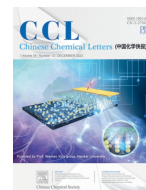




Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

DNA-based supramolecular hydrogels: From construction strategies to biomedical applications

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ARTICLE INFO

Article history:

Received 20 February 2023

Revised 26 May 2023

Accepted 29 May 2023

Available online 1 June 2023

Keywords:

DNA hydrogels

Supramolecular hydrogels

Self-assembly

DNA nanotechnology

Biomedical applications

ABSTRACT

DNA-based supramolecular hydrogels are important and promising biomaterials for various applications due to their inherent biocompatibility and tunable physicochemical properties. The three-dimensional supramolecular matrix of DNA formed by non-covalently dynamic cross-linking provides exceptional adaptability, self-healing, injectable and responsive properties for hydrogels. In addition, DNA hydrogels are also ideal bio-scaffold materials owing to their tissue-like mechanics and intrinsic biological functions. Technically, DNA can assemble into supramolecular networks by pure complementary base pairing; it can also be combined with other building blocks to construct hybrid hydrogels. This review focuses on the development and construction strategies of DNA hydrogels. Assembly and synthesis methods, diverse responsiveness and biomedical applications are summarized. Finally, the challenges and prospects of DNA-based supramolecular hydrogels are discussed.

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1. Introduction

Hydrogels are a class of three-dimensional (3D) networks swollen in an aqueous medium formed from cross-linked polymer chains [1]. The water-rich nature of hydrogels, combined with substantially tunable physicochemical properties, offer great potential for biotechnological and biomedical applications, including tissue engineering, cell culture, drug delivery, biosensing, and others [2–5]. In particular, supramolecular hydrogels connected by non-covalent interactions have great adaptability, self-healing, and stimuli-responsiveness due to their rapid phase transitions and relatively weak dynamic non-covalent bonds [6–8]. Typically, DNA-based supramolecular hydrogels, cross-linked through DNA-sequence-directed hybridization, have attracted extensive attention because of the distinctive properties of DNA, and are considered as promising soft materials for biological and therapeutic applications [9,10]. The DNA molecules with excellent biocompatibility and sequence programmability in the supramolecular 3D networks provide

vide hydrogels with extraordinary versatility, precise recognizability, and specific responsiveness, making them ideal for fabricating smart biomaterials.

In 2009, Liu's group fabricated a novel type of pure DNA supramolecular hydrogel completely based on DNA self-assembly by using short double-stranded DNA and quadruplex i-motif [11]. This research provides a new direction for the construction of DNA hydrogels. Besides, the developed supramolecular hydrogel can be switched to the non-gel state within minutes upon simply changing the environmental pH. Generally, due to the definite persistence length and rigidity of both duplex and i-motif structures, this kind of hydrogels based on DNA self-assembly have adjustable mechanical properties and permeability. Therefore, DNA-based supramolecular hydrogels as smart materials are considered as ideal candidate for bio-scaffolds. For example, the natural extracellular matrix (ECM) is a complex assembly of biopolymers that provides the structural, functional, and biochemical basis for cell survival. DNA supramolecular hydrogels that mimic ECM offer a promising option for cell engineering with minimal loss of cell viability and molecular integrity. This paper reviews the construction strategies and typical biomedical applications of DNA-based supramolecular hydrogels (Fig. 1) [12–24].

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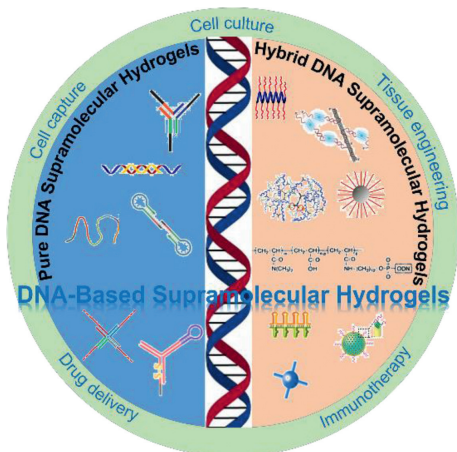


Fig. 1. Schematic illustration of construction strategies and typical biomedical applications of DNA-based supramolecular hydrogels. Reproduced with permission [11]. Copyright 2009, Wiley-VCH. Reproduced with permission [12]. Copyright 2017, Chinese Chemical Society. Reproduced with permission [13]. Copyright 2021, Wiley-VCH. Reproduced with permission [14]. Copyright 2019, Jilin University, The Editorial Department of Chemical Research in Chinese Universities and Springer-Verlag GmbH. Reproduced with permission [15]. Copyright 2016, American Chemical Society. Reproduced with permission [16]. Copyright 2015, American Chemical Society. Reproduced with permission [17]. Copyright 1996, Elsevier B.V. Reproduced with permission [18]. Copyright 2012, American Chemical Society. Reproduced with permission [19]. Copyright 2020, American Chemical Society. Reproduced with permission [20]. Copyright 2014, Royal Society of Chemistry. Reproduced with permission [21]. Copyright 2011, Royal Society of Chemistry. Reproduced with permission [22]. Copyright 2014, Royal Society of Chemistry. Reproduced with permission [23]. Copyright 2017, American Chemical Society. Reproduced with permission [24]. Copyright 2019, American Chemical Society.

2. Construction strategies of DNA-based supramolecular hydrogels

2.1. Pure DNA supramolecular hydrogels

DNA can be programmatically designed to construct supramolecular hydrogels with 3D networks through base complementary pairing. Until now, simple DNA hybridization reaction, clamped hybridization chain reaction (C-HCR), polymerase chain reaction (PCR), rolling circle amplification (RCA), etc. have been successfully applied to construct pure DNA supramolecular hydrogels. Due to their excellent biodegradability, precise structural controllability, adjustable mechanical strength, and specific stimuli responsiveness, the hydrogels formed by the cross-linking of DNA have attracted considerable attention in the construction of functional materials for great potential applications in biology and medicine.

2.1.1. DNA hydrogels self-assembled from branched DNA scaffolds

Luo and his colleagues assembled a pure DNA hydrogel in 2006 through enzyme-catalyzed cross-linking of branched DNA scaffolds [25]. However, the preparation of this hydrogel by enzymatic ligation requires multiple steps, which is time-consuming. A more important concern for biomedical applications is that the contaminating ligase may trigger unwanted anaphylactic responses [26]. The first pure DNA supramolecular hydrogel with well-defined compositions and structures was constructed by cross-linking Y-shaped DNA (Y-scaffold) building blocks through the formation of intermolecular i-motif structures [11]. As shown in Fig. 2A, Y-scaffolds with three half i-motif sequences sticking out are self-assembled from equal amounts of three oligonucleotides at pH 8. When adjusting the pH to 5, the intermolecular i-motif structures are formed between Y-scaffolds to yield the DNA hydrogel. Because of the fast transformation of i-motifs, such hydrogels can be switched

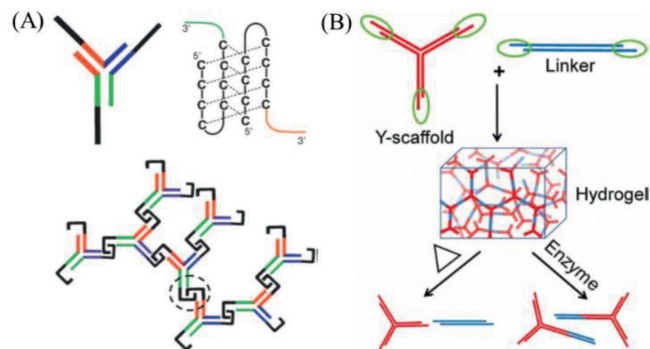


Fig. 2. (A) The nanostructure units of a pH responsive DNA hydrogel. Copied with permission [11]. Copyright 2009, Wiley-VCH. (B) A self-assembled DNA hydrogel with designable thermal and enzymatic response capability. Copied with permission [27]. Copyright 2011, Wiley-VCH.

between gel and sol states in minutes by changing the environmental pH. Thereby, this research provides a novel DNA hydrogel system in which cargoes can be released in a pH-dependent manner. However, this kind of DNA hydrogel can only form under acidic conditions, which limits its applications *in vivo*. Later, Liu *et al.* used linear DNA duplexes as linkers to assemble with Y-scaffolds to form a pure DNA hydrogel under neutral conditions [27]. As illustrated in Fig. 2B, through particularly designing the “sticky ends” of DNA building blocks, the Y-scaffolds and linkers can complement each other to construct DNA hydrogels rapidly without any treatment of chemical cross-linking. In particular, DNA hydrogels exhibit typical thermal and enzymatic responsiveness through customized sequences of DNA building blocks. In addition, the effective elasticity of the hydrogels can further be regulated by introducing flexible, non-binding bases into the linker DNA [28]. Thus, such pure DNA hydrogels with ordered structure and multiple responsiveness provide a new and general strategy for constructing functional biomaterials through DNA sequence-directed self-assembly.

