Bioactive Materials 40 (2024) 503–523

Contents lists available at ScienceDirect

Bioactive Materials

journal homepage: www.keaipublishing.com/en/journals/bioactive-materials

Review article

Recent research of peptide-based hydrogel in nervous regeneration

Chunmei Xie [a], Yueyang Chen [a], Lang Wang [a], Kin Liao [b], Bin Xue [c], Yulong Han [a,**], Lan Li [d,e,f,***], Qing Jiang [d,e,f,*]

[a] State Key Laboratory of Mechanics and Control of Mechanical Structures, Nanjing University of Aeronautics and Astronautics, Nanjing, 210016, China
[b] Advanced Digital and Additive Manufacturing Center, Khalifa University of Science and Technology, Po Box 127788, Abu Dhabi, United Arab Emirates
[c] National Laboratory of Solid State Microstructures, Department of Physics, Nanjing University, Nanjing, China
[d] State Key Laboratory of Pharmaceutical Biotechnology, Division of Sports Medicine and Adult Reconstructive Surgery, Department of Orthopedic Surgery, Drum Tower Hospital Affiliated to Medical School of Nanjing University, Nanjing, China
[e] Jiangsu Engineering Research Center for 3D Bioprinting, Nanjing, China
[f] Institute of Medical 3D Printing, Nanjing University, Nanjing, China

ARTICLE INFO

Keywords:
Self-assembled
Dipeptide
Cyclic dipeptide
Hydrogels
Nervous regeneration

ABSTRACT

Neurological disorders exert significantly affect the quality of life for patients, necessitating effective strategies for nerve regeneration. Both traditional autologous nerve transplantation and emerging therapeutic approaches encounter scientific challenges due to the complex nature of the nervous system and the unsuitability of the surrounding environment for cell transplantation. Tissue engineering techniques offer a promising path for neurotherapy. Successful neural tissue engineering relies on modulating cell differentiation behavior and tissue repair by developing biomaterials that mimic the natural extracellular matrix (ECM) and establish a three-dimensional microenvironment. Peptide-based hydrogels have emerged as a potent option among these biomaterials due to their ability to replicate the structure and complexity of the ECM.

This review aims to explore the diverse range of peptide-based hydrogels used in nerve regeneration with a specific focus on dipeptide hydrogels, tripeptide hydrogels, oligopeptide hydrogels, multidomain peptides (MDPs), and amphiphilic peptide hydrogels (PAs). Peptide-based hydrogels offer numerous advantages, including biocompatibility, structural diversity, adjustable mechanical properties, and degradation without adverse effects. Notably, hydrogels formed from self-assembled polypeptide nanofibers, derived from amino acids, show promising potential in engineering neural tissues, outperforming conventional materials like alginate, poly(ε-caprolactone), and polyaniline. Additionally, the simple design and cost-effectiveness of dipeptide-based hydrogels have enabled the creation of various functional supramolecular structures, with significant implications for nervous system regeneration. These hydrogels are expected to play a crucial role in future neural tissue engineering research. This review aims to highlight the benefits and potential applications of peptide-based hydrogels, contributing to the advancement of neural tissue engineering.

1. Introduction

Neurological injuries often create a neuroinhibitory environment within the central nervous system (CNS), and they also lead to incomplete tissue remodeling in the peripheral nervous system (PNS). Damage to the CNS, which includes the brain, spinal cord, and retina, leads to the loss of sensory, motor, and cognitive functions. Similarly, severe peripheral nerve injuries (PNIs) can significantly reduce patient quality of life [1]. In the United States alone, around a quarter of a million individuals experience spinal cord injuries (SCIs) every year, with

Peer review under responsibility of KeAi Communications Co., Ltd.

* Corresponding author. State Key Laboratory of Pharmaceutical Biotechnology, Division of Sports Medicine and Adult Reconstructive Surgery, Department of Orthopedic Surgery, Drum Tower Hospital affiliated to Medical School of Nanjing University, Nanjing University, No.321 Zhongshan Road, Nanjing, 210000, China.
** Corresponding author. State Key Laboratory of Mechanics and Control for Aerospace Structures, Nanjing University of Aeronautics and Astronautics, No. 29 Yudao Street, Nanjing, 210016, China.
*** Corresponding author. State Key Laboratory of Pharmaceutical Biotechnology, Division of Sports Medicine and Adult Reconstructive Surgery, Department of Orthopedic Surgery, Drum Tower Hospital affiliated to Medical School of Nanjing University, Nanjing University, No.321 Zhongshan Road, Nanjing, 210000, China.
E-mail addresses: hanyulong@nuaa.edu.cn (Y. Han), lanl17@163.com (L. Li), qingj@nju.edu.cn (Q. Jiang).

https://doi.org/10.1016/j.bioactmat.2024.06.013
Received 3 April 2024; Received in revised form 2 June 2024; Accepted 7 June 2024

approximately 3.5 million people affected by such injuries. Surprisingly, fewer than 1 % of these patients achieve full recovery upon hospital discharge. Additionally, an estimated 27–69 million new cases of traumatic brain injury (TBI) are reported each year [2], with most survivors experiencing moderate to severe disability even five years after the initial injury. These resulting disabilities often require rehospitalization, affecting individuals' quality of life and imposing a significant economic burden on society [3]. Although some degree of nerve damage can undergo regeneration, finding an optimal solution remains challenging. Consequently, nerve regeneration has attracted considerable attention.

Currently, autologous grafts are considered the gold standard for treating nerve defects [4]. However, these methods have limitations, including microstructural mismatch, the need for donor site surgery, limited donor availability, and issues related to excessive graft length [5]. Therefore, there is an urgent need to identify suitable alternative therapies, and tissue engineering techniques have emerged as the most effective strategies for repairing neural defects [6]. In the field of nerve regeneration tissue engineering, various materials are commonly used.

Materials commonly employed for nerve tissue regeneration can be classified into three categories [7]. Firstly, artificial synthetic materials like polylactic acid (PLA), polycaprolactone (PCL), and polyglycolic acid (PLGA) are utilized. When combines with bone marrow mesenchymal stem cells, PLA has been demonstrated to hasten peripheral nerve regeneration [8] and stimulate Schwann cell migration, facilitating the formation of normal neural structures [9]. PCL exhibits a nerve repair effect similar to autografts, surpassing PLA [10]. Furthermore, PCL can undergo metabolism and excretion from the body. PLGA shows commendable mechanical properties for repairing lengthy nerve defects [11]. Artificial synthetic materials demonstrate favorable biocompatibility and biodegradability. However, employing a single synthetic material necessitates a significant investment of time and financial resources. Additionally, these materials exhibit poor elasticity and hardness [12].

Natural biomaterials, including collagen, silk, and gelatin, are noteworthy for their extensive use in clinical applications. Among these, Type I collagen conduits stand out as the most commonly employed biomaterial. When applied to repair long gap defects, they demonstrate performance comparable to autografts, effectively fostering nerve regeneration and facilitating repair processes [13]. Silk fibroin materials exhibit remarkable capabilities in promoting the release of nerve growth factors and related factors, creating an enriched environment conducive to optimal nerve repair [14]. Additionally, they display excellent compatibility with dorsal root ganglion neurons, actively supporting their growth and development [15]. Gelatin materials contribute to the swift restoration of the blood-brain barrier following acute brain injury [16]. These natural biomaterials are esteemed for their exceptional biocompatibility and biodegradability. They are readily absorbed by the body, with abundant sources ensuring accessibility. However, it is imperative to recognize that each natural biomaterial possesses its own set of limitations. Some materials may exhibit brittleness, rendering them susceptible to fracture, while others may be prone to erosion in moist environments. Additionally, certain natural materials may have limited solubility in water and conventional organic solvents, which can restrict their application in certain scenarios.

As research progresses, an increasing array of new biodegradable materials finds application in nerve regeneration. Chitosan emerges as a pivotal player, offering support, protection, and guidance during the initial phases of nerve repair [17]. It establishes a relatively stable and localized microenvironment that facilitates the regenerative process. When paired with bone marrow mesenchymal stem cells, chitosan conduits effectively enhance the repair of peripheral nerve injuries [18]. Graphene, a two-dimensional carbon nanomaterial, offers remarkable optical, electrical, and mechanical properties. Integration of graphene nanoparticles into chitosan/gelatin scaffolds for rat sciatic nerve injury repair significantly boosts nerve regeneration [19,20]. Graphene not only mitigates inflammation but also expedites the migration of endogenous neural progenitor cells [21]. These innovative materials warrant further investigation to unveil their full spectrum of advantages and drawbacks.

The above synopsis offers an insight into three commonly utilized materials for neural tissue regeneration, delineating their respective merits and demerits. Nonetheless, the pursuit of biomaterials capable of providing a sustained and stable regenerative microenvironment for neural tissue remains an ongoing endeavor.

Peptide-based materials have attracted increasing attention in neural regeneration research in recent years, owing to several key factors.

a) Peptides synthesized via solid-phase methods can undergo molecular-level modifications, allowing for the creation of peptide-based nanomaterials with tailored properties [22].
b) Additional functionality can be imparted to peptide-based nanomaterials by intergrating external substances, such as enzymes, into the peptide nanostructures [23].
c) Precise manipulation of the self-assembly process of peptide-based materials is achievable by controlling the secondary structures of peptide building blocks, including α-helices and β-sheets [24].
d) Peptide-based materials accurately replicate the intricate structure and complexity of the extracellular matrix [25].

This unique characteristic enables their broad utilization across various domains, including drug delivery, tissue engineering, biosensors, protein separation, and wound healing [26].

This review examines various peptide-based hydrogels commonly used in nerve regeneration, such as dipeptide hydrogels, tripeptide hydrogels, oligopeptide hydrogels, multidomain peptides (MDPs), and amphiphilic peptide hydrogels (PAs). It examines the characteristics, design strategies, application modes, and mechanisms involved in promoting nervous tissue regeneration using peptide-based materials. Furthermore, this review provides insights into the future prospects of applying these materials in the field of nerve regeneration.

2. Design strategies for peptide-based hydrogels for nervous regeneration

2.1. Amino acids

In peptide-based hydrogels, amino acids serve as the fundamental building blocks of the three-dimensional matrix. Twenty different natural amino acids are utilized to synthesize peptides, resulting in a wide range of peptide sequences [27]. Table 1 provides the complete range and abbreviations of amino acids for the convenience of readers. The specific amino acid sequences within the peptides are crucial in designing various peptide-based hydrogels. By carefully modifying the side chain functionalities of the constituent amino acids in the peptide backbone, both intermolecular and intramolecular interactions can be adjusted. The number of peptide bonds (-CONH- amide bonds) between amino acids distinguishes short-peptide hydrogels from long-peptide

Table 1
Table of standard amino acid abbreviations. *Encode secondary amino acids.

Amino acids	3- and 1-letter symbols	Amino acids	3- and 1-letter symbols
Alanine	Ala/A	Arginine	Arg/R
Asparagine	Asn/N	Aspartate	Asp/D
Cysteine	Cys/C	Glutamine	Gln/Q
Glutamate	Clu/E	Glycine	Gly/G
Histidine	His/H	Isoleucine	Ile/I
Leucine	Leu/L	Lysine	Lys/K
Methionine	Met/M	Phenylalanine	Phe/F
Proline	Pro/P	Serine	Ser/S
Threonine	Thr/T	Tryptophan	Trp/W
Tyrosine	Tyr/Y	Valine	Val/V
Selenocysteine*	Sec/U	Pyrrolysine*	Pyl/O

hydrogels. Short peptides range from dipeptides to oligopeptides and most being generally more cost-effective and simpler to synthesize than long peptides. The differing number of peptide bonds results in variations in intermolecular hydrogen bonding, thereby influencing the physical properties of the peptides, including their mechanical properties. Additionally, the hydrophobic or hydrophilic nature of the amino acids in the peptides can affect the overall hydrophobicity or hydrophilicity of the hydrogel, contributing to distinct gel properties.

2.1.1. Short peptides

2.1.1.1. Dipeptide. Among short peptides, dipeptides represent the smallest units and consist of two amino acids, with one amino terminus referred to as the N-terminus and one carboxyl terminus (-COOH) known as the C-terminus (Fig. 1A) [28]. However, due to their relatively short sequence length, dipeptides alone may not exhibit adequate interactions to form a stable gel network. Hence, additional aromatic

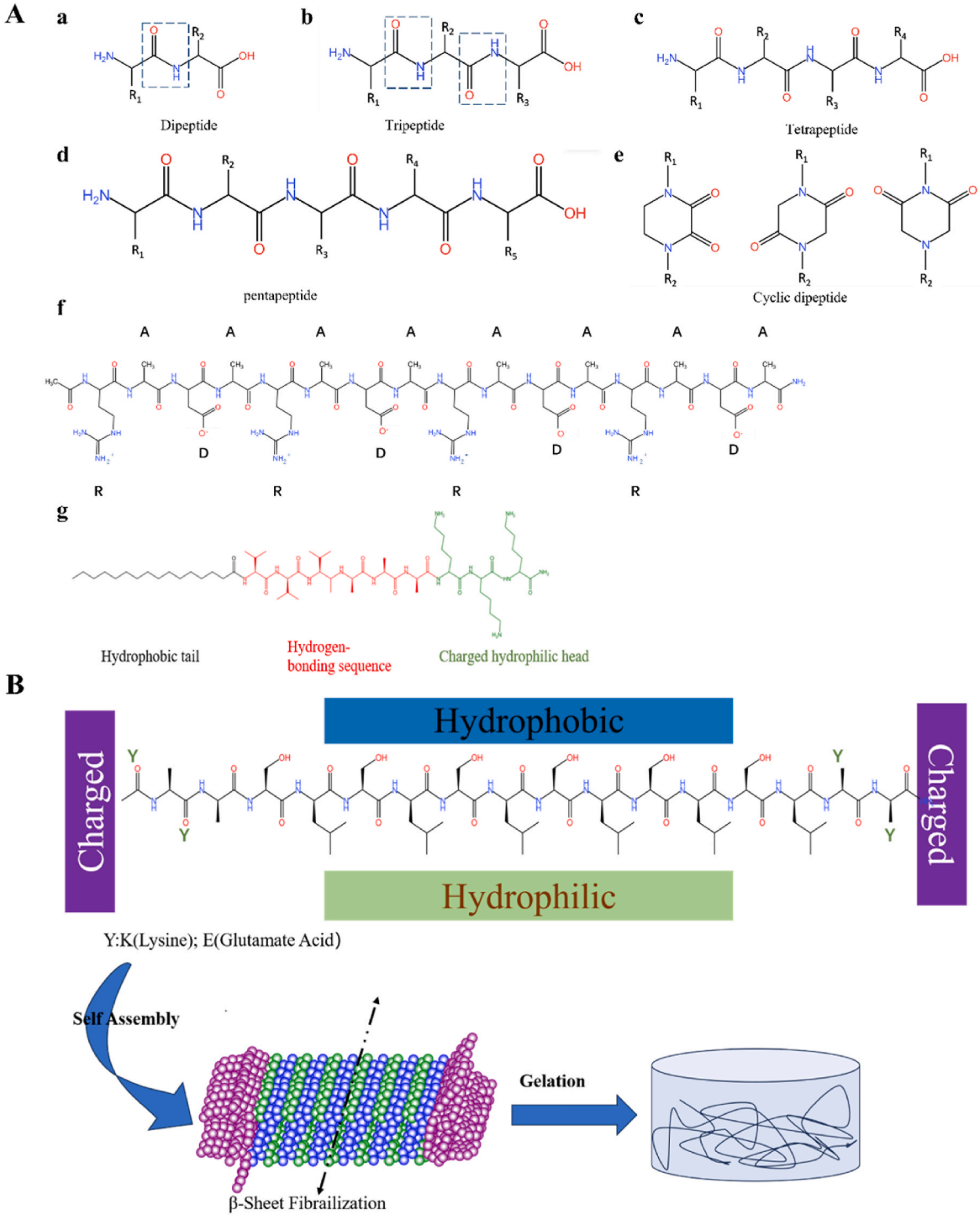

Fig. 1. (A) The core structures of dipeptide (a), tripeptide (b), tetrapeptide (c), pentapeptide (d), cyclic dipeptide (e), RADA 16 (f), PA (g). (B) The structure of MDPs and the self-assembly process. MDPs with a hydrophilic surface (green), a hydrophobic surface (blue), and two charged structural domains (purple) on both sides. Under physiological conditions, MDP self-assembles and occurs in β-sheet fibers. This led to the formation of MDP nanofibers and rapid gel formation into nanofiber hydrogels.

moieties are frequently incorporated into dipeptide structures to improve gel formation and enhance mechanical strength through self-assembly processes [29–31]. Aromatic rings have been shown to promote the gelation of bioactive peptides. Examples of such aromatic moieties include fluorene methoxycarbonyl (Fmoc), naphthalene (Nap), phenothiazine (PTZ), carboxybenzyl (Cbz), azobenzene (Azo), and pyrene (Pyr). These aromatic groups facilitate extensive π-π interactions, boosting the intermolecular interactions within the gel and promoting the self-assembly of non-gelling gelators under mild conditions. Research has demonstrated that dipeptides lacking aromatic groups are incapable of forming hydrogels [32].

Dipeptides can be classified based on various modifications of the aromatic ring. One prevalent modification involves the addition of the fluorene methoxycarbonyl (Fmoc) group, commonly utilized as a protective group in peptide synthesis [33]. Hydrogels formed by combining Fmoc with derivatives of glycine (Gly), alanine (Ala), leucine (Leu), and phenylalanine (Phe) exhibit favorable stability. Examples include Fmoc-Phe-Phe [34], Fmoc-Gly-Gly, Fmoc-Ala-Gly, Fmoc-Ala-Ala, Fmoc-Phe-Gly and Fmoc-Leu-Gly. However, most of these hydrogels undergo gelation only under very low pH conditions (pH < 4) [32], except for Fmoc-Phe-Phe, which can form hydrogels at physiological pH [35]. This pH hinders their applicability in biomedical settings. It is crucial to recognize that not all Fmoc-modified dipeptides possess the capability to form hydrogels under any circumstances.

Researchers are increasingly investigating alternative aromatic end groups, such as Nap (naphthalene). Nap-modified dipeptides have shown the capacity to form hydrogels by manipulating the solution pH. For example, as the solution pH decreases, Nap-Gly-Ala can undergo gelation and develop into a hydrogel, whereas Nap-Ala-Gly tends to assume a crystalline structure instead [36]. Nonetheless, it is critical to acknowledge that these functional groups frequently demonstrate toxicity, presenting hurdles for their use in biomedical applications [37].

