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REVIEW

Temperature-Responsive Supramolecular Hydrogels

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Hydrogels comprise a class of soft materials which are extremely useful in a number of contexts, for example as matrix-mimetic biomaterials for applications in regenerative medicine and drug delivery. One particular subclass of hydrogels consists of materials prepared through non-covalent physical crosslinking afforded by supramolecular recognition motifs. The dynamic, reversible, and equilibrium-governed features of these molecular-scale motifs often transcend length-scales to endow the resulting hydrogels with these same properties on the bulk scale. In efforts to engineer hydrogels of all types with more precise or application-specific uses, inclusion of stimuli-responsive *sol-gel* transformations has been broadly explored. In the context of biomedical uses, temperature is an interesting stimuli which has been the focus of numerous hydrogel designs, supramolecular or otherwise. Most supramolecular motifs are inherently temperature-sensitive, with elevated temperatures commonly disfavoring motif formation and/or accelerating its dissociation. In addition, supramolecular motifs have also been incorporated for physical crosslinking in conjunction with polymeric or macromeric building blocks which themselves exhibit temperature-responsive changes to their properties. Through molecular-scale engineering of supramolecular recognition, and selection of a particular motif or polymeric/macromeric backbone, it is thus possible to devise a number of supramolecular hydrogel materials to empower a variety of future biomedical applications.

1. Introduction

Hydrogels are a class of materials prepared from hydrophilic polymers which are rendered insoluble through crosslinking, enabling these to form hydrated percolated networks which imbibe several times their dry weight of water or physiological fluids.[1–3] Hydrogels have been widely used for a range of applications, including in the cosmetics, food, and petroleum industries.[4] In addition, hydrogels have shown particular utility as biomaterials for tissue engineering, regenerative medicine, and drug delivery.[5–8] In this role, their tunable composition and high water content are particularly appealing, and commonly these materials also possess excellent biocompatibility. These features support extensive exploration as artificial extracellular matrices which mimic the soft tissue microenvironment, as well as depots for the encapsulation and controlled release of therapeutic agents.

Hydrogels are classified in part by the nature of their crosslinking, which commonly is derived from either covalent (*chemical*) or non-covalent (*physical*) interactions.[9,10] Covalent crosslinking typically forms permanent interactions between polymer chains, which can lead to stable materials with superior mechanical properties, yet which lack the ability to dynamically restructure.[9,10] Importantly, chemical covalent crosslinks typically lack the ability to heal if broken in the course of material manipulation or use.[10] Hydrogels prepared from non-covalent physical crosslinks typically have more dynamic material properties due to relatively lower interaction energies and often equilibrium-governed reversibility of their underlying physical interactions, which can consist of chain entanglements as well as programmed non-covalent and/or supramolecular interactions.[11–13] Chemical interactions based on molecular dimerization or host–guest motifs have some similarities to a covalent chemical crosslink in the resulting material architecture and network topology, yet these are typically still classified as physical crosslinks due to their dynamic and reversible character. Physical crosslinks which are ruptured as a result of external mechanical forces or in response to other stimuli, such as a change in pH or temperature, can be reformed through healing of these dynamic interactions over time to reestablish a network structure. The dynamic nature which results from physical crosslinking leads to materials which exhibit a reduction in viscosity to flow under an applied force (*i.e.,* shear-thinning) yet rapidly reform their network upon cessation of the deforming force (*i.e.,* self-healing). Accordingly, this class of dynamic hydrogel materials is ideal for applications as minimally invasive injectable biomaterials.[14]

Given their many benefits, a variety of dynamic physically crosslinked hydrogels have been explored over the past several decades, spanning many types of non-covalent and/or dynamic interactions. Hydrogels prepared from physical (ionic) crosslinking of biopolymers such as alginate and chitosan have been widely explored, as reviewed in detail elsewhere.[15,16] Another related class of physically crosslinked hydrogels has been formed through metal-ligand coordination interactions.[17] A more recent advance in dynamic hydrogels is found in the developing body of literature using dynamic covalent interactions – covalent bonds which are equilibrium governed and form reversibly – to crosslink polymers and form dynamic hydrogel materials.[18,19]

This review will instead focus on the class of physically crosslinked hydrogels which leverage supramolecular interactions. Supramolecular chemistry, defined as chemistry beyond the molecule, is based on the rational design of specific, directional, tunable, reversible, and non-covalent molecular recognition motifs. Such interactions are typically incorporated in the formation of

hydrogels through one of two separate mechanisms.[20] In one manifestation, supramolecular interactions can be used to bridge two polymer chains through pendant or terminal presentation to give rise to a physically crosslinked network.[12,21] In its second manifestation, organized supramolecular interactions between small molecules (*e.g.,* one-dimensional stacking) can give rise to high aspect-ratio assemblies which then physically entangle to form a hydrogel.[22–24]

Engineering hydrogels with stimuli-responsive properties affords opportunities to create "smarter" materials which may respond to particular stimuli with some change in their formation or by modulation of properties such as their swelling, degradation, or extent of crosslinking. Supramolecular hydrogels have likewise been designed to respond to a variety of different stimuli, including osmolarity, pH, temperature, enzymes, or an applied external field.[25] Among these different stimuli used to direct supramolecular materials, strategies which are responsive to changes in temperature are particularly attractive for biomedical applications given the inherent temperature change associated with transitioning from an ambient to a physiologic setting. Accordingly, the different efforts which have been used specifically to create supramolecular hydrogels that exhibit temperature-responsive properties will be outlined in this review, highlighting hydrogels prepared from host–guest interactions, designed hydrogen bonding motifs, and molecular-scale peptide self-assembly. An emphasis in this coverage will be materials with properties which are responsive to temperatures in the range of typical physiologic and/or experimental conditions. The collection of works discussed offers design insight and inspires future application of temperature-responsive supramolecular hydrogels, in the hopes of informing the synthesis and use of this class of materials for biomedical applications.[26]

2. Host–Guest Supramolecular Hydrogels

The inclusion of a guest molecule within the portal of a macrocyclic host is one common route to enable physical crosslinking in hydrogel networks, typically by attaching hosts and their respective guests pendant to macromeric or polymeric backbones to leverage their interaction as a point of physical crosslinking.[21] A wide array of different host chemistries have been realized, including cyclodextrins (CDs), cucurbit[*n*]uril (CB[*n*]s), porphyrins, cryptophanes, carcerands, crown ethers, cyclophanes, catenanes, pillar[*n*]arenes, and calix[*n*]arenes, all of which bind reversibly to a variety of guests motifs.[27,28] For the cavitand class of hosts, which include CDs, CB[*n*]s and calix[*n*]arenes, guests typically bind within their enclosed portal leaving the external surface to interact with the solvent phase.[12] The interactions between a host and guest to form a complex are most commonly dynamic and equilibrium-governed, meaning these can

