Metabolite-Based Hydrogels

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Contributor: Om Shanker Tiwari , Sigal Rencus-Lazar , Ehud Gazit

Minimalistic peptide- and metabolite-based supramolecular hydrogels have great potential relative to traditional polymeric hydrogels in various biomedical and technological applications. Advantages such as remarkable biodegradability, high water content, favorable mechanical properties, biocompatibility, self-healing, synthetic feasibility, low cost, easy design, biological function, remarkable injectability, and multi-responsiveness to external stimuli make supramolecular hydrogels promising candidates for drug delivery, tissue engineering, tissue regeneration, and wound healing. Non-covalent interactions such as hydrogen bonding, hydrophobic interactions, electrostatic interactions, and π–π stacking interactions play key roles in the formation of peptide- and metabolite-containing low-molecular-weight hydrogels. Peptide- and metabolite-based hydrogels display shear-thinning and immediate recovery behavior due to the involvement of weak non-covalent interactions, making them supreme models for the delivery of drug molecules. In the areas of regenerative medicine, tissue engineering, pre-clinical evaluation, and numerous other biomedical applications, peptide- and metabolite-based hydrogelators with rationally designed architectures have intriguing uses.

peptide metabolite supramolecular hydrogel amino acids drug delivery

1. Introduction

Hydrogels are composed of molecular networks that can retain a substantial amount of water inside their structures (in most cases, water comprises most of their mass). These assemblies retain a solid structure and do not dissolve in water. Naturally occurring hydrogels include collagen and gelatin. Various synthetic molecular and supramolecular polymers have been shown to form hydrogels. The conventional hydrogel networks are produced during the initial stages of hydrogel growth using covalently cross-linked polymers such as poly(ethylene glycol) diacrylate (PEGDA), poly(ethylene glycol) monoacrylate (PEGMA), poly(ethylene glycol), poly(vinyl alcohol), polyacrylamide, and chitosan-collagen [1][2][3][4][5][6]. These inexpensive chemically cross-linked hydrogels have limited applicability in the field of regenerative medicine and other biomedical applications due to their high molecular weight and potentially toxic chemicals or catalysts, which require prudent inspection of the safety profile [7]. The foundations of bio-inspired materials design with an emphasis on the advantages and limitations of decellularized and reconstituted biopolymeric matrices as well as biohybrid and fully synthetic polymer hydrogel systems have been applied to enable specific organotypic and organoid cultures [8]. Furthermore, there are emerging adhesive qualities of soft and hydrated surfaces for the design of binding chemistry or adhesion junctions, whether covalent, dynamic covalent, supramolecular, or physical [9]. For a variety of biomedical applications, wet adhesion is helpful for adhering to or between tissues and implants. In the context of effective junction design, a number of recent and upcoming adhesive hydrogels for use in biomedicine have been reported.

The major objective is to control the adhesion strength, reversibility, stability, and sensitivity to environmental stimuli by engineering hydrogel adhesion through the molecular design of the junctions.

