Chinese Chemical Letters 35 (2024) 109558

Contents lists available at ScienceDirect

Chinese Chemical Letters

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

Research advancement of DNA-based intelligent hydrogels: Manufacture, characteristics, application of disease diagnosis and treatment

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ARTICLE INFO

Article history:
Received 29 September 2023
Revised 29 December 2023
Accepted 24 January 2024
Available online 26 January 2024

Keywords:
DNA-based hydrogel
Intelligent hydrogel
Manufacture
Characteristics
Disease diagnosis and treatment

ABSTRACT

DNA-based hydrogels are exceptional materials for biological applications because of their numerous advantages such as biodegradability, biocompatibility, hydrophilicity, super absorbency, porosity, and swelling. Among these advantages, the ability of DNA-based hydrogels to respond to specific physical and chemical triggers and undergo reversible phase transitions has garnered significant attention in the fields of disease diagnosis (biosensors) and treatment (drug delivery). This article focuses on the recent advancements in the research of DNA-based hydrogels and discusses the different types of these hydrogels, the synthetic methods, their unique properties, and their applications in biosensors and drug delivery. The types of DNA hydrogels are categorized based on their building blocks, and the process of synthesis as well as the unique characteristics of DNA-based hydrogels are described. Then, DNA-based responsive hydrogels utilized as intelligent materials for the development of biosensors are reviewed. Furthermore, this article also presents the current status of DNA-based responsive hydrogels in drug delivery for cancer treatment, wound healing, and other therapeutic applications. Ultimately, this paper discusses the current challenges in expanding the practical application of DNA-based hydrogels.

1. Introduction

Hydrogels, constructed from hydrophilic polymers through cross-linking, are hydrated porous materials with controllable pore sizes. Hydrogels are widely applied as new functional materials in various fields because of their high water expansion, environment friendly, and certain mechanical stability [1–4]. Recently, responsive hydrogels have become one of the research hotspots due to their controllable and reversible conversion from gel to sol under external stimuli [5–11]. This unique property makes hydrogel an intelligent material and further expands its applications. Commonly, selecting or synthesizing a responsive polymer backbone or cross-linking units is a key aspect of the procedure for preparing responsive hydrogels. Deoxyribonucleic acid (DNA), with multiple structural primitives and functional information, is commonly used as a base unit to precisely prepare two- and three-dimensional macroscopic products [12–17]. The programmability and predictability of DNA make it suitable for use as functional building blocks in the synthesis of responsive DNA hydrogels [18–23].

To date, two types of DNA-based hydrogels have been reported in the literature: pure DNA hydrogels [24–26] and heterogeneous DNA hydrogels [27–29]. Pure DNA hydrogels are synthesized through the self-assembly of DNA strands. Consequently, pure DNA hydrogel is an arbitrary three-dimensional polymer framework with the chemical characteristics of DNA and the physical attributes of a hydrogel. Pure DNA hydrogels can be synthesized by different nucleic acid reactions, such as the self-assembly of branching DNA [30–32], enzymatic ligation of branching DNA [33], and cross-linking of large DNA strands [34]. The heterogeneous DNA hydrogels, on the other hand, are prepared by attaching the short DNA sequences or pre-designed DNA strands [35] that form hairpins to hydrophilic polymer scaffolds. The hybridization reactions between DNA strands facilitate the formation of hydrogels [36]. Due to the benefits of hydrophilic polymers and DNA, heterogeneous DNA-based hydrogels possess the chemical stability, hydrophilicity, and accessibility of the polymer to enable DNA

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https://doi.org/10.1016/j.cclet.2024.109558
1001-8417/

programming capabilities. Responsive DNA-based hydrogels can change their physicochemical properties, such as cross-link density, mechanical stability, and optical properties, in response to external stimuli. These changes can further lead to detectable signals for readout [37–39] or facilitate the release of cargo for drug delivery [40–42]. For biosensor applications, functional DNA fragments play a crucial role in the formation and functioning of DNA-based hydrogels. They can induce a reversible, switchable sol-gel transition or release of payload (already encapsulated in DNA hydrogels) upon recognition of the analyte. This process generates a readout signal for detecting disease biomarkers such as protein, microRNA, viruses [43]. Moreover, DNA-based hydrogel also can used as a highly biocompatible matrix for immobilizing various functional motifs such as DNAzymes [44] and aptamers [45]. This integration grants the hydrogel with molecular recognition capabilities, high mechanical strength, specificity, and a wide range of target options. For drug delivery applications, responsive DNA hydrogels have optimal mechanical properties that enable them to retain drug molecules within a cross-linked porous network. This is due to their adaptable network structure and responsive properties. In the presence of external stimulation, the gel converts into a solution, accompanied by the release of the drug. Thus, DNA-based complementary pairing can be effectively designed to prolong drug release.

In this article, we discussed the techniques for creating DNA-based hydrogels and highlighted their applications in disease diagnosis and treatment including constructing various biosensors and drug carriers. In contrast to the reported reviews on DNA-based responsive hydrogels, our specific focus is on the mechanism of DNA-based hydrogels for the construction of different biosensors and drug delivery. We also present the current challenges in the development of DNA-based responsive hydrogels.

2. Synthesis of intelligent DNA-based hydrogel

2.1. Intelligent hydrogel based on pure DNA

Pure DNA hydrogels, also known as "all-DNA" hydrogels, are produced by polymerizing DNA through different biochemical reactions such as enzymatic polymerization, specific binding of DNA motifs self-hybridization. Generally, there are two methods to prepare pure DNA hydrogels: (1) Assembling hydrogels from branching DNA building blocks or DNA monomers; and (2) DNA extension.

The first pure DNA hydrogels reported by Luo and colleagues, in which three kinds of branched DNAs including T-DNA, X-DNA, and Y-DNA monomers were designed for the formation of the hydrogels by hybridization with T4 DNA ligase aided under mild reaction conditions [33]. Their properties such as shape, pore size, and mechanical stability can be adjustable by varying the types and concentrations of the three DNA monomers. In addition, a pure plasmid-based hydrogel that can be produced in large quantities at low cost through fermentation was prepared by Nöll and colleagues [46] in 2017 as following two steps: (1) The plasmid DNA was used as a basic unit to construct the linear DNA building blocks through enzymatic degradation, (2) the covalent bonds between the building blocks were formed under the action of ligase.