Table 1. Summary of host–guest interaction and binding affinity

Interaction Pair	K_{eq}	Ref #
β-CD • Adamantane Carboxylate	5×10^{4} M^{-1}	48
β-CD • Adamantane	5×10^{5} M^{-1}	56
β-CD • *cis*-Azobenzene	4.8×10^{3} M^{-1}	49
β-CD • *trans*-Azobenzene	2.3×10^{3} M^{-1}	49
CB[7] • Adamantylamine	4.2×10^{12} M^{-1}	75
CB[7] • Ferrocene(Trimethylammonium)	3.31×10^{11} M^{-1}	76
CB[8] • Adamantylamine	8.2×10^{8} M^{-1}	75
CB[8] • Methyl viologen • Naphthoxy	10^{11}~10^{12} M^{-2}	78
CB[8] • trans-Brooker's Merocyanine	8.5×10^{11} M^{-2}	88

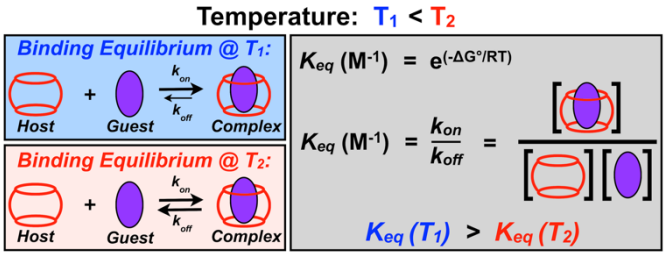

Figure 1. Guest recognition by a host macrocycle occurs with binding affinity (K_{eq}) that is a function of temperature, with affinities typically scaling inversely with increases in temperature.

be characterized by their equilibrium binding affinity (K_{eq}), as well as their dynamic rates of association (k_{on}) and dissociation (k_{off}) (**Figure 1**). A higher binding affinity is typically accompanied by concomitantly slower dynamic exchange of the interaction, which makes affinity a useful parameter to tune the resulting dynamic relaxation of a hydrogel network.[29] A range of affinities have thus been demonstrated for various host–guest motifs (**Table 1**). Additionally, competitive guests which have higher binding affinity than the motif used to form the network can be added to displace and disrupt these physical crosslinks. Here, routes are described which have prepared temperature-responsive supramolecular hydrogels using some common host macrocycle chemistries by designing either the affinity and/or dynamics of the host–guest motif, or by leveraging these motifs alongside temperature-sensitive polymeric backbones to use temperature change as a cue to vary properties of the hydrogel network.

2.1 Systems Based on Crown Ethers

The crown ethers, a class of cyclic polyethers, are one of the earliest demonstrated supramolecular hosts.[30] In their simplest form, crown ethers are cyclic oligomers of repeating ethylene oxide units (**Figure 2A**).[31] Crown ethers commonly bind organic and metallic cations in a size-dependent manner,[32,33] but modified variants have been used to bind larger guests such as paraquat (N, N'dimethyl-4,4'-bipyridinium).[34] The oxygen atoms in crown ethers also interact with guest molecules through hydrogen bonding. The exterior of the ring is somewhat hydrophobic, rendering many crown ethers poorly soluble in water. Traditional crown ethers also have somewhat low binding affinity for guests, though modified variants incorporating prosthetic aromatics and solubilizing charged groups have been reported which achieve binding on the order of 10^5 M^{-1} to larger guests.[35]

One approach to the creation of temperature-responsive hydrogels featuring crown ethers has combined their supramolecular recognition with polymers such as poly(N-isopropylacrylamide) (pNIPAAm) which undergoes a lower critical solution temperature (LCST) transition around physiologic conditions.[36–39] In these works, pNIPAAm chains were modified with crown ether derivative moieties, such as benzo[18]crown-6 and 15-crown-5. The pNIPAAm polymer backbone facilitates an LCST-mediated *sol-gel* transition, while the presence of metal ions such as K^+ and Na^+ complex with the crown ether, enabling host inclusion of metal ions to tune the hydrophilicity and LCST of the material.[36]

Low molecular weight gelators (LMWG) have also been reported from small aromatic molecules with pendant crown ethers which undergo thermally triggered assembly and hydrogelation.[40] In one study, an amphiphilic small molecule was prepared by modifying hydrophobic tetrafluorobenzene dicarboxylic acid with hydrophilic

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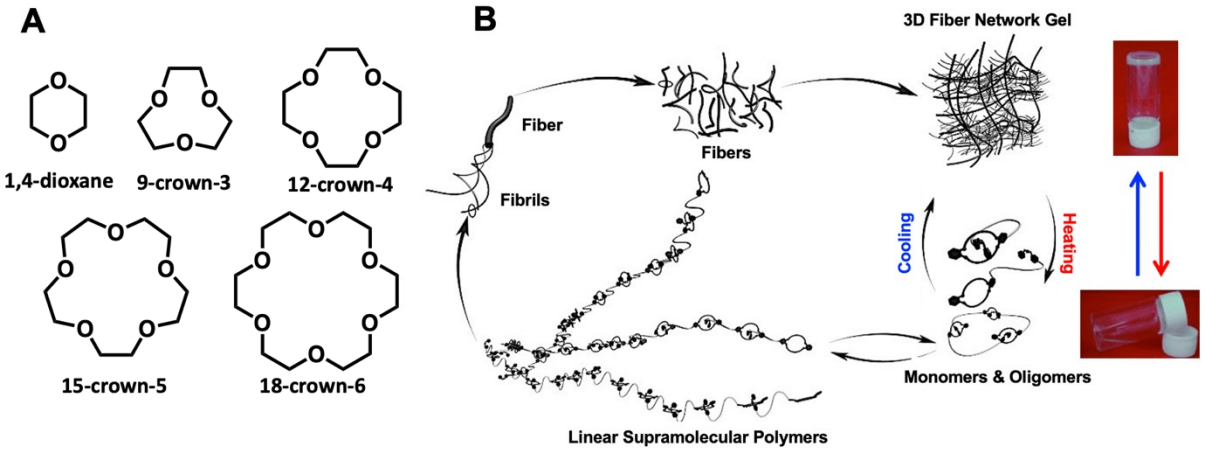


Figure 2. (A) Common crown-ether variants consisting of cyclo-oligomers of ethylene oxide. **(B).** Schematic illustration of a temperature-responsive supramolecular hydrogels mechanism: A–B monomers form linear supramolecular polymers through host–guest interactions between dibenzo[24]crown-8 hosts and a dibenzylammonium guest, which further entangle to form 3D fibrils and hydrogel networks which can be disrupted through heating. Panel B was modified with permission from reference 42.

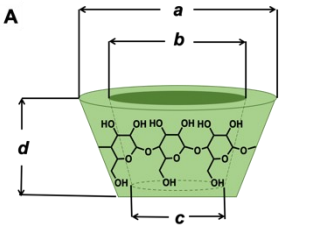
Benzo-21-crown-7 (B21C7) derivatives; this macrocycle has been previously shown to exhibit LCST-type behavior.[41] In this demonstration, B21C7 affords a temperature-responsive phase change, while the hydrophobic tetrafluorobenzene enables supramolecular gelation through hydrophobic association and π-π stacking. The resulting molecules undergo a formation process consisting first of LCST phase-separation followed by self-assembly of the gelator.

