic information [2]. The DNA molecule consists of two single strands of deoxyribonucleotides that adhere to the Watson–Crick base-pairing principle. These DNA strands are organized in a particular coding sequence to create a stable double-helix structure [3]. This highly selective base recognition and sequence coding design capability endows DNA with excellent assembly capabilities. In 1982, Seeman designed the first linear DNA double helix. Since then, artificial DNA synthesis and modification techniques have been developed and matured, and DNA can be easily designed and synthesized from known sequences. DNA molecule applications have gradually expanded from their biological roles to the field of material science [4]. DNA molecules can be precisely programmed with simple chemical modifications to build materials with desired mechanical, biological, and structural properties [5–7]. For instance, the DNA manipulation and modification using specific instrumental enzymes has led to the development of multifunctional DNA nanostructural units [8]. Additionally, introducing a variety of functional groups at different positions in the DNA strand, such as sulfhydryl and amino groups [9], topologies can be changed in vitro using simple enzymatic reactions. Various compounds have been developed based on specific DNA structural and functional changes that exhibit potential biological uses in different areas of biomedicine [10–12].

Hydrogels are attractive biomaterials owing to their high biocompatibility and physical characteristics that resemble biological tissues. New hydrogels with unique functions are frequently reported [13–15]. Among the various polymer materials, researchers have been interested in using DNA to construct hydrogels. This is because DNA hydrogels not only retain the hydrogel backbone, but their unique programmability allows precise control of polymer chain interactions, thus, researchers are able to determine the formation and behavior of hydrogels in unique ways not possible with traditional hydrogel materials. When designing synthetic hydrogel structures, researchers can insert functional DNA nanostructures into the polymer network to control the behavior of the hydrogel in different environments. Examples include DNA aptamers with specific affinities for targets, i-motif structures that form at specific pH values, DNA enzymes that catalyze different chemical reactions, and more. These functional DNA structures provide hydrogels with sensitive stimulus responsiveness and offer more possibilities for the development of hydrogels. Additionally, the three dimensional (3D) scaffold of DNA hydrogels has a certain degree of mechanical rigidity that provides a large number of attachment sites, enhancing their function of stabilizing the immobilized substrate [16], while the introduction of other nanomaterials, such as magnetic and metal nanoparticles (NPs), into DNA hydrogels can improve their functional properties [17, 18]. Moreover, compared with other synthetic polymer hydrogels, DNA is inherently biocompatible and is easily recognized by the human body, thus reducing practical application-related risks. Furthermore, the biodegradability of DNA eliminates the major concerns associated with most synthetic polymers [19]. DNA hydrogels offer many other advantages, such as specific molecular recognition, controlled phase transitions, and mechanical properties [20–23].

Different strategies have been devised to synthesize DNA hydrogels for biomedical engineering applications in various fields, such as biosensing, drug loading, tissue engineering, and cell culture. In this study, we provide an overview of significant recent advancements in DNA hydrogel technology. We outline the different design philosophies and methods of DNA hydrogel preparation, discuss their special physicochemical characteristics, and highlight the various uses of DNA hydrogels in biomedical domains. Finally, we elaborate on the difficulties facing DNA hydrogels and their potential for future development.

Materials for DNA hydrogel synthesis

Constructing abundant DNA strands is necessary for preparing DNA hydrogels. Whether relying on artificial synthesis or genome extraction, the cost of these two methods is high, and they often synthesize DNA strands of insufficient length and purity. To this end, researchers have developed various nucleic acid amplification methods to produce long DNA strands to meet research needs. Polymerase chain reaction (PCR), rolling circle amplification (RCA), and hybridization chain reaction (HCR) have been used to produce DNA hydrogels [24, 25]. RCA and HCR are amplification methods at a constant temperature, simpler to perform and more efficient than PCR. RCA and HCR have different advantages. RCA is a simple and effective enzymatic amplification technique that is performed at constant temperatures and uses a minor quantity of circular DNA template [26]. This amplification method results in the continuous extension of DNA to form ultra-long linear DNA strands [27–29]. The hybridization chain reaction eliminates the complex thermal cycling step and achieves ultra-high detection sensitivity similar to PCR. As RCA does not require coenzymes, it is cheaper to synthesize DNA hydrogels. Further, non-linear HCR forms multiple branching DNA nanostructures. Triggered by promoter sequences, specific hairpin structures are opened to form self-assembled DNA nanostructures. Compared with other nucleic acid amplification methods, HCR has higher sensitivity and selectivity [30, 31].

Functional DNA structures are important components of DNA hydrogels, such as i-motif structures, DNA enzymes, and aptamers, which provide molecular recognition to hydrogel polymers, further enriching the stimulus responsiveness of DNA hydrogels [32, 33]. DNA aptamers are commonly used functional DNA structures, obtained by in vitro screening, the systematic evolution of ligands by exponential enrichment (SELEX), and random DNA sequences and can bind to various small molecules. Therefore, aptamers are mostly used as targeting ligands to assist DNA hydrogels in delivering therapeutic drugs, such as small RNA (siRNA), specifically to diseased cells, so that normal cells will not be damaged and the effect of targeting therapy can be achieved [34]. Nucleic acid aptamers present notable advantages, such as small physical size for easy transportation, customizable structure, high thermal stability, and ease of chemical modification. These qualities allow DNA aptamers to be used for exosome isolation and bioanalysis [35, 36]. As biologically active molecules, DNA aptamers leave the physicochemical properties of the hydrogel unchanged and enable the DNA hydrogel to have a highly specific targeting function for various biomolecules [37]. Some DNA aptamers also undergo conformational changes in response to potassium ions, triggering a change in hydrogel volume, and can therefore be used for sensitive detection of potassium ions. [38]. In addition, these functional DNAs can act as cross-linking agents that allow

the hydrogels to self-assemble at near-body temperature, making them ideal for encapsulating cells.

DNA hydrogel construction

There are many different ways to categorize DNA hydrogels. Generally, they are divided into two categories according to their composition: pure DNA hydrogels prepared entirely by DNA assembly, which are assembled by constructing various DNA modules and patterns, or by nucleic acid amplification to obtain long DNA strands entangled to form DNA hydrogels; hybrid DNA hydrogels, which usually contain other natural or synthetic polymers where the DNA acts as a cross-linking agent to cross-link and form hydrogels. In this section, we will discuss the synthesis strategies based on these two components of hydrogels and how they can be applied in different fields.

Hybridized DNA hydrogels using DNA cross-linking

Hybridized DNA hydrogels are made by cross-linking DNA with other polymers. For hybridized DNA hydrogels, the hydrophilic polymer chains act as scaffolds for the main body of the gel, and the DNA chains mainly act as cross-links during the gelation process, which is significantly different from that of pure DNA hydrogels.

The first reported DNA hybridization hydrogel was synthesized by Nagahara and Matsuda in 1996 as a polyacrylamide-DNA hybridization hydrogel [39]. They crosslinked short DNA sequences modified with acrylates to polyacrylamide polymer chains. The authors then showed that there are two ways to achieve gelation; by hybridizing the DNA sequences with two other DNA strands attached to the polymer backbone and by attaching complementary DNA branched strands directly to the polymer backbone without adding external DNA connectors. Following this work, polyacrylamide hydrogels with different DNA cross-links have been produced. For example, Willner et al. [40] designed pH-controllable shape memory hydrogels. These two nucleic acid chains act as "connectors" that aggregate into an i-motif structure at pH 5.0 to form a stable hydrogel, and then dissociate from the i-motif structure at pH 8.0 to turn the hydrogel into a liquid (Fig. 1A). Also utilizing the i-motif as a cross-linking unit, Guo et al. [41] designed DNA hybridization hydrogels as thin-film structures; then, i-motif sequences were inserted into the active layer of bilayer polyacrylamide to direct the programmable stimulus response and reversible shape deformation of the hydrogels. As shown in Fig. 1B, the formation of the i-motif structure was induced by pH adjustment, thus changing the cross-linking density of the active layer and becoming swollen, while the passive layer, which was tightly adhered to the active layer, remained unchanged in volume, which induced the bending deformation of the hydrogel film. Liao et al. [42] proposed another method for assembling stimulus-responsive DNA-polyacrylamide hydrogels to stabilize microcapsules. They used HCR to generate a DNA crosslinked hydrogel coat encapsulating $CaCO_3$ particles. Due to the incorporation of cofactor-dependent DNAzyme units, the stiffness of the outer hydrogel decreases and porosity increases when the crosslinked DNAzyme substrate is cleaved by the corresponding cofactor, thereby releasing the loadings. Constructing a hydrogel based on a similar strategy, Sun et al. [43] developed a novel stimulus-responsive aptasensor. The DNA-acrylamide hydrogel formed by two polyacrylamide chains was functionalized by DNA hairpins and involved in chain-induced HCR. Upon fumonisin B (FB) exposure, the complexes formed by FB with the DNA functional units promote the dissociation of the crosslinked bridging units, leading to the disintegration of the encapsulated metal-organic framework (MOF) hydrogel shell. These polyacrylamide-based hybrid DNA hydrogels use DNA units as "bridges" to form hydrogels that undergo a solution-gel transition as the DNA polymerizes and dissociates. The properties of the polymer itself, such as chemical flexibility and stability, are well preserved in these hybrid hydrogels. In addition, other organic backbone materials have been gradually explored, and various hybridized DNA hydrogels, such as proteins and peptides, have been prepared [44]. Li et al. [45] prepared supramolecular peptide-DNA hydrogels using "X"-shaped DNA as a cross-linking agent (Fig. 1C). Under physiological conditions, the gelation process was rapid. Moreover, this hydrogel presents self-repairing ability. The peptide-DNA hydrogel blocks are modified into different colors for easy observation, they stick together upon contact, and after a few minutes, the fully bonded gel blocks can be picked up with tweezers. They can even be completely fused into a homogeneous whole. This is because DNA grafted polypeptides have the same cross-linked "sticky ends" as the "X-shaped" DNA linkers, so when they come into contact, the "sticky ends" of the "X-shaped" DNA linkers in one of the hydrogels dissociate from the polypeptide chain and form a new double strand with the DNA "sticky ends" on the polypeptide chain of the other hydrogel.

Inorganic nanomaterials, such as magnetic and carbon nanotube metal NPs [46, 47], have also been used to create hybridized DNA hydrogels in order to enhance their performance and give them additional functionality. For example, magnetic nanoparticles (MNPs) can form dynamic cross-linking points in the hydrogel network through physical entanglement. Yang et al. [48] developed a magnetically driven soft robot based on DNA hydrogel by incorporating MNPs into the hydrogel. RCA first amplifies the long ssDNA, and short ssDNA-modified MNPs are attached to the long ssDNA as cross-linking

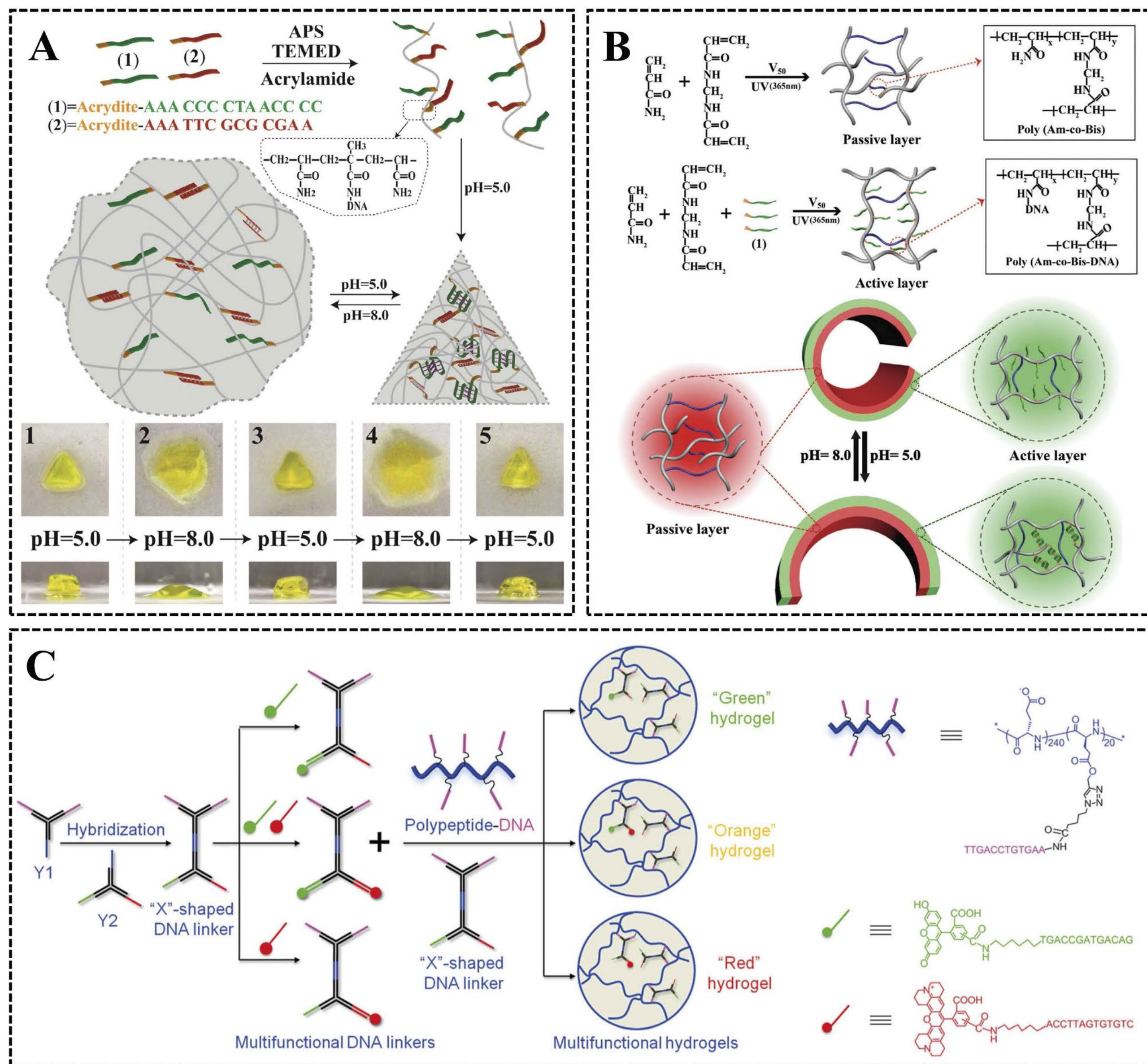


Fig. 1 (**A**) pH-stimulated DNA hydrogels with shape memory properties. Adapted reprinted with permission from Ref [40]. Copyright 2014, Wiley. (**B**) Smart bilayer polyacrylamide/DNA hybrid hydrogel. Adapted reprinted with permission from Ref [41]. Copyright 2020, Wiley. (**C**) Peptide-DNA hydrogel with multiple modification sites. Adapted reprinted with permission from Ref [45] Copyright 2014, Wiley

