Adhesive and self-healing materials for central nervous system repair

Cátia Correia, Rui L. Reis, Iva Pashkuleva, Natália M. Alves

PII: S2772-9508(23)00162-0

DOI: https://doi.org/10.1016/j.bioadv.2023.213439

Reference: BIOADV 213439

To appear in:

Received date: 11 February 2023

Revised date: 14 April 2023

Accepted date: 19 April 2023

Please cite this article as: C. Correia, R.L. Reis, I. Pashkuleva, et al., Adhesive and self-healing materials for central nervous system repair, (2023), https://doi.org/10.1016/j.bioadv.2023.213439

Adhesive and self-healing materials for central nervous system repair

Cátia Correia[a,b], Rui L. Reis[a,b], Iva Pashkuleva[a,b], Natália M. Alves[a,b,*]

[a] *3B's Research Group, I3Bs – Research Institute on Biomaterials, Biodegradables and Biomimetics, University of Minho, Headquarters of the European Institute of Excellence on Tissue Engineering and Regenerative Medicine, AvePark, Parque de Ciência e Tecnologia, Zona Industrial da Gandra, 4805-017 Barco, Guimarães, Portugal;*

[b] *ICVS/3B's–PT Government Associate Laboratory, Braga/Guimarães, Portugal*

***Corresponding author**

E-mail address: nalves@i3bs.uminho.pt;

Abstract

The central nervous system (CNS) has a limited ability to regenerate after a traumatic injury or a disease due to the low capacity of the neurons to re-grow and the inhibitory environment formed *in situ*. Current therapies include the use of drugs and rehabilitation, which do not fully restore the CNS functions and only delay the pathology progression. Tissue engineering offers a simple and versatile solution for this problem through the use of bioconstructs that promote nerve tissue repair by bridging cavity spaces. In this approach, the choice of biomaterial is crucial. Herein, we present recent advances in the design and development of adhesive and self-healing materials that support CNS healing. The adhesive materials have the advantage of promoting recovery without the use of needles or sewing while the self-healing materials have the capacity to restore the tissue integrity without the need for external intervention. These materials can be used alone or in combination with cells and/or bioactive agents to control the inflammation, formation of free radicals, and proteases activity. We discuss the advantages and drawbacks of different systems. The remaining challenges that can bring these materials to clinical reality are also briefly presented.

Keywords: Tissue adhesives; biomimetic adhesives; neural tissue engineering; regenerative medicine; spinal cord injury

List of Abbreviations

AD	Alzheimer's disease
ASTM	American Society for Testing and Materials
BBB	Blood-brain barrier
BMSC	Bone marrow stem cells
CNS	Central nervous system
CS	Chondroitin sulfate
CSF	Cerebrospinal fluid leakage
DF-PEG	PEGylated 4-formylbenzoic acid
ECM	Extracellular matrix
FDA	Food and Drug Administration
FN	Fibronectin
GC	Glycol chitosan
GeP@PDA	Germanium phosphide modified with polydopamine
HA	Hyaluronic acid
hiPSC	Human induced pluripotent stem cells
HRP	Horseradish peroxidase
hUCMSC	Human umbilical cord mesenchymal stem cells
L-DOPA	3,4-dihydroxyphenyl-L-alanine
LUT	Luteolin
MSC	Mesenchymal stem cells
NGF	Nerve growth factor
NHS	N-hydroxysuccinimide
NSC	Neuronal stem cells
NSPC	Neural stem/progenitor cells
PAINT	Pastable, adhesive, injectable, nanofibrous, and tunable matix
PC12	Pheochromocytoma 12 cells
PCE	Polycitrate-polyethylene glycol-polyethyleneimine
PCL	Polycaprolactone
PD	Parkinson's disease
PEG	Polyethylene glycol
PEO	Poly(ethylene oxide)
PF127	Pluronic F127
PLGA	Poly(lactic-co-glycolic acid)
PLL	Poly-l-lysine
PPy	Polypyrrole
ROS	Reactive radical species
SCI	Spinal cord injury
SD rats	Sprague Dawley rats
SH-SY5Y	Human neuroblastoma cell line

TA	Tannic acid
TBI	Traumatic brain injury
TE	Tissue engineering
VH	Venlafaxine hydrochloride

Statement of significance

Central nervous system (CNS) disorders, associated with traumas, infections, degenerations, or tumors, represent a considerable social and economic problem worldwide. Adhesive and self-healing materials are a feasible strategy for treating different types of neuronal lesions and have shown remarkable potential towards functional recovery. This review provides an overview of the most promising approaches that use adhesive and self-healing materials to promote cell attachment, tissue adhesion and scissure closing by creating an enhanced environment for axonal growth after a CNS lesion. The remaining challenges and possible breakthroughs that can improve the current clinical reality are also discussed.

1. Introduction

Diseases related to the neurological system constituted 12% of total deaths globally in 2006 and the World Health Organization estimates that neurological disorders will become a leading cause of disability worldwide, with a projected contribution of 103 millions of disability-adjusted life years in 2030 [1].

The brain and spinal cord are the main components of the central nervous system (CNS). When they are affected by a pathology or a disorder, different neurological and behavior complications can occur. The most common causes for CNS damage are car accidents, falls or sports-related traumas, and pathologies such as cancers and neurodegenerative disorders [2]. Regardless of the cause, the CNS damage triggers a series of events such as blood and immune cell infiltration, inflammation, wound healing processes, and glial scar formation **(Fig. 1)** [3-6]. These events lead to limited or no self-repair/regeneration, often causing paralysis and loss of sensation.