Another approach has demonstrated a crown ether-based dual-responsive supramolecular hydrogel from a heteroditopic A–B monomer linking dibenzo[24]crown-8 (DB24C8) and dibenzylammonium salt (DBA) *via* a flexible alkyl linker.[42] DBA and DB24C8 form a 1:1 supramolecular complex.[43] Thus, the host–guest interaction between DBA and DB24C8 results in linear supramolecular polymers from head-to-tail assembly of these A–B monomers. Linear supramolecular polymers further entangle to form 3-D fibrillar network hydrogels (**Figure 2B**). A *sol-gel* transition temperature of ~40 °C was reported, with further heating disrupting the gel network by decreasing the affinity of the host–guest interaction. These gels were also pH-sensitive, as at higher pH DBA deprotonation disrupted its host–guest interaction with DB24C8. Using the host–guest interaction between DBA and DB24C8, an alternative platform has also been reported by modifying the ends of four-arm star poly(ε-caprolactone) (PCL) with DB24C8 and then modifying the ends of two-arm PCL with DBA.[44] Upon mixing, the two polymers were crosslinked by host–guest interactions to form a gel. Yet, upon heating to ~60 °C, the reduced host–guest affinity resulted in crosslink rupture and a *gel-sol* transition in the material; these materials are likewise pH-responsive.

2.2 Systems Based on Cyclodextrins

Cyclodextrins (CDs) are a family of macrocycles formed from a defined number of glucose monomers linked through α-1,4-glucosidic bonds to form a cyclic oligomer in the shape of a truncated cone; common variants are comprised of 6 (αCD), 7 (βCD), or 8 (γCD) glucose units (**Figure 3A**).[45] The protruding hydroxyl groups are solvent-exposed, lending hydrophilicity and water solubility to the macrocycles, while the interior cavity is relatively hydrophobic, offering a portal for binding hydrophobic guest molecules. In terms of its electrostatic surface potential, CD macrocycles are primarily neutral (**Figure 3B**).[46] CD-based host–guest complexation is mainly driven by hydrophobic and van der Waals interactions.[47] CD macrocycles bind a wide array of small molecule guests with the typical range of binding affinity being 10^3 to 10^5 M^{-1}.[48,49] Whereas some macrocycles have a preference to complex with guests of a particular charge, CD binding is primarily charge-independent.[50] One of the most attractive properties of CD is an ability to enhance solubility through its binding to an included guest molecules, and CD macrocycles have therefore been used routinely as formulation excipients to enhance the solubility of drug compounds.[51] CD macrocycles are produced through an enzymatic process from an inexpensive starch feedstock, making these very accessible materials with industrially scaled manufacturing.[51,52]

Beyond an ability to bind small molecule guests, CDs can be threaded by polymers such as PEG, to create a linear supramolecular-nanostructured complex known as a poly(pseudo)rotaxane.[53,54] These threaded complexes are stabilized by a strong interaction between the hydrophobic cavity of the CD and the $–CH_2OCH_2–$ of the PEG backbone.[55] The resulting assembly is thermosensitive, with higher temperatures driving PEG chains to de-thread from the macrocycle, and accordingly temperature is a useful parameter to tune the equilibrium of this interaction; the length of the PEG chain and concentration of the CD species are also useful parameters to



	a [Å]	*b* [Å]	*c* [Å]	*d* [Å]
***α*-CD**	13.7	5.7	13.2	7.8
***β*-CD**	15.3	7.8	14.9	7.8
***γ*-CD**	16.9	9.5	16.1	7.8

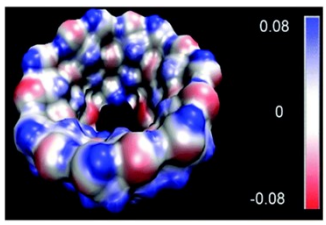


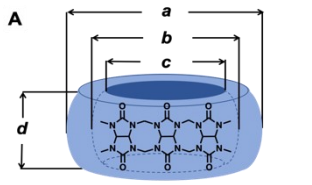
Figure 3. (A) Schematic illustration and tabulated dimensions of α-, β- and γ-CD macrocycles. **(B)** Electrostatic surface potential map for β-CD, with localized regions of positive (blue) and negative (red) charge indicated. Panel B was modified with permission from reference 46.

tune the properties of the resulting assembly.[55,56] Accordingly, this approach has yielded a well-studied supramolecular motif, with several groups utilizing poly(pseudo)rotaxane formation between CDs and PEG to create temperature-responsive hydrogels.[57–60] In one example, PEG chains (MW = 500, 1000, 2000 Da) modified with the hydrophobic anticancer drug camptothecin (CPT) were combined with αCD to create temperature-responsive drug-loaded hydrogels.[61] Of particular interest in this work, varying the length of the PEG chain and the amount of αCD added enabled the *gel-sol* transition temperature to be tuned within the range of 35-60 °C. PEG chains can also be grafted to synthetic co-polymers to enable temperature-responsive properties in the resulting hydrogels, with a demonstration of this use to tune a *gel-sol* transition within the range of 37-72 °C.[58] A related threading approach has explored a different temperature-responsive copolymer, Pluronic (PEG-PPO-PEG), which undergoes temperature-responsive micellation; the addition of αCD facilitates a *sol-gel* transition around 22 °C.[60]

The use of pNIPAAm has also been incorporated into supramolecular hydrogels based on CD, often by modifying the polymer with pendant CD and/or guest moieties.[62–65] In one example, a temperature-responsive hydrogel was prepared by using βCD dimers and guest-modified pNIPAAm copolymers; modifying pNIPAAm with adamantyl guests, the LCST decreased from 35 °C to 23 °C due to increased hydrophobicity of the guest-modified polymer.[66] Similarly, others have reported on a light and temperature dual-responsive hydrogel with CD dimers and pNIPAAm modified with an azobenzene guest.[67] As CDs preferably bind to *trans*-azobenzene, the use of light dictates the extent of supramolecular crosslinking in the network. In another manifestation, 8-arm PEGs were modified with an adamantyl guest, while βCD was modified with multiple pNIPAAm arms.[68] As temperature was increased, this system underwent a *sol-gel* transition due to reversible phase-separation of pNIPAAm arms which were bound to the 8-arm PEG through βCD–guest interactions.[60]

2.3 Systems Based on Cucurbit[*n*]urils

Cucurbit[*n*]urils (CB[*n*], *n*=5-8, 10) are symmetric macrocyclic oligomers prepared from [*n*] glycoluril units linked together *via* methylene bridges.[69,70] The portals of CB[*n*] macrocycles are fringed with carbonyl groups, while the hydrophobic cavity affords a site for inclusion of a variety of hydrophobic guests with often very high affinity.[71] The internal cavity diameter of CB[6] (3.9 Å), CB[7] (5.4 Å), and CB[8] (6.9 Å) are very similar to those of of αCD, βCD, and ɣCD, respectively, while the height is 9.1 Å for all variants (**Figure 4A**).[72] The solubility of CB[n]s in water exhibits an interesting odd-even trend, with CB[5] and CB[7] having relatively high water solubility in the range of 20-30 mM, while CB[6] and CB[8] have much lower water solubility of 0.018 and less than 0.01 mM, respectively.[73,74] Whereas CDs rarely achieve K_{eq} above ~10^4 M^{-1}, CB[*n*] and in particular CB[7] can achieve affinities spanning a broad range to various guests, with 10^2 to 10^{17} M^{-1} demonstrated.[75,76] Typically, CB[6] forms 1:1 complexes with protonated diaminoalkanes, while CB[7] can from 1:1 complexes with more three-dimensional guests, including ferrocene, adamantane, diamantine and bicyclooctane derivatives with high binding affinities, ranging from 10^7 to 10^{17} M^{-1}.[71] With its larger cavity, CB[8] can form ternary complexes by simultaneously binding two guests, with both heteroternary (1:1:1) and homoternary (1:2) complexes being demonstrated.[77] CB[n]s bind with enhanced affinity to hydrophobic guests flanked by cationic groups, while exhibiting virtually no binding to guests flanked by anionic groups.[50] These charge-dependent trends can be explained



	a [Å]	*b* [Å]	*c* [Å]	*d* [Å]
CB[6]	14.4	5.8	3.9	9.1
CB[7]	16.0	7.3	5.4	9.1
CB[8]	17.5	8.8	6.9	9.1