2.1.2. DNA hydrogels self-assembled from linear DNA scaffolds

In 2014, Noll *et al.* demonstrated that linear DNA scaffolds can form 3D DNA hydrogels by self-assembly [29]. They prepared a highly entangled DNA hydrogel solely from linear dsDNA building blocks with sticky ends (Fig. S1A in Supporting information). The rheological properties of the hydrogels are comparable to those of DNA hydrogels built from branched DNA motifs. However, the structural details of the hydrogel were still unclear. In 2017, Liu *et al.* constructed a DNA hydrogel by bending linear DNA scaffolds containing one dsDNA domain equipped with a half i-motif structure at both ends (Fig. S1B in Supporting information) [12]. When pH was slightly acidic, the linear DNA scaffolds were polymerized together to form interlocked loop structures through the formation of intermolecular i-motif. The resulting DNA hydrogel is a 3D network of interlocked rings. The rheological properties can be further tuned by adjusting the length and bending curvature of the linear duplex scaffolds. This approach provides a way to explore the relationship between hydrogel structures and linear DNA assemblies.

2.1.3. DNA hydrogels self-assembled from single-stranded DNA monomers

Besides the above methods of multi-stranded designs, pure DNA supramolecular hydrogels can also be obtained by self-assembly of single-stranded DNA monomers. For example, Ke *et al.* developed a low-cost, highly programmable DNA hydrogel by using single-stranded DNA containing multiple palindromic domains [30]. The hydrogel is formed by one-step cross-linking of individual strands with complementary domains (Fig. S2A in Sup-

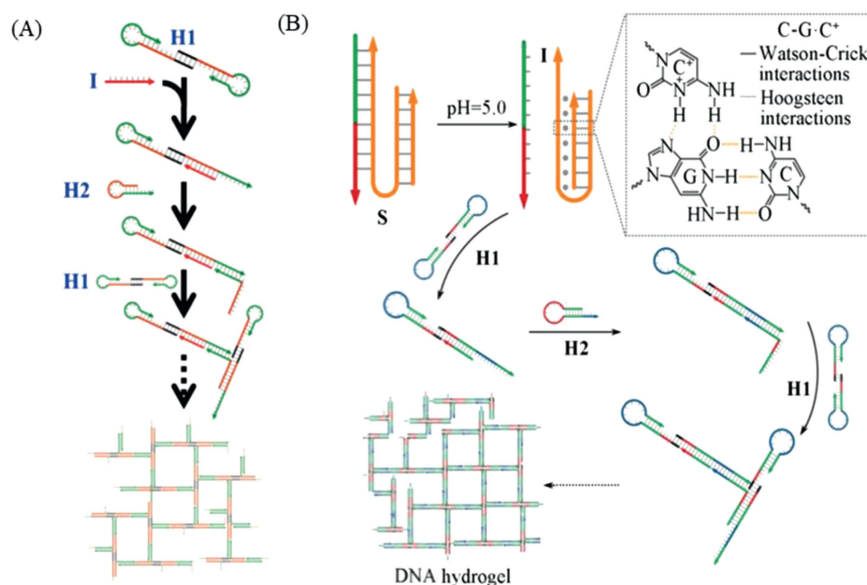


Fig. 3. (A) DNA hydrogels assembled by C-HCR. Copied with permission [33]. Copyright 2017, Wiley-VCH. (B) A pH-triggered DNA hydrogel based on HCR. Copied with permission [14]. Copyright 2019, Jilin University, The Editorial Department of Chemical Research in Chinese Universities and Springer-Verlag GmbH.

porting information). In addition, the thermal stability, mechanical properties, and payload capacity of the hydrogel assembled from one-stranded DNA monomers can be readily tuned by adjusting the sequences and lengths of DNA domains. Furthermore, Liu *et al.* constructed two pH-responsive supramolecular hydrogels using the single-stranded DNA monomer strategy. The first one, DNA nanowires self-assembled from monomers containing two self-complementary sequences and a half i-motif domain can form 3D hydrogels by cross-linking the half i-motif domains under slightly acidic conditions [31]. Since the hydrogels require only one strand of DNA, the construction of supramolecular hydrogels is greatly simplified. Moreover, they also assembled a DNA double-crossover (DX) backbone using a single-stranded DNA. Then, based on the kinetically interlocking multiple-units (KIMU) supramolecular polymerization strategy, a novel KIMU supramolecular polymer was successfully prepared by using the DNA DX monomers [32]. Particularly, a supramolecular hydrogel with high mechanical strength was further constructed with the rigid KIMU polymers (Fig. S2B in Supporting information) [13]. Overall, the principle of using one-stranded monomers to prepare DNA hydrogels avoid quantitative matching of each strand, and provides a simple, low-cost method to fabricate programmable biomaterials with good homogeneity.

2.1.4. DNA hydrogels self-assembled by hybridization chain reaction

Most pure DNA hydrogels based on self-assembly of DNA building blocks occur nonspecifically throughout the solution. The gelation process is spontaneous and homogenous. In order to accurately control sol-gel transitions in time and space, Liu *et al.* developed a new approach for constructing pure DNA hydrogels by a C-HCR [33]. As shown in Fig. 3A, the system includes three DNA strands: two hairpin strands H1, H2, and an initiator strand I. As triggered by a small amount of initiator I, the hybridizations between H1-dimer and H2 can lead to forming of 3D DNA hydrogels with three-arm and four-arm junctions. Moreover, by taking advantage of printed, surface-confined DNA initiators, 2D DNA hydrogel patterns without external confinements can also be fabricated. Later, Liu and colleagues constructed a pH-triggered DNA hydrogel based on HCR by using a DNA switch to release the initiator strand under pH stimuli (Fig. 3B) [14]. Wu, Shen and colleagues achieved intracellular invasive growth of DNA hydrogels for flu-

orescence imaging of miRNAs in living cells based on the palindromic end-mediated cross-linking HCR technique [34].