2.1.1.2. Tripeptide. Tripeptides represent a category of short peptides that can be either N-terminally protected or N-terminally unprotected [28]. Among these tripeptides, the arginine-glycine-aspartic acid (RGD) sequence holds particular significance. RGD is recognized as the smallest peptide sequence capable of promoting cell adhesion. When RGD binds to fibronectin, it aids in the activation and myelin formation of Schwann cells (SCs) post-injury. Additionally, it fosters axonal regeneration and boosts the expression of specific integrins α5 and β6 in the injured environment [38]. Integrating the adhesive ligand RGD presents an alternative method for enhancing peripheral nerve regeneration [39]. However, it is crucial to consider the positioning of the RGD sequence within the peptide structure, as it can influence cell adhesion. For instance, when the RGD sequence is introduced into peptide fibers initially containing the RADARADARADARADA sequence and RAD is substituted with RGD as the self-assembly unit, resulting peptide fibers with the RGDARADARADARADA sequence exhibit weaker cell adhesion compared to peptide fibers containing the RADARADARADARADA sequence [40].

Glutathione (γ-L-glutamyl-L-cysteinylglycine, GSH) is an endogenous tripeptide with potent antioxidant properties. Unlike other tripeptides, GSH features a distinct peptide linkage between the amino group of cysteine and the carboxyl group of glutamate. Elevated levels of reactive oxygen species (ROS) in the body lead to oxidative stress, closely associated with various neurodegenerative disorders, including Parkinson's disease [41]. GSH functions as a primary antioxidant in the brain, serving as a crucial cofactor for numerous enzymes. It acts as a safe reservoir of cysteine, a pivotal component in cellular antioxidant defenses. Additionally, GSH acts as a vital regulator and neurotransmitter in the central nervous system, contributing to proper neuronal signaling and function [42].

Furthermore, there exists a tripeptide known as glycine-proline-glutamate (GPE), naturally occurring as the N-terminal tripeptide of insulin-like growth factor-1 (IGF-1), cleaved by acidic proteases in brain tissue. *In vitro* studies have revealed its capacity to stimulate the release of acetylcholine and dopamine, as well as to shield neurons against various induced brain injuries. Moreover, GPE has demonstrated significant neuroprotective effects in animal models of numerous hypoxic-ischemic brain injuries and neurodegenerative diseases, such as Parkinson's disease, Alzheimer's disease, and Huntington's disease [43].

2.1.1.3. Oligopeptides. Oligopeptides are short-chain peptides consisting of more than two but fewer than twenty peptide bonds. Similar to other peptide-based hydrogels, oligopeptide-based hydrogels can form through self-assembly driven by non-covalent interactions. These hydrogels display three-dimensional networks and exhibit a diverse range of nanostructures, including β-sheets, helical structures, β-hairpin-based fibers, and nanotubes [44,45].

Tetrapeptides, a subtype of oligopeptide, can also self-assemble into three-dimensional nanostructured hydrogels through non-covalent interactions and find wide application in various fields. To date, several tetrapeptide sequences used for nerve regeneration, such as RGDS (arginine-glycine-aspartic acid-serine) and RADA (arginine-alanine-aspartate-alanine), have been identified. The RGDS sequence introduces serine (S), which provides additional hydrogen bonds and electrostatic interactions, increasing the binding affinity of RGDS to cell surface receptors. This promotes cell adhesion, signaling processes, and contributes to the regeneration potential of neural tissue [46]. Conversely, RADA can form β-sheet-rich nanofibers, creating an environment favorable for cell growth and tissue regeneration [47].

Pentapeptides hold significance for both synthetic and biological applications [48]. Among the pentapeptides include IKVAV (isoleucine-lysine-valine-alanine-valine) and YIGSR (tyrosine-isoleucine--glycine-serine-arginine). Notably, IKVAV facilitates neuron adhesion, differentiation, and axonal growth within the injured peripheral nerve area. It also inhibits glial cell adhesion and differentiation while mimicking the conducive microenvironment necessary for nerve cell growth during peripheral nerve repair [49]. On the other hand, YIGSR can promote cell adhesion [50].

Another noteworthy category of oligopeptides is cyclic peptides (CDPs). CDPs are unique polypeptide chains consisting of amino acids connected by amide bonds, forming a closed cyclic sequence. These cyclic structures can be derived from protein-derived or nonprotein-derived amino acids. CDPs possess favorable properties such as low toxicity, high binding affinity, and targeted selectivity, making them highly attractive for therapeutic drug development [46]. For example, CDPs, being the smallest cyclic peptides, can traverse the blood–brain barrier, rendering them suitable for the development of oral neuroprotective agents [47]. Due to their ability to transmembrane and penetrate cells, CDPs have been extensively studied as drug carriers [48]. They have also been explored for various biological activities [49–51], making them promising for biomedical applications.

2.1.2. Ionic complementary oligopeptides

Ionic complementary self-assembled oligopeptides are comprised of alternating charged hydrophilic and hydrophobic amino acids, enabling them to form supramolecular nanofiber hydrogels through self-assembly [51]. Since the development of EAK16-II [52], numerous ion-complementary self-assembled peptides with remarkable properties have been devised as promising biomaterials, including RADA16-1 [53], KLD12 [54], and KFE8 [55]. Of these peptides, RADA16-I stands out as extensively studied and representative in various fields.

RADA16-I (Ac-RADARADARADARADA-CONH2) is widely used as a self-assembling oligopeptide hydrogel known for its exceptional biocompatibility, minimal cytotoxicity, and three-dimensional structure

that supports cell growth [56]. RADA16 comprises four tetrapeptide repeats containing R (arginine, positively charged), A (alanine, hydrophobic), and D (aspartic acid, negatively charged) amino acid residues (Fig. 1A). RADA16 can self-assemble into a hydrogel capable of transporting neurotrophic substances to nerve cells, crucial for nerve regeneration, nerve cell adhesion, and axon elongation [57]. Yoshimatsu et al. reported the design of hydrogels of RADA16-I (+) and RADA16-I (−) to assess their effects on regenerating the recurrent laryngeal nerve in rats [58]. Results demonstrated the effectiveness of prepared RADA16-I peptides in promoting recurrent laryngeal nerve regeneration. Another notable example is the design of Ac-$(RADADA)_2$-$CONH_2$ (RADA16-II), RAD16-II, and EAK16-II scaffolds exhibiting good mammalian cell adhesion [59]. These peptides, along with many others in this class, have been successfully applied in tissue engineering, prospects for tailored functional biomaterials [53,60].

2.1.3. The multidomain peptides (MDPs)

MDPs, a type of SAP, are composed of ABA blocks. The term ABA denotes the arrangement of specific peptide blocks within the MDP structure. Block A comprises charged amino acids located at the terminal flanks, while block B contains alternating sequences of hydrophobic and hydrophilic amino acids (Fig. 1B) [61]. The hydrophobic residues within the MDPs play a pivotal role in forming a β-sheet conformation, resulting in a hydrophobic ABA sandwich structure. In an aqueous solution containing multivalent salts, MDPs dissolve. This dissolution causes the hydrophilic side chains of the amino acid residues to face outward, while the hydrophobic side chains face inward. As a result, antiparallel β-sheets form, followed by self-assembly into nanofibers. MDP hydrogels have garnered significant attention in nerve regeneration due to their biological activity and interaction capability with surrounding tissues. The unique characteristics of MDPs, including their self-assembly into nanofibers, render them suitable for various applications in regenerative medicine, particularly in the context of nerve regeneration [62].

2.1.4. Peptide amphiphiles (PAs)

Peptide amphiphiles (PAs) have attracted considerable attention due to their unique structure, comprising a hydrophobic tail and a hydrophilic structure [63]. This distinctive composition enables PAs to self-assemble in aqueous solutions, giving rise to diverse nanostructures with significant applications. In 2001, the Stupp Lab reported the first instance of self-assembled nanofibers formed by PA molecules. These molecules can create hydrogel biomaterials that mimic the properties of the extracellular matrix. The nanofibers can present biological signals on their surfaces and facilitate hydrogel formation by reducing the charge density on amino acid residues. Typically, PA molecules forming fibers consist of peptide sequences containing fewer than 10 amino acids, attached to aliphatic tails with more than 10 carbon atoms. (Fig. 1A). The addition of a hydrophobic tail to peptides gives PAs their amphiphilic characteristics, allowing them to self-assemble into structured formations. These amphiphilic self-assembled peptides are primarily classified into surfactant-like peptides and peptide amphiphiles. PAs offer great versatility and can form self-assembled nanostructures with adjustable properties, making them highly attractive for applications in tissue engineering, drug delivery, and regenerative medicine. Current research endeavors aim to further investigate and broaden the scope of PAs in these domains.

2.1.4.1. Surfactant-like peptides (SLP). Surfactant-like peptides (SLP) are characterized by one or two hydrophilic amino acid residues at the head and several hydrophobic amino acid residues at the tail. These peptides include cationic SLPs (such as Ac-A_3K–NH_2, Ac-A_6K– NH_2, Ac-A_9K– NH_2, and Ac–I_3K– NH_2) and anionic SLPs (such as Ac–V_6D-COOH, Ac–V_6D_2-COOH, and Ac-A_6D-COOH) [64]. One notable advantage of SLPs is their typically short sequence length, often comprising fewer than 10 amino acids. This characteristic renders them relatively easy to synthesize and more cost-effective than longer peptide sequences. However, not all surfactant-like peptides with short sequences have the ability to form hydrogels. Hydrogel formation is desirable for various applications, including tissue engineering and drug delivery. Therefore, future research in this field may focus on designing and exploring short surfactant-like peptides capable of forming stable hydrogels.

2.1.4.2. Amphiphilic peptides. Amphiphilic peptides fall under the category of peptide amphiphiles (PAs) and are a part of the PA class. In comparison to other peptide-based polymers, the peptide region within PAs plays a pivotal role in facilitating their self-assembly process. A notable feature of PAs is the connection between hydrophobic long-chain alkyl groups and hydrophilic peptides. These alkyl chains are typically incorporated into either the N-terminus or C-terminus of the peptide sequence. Additionally, the basic components of PAs resemble those found in natural lipid molecules [65]. Moreover, PAs can be designed as peptide polymers with 2–4 structural domains, allowing for the integration of new structures, functions, and affinities. This enhances their interaction with cell membranes or intracellular organelles [66]. Peptide amphiphilic compounds are commonly used as carriers for the targeted delivery of antitumor agents and nucleic acid drugs to specific sites.

2.2. The mechanism of peptide self-assembly

When peptides are dissolved in a solvent, they can adopt specific conformations that play a critical role in determining whether self-assembly occurs. Certain secondary structures, such as β-sheets, β-hairpins, and α-helices, are particularly favorable for peptide self-assembly, leading to different nanostructures (Fig. 2A) [67].

2.2.1. β-sheets

β-sheets are indeed frequently selected as secondary structures for crafting peptide-based hydrogels (Fig. 2B). In 1997, Boden et al. outlined key design principles for *β*-sheet type aggregates in solution: 1) Side chain functionalities' crosslinking forces are pivotal for *β*-sheet structure stabilization, achievable through diverse non-covalent interactions like hydrogen bonding, hydrophobic interactions, and electrostatic interactions. 2) Adjacent *β*-strands necessitate recognizing each other for one-dimensional lateral self-assembly. Failing these criteria may result in heterogeneous β-sheet structure aggregation. 3) Strong water adhesion to the *β*-sheets' surface was identified as an essential factor [68]. Following these guidelines, Aggeli et al. synthesized anionic and a cationic peptide [69]. IIndividual peptides typically adopt random coil structures in their monomeric state. However, in mixed aqueous solutions of cationic and anionic peptides, they can form polyelectrolyte complex fibrils, likely due to the spontaneous self-assembly of the original fiber network and columnar hydrogel generation [70]. This approach aligns with Boden's design principles and has been utilized by various groups to develop peptides capable of forming *β*-sheet structures and their corresponding hydrogels, such as FEFKFEFK (F8), FKFEFKFK (FK), FEFEFKFE (FE), FEFKFEFKK (F8K), and KFEFKFEFKK (KF8K) (F: phenylalanine; E: glutamic acid; K: lysine) [71–74]. Additionally, the hydrogel exhibits remarkable compatibility with nerve cells, fostering a conducive environment for cell adhesion and proliferation, thereby enhancing the potential utility of peptide hydrogels in neural tissue engineering [75,76].

2.2.2. β-hairpin

Another intriguing secondary structure is the *β*-hairpin (Fig. 2B). It entails the creation of a type II β-turn between two periodically repeating chains, featuring alternating hydrophilic and hydrophobic amino acids. The Schneider group empolyed a tetrapeptide containing a ^{D}Pro-^{L}Pro sequence flanked on both sides by two (VL)4 chains [77]. These peptides exhibited stimulus-driven folding into *β*-hairpin structures. In the folded state, the generated hairpin structure fosters

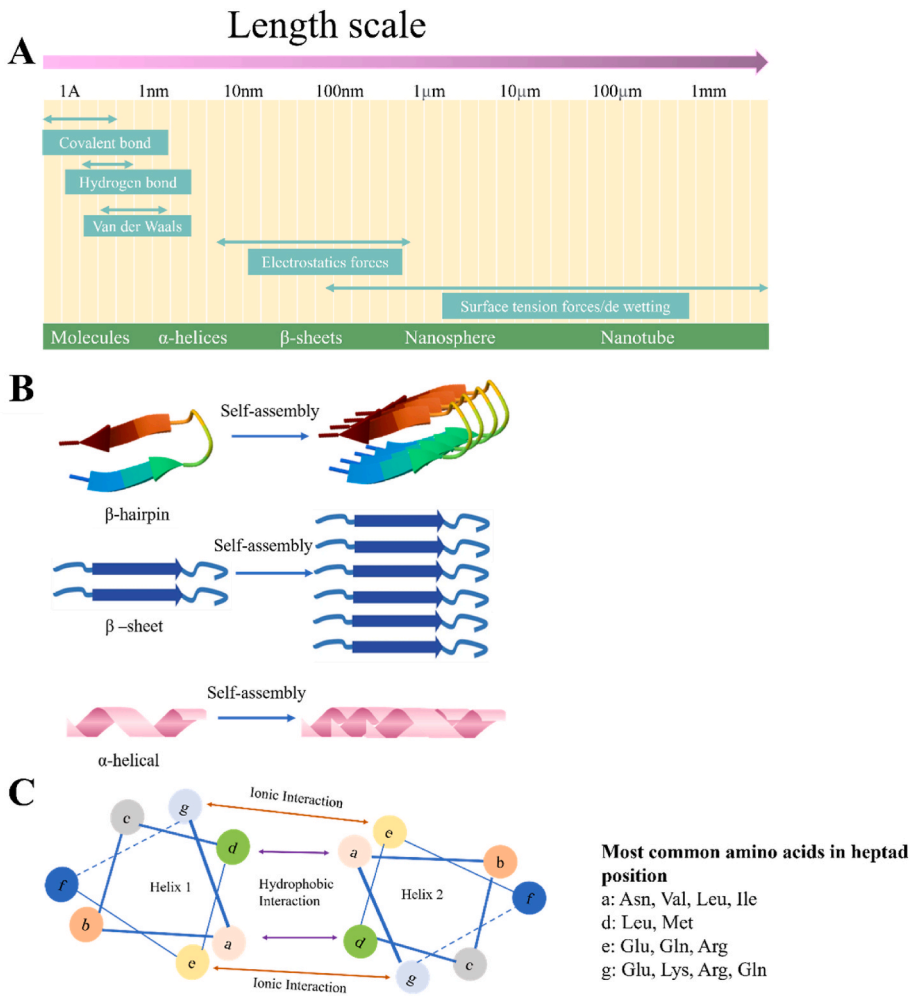

Fig. 2. (A) The patterns of forces involved in self-assembly and its generated structures. (B) Schematic representation of the *β*-hairpin, *β*-sheet, and *α*-helical structures. (C) Schematic illustration of the coiled-coil domain structure and interactions. The letters '*abcdefg*' represent seven amino acid residues comprising a hydrophobic heptad-repeat.

intermolecular hydrogen bond and hydrophobic face binding, facilitating higher-order self-assembly. The MAX family of peptides includes well-established *β*-hairpin peptides. MAX1 (VKVKVKVK-V^{D}PPT-KVKVKVKV-NH_2) serves as an illustration of a MAX peptide. In neutral or low-pH environments, MAX1 remains unfolded and irregularly curled due to repulsive forces between positively charged lysine side chains, particularly at low ionic strengths [78,79]. This prevents the peptide arms from adopting a parallel *β*-sheet conformation.

Similar peptide sequences forming *β*-hairpins comprise TSS1, IC1-R (CKIKIKIK–IDPPT–KIOIKIKC–NH_2) [80], IA-2 (H_2N-IKIKIKIK-IDPPT-KIOIKIKI-NH_2) [81]. These peptides feature the requisite amino acid motifs for *β*-hairpin formation. The stimulus-driven folding and self-assembly of *β*-hairpin peptides can be harnessed to fabricate responsive materials like hydrogels capable of undergoing conformational alterations in response to specific triggers such as pH, temperature, or the presence of certain molecules.

Overall, the *β*-hairpin structure in peptides offers a versatile foundation for crafting self-assembling biomaterials with tailored properties, applicable in areas such as drug delivery, tissue engineering, and biosensing.

2.2.3. *α-helical*

α-Helical peptides are relatively uncommon, likely due to the predominantly intramolecular hydrogen bonds associated with *α*-helices, rendering these secondary structures discrete entities. By incorporating the appropriate amino acids into the primary sequence, *α*-helices can self-assemble through hydrophobic and ionic interactions between two helices [82]. Peptide-based hydrogels typically consist of coiled coils comprising two or more α-helices. Coiled coils are typically designed with a seven-residue repeat (heptads), with amino acids labeled *a-g* (Fig. 2C) [83]. In a standard heptad, hydrophobic residues at positions a and d create a hydrophobic core, while ionic interactions between charged residues at positions e and g contribute to coiled-coil stability. Based on this model, Woolfson introduced a series of 28-residue peptides [84–86]. These peptides assemble into *α*-helical dimers with complementary sticky ends, and appropriate peptide sequence modifications result in temperature-responsive hydrogels. These temperature-responsive hydrogels, based on *α*-helical coiled coils, illustrate the potential of *α*-helical peptides in designing functional biomaterials.

In summary, although *α*-helical peptides are relatively less common, their capability to self-assemble via hydrophobic and ionic interactions presents opportunities for designing peptide-based hydrogels based on coiled-coil structures. Tailoring peptide sequences appropriately can lead to the formation of *α*-helical dimers and the creation of functional hydrogel materials with diverse applications.

2.3. *Methods for the synthesis of peptide-based hydrogels*

The extracellular matrix (ECM) serves as a dynamic system with specific mechanical attributes that significantly influence cellular

behavior. When developing hydrogels for cell culture, it is essential to replicate both *in vivo* and *in vitro* environments accurately. Research indicates that the destiny of mesenchymal stem cells is largely governed by the scaffold's stiffness [87,88]. This concept finds support in studies by Liepzig et al. [89] and Saha et al. [90], affirming that NSCs tend to differentiate into neurons on matrices with elastic moduli below 1 kPa, while scaffolds exceeding 1 kPa can induce differentiation into glial cell lineages. Hence, precise modulation of the stiffness or mechanical attributes of peptide-based hydrogels holds paramount importance.