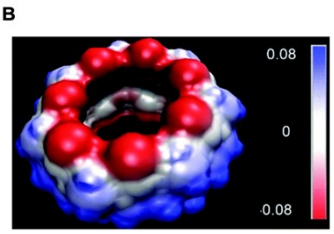


Figure 4. (A) Schematic illustration and tabulated dimensions of CB[6], CB[7], and CB[8] macrocycles. (**B)** Electrostatic surface potential map for CB[7], with localized regions of positive (blue) and negative (red) charge indicated. Panel B was modified with permission from reference 46.

from the electrostatic surface potential of CB[7] (**Figure 4B**). Though net-neutral, CB[7] has a partial negative charge on either portal due to the electron density of its carbonyl fringes which serves to enhance binding to guests that position a positive charge at the portal while disfavoring guests which place a negative charge in this sample position.[73]

Like most supramolecular motifs, CB[*n*]–guest interactions exhibit somewhat weakened binding affinities with increasing temperature. In particular, when ternary interactions are used for material crosslinking, elevated temperatures can enable a *gel-sol* transition for these motifs by disfavoring binding of the weaker second guest.[78,79] Yet the magnitude of affinity change for very high-affinity guests would not typically be sufficient to enable temperature-responsive materials on its own under reasonable environmental stimuli. Like with other host–guest motifs, most relevant examples have incorporated CB[*n*]–guest recognition in conjunction with thermosensitive polymers. Toward temperature-responsive dynamic hydrogels, CB[*n*] crosslinking of thermosensitive polymers such as pNIPAAm has been explored.[80–83] In one approach, pNIPAAm was copolymerized with groups presenting high-affinity adamantyl guests for CB[7].[80] The *sol-gel* transition temperature of these copolymers was then lowered by the presence of CB[7] bound to the presented guest on the copolymer. A similar approach was also shown for pNIPAAm-based copolymers presenting a good guest for CB[6].[83] It is noted that the CB[*n*]–guest interaction in these designs alters the hydrophobic transition and chain packing of the resulting polymers, but does not itself participate in physical crosslinking of the polymer chains.

In order to incorporate CB[*n*] macrocycles onto materials for the purposes of forming host–guest physical crosslinks, one synthetic challenge which has been addressed is the inclusion of reactive handles.[84–87] These modified variants can thus be attached as pendants on a material for host–guest physical crosslinking, as described for CD variants. Alternatively, the ability of CB[8] to simultaneously bind two guests within a complex affords a very useful approach of using the free unmodified macrocycle to simultaneously bind two pendant guests to form a ternary physical crosslink.[78,88] Other temperature-responsive polymers have thus been incorporated along with CB[*n*]–guest crosslinking to prepare responsive hydrogels. In one example, responsive pluronic-based copolymer surfactants were modified with CB[7], and when mixed with a multivalent guest formed hydrogels at ~32 °C upon host–guest crosslinking of thermally-induced pluronic micelles.[89] In a second approach, the guest used was a variant of *trans*-Brooker's merocyanine which forms homoterarny complexes with CB[8] and

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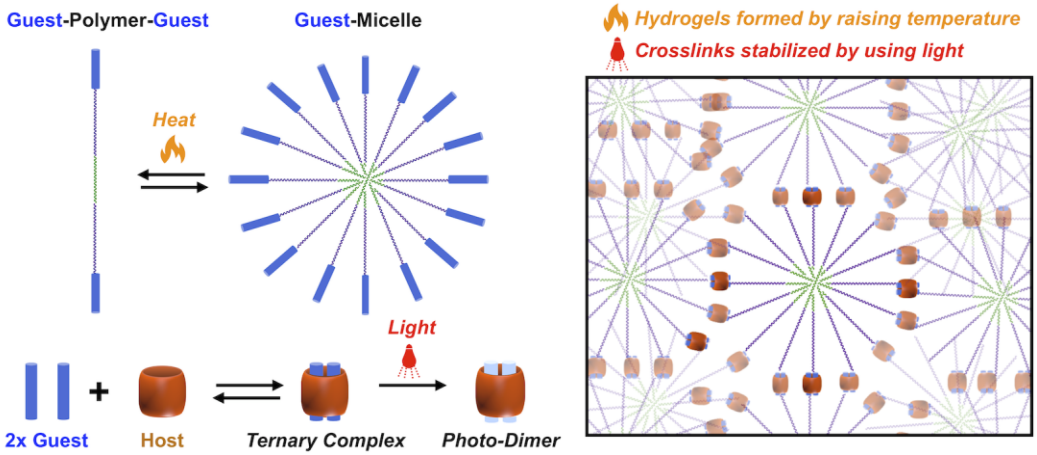

Figure 5. Schematic illustration of a temperature-responsive hydrogel based on both host–guest crosslinking of temperature-sensitive Pluronic F127 micelles through homoternary complex formation with CB[8] macrocycles; CB[8] further catalyzes a [2+2] photo-dimerization of the guest to convert physical supramolecular crosslinks to chemical covalent crosslinks. Figure reproduced with permission from reference 90.

can furthermore be converted into a covalent interaction within the CB[8] portal through a photo-mediated [2+2] cycloaddition (**Figure 5**).[90]

3. Supramolecular Hydrogen Bonding Motifs

Designed hydrogen bonding motifs are another class of commonly used supramolecular interactions, typically consisting of intermolecular interfaces which position hydrogen bond donors (e.g., -FH, -NH, or OH) in proximity to an electronegative hydrogen bond acceptor (e.g., C=O).[91,92] Hydrogen atoms only form one chemical covalent bond based on valence bond theory, yet the hydrogen atom is formally divalent in many cases, and the additional bond is defined as a hydrogen bond.[93] These chemical interactions are distinct from a traditional chemical crosslink in the underlying dynamic and reversible nature of the crosslink formed, thus more closely resembling a physical interaction. The interaction energy of a single hydrogen bond is relatively weak, and thus these motifs typically must capture simultaneous formation of multiple hydrogen bonds to achieve ordering. The additivity of these interactions can be seen in the change in affinity of dimerization with increasing number of hydrogen bonds between molecules (**Table 2**), which increases for representative complexes having two (10^2 M^{-1}), three (10^4-10^5 M^{-1}), four (10^7 M^{-1}), or six (10^9 M^{-1}) hydrogen bonds between dimers.[91,94–97] The strength of the interaction is also impacted by secondary interaction of adjacent hydrogen bonds.[92,95,98] The resulting secondary interaction rules stipulate that for molecular interactions derived from multiple acceptors (A) and donors (D), the binding constant for AAA–DDD hydrogen bonding is the highest (~10^4-10^5 M^{-1}), while ADA–DAD hydrogen bonding is the lowest (~10^2-10^3 M^{-1}).[92] Furthermore, an odd number of hydrogen bond donors/aceptors on each molecule requires hetero-complementary pairing (e.g., ADA–DAD), while an even number can form self-complementary pairs (e.g., AADD–DDAA). Much like other non-covalent interactions, the association of hydrogen bonding motifs is temperature-dependent, and accordingly increasing temperature typically facilitates reduced affinity and eventual rupture of these interactions.[99]