2.1.5. DNA hydrogels self-assembled from enzyme-polymerized DNA sequences

The above-mentioned methods for obtaining pure DNA hydrogels require a large number of oligonucleotides, even reaching the submillimolar level, which may greatly hinder their practical applications due to the high cost. On the other hand, the idea of efficiently acquiring substantial long DNA strands as building blocks for assembling DNA hydrogels has received significant attention. For example, Luo *et al.* used thermostable branched DNA nanostructures as modular primers for PCR, thus making PCR products novel building blocks for the formation of DNA supramolecular hydrogels [35]. Nie and colleagues reported a facile and cost-effective approach for the self-assembly of DNA hydrogels using enzymatically polymerized DNA sequences [15]. In this system, the extended DNA sequences by TdT polymerization can serve as stick-ends to form hydrogels (Fig. 4A), which significantly reduces the amount of original DNA motifs required. The DNA hydrogels can be further applied to protein encapsulation and enzyme/DNAzyme hybrid cascade reactions. Meanwhile, RCA is an efficient isothermal amplification technology mediated by single-stranded circular DNA templates to synthesize long periodic stretches of DNA, which offers a facile strategy for the fabrication of programmable DNA self-assembled structures [36–38] and mechanical metamaterials [39]. In particular, the employment of the RCA technique to construct DNA supramolecular hydrogels could not only further simplify the fabrication process, but also introduce the customized functions into DNA hydrogels by using tailor-designed template sequences. Based on this merit, Tian *et al.* constructed a functionalized DNA hydrogel with stable catalytic ability by a one-step RCA method [40]. In this study, they used circular cytosine-rich DNA templates to produce long ssDNA containing periodic guanine-rich sequences with the potential enzyme catalytic properties (Fig. 4B). Subsequently, the resulting RCA products prefer forming intermolecular parallel G-quadruplex structures, which could be served as cross-linking sites for the formation of supramolecular hydrogels. In addition, the hydrogels combined with hemins exhibit highly stable horseradish peroxidase-like (HRP) catalytic capability, and further integrated with glucose oxidase (GOx) can be applied to glucose

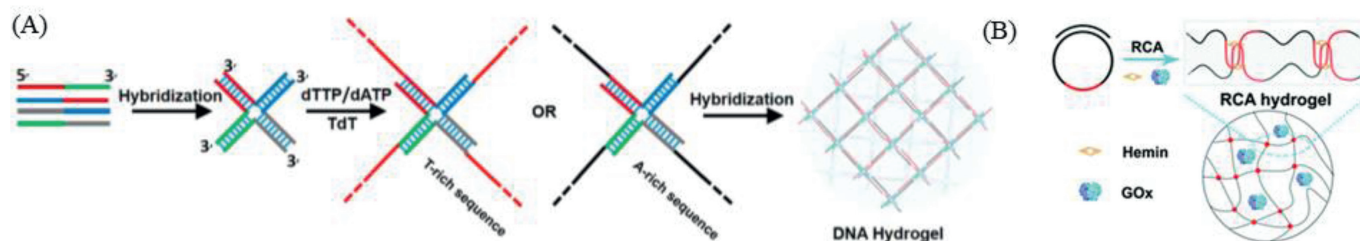


Fig. 4. (A) DNA hydrogels self-assembled from TdT-polymerized DNA sequences. Copied with permission [15]. Copyright 2016, American Chemical Society. (B) DNA hydrogels by a one-step RCA method. Copied with permission [40]. Copyright 2017, Royal Society of Chemistry.

detection. Furthermore, the authors also produced pH-responsive DNA hydrogels by introducing periodic i-motif-forming sequences into the polymeric RCA chains [41]. Very recently, Liu *et al.* reported that the mechanical strength of DNA supramolecular hydrogels could be reinforced by introducing polymeric multiple-unit linkers (PMULs), which were obtained through the hybridization between RCA products and their complementary chains [42]. In general, these RCA-based hydrogels with friendly cost and good performance are ready to be tailored for the fabrication of functionalized DNA hydrogels with broad applications.

2.1.6. DNA nanohydrogels based on self-assembly

In addition to bulk DNA hydrogels with macroscopic sizes, Tan and colleagues fabricated a DNA nanohydrogel with controllable size by confining random self-assembly of DNA at nanoscale [16]. As illustrated in Fig. S3A (Supporting information), three kinds of units are used in the system: a Y-scaffold monomer A (YMA) with three sticky ends as a building unit, a Y-scaffold monomer B (YMB) with only one sticky end as a blocking unit to limit the network expansion, and a DNA linker (LK) with two sticky ends as a linking unit. By varying the ratio of YMA to YMB, the hybridizations of monomers and LKs can lead to generating DNA nanohydrogels with controllable size. Furthermore, they also incorporated aptamers and disulfide linkages into the building units to generate targeted and stimuli-responsive nanohydrogels for gene therapy.

DNA nanohydrogels bear the relative merits of both hydrogels and nanoscale materials. He *et al.* assembled multifunctional DNA nanohydrogels as nanoreactors for efficient cancer therapy using the building blocks of X-shaped DNA monomers (XMA, XMBs) and LKs (Fig. S3B in Supporting information). The XMBs contained the aptamers to target cancer cells and control the nanohydrogel size. The LKs designed as i-motif sequences were modified with ferrocene (Fc). The three building blocks formed nanohydrogels through the hybridization of sticky ends at neutral conditions and successfully encapsulated GOx at the same time. In acidic tumor microenvironments, the DNA nanohydrogels were disassembled by forming i-motif structures to release GOx and Fc for the combination of starvation and chemodynamic therapies [43]. Zhu, Bi, and colleagues achieved DNA nanoassemblies using two DNA hairpins, an initiator, and a DNA polymerase in a cascade manner, and further used the nanoassemblies as building blocks to construct DNA nanohydrogels driven by liquid crystallization and dense packaging of DNA [44].

2.2. Hybrid DNA supramolecular hydrogels

In order to overcome the limitations of DNA as the only module of supramolecular materials and expand the performance of DNA hydrogels, new building blocks are desired to incorporate into the DNA systems to construct hybrid supramolecular hydrogels. Actually, hybrid DNA supramolecular hydrogels have been constructed by hybridizing DNA with polymers or nanomaterials, which can not only reduce the required concentration of DNA for

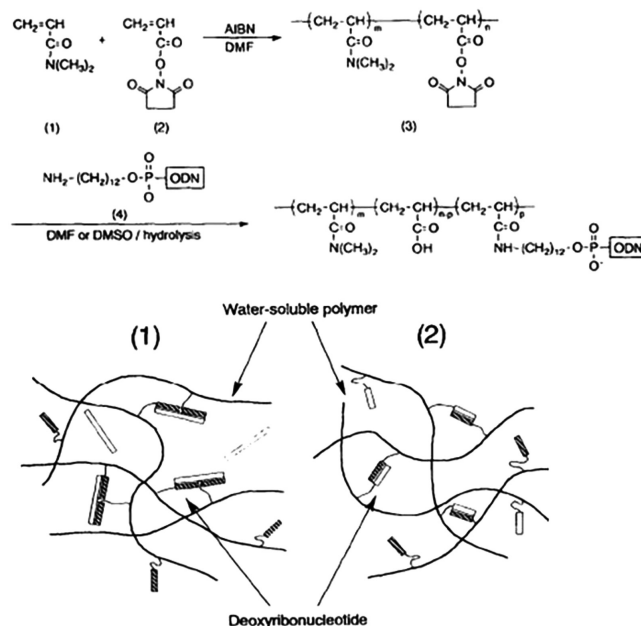


Fig. 5. Hybrid supramolecular hydrogels with polyacrylamide–DNA synthesized by the coupling reactions of active ester and amine. Copied with permission [17]. Copyright 1996, Elsevier B.V.

gelling, but also combine the advantages of multiple materials to improve the performance. Various integration strategies of hybrid DNA supramolecular hydrogels have important guiding significance for the development of novel biomaterials. In practice, the properties of supramolecular systems can be significantly enhanced by the incorporation of composites into the hydrogels.

2.2.1. DNA–polymer supramolecular hydrogels

DNA–polyacrylamide supramolecular hydrogels: The first DNA–polymer supramolecular hydrogel was prepared by Nagahara and Matsuda in 1996 [17]. In the study, short DNA strands were grafted onto poly(*N,N*-dimethylacrylamide-*co-N*-acryloyloxysuccinimide)s by coupling reactions of active ester and amine to establish stable amide bridges, and then the polyacrylamide–DNA hybrid hydrogels were formed through the hybridization of the modified side-chain DNA (Fig. 5). Another strategy to obtain DNA-grafted polyacrylamide is based on attaching DNA chains to the polymerizable monomer units, which are subsequently incorporated into the polyacrylamide backbone by copolymerization with acrylamide. According to this idea, Langrana *et al.* produced a DNA-crosslinked polyacrylamide hydrogel [45]. Meanwhile, by incorporating toe-hold regions into the cross-linker DNA strands, the mechanical properties of the hydrogel could be regulated reversibly with chain exchanging reactions through introducing full-length complementary sequences of the linker DNA. These studies of cross-linking

polyacrylamide chains by DNA provide a versatile means to yield smart and responsive hydrogels. Since then, a series of functional DNA strands including aptamers, G-quadruplex, i-motifs, triplex nucleic acids, and catalytic nucleic acids have been used as cross-linkers to construct polyacrylamide–DNA hybrid hydrogels for bioanalysis and biomedical applications [46].