sites. These cross-linking sites change position as the long ssDNA strand slides, and short ssDNA also serves as a primer for the long-stranded ssDNA, triggering re-amplification. The long-stranded DNA is entangled to form a stable magnetic hydrogel network, and the navigational motion of the DNA hydrogel is driven by MNPs. The magnetic nanomaterials have a synergistic effect with the DNA, making the hydrogel highly adaptable. For example, it is shape-adaptive, allowing it to change shape flexibly in various environments, and can be used to efficiently transport molecular drugs. DNA gelation with a variety of materials to form hydrogels is mainly achieved using chemical cross-linking and physical entanglement, as opposed to chemical cross-linking, which has a permanent and irreversible covalent effect. Physical cross-linking is relatively dynamic and flexible [49, 50]. However, Tang et al. [51] showed that DNA hydrogelation is possible by DNA strands and upconversion nanoparticles (UCNPs) to prepare hybridized DNA hydrogels. The distance between DNA strands (negatively charged) and UCNPs (positively charged) is shortened by electrostatic attraction. Through electrostatic interactions (EIs), UCNPs and DNA strands bind together at the interface to form a hydrogel network. Remarkably, this process

results in the formation of a large number of hydrogels in only 1 s, providing a new paradigm for the preparation of DNA hydrogels.

In summary, hybridized DNA reduces the concentration of DNA required for gelling, which alleviates the disadvantages of rate-pure DNA-based hydrogels such as limited stability, high synthesis cost, and low yield, and scales up production. However, synthetic polymer materials within the hybridized DNA hydrogels can still limit hydrogel biocompatibility. Therefore, this should be considered when selecting suitable polymer materials for cross-linking to form hydrogels.

Pure DNA hydrogels prepared based on DNA self-assembly enzymatic cross-linking

Pure DNA hydrogels are synthesized using DNA as the only component of the hydrogel, and there are two strategies for synthesizing them: one is to use DNA strands as building blocks, which are self-assembled or enzymatically ligated and cross-linked to form a polymeric network. The other is to directly wind long DNA strands from nucleic acid amplification into a hydrogel. Self-assembling DNA hydrogels require multiple building blocks with repetitive sequences, usually linear and branched DNA structures. In general, branched DNA structures are more customizable and ordered than linear DNA, but whether linear or branched, these building blocks usually contain special sticky end structures with complementary nucleotide sequences that form hydrogen bonds. Therefore, the networks of these DNA hydrogels are formed by recognizing and assembling the sticky ends of DNA.

In 2006, Luo et al. reported hydrogels made entirely of branched DNA, which was the first time DNA hydrogels were formed by complementary hybridization of sticky ends. Rational self-assembly of ssDNA strands produces various branched DNA modules, such as X-type or T-type DNA [52]. As shown in Fig. 2A, various branched DNA modules, i.e., X-type, T-type, or Y-type DNA, were generated by the rational self-assembly of ssDNA strands. Each branched DNA strand had a different number of complementary sticky ends, which hybridized and combined with each other, guiding the branched DNA into a network and forming a stable DNA hydrogel. For the first time, the entire preparation process was accomplished under physiological conditions. The advantage of this method is that it is simple and inexpensive, but a large number of palindromic sequences are used in the preparation process, resulting in inhomogeneous DNA hydrogels. Therefore, Liu et al. [53] assembled DNA hydrogels using a Y-type scaffold and a linker (Fig. 2B). The Y-type scaffold consists of three ssDNA strands and a linker, which is a linear double strand composed of two ssDNA strands. The Y-scaffold and linker are also designed with sticky ends for complementary cross-linking, but their sticky ends minimize the use of palindromic sequences so that the DNA hydrogel formed can be more homogeneous. Additionally, enzymes are important molecular tools that aid in sticky end joining. The main enzymes used to construct DNA hydrogels are DNA ligases and polymerases. Ligases repair gaps in the assembly of branched DNA. Luo et al. proposed another novel cellular protein synthesis method to synthesize DNA hydrogels [54]. They added plasmid DNA to the hydrogel and then used T4 DNA ligase to join the gaps between the X-DNA and the linear plasmid to form a DNA hydrogel network. This DNA hydrogel is mainly used for efficient cell-free production. Notably, unlike other polymerases that require templates and primers to synthesize DNA strands, terminal deoxynucleotidyl transferase (TdT) catalyzes the synthesis of DNA from random mononucleotide dNTP only in the presence of primers, which greatly improves the efficiency of DNA hydrogel preparation [55, 56].

Hydrogels with 3D network structures can also be prepared by using nucleic acid amplification to obtain long DNA strands. Wang et al. [57] used clamp HCR to prepare self-assembled DNA hydrogels (Fig. 2C). Three DNA strands are involved in this system, and unlike other long DNA strands that spontaneously form homogeneous hydrogels, the DNA initiator induces a sol-gel transition that controls the hydrogel in three-dimensional space and time. This hybridization reaction, precisely triggered by the initiator strands, offers the possibility of constructing custom-shaped DNA hydrogels. RCA is another stable and rapid method of nucleic acid amplification that can be used to obtain long DNA strands. In the process of successive replication of DNA sequences to form long strands of DNA, the physicochemical properties of the polymerization network can also be improved by the addition of different repetitive functional sequences and complementary regions, thus enabling the functionalization of the hydrogel. Guo et al. [58] synthesized DNA network structures with different crystallinity based on RCA (Fig. 2D) and controlled the crystallinity of inorganic magnesium pyrophosphate (MgPPi) by adjusting the conditions of RCA to change the size of the hydrogel network gaps. Both RCA and HCR are thermostatic amplification methods that are simple and efficient. Using these amplification methods, repetitive functional DNA sequences can be obtained, and as with hybridized DNA hydrogels, insertion of these functional DNA structures into a polymer network allows for the preparation of DNA hydrogels that are responsive to a variety of factors [59–61]. Hu et al. [62] synthesized smart DNA hydrogels using single-stranded DNA capable of assembling functional units. Under slightly acidic conditions, the ssDNA strands self-assemble to form a linear

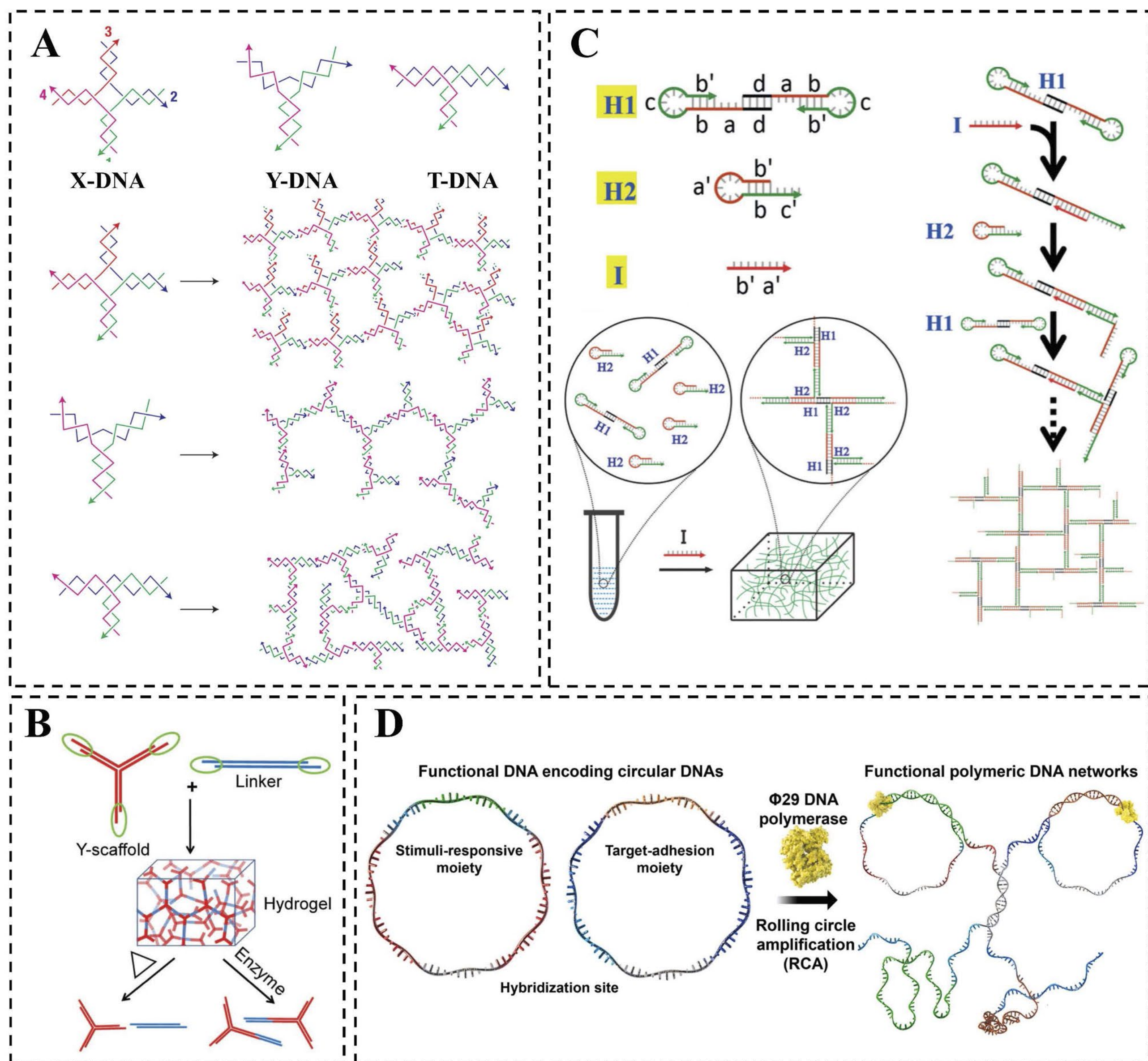


Fig. 2 (**A**) DNA hydrogels assembled from DNA building blocks. Adapted reprinted with permission from Ref [52]. Copyright 2006, Springer Nature Ltd. (**B**)Preparation of DNA hydrogels by of Y-scaffolds and linkers. Adapted reprinted with permission from Ref [53]. Copyright 2010, Wiley. (**C**) DNA initiator-induced HCR and gelation process. Adapted reprinted with permission from Ref [57]. Copyright 2017, Wiley. (**D**) RCA-based DNA hydrogels. Adapted reprinted with permission from Ref [58]. Copyright 2023, Elsevier Ltd

DNA structure containing an i-motif structure, which then naturally breaks down under slightly alkaline conditions, leading to cross-linking of the hydrogel. Therefore, the DNA hydrogel can be reversibly transformed from hydrogel to solution in pH-controlled conditions.

In summary, the self-assembly strategy of DNA modules based on the sticky end makes the formation and post-formation behavior of hydrogels more controllable, and the efficient nucleic acid amplification can in turn provide us with a large amount of nucleic acids while reducing the cost. Moreover, compared to hybridized DNA hydrogels, pure DNA hydrogels without the use of other polymers are not only chemically similar to DNA molecules with good biocompatibility and enzyme degradation, but also show good biodegradability, precise structural controllability, and responsiveness to specific stimuli, which is promising for biomedical fields.

Physicochemical properties of DNA hydrogels

Among many hydrogel materials, DNA hydrogels have outstanding mechanical properties and stimulus responsiveness. Different textures of DNA hydrogels perform unique functions. For example some DNA hydrogels can be used as intelligent soft robots [63], and others with

higher mechanical strength are used as cartilage substitutes for cartilage repair [64]. The mechanical strength of DNA hydrogels is related to the construction method and hydrogel composition. In general, DNA hydrogels assembled from DNA modules have a higher shear modulus than hydrogels formed from continuously elongated ultralong DNA strands, indicating that the latter are mechanically stiffer [65] and the former can exhibit higher elasticity, such as ssDNA hydrogels constructed on the basis of the RCA reaction [28, 66]. This is due to the physical entanglement between the ultra-long ssDNA, and DNA hydrogels are usually soft in texture. Such DNA hydrogels have good shape adaptation, making up injectable DNA hydrogels with good thixotropic properties [64].