To overcome the drawbacks of enzymatic ligation, Liu *et al.* designed three-armed DNA nanostructures (Y-units) for the self-assembly formation of inter-molecular i-motif structures, rapidly achieving pH-responsive DNA hydrogels [47]. The hydrogels can be simply transformed to a non-gel state within 1 min using changes in environmental pH. The stability of the above pure DNA hydrogels is unsatisfactory under physiological conditions, limiting their application *in vivo*. Thus, Liu *et al.* further prepared a pure DNA hydrogel by appropriate treatment of the "sticky ends" of the DNA building blocks (Y-strand and linker) [31]. Moreover, a highly entwined DNA hydrogel has been prepared using linear double strands DNA (dsDNA) as monomers that can self-assemble by sticky ends, and their rheological properties were equivalent to those of pure DNA hydrogels achieved from more complex branched components [48]. However, all the above DNA random self-assembly methods suffer from the drawbacks of the inevitable accumulated errors at high concentrations. Therefore, template-based DNA-ordered assembly technologies such as hybridization chain reaction (HCR), rolling circle amplification (RCA), and multiple chain amplification (MCA) were mainly utilized to synthesize pure DNA hydrogels. Walther's group prepared a pure DNA hydrogel based on the RCA technique (Fig. 1A) [49]. Firstly, two small cyclic oligonucleotides are designed as templates (templates A and templates B). After RCA, two complementary "multi-block" ssDNA of several thousand nucleotides in length are generated as hydrogel precursors (precursors A and precursors B). When mixed and annealed the two precursors, the complementary cross-linked structural domains between the two precursors are hybridized to form a DNA hydrogel by supramolecular bilayers.

A similar method was reported by Yang's group which used circular DNA as a template to form two long DNA strands by a double-RCA strategy, and these two long DNA strands intertwined and self-assembled to form physical cross-linked DNA hydrogels (Fig. 1B) [50]. In addition, other nucleic acid amplification technology was mostly used in conjunction with RCA to prepare pure DNA hydrogel. Luo *et al.* designed a pure DNA hydrogel to functionalize the tiles using its mechanical and biological properties, wherein the superhelical plasmid DNA (double-stranded circular DNA) was converted into single-stranded circular (sscirc) templates which are amplified by RCA and MCA (Fig. 1C) [51]. The above process produced a hydrogel of physically entangled and hydrogen-

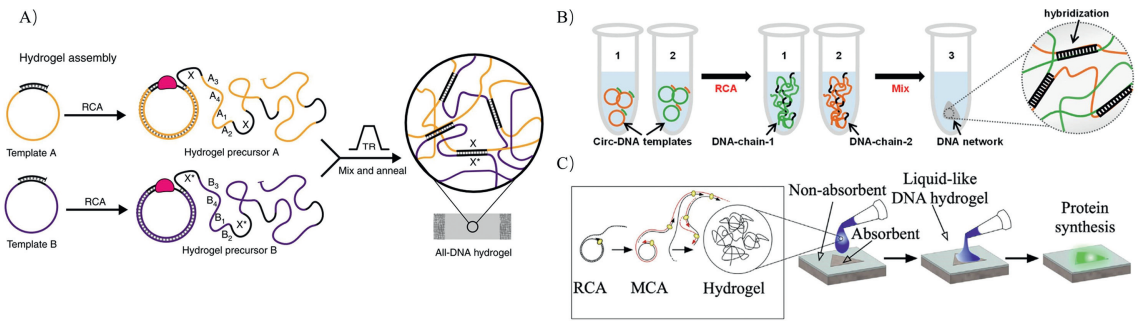

Fig. 1. Synthesis of template-based DNA hydrogels. (A) DNA hydrogels are prepared by self-assembling two DNA strands. Copied with permission [49]. Copyright 2019, American Chemical Society. (B) The synthetic ultra-long DNA strands of RCA form three-dimensional DNA networks through intertwining and self-assembly. Copied with permission [50]. Copyright 2020, American Chemical Society. (C) The preparation of DNA hydrogel by combining RCA and MCA. Copied with permission [51]. Copyright 2021, Elsevier Ltd.

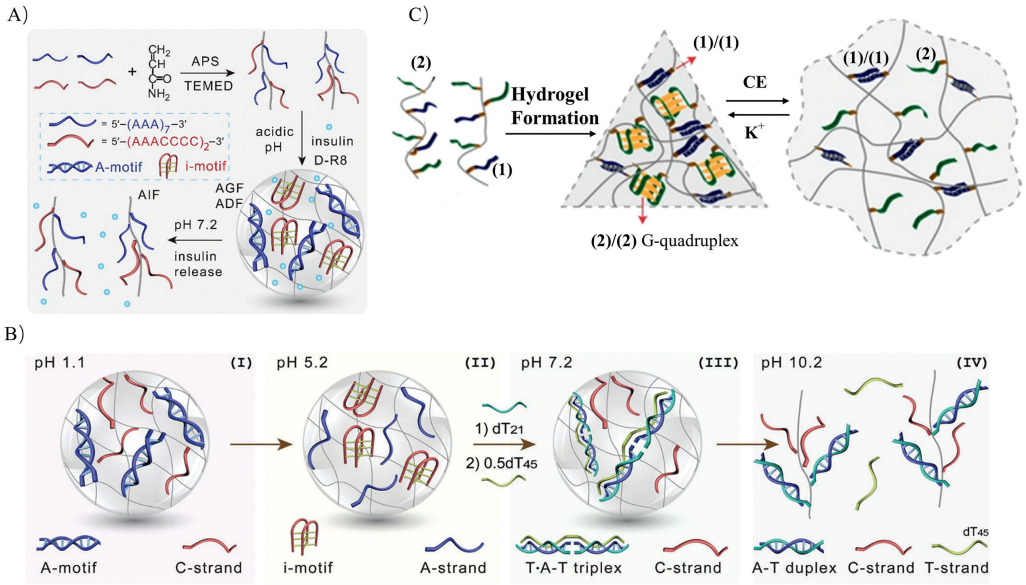

Fig. 2. (A) Development of heterogeneous DNA hydrogels with resistance to acid and responsiveness to physiological pH. Copied with permission [56]. Copyright 2022, American Chemical Society. (B) Schematic representation of cascade DNA hydrogels with different pH values. (I) DNA hydrogels were stabilized by parallel A-motif double-stranded under highly acidic conditions. (II) DNA hydrogels are stabilized by i-motif tetramer stabilized gels under weakly acidic conditions. (III)Under physiological conditions, DNA hydrogels are stabilized by the addition of the helper strands dT21 and dT45 through the T-A-T triple structure. (IV) DNA hydrogel disintegration to liquid. Copied with permission [57]. Copyright 2023, Wiley-VCH GmbH. (C) synthesis of heterogeneous DNA hydrogels using the duplex and G-quadruplex as cross-linkers with shape memory. Copied with permission[64]. Copyright 2015, American Chemical Society.

bonded cross-linked long single- and double-stranded DNA. The prepared hydrogel has a nonlinear stretch response, however, in air that exhibits liquid-like properties. This property is an important factor in their ability to cover and eventually adsorb to solid surfaces, a strategy that opens up new avenues for biosensors, protein patterning, detection, and diagnostics.

Although pure DNA hydrogels possess numerous distinct characteristics, DNA exhibits inherent constraints, such as an exceedingly adverse overall charge, restricted durability, and an absence of functional clusters for subsequent alterations, which restrict the applications of pure DNA hydrogel.