Supramolecular hydrogels based on conjugating DNA with biocompatible and biodegradable polymers: Beyond polyacrylamide, other hydrophilic polymers, especially those with biocompatibility and biodegradability, have been continuously explored to construct hybrid DNA supramolecular hydrogels. Typically, polyethylene glycols (PEG), as a well-known biocompatible material, pegylated hydrogels have attracted wide attention in biomedical fields such as drug delivery and tissue engineering due to their great biocompatibility. Based on this advantage, Kuzuya *et al.* coupled oligonucleotides to the ends of linear or branched PEGs by applying liquid-phase large-scale DNA synthesis technique (Fig. S4A in Supporting information). The obtained DNA–PEG conjugates at least on a gram scale were further used to construct intelligent and biodegradable hydrogels with G-quadruplexes [47] or i-motifs [48] as cross-linking points. On the other hand, the oligonucleotides with active end groups, such as amino, sulfhydryl, and azide, are readily available commercially. Therefore, DNA–polymer hybrids can be conveniently constructed based on the post-modification strategy, in which DNA strands are attached to the natural or synthetic polymer backbones through efficient coupling reactions. For example, carboxymethyl cellulose is an anionic, water-soluble derivative of cellulose, which could be functionalized with the amino-modified DNA through EDC–NHS chemistry (Fig. S4B in Supporting information). Willner's group used the resulting hybrid products to prepare redox-switchable hydrogels and photo-responsive hydrogels [49,50]. As another example, synthetic polypeptides with well-defined secondary structures have attracted extensive attention owing to their good biocompatibility and biodegradability. By a copper(I) catalyzed cycloaddition click reaction, azide-terminated DNA was conjugated to polypeptide backbones (Fig. S4C in Supporting information) [18]. The prepared DNA-grafted polypeptides were further applied to construct DNA–polypeptide hydrogels by hybridization with DNA linkers. These hybrid hydrogels not only can be easily decorated with functional groups [51], but also possess extraordinary healing properties and adjustable rheological properties [52]. Based on all of the unique performances, the DNA–polypeptide supramolecular hydrogels were subsequently explored for in-situ 3D multilayer bioprinting [53].

Hybrid hydrogels based on supramolecular interactions between DNA and polymers: DNA can form hybrid hydrogels with polymers through supramolecular interactions (such as electrostatic interactions, chelation interactions, hydrogen bonding) besides chemical coupling. Several kinds of polymers have been introduced into composite systems to construct DNA hybrid hydrogels without involving chemical cross-linking processes. Wang *et al.* [54] fabricated a fluorescent supramolecular hydrogel by mixing double-stranded DNA with positively charged conjugated polymers synthesized by *in-situ* polymerization (Fig. 6A), which was exploited to monitor drug loading and release by fluorescence technique. Later, they developed a multifunctional hydrogel self-assembled from salmon-sperm DNA and anionic polythiophene derivatives (PT–COOH) through the chelation of gadolinium ions (Gd^{3+}) *in situ*. Due to the efficient energy transfer from PT–COOH to Gd^{3+} ions and the production of reactive oxygen species (ROS) under light irradiation, the assembled hydrogels have the ability to image, encapsulate, and kill cells simultaneously [55]. Furthermore, DNA can also hybridize with RNA through hydrogen bonding. Based on this, exploiting DNA and RNA as building blocks obtained by stepwise dual-enzyme polymerization method of RCA and rolling circle transcription, respectively, Lee *et al.* constructed a DNA–RNA hybrid

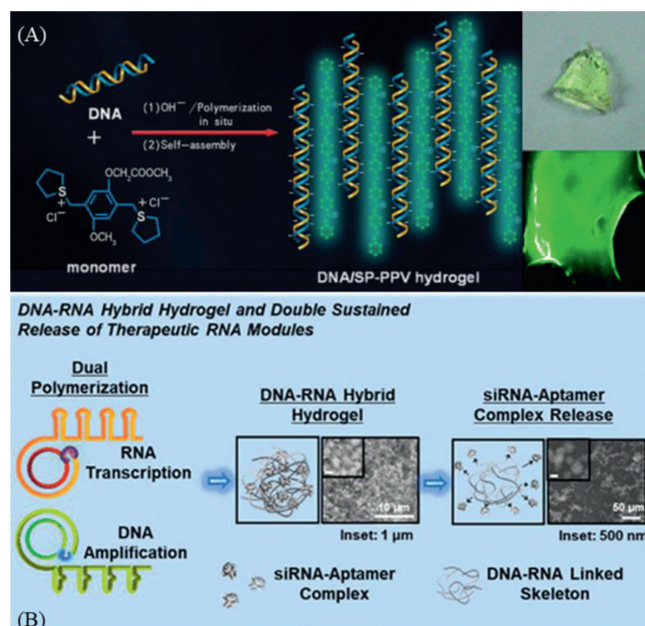


Fig. 6. (A) A fluorescent supramolecular hydrogel self-assembled from DNA and poly(phenylenevinylene). Copied with permission [54]. Copyright 2009, Royal Society of Chemistry. (B) A DNA–RNA hybrid hydrogel. Copied with permission [19]. Copyright 2020, American Chemical Society.

hydrogel in site upon repeated hybridization of functional DNA aptamers and multimeric short hairpin RNAs (Fig. 6B) [19].

DNA–protein hybrid hydrogels: Proteins as natural polymers possess many advantageous characteristics, including inherent biocompatibility, precisely defined chain lengths and amino acid sequences. Thereby, protein–DNA hybrid hydrogels can combine the unique features of each macromolecular building block. For example, a versatile hybrid material with tuneable stiffness, high biocompatibility and controllable enzyme-mediated degradation was prepared by cross-linking denatured human serum albumin (HSA) with multi-arm DNA, which was further used for specific loading and controlled release of active proteins (Fig. S5A in Supporting information) [20,56]. Furthermore, a DNA–protein hybrid hydrogel was fabricated by a programmable assembly approach using streptavidin as the cross-linker. The biocompatible hydrogel with flower-like porous structures could be served as a biomimetic physiologic matrix for highly efficient enzyme encapsulation and immobilization (Fig. S5B in Supporting information) [57].

2.2.2. DNA supramolecular hydrogels based on hybridization of DNA with functional nanomaterials

Using DNA as the supramolecular cross-linking agent, various nanomaterials with unique structures and excellent physicochemical properties have been integrated into the hydrogels to obtain supramolecular hybrid materials with ideal photoelectric features and stimuli-responsiveness. The nanomaterials used to construct hybrid DNA supramolecular hydrogels cover a wide variety of categories, ranging from carbon-based nanomaterials (*i.e.*, carbon nanotubes, graphene, carbon dots), and porous nanomaterials (*i.e.*, silica and metal-organic framework nanoparticles), to plasma (*i.e.*, gold nanoparticles), photoluminescent nanoparticles (*i.e.*, inorganic quantum dots and upconversion nanoparticles), and magnetic nanoparticles (*i.e.*, Fe_3O_4 nanoparticles). Either way, the incorporation of nano-scale materials into large-scale hydrogels can confer the composites' additional functions and performance with synergistic effects.