Moreover, due to their highly structured assembly patterns, biological origins, bioactivity, easy synthesis, characterization, chemical diversity, high stability, biocompatibility, low cost, and biodegradability, peptide- and metabolite-based materials, which are present everywhere in nature, are able to carry out specialized biological tasks. Self-assembly through noncovalent interactions such as electrostatic, hydrophobic, and hydrogen bonding, as well as π–π stacking interactions, can mediate a variety of supramolecular nanoarchitectures, including nanotubes, nanoparticles, nanofibers, nanobelts, and hydrogels [10][11][12][13][14][15][16][17][18]. Non-covalent interactions, which are often weaker than covalent bond interactions and allow supramolecular gelators to self-assemble into hydrogels, are primarily responsible for this phenomenon [19]. Amino acids and their derivatives are a family of supramolecular gelators, and the fundamental mechanism underlying their gelation is intermolecular hydrogen bonding between amide bonds [20][21][22][23]. With a focus on understanding the relationships between their structures, properties, and functions, the current progress in the preparation of peptide and amino acids-based hydrogels under various types of external stimuli, as well as the in situ encapsulation of cells into the hydrogels have been reported [24]. The applications of peptide- and amino-acid-based hydrogelators with rationally chosen architectures in regenerative medicine, tissue engineering, and pre-clinical testing seem promising. Furthermore, the development of biomacromolecules, including peptide-based multifunctional hydrogels with a combination of various characteristics and functions, such as antioxidant, antibacterial, bioadhesive, and sustaining mechanical properties, as well as their effect on wound healing, seems to offer similar promise [25]. The peptide-based multi-responsive hydrogels with unique and improved properties using coarse-grained and atomistic simulations can be useful in exosome delivery, with an emphasis on bioadhesion, organoids, and tissue engineering [26]. The remarkable properties of peptide- and metabolite-based hydrogels suggest their potential use in 3D bioprinting, tissue engineering, antibacterial and wound-healing materials, drug delivery, anti-bacterial, tumor therapy, tissue engineering, water remediation, and other biomedical applications [27][28][29][30][31][32][33][34][35][36][37][38][39][40][41][42][43][44][45][46][47][48][49][50][51][52][53][54][55][56][57][58][59][60][61][62][63][64][65][66].

2. Metabolite-Based Hydrogels

Metabolites are small molecules that are found as intermediate or end products of the metabolic network of various organisms. Key metabolites include amino acids, nucleobases, vitamins, saccharides, and lipids. Recent studies have indicated the ability of metabolites to form supramolecular assemblies.

2.1. Nucleobase-Based Hydrogels

Guanine-based hydrogels have been produced since the early 20th century, when it was discovered that 5′-guanosine monophosphate (5′-GMP) can accumulate into polycrystalline gels at millimolar concentrations [67]. The discovery that 5′-GMP can self-assemble into left-handed columnar aggregate particles that can pack into left-handed cholesteric mesophase liquid crystals at higher concentrations is the result of the prospective capacity to alter the properties of these assemblies [68]. Giraud et al. demonstrated the preparation of hydrogels from a new

series of hybrid nucleopeptides by incorporating DNA-nucleobases to produce their peptide nucleic acid (PNA) forms [69][70]. Thus, the physicochemical and mechanical properties of the resulting hydrogels can be significantly improved and fine-tuned depending on the type of nucleobase (i.e., thymine, cytosine, adenine, or guanine), with, for example, enhancement of both the gel stiffness (up to 70-fold) and the gel resistance to external stress (up to 40-fold), and the generation of both thermo-reversible and uncommon red-edge excitation shift (REES) phenomena.

2.2. Amino-Acid-Based Hydrogels

Single amino acids have also been shown to construct 3D networks of nanostructures capable of encasing solvent molecules and producing supramolecular gels. Furthermore, the crystalline gel state of L-Phe, the smallest molecule known to date to form gel networks in water, is particularly interesting because of its crystalline gel condition [17][18][71][72]. Zaguri et al. demonstrated the mechanical properties of the Phe single amino acid along with the associated supramolecular fibrillar structures, using scanning electron microscopy and atomic force microscopy [73]. Furthermore, Phe self-assembled fibrils, exhibiting a remarkable Young's modulus (30 GPa), were comprised of interlaced protofilaments in a helical or twisted ribbon-like supramolecular structure. Furthermore, the crystalline, highly homogeneous, and self-healing Phe hydrogel was formed in H_2O or PBS at a concentration of 0.24 M following heating at 90 °C and cooling after 5 h, resulting in significantly higher storage and loss moduli compared to other biocompatible fibrillar supramolecular structures. Moreover, Phe could form a hydrogel with high stiffness and nanofibrillar supramolecular structural properties, which may be used in various biomedical and technological applications, such as load-bearing 3D frameworks, self-healing, 3D printing, sensing, and tissue engineering.