2.2. Synthesis of heterogeneous DNA hydrogels

To overcome the drawbacks of pure DNA hydrogel, heterogeneous DNA hydrogels were explored by functionalizing the polymer backbone with DNA that can be used as cross-linker in hydrogel preparation. The heterogeneous DNA hydrogels incorporate the programmable and intelligent properties of DNA with the advantages of the polymers including chemical stability, flexibility, and accessibility, breaking through the limitations of pure DNA hydrogel. In 1996, Nagahara *et al.* first produced heterogeneous DNA hydrogels by grafting short DNA sequences onto poly(acrylamide) chains [36], then, the gelation of polymer chains induced by direct hybridization between two short DNA strands modified to the polymer strand or hybridizing soluble DNA sequences with two DNA strands attached to the polymer backbone. After that, numerous and diverse DNA-functionalized polymers have been explored [52–55]. Subsequently, smart-responsive hydrogels obtained by rational design of DNA sequences have also been reported. pH-driven A-motif, i-motif, and T-A-T triple helix structures, K^+ triggered G-quadruplex, and specific ligand-DNA aptamer complexes were applied as DNA cross-linking motifs to prepare stimulus-responsive hydrogel. For example, Ying *et al.* rationally designed adenine-rich (poly A) and cytosine-rich (poly C) DNA strands to form copolymers with acrylamide monomers by free radical polymerization, and acid-resistant and physiological pH-responsive hydrogels by cross-linking parallel A-motif double-stranded (pH 1.2–3.0) and tetradentate i-motif (pH 4.0–6.0) strands (Fig. 2A) [56]. Willner *et al.* synthesized cascade DNA hydrogels adapted to different pH values based on the A-motif, i-motif, and T-A-T triple helix structures (Fig. 2B) [57]. They formed copolymers with polyacrylamide as the main chain, poly C-sequence, and poly A as the side chain, and introduced thymidine-rich (poly T) into the system under physiological conditions (pH 7.2). The stability of the DNA hydrogel can be maintained at pH 1.1, pH 5, and pH 7.2 by the triple helix structure of A-primer, i-primer, and T-A-T, whereas at pH 10.2, the deprotonation of thymidine leads to the dissociation of the hydrogel. This design principle of multiple cascade pH-responsive DNA hydrogels may trigger its application in drug delivery and multiple pH sensing sensors. Based on the same principle, the K^+ ions responsive acrylamide hydrogels were synthesized by forming the K^+-G-quadruplex-cross-linker [58,59], which dissociates upon the addition of 18 crown-6 ether that can capture the K^+ ions form K^+-G-quadruplex-cross-linker (Fig. 2C). The "ON"-"OFF" G-tetramer cross-linked hydrogels were used to achieve the catalytic function and the convertible catalytic function. In addition, aptamer-contained cross-linked hydrogels are prepared by hybridizing the aptamer with its partially complementary DNA, where the aptamer and its complement fragment were anchored onto the polymer respectively [60]. Hu *et al.* copolymerized acrylic acid-modified DNA strand A (S1) and DNA strand B (S2) with acrylamide monomers to form DNA-polyacrylamide polymers P-S1 and P-S2. The aptamer of alpha-fetoprotein was designed as the connecting strand to hybridize with S1 and S2, thus forming an aptamer-responsive DNA hydrogel (Fig. 3A) [61]. Similarly, Kang *et al.* used the substrate sequence of ractopamine aptamer as a cross-linking agent, which was partially complementary to the DNA-polyacrylamide polymer to form target-responsive DNA hydrogels by cross-linking through base complementary pairing (Fig. 3B) [62]. Meanwhile, different polymer backbones can also be introduced, for example, Lin's group constructed Aflatoxin B1 (AFB1) target-responsive double-crosslinked hydrogels by using linear hyaluronic acid grafted single-stranded DNA complexes as the backbone, and AFB1 aptamer and polyethyleneimine as the cross-linking agent [63]. Due to the above unique properties, the

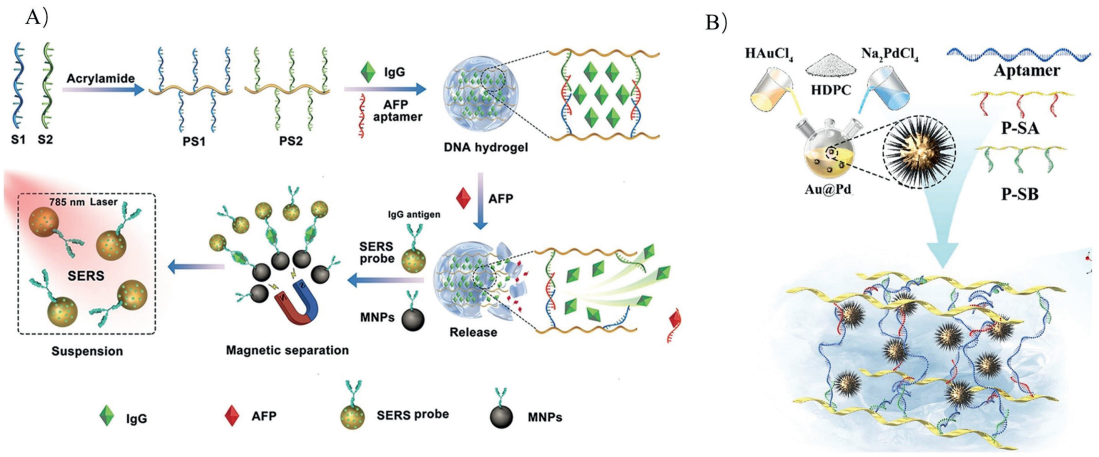

Fig. 3. (A) Synthesis of heterogeneous DNA hydrogels by using α-Fetoprotein-aptamer as cross-linker. Copied with permission [61]. Copyright 2020, American Chemical Society. (B) Synthesis of ractopamine-targeted responsive DNA hydrogels. Copied with permission [62]. Copyright 2023, Elsevier B.V.

heterogeneous DNA hydrogels have great potential applications in multiple fields.

3. Properties of DNA-based hydrogels

Whether it is pure DNA hydrogel or hybrid DNA hydrogel, DNA-based hydrogels have the unique properties of DNA, such as self-assembly, programmability, stimuli-response, and the physicochemical properties of the hydrogel, such as expansion, porosity, hydrophilicity, sol-gel transition. The practical applications of DNA hydrogels in biosensors and drug delivery are intricately linked to their exceptional physical and chemical properties.

3.1. Stimuli-response and self-assembly

The programmability of DNA sequences allows DNA to independently design specific oligonucleotide sequences, such as aptamers [22,65–67], DNAzymes [68–71], C-rich sequences [72–74], and G-rich sequences [75–77], as required, conferring stimuli-responsive properties to DNA-based hydrogels. DNA also has inherent base complementarity reactions, and by rationally designing DNA strands with complementary sequences, it is possible to prepare DNA hydrogels by self-assembly. of DNA strands with complementary sequences, hydrogels of DNA can be prepared by self-assembly. Therefore, in the preparation of DNA hydrogels, DNA fragments can be used not only as cross-linking units but also as stimuli-responsive elements, thus realizing the controlled formation of gels. For example, Willner *et al.* prepared a novel hybridized DNA hydrogel using glucosamine-borate crosslinked polyacrylamide chains as the backbone and potassium ion-stabilized G-quadruplex bridges synergistically crosslinked, in which the closure and dissociation of stimulus-responsive units can confer shape memory and self-healing functions to the gel for a stimulus-responsive material for switchable and controlled drug release [78].