Physically crosslinked DNA hydrogels are mainly stabilized by various non-covalent interactions. In contrast to the high strength and stable covalent bonds, these non-covalent bonds reversibly break and form by the external environment [67, 68]. Wang et al. [69] prepared pure DNA hydrogels with different concentrations of hydrogen bonds (Fig. 3A). They prepared three sets of DNA hydrogels based on double RCA and self-assembly, in which the ultra-long single-stranded DNA precursors contained different amounts of hydrogen bonds. The experimental results showed that the higher degree of hydrogen bonding in the precursor DNA, the denser the network inside the hydrogel, the higher the mechanical properties, and the better the capture efficiency. On the other hand, DNA hydrogels based on chemical crosslinking are usually more stable, and the range of hydrogel applications, such as shear-thinning and injectable properties, can be further expanded by introducing dynamic covalent bonds. This is due to the fact that dynamic covalent bonds open under shear and can be spontaneously reconnected after the shear force is removed [70]. In addition, rational design of the backbone structure of DNA hydrogels is another effective approach. Liu et al. [71] assembled a DNA double cross (DX) backbone rigid hydrogel. The rigidity of the DNA double helix can improve the polymerization in the kinetic interlocking multiple unit (KIMU) strategy, so they designed the DNA DX single strand as the DX backbone (Fig. 3B), on which the DX supramolecular polymer was prepared with high molecular weight and high stability. Finally, the supramolecular hydrogels further constructed by utilizing DX polymers as rigid backbones have ultra-high mechanical strength. Similarly, Yang et al. [72] developed a new L-DNA hydrogel (Fig. 3C). The L-DNA hydrogel exhibits superior biostability in comparison to the mirror-image isomer deoxyribose, and after 30 days of co-cultivation with fetal bovine serum, there is no discernible loss in mechanical strength. Moreover, it does not cause the body to manifest an inflammatory response. In 2024, Shi et al. [73] synthesized three DNA scaffolds with different shapes and sequentially increasing stiffness, connected them with DNA linkers of different stiffnesses, and formed hydrogels with simple mixing. They further revealed the close relationship between the rigidity and structure of DNA hydrogels. Furthermore, during the synthesis of hydrogels, by adjusting the ratio of hairpin chains in the hybridization chain reaction, the mesh size of the hydrogel can be altered to meet various clinical needs [74].

Stimulus responsiveness of DNA hydrogels refers to the behavior of base complementary pairing between DNA strands or functional nucleic acid structure changes triggered by various factors, which affects the volume of the hydrogel or changes in physicochemical properties [75]. Sequences of functional DNA units can be introduced to programmatically alter the response properties of hydrogels to exhibit dynamic volume changes in response to targets. Among them, hydrogels with pH-responsive behavior usually contain special structures such as i-motif structure, T-A-T triple helix structure, and C-G-C+triple helix structure [76–78]. Among them, the i-motif is a cytosine C-rich structure, and after being protonated, it becomes sensitive to pH changes. Therefore, special DNA functional modules can be used to trigger the solution-gel transition in hydrogels. Liao et al. [60] designed stimulus-responsive DNA hydrogel microcapsules, where the hydrogel consisted of a functional DNA structure, an i-motif structure, and a polyacrylamide, and under acidic conditions, the i-motif structure formed a "connecting bridge" that separated the i-motif-connected double-stranded units, which led to the separation of the microcapsule shell. Nucleic acid aptamers are another commonly used functional unit of DNA that specifically recognizes and binds to target molecules. When the aptamer binds to the target molecule, the structure of the hydrogel network is changed [79]. DNA enzymes do the same by disintegrating the substrate strand to disintegrate the DNA network structure, dissolving the hydrogel. Gao et al. [80] also methylated the edges of the DNA tetrahedra with DNA adenine methyltransferase (Dam), and methylation-sensitive restriction endonucleases then cleaved the DNA tetrahedra to release amyloglucosidase, which catalyzes glucose production, and finally quantitative readings were taken using PGM. Li and Yang [81] developed a handheld glucometer based on a multicomponent nuclease-based DNA hydrogel. When the target miRNA is added, the active nuclease triggers the hydrogel to break down and release the encapsulated amylase. Metal ion-dependent DNAzyme binds to metal cofactors and activates DNAzyme to degrade the substrate. Various DNAzyme-based DNA hydrogels have been reported for metal ion detection. Guo et al. [82] developed a bilayer DNA hydrogel membrane. The lead (Pb^{2+}) or uranyl

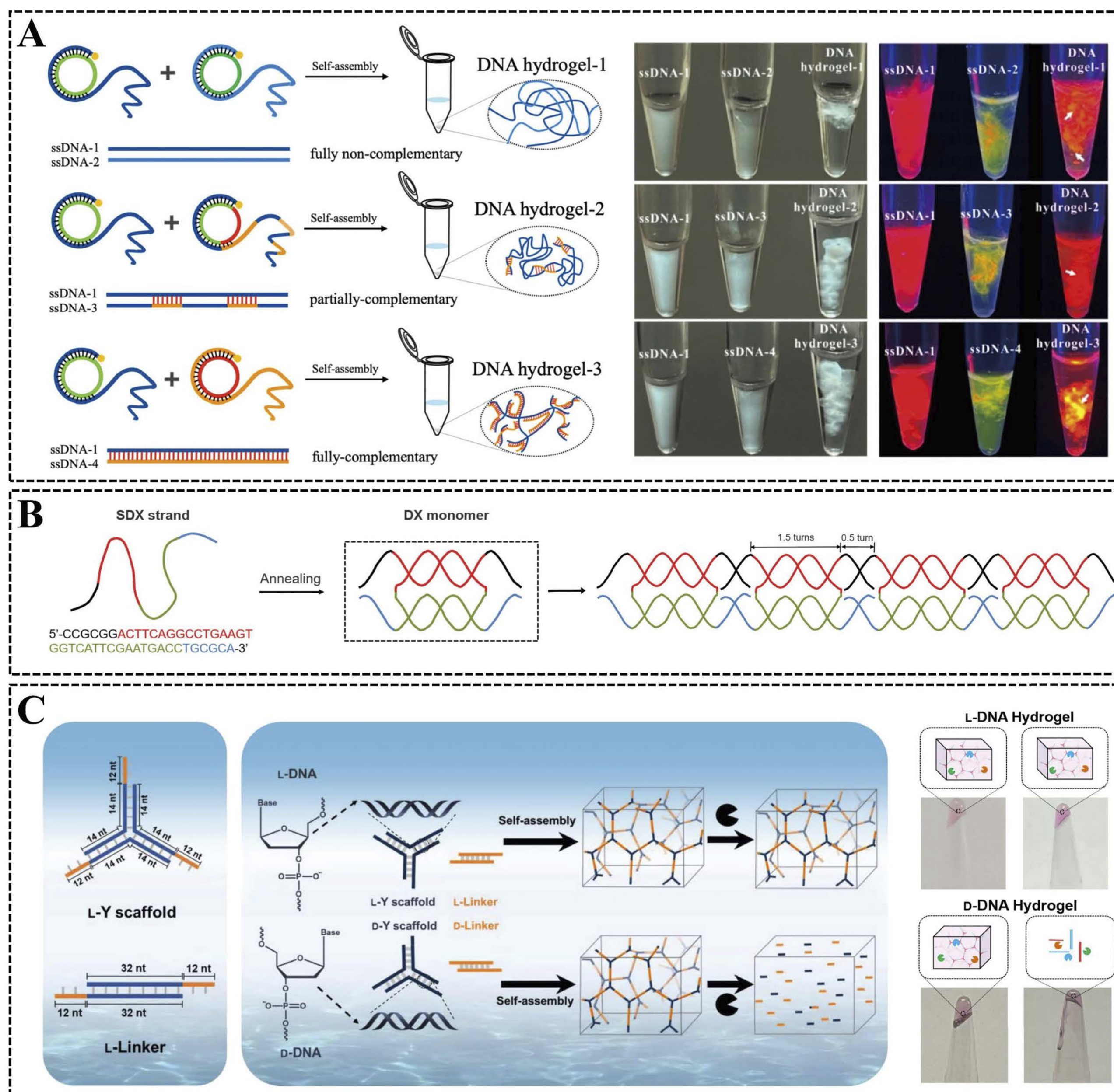


Fig. 3 (**A**) Schematic representation of DNA hydrogels prepared from long-stranded DNA with different degrees of hydrogen bonding. Adapted reprinted with permission from Ref [69]. Copyright 2023 Biosensors (**B**) Schematic representation of DNA double cross-linking hydrogels. Adapted reprinted with permission from Ref [71]. Copyright 2022, Wiley. (**C**) D-DNA and L-DNA hydrogels with special strengths. Adapted reprinted with permission from Ref [72]. Copyright 2021, Wiley

(UO^{22+}) ions can activate the DNA enzyme to cleave the substrate strand and release the negatively charged cleavage fragments. The negative charge density of the active layer decreases and shrinkage occurs, which triggers the large macroscopic shape of the bilayer hydrogel membrane to change significantly. This DNA hydrogel combines target introduction, signal amplification, and signal output to build a smart offloading system of biosensors for rapid detection of target molecules or drugs to meet the requirements of clinical portability and sensitivity [83–85].

There is a tendency to develop dynamic hydrogels in which various factors modulate the change in hydrogel structure. For example, Quan et al. [86] added cations to the hydrogel to control cross-linking and disassembly between DNA strands and spermine. The most straightforward approach is to introduce a response structure. Such structures can be responsive DNA structures or responsive polymer chains [87, 88]. Designing these

different functional DNA hydrogels as smart sensors has attractive applications in the field of bioengineering.

Biomedical application of DNA-based hydrogel construction

Drug delivery and therapy

Controlled release and targeted delivery of therapeutic drugs are important issues in modern biomaterial research. Conventional drug delivery systems usually suffer from low drug bioactivity and unsatisfactory therapeutic effects owing to systemic toxicity, repeated administration, and changes in the internal environment. Moreover, the difficulty in precisely controlling drug targeting and release often results in insufficient efficacy or severe side effects. Therefore, finding an ideal mode of drug delivery is critical. DNA hydrogels can be used as a carrier for topical drug delivery, delivering high doses of active biomolecules to the target site continuously and slowly [89–91].

A suitable scaffold that can prevent the drug from spreading beyond the treatment site during administration to avoid side effects while simultaneously ensuring that the drug is released slowly at a certain rate to maintain its therapeutic activity is urgently required. The porous microstructure and cross-linking network of the DNA hydrogel can effectively bind to the drug molecule. In addition, by integrating stimulus-responsive structures into the DNA backbone or DNA junctions of the DNA hydrogel, the DNA hydrogel disintegrates under specific triggers, thus ensuring that the drug can be released exactly at the target site [92, 93]. Li et al. [94] developed a multifunctional hydrogel (Agevgel) based on DNA scaffolds, in which the DNA strands act both as shape-variable scaffolds for loading immunomodulatory M2 macrophage-derived extracellular vesicles (M2EVs) and as antimicrobial building blocks (Fig. 4A). The adherent DNA hydrogels not only ensure the time-dependent sustained release of silver nanoclusters (AgNCs) and M2EVs, but also serve as artificial extracellular matrices suitable for different shapes of diabetic alveolar bone defects (DABDs) and avoid unfavorable external environmental factors. Another strategy is to use the enzymatic action of the DNA hydrogel to disintegrate the hydrogel structure, resulting in a slow release of the encapsulated drug. Zhang et al. [95] used an enzyme-responsive DNA hydrogel (DSH) as a metformin (MET) delivery vehicle for the treatment of osteoarthritis (OA). With the degradation of DSH by DNAzyme, MET was slowly released into the joint cavity. This approach protected MET from rapid clearance by synovial fluid, and exerted a greater anti-inflammatory effect. In addition to delivering various types of small molecule drugs, the injectable DNA hydrogel can be designed to contain immunostimulatory motifs that bind to pathogen pattern recognition receptors, inducing an immune response. This promotes immune activation of the vaccine in vivo to enhance vaccine efficacy. Guo et al. [96] developed a nanotoxin-embedded DNA hydrogel. The DNA hydrogel contains both immunostimulatory CpG sequences and is enriched with guanine that can form a G-quadruplex structure, which stabilizes the structure of the DNA hydrogel and prolongs the retention time of the nanotoxin.

Traditional cancer immunotherapy often suffers from low immune response rates and poor targeting. DNA hydrogels have excellent targeting capabilities, and they can be loaded with immunotherapeutic agents, chemotherapeutic agents, phototherapeutic agents, and other agents to the tumor site, thus allowing for the precise controlled release of drugs and triggering long-term anti-tumor effects [97]. However, these tumor immunotherapy monotherapies may suffer from insufficient immune activation and unsatisfactory immunosuppressive effects. DNA hydrogel-mediated combinatorial immunotherapies can play an important role in enhancing therapeutic efficiency. In 2024, Yang et al. [98] developed a smart DNA hydrogel (Fig. 4B). The hydrogel is constructed from two ultra-long DNA strands containing three complementary functional units. One DNA strand is designed to contain an aptamer and an immunostimulatory sequence, CpG, which is used to load exosomes with antitumor effects, and the other DNA strand contains a multivalent G-quadruplex, which is used to load photodynamic agents. Additionally, in order to exert the combination immunotherapeutic effect, restriction endonuclease sites are designed between the functional units, and the hydrogel is stimulated to break down and release the functional units from the tumor location. The outcomes of the experiment demonstrated that the DNA hydrogel effectively activated the immune system, killed tumors, and dramatically prevented tumor growth.