Peptide-based hydrogels can be synthesized through two main methods (Fig. 3), physical crosslinking and chemical crosslinking [91]. Table 2 illustrates some notable examples of both physical and chemical approaches. These methodologies offer distinct benefits and enable the adjustment of various hydrogel properties. Subsequently, we will investigate a detailed discussion of these two synthesis techniques.

2.3.1. Physical crosslinking by non-covalent interactions

Physical crosslinking relies on non-covalent interactions, including ionic/electrostatic interactions [23], hydrophobic/hydrophilic interactions [24], hydrogen bonding [25], and π-π interactions [26]. The dynamic interplay between intra- and intermolecular self-assembly [97] confers peptides with hierarchical structures possessing diverse functionalities. Therefore, physical crosslinking represents a prevalent strategy in polypeptide hydrogel synthesis.

Ionic/electrostatic interactions form the basis of conventional physical crosslinking between two molecules with opposite charges. These interactions underpin physical crosslinking and enable hydrogels to manifest self-healing properties. Under high stress, the hydrogel structure can break, only to reform once the stress abates. However, it is worth noting that this self-healing ability often compromises mechanical strength, which can limit the utility of such hydrogels. Collagen, the primary protein in the natural ECM, features regularly repeated Gly-XY sequences (where X is usually proline and Y is hydroxyproline) [98]. In a study by Vijay et al. [99], two phenylalanine (Phe) residues were introduced at the N-terminus of collagen-derived motifs to enhance self-assembly through π-π interactions. Furthermore, proline's intermediate position within the motif was replaced with a positively charged lysine residue and a negatively charged aspartate residue. This substitution facilitated interactions between complementary charges on the residues, leading to the formation of a complex hierarchical structure.

Table 2
Some representative examples of physical and chemical methods for the synthesis of peptide-based hydrogels.

Synthesis method	Hydrogel Composition	Hydrogel Composition	Reference
Physical crosslinking	vancomycin-pyrene	Hydrogen bonds	[92]
	Fmoc-FFpY	Electrostatic interactions	[93]
	Fmoc	Hydrophobic interactions	[94]
Chemical crosslinking	β-hairpin peptide	Photo-polymerization	[28]
	poly(l-glutamic acid)	Enzyme polymerization	[95]
	MAX7CNB	Photosensitive polymerization	[96]

Consequently, a range of pentapeptide gels with distinct properties emerged. The peptides in the study displayed a significant inclination to form self-supporting hydrogels based on their overall surface charge. However, this characteristic confines their biomedical applications, as these hydrogels typically form under acidic or alkaline pH conditions. Nonetheless, an intriguing revelation surfaced when a 1:1 mixture of two collagen mimetic peptides with opposing charges was employed. This mixing process resulted in the complete neutralization of charges, effectively shifting the sol-to-gel transition to a physiological pH range. This discovery underscores the potential of utilizing the shortest bioactive pentapeptide sequence of collagen mimetics with opposing charges, offering novel opportunities for targeted applications in the biomedical field.

Hydrogels formed via hydrophobic/hydrophilic interactions exhibit a high water content and demonstrate excellent biocompatibility with cells. Typically, in these hydrogels, the peptide sequence at the N-terminus comprises an aliphatic nonpolar amino acid tail, contributing to reduced hydrophobicity. Conversely, the C-terminus consists of a hydrophilic amino acid that can be alkaline, neutral, or acidic in nature. Hexapeptides, such as Ac-LIVAGD, are renowned for their capacity to form hydrogels. These peptides self-assemble into amyloid β-type fiber aggregates, with intermediate α-helical structures [100]. The combination of hydrophobic interactions and electrostatic interactions can lead to the formation of a more stable peptide hydrogel. Peptide hydrogels based on the RADA sequence a are characterized by high mechanical

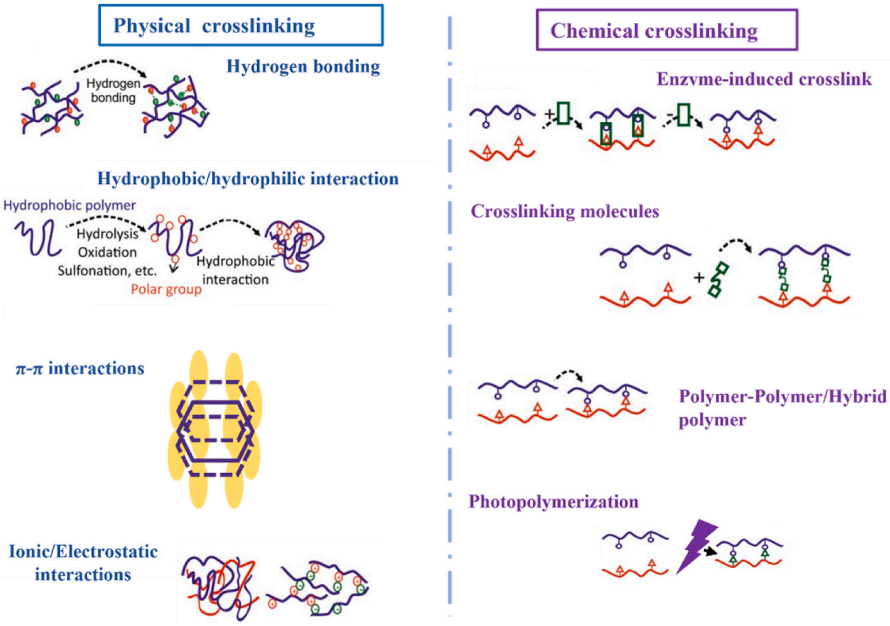

Fig. 3. Schematic diagram of hydrogels synthesized by two crosslinking methods.

strength. Substituting the alanine residue with glycine further enhances the mechanical strength of the hydrogel [101].

Hydrogen bonding plays a crucial role as a non-covalent interaction in hydrogel formation [102]. However, a single hydrogen bond alone is often inadequate to support robust hydrogel formation. Multiple multivalent hydrogen bonds are typically created to improve the strength of the hydrogel network. One effective strategy involves the utilization of molecules with multiple hydrogen bond acceptors and donor sites. For example, incorporating ureidopyrimidinone moieties in the peptide sequence can facilitate the formation of a robust network through the establishment of multiple multivalent hydrogen bonds [103]. This approach enhances the stability and mechanical strength of the resultant hydrogel. By maximizing the number of hydrogen bonding interactions, the overall structure of the hydrogel is fortified, leading to improved gel properties.

π-π interactions play a significant role in constructing peptide-based hydrogels [104]. For instance, diphenylalanine (FF), a dipeptide, thas the ability to form hydrogels. The interactions between the aromatic rings of phenylalanine residues in diphenylalanine (FF) contribute to stabilizing the resulting β-sheet structures within the hydrogel [105]. These interactions reinforce the gel network and enhance its overall stability.

Physically crosslinking hydrogels offer advantages such as good solubility of the unmixed polypeptide in physiological liquid, injectability, and minimal side effects or toxicity. However, the weak nature of non-covalent interactions in these hydrogels makes them sensitive to external stimuli, including pH, ionic strength, temperature, and light [106]. pH and ionic strength can effectively control the mechanical properties of hydrogels [107,108]. pH fluctuations can alter hydrogen bonds and salt bridges, thereby influencing peptide structure [109]. For instance, most dipeptides conjugated with Fmoc or Nap groups form hydrogels at low pH (<4) [110]. By adjusting the solution pH, the positive and negative charges of the peptide chains can be modified, thereby modulating the peptide assembly process. This enables the formation of adaptive hydrogels with varying densities and pore structures, facilitating the long-term release of drugs in the region of peripheral nerve injury to promote neural proliferation and repair [111].

The elasticity of the hydrogel can be controlled by changing the ionic strength of the system. Several studies have shown that the addition of salt can significantly improve the mechanical properties of hydrogels [47,91,112]. A histidine-containing peptide-based amphiphile (P1) was used to form a transparent hydrogel in a phosphate buffer solution within a pH range of 5.5–8. Dipayan et al. adjusted the mechanical strength of hydrogels by adding different dicarboxylic acids (oxalic acid, succinic acid, glutaric acid, and octanoic acid). These acids promoted non-covalent interactions between the histidine-containing, N-terminal-free peptide molecules. Among all tested acids, the addition of succinic acid notably enhanced the stiffness of the gel ($G' = 4$ kPa) [113]. It was also observed that hydrogels with relatively low stiffness ($G' = 4$ kPa) was highly suitable for 3D cell culture. This is because it facilitated the selective infiltration of cells into the gel phase while increasing the stiffness above the cell traction stress, providing a platform for 2D cell culture on the surface of the hydrogel. By adjusting their the mechanical properties, hydrogels can be tailored to provide an environment conducive to specific cell culture applications.

2.3.2. Chemical crosslinking by non-covalent interactions

Chemical crosslinking involves the formation of covalent bonds within or between polymer molecules, providing enhanced structural integrity [114]. Compared with physical crosslinking, chemical crosslinking methods offer improved mechanical properties and stability. Various techniques can be used for chemical crosslinking, including free radical polymerization crosslinking, photopolymerization [115], and enzyme-induced crosslink [116]. These methods enable the creation of stable covalent bonds, enhancing the mechanical strength and resilience of hydrogels against environmental fluctuations. Chemical crosslinking establishes a sturdy and durable framework for hydrogels, rendering them suitable for prolonged usage and ensuring structural integrity amidst diverse physiological conditions.

A common chemical crosslinking method involves the conjugation of crosslinked molecules in polymer chains or in direct combination with each other. For example, Liu et al. synthesized a peptide/polymer mixed double network (DN) hydrogel composed of both supramolecular and covalent polymers [117]. The DN hydrogel was created by merging two networks. The initial network comprised self-assembled pentafluorobenzyl diphenylalanyl aspartate acid (PFB-FFD) tripeptide, which formed nanostructures via non-covalent interactions. The second network consisted of a polymerized PNIPAM-PEGDA copolymer. During DN hydrogel formation, the self-assembled peptide nanostructures crosslinked with the polyacrylamide groups in the polymer network via non-covalent interactions. In comparison to the PNIPAM-PEGDA copolymer alone, the PNIPAM-PEGDA: PFB-FFD hydrogel demonstrated greater mechanical stiffness ($G' \sim 2$ kPa). Moreover, by adjusting the UV irradiation duration during synthesis, the stiffness of the PNIPAM-PEGDA: PFB-FFD hydrogel could be quadrupled.

Disulfide bonds in cysteine residues and electrostatic interactions with lysine or aspartic acid residues are commonly utilized as crosslinking points in hydrogels. Substituting specific amino acids within the hydrogel can lead to significant changes in its mechanical properties. For instance, Aulisa et al. replaced glutamine in the hydrophilic part of the B domain of MDP, resulting in notable alterations in mechanical properties. In the presence of phosphate-buffered saline (PBS), the storage modulus of the hydrogel containing positively charged peptides increased from 108 Pa with glutamine to 190 Pa with serine. Conversely, hydrogels with negatively charged peptides exhibited more substantial changes in the presence of Mg^{2+} ions, with storage moduli ranging from 99 Pa for glutamine to 482 Pa for serine. Additionally, hydrogels containing serine showed shear-thinning behavior, decreasing viscosity under shear stress and facilitating injection or application. These peptides containing serine underwent shear thinning and recovered approximately 80 % of their mechanical strength within 1 min, whereas peptides containing glutamine only recovered approximately 50 % of their original storage modulus after cleavage [118].

Photopolymerization is extensively employed in hydrogel formation and cytokine encapsulation due to several key advantages. Notably, photopolymerization enables rapid gel network formation at room temperature and under mild conditions [119]. Exposure of the precursor solution or formulation to specific wavelengths of lightlight initiates and completes the gelation process within a short period. This allows for convenient and efficient gelation without requiring high temperatures or harsh chemical initiators. Furthermore, photopolymerization offers tunability of the resulting hydrogel's mechanical properties [120]. Parameters such as light intensity, exposure time, and initiator concentration can be adjusted to control the crosslinking reaction, influencing the mechanical strength and stiffness of the hydrogel. Moreover, photopolymerization provides precise control over crosslinking sites within the hydrogel. Photoinitiators, like phenyl-2,4,6-trimethylbenzoylphosphinate (LAP), absorb specific wavelengths of light to produce free radical-initiating species [121]. In summary, photopolymerization is a versatile and efficient method for hydrogel formation, offering rapid gelation, tunable mechanical properties, and precise control over crosslinking sites, making it valuable for various applications in hydrogel engineering.

Enzymes, as bioactive macromolecules, possess excellent biosafety and biological affinity, rendering enzymatic crosslinking an attractive method for preparing hydrogels [122]. The incorporation of enzymes into hydrogel systems enables specific degradation of desired target groups within peptide chains, offering precise control over the crosslinking process. For instance, enzymes like glutamine transaminase (TGase) and peroxidase catalyze the crosslinking reaction between polymer chains, facilitating rapid gelation and the formation of a stable, non-toxic hydrogel. Maria et al. synthesized a series of self-assembling

peptide sequences using type 2 TGase as the crosslinking enzyme, resulting in enhanced storage modulus of the crosslinked SAP hydrogels without compromising maximum failure stress [123]. This enhancement in mechanical properties through enzymatic crosslinking indicates improved robustness of the hydrogel. Moreover, *in vitro* tests revealed that the SAP hydrogel crosslinked with TGase did not adversely affect the viability or differentiation of seeded neural stem cells (hNSCs), suggesting safe in situ crosslinking reactions *in vivo*, which holds promise for tissue engineering and regenerative medicine applications.

In a groundbreaking study utilizing ultrasonic standing wave (USW) technology to align nerve cells, cells were directly patterned in a 3D hydrogel system, and PC12 cells aligned with USW exhibited no adverse effects on viability or proliferation [124]. The key design strategy involved the oxidative coupling of hydroxyphenylpropionic acid (HPA) catalyzed by hydrogen peroxide and horseradish peroxidase, enabling rapid crosslinking of gelatin-HPA hydrogel within 90 s to synthesize the "gel block" for arranging cells. This technology represents a promising alternative method for guiding nerve regeneration.

3. Application of peptide-based hydrogels in nervous regeneration

In the pursuit of innovative therapies for neural tissue ailments, a notable challenge stems from the limited potential for nerve tissue regeneration post-injury [125]. Within the central nervous system, the presence of glial scars impedes neuronal regeneration and neurite growth, leading to a prolonged recovery process spanning several months [126]. Hence, there is an urgent need to develop effective and improved treatment strategies that can accelerate the regeneration of damaged neural pathways and facilitate the functional restoration of neural tissue.

Promising advancements in nerve tissue regeneration therapy center on the utilization of stem cells, while the extracellular matrix assumes a pivotal role in supporting and regulating cell survival and activity [127, 128]. Consequently, numerous studies have actively investigated the creation of simulated extracellular matrix microenvironments based on neural regeneration principles to promote axonal bridging. In this context, peptide-based hydrogels have emerged as promising candidates, offering significant application potential. The subsequent sections will explore the notable and recent advancements concerning peptide-based hydrogels utilized for nerve regeneration.

3.1. Dipeptide hydrogels

A recent investigation showed the development of a biocompatible and durable dipeptide hydrogel with adjustable mechanical properties and cell growth characteristics, demonstrating its capacity to foster glial cell proliferation [129]. Through self-assembly in various solvents and salt concentrations, researchers successfully engineered a dipeptide gel, as depicted in Fig. 4A. *In vitro* experiments validated the growth of glial cells (C6) on the biocompatible and resilient dipeptide hydrogel. Furthermore, as depicted in Fig. 4A, the cytoskeletal composition increased proportionally with rising sodium acetate concentration, indicating a positive association between sodium acetate concentration and glial cell growth.

Adak et al. devised an injectable and biocompatible peptide hydrogel incorporating sulfonyl functionality. The hydrogel, derived from the Phe-Phe dipeptide, featured a peptide segment with a sulfate functional group prepared using *para*-mercaptobenzoic acid at the N-terminus. At the C-terminus, the neuroprotective hexapeptide (NV) was tethered via a PLGL tetrapeptide linker, as illustrated in Fig. 4B [130]. The FFPLGLNAVIQ hydrogel exhibits remarkable attributes. It not only

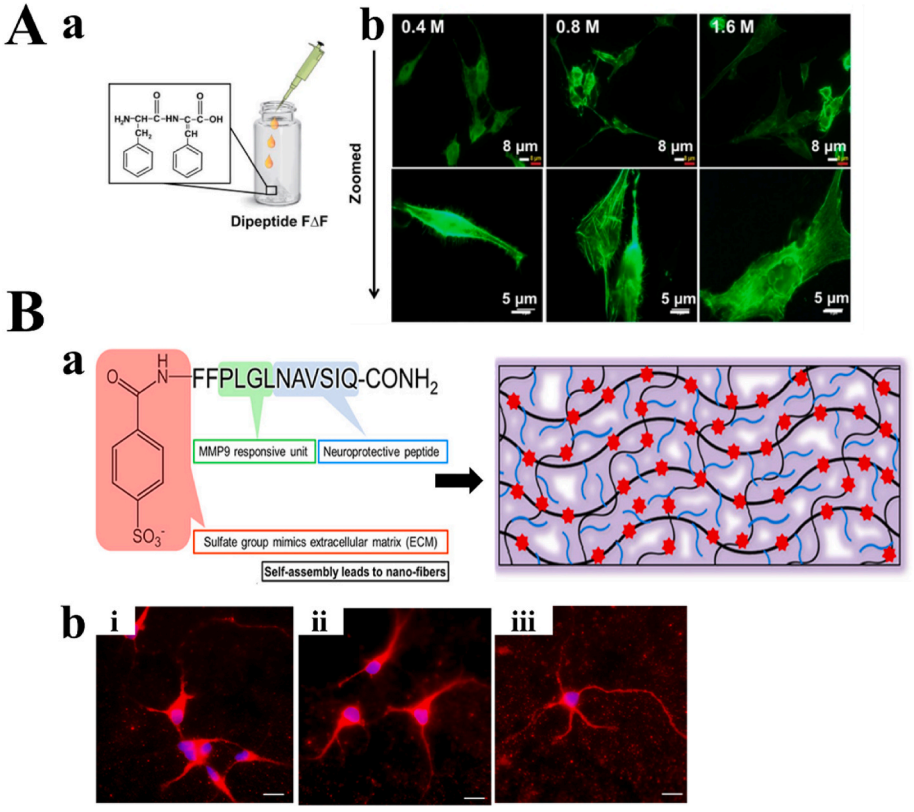

Fig. 4. The application of dipeptide hydrogels in nerve regeneration. (A) Fluorescence microscopic images of C6 glial cells cultured on Phe-Phe hydrogels prepared at various concentrations of sodium acetate. Reprinted from Ref. [129]. (B) Primary culture of cortical neurons from a rat brain in the presence of the SFNV hydrogel (a) at day 1, (b) at day 3, and (c) at day 7. Reprinted from Ref. [130].

stimulated neurite outgrowth in PC12-derived neurons and primary neurons but also effectively mitigated the neurotoxic effects of anti-NGF on neurons. Additionally, the hydrogel augmented the expression of pivotal neuronal markers in the primary cortical neurons of rats, highlighting its potential for nerve regeneration. In a mouse model of sham injury, the hydrogel expedited brain recovery.