3.2. Swelling

The preparation method of hydrogel exhibited that the hydrogel skeleton contains a large number of hydrophilic groups. Therefore, When the hydrogel is placed in an aqueous environment, its volume can expand up to 3–6 times the original volume. This property is beneficial for the release of drugs from the cargo [65,79–81]. It should be noted that both the ionic strength of the solutions and the density of cross-linkers influenced the swelling capability of DNA hydrogel [28,82–84]. Thus, the optimal ionic strength and density of cross-linkers need to be optimized in the experiment.

3.3. Adjustable porous structure

DNA hydrogels are three-dimensional porous structures, and porosity is an important property of hydrogels, which can be adjusted by controlling the length and density of the cross-linking agent, as well as by gel synthesis [19,49,85]. Because of the different pore size requirements in various applications, pore size needs to be considered when designing applications. For example, Yang *et al.* constructed a DNA hydrogel that can specifically and non-destructively isolate lipid bilayer vesicle exosomes (EXOs) secreted by cells with diameters of 30–150 nm, and its three-dimensional porous structure can reach the microscale [86]; Guo *et al.* developed a pore structure consisting of larger pores (≈30–60 μm) and smaller pores (≈2–5 μm), a hierarchical porous structure responsive DNA gel composed of larger pores (≈30–60 μm) and smaller pores (≈2–5 μm), which has higher mechanical strength and can withstand 90% strain compression without rupture compared to the uniform porous structure hydrogel with pore sizes of 6–10 μm [87].

3.4. Gel-sol transition

The gel-sol transition is a key property of DNA hydrogels. This macroscopic phase transition process makes DNA hydrogels special materials for encapsulating signaling molecules, which can be released for rapid readout when used as a targeted assay, expanding their applications in disease diagnosis and treatments. Many external triggers affect the assembly of DNA hydrogels and initiate the phase transition, such as temperature [88], light [89–91], enzymes [87], pH [92], magnetic field [93], and aptamer-target [94] interactions. Typical examples are i-motif structures, T-A-T triple helices, and C-G-C^+ triple helices, which show a reversible response to pH changes; in addition, aptamer DNA hydrogels also competitively bind to crosslinker aptamer chains in the presence of the target substance, leading to the gradual disintegration of the hydrogel structure. This property has been widely used for the controlled release of signaling molecules or drugs.

4. DNA-based hydrogels applications

4.1. Applications of DNA-based hydrogels in disease diagnosis

Early and accurate diagnosis of diseases is beneficial for their treatment and recovery of health. Currently, early diagnosis of diseases still poses challenges. Due to the high biocompatibility and the ability to respond to the stimulates, a series of disease diag-

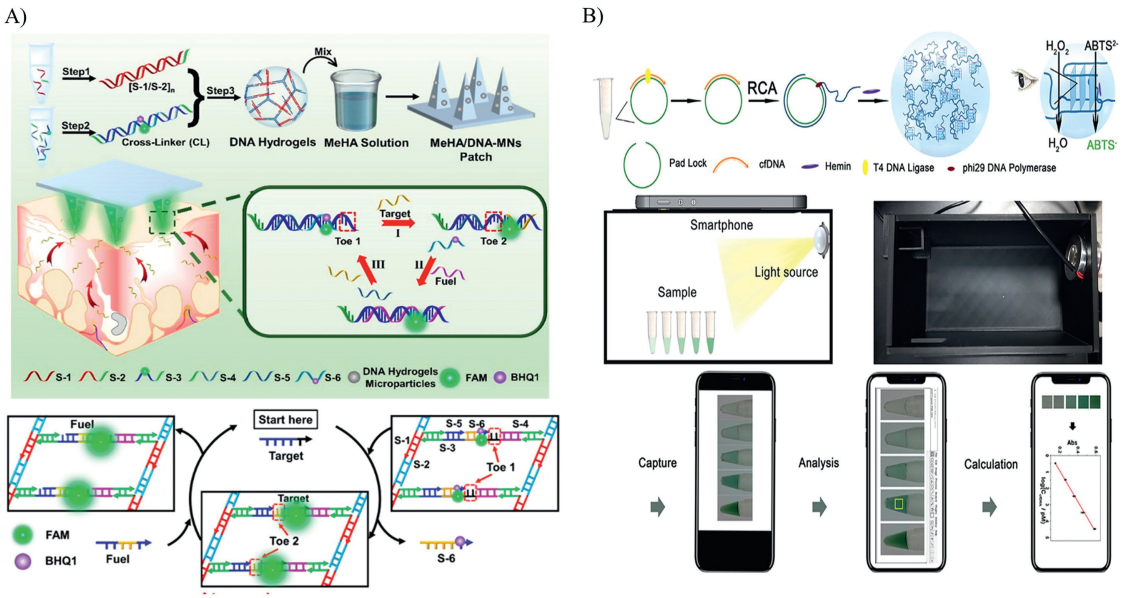

Fig. 4. (A) Structure and strand substitution process of DNA-based fluorescent hydrogels and their sensitivity to microRNA sensing. Copied with permission [96]. Copyright 2022, American Chemical Society. (B) DNA-based hydrogel combined with a portable visual smartphone for cfDNA detection platform. Copied with permission [97]. Copyright 2022, American Chemical Society.

nosis methods based on hydrogels have been reported. In these methods, hydrogels can be used as soft substrates to immobilize probes, special materials to enrich signal molecules, barriers to prevent molecular diffusion, and carriers to adsorb signal molecules.

4.1.1. DNA hydrogels as a soft matrix for immobilizing DNA probe

For disease diagnosis, DNA hydrogels are commonly designed as matrices to immobilize DNA probes that can respond to biomarkers such as aptamer, DNA segment, and DNAzyme. When the target binds to the aptamer or DNA segment, the physical and chemical properties of hydrogel change, to output the detection signal related to the concentration of the target. For example, Chen *et al.* constructed a DNA hydrogel for the specific detection of the tumor marker epithelial cell adhesion molecule(EpCAM) using EpCAM aptamer as a cross-linker and polyacrylamide as a backbone [95]. The thermal reversibility of the polyacrylamide DNA hydrogel was utilized to connect it to one end of the capillary to form a DNA hydrogel membrane. When the target analyte binds to the aptamer, the DNA hydrogel membrane will undergo different degrees of disruption. The degradation of the gel increases with the increase of the concentration of EpCAM, resulting in the increased permeability of the DNA hydrogel membrane. By using the self-driven effect of capillary, the different permeability of DNA hydrogel membrane will result in the sample solution being more specific for the tumor marker EpCAM. Ding *et al.* crosslinked recognition DNA probes with DNA strands grafted onto linear polyacrylamides to construct hybridized DNA hydrogels, which were immobilized on silanized ITO for the detection of lung cancer-specific microRNA-21 [39]. When the recognition probe hybridizes with the target microRNA-21, the hydrogel dissolves, producing a loss of ferrocene labeling and a decrease in current, a change that can be demonstrated by cyclic voltammetry and differential pulse voltammetry. Since the expression level of microRNAs in interstitial skin fluid is low and the sample volume is limited, therefore, Dong *et al.* constructed a microneedle patch consisting of a smart DNA hydrogel for rapid sampling and sensitive detection of microRNA-155 in interstitial skin fluid (ISF) (Fig. 4A) [96]. The DNA hydrogel was prepared from six single strands (S-1 to S-6) and encapsulated in methacrylic acid hyaluronic acid, which conferred strong hydrophilicity and provided sufficient ISF samples for miRNA-155 analysis. The target microRNA-155 triggered the substitution of the S-6 strand to restore the fluorescence signal, and the addition of the fuel probe further led to the dramatic increase of fluorescence signal, which was sensitive for the detection of low-abundance miRNA-155 as low as 241.56 pmol/L. Zhang *et al.* developed a hydrogel platform consisting of multiple G-quadruplex DNA enzymes for visible and portable detection of the tumor marker cell-free DNA (cfDNA) (Fig. 4B) [97]. Ferroheme chloride was embedded in G-quadruplex deoxyribonucleases conferring horseradish peroxidase-like catalytic activity. When the target cfDNA triggers to form G-quadruplex DNAzyme-contained hydrogel, it can catalyze the conversion of 2,2′-azidobis(3-ethylbenzothiazoline-6-sulfonic acid) ($ABTS^{2-}$) to the green oxidation product $ABTS^{-}$ with accompanying color change, enabling visual detection of cfDNA. In addition, the concentration value of cfDNA can be converted into an optical signal by the catalytic ability of the DNAzyme hydrogel, which can be recorded and quantified using a smartphone platform.