Aptamers present a good choice for targeted transportation. A DNA-containing hydrogel can accurately bind to the target and target cancer cells, making chemotherapeutic molecules more drug-toxic and tumor-specific, thus increasing efficacy while minimizing multidrug resistance and side effects. Lee et al. [99] developed an immune checkpoint blocking DNA aptamer hydrogel (PAH). The DNA strands were designed to contain DNA of the programmed death receptor PD-1 aptamer and a single-stranded guide RNA sgRNA targeting sequence. In this way, CRISPR-associated protein 9 (Cas9) is able to exactly recognize and cut the sgRNA-guided DNA double-stranded structure. When Cas9 binds to the sgRNA, it triggers the hydrogel to degrade and release the PD-1 DNA aptamer, resulting in an effective anti-tumor effect over a long time. However, the retention time of this hydrogel was only a few days at the injection site; thus, multiple treatment repetitions were required, and the

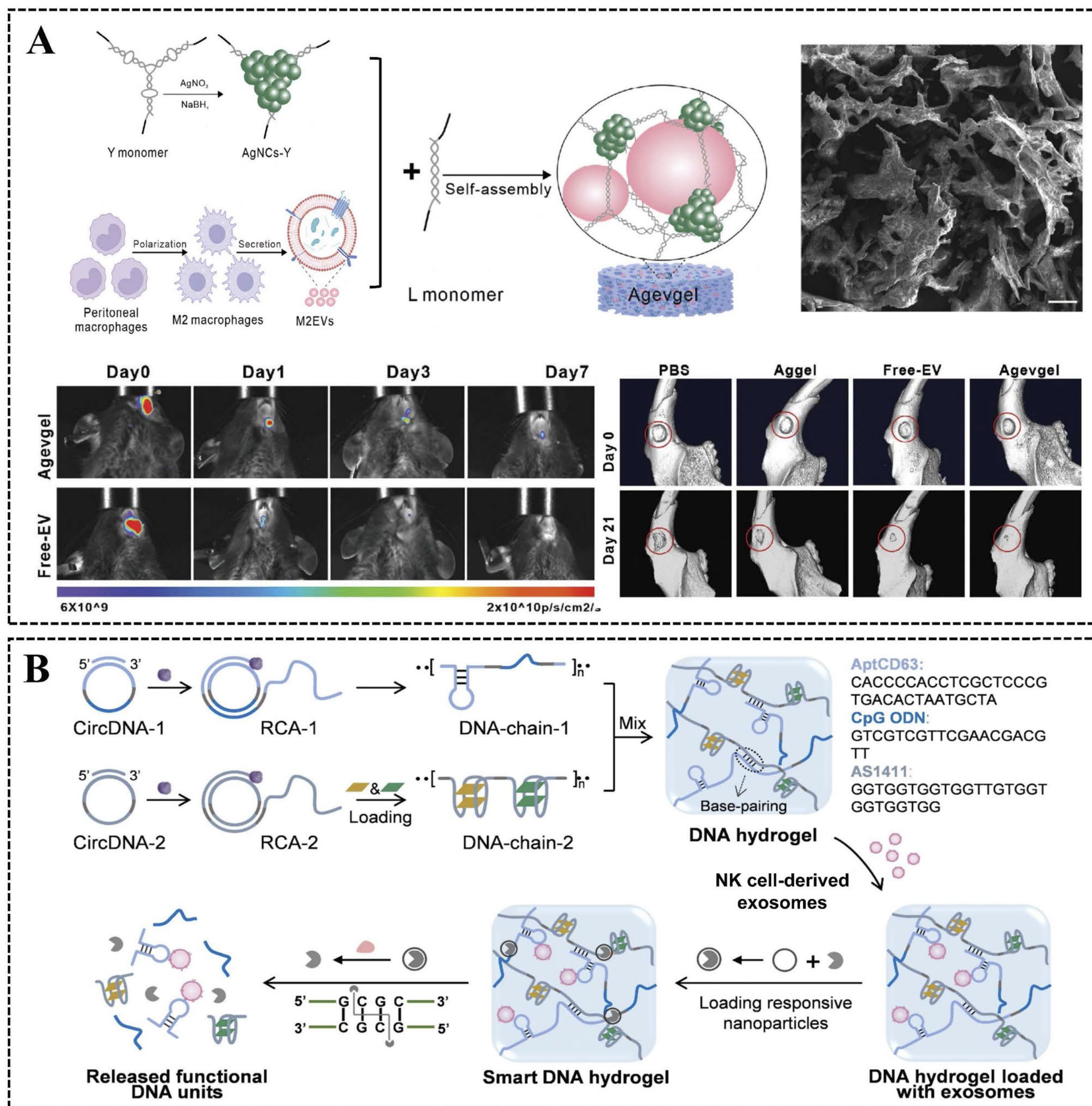


Fig. 4 (**A**) Multifunctional hydrogel for delivery of extracellular vesicular DNA promotes reconstruction of diabetic alveolar bone defects. Microscopic CT images of the treatment group in the area of the bone defect after treatment. Adapted reprinted with permission from Ref [94]. Copyright 2023, Wiley. (**B**) DNA hydrogel-mediated combination immunotherapy loaded with natural killer cells and photodynamic agents. Adapted reprinted with permission from Ref [98]. Copyright 2024, Wiley

immunogenicity problem has not yet been solved. In 2023, Zhu et al. [100] used direct self-assembly of DNA molecules to fabricate DNA nanogels (DNGs). The preparation method is simple, and the DNGs are highly stable against physical forces and can be stored in concentrated solutions or powders for long periods of time. As shown in Fig. 5A, by encoding specific DNA aptamers onto dendritic DNA molecular branches and encapsulating the chemotherapeutic drug doxorubicin, DNG can selectively target cancer cells to enhance chemotherapeutic drug efficacy and tumor specificity. Thus, the therapeutic efficacy can be improved while minimizing the side effects.

Additionally, DNA hydrogels are prepared as smart carriers that respond to various external and internal stimuli [101], which not only improves drug efficacy

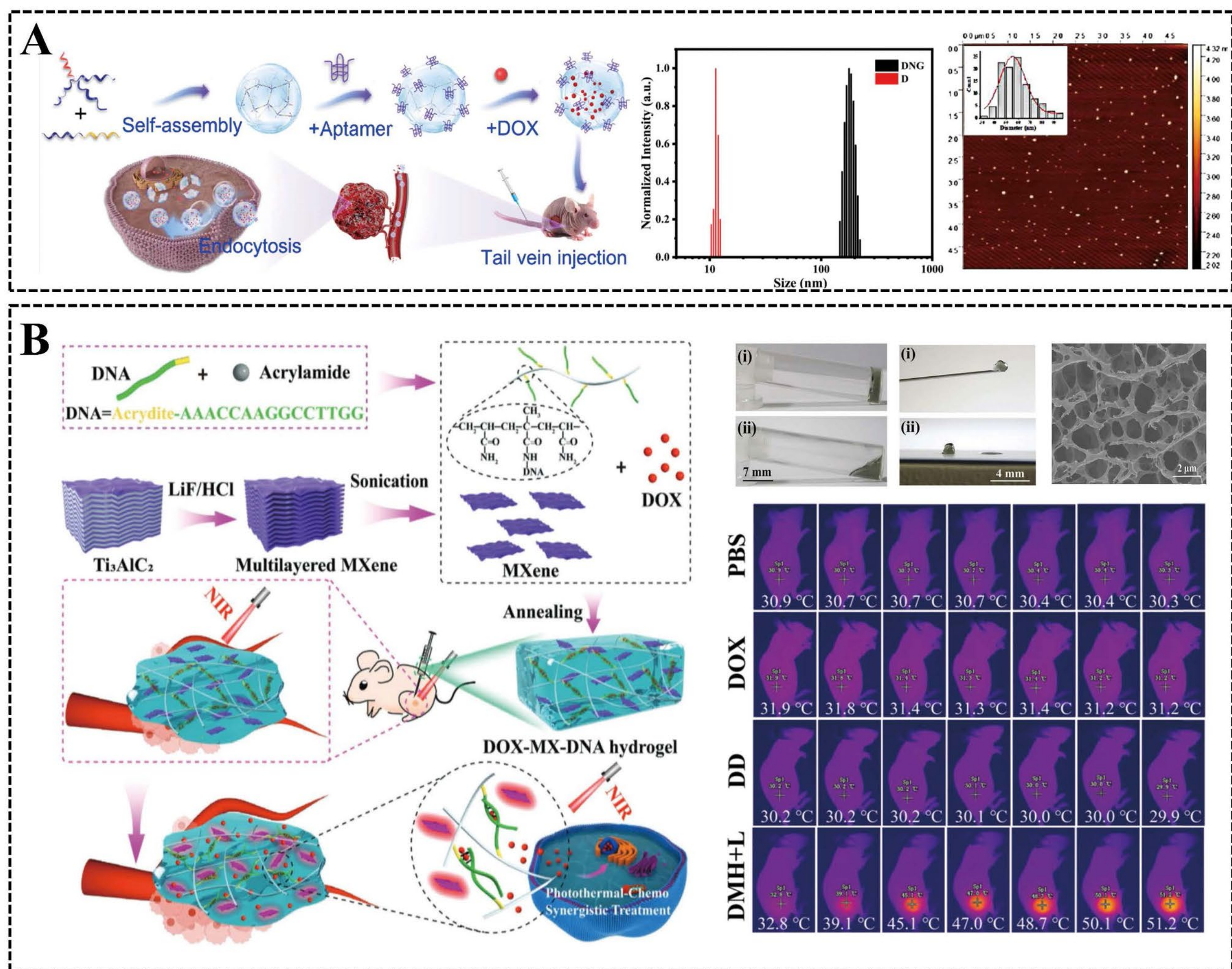


Fig. 5 (**A**) Targeted DNA hydrogel for slow release of doxorubicin. Adapted reprinted with permission from Ref [100]. Copyright 2024, Elsevier Ltd. (**B**) MXene-DNA hydrogel for light-triggered localized photothermal chemotherapy for the treatment of rhabdomyosarcoma mice, where the hydrogel undergoes adaptive shape changes according to the shape of the mold in the presence of near-infrared radiation. Adapted reprinted with permission from Ref [104]. Copyright 2022, Wiley

but also minimizes cytotoxicity. In recent years, photothermal therapy has been gradually applied to the local treatment of tumors. The hydrogel network structure can be loaded with photothermal nano-agents and chemotherapeutic agents, and the development of DNA hydrogels with photothermal properties can realize efficient controlled drug release [102, 103]. Guo et al. [104] established a photothermal-chemotherapeutic synergistic cancer treatment system by combining DNA hydrogels with MXene nanosheets. As shown in Fig. 5B, hybrid DNA hydrogel with temperature-induced solution-gel transition was first prepared, and then the photothermal MXene nanosheets would be uniformly dispersed within the hydrogel. Under near-infrared light (NIR) irradiation, the temperature of the nanosheets increased, which induced the disintegration of the DNA double-stranded cross-linking structure, thus triggering the transformation of the hydrogel matrix into a solution. The DNA double strands were re-cross-linked and reformed into a hydrogel matrix after the NIR irradiation stopped. This property can also be used to design different shapes of hydrogels using models. Experimental results showed that DNA hydrogels loaded with the therapeutic agent doxorubicin were effectively released in a murine tumor model, causing direct damage to the tumor tissue, thus demonstrating efficient therapeutic properties against local cancer.

Biosensing

When a stimulus-responsive DNA molecule dissociates or undergoes a conformational change upon binding to an external analyte, the structure of the hydrogel changes accordingly, releasing the probe encapsulated in the gel [105–108]. The detection process converts the target

input into various physical or chemical outputs (mechanical, acoustic, optical, and electrical signals), thereby transforming various analytes into easily processed sensing signals for biosensing. DNA hydrogel sensors were developed based on their ability to respond to a variety of stimuli. Additionally, DNA hydrogels are good platforms for encapsulating catalytic substances, which are released to further catalyze the reaction [109]. The release of catalytic substances can further catalyze the reaction to produce amplified output signals [110–112].