Table 2. Summary of hydrogen bonding motif and binding affinity

# H-bonds	Motif	K_{eq}	Ref. #
2	Adenine • Thymine	~10^2 M^{-1}	91
3	Guanidine • Cytosine	~10^5 M^{-1}	95
4	UPy • UPy	10^5~10^6 M^{-1}	96
6	Oligoamide Strands	~10^9 M^{-1}	94

3.1 Ureido-Pyrimidone Motifs

In the context of supramolecular materials and hydrogels, quadruple hydrogen bonding motifs, such as the ureido-pyrimidone (UPy), have been the most extensively explored.[100–104] The UPy moiety can dimerize through self-complementary quadruple hydrogen bond formation to yield rigid and planar complexes (**Figure 6A**).[96,101] As expected, the dissociation rate of the UPy dimer increases as temperature is increased.[101]

The dimerization of UPy affords a directing interaction to prepare a number of nanostructures and materials.[105,106107,108] Similar to pendant host–guest motifs, polymer modification with UPy moieties can enable physical crosslinking *via* self-complementary complex formation, giving rise to hydrogels.[109] This includes work to create an injectable, multi-stimuli responsive UPy-based hydrogel, wherein UPy-modified methacrylate was copolymerized with temperature and pH dual-responsive poly[(2-(dimethylamino)ethyl methacrylate) (PAEA).[110] In this system, a hydrogel was formed through crosslinking by UPy dimerization, while the LCST properties of PAEA afforded a transition around 45 to 50 °C that disrupted the hydrogel and destabilized UPy hydrogen bonds.

To prepare a temperature- and pH-responsive hydrogels, PEG chains have been terminally modified with UPy moieties.[111–114] Upon cooling from 50 °C, the system self-assembles through UPy association, fibrillization, and phase separation into entangled bundles of fibrils to form a hydrogel (**Figure 6B**). This PEG-rich hydrogel is biocompatible and has been explored for a variety of biomedical applications (**Figure 6C**). In an effort to improve the mechanical properties of these materials, a tough UPy-based hydrogel with shape-memory properties was prepared by co-polymerization of UPy and PEG to create chain-extended polymers which were crosslinked by UPy dimerization to form a hydrogel.[109] This hydrogel exhibited a temperature-dependent change in mechanical properties, as well as a thermally activated phase

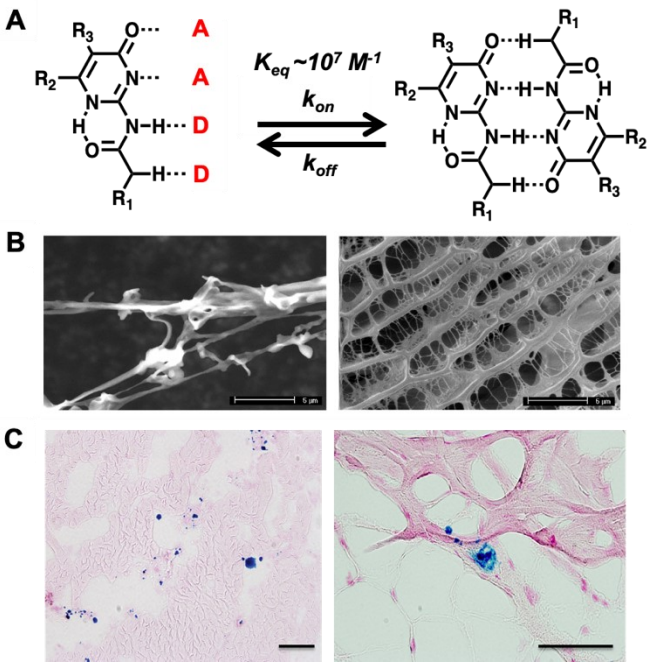

Figure 6. (**A)** Dynamic self-complimentary homodimer formation between two Upy moieties (A: H-bond acceptor, B: H-bond donor). **(B).** Scanning electronic microscopy images of a UPy-modified PEG, showing a globular fibrous morphology (left) as well as the percolated network of the material in its gel state (right). Panel B reproduced with permission from reference 111. (**C)** Representative microscopic images of *Prussian Blue*-stained peri-infarct sections after intramyocardial injection of PEG-Upy hydrogels. (Scale bars: 125 µm). Panel C reproduced with permission from reference 112.

transition which enabled shape-memory function at temperatures equal to or above the melting point of PEG (~70 °C).

3.2 Nucleic Acid-inspired Motifs

DNA is a ubiquitous genetic material in all living species. Beyond its common biological function encode and transmit genetic information, the stability of DNA as well as its flexibility and ability to be programmed and modified offer interesting properties for its incorporation into materials.[115,116] DNA is a polymer constructed from four nucleotide subunits, adenine (A), cytosine (C), guanine (G) and thymine (T), with each nucleotide composed of a five-carbon phosphorylated sugar moiety and a nitrogenous base. Single-stranded DNA (ssDNA) can arranged into antiparallel double-stranded DNA (dsDNA) through non-covalent hydrogen bonding between their nitrogenous bases following Watson-Crick base pairing rules, which are A pairs with T and G pairs with C.[115–117] The hydrogen bonds between nucleotides are temperature-responsive, with hybridization or disassociation occurring as a function of the annealing temperature of the sequence. The annealing temperature meanwhile depends on the length, base composition, and concentration of the associating DNA strand.[115] Y-shaped DNA has been designed from three ssDNA, resulting in free interlocking domains that crosslink with each other by forming i-motif to yield reversible hydrogels that are both pH- and temperature-responsive.[118,119] This type of pure DNA gel showed a dramatic decrease in storage modulus *G'* upon heating to ~30 °C.