4.1.2. DNA hydrogels as special materials to enrich signal molecules

The hydrophilic network structure of the DNA hydrogel facilitates the wrapping of the signaling molecules, while the specific recognition function of the DNA hydrogel allows the hydrogel to undergo a phase transition that can release the signaling probe. Based on these mechanics, numerous biosensors for biomarker detection were developed. For example, Liao *et al.* have designed a DNA-based acrylamide hydrogel microencapsulated sensor that utilizes competitive accounting substitutions to detect microRNA using fluorescent quantum dots (QDs) as the readout signal (Fig. 5A) [98]. The DNA hydrogel-coated microcapsules were synthesized using $CaCO_3$ particles loaded with QDs as the core template, and the bridging DNA-acrylamide hydrogel with sandwich-type structure as a cage-like shell with a microRNA response function. The target microRNA-141 specifically binds to the bridging DNA in the microcapsule shell by a competitive sequence substitution reaction, leading to the DNA hydrogel microcapsules unlocking and releasing fluorescent QDs. It was also possible to combine controlled release systems for hydrogels with various readout strategies, such as chemiluminescent (ECL), Lin *et al.* constructed a highly sensitive target-responsive ECL

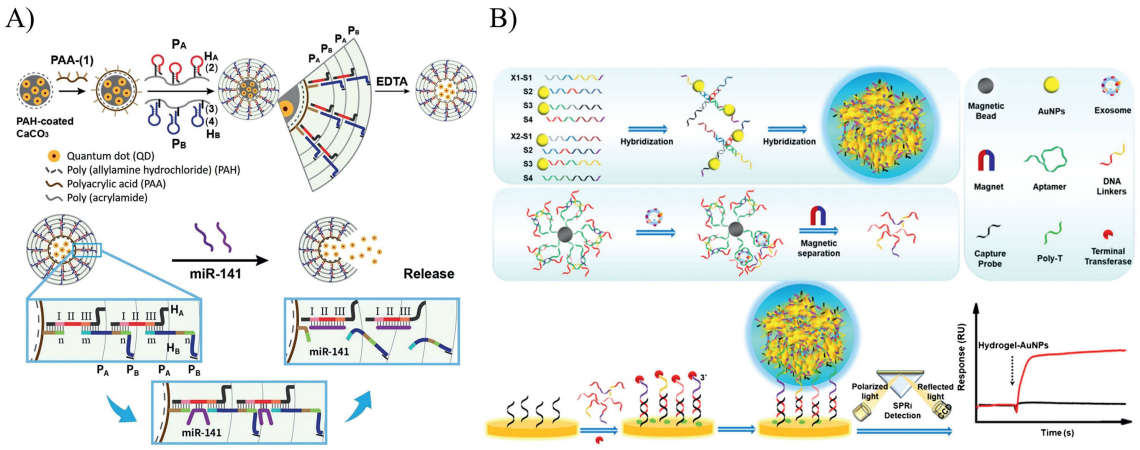

Fig. 5. (A) The process of synthesizing DNA hydrogel microcapsules and the mechanization of unlocking the hydrogel microcapsules for the release of the QDs. Copied with permission [98]. Copyright 2021, Royal Society of Chemistry. (B) The process of constructing a DNA hydrogel-based Surface plasmon resonance(SPR)biosensor for the determination of EXOs [100]. Copied with permission. Copyright 2020, Springer-Verlag GmbH Austria, part of Springer Nature.

DNA hydrogel-based biosensor for the detection of Dam methyltransferase (MTase) [99]. The hydrogel was prepared by using hyaluronic acid sodium salt as polymer monomer, two amine-modified dsDNA with methylation site as cross-linker, a little polyethyleneimine (PEI) as ECL signal enhancer. Moreover, a large amount of $(Ru(bpy)^{+}$-doped SiO_2 nanoparticles were wrapped in the prepared DNA hydrogel for ECL signal readout. In the presence of target Dam MTase, the methylation site in dsDNA can be recognized by Dam MTase and the dsDNA can be specifically decomposed by DpnI. As a result, the dsDNA cross-linker in the hydrogel was degraded, resulting in the release of signal probes from the hydrogel's strong ECL signal readout.

DNA hydrogels, as three-dimensional network-structured materials, are often considered carriers for encapsulating and releasing functional molecules, but the dense structure and mechanical stiffness of DNA hydrogels induce confinement effects, which play a great role in retarding and hindering the diffusion of substances. For example, Ding's group developed a SPR biosensor based on the gold nanoparticles (AuNPs)-encapsulated hydrogel supramolecular sphere for specific detection of prostate cancer cell-derived EXOs [100]. As shown in Fig. 5B, the two X hydrogel units (X1 and X2) were synthesized *via* hybridizing between DNA chains. The network hydrogel was formed by using four overhang arms DNA as cross-linkers to connect the two X hydrogel units by hybridizing. The target-DNA probe containing target-specific aptamer was immobilized on the surface of magnetic bead. when the target is bound to a DNA probe, triple DNA linkers will be released and then purified by magnetic separation. The obtained DNA linkers can hybridize with the capture probe modified on the electrode surface. Then, the enzyme TDT was dropped onto the electrode and catalyzed the formation of poly-A tails at the exposed terminals of DNA linkers. Subsequently, the synthesized hydrogel-AuNPs was added and fixed by hybridizing with the poly-A tails for signal amplification. Finally, the SPR signal can be read out due to the existence of poly-A tails and hydrogel-AuNP complex by using SPR instruments, which was proportional to the concentration of the target EXOs.