Furthermore, Ramalhete et al. showed that L-Phe hydrogels could be employed as model materials for a nuclear magnetic resonance (NMR)-based analytical method for understanding supramolecular gelation [71]. This method made it possible to pinpoint the additional molecules that changed the material's characteristics. Amino-acid-containing L-Tryptophan (L-Trp)-based cationic amphiphilic hydrogelators with varied degrees of hydrophobicity were produced by Roy et al. [74]. These hydrogelators showed exceptional bactericidal action against a variety of Gram-positive (MIC = 0.1–75 μg/mL) and Gram-negative (MIC = 0.5–5 μg/mL) bacteria. Nebot et al. provided insight into the aggregation thermodynamics associated with hydrogel formation by molecular gelators derived from L-Val and L-Isoleucine (L-Ile) [75]. Liberato et al. presented His-based hydrogels obtained using photooxidation [76]. The His-based hydrogels were used to produce polymers comprising chondroitin sulfate functionalized with His and recombinant elastin-like peptide (ELP) using a unique mechanism for hydrogel formation via His photooxidation mediated by the singlet oxygen. Furthermore, two new hydrogels were synthesized by Yang et al. through the self-assembly of β-amino acid derivatives [77]. The confirmation of β-amino-acids-based hydrogelators should offer a new way to customize the stability of hydrogels in biological environments and ultimately broaden the ranges of applications of the hydrogels as biomaterials, because β-amino acids are less prone to biodegradation and are therefore expected to be available for longer times. Compared to hydrogels made from α-amino acid derivatives, this type of hydrogel should have a longer bioavailability under biological conditions. Pyrene-conjugated protein amino-acid-based super hydrogels have been shown to form a hydrogel in a variety of aqueous solutions across a wide pH range (7.46–14) [78].

Li et al. developed three-component luminous hydrogels made of melamine, riboflavin, and perylene derivatives functionalized with amino acids [79]. In the hybrid gel systems, hydrogen bonds, triple hydrogen bonds, and π–π stacking interactions form acid-functionalized perylene derivatives. A perylene core and two amino-acid residues were present as the terminal groups, as in the glutamate-functionalized perylene derivatives (GP) and tyrosine-functionalized perylene derivatives (TP). The homogenous self-assembly of the amino acids, together with the fluorescent riboflavin and perylene derivatives resulted in the formation of supramolecular luminescent hydrogel systems. These luminous hydrogels showed exceptional mechanical strength (>104 Pa) and low cell toxicity, which might be used to drive drug release in a regulated manner. Yang et al. showed that, based on self-assembled nanofibers of a β-amino acid derivative, supramolecular hydrogels were enzymatically formed in vitro and in vivo [80]. Juriga et al. evaluated the suitability of various hydrogels composed entirely of amino acids for use in tissue engineering and drug release [81]. Under various circumstances, the impact of the chemical makeup of these hydrogels on their mechanical and swelling capabilities was investigated. Different molar ratios of Lys and Cys were utilized as cross-linkers to produce poly(aspartic acid) (PASP)-based hydrogels. By modifying the chemical structure of the hydrogels using amino acids, PASP-based hydrogels were shown to be promising materials for both medical and pharmaceutical applications.

As demonstrated by Bratskaya et al., amino acids can also be utilized as chemical effectors to promote a transamination reaction that dissolves salicylimines hydrogels [82]. At pH 8, lysine significantly improved the solubility of N-substituted carboxyethylchitosan (CEC)-salicylimine, reaching 100% at an amino-acid concentration of 20 g/L. Salicylaldehyde's interaction with carboxy-alkyl-chitosan thus exhibits a new opportunity for the production of biopolymers that are usable over a far wider pH range than previously known for chitosan. Peres et al. showed that using free radical polymerization, pH-responsive hydrogels, and nanogels were produced using N-acryloyl-L-glutamic acid (L-AGA) [83]. By using solution homo-polymerization reactions with a monomer concentration of >30% *w*/*v*, physically cross-linked hydrogels were produced. It is interesting to note that less than 20% of the monomer was required to produce fully water-soluble polymers. A hydrophilic drug was successfully loaded into the nanogels, with an encapsulation efficiency of >83% and a drug content of >41 mg_{DOX}/g_P (mg of doxorubicin (DOX) per gram of polymer). Altogether, these results contribute to the rational design of molecular hydrogelators which could be used for the tailored preparation of this type of soft material for diverse applications.