The most common functional unit of stimulus-responsive DNA hydrogels is the aptamer, and the synthesis of sensitive biosensors using a variety of aptamers that bind to the molecule to be tested is a conventional strategy for the preparation of DNA hydrogels applied to biosensing [113]. Researchers have also developed a fluorescent DNA hydrogel system for prostate-specific antigen (PSA) detection [114]. Y-type DNA is used as a building block and is designed to be enriched with C-sequences to serve as a substrate for AgNCs with optical properties, whose fluorescence emission increases due to aggregation-induced emission (AIE) and a hydrogel structure that facilitates the formation of highly fluorescent signals [115]. These act as cross-linking agents to form dense hydrogels, which insulate AgNCs from environmental influences and produce strong fluorescence emission. When the target PSA binds to its specific aptamer, the DNA network structure disintegrates and the hydrogel collapses and dissolves, thus reducing the emission intensity. Also inspired by the excellent properties of DNA aptamer hydrogels, several target-responsive hydrogels have been designed as monitoring devices for ochratoxin A (OTA) detection. The existing single-mode OTA monitoring strategies are susceptible to various factors such as the environment, instrumentation, and operation, and the reliability and accuracy of the detection results requires improvement [116]. Therefore, Fan et al. [61] created a heme-based CuNCs-modified DNA hydrogel sensor for ochratoxin. Colorimetric detection is both sensitive and quick. OTA aptamers were used to create DNA hydrogels, which were then embedded with heme, cross-linked, and in situ encapsulated with fluorescent copper nanoclusters (CuNCs). When OTA appeared, the DNA aptamer formed a G-quadruplex structure by preferential binding. This enabled fluorescence and caused the CuNCs to burst. After OTA competitively attaches to the aptamer to create a G-quadruplex structure, the network structure of the DNA hydrogel is dissociated, causing hemoglobin to be released and CuNCs to fluoresce. The signaling cascade is amplified when the liberated heme attaches to the G-quadruplex to generate a DNAzyme that enables the CuNCs to fluoresce again. However, these aptamer-based hydrogels require "one-to-one" binding to the target, which can lead to less sensitive detection. Nucleic acid amplification techniques such as HCR, RCA, etc., have also been used for various signal amplifications, but these amplification strategies increase the sensitivity while being limited by the high concentration of DNA as well as the stringent conditions such as temperature and pH. Some DNA polymers such as G-quadruplexes are not only able to bind to the target, but also amplify the signal by reassembling into a special structure under the action of triggers to connect with the biosensor substrate [117]. Lu et al. [118] developed another approach to enhance signal sensing. The DNA hydrogel consists of layers of micropores that are interconnected to help enhance signal transmission. Moreover, the hydrogel makes it easier to monitor the sensed signals by connecting it to a smartphone sensing platform. Metal ion-dependent DNA enzymes are reaction units and cross-linkers in hydrogels and can be used for a variety of metal ion assays. Jiang et al. [119] developed a smart DNA hydrogel capillary sensor to convert Pb^{2+} concentration into macroscopically visible changes in solution behavior (Fig. 6A). The Pb^{2+}-dependent DNA enzyme is the response unit and cross-linking unit of the hydrogel. The capillary is fixed at the origin of the calibration scale, and the crosslinked and stabilized hydrogel membrane completely blocks the capillary to prevent solution inflow. In the presence of Pb^{2+}, the crosslinker substrate strand is cleaved by the activated DNA enzyme, the pores of the hydrogel membrane at the end of the blocked capillary enlarge and break, and the solution flows into the tube. The concentration of Pb^{2+} is quantified by reading the distance and duration of the solution in the capillary. In this way the DNA hydrogel membrane translates the Pb^{2+} concentration into a visualization of the flow behavior of the solution in the tube to facilitate detection.

The electrochemical sensing properties can also be used to detect small molecules, providing valuable information for the diagnosis of a variety of diseases. For example, Yao et al. [120] developed an electrochemical sensing strategy by combining the hybridization chain reaction-activated Cas12a enzyme with DNA hydrogels. As shown in Fig. 6B, the target protein binds to a specific region of DNA to form a complex that protects the DNA from being digested by nucleic acid exonuclease, and simultaneously, the long double stranded DNA produced by HCR activates Cas12a enzyme, which cleaves the DNA junction of the crosslinked DNA gels and releases a large amount of electroactive substances embedded in the gel, which exhibit highly amplified current signals under specific conditions, thus achieving signal amplification and sensitively detecting nuclear factors. Guo et al. [121] proposed a new nano-impact electrochemical (NIE) sensing strategy to prepare highly sensitive DNA hydrogels based on CRISPR technology. AgNPs were encapsulated

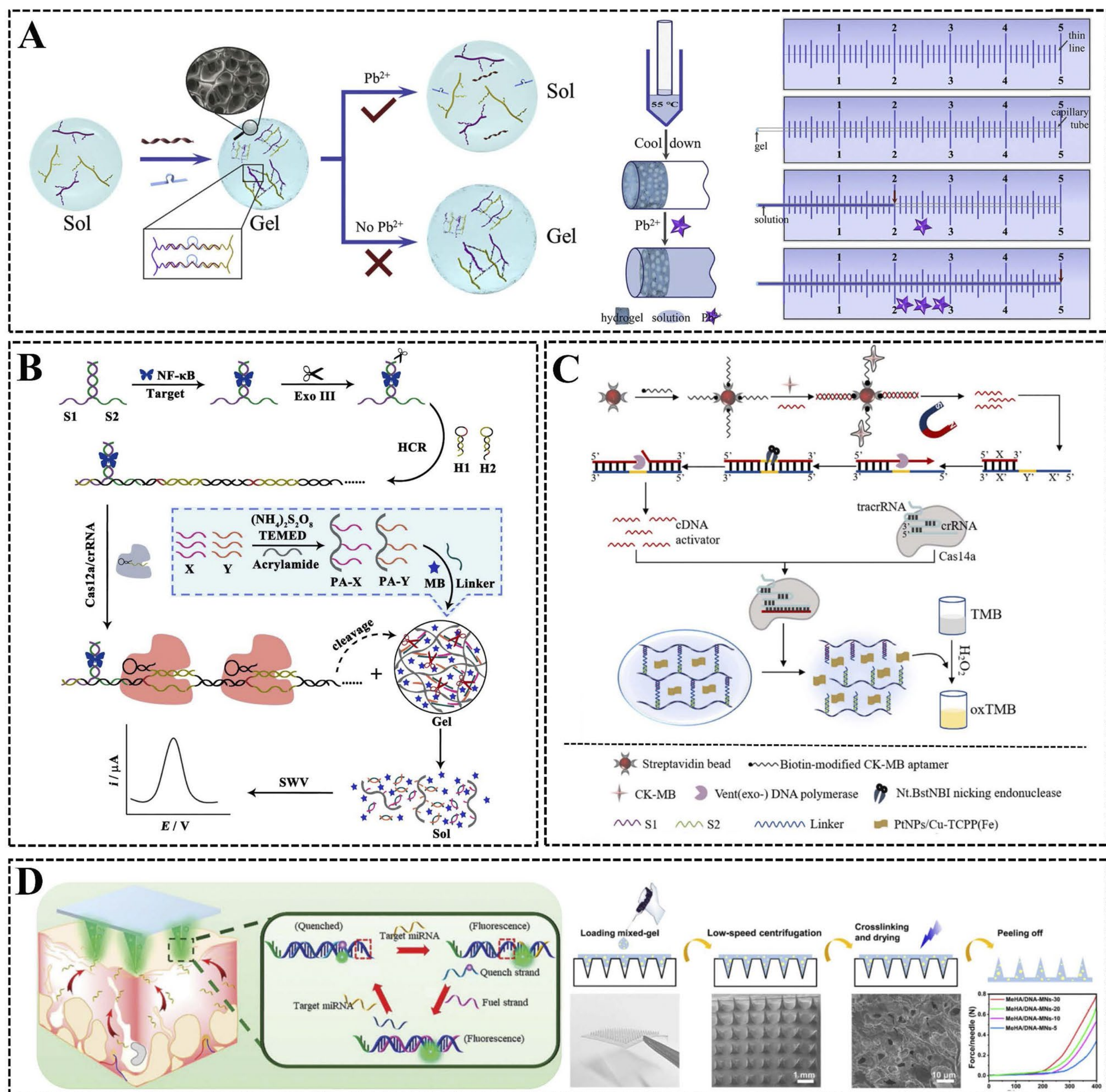


Fig. 6 (**A**) Schematic of DNA hydrogel-based Pb^{2+} capillary sensor. Adapted reprinted with permission from Ref [119]. Copyright 2020, Elsevier Ltd. (**B**) DNA hydrogel-integrated electrochemical sensing method for detection of NF-κB p50. Adapted reprinted with permission from Ref [120]. Copyright 2022, Elsevier Ltd. (**C**) Detection of CK-MB system based on Cas14a cleaved DNA hydrogel. Adapted reprinted with permission from Ref [125]. Copyright 2021, Wiley. (**D**) Construction scheme and characterization data of DNA hydrogel-encapsulated microneedle arrays for sensing miRNA cross-linked microneedle patches [127]. Copyright 2022, American Chemical Society

within the DNA hydrogel to avoid adhesion of NPs on the electrode surface. The disintegrated hydrogel releases AgNPs that collide with the electrode material, resulting in a significant electrochemical signal. The sensitivity of the DNA hydrogel assay is very high, and the detection limit of this NIE biosensing strategy for miR-141 is as low as 4.21 aM, which is highly specific for practical applications. The drawback of limiting the sensitivity because of the low effective collision frequency was improved. Electrochemiluminescence (ECL) is another emerging effective analytical method for the sensitive determination of biomolecules, which has garnered substantial attention. Zhao et al. [122] constructed a target-induced DNA hydrogel biosensing platform. miRNA let-7a triggered strand displacement amplification, and the product then underwent cyclic amplification and induced HCR to

generate dendritic DNA hydrogel structures. A positively charged amphiphilic perylene derivative (PTC-DEDA) was then intercalated into the DNA grooves of the hydrogel. PTC-DEDA, as the core of the ECL reaction, has a very high binding stability with the DNA hydrogel, which enables the dendrimer to generate a stable ECL reaction and thus obtain a strong ECL signal.

Proteins and nucleic acids are used as biomarkers to reflect the health changes of the organism, and sensitive detection of abnormal activities of DNA, miRNA, or nucleic acid-related enzymes provides important information for the development of various diseases [123–126]. Chen et al. [125] constructed a hybrid DNA hydrogel for the detection of creatine kinase (CK-MB) by combining the technical amplification technology (EXPAR) and the CRISPR/Cas14a system. As shown in Fig. 6C, CK-MB dissociates the aptamer-DNA complex by competitive magnetic separation, and the DNA strand forced to dissociate from the aptamer initiates the EXPAR system to generate the target ssDNA, which in turn activates the cleaving enzyme activity of Cas14a to disintegrate the hydrogel network. Thus, metal-organic framework nanosheets coated with platinum nanoparticles (PtNPs) decorated on the hydrogel were released and detected. The detection limit of the system for CK-MB was 0.355 pM, which is far below the clinically abnormal detection value. To achieve rapid, easy, and portable instant detection, microfluidic chips and microneedle patches around DNA hydrogels are becoming a new research hotspot. Yang et al. [127] reported a DNA hydrogel microneedle (MN) array based on strand substitution to achieve limiting signal amplification for the rapid detection of interstitial skin fluids (ISF). As shown in Fig. 6D, the microneedle patch can easily penetrate the skin to reach the dermis, and when the target miRNA is present in the skin mesenchyme, a substitution reaction occurs within the DNA hydrogel. The DNA strand modified by the quenching group is replaced by the miRNA to produce a fluorescent signal, and then the DNA strand with the fuel probe immediately replaces the miRNA again, which is released to continue to induce the next substitution. This cycle ensures that enough ISF can be extracted in a short time for miRNA detection. This invasive sampling method provides a new idea for ISF extraction.

Tissue engineering

DNA hydrogels not only serve as three-dimensional skeletal materials that provide a good matrix for cell culture and proliferation in vitro [128], but they are also widely used in bone defect repair, wound healing, and nerve repair owing to their ability to precisely adjust the composition and structure within the hydrogel to guide cell differentiation and promote neoplastic tissue growth, as well as their ability to deliver regenerative medicines to the tissues [129, 130].

Biomaterials used to promote tissue regeneration must have strong mechanical strength to organize various living cells and functional factors in three dimensions. Specifically, DNA hydrogels containing bone marrow stem cells (BMSC) are injected directly into cartilage defects to construct cartilage-like organs. The DNA hydrogels provide a three-dimensional network scaffold that is comparable to the extracellular matrix (ECM) of cartilage, guiding and supporting the proliferation of chondrocytes while maintaining their physiological functions [131]. Hybridized DNA hydrogels have superior mechanical properties compared to pure DNA hydrogels [132]. In 2023, Zhou et al. [133] pioneered the construction of a dual-network DNA-silk fibronectin (SF) hydrogel. The first network consists of DNA through base complementary pairing to form a constraining supramolecular network, and SF molecules can form a second network structure through enzymatic cross-linking that acts as a molecular scaffold for DNA. The moderate surface stiffness of dual-network DNA-SF hydrogels is also able to promote collagen expression in the extracellular matrix and induce chondrogenic BMSC differentiation, synergistically promoting cartilage regeneration and repair. Compared to discrete DNA nanostructures, DNA-SF hydrogels maintain a more localized effect due to their polymerization and confinement to a defective region. Furthermore, in addition to excellent mechanical strength, for hydrogel dressings applied to wounds, good fit and gripping power are essential, and Ye et al. [134]. prepared a DNA hydrogel dressing with good fluid absorption and stable adhesion (Fig. 7A), and on mouse liver, the DNA hydrogel quickly adhered to the wound and stopped bleeding. Similarly, Zhou et al. [135] designed biomimetic macro deformed DNA gel microneedles. Unlike the traditional MN array structure, MNs were designed to approximate a crab-claw-like structure and a shark microgroove structure, which improved the stability and gripping power (Fig. 7B). The hydrogel adheres to the joint and remains stable after repeated deformation, which improves the comfort of patients with joint wounds. In conclusion, this DNA gel MN one-piece dressing is stable enough to regulate the wound microenvironment and promote high-quality wound healing.