4.1.3. DNA-based hydrogels as a physical barrier to hinder interactions

Due to the mechanical properties of DNA hydrogels, they can also act as a physical barrier to hinder interactions between substances. Once the probe recognizes the target, the physical barriers are lifted because of hydrogel degradation, achieving the output of the detection signal. For example, Li *et al.* developed a novel surface-enhanced Raman scattering (SERS) sensor array based on a DNA-zyme functionalized hydrogel that responds to miRNA targets, allowing simultaneous detection of multiple tumor-associated miRNAs in a sample [101]. When microRNA is lacking, the two parts (EA and EB) of each multicomponent nucleases (MNA-zymes) form an inactive DNA-zyme structure and the responsive DNA hydrogel is "OFF". Therefore, SERS tags cannot cross the hydrogel barriers and be captured by the detection region, thereby weakening the Raman signal. Once target microRNAs were introduced, MNA-zymes resume activity, DNA hydrogel substrate strands are cleaved, SERS tags are captured by the detection region, and the responsive DNA hydrogel is in the "ON" state, showing a strong Raman signal. Zhang *et al.* designed a DNA hydrogel as a barrier for the coupling of graphitic carbon nitride (g-C_3N_4) with CdS QDs, thereby developing a label-free PEC biosensor for the detection of miRNA-21 (Fig. 6A) [102]. CdS quantum dots can be efficiently attached to the photoelectrically responsive composite material g-C_3N_4 to form heterojunction structures through click reactions that obtain enhanced photocurrent signals. Based on this, dibenzocyclooctene (DBCO) moiety and g-C_3N_4-modified ITO electrodes (DBCO-C_3N_4/ITO) were prepared, and then, the coupling between g-C_3N_4 and CdS quantum dots could be blocked by dropping a prepared DNA hydrogel onto the above-modified electrodes to obtain a very low photocurrent signal. The RCA reaction occurs in the presence of the target microRNA-21, and the generated long ssDNA activates Cas12a, which cleaves the crosslinked ssDNA in the DNA hydrogel, thus dissolving the DNA hydrogel. As a result, photoactive CdS@g-C_3N_4 heterojunctions were formed due to the proximity of CdS-N_3 to DBCO-C_3N_4, and high photocurrents were obtained for microRNA-21 detection.

4.1.4. DNA-based hydrogel as carriers to adsorb signal molecules

Due to the functional groups of DNA itself and its negatively charged properties, DNA hydrogels can adsorb some signal molecules through chemical adsorption or electrostatic adsorption, thus developing biosensors for the detection of disease markers. For example, Feng *et al.* prepared a C-Ag(I)-C-based hydrogel by the specific interaction between cytosine and Ag(I) [103]. When target miRNA-21 was introduced, the C-Ag(I)-C hydrogel was firmly immobilized on the electrode surface by the formation of a three-way junction which can load a large number of silver ions, generating different peak currents of oxidation by square wave voltammetry. The peak currents increased with the increment of the concentration of miRNA-21, leading to a sensitive and specific detection of miRNA-21. In 2020, Zhuo *et al.* constructed

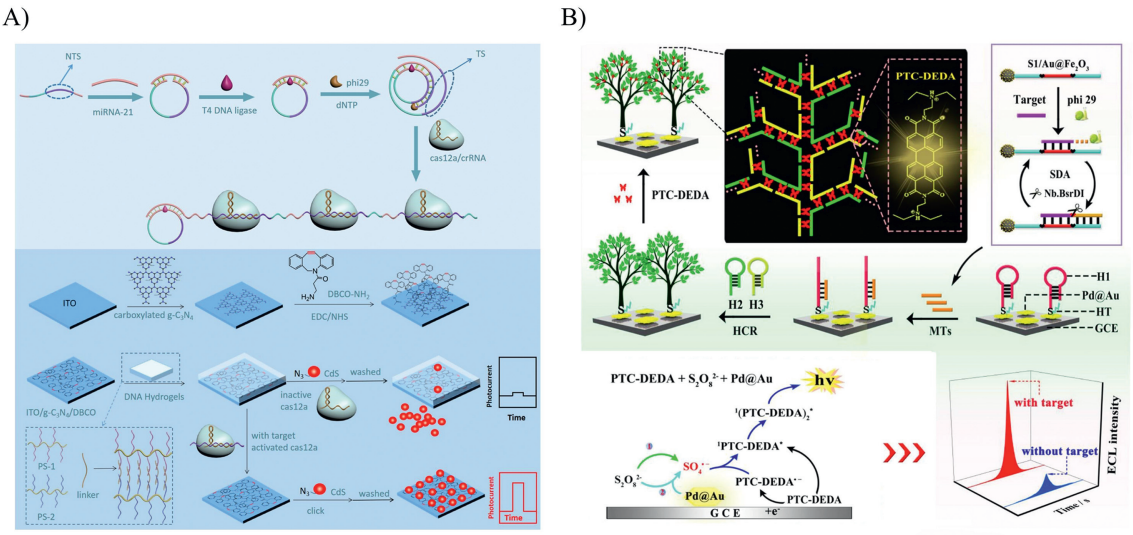

Fig. 6. (A) Construction of a novel label-free PEC biosensor based on a Cas12a system-responsive DNA hydrogel. Copied with permission [102]. Copyright 2022, American Chemical Society. (B) Schematic diagram of target-trigger DNA hydrogel-based ECL biosensor for sensitive assay of microRNA let-7a. Copied with permission [104]. Copyright.2020, American Chemical Society.

DNA hydrogel-based ECL biosensors using amphiphilic perylene derivative (PTC-DEDA) as DNA intercalators which also acted as ECL emitter for the sensitive quantification of microRNA let-7a (Fig. 6B) [104]. when target microRNA let-7a was introduced onto the modified electrode surface, the microRNA let-7a triggered nonlinear HCR, resulting *in situ* formication of DNA hydrogel with numerous dendritic DNA structures. The formed hydrogel possessed a large loading capacity to entrap massive PTC-DEDA due to electrostatic adsorption between dendritic DNA and PTC-DEDA, achieving a strong ECL signal. Due to the excellent loading ability of DNA hydrogel and the strong ECL signal of PTC-DEDA, the DNA hydrogel-based biosensor exhibited high stability and sensitivity for the detection of microRNA let-7a with a wide linear range (10 fmol/L to 10 nmol/L) and a low detection limit (1.49 fmol/L).

4.2. DNA-based intelligent hydrogels for the disease treatment

Drug delivery vehicles involve spatially and temporally storing and releasing drug molecules in a controlled manner, which plays an important role in disease treatment. Heretofore, various materials including inorganic nanoparticles, polymers, proteins, and liposomes have been used as drug delivery platforms. However, these materials suffer from difficult biodegradation and non-specific coalescence. DNA hydrogels, on the other hand, have excellent biocompatibility, degradability, and biostability, and the DNA in the hydrogels is uniquely recognized and highly programmable, with properties that are widely used in cancer, wound healing, and many other therapies.