2.2.1. Composite Amino-Acid-Based Hydrogels

Abenojar et al. designed a special thermo-responsive magnetic glycol chitin-based nanocomposite that contained iron oxide nanoparticles and D-amino acids [84]. This material could be delivered and transformed from a solution to a gel state at physiological temperature for sustained release of D-amino acids and magnetic field-activated thermal treatment of targeted infection sites. The D-amino acids in the hydrogel nanocomposite prevented the growth of new biofilms and dislodged those that already existed. Furthermore, loading the hydrogel nanocomposite with magnetic nanoparticles allowed combination thermal therapy after magnetic field stimulation (magnetic hyperthermia); infections resistant to conventional antibiotics were not completely eradicated by separate D-amino acid and magnetic hyperthermia treatments. Using this novel two-step approach which utilized an externally actuated gel-nanocomposite system for thermal treatment after initial disruption with D-amino acids, the authors

could demonstrate the complete eradication of the *Staphylococcus aureus* biofilms in vitro. Wang et al. successfully used L-Phe derivatives to self-assemble chiral twisted and non-twisted nanofibers in the presence of different metal ions [85]. They prepared two L-Phe-based hydrogelators such as LPF and LPPG. Through the coordination interaction between metal ions and supramolecular hydrogelators composed of L-Phe, a simple method was developed to produce the chiral nanotwists. The inverted test tube method showed that the hydrogels were produced after adding LPF to a variety of metal ions solutions, with the exception of the Eu^{3+} solution. Except for Li^{+} and Na^{+} complexes, the LPPG complexes with the aforementioned metal ions could also produce hydrogels. The self-assembled nanostructures' handedness, twist pitch, and diameter could be easily controlled [85]. These chiral twists have tremendous potential in electrochemical sensing, asymmetric catalysis, or chiroptics, and this technology can be used in complementary investigations of controlling the chirality of nanostructures.

Furthermore, Roy et al. showed a self-healing hydrogel composed of amino acids and (11-(4-(pyrene-1-yl)butanamido)undecanoic acid) [86]. Intriguingly, by introducing carbon-based nanomaterials such as graphene, pristine single-walled carbon nanotubes (Pr-SWCNTs), and both graphene and Pr-SWCNTs into the native gel system, it was possible to successfully control the self-healing, thixotropy, and stiffness of the hydrogel. Hybrid gels with RGO and/or Pr-SWCNTs also showed intriguing semiconductive activity.

2.2.2. Fmoc-Protected Amino-Acid-Based Hydrogels

Roy et al. showed that Fmoc-L-Phenylalanine-OH (Fmoc-Phe-OH), an N-terminally Fmoc-protected single amino acid, could produce an effective, stable, and transparent hydrogel at a minimum gelation concentration of 0.1% *w*/*v* [87]. Fluorescent few-atom silver nanoclusters have been produced and stabilized using this hydrogel. Intriguingly, silver ions were complexed with the carboxylate group of the Fmoc-Phe-OH gelator in a water medium in the absence of any hazardous reducing agents. The silver ions were spontaneously reduced at physiological pH and room temperature to produce silver nanoclusters. These chemically stable Ag nanoclusters that emit red light can be used for sensing and other applications. Furthermore, Yang et al. described various Fmoc-modified amino acids, such as Fmoc-Tyr, which were employed as effective hydrogelators, while unmodified amino acids without aromatic capping did not form hydrogels [88]. The group further demonstrated the utilization of a brand-new green Fmoc-Tyr-OH-amygdalin hydrogel for sustained release of amygdalin [89]. This hydrogel exerted neuroprotection by enhancing neurological performance and reducing neuroinflammation. Xie et al. showed that Fmoc-Trp, Fmoc-Methionine (Fmoc-Met), and Fmoc-Tyr were self-assembled to produce transparent, stable self-supporting hydrogels [90]. The antibacterial efficiency of all three forms of hydrogel was excellent against Gram-positive bacteria but minimal against Gram-negative bacteria in the sequence Fmoc-Trp hydrogel > Fmoc-Met hydrogel > Fmoc-Tyr hydrogel. The outstanding antibacterial characteristics of the amino-acid-based antibacterial hydrogels suggest their significant biomedical potential.