DNA hydrogels meet most of the requirements for an ideal material for transplantation of neural stem cells (NSCs). Sequentially engineered DNA hydrogels serve as carriers for NSC transplants, and their permeability ensures the successful diffusion of nutrients and molecular signals into the tissue. In 2021, Liu et al. [136] reported a DNA supramolecular hydrogel with high permeability to repair spinal cord transection injury. The

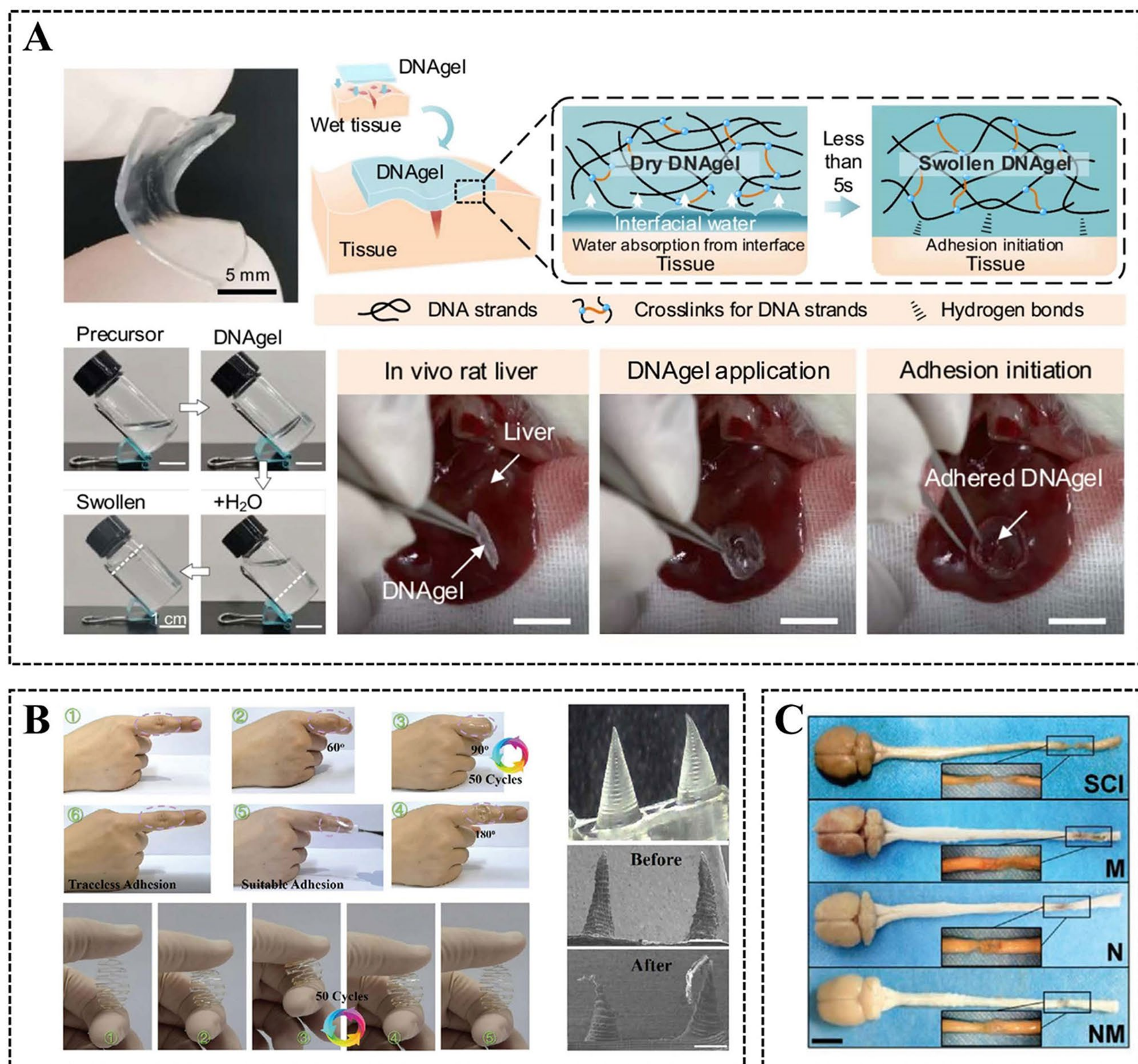


Fig. 7 (**A**) Adhesive DNA Hydrogel Band-Aid for Hemostasis. Adapted reprinted with permission from Ref [134]. Copyright 2024, Springer Nature Ltd. (**B**) Dual bionic deformable DNA hydrogel microneedle-guided tissue regeneration in diabetic ulcer wounds, mechanical strength testing, capsule adhesion effect on joints and deformation testing. Adapted reprinted with permission from Ref [135]. Copyright 2023, Wiley. (**C**) Highly permeable DNA hydrogel promotes spinal cord repair. SCI: Injury-only group Injury-only group. M: Hydrogel without NSCs group, N: NSCs without hydrogel group, NM: Hydrogel loaded NSCs group Hydrogel with NSCs group. Adapted reprinted with permission from Ref [136]. Copyright 2021, Wiley

hydrogel was self-assembled from DNA double strands to host homologous neural stem cells, and the spacing of cross-linking sites between DNA double strands in the hydrogel was designed to be 20 nm (60 bp), which avoids the formation of small lattices preventing permeation and ensures that the hydrogel is useful for the rapid diffusion of neuronally relevant growth factors and other nutrients in the tissues. Injecting DNA hydrogels and NSCs into a surgically formed murine spinal cord defect model filled most of the defective cavities after eight weeks (Fig. 7C). Furthermore, motor-evoked potential signals were detected in the hind limbs of the mice, suggesting that the hydrogel had successfully improved the regeneration of the tissues and recovered function. Also using DNA hydrogels to carry cells for tissue repair, Zhou et al. [137] designed a dual network hydrogel microsphere structure based on photocrosslinking. Compared to conventional block hydrogels, hydrogel microspheres are more efficient in solute diffusion and more conducive to promoting enhanced oxygen and nutrient exchange

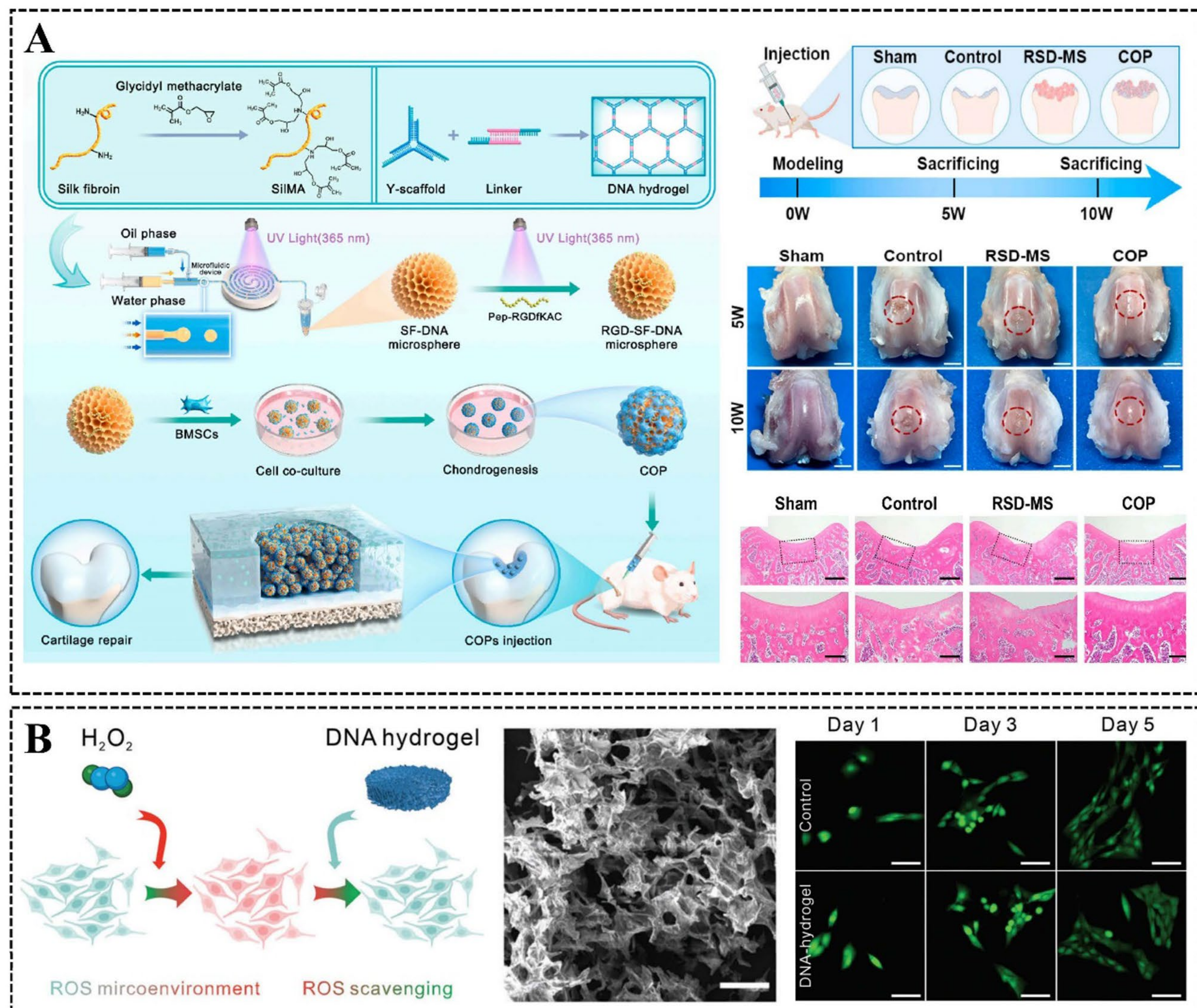


Fig. 8 (**A**) Schematic diagram of synthesis and promotion of cartilage repair by RGD-SF-DNA hydrogel microspheres. Sham group: positive control, Control group: untreated group, RSD-MS group: hydrogel with RSD-MSs only, COP group: hydrogel with COPs only. Adapted reprinted with permission from Ref [137]. Copyright 2024, Elsevier Ltd. (**B**) Antioxidant DNA Hydrogels Deliver Cytokines to Promote Diabetic Wound Healing Hydrogel. Electron microscopy images and schematic diagrams of ROS scavenging, live/dead staining images of human keratinocytes cells cultured for 24 h in DNA hydrogel and no DNA hydrogel. Adapted reprinted with permission from Ref [141]. Copyright 2022, Wiley

to enhance cell activity and differentiation potential. As shown in Fig. 8A, the mixed hybrid filipin protein-DNA droplets were in the aqueous phase, which were encapsulated by the outer oil phase to form microspheres, and hydrogel microspheres with a bilayer network structure were formed under UV irradiation. Microspheres with a large specific surface area can enhance the cell diffusion rate and cell-cell interaction, which promotes the proliferation of attached cells and facilitates the construction of cartilage-like organs.

Wound dressings stop bleeding, maintain moisture, prevent bacterial invasion, and promote wound healing. Multi-functional DNA hydrogels are considered an ideal skin substitute and wound dressing due to their excellent biodegradability, tissue adhesion, and capacity to carry a range of big and small molecule medications [138]. Antimicrobial peptides have attracted interest as structural templates for novel anti-infective drugs due to their low susceptibility to multidrug resistance mechanisms [139]. For example, the electrostatic interaction of a polyanionic DNA backbone and a cationic antimicrobial peptide (AMP) was used to form a physically cross-linked DNA hydrogel network. The release of the antimicrobial L12 peptide is modulated in the presence of DNA enzymes [140]. This DNA hydrogel loaded with antimicrobial L12 peptide showed significant efficacy in *Staphylococcus aureus*-infected porcine wounds. Treating chronic wounds, especially diabetic infected wounds, is one of

the key problems to be solved in regenerative medicine and since the microenvironment of diabetic wounds is complex, physicians usually choose DNA hydrogels with various functions such as anti-inflammatory, antioxidant, and pro-angiogenic. For example, a physically crosslinked DNA hydrogel that ensures cytokine bioactivity and sustained release has been developed [141]. As shown in Fig. 8B, an equiproportional mix of IL-33 and DNA monomers ensured uniform encapsulation of the cytokine. Under physiological conditions, this DNA gel sustains the release of IL-33 in the wound for at least seven days and is effective in inducing the local accumulation of immune cells to promote localized wound inflammation to subside. In addition, the DNA strand eliminated excess reactive oxygen species (ROS), which affect diabetic wound healing. Based on the same strategy, Yang et al. [142] designed a novel injectable DNA hydrogel dressing. Diversifying from the commonly used antimicrobial AgNCs, they physically encapsulated magnesium pyrophosphate crystals as an antimicrobial functional unit in a DNA polymer network, which slowly releases magnesium ions to promote wound angiogenesis in the wound microenvironment. The anti-inflammatory and antioxidant curcumin and antibiotic ciprofloxacin (CIP) were added, and the DNA hydrogel under the synergistic effect of the three showed excellent ROS scavenging and anti-inflammatory and antibacterial abilities, which effectively accelerated the healing of the infected wounds of diabetic patients.

Bio-3D printing

Using biomaterials to build three-dimensional tissue structures through interactions between cells and materials, 3D bioprinting is a sensitive tissue creation technique that may be used to repair damaged tissue and restore function. Precisely designed DNA hydrogels can meet the needs of 3D bioprinting. 3D bioprinting has gained attention for its ability to accurately print complex structures; however, selecting the correct scaffold material as bioink is the key to bioprinting. Hydrogels as scaffold materials have been widely reported due to their similarity to the natural extracellular matrix. However, the use of various natural products as scaffold materials for bioprinting has many drawbacks, such as high temperature-induced deformation of hydrogel formation and lack of responsiveness and customizability. Synthetic polymers in turn reduce the biodegradability and biocompatibility of hydrogels. Combining the concept of dynamic DNA nanotechnology with 3D bioprinting enables the production of hydrogel structures functionalized with DNA at the millimeter to centimeter scale [143].