Based on the preferred pairing of DNA, polymers can be crosslinked non-covalently through DNA hybridization.[120–122] DNA has thus been appended to PNIPAAm to facilitate multi-stimuli responsive hydrogels.[123] By selecting C-rich sequences, DNA can self-assemble into an i-motif structure at acidic pH or form duplexes bridged by Ag^+ ions, which reversibly form a hydrogel, while the thermoresponsive PNIPAAm backbone enables a reversible transition upon heating to ~45 °C.[123,124] Related work has explored hybrid interactions between polymers appended with peptide nucleic acids – a synthetic DNA analogue which append nucleotide bases to a peptide backbone[125] – which can then we crosslinked by temperature-responsive hybridization with DNA.[120] In another example, DNA-modified gold nanoparticles were created to form a temperature-responsive network actuated by the ability of nanoparticles to absorb infrared and near-infrared light and facilitate a local increase in temperature.[126] Gold-silver nanorods have similarly been impeded into hydrogel networks prepared from DNA-modified polyacrylamide, wherein near-infrared irradiation increases the local temperature and disrupts the hydrogel to release an encapsulated drug.[127]

3.3 Discotic H-bonding Motifs

Whereas UPy and DNA-inspired motifs leverage dimeric H-bonding interactions, another class of designed H-bonding motifs interact through one-dimensional stacking of monomers templated by H-bond donor–acceptor interactions between molecules. One commonly explored motif is the benzene tricarboxamide (BTA), a C_3-symmetric discotic molecule consisting of a benzene core with three amide-linked appendages that have a propensity for assembly into one-dimensional columnar aggregates through intermolecular hydrogen bonding of amides and planar co-orientation of hydrophobic arene cores.[128,129] The stacking of these molecules exhibits temperature-dependent nucleation and elongation formation mechanisms.[128] Many BTA molecules assemble and form organogels readily in organic solvents.[130–133] However more recent reports have shown BTA designs which enable hydrogel formation through one-dimensional stacking of BTA motifs bearing solubilizing appendages, and subsequent physical entanglements of these one-dimensional structures.[134–138] In many of these cases, BTA stacks and the concomitant materials they form are reversibly disrupted upon heating, though the stability of assemblies arising from these motifs may necessitate temperatures well in excess of those which are physiologically relevant. Temperature-responsive hydrogels have been realized from related C_3-symmetric cores wherein triazole linkers replace the amides common for a BTA, with appended peptides instead offering one-dimensional H-bonding.[139] Related work has explored cores based on perylene bisimide dyes with adjacent hydrogen bonding motifs such as amides.[140] The appendage of temperature-responsive oligoethylene glycol units to this core has revealed materials with tunable LCST behavior in the range of 26-51 °C.[141]

4. Supramolecular Peptide Assembly

Supramolecular self-assembly is a useful way to obtain diverse and intricate materials which are often organized across multiple length-scales.[142–145] The process by which molecules spontaneously organize into ordered structures is driven by free energy minimization of the system. An advantage of molecular self-assembly arises in the facile tuning of resulting material structure through molecular design to alter the affinity/dynamics of intermolecular association as well as by control of environmental parameters such

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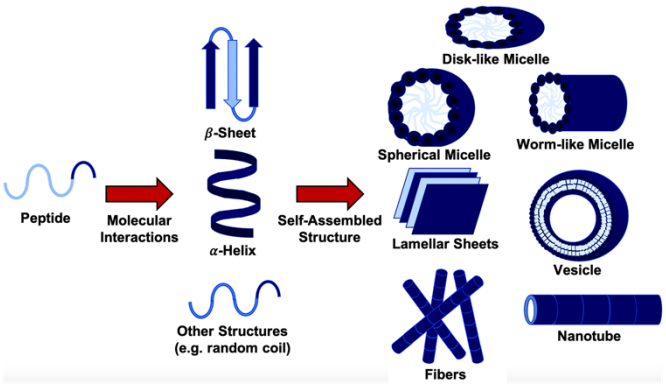

Figure 7. Schematic illustration of the diversity of nanostructures which may be achieved through peptide self-assembly, on the basis of various underlying intermolecular and intramolecular interactions and motifs. Figure modified with permission from reference 149.

as temperature, pH, and solvent. Within supramolecular self-assembly, and particularly for materials which interface with biology, peptides are useful due to their biological origin, modular and sequence-controlled synthesis, and their readiness to form robust secondary (*and even higher order*) structures through hydrogen bonding.[146] Peptides thus constitute an important design motif in creating supramolecular materials, wherein short amino acid sequences are prepared which aggregate spontaneously through multiple ordered and additive interactions including hydrogen bonding, hydrophobic interactions, and electrostatic interactions.[147,148] Peptides can also self-assemble into various nanostructure shapes, including micelles, fibers, vesicles, nanotubes, and nanosheets (**Figure 7**).[149] An important mode of peptide self-assembly is driven by the formation of β-sheet hydrogen bonding networks to yield high aspect-ratio assemblies.[22] The thermostability of β-sheets depends on interactions between side chains of adjacent amino acids as well as hydrogen binding of the amide backbone.[150] Accordingly a higher number of hydrogen bonds typically correlates with more stable β-sheets, while H-bonds near a turn or at the ends of a β-strand are less influential compared to those shielded within a hydrophobic region.[151,152] High aspect-ratio self-assembled structures arising from β-sheet formation can furthermore physically entangle to form percolated hydrogel networks. Though peptides constitute a useful design strategy to yield supramolecular materials, the inclusion of temperature-responsive properties in these materials has been less readily explored, in part due to the denaturing effect of heat on peptide sequences. Yet, some examples wherein temperature is used to direct changes in the property of peptide assemblies or hydrogels are provided here for different classes of peptide-based materials.

Macromolecular self-assembly arising from controlled and intermolecular interactions of high molecular weight block copolymers or polypeptides affords another related strategy which has been explored to generate temperature-responsive hydrogels. Synthetic block copolymers can be designed with thermosensitive blocks to enable *sol-gel* transitions upon heating.[153–157] There is also a large body of work describing thermo-responsive polypeptide gelators, such as recombinant elastin-like polypeptides, to prepare temperature-responsive assemblies and hydrogels.[158–164] However, these approaches typically leverage less ordered intermolecular interactions (*e.g,* purely hydrophobic interactions) than typical for a supramolecular material and thus are not be discussed at length here, though the reader is nonetheless encouraged to also explore this related body of literature.

4.1 Oligopeptide Gelators

One commonly used peptide motif to prepare supramolecular materials has explored sequences of alternating hydrophobic and hydrophilic amino acids which self-assemble into β-sheet structures and entangle to form hydrogels.[165–167] In particular, variants of these supramolecular peptide assemblies have been used as artificial extracellular matrices for tissue engineering applications.[168–172] In one example of a temperature-responsive peptide, an alternating charged and hydrophobic sequence was installed flanking a tetrapeptide with a high propensity to form type II' β-turn.[173] Upon heating, this peptide assembled into elongated fibrils through intermolecular hydrogen bonding and hydrophobic interactions which further entangled to form a hydrogel. The temperature of transition in this peptide was then tuned by sequence modification. A different oligopeptide motif has been reported which included sequences derived from elastin, a natural temperature-responsive protein.[174] These short peptide mimics of elastin showed continued increase in their β-sheet character yielding elongated fibrils upon heating from 20 °C to 80 °C.