These findings underscore the substantial potential of biocompatible and resilient dipeptide hydrogels as versatile platforms for fostering glial cell growth and establishing an optimal microenvironment for neural tissue regeneration.

3.2. Tripeptide hydrogel

Mauri et al. underscored the advantages of utilizing RGD-functionalized hydrogels as optimized materials for neural tissue engineering [131]. In comparison to hydrogels lacking tripeptide modification, RGD-modified peptide hydrogels demonstrate enhanced properties. The inclusion of the RGD tripeptide enables the hydrogel to accommodate a larger population of non-quiescent cells, fostering a more conducive biological environment for NSCs. Zaviskova and collaborators devised an injectable hydrogel employing a modified version of hyaluronic acid (HA-PH) with hydroxyphenyl groups, incorporating RGD for improved cell interaction. The hydrogel was enzymatically crosslinked, yielding a soft and injectable formulation, as illustrated in Fig. 5A [132]. Furthermore, they formulated a variant of the HA-PH-RGD hydrogel by integrating fibrinogen (HA-PH-RGD/F). Fibrinogen facilitated the proliferation of human Wharton's jelly-derived mesenchymal stem cells (hWJ-MSCs) on the HA-PH-RGD hydrogel. These cells were injected into the defect site of rats. Both HA-PH-RGD or the HA-PH-RGD/F hydrogel alone promoted axon growth in the lesion. When HA-PH-RGD/F was combined with hWJ-MSCs, this effect was further enhanced. Although no significant effects on blood vessel ingrowth or glial scar density were observed, this study successfully developed and characterized an injectable HA-PH-RGD-based hydrogel. This innovative approach introduces a new concept for peptide-based hydrogel materials in the realm of nerve regeneration. In the latest research, a silk-inspired phototriggered gelation method was devised to produce a novel hydrogel system. Through photocrosslinking, RGD peptides were efficiently bound to the T30@SFRGD hydrogel. This integration facilitated the robust adhesion of Schwann cells to the RGD peptide hydrogel, enabling them to guide cell growth using microgroove models. Consequently, this approach facilitated rapid axon regeneration and accelerated the repair of large-gap peripheral nerve damage [133].

Turkez et al. investigated the potential therapeutic effects of novel GPE analogs (GPE1, GPE2, and GPE3) concerning Alzheimer's disease. These analogs were synthesized by reducing the peptide bonds between Gly-Pro (GPE3) or Pro-Glu (GPE1) or at both connection sites (GPE2), resulting in the formation of aminomethyl groups (Fig. 5B) [134]. Various techniques were utilized to evaluate the anti-Alzheimer's disease potential of these GPE peptide analogs. The results revealed significant properties of the GPE analogs in regulating oxidative stress, mitigating acetylcholine depletion, inhibiting α-secretase inactivation, and affecting cellular apoptosis and necrotic cell death. The neuroprotective effects of the GPE analogs are underscored, suggesting their promise as therapeutic agents for Alzheimer's disease.

Bernardes et al. synthesized a snake venom peptide (p-BTX-I) derived from the natural tripeptide Glu-Val-Trp [135]. The research aimed to investigate the potential neuroprotective effects of this peptide by simulating the neurotrophic actions of nerve growth factors. The findings revealed that p-BTX-I strongly protected PC12 cells from the toxic effects of 1-methyl-4-phenylpyridinium (MPP+) and inducing

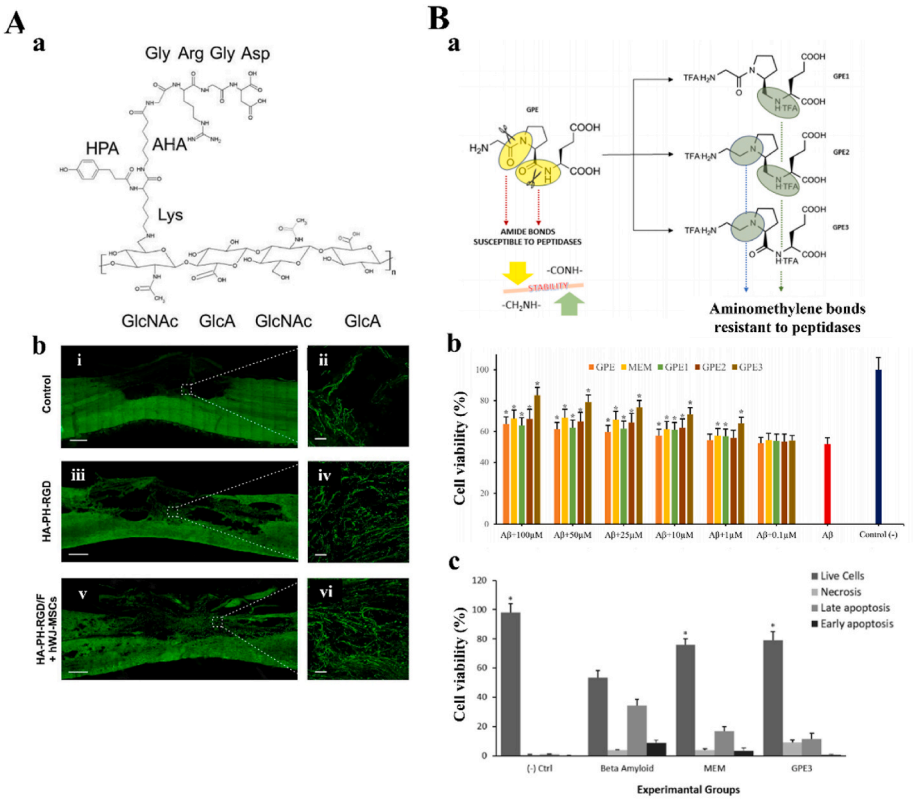

Fig. 5. (A) An injectable hydrogel was developed to promote the growth of axons in lesions. (a) The chemical structure of the HA-PH-RGD hydrogel. (b) RHA-PH-RGD/F hydrogels combined with hWJ-MSCs promoted the growth of axons in the lesion. Reprinted from Ref. [132]. (B) GPE peptidomimetics have neuroprotective effects. (a) Design and development of GPE peptidomimetics starting from native GPEs. (b) The neuroprotective effects of GPE, MEM, GPE1, GPE2, and GPE3 against *in vitro* Ab1-42 exposure. (c) Flow cytometric analysis of Annexin V-FITC (FL1)/PI (FL2) double-labeled cells in a cellular model of AD. Reprinted from Ref. [134].

neurogenesis in these cells. These results suggest that p-BTX-I holds promise as a therapeutic agent for promoting neuronal survival and regeneration.

3.3. Oligopeptide hydrogel

Huang et al. engineered a hydrogel film (ChT-PEDOT-p) with enhanced properties by incorporating conductive poly(3,4-ethylenedioxythiophene) nanoparticles (PEDOT NPs) and the cell-adhesive tetrapeptide Cys-Arg-Gly-Asp (CRGD) [136]. As shown in Fig. 6A, the hydrogel film exhibited remarkable mechanical strength and promoted the attachment and proliferation of Schwann cells and enhanced vascularization. Importantly, this ChT-PEDOT-p hydrogel film showed promising results in inducing the regeneration of damaged sciatic nerves.

IKVAV, a pentapeptide widely employed in neural regeneration, exhibits remarkable capability in enhancing neuronal vitality and maturation by binding to the β1-integrin subunit, thereby promoting the differentiation of neural progenitor cells into neurons [137]. Hydrogels incorporating IKVAV have been shown to prompt rapid differentiation of neural progenitor cells into neurons and neurites. Yin et al. prepared a three-dimensional pentapeptide IKVAV-functionalized poly(lactide ethylene oxide fumarate) (PLEOF) hydrogel was prepared (Fig. 6B) [138], which demonstrated excellent compatibility with cells and tissues. This IKVAV-PLEOF hydrogel facilitated the adhesion, growth, proliferation, and differentiation of NSCs and spheroids into neurons, while creating a regenerative environment for NSCs, thus alleviating spinal cord injury. *In vivo* implantation of the hydrogel for a period of 4 weeks demonstrated its favorable biocompatibility and highlighted its potential application prospects in the repair of spinal cord injuries.

YIGSR, another pentapeptide with significant potential in neural regeneration, has been studied extensively. Transplantation of YIGSRs into a composite hydrogel consisting of polyacrylamide, graphene oxide, collagen, and sodium alginate has been shown to enhance the growth of Schwann cells *in vitro* and facilitate sciatic nerve regeneration *in vivo* [139,140]. Recent research has revealed its ability to regulate the orientation growth of Schwann cells effectively through anisotropic hydrogel micropatterns (Fig. 6C) [141]. Additionally, Chen et al. synthesized a YIGSR-based hydrogel catheter with biological activity and implanted it into the sciatic nerve gap of rats, demonstrating its efficacy in promoting nerve regeneration through histological analyses [140].

Cyclo(L-His-L-Pro) is the first CDP found in mammals, which exhibits significant anti-inflammatory properties within the CNS. As illustrated in Fig. 7, it has demonstrated the ability to counteract reactive gliosis induced by lipopolysaccharide, suggesting its potential as an alternative therapeutic strategy for neuroinflammatory degenerative diseases. By inhibiting the inflammatory pathway in glial cells, Cyclo(L-His-L-Pro) plays a protective role in neuronal preservation. Moreover, it enhances antioxidant protection by modulating the interplay between the nuclear factor-like 2 (Nrf2) and nuclear factor kappa B (NF-kB) signaling pathways, while concurrently suppressing proinflammatory responses [136]. In Streptozotocin (STZ)-induced diabetes rats, Cyclo(L-His-L-Pro) romotes progenitor cell proliferation and increases the population of neural progenitor cells and immature neurons. Furthermore, zinc-supplemented Cyclo(L-His-L-Pro) exhibits a positive impact on early neurogenesis in STZ-induced diabetic rats [137]. However, despite these promising attributes, CDPs encounter challenges such as complex synthesis procedures, high structural rigidity, limited water solubility, and low bioavailability, which may impede their utilization in research [138].

3.4. Ionic complementary peptides hydrogel

In early studies, RADA16 was successfully functionalized with laminin-derived motifs (IKVAV, RGDS, and PDSGR) [142–144], bone marrow homing motifs (SKPPGTSS and PFSSTKT) [145,146], and cell adhesion motif RGD [147,148]. These functionalized RADA16 hydrogels not only promoted neuronal cell proliferation and adhesion but also induced neurite growth and synaptic formation. More recently, bifunctional hydrogels have been developed by combining two functionalized RADA16 peptides carrying IKVAV and RGD epitopes. Compared to monofunctional hydrogels, bifunctional hydrogels can enhance the viability and differentiation of NSCs into neurons and astrocytes [149]. In a study conducted by Lu et al. [75], as shown in Fig. 8A, a functional self-assembled peptide nanofiber hydrogel was synthesized by adding CTDIKGKCTGACDGKQC and RGIDKRHWNSQ (derived from NGF and BDNF, respectively) to RADA16-I, a functional self-assembled peptide. The impact of these hydrogels on neurite growth using PC12 cells was evaluated. The findings demonstrated that hydrogels incorporating CTDIKGKCTGACDGKQC and RGIDKRHWNSQ peptides significantly augmented neurite growth in PC12 cells compared to nonfunctional peptides. This observation underscores the beneficial impact of these functional peptides in promoting neurite outgrowth. To explore their potential applications further, *in vivo* experiments were conducted using a chitosan tube to bridge a 10 mm sciatic nerve defect in rats with the hydrogel inserted inside. Remarkably, the combination of CTDIKGKCTGACDGKQC and RGIDKRHWNSQ expedited axonal regeneration, leading to robust functional recovery and collaborative enhancement of peripheral nerve regeneration. These findings underscore the promising role of functional self-assembled peptide nanofiber hydrogels containing specific NGF and BDNF-derived peptides in stimulating neurite growth and facilitating the regeneration of peripheral nerves.

Currently, RADA16 PA hydrogels have shown significant potential for promoting brain injury regeneration. For instance, as shown in Fig. 8B, the RADA16 peptide hydrogel has been utilized as a cell carrier for cotransplantation of human adipose-derived stem cells and epilepsy brain-derived human neural stem cells (hNSCs). This approach has been shown to facilitate functional recovery in a rat model of traumatic brain injury, concurrently reducing neuroinflammation, injury volume, and reactive glial cell proliferation at the injury site [150]. Subsequently, Ghandy et al. developed a novel RADA-16 peptide-based hydrogel incorporating stromal cell-derived factor-1α (SDF-1α) and cotransplanted it with human neural stem cells. The results demonstrated a decrease in the inflammatory response and cell apoptosis in a traumatic brain injury model, fostering a more supportive microenvironment for tissue regeneration [151]. In another study, a zebrafish brain injury model was utilized to investigate the effects of RADA16, alone or in combination with SVVYGLR (an angiogenic A integrin-binding sequence derived from osteopontin), at the wound site [152]. A 1 % RADA16 hydrogel with or without SVVYGLR was applied, and its impact on various aspects of tissue evaluated. The findings showed that this application not only enhanced the endogenous differentiation of neural stem cells but also promoted neurogenesis, functional recovery, and the formation of new blood vessels. These results underscore the potential of RADA16 and its variants in promoting peripheral nerve growth.

In brief, the unique advantages of RADA16 and its self-assembled peptide nanofiber hydrogels have positioned them as highly biomimetic extracellular matrices in the field of biomedical engineering. Compared to other currently available polymer biomaterials, these hydrogels have multiple potential applications in neural tissue engineering [153].

3.5. MDP hydrogel

In vitro assessments showed that various lysine-based MDPs stimulate neurite growth. To evaluate their effectiveness *in vivo* for nerve regeneration, Lopez Silva et al. developed a representative MDP named $K_2(SL)_6K_2$. AThey incorporated biologically active motifs like ECM proteins and GF peptide sequences into the MDP, creating a bioactive MDP hydrogel with multiple biological functions. This hydrogel was directly administered to the site of injury in rats with sciatic nerve crush

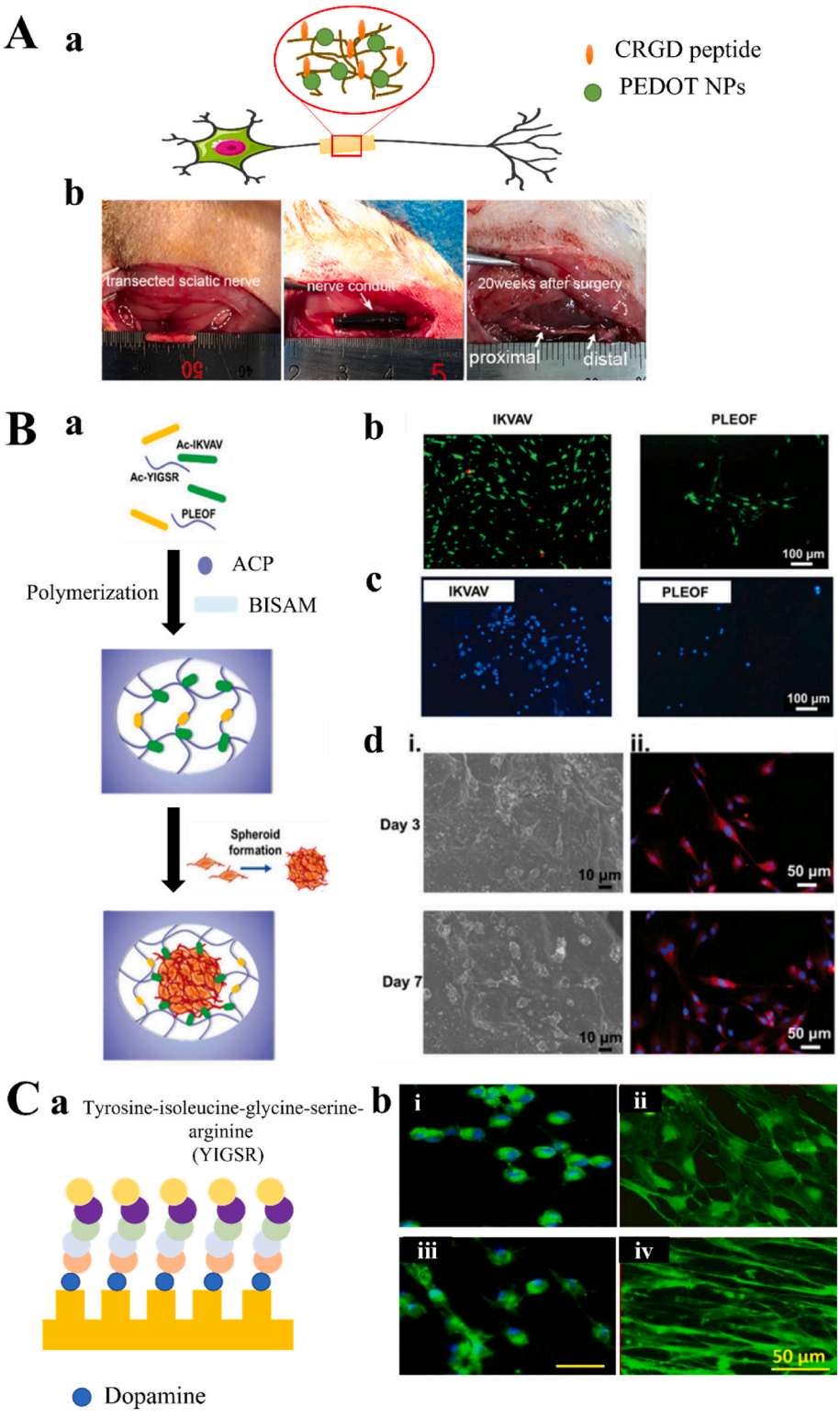

Fig. 6. (A) The ChT-PEDOT-p hydrogel film promoted angiogenesis and accelerated nerve regeneration. (a) Schematic diagram of the ChT-PEDOT-p hydrogel. (b) The ChT-PEDOT-p hydrogel promoted nerve regeneration. Reprinted from Ref. [136]. (B) The IKVAV-PLEOF hydrogel can support neural stem cell attachment, growth, proliferation, and differentiation. (a) Fabrication of the pre-gel mixture. Evaluation of cell viability(b), adhesion (c), and differentiation (d) on the IKVAV-PLEOF hydrogel surface. Reprinted from Ref. [138]. (C) YIGSR-based hydrogel can effectively regulate the orientation growth of Schwann cells through anisotropic hydrogel micropatterns. (a) Schematic diagram of the preparation of biofunctionalized anisotropic hydrogel micropatterns. (b) YIGSR peptide hydrogel promotes the distribution and cytoskeletal organization of Schwann cells. Reprinted from Ref. [141].