Li et al. [144] printed peptide-DNA hydrogels using two bioinks with different compositions. As shown in Fig. 9A, bioink A is a peptide backbone with five to six ssDNA motifs reconnected to create enough cross-linking sites. Bioink B is a double-stranded DNA (dsDNA) containing sticky ends that are complementary to the Bioink A ssDNA and act as DNA junctions. Once the printed droplets touch and mix, the two bioinks rapidly crosslink to form a supramolecular DNA hydrogel in less than a second. The hydrogels formed by this 3D printing are very rapid compared to hydrogel formation by manual mixing. The bioprinter can also be programmed to precisely control the position and distance of the printed droplets. This printed DNA hydrogel has borderless geometric homogeneity and maintains millimeter-scale shapes without collapsing, exhibiting good mechanical flexibility and healing properties. In addition, they added cells to the ink for testing, and unexpectedly, the specific viscosity and surface tension of the bio-ink not only met the requirements of the nozzle technology, but also the cells were able to remain stable in suspension and had high viability and normal biological functions. Therefore, with this bioprinting system, not only 3D patterns and structures of arbitrary scale and size can be constructed, but also long-term cell cultures are promising. Researchers developed a low-cost method for 3D bioprinting based on a commercially available extrusion printer [145], to develop a bioink covalently modified with DNA molecules. Agarose was modified with ssDNA strands to form the bioink, and DNA-functionalized hydrogels of various shapes were printed.

Another advantage of 3D printing is the ability to precisely fabricate porous scaffolds with controllable shapes, and the printed structures can maintain millimeter-scale porous shapes without collapsing. Chen et al. [146] supramolecularly co-assembled amyloid fibrillar proteins (AFs), clay nanosheets, and DNA chains to develop a hybrid DNA hydrogel (DAC) with 3D printing properties. DNA hydrogels are formed by electrostatic interactions between the positively charged amyloid fibrillar protein and the negatively charged DNA chains and clay nanosheets. A patterned macroporous structure was generated by a regular arrangement of hydrogel filaments in which a significant number of interconnecting pores were evenly distributed owing to freeze-drying, as seen in Fig. 9B for the DAC hydrogel scaffolds made in various forms by 3D printing. Additionally, the 3D printed DAC hydrogel scaffold exhibited potential for withstanding the somewhat acidic environment of in vivo wounds since it remained stable in various pH settings without experiencing appreciable swelling or disintegration. Cunniffe et al. [147] designed a novel printing ink consisting of alginate and nanohydroxyapatite (nHA) complexed with plasmid DNA (pDNA). Bone marrow mesenchymal stem cells were placed in the ink, which can form a stable network structure to provide mechanical stability to the constructs during printing.

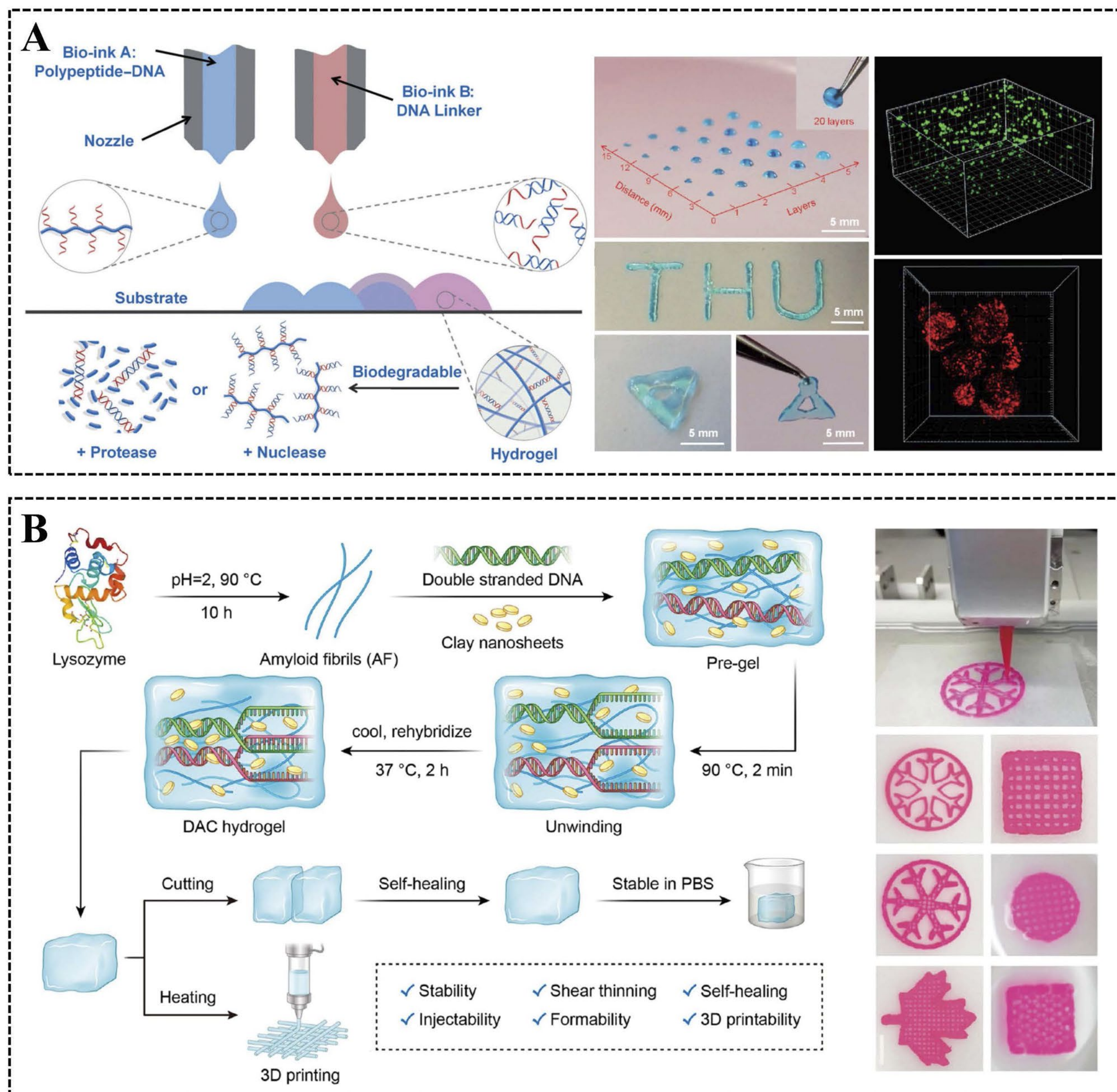


Fig. 9 (**A**) 3D bioprinting of peptide-DNA hydrogels. Adapted reprinted with permission from Ref [144]. Copyright 2023, American Chemical Society. (**B**) 3D printed dual nanoengineered dynamic DNA hydrogel 3D printing technique to make symmetric DAC1.0 hydrogel scaffolds. Adapted reprinted with permission from Ref [146]. Copyright 2015, Wiley

In addition, the four different extragenic genes used in the printing process transfect reporter and therapeutic genes onto the MSCs, thereby allowing the bone marrow MSCs to differentiate into osteoblasts and promoting osteogenic differentiation. Thus, this hydrogel induces MSC differentiation and bone regeneration through bioprinting. In addition, the construct containing nHA-pDNA showed enhanced osteogenic capacity compared to the construct containing nHA alone.

DNA hydrogels are ideal materials for bioprinting. Most of the existing DNA hydrogels for 3D bioprinting are mainly based on the bottom-up strategy, i.e., the preparation of hydrogels that can be rapidly gelatinized and then made into bioinks for printing. When DNA hydrogels are used as bioinks for 3D printing, complex and customized skeletal structures can be fabricated through sophisticated instrumentation, which can improve the efficiency of DNA hydrogel preparation. Notably, tissue structures printed using hybrid or pure

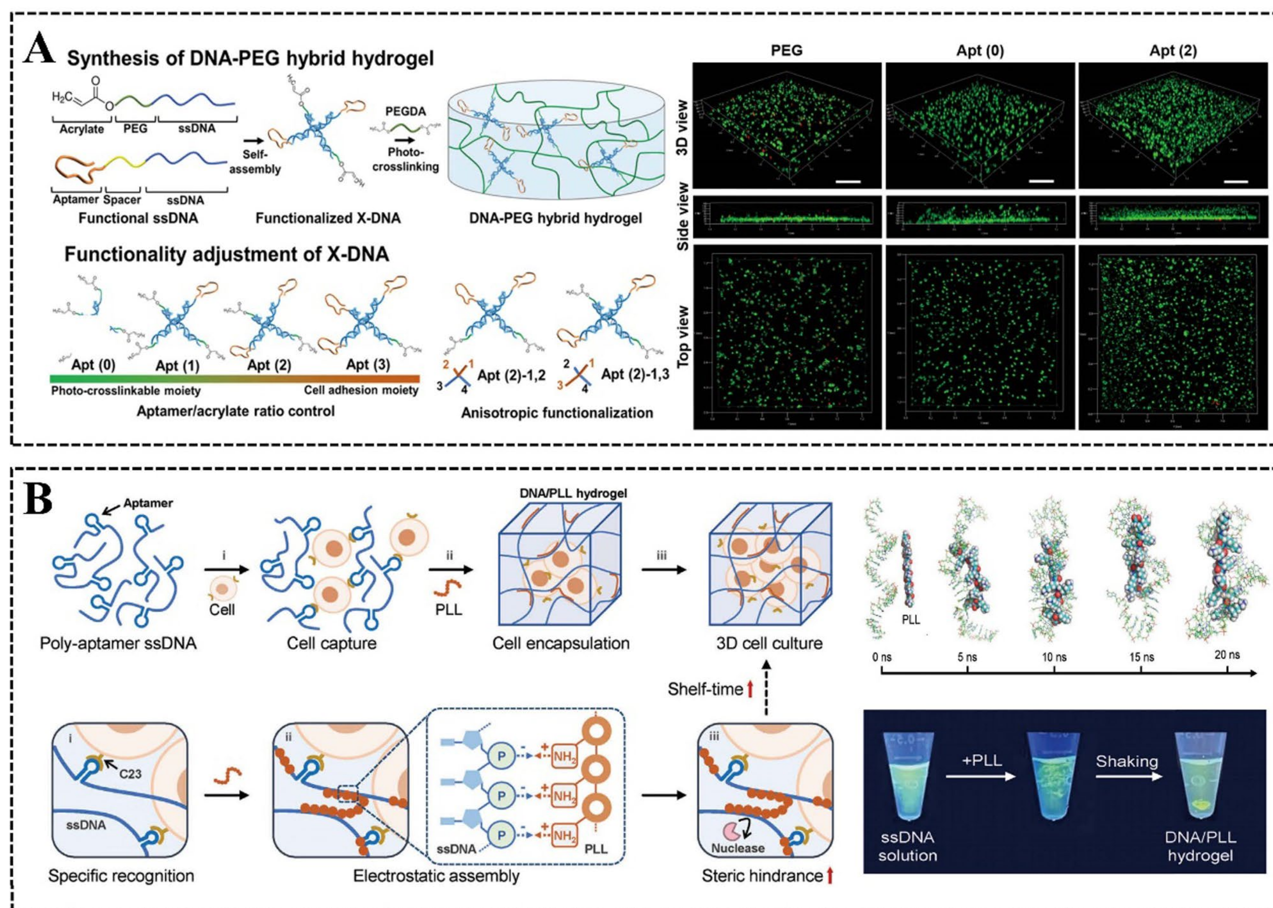


Fig. 10 (**A**) Functionalized Aptamer-DNA nanostructures for enhanced cell culture. Adapted reprinted with permission from Ref [150]. Copyright 2021, American Chemical Society. (**B**) DNA/polylysine hydrogels for three-dimensional cell culture. Adapted reprinted with permission from Ref [156]. Copyright 2024, Wiley

DNA bioinks may exhibit reduced levels of inflammation or foreign body reactions, and their biocompatibility may be somewhat weakened [139]. Challenges remain that need to be resolved in order to maximize the printing process. For example, DNA hydrogels for fabricating tissues and organs require large amounts of polymers and are costly [148]. Moreover, the mechanical properties and stability of printed DNA hydrogels are poor, which makes it difficult to guarantee the long-term activity of loaded cells in tissue engineering applications. In summary, DNA hydrogel 3D printing presents great potential and requires additional in-depth studies.

Cell culture and capture

A vital component of the cellular environment, the ECM, is a dynamic network of collagen, glycoproteins, enzymes, and other macromolecules that regulates cell activity [149]. Due to their high water content, DNA hydrogels resemble the ECM in that they exhibit gel-like characteristics. Additionally, their porous structure facilitates the flow of nutrients and metabolic wastes, hence promoting high cellular viability. High cell viability is maintained by the porous structure, which permits the flow of nutrients and metabolic wastes. DNA hydrogels are therefore ideally suited for significant cell culture-based applications.