4.2 Peptide-Aliphatic Conjugates

Peptide amphiphiles (PAs), which comprise a class of synthetic peptides modified with a prosthetic aliphatic group to realize surfactant-like features, have been widely explored to create supramolecular materials.[175–179] Their mechanism of self-assembly in water arises from the amphiphilic character of the PA sequence, as lipid-like alkyl tails self-associate by hydrophobic collapse to limit contact with the water bulk, leaving more hydrophilic amino acid residues solvent-exposed. Through molecular design, including the inclusion of ordered β-sheet hydrogen bonding interactions between peptide segments, the interfacial curvature and aspect-ratio of these assemblies can be controlled. In particular, peptides which form robust hydrogen bonding networks leading to their stacking into high aspect-ratio fibers can physically entangle to form hydrogel networks; entanglement is often aided by controlling surface charge on the nanostructure through pH or the addition of counterions which screen or bridge charged residues.[175] The stiffness and mechanical properties of the resulting hydrogels are also tunable through pre-heating a PA solution to induce liquid-crystalline bundling prior to inducing gelation with counterion addition (**Figure 8**).[180] Ni^{2+} ions, were also reported to exhibit a *gel-sol* transition upon heating, with the transition temperature controlled by the concentration of Ni^{2+}.[181] Other PAs bearing a single *L*-carnosine were shown to self-assemble into hydrogels which were sensitive to salt, pH and temperature, in particular exhibiting a *gel-sol* transition around 50 °C.[182]

Another common supramolecular peptide motif is based on short peptides modified at their *N*-terminus with a hydrophobic aromatic group, such as fluorenylmethoxycarbonyl (Fmoc).[183] These Fmoc-modified short peptides self-assemble into fibrillar nanostructures through β-sheet hydrogen bonding and π–π stacking, with many variants further forming hydrogels at physiological pH.[184,185] Other work with Fmoc-modified short peptides revealed thermoreversible hydrogelation upon cooling, enabling the creation of hydrogels for use in raising antibodies to a presented antigen.[186] An Fmoc-protected dipeptide containing β-alanine was found to self-assemble and form a hydrogel upon heating to physiologic temperature.[187] In a related system, screening a library of naphthalene-dipeptides found gelation which was affected by the

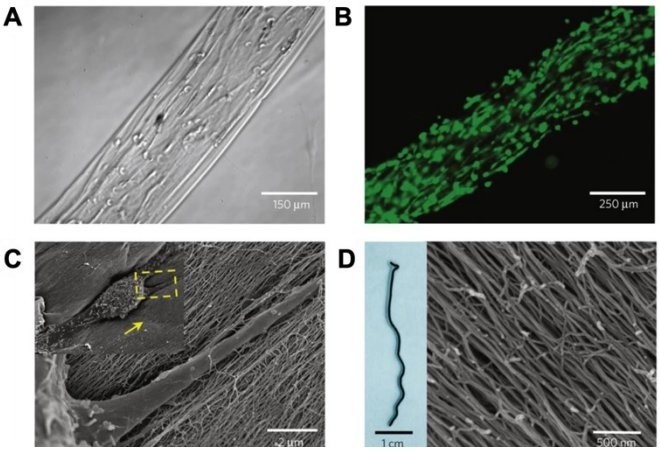

Figure 8. **(A)** Heat-treating a solution of a charged peptide amphiphile prior to inducing gelation by extrusion into a calcium bath yields massively parallel bundles of nanofibers which can support cells, as visualized by phase-contrast microscopy and **(B)** fluorescence microscopy. **(C)** These aligned macroscopic hydrogels serve to orient encapsulated cells, (D) and can furthermore encapsulate and align carbon nanotubes to enable electrically conductive hydrogel substrates. Figure modified with permission from Ref 180.

pK_a of dipeptides and the pH of solution.[188] This work further showed that the apparent pK_a was temperature-dependent, with higher temperatures resulting in lower pK_a, a phenomenon explained from thermal impact on the underlying temperature-sensitivity of the hydrogen bonds which drive hydrogelation. A biphenyl-terminated dipeptide was also found to self-assemble into hydrogels which were responsive to both temperature and ions.[189] Specifically, by attaching 4-biphenylacetic acid to the N-terminus of Phe-Phe dipeptide, hydrogels were then formed when the *sol* was first heated to 95 °C and then cooled back to room temperature.

4.3 Ultra-Short Peptide Gelators

An expanding body of recent work has sought to prepare supramolecular assemblies and hydrogels from ultra-short peptides, often of only 2-4 amino acids in length.[190–195] Compared to other peptide-based materials, the synthetic simplicity of this route to prepare materials offers an advantage, while still enabling the resulting materials to be used for biological applications.[196–198] Short peptides can be linear, cyclic or branched.[196] The underlying intermolecular forces enable these short peptides to associate through hydrogen bond or *via* hydrophobic or π-π interaction to give rise to ordered structures which may form hydrogels.[197] A short peptide of sequence Ile-Phe was also found to self-assemble into ordered fibrillar nanostructures which further entangle into hydrogels, yet heating of these hydrogels to ~40 °C induced a *gel-sol* transition.[199] While a gel-sol transition upon heating is most common for these short peptides due to their relatively weak cohesive forces, dipeptides have also been reported which form hydrogels that withstand extreme heating to temperatures up to 90 °C.[200]

An extension of this work in ultra-short peptide self-assembly has evaluated short peptides conjugated to polymers. For instance, a temperature-responsive hydrogel was reported by end-capping PEG with a dipeptide such as Phe-Phe or Tyr-Tyr.[201] Peptide self-assembly *via* β-sheet formation resulted in fibrillar nanostructures that further assemble to form a hydrogel by π–π stacking. This material underwent a *gel-sol* transition when heated to physiological temperature. A tetrapeptide was also conjugated to pNIPAAm, wherein the peptide association coupled to the LCST transition of the polymer resulted in a *sol-gel* transition around 32°C and temperature-induced hardening.[153] Longer peptides with antibacterial function have also been incorporated into this same design to prepare temperature-responsive hydrogels.[202]

4.4 Collagen-Inspired Supramolecular Peptide

Collagen is one of the main protein components of skin and connective tissue, and is among the most abundant proteins in the body.[203] Though there are various forms of collagen, classified as either fibrillar or non-fibrillar, the fibrillar Type-I collagen accounts for over 90% of all collagen in the body. An individual collagen chain forms a left-handed helix, with three such chains then entangling to form right-handed triple-helical tropocollagen. These triple-helical building blocks further assemble across length-scales to first form fibrils which then bundle to make large fibers.[204,205] The initial triple-helical structure arises from chains which commonly have a repeating Gly-X-Y sequence, with the X and Y positions typically occupied by proline and hydroxyproline residues. The development of short peptides which capture the sequence and self-assembly of native collagen, known as collagen-mimetic peptides, has thus been explored to create fibrillar materials and hydrogels, which due the collagen-based design have obvious applications as biomaterials for the support and growth of cells and tissues.[206–208] Collagen-mimetic peptides usually consist of 15-40 amino acids and are much shorter than natural collagen, for which single chains can be upwards of 1000 amino acids in length. Yet, with specific design, these short peptides can still self-assemble into ordered triple-helical architectures and even higher-order assemblies. Synthetic short collagen fragments form intermolecular triple helix, which further self-assemble to fibrils resemble natural collagen (**Figure 9A**).[207] Collagen-mimetic peptides experience temperature-reversible behavior arising from melting of these triple-helices at elevated (and tunable) temperatures, and can be further stabilized by designing heterocomplexes of triple-helices prepared from three strands of different sequence.[209–211] Toward reversible temperature-responsive hydrogels, collagen-mimetic sequences have been designed to incorporate cysteine residues to use disulfides in order to template a triple-helical building block.[212] These disulfide-linked trimers were then able to self-assemble into elongated triple-helices and bundle to form fibrillar hydrogels, where the *gel-sol* transition temperature was furthermore tunable by varying molecular design.