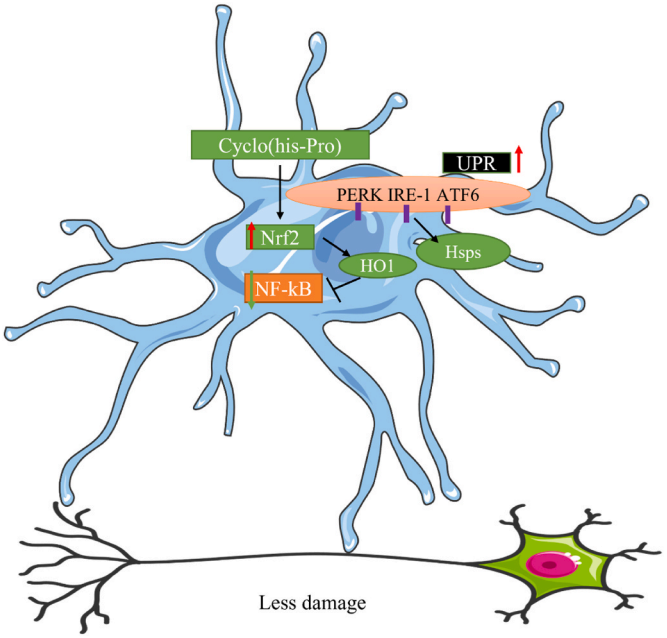

Fig. 7. Cyclo(His-Pro) can protect neuronal cells from neurotoxic damage, by increasing the protective unfolded protein response (UPR), activating the antioxidant response through Nrf2 induction, and downregulating the proinflammatory response through NF-κB inhibition in microglia.

injury. Results demonstrated that the bioactive MDP hydrogel promoted nerve regeneration by inducing acute macrophage infiltration, supporting axonal growth, and aiding in myelin sheath regeneration in Fig. 9A [62]. These findings suggest that MDP facilitates neurite growth and initiates a multicellular regenerative response in peripheral nerve injury.

Another frequently used MDP sequence is $K_2(QL)_6K_2$, which forms β-sheets at neutral pH [111]. In SCI, injecting $K_2(QL)_6K_2$ into the injury site was observed to reduce glial scar formation and enhance neurological function recovery [154]. In a related study, neural precursor cells (NPCs) were conjugated to $K_2(QL)_6K_2$ self-assembled peptides and then injected into the spinal cord of rats. Neural function was assessed weekly for 8 weeks. Results showed that animals treated with self-assembled peptides had a higher survival rate of NPCs and increased differentiation of these cells into neurons and oligodendrocytes in Fig. 9B [155].

Recently, the Hartgerink team introduced a bioactive MDP hydrogel-filled PCL catheter to facilitate regeneration of the transected sciatic nerve [156]. PCL catheters infused with anionic MDP hydrogel notably enhanced functional recovery at 16 weeks post-surgery. These catheters demonstrated superior composite muscle action potentials, preserved gastrocnemius muscle weight, and earlier onset of flexion contractures. Conversely, PCL catheters containing cationic MDP hydrogels exhibited the lowest degree of myelination and limited functional recovery. This observation underscores the superior nerve regeneration promotion ability of anionic MDP hydrogel over cationic counterparts, emphasizing the importance of peptide sequence design and optimization in manufacturing functional peptide-based hydrogels.

These findings collectively demonstrate MDP's efficacy in promoting nerve regeneration and aiding the healing process of nerve injuries, offering valuable insights into its potential as a biomaterial for nerve regeneration and broader clinical applications.

3.6. Peptide amphiphiles hydrogel

PA hydrogels offer versatility in biofunctionalization with various motifs, thereby imparting biological activity to the surrounding microenvironment conducive to nerve cell growth. Additionally, surfactant-like peptides have emerged as effective agents in neural regeneration. In this study, the self-assembled ultrashort surfactant-like peptide I_3K, characterized by positively charged lysine head groups and hydrophobic isoleucine tails, was chosen. These peptides can spontaneously assemble into nanofiber structures and strongly interact with silk fibroin (SF) scaffolds, creating a conducive environment for neuronal cell attachment and proliferation. Atomic force microscopy (AFM) was utilized to visualize the morphology and formation of neural processes in PC12

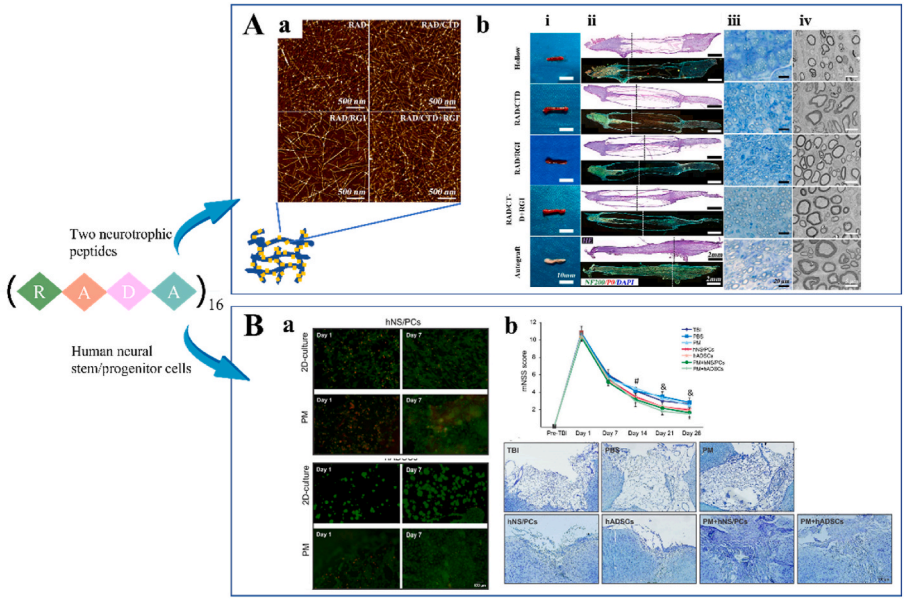

Fig. 8. (A) Bifunctional RADA16 hydrogels promote peripheral nerve regeneration. (a) AFM images of RADA16-I and solutions of various functionalized, self-assembling peptides mixed with RADA16-I. (b) Bifunctional RADA16 hydrogels promote nerve fiber regeneration at 12 weeks after surgery. Reprinted from Ref. [75]. (B) Human neural stem/progenitor cells derived from the epileptic human brain via the RADA16 peptide improve traumatic brain injury in rats. (a) Transplantation of hNS/PCs or hADSCs seeded in PM significantly increased the number of surviving cells. (b) Transplantation of hNS/PCs or hADSCs seeded in PM diminished inflammatory responses in the damaged brain parenchyma after TBI. Reprinted from Ref. [150].

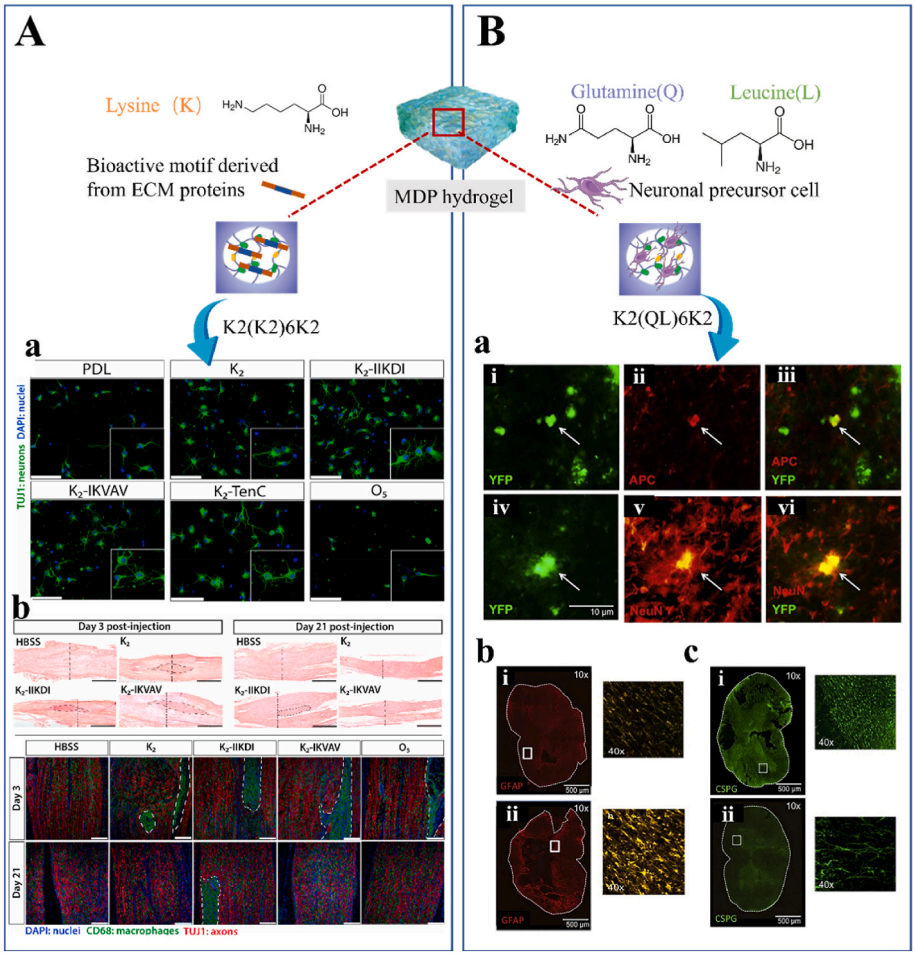

Fig. 9. (A) An injectable K_2-based bioactive MDPs can accelerate peripheral nerve regeneration after crush injury. a) K_2-based bioactive MDPs can promote neurite outgrowth *in vitro*. b) K2-based hydrogels may improve the early injury response and enhance immune cell recruitment after injury. Reprinted with permission from Ref. [62]. (B) QL6 MDPs optimize the post-traumatic milieu and synergistically enhance the effects of neural stem cell therapy after cervical spinal cord injury. (a) Mice that received QL6 pretreatment one day after trauma had a significantly greater number of surviving NPCs. The combination of SAPs injected into the lesion epicenter 24 h after SCI may have inhibited astrogliosis (b) and tissue scarring (c). Reprinted with permission from Ref. [155].

cells. The findings demonstrated that self-assembled I_3K nanofibers effectively supported the formation of neural processes in PC12 cells (as shown in Fig. 10). Furthermore, immunolabeling techniques revealed that coating I_3K nanofibers onto the SF scaffold surface not only increased the percentage of cells with neural processes but also enhanced the average maximum length of these neural processes [157].

PAs have shown promise in forming stable complexes with various drugs; thus, reducing drug toxicity, facilitating drug transport across nerve cell membranes, and enabling controlled and sustained release of neurotrophic drugs. This property promotes targeted growth and migration of nerve cells, enhancing the therapeutic effectiveness of drugs for peripheral nerve injury. However, a drawback of PA hydrogels is their relatively low mechanical strength [158]. Chemical modifications are often utilized to crosslink the PA molecules to address this issue, thereby enhancing the mechanical properties of the hydrogel [159]. Introducing crosslinking agents or modifying the chemical structure of PAs can result in hydrogels with improved mechanical strength suitable for nerve tissue engineering applications. Moreover, PAs can be chemically or physically linked to other biomaterials, such as polymers or scaffolds, to create composite scaffolds [64] with enhanced mechanical properties, rendering them more suitable for use in nerve tissue engineering and regeneration.

In conclusion, while the mechanical strength of PA hydrogels may be limited, this challenge can be overcome through chemical modifications and the development of composite scaffolds. These strategies contribute to the progress of PA-based biomaterials, enabling their effective utilization in promoting nerve tissue regeneration and repair.

4. The advantages of peptide-based hydrogels in nerve regeneration

Peptide-based self-assembled hydrogels have garnered significant attention in tissue engineering [160]. Their physical and chemical properties, coupled with high water content, closely resemble the viscoelastic properties of the tissue ECM. Additionally, their fiber morphology and entanglement network mimic those of the natural ECM in terms of shape, size, and porosity, enabling them to simulate the ECM and provide a conducive environment for nervous system regeneration [161]. Consequently, they find various applications in neural tissue engineering (Fig. 11A). Coculturing nerve cells with self-assembled peptide-based hydrogels offers several advantages. Firstly, it can mitigate neuronal apoptosis, thereby promoting the survival, growth, and proliferation of new nerve cells [162]. The hydrogel scaffold offers mechanical support and establishes a favorable microenvironment that sustains cell viability and functionality. Secondly, these hydrogels can guide nerve axon outgrowth, facilitating the formation of organized neural networks [163]. Incorporating specific bioactive sequences within the hydrogel structure enables them to direct nerve axon growth in specific directions, promoting the establishment of active synapses between neurons. This fosters neural connectivity and enhances

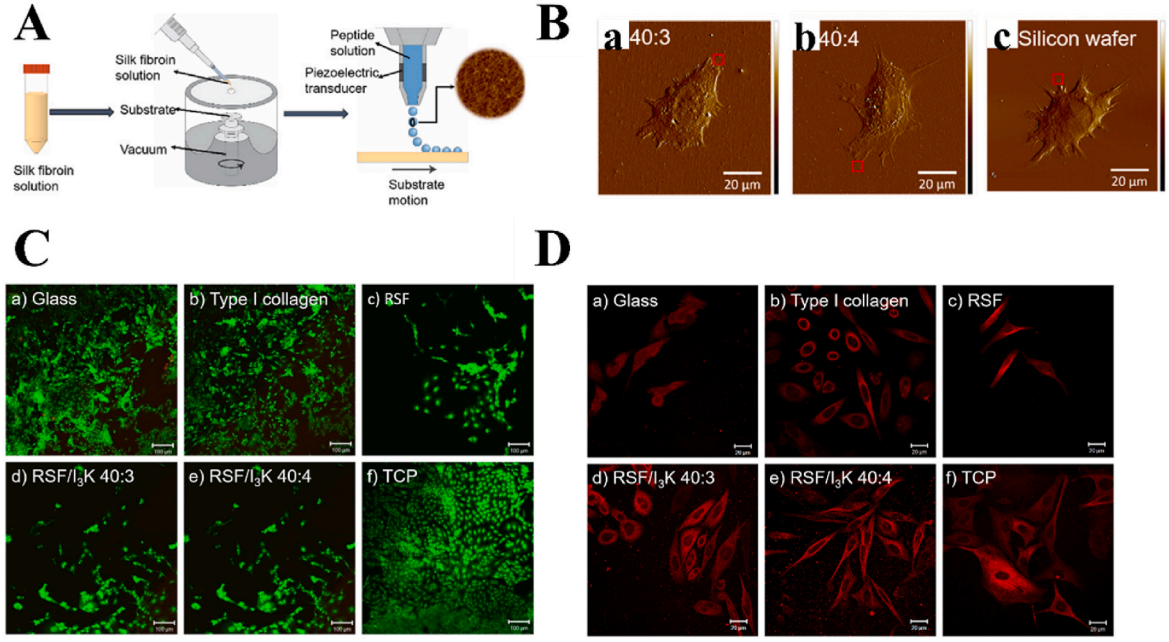

Fig. 10. Self-assembled I_3K nanofibers were fabricated to guide neuronal cell attachment. (A) Schematic diagram of the preparation process of the RSF/I_3K peptide. (B) I_3K can activate the cell adhesion process, inducing cell spreading and flattening. (C) RSF/I_3K improved cell growth and proliferation overall. (D) The concentration of I_3K directly affects the length of neurites. Reprinted from Ref. [157].

functional recovery in regions affected by peripheral nerve injuries [164]. Consequently, peptide-based hydrogels are considered optimal biomaterials for promoting nerve cell differentiation and growth in regenerative medicine applications [165,166].

Peptide-based hydrogels, capable of replicating the ECM microenvironment, hold the potential for transplanting exogenous neural stem cells (NSCs). NSCs, with the ability to differentiate into glial cells and neurons [167], can stimulate endogenous NSCs, emerging as advanced therapy for central nervous system (CNS) injuries [168]. This method entails secreting various growth factors or neurotrophic proteins, such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), ciliary neurotrophic factor (CNTF), and glial cell line-derived neurotrophic factor (GDNF), in the vicinity of damaged tissue [169] (Fig. 11B). These growth factors foster a conducive environment for neural regeneration. For instance, BDNF crucially promotes neuronal survival, synaptic plasticity, and neurogenesis. Employing LN and BDNF to emulate epitope-functionalized self--assembled peptide hydrogels synergistically enhances peripheral nerve regeneration [170]. GDNF is pivotal in supporting motor neuron survival and nourishment and in regulating neuron development and differentiation [171].

Peptide-based hydrogels can directly serve as carriers for encapsulating growth factor mixtures. Through controlled and sustained release of these encapsulated growth factors, endogenous NSCs can be stimulated, promoting intrinsic repair of damaged neurons and glial cells. This controlled release mechanism enhances growth factor penetration through cell membranes and mitigates potential adverse effects of degradation products on drug efficacy [172]. By providing a conducive regenerative environment, peptide-based hydrogels contribute to central nervous system wound healing.

Peptide-based hydrogels offer a versatile platform for controlled drug delivery to specific sites of nerve injury (Fig. 11C). One intriguing application involves utilizing Taxol, known for its efficacy in stabilizing microtubules and aiding neurite regeneration and functional recovery post-SCI, albeit limited by its ability to penetrate the blood–brain barrier (BBB), necessitating localized administration [173]. To address this, Xiao et al. synthesized a novel peptide, RADA16-FGL, incorporating the neurocyte adhesion molecule motif FGL (EVYVVAENQGKSKA) for controlled Taxol release [174]. After T9 contusion, SAPs were injected into the injury site and evaluated in rats after 8 weeks of injury. As shown in Fig. 12A, rats injected with Taxol loaded scaffolds exhibited maximum functional recovery, reduced glial scar formation, and increased the number of nerve fibers. In addition, rats treated with Taxol loaded stents exhibited preserved neural processes, smaller cavity size, and reduced inflammation and demyelination. These findings underscore the positive impact of Taxol delivery via the peptide-based hydrogels in promoting recovery and mitigating spinal cord injury effects.