Supramolecular hydrogels based on hybridization of DNA with carbon-based nanomaterials: Carbon-based nanomaterials, such as

graphene oxide (GO) [58–60], single-walled carbon nanotubes (SWNTs) [21,61], and carbon quantum dots (CDs) [62–65] have been applied to the construction of hybrid DNA supramolecular hydrogels due to their structural diversity, high biocompatibility, unique electrical and optical properties. For instance, Shi *et al.* [58] fabricated a self-assembled multifunctional hydrogel with GO sheets and DNA by a one-step heating process (Fig. S6A in Supporting information). The hybrid hydrogel exhibits high mechanical strength, environmental stability, dye-adsorption capacity, and excellent self-healing functions. Furthermore, the DNA–GO hybrid hydrogel was developed to produce a hybrid electrode, which showed high sensitivity and selectivity for detecting mitochondrial DNA by an impedimetric approach [59]. Liu and Deng prepared a DNA–SWNT hybrid hydrogel with pH responsiveness and tunable strength (Fig. S6B in Supporting information) [21]. Instead of carbon nanotubes covalently binding to DNA strands *via* chemical reactions [66], the ssDNA chains in this study were helically wrapped to the surface of SWNT by (GT)₂₀ repeat units through π -stacking, leaving multiple sticky ends sticking out. The sticky domains can then hybridize with specially designed DNA strands, which contain cytosine-rich domains at their ends for subsequent formation of hydrogel networks. With the assistance of linear DNA units containing 12 bp long duplexes and two stretches of cytosine at each end, a hydrogel cross-linked by intermolecular i-motif structures could be formed after changing pH to 5.0, composing of long linear DNA assembly structures and SWNTs. In particular, this hybrid hydrogel could be switched between sol-gel states by controlling the pH value, and its mechanical property could also be adjusted by changing the ratio of linear DNA units to cross-linking SWNTs units. In addition, Hersam *et al.* presented an optothermally reversible DNA–SWNT supramolecular hybrid hydrogel by employing DNA base pairing as the cross-linking interaction [61]. However, graphene and carbon nanotubes have the disadvantage of easy aggregation and low solubility, and usually require oxidation to achieve surface functionalization and water-phase dispersion. CDs, as another kind of carbon-based nanomaterials, are water-soluble and have numerous inherent surface functional groups, especially with good biocompatibility, low cost, excellent fluorescence emission, and long-term photostability. Based on these performances, Das and co-workers constructed a DNA–CD hybrid hydrogel for targeted and sustained release of drug molecules [62]. By further coupling with protoporphyrin IX [63] and poly(vinylpyrrolidone) [64], respectively, they armored the hydrogels with worthy antimicrobial activity, self-healing and shape memory features.

Supramolecular hydrogels based on hybridization of DNA with porous nanomaterials: Highly porous nanomaterials have triggered immense enthusiasm as nano-carriers for controlled drug release owing to their good biocompatibility, intrinsic nano-cavities, and versatile surface characteristics [67,68]. Until now, mesoporous silica nanoparticles (SiNPs) [22,69], clays [70–74], and metal-organic framework nanoparticles (NMOFs) [75] have been integrated into DNA systems to construct DNA-based supramolecular nanocomposite hydrogels.

Typically, mesoporous SiNPs with controlled sizes have inherent biocompatibility, which is conducive to acting as reliable drug carriers to permeate cell membranes. Further on the basis of SiNPs coated with DNA cross-linked hydrogels (Fig. S7A in Supporting information), Ren and Qu *et al.* developed an intelligent bioreactor system whose function can be controlled by external stimuli [22]. Ding *et al.* constructed a series of nano-sensors for the detection of adenosine triphosphate [69]. Similarly, Luo and Wang *et al.* proposed magnetic mesoporous SiNPs capped with DNA cross-linked hydrogels for chemiluminescence sensing of adenosine [76]. Furthermore, Niemeyer *et al.* developed a class of nanocomposite hydrogels in which SiNPs were interwoven with carbon nanotubes by DNA polymerization. Importantly, the hybrid hydrogel materials

were exploited as substrates to control cellular adhesion, proliferation and transmigration [77].

Clays, owing to the high polarity of their charged surfaces, can be directly mixed with DNA as building blocks to construct nanocomposite hydrogels. The incorporation of nano-clays into hydrogels can significantly improve the performance of hybrid systems. Several supramolecular hydrogels composed of clays and DNA have been reported. In 2012, Takahara *et al.* successfully produced an imogolite–DNA hybrid hydrogel by mixing positively charged imogolite with DNA (Fig. S7B in Supporting information) [70]. The construction power of this hybrid hydrogel mainly comes from the strong affinity between phosphate groups outside the DNA double helix and protonated aluminol groups on the outer wall of the imogolite nanofibers. Similarly, Okamoto *et al.* prepared a series of DNA-based hybrid supramolecular hydrogels using synthetic hectorite [71] and natural allophane [72], respectively. Such nanocomposite hydrogels composed of DNA molecules and nano-clays, should be useful in designing novel forms of drug delivery systems with high dosages due to their large specific surface areas. Indeed, just as the nucleic acids enriched in clay hydrogels have anti-nuclease activities [78], the DNA in DNA/clay nanocomposite hydrogels can also be effectively protected by hybridization with clays [70], which is beneficial for biological and biomedical applications. Additionally, using synthetic Laponite clay as a dynamic cross-linking agent, Guney, Okay, and colleagues prepared two DNA/clay hybrid hydrogels, one temperature-sensitive and high-strength nanocomposite hydrogel containing poly(*N*-isopropylacrylamide) [73], and another self-healing and high-stretch nanocomposite hydrogel containing poly(*N,N*-dimethylacrylamide) [74].

NMOFs, as highly porous materials, provide a versatile platform for controlled drug delivery [79]. Typically, Willner's group reported doxorubicin-encapsulated NMOFs coated with stimuli-responsive DNA-based polyacrylamide hydrogels by using the “click chemistry” principle and HCR process. Moreover, the drug-loaded, ATP-responsive, hydrogel-coated NMOFs exhibit selective and effective cytotoxicity against targeted cancer cells [75].

Supramolecular hydrogels based on hybridization of DNA with inorganic functional nanoparticles: Inorganic nanoparticles with special optical, electrical and magnetic properties have attracted growing attention. Therefore, the combination of multifunctional nanoparticles and DNA hydrogels offers the possibility to construct versatile soft materials. On basis of the above considerations, the utility of diverse inorganic nanoparticles, such as inorganic quantum dots (QDs), magnetic nanoparticles (MNPs), gold nanoparticles (AuNPs), and upconverting nanoparticles (UCNPs), acting as building blocks to expand and enhance the performance of DNA hydrogels has been established.

Kelley *et al.* introduced DNA-templated QDs with tunable sizes and spectra into DNA hydrogel networks in one step (Fig. 7A) [80]. Unlike the CDs-integrated DNA hydrogels mentioned above through chemical conjugation [62–64], Kelley group's method does not require additional reagents and complex multi-step fabrication, thus ensuring the uniform structure of the final constructs. Especially, by utilizing DNA-guided interactions, they enabled the hybrid hydrogel with multi-functionality, which can act as excellent nano-carriers for cell-specific targeting and drug delivery in biological systems.

MNPs have caused wide concern due to their many merits (*e.g.*, high chemical stability, good aqueous dispersibility, and unique magnetic properties). Wang and Liu *et al.* integrated DNA-modified MNPs into the mainframe of DNA hydrogels to form DNA–MNP hybrid hydrogels (Fig. 7B) [23]. Interestingly, driven by a magnetic field, the hydrogels can be remotely controlled to form a variety of shapes, jump between two planes and even climb mountains.