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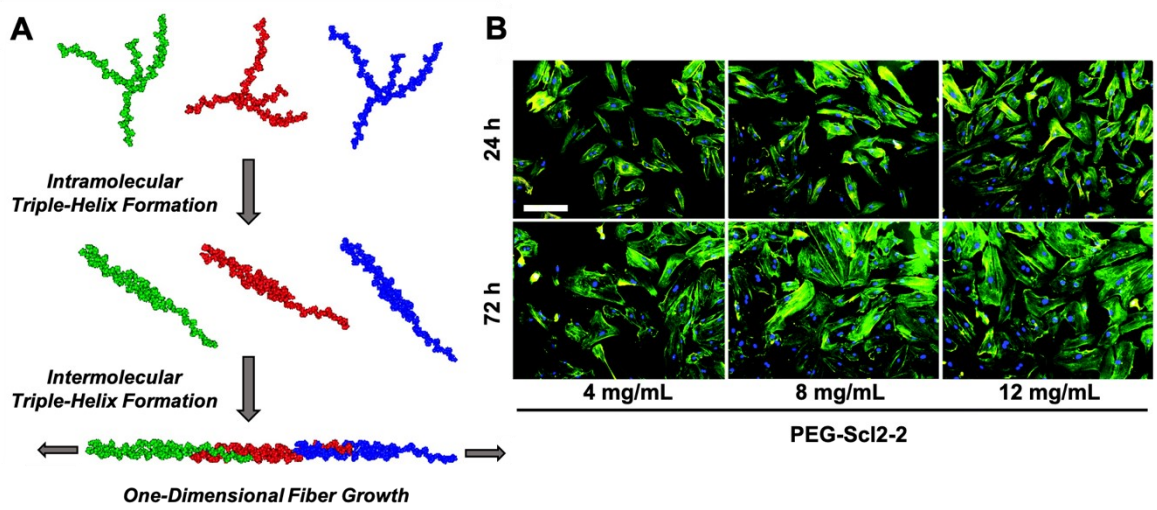

Figure 9. (A) Schematic representation of the self-assembly of collagen-mimetic peptides templated by three peptide chains connected by disulfide bonds. Panel A modified with permission from reference 207 (Copyright 2006 National Academy of Sciences). **(B)** Representative images of endothelial cells grown on substrates of a PEG-Scl2-2 hydrogel (PEG modified triple-helical collagen-mimetic segment and containing a cell-adhesion sequence) and stained with phalloidin (green) and DAPI (blue). The number of adherent HAECs increased with increasing Scl2-2 concentration. (Scale bar: 200 μm). Panel B modified with permission from reference 214.

The use of collagen-mimetic sequences has also been explored to enable dynamic physical crosslinking of four-arm PEG macromers.[213] Below the melting temperature of the triple-helix (~71°C), the interaction of these appended peptides yielded a three-dimensional hydrogel network, but upon heating these peptides underwent a reversible *gel-sol* transition. PEG-based materials modified with collagen-mimetic sequences were also explored for endothelial cell adhesion, migration and maturation, which showed potential for artificial extracellular matrices and tissue engineering based applications (**Figure 9B**).[214] A similar concept has been explored for a triblock copolymer design bearing collagen-based end blocks and a random coil mid-block.[215] This polymer is crosslinked through recognition and assembly of these collagen end-blocks, resulting in a dynamic supramolecular hydrogel with temperature-induced *sol-gel* transition. The inclusion of collagen-derived sequences on a PAMAM dendrimer also allowed for triple-helix formation to facilitate hydrogel formation, with the *sol-gel* transition temperature able to be tuned by varying concentration.[216]

Conclusions

The general approach to engineer materials with stimuli-responsive features seeks smarter and more capable technologies to empower a variety of material-dependent applications. In the context of creating new biomaterials, the temperature stimulus is a particularly useful trigger, especially if the response is tuned to enable a material transformation upon transitioning from ambient to physiologic conditions. The possibilities from such an approach are many. For example, one could envision a minimally invasive method to apply a biomaterial, beginning outside the body as a low-viscosity *sol* which is then extruded through a small needle or catheter, subsequently forming a solid material once *in situ* for use in regenerating tissues or locally delivering a drug. For example, this general approach has used easily applied supramolecular hydrogel materials to support and retain therapeutic cell populations within a tissue site of interest,[217,218] or to deliver pro-regenerative growth factors or related cues to drive minimally invasive tissue healing.[219–221] By incorporating *sol-gel* triggered material formation, the viscosity of the injectant and, correspondingly, the size of the needle or catheter used could be reduced to enable even more facile administration. Alternatively, a reverse *gel-sol* transition could likewise have uses in a biomedical context. For example, some have explored the use of hydrogels to stabilize protein drugs in formulation.[222] From here, one could envision a protein-protecting gel for drug storage or transport that was then gently warmed to a *sol* prior to therapeutic administration. In a related concept, a topical (*e.g.,* skin) medication could be formulated as an extruded hydrogel for ease in initial application, but upon contact with the warm skin transition to a *sol* for ease in spreading and improved surface coverage. In addition, coupling temperature-responsive hydrogels with plasmonic nanostructures based on gold could enable the triggered release of a therapeutic through achieving local temperatures well in excess of normal physiology. Surely, these are just some of the many uses which might be enabled through the creation of temperature-responsive supramolecular hydrogel biomaterials. It is therefore envisioned that the design strategy described herein, which is firmly rooted in engineered and controlled intermolecular interactions, coupled with several exemplary uses of these materials to date, will inspire future efforts in temperature-responsive supramolecular hydrogels for use as new biomaterials. We are enthusiastic about a future which includes supramolecular hydrogel biomaterials with temperature-triggered formation or dissolution as a growing component of the arsenal of available healthcare technologies in combating disease with improved therapeutic delivery or accelerating tissue regeneration following disease, injury, or dysfunction.

Conflicts of interest

There are no conflicts to declare.

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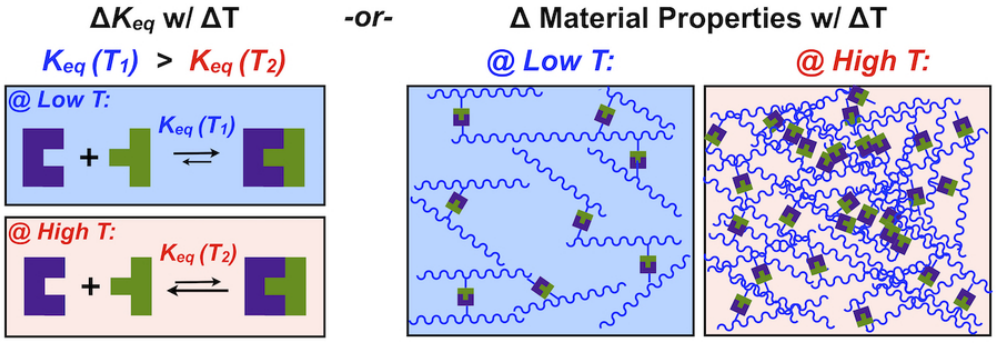

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