4.2.1. DNA-based intelligent hydrogels for delivery of drugs for cancer therapies

Cancer is a serious public health problem all over the world, and drug delivery systems play a huge role in cancer treatment. To overcome the non-specificity and inefficacy of chemotherapeutic drugs, Chen's group designed a dual-targeting-responsive and multivalent aptamer-modified DNA hydrogel as drug carriers to synergistically deliver the chemotherapeutic doxorubicin (DOX) and the aptamer nucleic acid drugs into the target cells for treating HER2-positive breast cancer [105]. However, DNA-based hydrogels for drug delivery take a long time to treat cancer, which will limit application in real cancer therapy. Thus, researchers combined DNA hydrogels with other therapeutic methods to construct an efficient synergistic treatment system. Guo's group established an efficient photothermal-chemical synergistic cancer treatment platform based on DNA hydrogels, in which MXene nanosheets (MX) acted as a photothermal agent and the anti-cancer drug DOX as a chemotherapeutic agent [106]. Under near-infrared light irradiation, MX can convert light into heat energy, which induces a reversible gel-sol transition of the DNA hydrogel and releases DOX for effective localized cancer treatment. Li *et al.* constructed an amplified photodynamic therapy synergistic hunger treatment platform based on DNA hydrogel (Fig. 7A) [107]. A cancer-targeted "domino" cascade reactor was constructed for synergistic starvation therapy and amplifies photodynamic therapy by the load with hypoxia-inducible factor 1α (HIF-1α) and photosensitizer chlorin e6 (Ce6). Firstly, a DNA hydrogel was prepared by RCA from a circular DNA template containing complementary sequences of AS1411 aptamer and antisense DNA of HIF-1α. In the hydrogel, a cancer-targeting "domino" cascade reactor can be formed by assembling hemin that can be conjugated with G-quadruplex of AS1411 and GOx for starvation therapy and amplified photodynamic therapy (PDT). The GOx can catalyze the glucose to form gluconic acid and hydrogen peroxide which can be further catalyzed by the hemin to produce oxygen. Then, Ce6 converts the generated oxygen to mono-linear oxygen ($^1O_2$) with cytotoxicity, thus inhibiting tumor growth. Because the inherent drug resistance and biological barriers of tumor tissues can weaken the cancer treatment effect, Wen *et al.* designed a novel nano-photothermal DNA hydrogel to enhance tumor therapy and validated its safety and efficacy in solid tumors in mice [108]. Briefly, the black phosphorus quantum dots (BPQDs) with negative charge adsorbed to positively charged PEI to form photothermal composite materials PEI@BPQD (Fig. 7B). Then, nano-photothermal DNA hydrogel (PEI@BPQDs-DNA hydrogel) can synthesize by X-shaped DNA molecules, which can regulate their sizes under the effect of electrostatic and hydrogen bonding. The positively charged PEI@BPQDs-DNA hydrogel promoted phagocytosis and exhibited excellent cell permeability, and the BPQDs can increase the sensitivity of tumor cells to photothermal therapy and photodynamic therapy. Cellular and mouse model experiments showed that PEI@BPQDs-DNA hydrogel can deliver anticancer drugs DOX "on-demand".

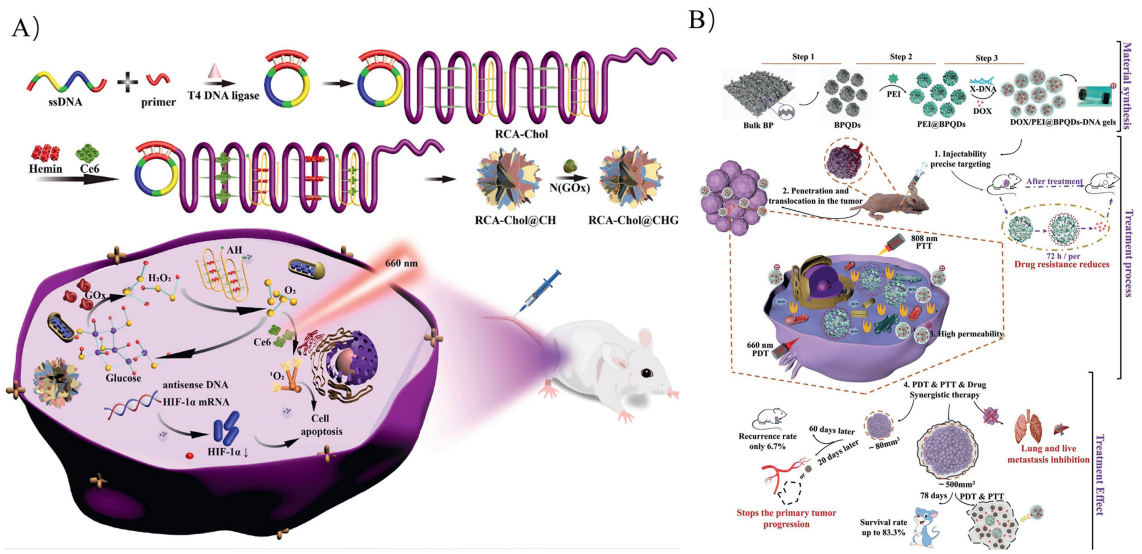

Fig. 7. (A) Construction of cancer-targeted "domino" cascade reactors and the regulatory mechanism of synergistic starvation therapy by photoconductive therapy. Copied with permission [107]. Copyright 2023, Elsevier Masson SAS. (B) Schematic of the synthesis route of injectable PEI@BPQDs-DNA gels and efficient drug delivery to tumor cells *via* PDT and PTT. Copied with permission [108]. Copyright 2021, Royal Society of Chemistry.