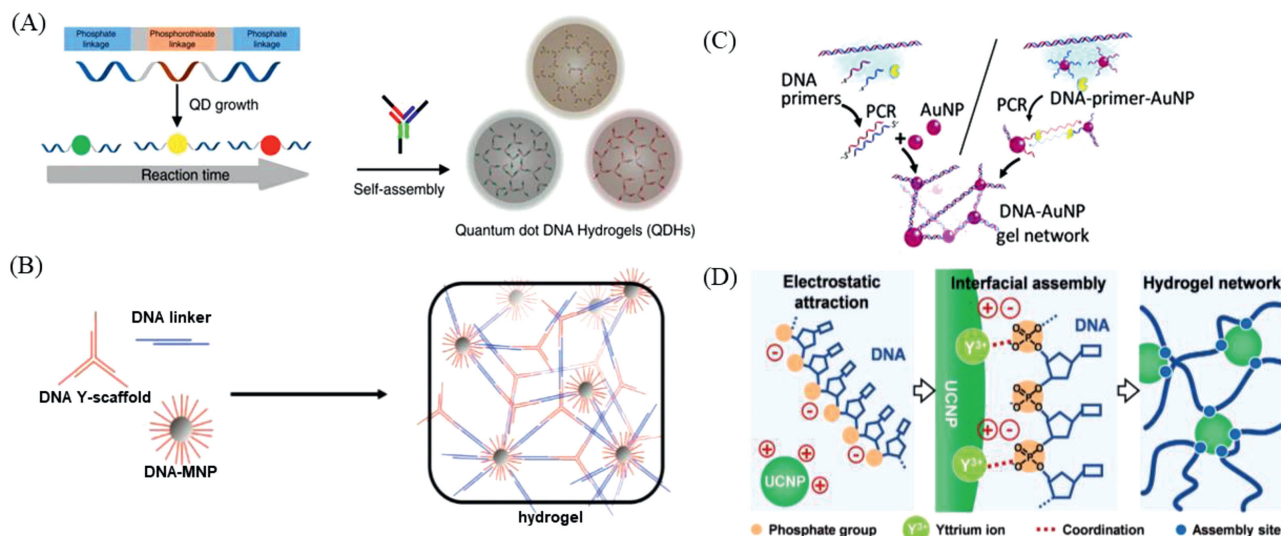


Fig. 7. (A) DNA-inorganic quantum dot hybrid hydrogels [80]. (B) DNA-magnetic nanoparticle hybrid hydrogels. Copied with permission [23]. Copyright 2017, American Chemical Society. (C) DNA-gold nanoparticle hybrid hydrogels. Copied with permission [81]. Copyright 2017, Royal Society of Chemistry. (D) DNA-upconverting nanoparticle hybrid hydrogels. Copied with permission [86]. Copyright 2022, Wiley-VCH.

AuNPs owing to their large surface area, unique optical activity, and high photothermal effect, have attracted extensive attention in biodetection and biondiagnostics. In 2017, Maruyama *et al.* [81] prepared a novel DNA-AuNP hybrid hydrogel, in which DNA strands were extended to controlled lengths by using PCR, and AuNPs were used as cross-linkers to construct supramolecular 3D networks through Au-S coordination bonds (Fig. 7C). Due to the inherent properties of DNA and AuNPs, this well-defined hybrid hydrogel exhibits gel-sol transitions under appropriate stimuli (heating, restriction enzymes, or laser irradiation). On the other hand, DNA nanohydrogels have aroused considerable interest in the fields of biosensing, cancer-targeted drug delivery and release-controlled therapeutics. By mixing DNA nanohydrogels containing disulfide bonds in DNA strands with AuNPs solution, Zhang *et al.* constructed DNA nanohydrogel-protected AuNPs (Gel@AuNPs) via ligand exchange reactions [82]. Significantly, the disulfide linkages in the building units are relatively unstable in the presence of reductants like glutathione, causing the collapse of the DNA nanohydrogels and further inducing the aggregation of AuNPs. On this basis, the proposed Gel@AuNPs were used as a sensitive profiling platform for small molecule reductants in rat brains. Furthermore, Roh *et al.* [83] fabricated oligonucleotide-adsorbed AuNPs by exploiting polyadenine (polyA) as an effective anchor block for preferentially binding to AuNP surface, unlike thiolated oligonucleotides using Au-S binding affinity. The DNA density on AuNP surface could be adjusted by simply changing the length of the polyA tail [84]. Then, the appended recognition blocks acting as sticky ends self-assembled with aptamer functionalized building units and DNA linkers to form multifunctional DNA nanohydrogels. Significantly, the aptamers and AuNPs in the system enabled the nanohydrogel platform to be cancer-specific targeting and photoinduced temperature responsive, respectively. Most recently, Liu and colleagues combined frame-guided assembly with C-HCRs to guide the growth of 3D DNA networks on the surface of AuNPs. The size of the prepared DNA nanohydrogels can be well controlled, and programmable targets such as fluorescence-labeled ssDNA can be loaded and released on demand [85].

UCNPs, as unique anti-Stokes optical materials, can convert low-energy excitation into higher-energy emission, and have been proved to be very useful tools for medical diagnostics and optical imaging. On this basis, Yang and Yao *et al.* prepared a DNA-UCNPs

hybrid supramolecular hydrogel within one second (called flash synthesis) by combining electrostatic attraction, interfacial assembly, and DNA chain cross-linking on the surface of UCNPs (Fig. 7D). The rationally designed DNA in the hybrid materials could accurately recognize and selectively isolate specific cells, while the UCNPs endowed the hydrogels with up-conversion effects to protect target cells from near-infrared (NIR) light-induced damage [86]. Furthermore, Yang, Su, Wang and colleagues developed a novel NIR-responsive and injectable DNA-inorganic hybrid hydrogel by electrostatic complexation of DNA and UCNP-Au hybrid NPs. The bio-inorganic hybrid hydrogels with good biocompatibility, high photothermal efficiency, and thermal stability can be accurately loaded around the tumors by injection. More notably, efficient tumor eradication without recurrence was successfully achieved through local management [87].

2.2.3. DNA supramolecular hydrogels based on other hybrids

Besides the aforementioned polymers and nanomaterials being exploited for the construction of hybrid DNA supramolecular hydrogels, other alternatives, such as organic small molecules, metal ions, metal ion-based complexes, and liposomes, can also cross-link DNA into 3D networks through synergies of multiple non-covalent driving forces, including intermolecular electrostatic interactions, hydrogen bonding, metal coordination, hydrophobic interactions, intercalation, and so on. For example, using tannic acid as a molecular glue to bind reversibly with DNA phosphodiester bonds, Lee *et al.* constructed a novel DNA hybrid supramolecular hydrogel with biodegradability, extensibility, tissue adhesiveness, and hemostatic ability (Fig. S8A in Supporting information) [88]. Similarly, based on the electrostatic interactions and hydrogen bonding between DNA and tetrakis (hydroxymethyl) phosphonium sulfate (THPS), a potential wound dressing hydrogel with self-healing, shear-thinning, and injectability was prepared via one-pot self-assembly (Fig. S8B in Supporting information) [24]. On the other hand, based on specific dynamic recognition between biomacromolecules and metal ions, Willner *et al.* prepared Ag⁺-cross-linked DNA hydrogels by the formation of cytosine-Ag⁺-cytosine complexes and dissociated the hydrogels into solution phase by eliminating Ag⁺ ions with cysteamine [89]. Moreover, driven synergistically by intercalation, coordination, π - π stacking and intermolecular hydrogen bonding interactions, Yu *et al.*

proposed a bioinspired hydrogel composed of DNA and Zn^{2+} -based complexes containing terpyridine and sugar groups linked by ethylenediamine units [90]. In other ways, Guo *et al.* cross-linked cholesterol-DNA-functionalized acrylamide chains with liposomes as non-covalent cross-linkers, and developed a stimuli-responsive hydrogel to controlled-release of small molecular payloads [91].

3. Stimuli responsiveness of DNA-based supramolecular hydrogels

Responsive DNA-based supramolecular hydrogels can be designed by incorporating responsive DNA sequences, polymers, or nanomaterials into the networks to achieve stimuli-responsive changes in mechanical properties, shapes, phases and others [92]. Especially, DNA hydrogels integrated with nucleic acid-based recognition moieties and active groups could be rationally designed at the molecular level, which can explore diverse stimuli for triggering responses in the development of smart functional biomaterials [93,94]. For example, DNA nanomotors based on i-motif sequence were integrated into DNA supramolecular hydrogels. The reversible transition of i-motif conformation changes the distance between the cross-linking points of DNA networks, while tunes the mechanical properties of the hydrogels [95]. In addition, ATP aptamer sequences were inserted into the backbone of DNA hydrogel networks. Based on the high permeability of hydrogels and the conformational transition of ATP aptamers, the mechanical strength of DNA hydrogels could be regulated in three phases [96]. Noticeably, Cangialosi *et al.* fabricated DNA-triggered shape-changing polyacrylamide/DNA hydrogels with high-degree swelling. Up to 100-fold hydrogel volume expansion was realized through HCR-mediated extension of cross-links. In the study, the macroscopic shape changes of centimeter-sized hydrogels can be controlled in complicated and programmable ways with specific DNA sequences [97]. Based on solid-phase synthesis and precise DNA self-assembly, thermo-responsive macromolecules (polypropylene oxide, PPO) were evenly inserted into the 3D DNA network. Especially, since PPO chains were uniformly dispersed and separated by the rigid DNA-assembled scaffolds, their self-collapsing process could be studied at the single-molecule level [98].