2.2.3. Co-Assembly-Based Amino Acid Hydrogels

Croitoriu et al. employed a pH-switch and a polar solvent strategy for the Fmoc-Trp-OH and the Fmoc-Lys-Fmoc-OH stock solution, respectively. In oscillatory shear experiments, stable structures with transparent and solid-like

characteristics were produced as a result of the co-assembly of the amino acids in various volumetric ratios [91]. Irwansyah et al. reported a unique supramolecular hydrogel platform formed by Fmoc-Phe which can be easily established by the intermolecular stacking interactions between Fmoc and the phenyl group [92]. Additionally, by combining the Fmoc-Phe hydrogelator with Fmoc-Leu as an antimicrobial building-block, antimicrobial properties could be conferred upon this supramolecular hydrogel platform via a co-assembly method. While showing biocompatibility towards cultured mammalian cells, the co-assembled (Fmoc-Phe + Fmoc-Leu) supramolecular hydrogel demonstrated selective Gram-positive bactericidal activity through a mechanism involving cell wall and membrane rupture. In contrast to the edges and smooth bodies observed for native bacteria, cellular deformation, and surface collapse were detected in *Staphylococcus aureus* cells following a 2-h incubation with the hydrogel, as also supported by live/dead bacterial staining assay. In contrast to commonly used antimicrobial hydrogels based on cationic materials, the fabrication of this antimicrobial hydrogel relies on the co-assembly of commercially available Fmoc-amino acids, allowing for the quick and affordable production of a biocompatible antimicrobial hydrogel without the need for time-consuming organic synthesis and purification procedures.

Furthermore, multi-component supramolecular hydrogels have also been reported to form when ε-Fmoc-Lys was combined with either Fmoc-Phe or Fmoc-Leu [93][94]. Guilbaud-Chereau et al. showed that various Fmoc-protected amino acids spontaneously self-assembled into a 3D fibrous network, resulting in the formation of hydrogels [95]. The authors examined binary mixtures of Fmoc-Tyr-OH and Fmoc-Tyr(Bzl)-OH or Fmoc-Phe-OH and Fmoc-Tyr(Bzl)-OH gels. Various microscopy and rheology methods were used to evaluate the structural and physical characteristics of these gels. These hydrogels contained oxidized carbon nanotubes (ox-CNTs) and graphene oxide (GO), which displayed a good interface with the fibrils, particularly the nanotubes. As a high-concentration model hydrophilic drug, L-Ascorbic acid was incorporated into the gels. With the potential for numerous applications, including drug delivery, the heat produced by the carbon nanomaterials upon NIR light irradiation stimulated the rapid release of the drug. Furthermore, Zhao et al. reported a novel conjugated oligomer, oligo(thiophene ethynylene) (OTE)-D-Phe, which was synthesized by adding D-Phenylalanine (D-Phe) to the side chain of conjugated OTE [96]. A novel and biocompatible low-molecular-weight hydrogel (HG-2) was produced through self-assembly by combining Fmoc-L-Phe and OTE-D-Phe. Xing et al. showed smart high-quality hydrogel materials with light irradiation-triggered luminescence using the co-assembly of Phe with bipyridines [97]. Hydrogel obtained from the co-assembly of Phe and bipyridines resulted in fluorescently imprinted materials without showing any photobleaching or phase separation during the irradiation of UV light. Fichman et al. demonstrated the ability to synthesize Fmoc-Tyr, Fmoc-3,4-dihydroxyphenylalanine (Fmoc-DOPA) two-component hydrogels with functional properties of the catechol groups and mechanical properties similar to those of the Fmoc-Tyr gel [98]. Such a multi-component arrangement could potentially enable researchers to take advantage of the Fmoc-DOPA antioxidant activity, radical trapping, and metal chelation functions in addition to its reduction activity. This is an excellent example of how the complementary qualities of different building blocks can be combined to generate new functionalities.

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