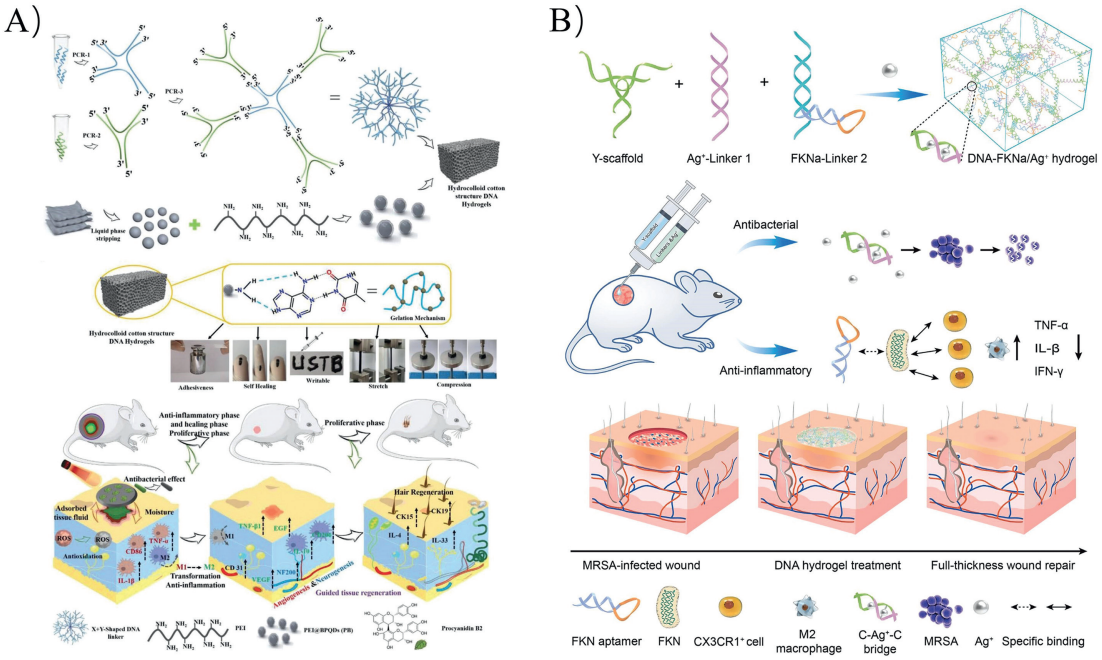

Fig. 8. (A) Preparation of a multifunctional DNA hydrogel, demonstration of its properties, and description of its mechanism for diabetic wound healing. Copied with permission [109]. Copyright 2021, Wiley-VCH GmbH. (B) Synthesis of DNA-FKNa/Ag^+hydrogel and schematic diagram of its antimicrobial and anti-inflammatory capacity verified in animal experiments. Copied with permission [111]. Copyright 2023, Elsevier B.V.

4.2.2. DNA-based intelligent hydrogel for delivery of drugs for wound healing

Wound infections have now become a major healthcare burden globally. DNA hydrogels with biosafety, wettability, and breathability have been considered ideal dressings for wound healing. Recently, Wen *et al.* designed a multifunctional DNA-based hydrogel dressing for diabetic wound infection and tissue regeneration [109]. The DNA-based hydrogels were prepared by dynamically cross-linking X + Y shaped DNA strand structures through the principle of base complementary pairing, where the cationic polymer PEI functionalized-BPQDs (PEI@ BPQDs) and procyanidin B2 were enwrapped to form active DNA hydrogels (Fig. 8A). The loaded procyanidin B2 endowed the DNA hydrogel with free radical scavenging and antioxidant properties, the BPQDs endowed it with a photothermal effect that appeared to have different therapeutic effects at different treatment periods, and the PEI enhanced the hydrogel's ability to absorb tissue fluids. Importantly, the prepared DNA hydrogel dressing can promote tissue regeneration by activating adaptive immunity by recruiting myeloid cells. Zheng *et al.* developed interleukin-33 (IL-33)-encapsulated DNA hydrogel as wound dressings to accelerate wound closure [110]. The IL-33 was encapsulated into the DNA hydrogel to obtain IL-33 functionalized hydrogel, which possesses biodegradability, biocompatibility, antioxidant, and anti-inflammatory properties. The encapsulated IL33 can sufficiently induce groups 2 innate lymphocytes and regulatory T cells in the localized accumulation in diabetic wound areas

and accelerate wound closure. To prevent methicillin-resistant Staphylococcus aureus (MRSA) infection, Li *et al*. designed an injectable DNA hydrogel with antibacterial and anti-inflammatory properties as wound healing materials based on DNA self-assembly [111]. The numerous DNA strands including recombinant human membrane-bound chemokine (FKN) aptamer, Ag(I)-conjugate, and Y-shaped DNA subunit self-assembled through base complementation, leading to the formation of DNA-FKNa/ Ag(I) hydrogel in the presence of Ag^+ (Fig. 8B). The FKN aptamer specifically binds to chemokine FKN and then recruits $CX3CR1^+$ cells, which leads to an increase in the concentration of M2 macrophages and release of anti-inflammatory factors. The C-Ag(I)-C bridge formed can delay the release of Ag(I) to give the hydrogel long-lasting antibacterial activity. Meanwhile, the DNA hydrogel facilitates skin tissue regeneration and wound healing in the MRSA-infected rat model, which provides the possibility of clinical translation.

4.2.3. DNA-based intelligent hydrogels for delivery drugs for other therapies

In addition, by utilizing the cytidine (C)-rich sequences functionalized-DNA hydrogels, the pH-responsive DNA hydrogels can also be used to transport drugs. Zhu *et al*. prepared an intelligent pH-responsive nano-DNA hydrogel to solve the problem that naked messenger RNA) is easily degraded and cannot be manipulated for protein expression through cell membranes [112]. An "X"-shaped DNA scaffold with pH-responsive i-substituents was crosslinked to form a DNA hydrogel to carry messenger RNA. Only when the i-motif was formed in the acidic microenvironment of lysosomes (pH 4.5–5.0), did the DNA hydrogel dissolve and release messenger RNA to encode proteins to overcome infection and mutation risk problems in transgenics. Ying *et al*. developed an acid-resistant and physiological pH-responsive DNA hydrogel by utilizing the structure of A-motif formed by adenine (A)-rich sequences under extreme acidity and i-motif formed by cytidine (C)-rich sequences under weak acidity, which was used as a novel carrier for insulin encapsulation and oral delivery [56]. The resulting DNA hydrogel acts as an insulin-protecting agent at acidic pH (1.2–6.0) in the stomach due to the formation of A-motif and i-motif, whereas at physiological pH, the A-motif and i-motif short cross-linker dissociate into a long single strand that releases insulin in the small intestine for the treatment of diabetes mellitus.

5. Conclusions and outlooks

Intelligent hydrogels, which can undergo controllable changes in their physical and chemical properties in response to specific external stimuli or triggers, have the potential to be utilized in various fields, particularly in disease diagnosis and treatment. DNA has emerged as an ideal responsive component for constructing intelligent hydrogels. A more comprehensive overview of the synthesis methods for DNA and DNA-derived hydrogels, along with their distinctive properties, is provided in this article. The intelligent DNA-based hydrogels, which can respond to specific external stimuli, provide a promising material for constructing biosensors and are considered ideal bio-scaffolds for drug delivery. Although significant progress has been made in the development of DNA-based hydrogels, there are still some major technical barriers that hinder their application in biosensors and drug delivery. Therefore, some challenges need to be addressed before applying it in practice. Firstly, during the process of preparing DNA hydrogel, the conditions are relatively harsh, and the success rate is low. Secondly, the cost of constructing DNA hydrogels is still quite high because the DNA often needs to undergo chemical modifications to meet the requirements of applications. Thus, the development of cost-effective and efficient methods for DNA modification is necessary. Polyacrylamide, a fundamental component of DNA hydrogels, has finally been found to exhibit a certain level of biological toxicity. Therefore, it is necessary to evaluate the toxicological characteristics of DNA hydrogels for controlled drug release before they can be used in clinical settings. After successfully resolving the aforementioned problems, we will achieve DNA hydrogels with improved properties. These properties include a high success rate of preparation, low cost, accurate delivery and release *in vivo*, and ultra-sensitive sensing. The applications will be expanded from the laboratory to include clinical testing and analysis of real samples.

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

This work was financially supported by the National Natural Science Foundation of China (No. 21804014), the Natural Science Foundation of Chongqing Science & Technology Commission (No. 2023jcyjA3529), the Science and Technology Research Program of Chongqing Municipal Education Commission (No. KJQN202200832). Construction of Graduate Joint Training Base of Chongqing Municipal Education Commission (No. yjd223005).

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