4. Biomedical applications of DNA-based supramolecular hydrogels

DNA hydrogels as 3D constructs hold great potential in biomedical applications owing to their tissue-like mechanics, self-healing, biocompatibility, and biodegradability [99].

4.1. Cell culture

DNA hydrogels are one of the best candidates for cell culture due to their high-water content, biocompatibility, intrinsic biological functions, and gelatinous character like natural ECMs. For example, single cells were enveloped in microwells using the permeable DNA supramolecular hydrogels, which can be further triggered by specific restriction enzymes for release (Fig. 8A) [100]. Importantly, due to the permeability of DNA 3D networks, nutrients and waste can pass through the hydrogel cover, keeping the cells enveloped alive. This research shows a universal platform to position and manipulate single cells, and provides an ideal material for 3D living cell culture. Furthermore, as a proof of concept, tissue-like complex structures were fabricated from cell-laden DNA hydrogel bricks [101]. Based on a stepwise building strategy, multiple cell types were first encapsulated in DNA supramolecular hydrogel bricks and then a “brick-to-wall” technology was applied to fabricate 3D tissue-like structures. On the other hand, Liu's group de-

signed and prepared a three-armed chemically branched DNA unit based on solid-phase synthesis technology by using a commercially available branched monomer. By mixing these building blocks with self-dimer DNA linkers, supramolecular DNA hydrogels with shear thinning and designable responsiveness could be easily constructed in a few seconds. Particularly, due to their rapid, spontaneous gelation behavior and tunable modulus, the excellently biocompatible and highly permeable DNA hydrogels could also be further applied in 3D cell culture [102].

4.2. Cell capture

A responsive DNA hydrogel capable of encapsulating and releasing circulating tumor cells (CTCs) was prepared by the aptamer-triggered clamped hybridization chain reaction (atcHCR) [103,104]. In the system, a DNA strand with aptamer-initiator biblocks is used to bind to the epithelial cell adhesion molecule (EpCAM) on the tumor cell surface, and then triggers the atcHCR to form DNA hydrogels to recognize CTCs (Fig. 8B). The DNA hydrogel networks can capture CTCs *in situ* with minimal cell damage. Subsequent chemical stimuli with ATP enable release CTCs for cell culture and live-cell analysis. Yang's groups constructed a DNA hydrogel for fishing stem cells through the intertwining and self-assembly of ultra-long DNA chains. In the study, two ultra-long DNA chains were synthesized by a double-RCA method. One of the DNA chains included aptamer sequences to ensure specific anchoring with bone marrow mesenchymal stem cells (BMSCs). The hybridization of the two ultra-long DNA chains cross-linked the cell-anchored DNA strands to form a 3D network. The resulting DNA hydrogel could be used for capture, encapsulation, and enzyme-triggered release of BMSCs [105]. Furthermore, polyvalent multimodule with multifunctional roles generated by RCA were integrated into two ultra-long DNA chains. One DNA contained programmed death-1 aptamers for specific capture and *in situ* incubation of T lymphocytes (T-cells); another DNA contained CpG ODNs to activate antigen-presenting cells and enhance immunotherapy. The mutually complementary sequences of these two DNA chains facilitated DNA networks formation and T-cells encapsulation, while also providing restriction enzyme cleavage sites for responsive release of T-cells and immune adjuvants [106].

4.3. Tissue engineering

Due to the great potential as substrates for delivering and supporting living cells, DNA supramolecular hydrogels have been employed as delivering materials for mesenchymal stem cells (MSCs) to treat severe osteoarthritis (OA) [107]. The research results indicate that the DNA supramolecular hydrogel could significantly improve the vitality of bone marrow MSCs owing to the effective protection against the shear forces during injection, and could promote repair and regeneration of cartilage under the high friction conditions of OA. Furthermore, the DNA supramolecular hydrogel with well design could effectively carry homologous neural stem cells (NSCs) to repair completely transected spinal cord defects in Sprague-Dawley rats (Fig. 8C). Under the support and protection of the highly permeable DNA hydrogels, a continuous renascent neural network was formed at the lesion site *via* the sufficient migration, proliferation and differentiation of both implanted and endogenous NSCs [108]. Therefore, it can be predicted that DNA supramolecular hydrogels with adjustable mechanical strength, excellent thixotropic properties, good biocompatibility and degradability, would be a promising carrying system of stem cells for clinical therapy.