Introducing a sequence of materials into DNA hydrogels increases their versatility in cell culture. DNA sequences bind to specific cellular receptors in a targeted manner, thus ensuring cell immobilization and cell culture. However, the rigidity of the DNA structure reduces the mechanical properties of the hydrogel, which is prone to collapse when insufficient support is provided. Therefore, researchers have developed multifunctional DNA nanostructures for assisting target-specific adhesion and cell proliferation in cell cultures [150]. As shown in Fig. 10A, four complementary ssDNA sequences were first functionalized with acrylates (as photo-crosslinkers) or peptidomers (as cell adhesion molecules), respectively, to prepare multifunctional nanostructures of X-DNA, and hybrid hydrogels formed by photo-crosslinking rapidly under mild reaction conditions. Various types of functionalized X-DNA (AptX-DNA) can be synthesized

by controlling the ratio of photocrosslinker to aptamer added to X-DNA. Furthermore, aptamers were inserted into the branched strands to optimize the cell adhesion of X-DNA and promote cell proliferation. In the same year, another study introduced polyacrylamide hydrogels as additional networks. Gao et al. [151] developed a new strategy for constructing DNA-polyacrylamide (PAAm) hybridization hydrogel preparation. The dual network formed by the DNA strands and polyacrylamide improves the tensile and shear strength of the hydrogel and ensures that it remains stable during performing immunostaining and cellular imaging to visualize the cellular behaviors and functions in a 3D environment.

Traditional 2D cell culture systems performed on planar scaffolds lack cell-cell and cell-environment interactions [152–154]. However, hydrogels with a jelly-like texture with high water content not only provide effective physiological and structural support for 3D cell growth, but can also be tuned with biochemical and physical properties to mimic the extracellular matrix, which shows great potential in 3D cell culture [155]. However, nucleases in the culture medium degrade the hydrogel structure, leading to a significant reduction in the shelf life of DNA hydrogels. Yao et al. [156] proposed a novel strategy for extending the validity period of DNA hydrogels. Poly (L-lysine) (PLL) was used as a cross-linking agent to connect single-stranded DNA integrated with an aptamer for the rapid assembly of the hydrogel network (Fig. 10B). PLL served as a protective coating to increase the resistance between the nuclease and the phosphodiester bond, effectively preventing nuclease damage to the DNA hydrogel network. After 15 days of cell culture, cells encapsulated in the hydrogel were able to proliferate and eventually form cell spheroids, indicating that the coating improves the stability of the hydrogel structure without affecting the ability of the aptamer to target and recognize cells.

In addition to cell culture, DNA hydrogels can capture specific cells efficiently while maintaining high cell viability. Yao et al. [157] introduced a DNA hydrogel network for the efficient capture of bone marrow MSCs. As shown in Fig. 11A, in the RCA-based synthesis of two complementary DNA long strands, they were mixed and entwined to form a hydrogel. The sequence of one of the DNA strands contains an aptamer with high affinity to the special protein on the membrane of BMSCs, which is used to specifically capture BMSCs from bone marrow, whereafter the DNA strand is deconstructed by the addition of nuclease to release the captured cells. Distinguishing from the use of long DNA strands to construct a web to encapsulate cells, Tang et al. [51] reported another hydrogel formed using electrostatic attraction and interfacial assembly of long DNA strands and UCNPs. The addition of NPs caused rapid hydrogel formation from the mixed solution, which selectively captured the target cells. Tumor cell detection and consolidation therapy are important for patients with cancer after surgery. If live circulating tumor cells (CTCs) are accurately and efficiently isolated from peripheral blood and monitored in real time, tumor recurrence can be sensitively detected, which is important for the prevention of secondary metastasis. The programmability of a DNA molecule allows DNA networks to have the desired structure and specific functions. In 2020, Li et al. [158] synthesized physically cross-linked DNA hybrid DNA hydrogels containing ATP-responsive aptamers (Fig. 11B). When the aptamer binds to epithelial adhesion molecules on the surface of tumor circulating cells, it triggers the formation of porous DNA hydrogels. Using this system, blood from cancer patients successfully encapsulated and released CTCs, identifying as few as 10 tumor cells in 2 μL of whole blood, and the special composition of the DNA hydrogel can both capture and kill cells. It is worth mentioning that, also utilizing aptamers for cell-targeted capture, Mu et al. [159] designed an anisotropic DNA hydrogel. This specially structured hydrogel consists of unidirectional pore channels, and compared with the control DNA hydrogel without macroporous channels, the DNA hydrogel with macroporous channels exhibits more efficient cell capture. Recently, Wang et al. [160] developed a local photodynamic immunomodulatory DNA hydrogel. One ssDNA strand contained the complementary sequence of the immune adjuvant CpG and the PDL1 aptamer, and the other contained the ATP sensor. When the PDL1 aptamer binds to the PDL1 protein on the surface of the tumor cell, the tumor cell is anchored and aggregates, the local ATP concentration increases, the ATP sensor emits fluorescent signals, and the photosensitizer added in advance induces the hydrogel to decompose by local laser irradiation, releasing CpG and PDL1 aptamers, and inducing the immune response to kill the tumor cells. The more PDL1 aptamers are released from the hydrogel, the more tumor cells are captured, the stronger the fluorescence signal is, and the more hydrogel is released from the hydrogel decomposition, forming a benign signal amplification cycle. However, the hydrogel is only able to monitor part of the tumor site, the tumor may still recur, and the stability of the hydrogel in the body remains to be considered.

In 2021, Jiang et al. [161] established a Zn^{2+}-dependent DNA enzyme responsive DNA hydrogel (Fig. 11C). Similar to the above strategy, the hydrogel is constructed by intertwining and hybridizing two polymerized DNA strands (R1 and R2), the R1 strand containing the aptamer sequence and DNAzyme sequence, and the R2 strand containing the corresponding DNAzyme substrate sequence. When R2 is added to the R1 solution, R2 is entangled with the R1

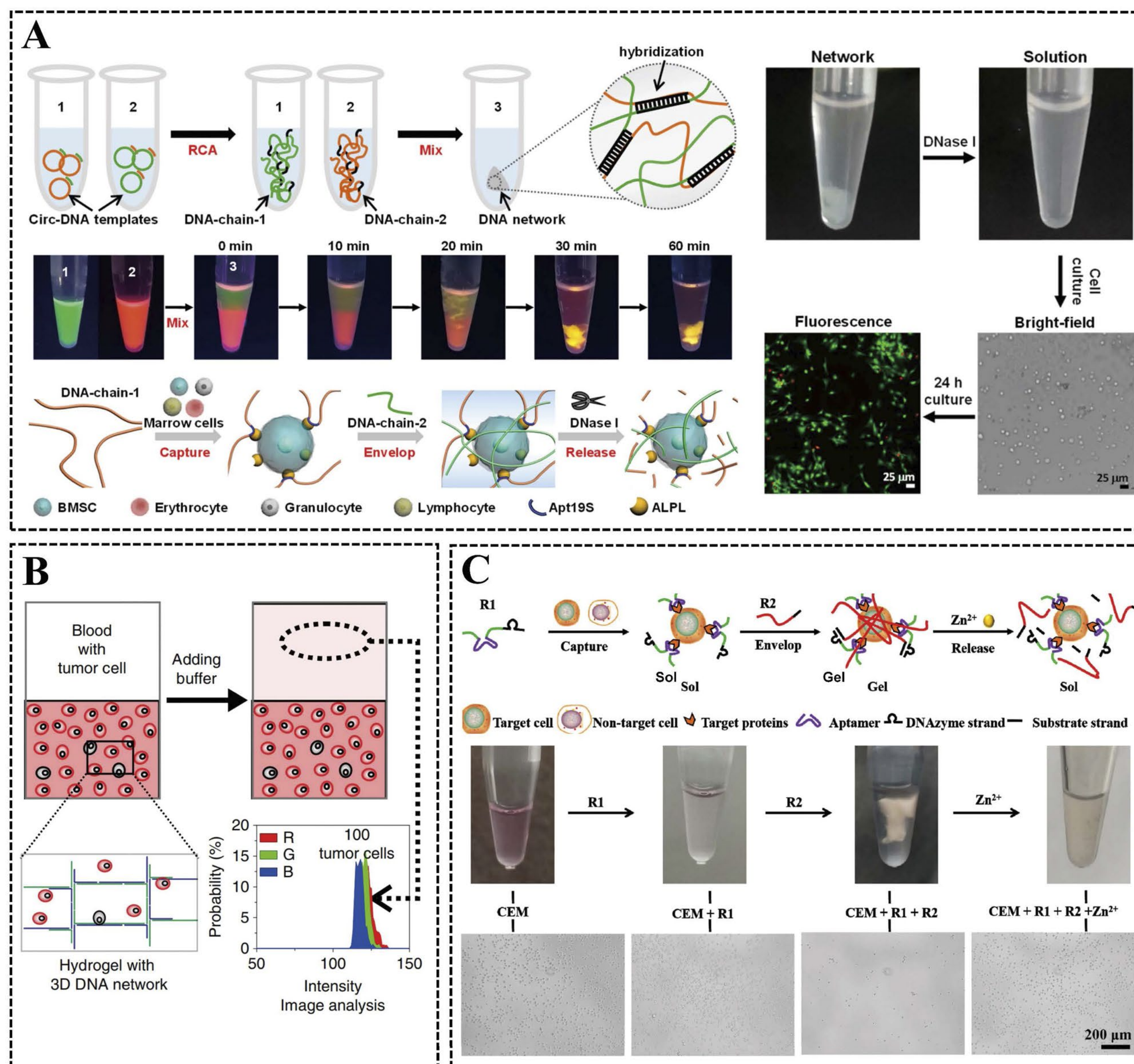


Fig. 11 (**A**) Physical crosslinked DNA networks for stem cell harvesting. Adapted reprinted with permission from Ref [157]. Copyright 2020, American Chemical Society. (**B**) Encapsulation of live tumor cells in blood using a hydrogel that reacts with hybridization chains. Adapted reprinted with permission from Ref. The process of ultra-long DNA strands to obtain three-dimensional DNA networks as well as the process of capturing, encapsulating and releasing BMSCs [158]. Copyright 2021, American Chemical Society. (**C**) DNA enzyme-triggered solution-gel-solution transition of the hydrogel enriches target cells. Adapted reprinted with permission from Ref [161]. Copyright 2020, Springer Nature Ltd

strand of the target cell already captured in the solution to form a DNAzyme hydrogel, and the target cell is separated by solution-gel conversion. The DNAase hydrogel disassembles and releases the captured cells when triggered by Zn^{2+}. The entire process of Zn^{2+} has minimal cytotoxicity, and the capture and release of the DNA hydrogel are performed in mild conditions, which is expected to be suitable for the use of clinical samples.

Conclusion and prospects

Nowadays, many ingenious strategies for the preparation of DNA hydrogels have been developed through various precise structural designs. Pure DNA hydrogel network gels based on hydrogen bonding of base complementary pairing usually have stable and controllable structures. Hydrogels for nucleic acid amplification to obtain ultra-long DNA strands that are then physically wound is an easy alternative. Gradually, researchers have added single or multiple functional materials with

excellent properties to the hydrogels, such as functional DNA groups, natural and synthetic polymers, and various new nanomaterials, as well as DNA as a crosslinking agent to tightly connect various functional materials to each other, so as to make them have the required optical, electronic, and other physical properties, to realize different DNA hydrogel functions. The mechanical, optical, and encapsulating capabilities of these functionalized DNA hydrogels are used in the biosensing area to meet the requirements of high sensitivity and accuracy in sensing detection. To achieve the accurate distribution of loaded pharmaceuticals using DNA hydrogels, we concentrated on discussing functional DNA hydrogels with high mechanical capabilities and stimulation response properties for use in targeted therapy and drug delivery. DNA hydrogels must have strong molecular permeability, thixotropy, self-healing, and antibacterial qualities in tissue engineering and cell culture applications to adjust to the right environments for cell growth and differentiation. However, DNA hydrogels have many drawbacks. For example, as the preparation cost of DNA hydrogels is still too high to meet the requirements for scaling up production, it is hoped that simpler synthesis methods can be developed to reduce costs, and the mechanical properties of DNA hydrogels need to be improved, especially as biomedical materials used in clinical applications should have repair and stretching capabilities similar to human tissues, while the biocompatibility of the hydrogel material should be ensured; therefore, programmable DNA scaffolds with adjustable stiffness are ideal. When testing metrics of biological systems, it may be possible to integrate DNA hydrogel assay designs with mobile apps to allow for more intuitive real-time monitoring, thus developing more individualized treatments tailored to the patient. Furthermore, the development of specific DNA sequences in hydrogels for binding to biomolecules of interest is important for guiding both cell behavior and tissue engineering. In addition, many hybrid DNA hydrogels contain other materials as structural scaffolds, and when these hydrogels are used in the in vivo environment, we have to consider the toxic effects and biodegradability of the materials involved. We can use more biocompatible materials such as exosomes, herbal molecules with anti-inflammatory properties. Extensive studies using animal models and perhaps clinical trials must be conducted going forward. To address the remaining issues in hydrogel application, the properties of DNA hydrogels should be continuously optimized and expanded. We look forward to a broad future for DNA hydrogels.

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Author contributions
R.W. wrote and revised the main manuscript. W.L. conceived the project. P.Y., N.S., A.Y., X.L., Y.J. reviewed the manuscript. L.L. and BF conceived and designed the manuscript. All authors read and approved the final manuscript.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
We give our consent for the manuscript to be published in Journal of Nanobiotechnology.

Competing interests
The authors declare no competing interests.

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