These hydrogels can encapsulate drugs or therapeutic molecules and for gradual release over time. Importantly, the metabolites from hydrogel degradation are safe and non-toxic [175]. Four main strategies for drug delivery include (i) nanoparticle carriers, (ii) non-specific mediated release, (iii) bound release, and (iv) rapid targeted delivery via cell penetration. For instance, drug-loaded SAP hydrogels can encapsulate hydrophobic compounds, enhancing their permeability for efficient release and targeted delivery to the nerve injury site. The tunable three-dimensional structure of self-assembled peptide-based hydrogels enables versatile slow-release vehicle applications for various drugs. In a recent study, Adak et al. developed the neuro-compatible peptide-based hydrogel (abbreviated as PA-NK) [176], gradually degrading enzymatically for controlled release of the neuroprotective peptide NAPVSIPQK. As shown in Fig. 12B, PA-NK promoted neurite growth and showed remarkable neuroprotective effects against SNGF-induced neuronal cytotoxicity. It served as an effective carrier for encapsulating the hydrophobic drug curcumin, inhibiting neuronal cancer cell sphere growth. With high biocompatibility, the hydrogel serves as a platform for various applications, including neuronal cell adhesion, growth, and transplantation for brain damage repair, and as a delivery vehicle for neuroprotective agents targeting Alzheimer's disease and cancer.

Moreover, self-assembled peptides exhibit low immunogenicity. The formation of long, unbranched nanofibers effectively encapsulates the antigenic epitopes of immunogenic prodrugs, reducing the required level of immunity *in vivo* and minimizing adjuvant effects [177]. In

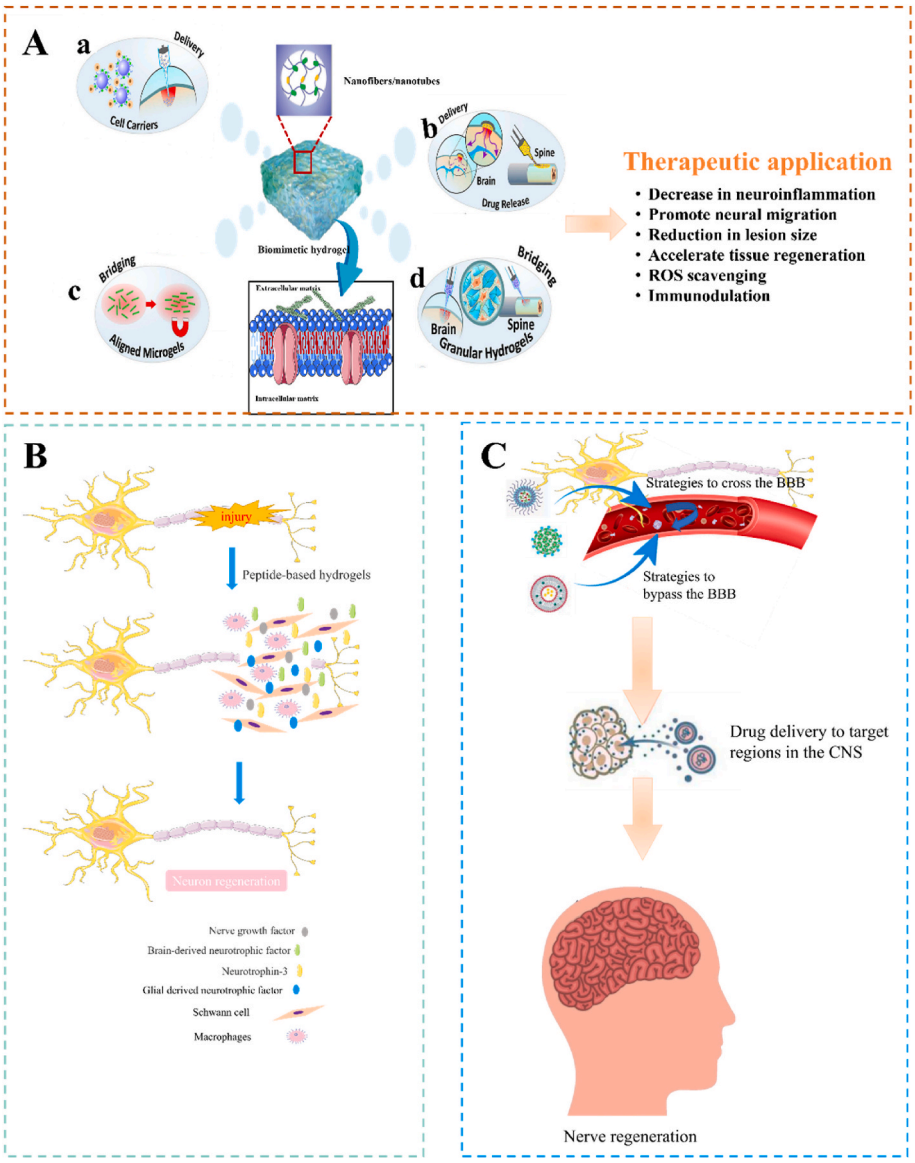

Fig. 11. (A) Peptide-based hydrogels in diverse applications associated with neural regeneration and therapy. (B) By transplanting exogenous neural stem cells through peptide-based hydrogels, the secretion of various growth factors and neurotrophic proteins can be promoted near damaged tissues, creating a favorable environment for nerve regeneration. (C) Graphical overview of the process toward of peptide-mediated treatment of neurological diseases.

immunology, SAP hydrogels serve as carriers for antigens and antibodies, genes and proteins, and biosensors for recognizing and regulating gene expression, thereby modulating stem cell behavior. Compared with conventional antibodies, SAP hydrogels offer advantages such as low production cost, low immunogenicity, good permeability, and potent anti-inflammatory effects. Consequently, the development of SAPs incorporating immunogenic antigens holds promising application prospects [58].

In summary, peptide-based hydrogels provide versatile platforms for drug delivery and nerve regeneration. Their adjustable three-dimensional structure, compatibility with nerve cells, and controlled release capabilities make them valuable tools for promoting nerve tissue regeneration.

5. Conclusion and outlook

Recent advancements in peptide-based hydrogels have been outlined in terms of their type, design strategies, application methods, and neural regeneration mechanisms. Short-chain peptide-based hydrogels, comprising dipeptides to oligopeptides, can be differentiated from long-chain peptide-based hydrogels based on the number of peptide bonds (-CONH- amide bonds). Design strategies for peptide-based hydrogels include the selection of amino acid sequences, secondary structures, and synthetic methods.

Peptide-based hydrogels exhibit tremendous practical applications in neural regeneration. They serve as suitable matrices for nurturing neural cells, promoting cell adhesion, infiltration, proliferation, migration, differentiation, and synaptic formation within the injured neural area without causing cellular toxicity. Additionally, these hydrogels function as specific hydrophobic drug delivery carriers, enabling high payload delivery to specific sites of nerve injury. Therefore, designed peptide-based hydrogels must possess good biocompatibility and should not induce inflammatory reactions after implantation at the injured site. Furthermore, these scaffolds should support cell migration, allowing cells to grow and survive in the reactive microenvironment of damaged tissue, thereby establishing an acceptable graft-host interface. By considering these factors and designing peptide-based hydrogels with appropriate properties, researchers can develop scaffolds that effectively

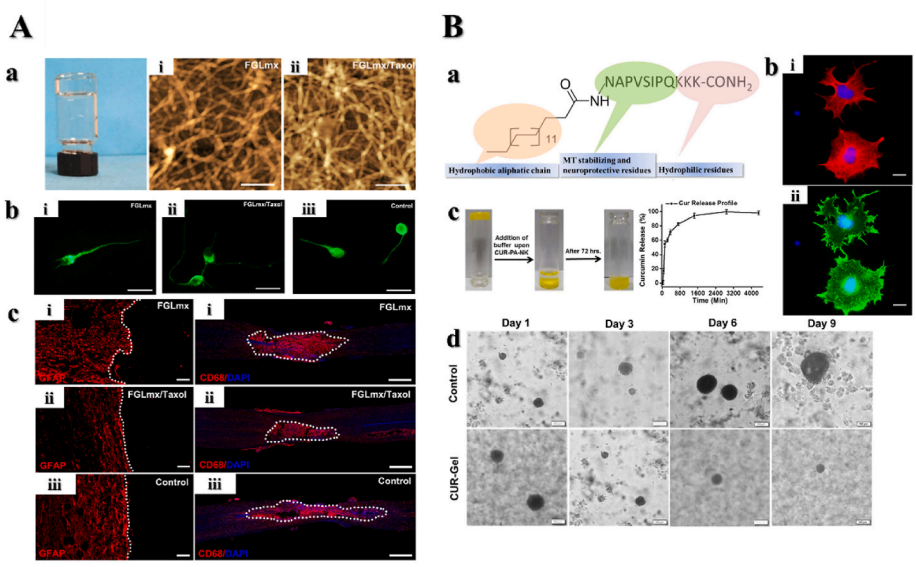

Fig. 12. (A) Local delivery of Taxol from FGL-functionalized SAPs promote drecovery after SCI. (a) AFM images of the ultramicrostructures of the FGLmx (i) and FGLmx/Taxol (ii) nanofiber scaffolds. (b) Taxol released from FGLmx/Taxol increased neurite outgrowth from primary cortical neurons *in vitro*. (c) Local delivery of FGLmx/Taxol decreased glial scar formation and inflammation. Reprinted from Ref. [174]. (B) The PA-NK hydrogel delivers an anti-Alzheimer drug and has significant neuroprotective effects. (a) Chemical structure of palmitic acid (PA) conjugated with the NK peptide (PA-NK). (b) PA-NK promotes neurite growth in neuronal cells. The slow release of curcumin (c) from the hydrogel significantly inhibited the growth of three-dimensional neuronal cancer cell spheres (d). Reprinted from Ref. [176].

support neural cell functions, exhibit biocompatibility, enable targeted drug delivery, and contribute to the overall success of neural regeneration efforts.

Although peptide-based hydrogels have the potential to promote nerve regeneration, the problem of their stability *in vivo* must be addressed before realizing their clinical potential. These hydrogels should retain their structural integrity, mechanical properties, and bioactive functionalities over an extended period. Strategies such as incorporating crosslinking moieties or modifying peptide sequences can enhance the stability and durability of hydrogels, allowing them to withstand degradation and maintain their therapeutic efficacy.

Peptide-based hydrogels face challenges in loading drugs and cells and then crosslinking them as prefabricated *in vitro* matrices. Overcoming these challenges associated with incorporating bioactive molecules or cells into a hydrogel matrix without compromising its structural integrity and bioactivity is crucial. Techniques such as preencapsulation, surface modification, or covalent conjugation can be explored to optimize drug and cell loading within hydrogel scaffolds.

Designing peptide-based hydrogels as cell scaffolds poses a significant challenge in integrating multiple bioactive epitopes to emulate the dynamic microenvironment of the extracellular matrix while preserving the hydrogel's physical properties. Thoughtful selection and arrangement of bioactive sequences within the hydrogel structure are essential to provide appropriate cues for cell adhesion, migration, proliferation, and differentiation while maintaining structural stability and bioactivity.

Several technical hurdles must be overcome for successful clinical translation of peptide-based hydrogels. These include scalability of manufacturing, ensuring sterility and safety, adaptability to diverse clinical scenarios, and cost-effectiveness. Enhancing manufacturing processes, complying with regulations, and optimizing production and storage are crucial steps to enhance the clinical viability of peptide-based hydrogels.

Focusing on these research areas will drive advancements in peptide-based hydrogels, fostering their continued growth in biomedical applications. The development of sustainable and economical hydrogels will broaden their clinical utility, benefiting patients and advancing regenerative medicine.

CRediT authorship contribution statement

Chunmei Xie: Writing – original draft. **Yueyang Chen:** Data curation. **Lang Wang:** Data curation. **Kin Liao:** Methodology. **Bin Xue:** Methodology. **Yulong Han:** Writing – review & editing, Supervision. **Lan Li:** Writing – review & editing, Supervision. **Qing Jiang:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

None.

Acknowledgment

This study was supported by the National Natural Science Foundation of China (32271408, 32271296, 12202193), National Basic Research Program of China (2021YFA1201404), Natural Science Foundation of Jiangsu Province (BK20232023), Nanjing Health Technology Development Special Project (JQX23002), Jiangsu Provincial Key Medical Center Foundation, Jiangsu Provincial Medical Outstanding Talent Foundation, the Youth Innovation Team of Shaanxi Universities, China.

References

[1] B. Schlosshauer, L. Dreesmann, H.-E. Schaller, N. Sinis, Synthetic nerve guide implants in humans: a comprehensive survey, Neurosurgery 59 (4) (2006) 740–748.
[2] B. Guan, D.B. Anderson, L. Chen, S. Feng, H. Zhou, Global, regional and national burden of traumatic brain injury and spinal cord injury, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019, BMJ Open 13 (10) (2023) e075049.
[3] N.H.B.N.H. White, Spinal cord injury (SCI) 2016 facts and figures at a glance, J Spinal Cord Med 39 (4) (2016) 493–494.
[4] L. Yan, Z. Yao, T. Lin, Q. Zhu, J. Qi, L. Gu, et al., The role of precisely matching fascicles in the quick recovery of nerve function in long peripheral nerve defects, Neuroreport 28 (15) (2017) 1008–1015.
[5] E. Suzanne, Chloe Thomson, Carol-Anne Charalambous, et al., Microtopographical cues promote peripheral nerve regeneration via transient mTORC2 activation - ScienceDirect, Acta Biomater. 60 (2017) 220–231.

[6] A. Kirillova, T.R. Yeazel, D. Asheghali, S.R. Petersen, S. Dort, K. Gall, et al., Fabrication of biomedical scaffolds using biodegradable polymers, Chem. Rev. 121 (18) (2021) 11238–11304.

[7] H. Zhang, J. Guo, Y. Wang, L. Shang, R. Chai, Y. Zhao, Natural polymer-derived bioscaffolds for peripheral nerve regeneration, Adv. Funct. Mater. 32 (41) (2022) 2203829.

[8] S.M. Kim, M.S. Lee, J. Jeon, D.H. Lee, K. Yang, S.W. Cho, et al., Biodegradable nerve guidance conduit with microporous and micropatterned poly (lactic-co-glycolic acid)-accelerated sciatic nerve regeneration, Macromol. Biosci. 18 (12) (2018) 1800290.

[9] Q. Su, M.I. Nasser, J. He, G. Deng, Q. Ouyang, D. Zhuang, et al., Engineered Schwann cell-based therapies for injury peripheral nerve reconstruction, Front. Cell. Neurosci. 16 (2022) 865266.

[10] L. Zhu, S. Jia, T. Liu, L. Yan, D. Huang, Z. Wang, et al., Aligned PCL fiber conduits immobilized with nerve growth factor gradients enhance and direct sciatic nerve regeneration, Adv. Funct. Mater. 30 (39) (2020) 2002610.

[11] F.G. Roca, L.G. Santos, M.M. Roig, L.M. Medina, C. Martínez-Ramos, M. M. Pradas, Novel tissue-engineered multimodular hyaluronic acid-polylactic acid conduits for the regeneration of sciatic nerve defect, Biomedicines 10 (5) (2022) 963.

[12] H. Gregory, J.B. Phillips, Materials for peripheral nerve repair constructs: natural proteins or synthetic polymers? Neurochem. Int. 143 (2021) 104953.

[13] W.-H. Huang, S.-L. Ding, X.-Y. Zhao, K. Li, H.-T. Guo, M.-Z. Zhang, et al., Collagen for neural tissue engineering: materials, strategies, and challenges, Materials Today Bio (2023) 100639.

[14] A. Magaz, A. Faroni, J.E. Gough, A.J. Reid, X. Li, J.J. Blaker, Bioactive silk-based nerve guidance conduits for augmenting peripheral nerve repair, Adv. Healthcare Mater. 7 (23) (2018) 1800308.

[15] C. Wang, Y. Jia, W. Yang, C. Zhang, K. Zhang, Y. Chai, Silk fibroin enhances peripheral nerve regeneration by improving vascularization within nerve conduits, J. Biomed. Mater. Res. 106 (7) (2018) 2070–2077.

[16] L.S. Kumosa, V. Zetterberg, J. Schouenborg, Gelatin promotes rapid restoration of the blood brain barrier after acute brain injury, Acta Biomater. 65 (2018) 137–149.

[17] A. Boecker, S.C. Däschler, U. Kneser, L. Harhaus, Relevance and recent developments of chitosan in peripheral nerve surgery, Front. Cell. Neurosci. 13 (2019) 104.

[18] M. Moattari, H.M. Kouchesfehani, G. Kaka, S.H. Sadraie, M. Naghdi, K. Mansouri, Chitosan-film associated with mesenchymal stem cells enhanced regeneration of peripheral nerves: a rat sciatic nerve model, J. Chem. Neuroanat. 88 (2018) 46–54.

[19] S. Grijalvo, D.D. Diaz, Graphene-based hybrid materials as promising scaffolds for peripheral nerve regeneration, Neurochem. Int. 147 (2021) 105005.

[20] R. Fabbri, E. Saracino, E. Treossi, R. Zamboni, V. Palermo, V. Benfenati, Graphene glial-interfaces: challenges and perspectives, Nanoscale 13 (8) (2021) 4390–4407.

[21] L. Ou, X. Tan, S. Qiao, J. Wu, Y. Su, W. Xie, et al., Graphene-based material-mediated immunomodulation in tissue engineering and regeneration: mechanism and significance, ACS Nano 17 (19) (2023) 18669–18687.

[22] C. Petrou, Y. Sarigiannis, Peptide synthesis: methods, trends, and challenges, Peptide applications in biomedicine, biotechnology and bioengineering (2018) 1–21.

[23] G.B. Qi, Y.J. Gao, L. Wang, H. Wang, Self-assembled peptide-based nanomaterials for biomedical imaging and therapy, Adv. Mater. 30 (22) (2018) 1703444.

[24] A. Levin, T.A. Hakala, L. Schnaider, G.J. Bernardes, E. Gazit, T.P. Knowles, Biomimetic peptide self-assembly for functional materials, Nat. Rev. Chem 4 (11) (2020) 615–634.

[25] N. Bakhtiary, B. Ghalandari, F. Ghorbani, S.N. Varma, C. Liu, Advances in peptide-based hydrogel for tissue engineering, Polymers 15 (5) (2023) 1068.

[26] P. Tiwari, A. Basu, S. Sahu, S. Gound, R.M. Christman, A.K. Tiwari, et al., An auxin–tyrosine derivative based biocompatible supergelator: a template for fabrication of nanoparticles for sustained release of model drugs, New J. Chem. 10 (2018) 1039.

[27] Recent progress in quantitative analysis of self-assembled peptides, in: X. Cai, W. Xu, C. Ren, L. Zhang, C. Zhang, J. Liu, et al. (Eds.), Exploration, Wiley Online Library, 2024.

[28] S. Mondal, S. Das, A.K. Nandi, A review on recent advances in polymer and peptide hydrogels, Soft Matter 16 (6) (2020) 1404–1454.

[29] R. Jain, G. Khandelwal, S. Roy, Unraveling the design rules in ultrashort amyloid-based peptide assemblies toward shape-controlled synthesis of gold nanoparticles, Langmuir 35 (17) (2019) 5878–5889.

[30] R. Misra, A. Sharma, A. Shiras, H.N. Gopi, Backbone engineered gamma-peptide amphitropic gels for immobilization of semiconductor quantum dots and 2D cell culture, Langmuir 33 (31) (2017) 7762–7768.