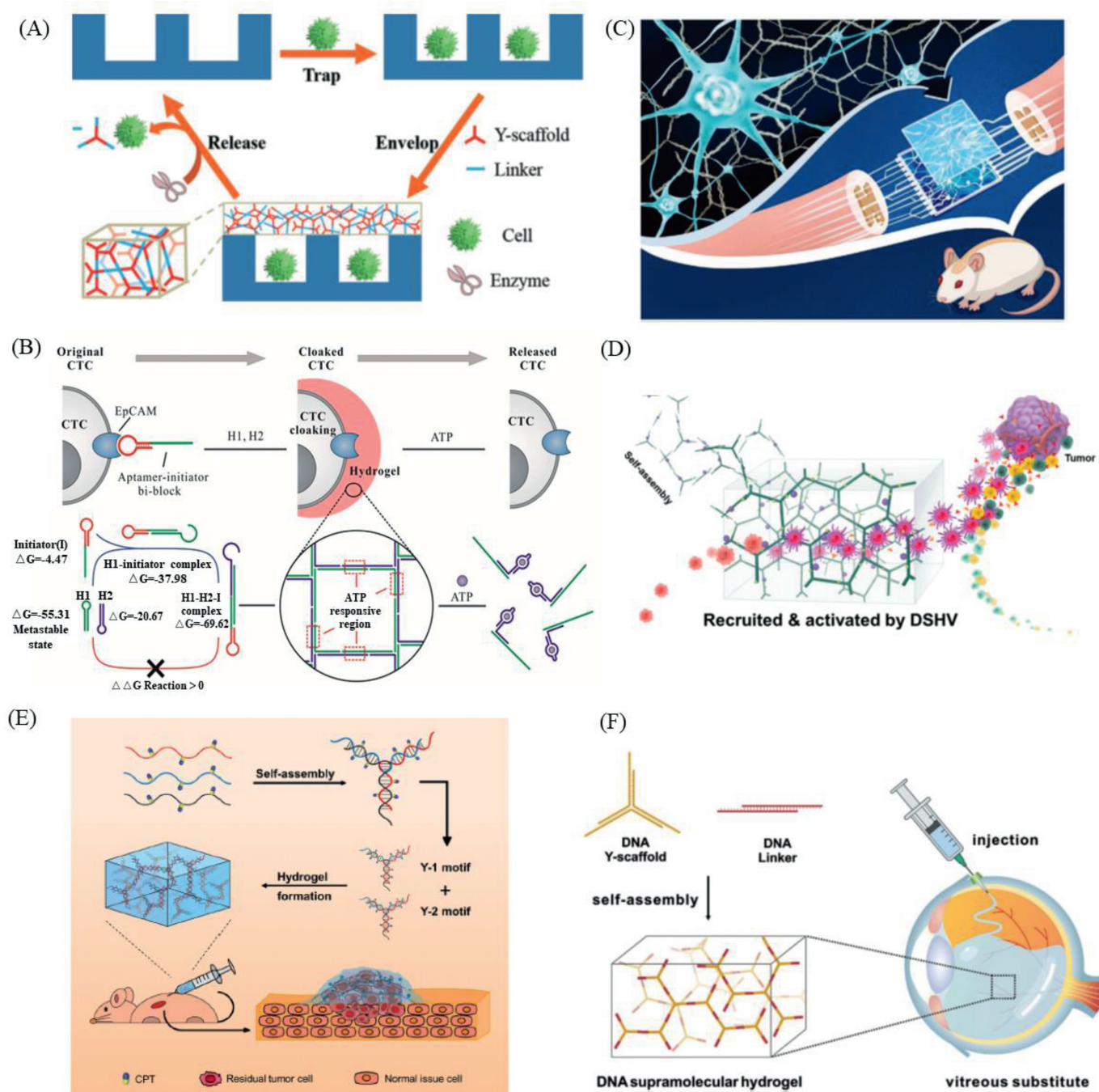


Fig. 8. (A) A DNA hydrogel cover that can be triggered to envelop and release single cells. Copied with permission [100]. Copyright 2013, Wiley-VCH. (B) A DNA hydrogel with aptamer-toehold-based recognition, cloaking, and decloaking of circulating tumor cells. Copied with permission [104]. Copyright 2017, American Chemical Society. (C) A DNA hydrogel promotes neurogenesis and functional recovery. Copied with permission [108]. Copyright 2021, Wiley-VCH. (D) A designable immune therapeutical vaccine system based on DNA hydrogels. Copied with permission [110]. Copyright 2018, American Chemical Society. (E) An injectable drug-conjugated DNA hydrogel for local chemotherapy. Copied with permission [112]. Copyright 2020, American Chemical Society. (F) A DNA hydrogel as a biocompatible artificial vitreous substitute. Copied with permission [114]. Copyright 2022, Wiley-VCH.

4.4. Immunotherapy

DNA containing unmethylated cytosine-phosphate-guanine (CpG) dinucleotides can activate innate immune responses through the Toll-like receptor, TLR9 [109]. Nishikawa *et al.* developed an injectable, immunostimulatory DNA hydrogel through spontaneous self-assembly using ODNs containing CpG motifs. Moreover, ovalbumin can be incorporated into the supramolecular networks and further be efficiently delivered to induce antigen-specific immune

responses [26]. Subsequently, a designable immunotherapeutic vaccine system was constructed based on DNA supramolecular hydrogels with the CpG motifs suspending on dsDNA networks as single strands (Fig. 8D) [110]. The study presents that the injectable DNA supramolecular hydrogel vaccines (DSHV) system can effectively recruit and activate antigen-presenting cells through a high local concentration of CpG. Meanwhile, peptide (P1) as a model antigen, containing a B cell epitope, a T-helper cell epitope, and seven lysine residues, was also loaded and evenly dispersed

in the DNA hydrogel network. Through the synergetic effect of the antigens and CpG adjuvants, the DSHV system showed robust immune responses and antitumor effects.

4.5. Drug delivery

The abundant anionic phosphate groups and high surface area in the DNA hydrogel networks facilitate the loading of cationic drugs through high-affinity electrostatic interactions. For example, Obuobi *et al.* reported a facile strategy to encapsulate cationic antimicrobial peptides (AMPs) with DNA hydrogels for wound therapy based on the electrostatic binding of AMPs to the polyanionic backbone of DNA [111]. The hydrogel dressings can serve as drug depots for sustained and controlled release of antimicrobials to prevent wound infections. Zhang *et al.* developed an injectable drug-conjugated DNA supramolecular hydrogel for local delivery of chemotherapy drugs to prevent cancer recurrence (Fig. 8E) [112]. In the system, camptothecin (CPT) as a model drug molecule was grafted onto the skeleton of phosphorothioate oligonucleotides. The obtained CPT-grafted DNA strands were further hierarchically assembled into supramolecular hydrogels through sequence-directed hybridization. The resulting CPT-containing DNA hydrogels showed good injectable, persistent and responsive properties, which can be used to construct drug delivery systems (DDSs) for local drug administration. This DNA hydrogel-based DDS can significantly inhibit cancer cell regeneration and effectively prevent tumor recurrence with the sustained release of CPT. In addition, drugs could also be incorporated into the interspace of DNA hydrogels and subsequently released under appropriate stimuli [113].

4.6. Others

Moreover, DNA supramolecular hydrogels are suitable as potential substitutes for natural vitreous because they are injectable, biocompatible, colorless, transparent, and have a density similar to human vitreous (Fig. 8F) [114]. In other fields, the polypeptide-DNA supramolecular hydrogels owing to their excellent self-healing and high mechanical strengths were used as bio-inks for rapid *in situ* multilayer 3D bioprinting. Particularly, due to the biocompatibility and permeability of hybrid supramolecular hydrogels, the designed structures containing living cells with normal functions could be constructed by alternative deposition of two complementary bio-inks at programmed locations [53].

5. Conclusions and perspectives

DNA-based supramolecular hydrogels represent an important and promising class of biomaterials possessing intrinsic biocompatibility and tunable physicochemical properties. Wherein the bonding forces between their components are mainly noncovalent, including hydrogen bonding, metal-ligand bonding, electrostatic interactions, π - π stacking, hydrophobic interactions, and host-guest interactions. Among them, pure DNA hydrogels assembled completely from DNA building blocks have the advantages of simple preparation, superior programmability and good biocompatibility, while DNA hybrid supramolecular hydrogels show multifunctional features due to the synergistic interactions between DNA and other components, which further promotes their corresponding applications. Although DNA-based supramolecular hydrogels are relatively stable owing to the unique complementary base pairing of DNA. The building blocks of supramolecular hydrogels maintain an equilibrium between assembly and disassembly within the systems due to the dynamic interactions. Therefore, the mechanical strength of DNA supramolecular hydrogels is generally lower than that of chemical hydrogels, which may limit their applications in tissue engineering when high modulus is required. Interestingly,

a supramolecular double-network hydrogel comprised of DNA and cucurbit[8]uril interpenetrating networks was fabricated based on DNA hybridization and host-guest recognition [115]. Unlike the double-network hydrogels with entirely chemical cross-links, the supramolecular system was constructed through precise and specific recognition by a “one-pot” mixing approach. The physically interpenetrating behavior provides increased mechanical properties and thermal stability as well as excellent stretchability and ductility for the supramolecular hydrogel. Moreover, the biodegradable double-network hydrogels have the properties of shear thinning and thixotropy, showing great potential as injectable soft materials.

However, some limitations and challenges still exist. First, the accumulated errors cannot be avoided during DNA self-assembly at high concentrations, which may affect the precise control of cross-linking position and pore size in pure DNA hydrogel networks by the persistence length of the DNA duplex. Therefore, in order to obtain hydrogels with more controllable structures, the structural rigidity and melting temperature of the building blocks, affinity and flexibility of the linkers and spatial availability of cross-linking points should be considered comprehensively when designing DNA hydrogels. Second, the immune system *in vivo* is highly sensitive to foreign DNA and nanomaterials, which may lead to the passive elimination of DNA hydrogels. It is necessary to completely remove or minimize harmful reaction residues and allergenic materials to reduce unnecessary immune reactions in the biomedical applications of DNA supramolecular hydrogels. Very recently, Liu, Dong, and colleagues reported a biostable L-DNA hydrogel with low inflammatory response for long-term applications [116], which provides a novel DNA-based platform with excellent biocompatibility for the biomedical field.

Overall, DNA-based supramolecular hydrogels have broad development prospects and have a significant impact on the development of biomaterials and biomedicine.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors acknowledge the financial support from the Shanghai Municipal Science and Technology Major Project (No. 2021SHZDZX0100), the National Natural Science Foundation of China (Nos. 22109117, 22272119), the Science and Technology Committee of Shanghai Municipality (No. 2022-4-ZD-03), Shanghai Pilot Program for Basic Research, China Postdoctoral Science Foundation (No. 2021M692418), and the Fundamental Research Funds for the Central Universities.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ccl.2023.108627.

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