[31] N. Brown, J. Lei, C. Zhan, L.J.W. Shimon, L. Adler-Abramovich, G. Wei, et al., Structural polymorphism in a self-assembled tri-aromatic peptide system, ACS Nano 12 (4) (2018) 3253–3262.

[32] L. Li, L. Xie, R. Zheng, R. Sun, Self-assembly dipeptide hydrogel: the structures and properties, Front. Chem. 9 (2021) 739791.

[33] N.K. Wijerathne, M. Kumar, R.V. Ulijn, Fmoc-dipeptide/porphyrin molar ratio dictates energy transfer efficiency in nanostructures produced by biocatalytic Co-assembly, Chem.–Eur. J. 25 (51) (2019) 11847–11851.

[34] T. Yoshitomi, H. Zheng, K. Yoshimoto, Investigations of chirality effects on undifferentiated state of mesenchymal stem cells using soft nanofibrous oligopeptide hydrogels, Anal. Sci. 37 (3) (2021) 539–543.

[35] C.P. Apostolidou, C. Kokotidou, V. Platania, V. Nikolaou, G. Landrou, E. Nikoloudakis, et al., Antimicrobial potency of fmoc-phe-phe dipeptide hydrogels with encapsulated porphyrin chromophores is a promising alternative in antimicrobial resistance, Biomolecules 14 (2) (2024) 226.

[36] L. Chen, K. Morris, A. Laybourn, D. Elias, M.R. Hicks, A. Rodger, et al., Self-assembly mechanism for a Naphthalene−Dipeptide leading to hydrogelation, Langmuir 26 (7) (2010) 5232–5242.

[37] A.D. Martin, P. Thordarson, Beyond Fmoc: a review of aromatic peptide capping groups, J. Mater. Chem. B 8 (5) (2020) 863–877.

[38] J.L. Zou, S. Liu, J.H. Sun, W.H. Yang, Y.W. Xu, Z.L. Rao, et al., Peripheral nerve-derived matrix hydrogel promotes remyelination and inhibits synapse formation, Adv. Funct. Mater. 28 (13) (2018) 1705739.

[39] K. Yao, G. Gong, Z. Fu, Y. Wang, L. Zhang, G. Li, et al., Synthesis and evaluation of cytocompatible alkyne-containing poly (β-amino ester)-based hydrogels functionalized via click reaction, ACS Macro Lett. 9 (9) (2020) 1391–1397.

[40] A. Ishida, M. Oshikawa, I. Ajioka, T. Muraoka, Sequence-dependent bioactivity and self-assembling properties of RGD-containing amphiphilic peptides as extracellular scaffolds, ACS Appl. Bio Mater. 3 (6) (2020) 3605–3611.

[41] G. Bjørklund, M. Peana, M. Maes, M. Dadar, B. Severin, The glutathione system in Parkinson's disease and its progression, Neurosci. Biobehav. Rev. 120 (2021) 470–478.

[42] K. Aoyama, Glutathione in the brain, Int. J. Mol. Sci. 22 (9) (2021) 5010.

[43] I. Cacciatore, C. Cornacchia, L. Baldassarre, E. Fornasari, A. Mollica, A. Stefanucci, et al., GPE and GPE analogues as promising neuroprotective agents, Mini Rev. Med. Chem. 12 (1) (2012) 13–23.

[44] J.A. Hutchinson, I.W. Hamley, C.J.C. Edwards-Gayle, V. Castelletto, C. Piras, R. Cramer, et al., Melanin production by tyrosinase activity on a tyrosine-rich peptide fragment and pH-dependent self-assembly of its lipidated analogue, Org. Biomol. Chem. 17 (18) (2019) 4543–4553.

[45] N. Hauptstein, L.M. De Leon-Rodriguez, A.K. Mitra, Y. Hemar, I. Kavianinia, N. Li, et al., Supramolecular threading of peptide hydrogel fibrils, ACS Biomater. Sci. Eng. 4 (8) (2018) 2733–2738.

[46] E. Rosa, L. De Mello, V. Castelletto, M.L. Dallas, A. Accardo, J. Seitsonen, et al., Cell adhesion motif-functionalized lipopeptides: nanostructure and selective myoblast cytocompatibility, Biomacromolecules 24 (1) (2022) 213–224.

[47] J. Lu, X. Sun, H. Yin, X. Shen, S. Yang, Y. Wang, et al., A neurotrophic peptide-functionalized self-assembling peptide nanofiber hydrogel enhances rat sciatic nerve regeneration, Nano Res. 11 (2018) 4599–4613.

[48] D.E. Clarke, C.D.J. Parmenter, O.A. Scherman, Tunable pentapeptide self-assembled β-sheet hydrogels, Angew Chem. Int. Ed. Engl. 57 (26) (2018) 7709–7713.

[49] R. Patel, M. Santhosh, J.K. Dash, R. Karpoormath, A. Jha, J. Kwak, et al., Ile-Lys-Val-ala-Val (IKVAV) peptide for neuronal tissue engineering, Polym. Adv. Technol. 30 (1) (2019) 4–12.

[50] H. Gao, Y. Liu, W. Guan, S. Sun, T. Zheng, L. Wu, et al., Surface topologized ovalbumin scaffolds containing YIGSR peptides for modulating Schwann cell behavior, Int. J. Biol. Macromol. 253 (2023) 127015.

[51] K.F. A, H.W. B, Z.S. A, Self-assembling peptide-based hydrogels: fabrication, properties, and applications, Biotechnol. Adv. 49 (2021) 107752.

[52] S. Zhang, T.C. Holmes, C.M. DiPersio, R.O. Hynes, X. Su, A. Rich, Self-complementary oligopeptide matrices support mammalian cell attachment, Biomaterials 16 (18) (1995) 1385–1393.

[53] F. Gelain, Z. Luo, S. Zhang, Self-assembling peptide EAK16 and RADA16 nanofiber scaffold hydrogel, Chem. Rev. 120 (24) (2020) 13434–13460.

[54] J. Lu, X. Wang, Biomimetic self-assembling peptide hydrogels for tissue engineering applications, Biomimetic Med. Mater.: From Nanotechnol. 3D Bioprinting (2018) 297–312.

[55] J. Bertouille, S. Kasas, C. Martin, U. Hennecke, S. Ballet, R.G. Willaert, Fast self-assembly dynamics of a β-sheet peptide soft material, Small 19 (20) (2023) 2206795.

[56] J. Liu, H. Song, L. Zhang, H. Xu, X. Zhao, Self-assembly-peptide hydrogels as tissue-engineering scaffolds for three-dimensional culture of chondrocytes in vitro, Macromol. Biosci. 10 (10) (2010) 1164–1170.

[57] R. Wang, Z. Wang, Y. Guo, H. Li, Z. Chen, Design of a RADA16-based self-assembling peptide nanofiber scaffold for biomedical applications, J. Biomater. Sci. Polym. Ed. 30 (9) (2019) 713–736.

[58] M. Yoshimatsu, R. Nakamura, Y. Kishimoto, H. Yurie, Y. Hayashi, S. Kaba, et al., Recurrent laryngeal nerve regeneration using a self-assembling peptide hydrogel, Laryngoscope 130 (10) (2020) 2420–2427.

[59] Y. Wen, S.L. Roudebush, G.A. Buckholtz, T.R. Goehring, N. Giannoukakis, E. S. Gawalt, et al., Coassembly of amphiphilic peptide EAK16-II with histidinylated analogues and implications for functionalization of β-sheet fibrils in vivo, Biomaterials 35 (19) (2014) 5196–5205.

[60] F. Gelain, Z. Luo, M. Rioult, S. Zhang, Self-assembling peptide scaffolds in the clinic, npj Regenerative Med. 6 (1) (2021) 9.

[61] A.N. Moore, J.D. Hartgerink, Self-assembling multidomain peptide nanofibers for delivery of bioactive molecules and tissue regeneration, Accounts Chem. Res. 50 (4) (2017) 714–722.

[62] A. Ls, D. Cdcb, A. Csel, A. La, D. Hklbc, A. Jdh, Self-assembling multidomain peptide hydrogels accelerate peripheral nerve regeneration after crush injury, Biomaterials 265 (2020).

[63] J.J. Greene, M.T. McClendon, N. Stephanopoulos, Z. Álvarez, S.I. Stupp, C. P. Richter, Electrophysiological assessment of a peptide amphiphile nanofiber nerve graft for facial nerve repair, J. Tissue Eng. Regenerative Med. 12 (6) (2018) 1389–1401.

[64] W. Sun, D.A. Gregory, X. Zhao, Designed peptide amphiphiles as scaffolds for tissue engineering, Adv. Colloid Interface Sci. 314 (2023) 102866.
[65] Q. Feng, C. Yongzhu, T. Chengkang, Z. Xiaojun, Amphiphilic peptides as novel nanomaterials: design, self-assembly and application, Int. J. Nanomed. 13 (2018) 5003–5022.
[66] X. Zhang, Y. Li, C. Hu, Y. Wu, D. Zhong, X. Xu, et al., Engineering anticancer amphipathic peptide-dendronized compounds for highly-efficient plasma/organelle membrane perturbation and multidrug resistance reversal, ACS Appl. Mater. Interfaces 10 (37) (2018) 30952–30962.
[67] S. Das, D. Das, Rational design of peptide-based smart hydrogels for therapeutic applications, Front. Chem. 9 (2021) 770102.
[68] K.M. Wong, A.S. Robang, A.H. Lint, Y. Wang, X. Dong, X. Xiao, et al., Engineering β-Sheet peptide coassemblies for biomaterial applications, J. Phys. Chem. B 125 (50) (2021) 13599–13609.
[69] A. Aggeli, M. Bell, L.M. Carrick, C.W.G. Fishwick, R. Harding, P.J. Mawer, et al., pH as a trigger of peptide β-sheet self-assembly and reversible switching between nematic and isotropic phases, J. Am. Chem. Soc. 125 (32) (2003) 9619–9628.
[70] A. Aggeli, M. Bell, N. Boden, L.M. Carrick, A.E. Strong, Self-assembling peptide polyelectrolyte beta-sheet complexes form nematic hydrogels, Angew Chem. Int. Ed. Engl. 42 (45) (2003) 5603–5606.
[71] J.K. Wychowaniec, A.M. Smith, C. Ligorio, O.O. Mykhaylyk, A.F. Miller, A. Saiani, Role of sheet-edge interactions in β-sheet self-assembling peptide hydrogels, Biomacromolecules 21 (6) (2020) 2285–2297.
[72] M.A. Elsawy, J.K. Wychowaniec, L.A. Castillo Díaz, A.M. Smith, A.F. Miller, A. Saiani, Controlling doxorubicin release from a peptide hydrogel through fine-tuning of drug–peptide fiber interactions, Biomacromolecules 23 (6) (2022) 2624–2634.
[73] Z. Liu, A. Miller, A. Saiani, R. Curtis, Self-Assembly Peptide Based Double-Network Hydrogel, University of Manchester, 2023.
[74] C.J. Edwards-Gayle, J.K. Wychowaniec, Characterization of Peptide-Based Nanomaterials. Peptide Bionanomaterials: from Design to Application, Springer, 2023, pp. 255–308.
[75] C.F. Lu, Y. Wang, S.H. Yang, C. Wang, X. Sun, J.J. Lu, et al., Bioactive self-assembling peptide hydrogels functionalized with brain-derived neurotrophic factor and nerve growth factor mimicking peptides synergistically promote peripheral nerve regeneration, ACS Biomater. Sci. Eng. 4 (8) (2018) 2994–3005.
[76] C. Ligorio, M. Zhou, J.K. Wychowaniec, X. Zhu, C. Bartlam, A.F. Miller, et al., Graphene oxide containing self-assembling peptide hybrid hydrogels as a potential 3D injectable cell delivery platform for intervertebral disc repair applications, Acta Biomater. 92 (2019) 92–103.
[77] J.P. Schneider, D.J. Pochan, B. Ozbas, K. Rajagopal, L. Pakstis, J. Kretsinger, Responsive hydrogels from the intramolecular folding and self-assembly of a designed peptide, J. Am. Chem. Soc. 124 (50) (2002) 15030–15037.
[78] K. Nagy-Smith, P.J. Beltramo, E. Moore, R. Tycko, E.M. Furst, J.P. Schneider, Molecular, local, and network-level basis for the enhanced stiffness of hydrogel networks formed from coassembled racemic peptides: predictions from Pauling and Corey, ACS Cent. Sci. 3 (6) (2017) 586–597.
[79] K. Nagy-Smith, E. Moore, J. Schneider, R. Tycko, Molecular structure of monomorphic peptide fibrils within a kinetically trapped hydrogel network, Proc. Natl. Acad. Sci. U.S.A. 112 (32) (2015) 9816–9821.
[80] Y. Zhu, L. Wang, Y. Li, Z. Huang, S. Luo, Y. He, et al., Injectable pH and redox dual responsive hydrogels based on self-assembled peptides for anti-tumor drug delivery, Biomater. Sci. 8 (19) (2020) 5415–5426.
[81] X. Li, M. Fu, J. Wu, C. Zhang, X. Deng, A. Dhinakar, et al., pH-sensitive peptide hydrogel for glucose-responsive insulin delivery, Acta Biomater. 51 (2017) 294–303.
[82] A.N. Lupas, J. Bassler, Coiled coils - a model system for the 21st century, Trends Biochem. Sci. 42 (2) (2017) 130–140.
[83] D.N. Woolfson, Coiled-coil design: updated and upgraded, Subcell. Biochem. 82 (2017) 35–61.
[84] M.G. Ryadnov, D.N. Woolfson, Engineering the morphology of a self-assembling protein fibre, Nat. Mater. 2 (5) (2003) 329–332.
[85] D. Papapostolou, A.M. Smith, E.D. Atkins, S.J. Oliver, M.G. Ryadnov, L.C. Serpell, et al., Engineering nanoscale order into a designed protein fiber, Proc. Natl. Acad. Sci. U. S. A. 104 (26) (2007) 10853–10858.
[86] E.F. Banwell, E.S. Abelardo, D.J. Adams, M.A. Birchall, A. Corrigan, A.M. Donald, et al., Rational design and application of responsive alpha-helical peptide hydrogels, Nat. Mater. 8 (7) (2009) 596–600.
[87] W. Zhang, G. Chu, H. Wang, S. Chen, B. Li, F. Han, Effects of matrix stiffness on the differentiation of multipotent stem cells, Curr. Stem Cell Res. Ther. 15 (5) (2020) 449–461.
[88] J. Li, K. Narayanan, Y. Zhang, R.C. Hill, F. He, K.C. Hansen, et al., Role of lineage-specific matrix in stem cell chondrogenesis, Biomaterials 231 (2020) 119681.
[89] N.D. Leipzig, M.S. Shoichet, The effect of substrate stiffness on adult neural stem cell behavior, Biomaterials 30 (36) (2009) 6867–6878.
[90] K. Saha, A.J. Keung, E.F. Irwin, Y. Li, L. Little, D.V. Schaffer, et al., Substrate modulus directs neural stem cell behavior, Biophys. J. 95 (9) (2008) 4426–4438.
[91] S. Peressotti, G.E. Koehl, J.A. Goding, R.A. Green, Self-assembling hydrogel structures for neural tissue repair, ACS Biomater. Sci. Eng. 7 (9) (2021) 4136–4163.
[92] B. Hu, C. Owh, P.L. Chee, W.R. Leow, X. Liu, Y.-L. Wu, et al., Supramolecular hydrogels for antimicrobial therapy, Chem. Soc. Rev. 47 (18) (2018) 6917–6929.
[93] Gonzalez M. Criado, D. Wagner, J. Rodon Fores, C. Blanck, M. Schmutz, A. Chaumont, et al., Supramolecular hydrogel induced by electrostatic interactions between polycation and phosphorylated-fmoc-tripeptide, Chem. Mater. 32 (2020).
[94] A. Croitoriu, L.E. Nita, A.P. Chiriac, A.G. Rusu, M. Bercea, New physical hydrogels based on Co-assembling of FMOC-amino acids, Gels 7 (4) (2021).
[95] O. Maslova, O. Senko, E. Efremenko, Aspartic and glutamic acids polymers: preparation and applications in medicinal chemistry and pharmaceutics, Russ. Chem. Bull. 67 (2018) 614–623.
[96] D. Wu, X. Xie, A.A. Kadi, Y. Zhang, Photosensitive peptide hydrogels as smart materials for applications, Chin. Chem. Lett. 29 (7) (2018) 1098–1104.
[97] Sotirios Koutsopoulos, Self-assembling peptide nanofiber hydrogels in tissue engineering and regenerative medicine: progress, design guidelines, and applications, J. Biomed. Mater. Res. 104 (4) (2016) 1002–1016.
[98] W. Zhang, X. Yu, Y. Li, Z. Su, K.D. Jandt, G. Wei, Protein-mimetic peptide nanofibers: motif design, self-assembly synthesis, and sequence-specific biomedical applications, Prog. Polym. Sci. 80 (2018) 94–124.
[99] V.K. Pal, R. Jain, S. Roy, Tuning the supramolecular structure and function of collagen mimetic ionic complementary peptides via electrostatic interactions, Langmuir 36 (4) (2019) 1003–1013.
[100] Y. Zhao, W. Yang, C. Chen, J. Wang, L. Zhang, H. Xu, Rational design and self-assembly of short amphiphilic peptides and applications, Curr. Opin. Colloid Interface Sci. 35 (2018) 112–123.
[101] A. Ishida, G. Watanabe, M. Oshikawa, I. Ajioka, T. Muraoka, Glycine substitution effects on the supramolecular morphology and rigidity of cell-adhesive amphiphilic peptides, Chem.–Eur. J. 25 (59) (2019) 13523–13530.
[102] P. Song, H. Wang, High-performance polymeric materials through hydrogen-bond cross-linking, Adv. Mater. 32 (18) (2020) 1901244.
[103] J. Verjans, R. Hoogenboom, Supramolecular polymer materials based on ureidopyrimidinone quadruple hydrogen bonding units, Prog. Polym. Sci. (2023) 101689.
[104] G.B. Qi, Y.J. Gao, L. Wang, H. Wang, Self-assembled peptide-based nanomaterials for biomedical imaging and therapy, Adv. Mater. 30 (22) (2018) e1703444.
[105] H. Zhang, S. Lou, Z. Yu, Polar− π interactions promote self-assembly of dipeptides into laminated nanofibers, Langmuir 35 (13) (2019) 4710–4717.
[106] A. Vedadghavami, F. Minooei, M.H. Mohammadi, S. Khetani, A. Rezaei Kolahchi, S. Mashayekhan, et al., Manufacturing of hydrogel biomaterials with controlled mechanical properties for tissue engineering applications, Acta Biomater. 62 (2017) 42–63.
[107] M.Y. Folikumah, M. Behl, A. Lendlein, Thiol–thioester exchange reactions in precursors enable pH-triggered hydrogel formation, Biomacromolecules 22 (5) (2021) 1875–1884.
[108] N.J. Sinha, M.G. Langenstein, D.J. Pochan, C.J. Kloxin, J.G. Saven, Peptide design and self-assembly into targeted nanostructure and functional materials, Chem. Rev. 121 (22) (2021) 13915–13935.
[109] P. Tufféry, P. Derreumaux, A refined pH-dependent coarse-grained model for peptide structure prediction in aqueous solution, Frontiers in Bioinformatics 3 (2023) 1113928.
[110] S. Chibh, J. Mishra, A. Kour, V.S. Chauhan, J.J. Panda, Recent advances in the fabrication and bio-medical applications of self-assembled dipeptide nanostructures, Nanomedicine 16 (2) (2020) 139–163.
[111] T.L. Lopez-Silva, D.G. Leach, I.C. Li, X. Wang, J.D. Hartgerink, Self-assembling multidomain peptides: design and characterization of neutral peptide-based materials with pH and ionic strength independent self-assembly, ACS Biomater. Sci. Eng. 5 (2) (2019) 977–985.
[112] P. Sharma, V.K. Pal, S. Roy, An overview of latest advances in exploring bioactive peptide hydrogels for neural tissue engineering, Biomater. Sci. 9 (11) (2021) 3911–3938.
[113] D. Bairagi, P. Biswas, K. Basu, S. Hazra, D. Hermida-Merino, D.K. Sinha, et al., Self-assembling peptide-based hydrogel: regulation of mechanical stiffness and thermal stability and 3D cell culture of fibroblasts, ACS Appl. Bio Mater. 2 (12) (2019) 5235–5244.
[114] N. Kulkarni, P. Rao, G.S. Jadhav, B. Kulkarni, N. Kanakavalli, S. Kirad, et al., Emerging role of injectable dipeptide hydrogels in biomedical applications, ACS Omega 8 (4) (2023) 3551–3570.
[115] G.C. Lindberg, K.S. Lim, B.G. Soliman, A. Nguyen, G.J. Hooper, R.J. Narayan, et al., Biological function following radical photo-polymerization of biomedical polymers and surrounding tissues: design considerations and cellular risk factors, Appl. Phys. Rev. 8 (1) (2021).
[116] X. Wang, Q. Wang, Enzyme-laden bioactive hydrogel for biocatalytic monitoring and regulation, Accounts Chem. Res. 54 (5) (2021) 1274–1287.
[117] Y.S. Liu, R.D. Chakravarthy, A.A. Saddik, M. Mohammed, H.C. Lin, Supramolecular polymer/peptide hybrid hydrogels with tunable stiffness mediated by interchain acid-amide hydrogen bonds, RSC Adv. 12 (22) (2022) 14315–14320.
[118] L. Aulisa, H. Dong, J.D. Hartgerink, Self-assembly of multidomain peptides: sequence variation allows control over cross-linking and viscoelasticity, Biomacromolecules 10 (9) (2009) 2694–2698.
[119] H. Samadian, H. Maleki, Z. Allahyari, M. Jaymand, Natural polymers-based light-induced hydrogels: promising biomaterials for biomedical applications, Coord. Chem. Rev. 420 (2020) 213432.

[120] B. van Bochove, D.W. Grijpma, Photo-crosslinked synthetic biodegradable polymer networks for biomedical applications, J. Biomater. Sci. Polym. Ed. 30 (2) (2019) 77–106.
[121] K.-H. Yang, G. Lindberg, B. Soliman, K. Lim, T. Woodfield, R.J. Narayan, Effect of photoinitiator on precursory stability and curing depth of Thiol-Ene Clickable gelatin, Polymers 13 (11) (2021) 1877.
[122] R.M. Maddock, G.J. Pollard, N.G. Moreau, J.J. Perry, P.R. Race, Enzyme-catalysed polymer cross-linking: biocatalytic tools for chemical biology, materials science and beyond, Biopolymers 111 (9) (2020) e23390.
[123] M.G. Ciulla, A. Marchini, J. Gazzola, M. Forouharshad, R. Pugliese, F. Gelain, In situ transglutaminase cross-linking improves mechanical properties of self-assembling peptides for biomedical applications, ACS Appl. Bio Mater. 7 (3) (2024) 1723–1734.
[124] K.W. Cheng, L. Alhasan, A.R. Rezk, A. Al-Abboodi, P.M. Doran, L.Y. Yeo, et al., Fast three-dimensional micropatterning of PC12 cells in rapidly crosslinked hydrogel scaffolds using ultrasonic standing waves, Biofabrication 12 (1) (2019) 015013.
[125] T. Liu, W. Zhu, X. Zhang, C. He, X. Liu, Q. Xin, et al., Recent advances in cell and functional biomaterial treatment for spinal cord injury, BioMed Res. Int. 2022 (2022) 5079153.
[126] A.M. Nicaise, A. D'Angelo, R.B. Ionescu, G. Krzak, C.M. Willis, S. Pluchino, The role of neural stem cells in regulating glial scar formation and repair, Cell Tissue Res. 387 (3) (2022) 399–414.
[127] S. Yi, Y. Zhang, X. Gu, L. Huang, K. Zhang, T. Qian, et al., Application of stem cells in peripheral nerve regeneration, Burns & trauma 8 (2020) tkaa002.
[128] A. Lavorato, S. Raimondo, M. Boido, L. Muratori, G. Durante, F. Cofano, et al., Mesenchymal stem cell treatment perspectives in peripheral nerve regeneration: systematic review, Int. J. Mol. Sci. 22 (2) (2021) 572.
[129] S. Mandal, T. Dube, A.K. Mohapatra, S. Choudhury, F. Khanam, P. Yadav, et al., Engineered biocompatible and stable dipeptide hydrogel with tunable mechanical and cell growth properties to embolden neuroglial cell growth, Int. J. Pept. Res. Therapeut. 27 (2021) 2795–2808.
[130] A. Adak, G. Das, J. Khan, N. Mukherjee, V. Gupta, R. Mallesh, et al., Extracellular matrix (ECM)-mimicking neuroprotective injectable sulfo-functionalized peptide hydrogel for repairing brain injury, ACS Biomater. Sci. Eng. 6 (4) (2020) 2287–2296.
[131] E. Mauri, A. Sacchetti, N. Vicario, L. Peruzzotti-Jametti, F. Rossi, S. Pluchino, Evaluation of RGD functionalization in hybrid hydrogels as 3D neural stem cell culture systems, Biomater. Sci. 6 (3) (2018) 501–510.
[132] K. Zaviskova, D. Tukmachev, J. Dubisova, I. Vackova, A. Hejcl, J. Bystronova, et al., Injectable hydroxyphenyl derivative of hyaluronic acid hydrogel modified with RGD as scaffold for spinal cord injury repair, J. Biomed. Mater. Res. 106 (4) (2018) 1129–1140.
[133] X. Tang, X. Gu, T. Huang, X. Chen, Z. Zhou, Y. Yang, et al., Anisotropic silk-inspired nerve conduit with peptides improved the microenvironment for long-distance peripheral nerve regeneration, ACS Macro Lett. 10 (12) (2021) 1501–1509.
[134] H. Turkez, I. Cacciatore, L. Marinelli, E. Fornasari, M.E. Aslan, K. Cadirci, et al., Glycyl-L-prolyl-L-glutamate pseudotripeptides for treatment of Alzheimer's disease, Biomolecules 11 (1) (2021) 126.
[135] C.P. Bernardes, N.A.G. Santos, F.M. Sisti, R.S. Ferreira, N.A. Santos-Filho, A.C. O. Cintra, et al., A synthetic snake-venom-based tripeptide (Glu-Val-Trp) protects PC12 cells from MPP(+) toxicity by activating the NGF-signaling pathway, Peptides 104 (2018) 24–34.
[136] L. Huang, X. Yang, L. Deng, D. Ying, A. Lu, L. Zhang, et al., Biocompatible chitin hydrogel incorporated with PEDOT nanoparticles for peripheral nerve repair, ACS Appl. Mater. Interfaces 13 (14) (2021) 16106–16117.
[137] A. Farrukh, F. Ortega, W. Fan, N. Marichal, J.I. Paez, B. Berninger, et al., Bifunctional hydrogels containing the laminin motif IKVAV promote neurogenesis, Stem Cell Rep. 9 (5) (2017) 1432–1440.
[138] Y. Yin, W. Wang, Q. Shao, B. Li, D. Yu, X. Zhou, et al., Pentapeptide IKVAV-engineered hydrogels for neural stem cell attachment, Biomater. Sci. 9 (8) (2021) 2887–2892.
[139] Y. Zhao, Y. Wang, C. Niu, L. Zhang, G. Li, Y. Yang, Construction of polyacrylamide/graphene oxide/gelatin/sodium alginate composite hydrogel with bioactivity for promoting Schwann cells growth, J. Biomed. Mater. Res. 106 (7) (2018) 1951–1964.
[140] S. Chen, Y. Zhao, X. Yan, L. Zhang, G. Li, Y. Yang, PAM/GO/gel/SA composite hydrogel conduit with bioactivity for repairing peripheral nerve injury, J. Biomed. Mater. Res. 107 (6) (2019) 1273–1283.
[141] G. Li, S. Li, L. Zhang, S. Chen, Z. Sun, S. Li, et al., Construction of biofunctionalized anisotropic hydrogel micropatterns and their effect on Schwann cell behavior in peripheral nerve regeneration, ACS Appl. Mater. Interfaces 11 (41) (2019) 37397–37410.
[142] L.-A. Feng, J. Shi, J.-Y. Guo, S.-F. Wang, Recent strategies for improving hemocompatibility and endothelialization of cardiovascular devices and inhibition of intimal hyperplasia, J. Mater. Chem. B 10 (20) (2022) 3781–3792.
[143] C.M. Motta, K.J. Endres, C. Wesdemiotis, R.K. Willits, M.L. Becker, Enhancing Schwann cell migration using concentration gradients of laminin-derived peptides, Biomaterials 218 (2019) 119335.
[144] C. Ligorio, A. Mata, Synthetic extracellular matrices with function-encoding peptides, Nature Rev. Bioeng. 1 (7) (2023) 518–536.
[145] Z. Hao, H. Li, Y. Wang, Y. Hu, T. Chen, S. Zhang, et al., Supramolecular peptide nanofiber hydrogels for bone tissue engineering: from multihierarchical fabrications to comprehensive applications, Adv. Sci. 9 (11) (2022) 2103820.
[146] B. Cao, Y. Li, T. Yang, Q. Bao, M. Yang, C. Mao, Bacteriophage-based biomaterials for tissue regeneration, Adv. Drug Deliv. Rev. 145 (2019) 73–95.
[147] N. Huettner, T.R. Dargaville, A. Forget, Discovering cell-adhesion peptides in tissue engineering: beyond RGD, Trends Biotechnol. 36 (4) (2018) 372–383.
[148] Q. Liu, S. Zheng, K. Ye, J. He, Y. Shen, S. Cui, et al., Cell migration regulated by RGD nanospacing and enhanced under moderate cell adhesion on biomaterials, Biomaterials 263 (2020) 120327.
[149] Y. Sun, W. Li, X. Wu, N. Zhang, Y. Zhang, S. Ouyang, et al., Functional self-assembling peptide nanofiber hydrogels designed for nerve degeneration, ACS Appl. Mater. Interfaces 8 (3) (2016) 2348–2359.
[150] A. Jahanbazi Jahan-Abad, S. Sahab Negah, H. Hosseini Ravandi, S. Ghasemi, M. Borhani-Haghighi, W. Stummer, et al., Human neural stem/progenitor cells derived from epileptic human brain in a self-assembling peptide nanoscaffold improve traumatic brain injury in rats, Mol. Neurobiol. 55 (2018) 9122–9138.
[151] N. Ghandy, A. Ebrahimzadeh-Bideskan, A. Gorji, S.S. Negah, Co-transplantation of novel Nano-SDF scaffold with human neural stem cells attenuates inflammatory responses and apoptosis in traumatic brain injury, Int. Immunopharm. 115 (2023) 109709.
[152] T.W. Wang, K.C. Chang, L.H. Chen, S.Y. Liao, C.W. Yeh, Y.J. Chuang, Effects of an injectable functionalized self-assembling nanopeptide hydrogel on angiogenesis and neurogenesis for regeneration of the central nervous system, Nanoscale 9 (2017).
[153] Y. Zhao, R. Zhu, X. Song, Z. Ma, S. Chen, D. Wu, et al., Assembly pathway selection of designer self-assembling peptide and fabrication of hierarchical scaffolds for neural regeneration, ACS Appl. Mater. Interfaces 10 (31) (2018) 26128–26141.
[154] M. Yousefifard, F. Ramezani, A.R. Vaccaro, M. Hosseini, V. Rahimi-Movaghar, The role of intraspinal administration of self-assembled peptide on locomotion recovery after spinal cord injury: a systematic review and meta-analysis study, Neuromodulation: Technol. Neural Interface 26 (6) (2022) 1171–1178.
[155] K. Zweckberger, C.S. Ahuja, Y. Liu, J. Wang, M.G. Fehlings, Self-assembling peptides optimize the post-traumatic milieu and synergistically enhance the effects of neural stem cell therapy after cervical spinal cord injury, Acta Biomater. 42 (2016) 77–89.
[156] C.S.E. Lai, V. Leyva-Aranda, V.H. Kong, T.L. Lopez-Silva, A.C. Farsheed, C. D. Cristobal, et al., A combined conduit-bioactive hydrogel approach for regeneration of transected sciatic nerves, ACS Appl. Bio Mater. 5 (10) (2022) 4611–4624.
[157] W. Sun, C.S. Taylor, Y. Zhang, D.A. Gregory, M.A. Tomeh, J.W. Haycock, et al., Cell guidance on peptide micropatterned silk fibroin scaffolds, J. Colloid Interface Sci. 603 (2021) 380–390.
[158] H. Chang, C. Li, R. Huang, R. Su, W. Qi, Z. He, Amphiphilic hydrogels for biomedical applications, J. Mater. Chem. B 7 (18) (2019) 2899–2910.
[159] C. Redondo-Gómez, Y. Abdouni, C.R. Becer, A. Mata, Self-assembling hydrogels based on a complementary host–guest peptide amphiphile pair, Biomacromolecules 20 (6) (2019) 2276–2285.
[160] A.K. Das, P.K. Gavel, Low molecular weight self-assembling peptide-based materials for cell culture, antimicrobial, anti-inflammatory, wound healing, anticancer, drug delivery, bioimaging and 3D bioprinting applications, Soft Matter 16 (44) (2020) 10065–10095.
[161] T. Guan, J. Li, C. Chen, Y. Liu, Self-assembling peptide-based hydrogels for wound tissue repair, Adv. Sci. 9 (10) (2022) 2104165.
[162] S. Lee, T.H. Trinh, M. Yoo, J. Shin, H. Lee, J. Kim, et al., Self-assembling peptides and their application in the treatment of diseases, Int. J. Mol. Sci. 20 (23) (2019) 5850.
[163] S. Yang, J. Zhu, C. Lu, Y. Chai, Z. Cao, J. Lu, et al., Aligned fibrin/functionalized self-assembling peptide interpenetrating nanofiber hydrogel presenting multi-cues promotes peripheral nerve functional recovery, Bioact. Mater. 8 (2022) 529–544.
[164] X. Ma, M. Wang, Y. Ran, Y. Wu, J. Wang, F. Gao, et al., Design and fabrication of polymeric hydrogel carrier for nerve repair, Polymers 14 (8) (2022) 1549.
[165] A.D. Noblett, K. Baek, L.J. Suggs, Controlling nucleopeptide hydrogel self-assembly and formation for cell-culture scaffold applications, ACS Biomater. Sci. Eng. 7 (6) (2021) 2605–2614.
[166] J. Lu, X. Wang, Biomimetic self-assembling peptide hydrogels for tissue engineering applications, Adv. Exp. Med. Biol. 1064 (2018) 297–312.
[167] L.R. Pinosanu, B. Capitanescu, D. Glavan, S. Godeanu, I. Ferna, T.R. Doeppner, et al., Neuroglia cells transcriptomic in brain development, aging and neurodegenerative diseases, Aging Dis. 14 (1) (2023) 63.
[168] L.Y. Liao, B.W. Lau, D.I. Sánchez-Vidaña, Q. Gao, Exogenous neural stem cell transplantation for cerebral ischemia, Neural Regen. Res. 14 (7) (2019) 1129–1137.
[169] Y. Li, D. Fraser, J. Mereness, A. Van Hove, S. Basu, M. Newman, et al., Tissue engineered neurovascularization strategies for craniofacial tissue regeneration, ACS Appl. Bio Mater. 5 (1) (2021) 20–39.
[170] S. Yang, C. Wang, J. Zhu, C. Lu, H. Li, F. Chen, et al., Self-assembling peptide hydrogels functionalized with LN-and BDNF-mimicking epitopes synergistically enhance peripheral nerve regeneration, Theranostics 10 (18) (2020) 8227.

[171] A.F. Cintrón-Colón, G. Almeida-Alves, J.M. VanGyseghem, J.M. Spitsbergen, GDNF to the rescue: GDNF delivery effects on motor neurons and nerves, and muscle re-innervation after peripheral nerve injuries, Neural Regenerat. Res. 17 (4) (2022) 748–753.
[172] K.M. Prautsch, L. Degrugillier, D.J. Schaefer, R. Guzman, D.F. Kalbermatten, S. Madduri, Ex-vivo stimulation of adipose stem cells by growth factors and fibrin-hydrogel assisted delivery strategies for treating nerve gap-injuries, Bioengineering 7 (2) (2020) 42.
[173] M. Tian, Z. Ma, G.-Z. Yang, Micro/nanosystems for controllable drug delivery to the brain, Innovation 5 (1) (2024).
[174] Z. Xiao, Y. Yao, Z. Wang, Q. Tian, J. Wang, L. Gu, et al., Local delivery of Taxol from FGL-functionalized self-assembling peptide nanofiber scaffold promotes recovery after spinal cord injury, Front. Cell Dev. Biol. 8 (2020) 820.
[175] X. Xiao, C.-T. He, S. Zhao, J. Li, W. Lin, Z. Yuan, et al., A general approach to cobalt-based homobimetallic phosphide ultrathin nanosheets for highly efficient oxygen evolution in alkaline media, Energy Environ. Sci. 10 (4) (2017) 893–899.
[176] A. Adak, G. Das, S. Barman, S. Mohapatra, D. Bhunia, B. Jana, et al., Biodegradable neuro-compatible peptide hydrogel promotes neurite outgrowth, shows significant neuroprotection, and delivers anti-Alzheimer drug, ACS Appl. Mater. Interfaces 9 (6) (2017) 5067–5076.
[177] Chesson C. Brent, R.E. Alvarado, J.S. Rudra, Microwave-assisted synthesis and immunological evaluation of self-assembling peptide vaccines, Methods Mol. Biol. 1777 (2018) 249–259.