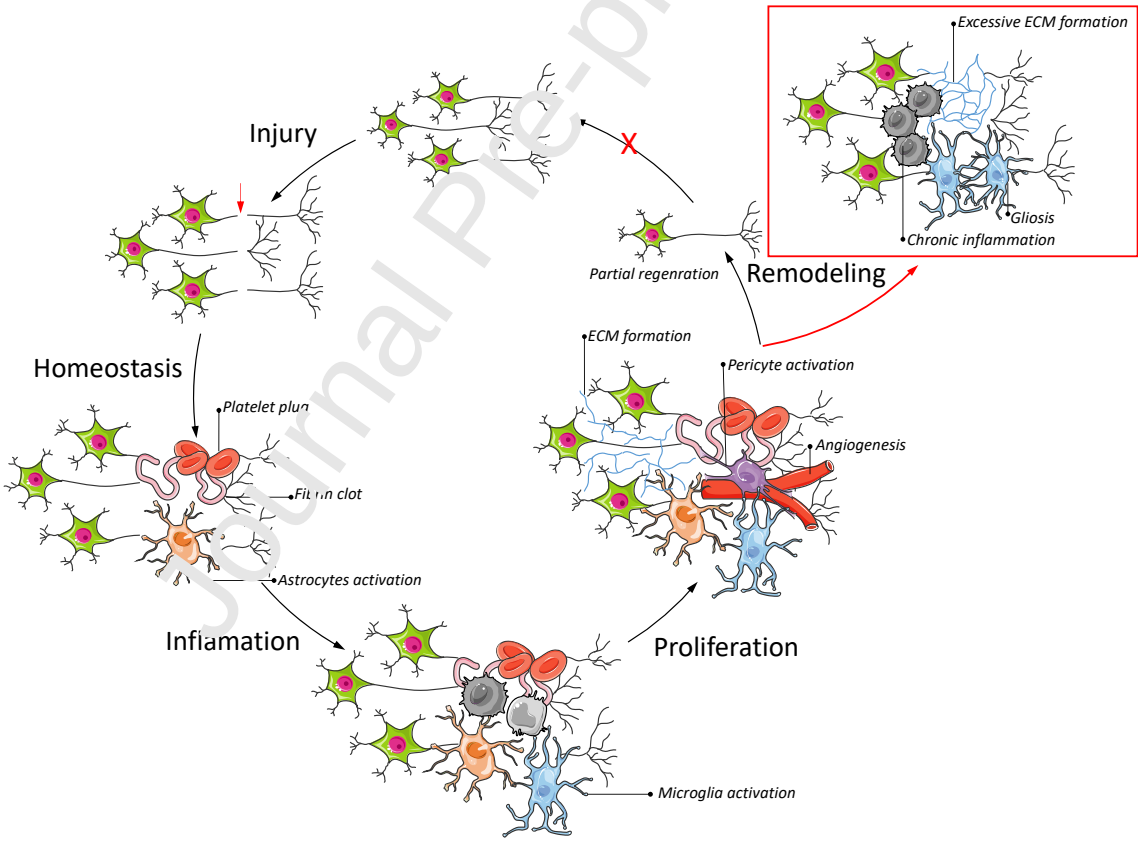


Figure 1. The damage of CNS triggers a cascade of events that lead to a limited (black arrows) or no (red arrow) regeneration. After the injury, an immune response is triggered to maintain the homeostasis. This response is followed by microglia activation and the recruitment of the peripheral macrophages from the bloodstream that are involved in a glial scar formation. The glial scar has an important role to constrain the damage, however, it can also hinder the passage of

axons throughout the lesion and inhibits the activity of the inflammatory cells [7, 8]. Adapted with permission from [9].

Different factors contribute to this CNS regeneration incapacity: lack of trophic support similar to the one provided by Schwann cells in the peripheral nervous system; mature neurons that cannot regenerate; inefficient and slow clearance of damaged axon fragments and myelin debris; fast infiltration of host cells (*e.g.* fibroblasts, endothelial cells) within the injury site; physical barrier established by the formed glial scar; elevated expression of myelin-associate inhibitors such as chondroitin sulfates among others [10, 11].

The complex anatomical and histological structure of CNS makes challenging the treatment of injuries such as spinal cord injury (SCI) or traumatic brain injury (TBI) [7]. Currently, SCI/TBI therapies involve palliative treatment and standard surgical interventions that aim to decompress the injured site [12, 13]. In the case of tumors, the most common treatment is chemotherapy, which is often related to severe side effects and commonly fails to eradicate diffuse cancer cells, and thus, recurrence might occur [14].

The inefficiency of the current therapies for the treatment of CNS diseases motivated the development of alternative interdisciplinary approaches that can be generally classified in three groups: 1) pharmacological therapeutic with immunomodulatory functions, which reduces the inflammation and limit the progression of secondary injuries; 2) transplantation of stem or neural cells; 3) transplantation of a scaffold for nerve guidance to bridge the lesion gap [11, 15]. Each of these approaches has its advantages, challenges and drawbacks. The main challenge associated with the first approach is the systematic use of high doses over long periods. Additionally, none of the currently used pharmacological therapeutics treat neurodegeneration efficiently, *i.e.*, they are mainly used to treat cognitive symptoms at an early stage [16]. On the other hand, cell therapies have a promising therapeutic outcome: preclinical studies that use stem and progenitor cells for the treatment of SCI, TBI, brain tumor, and neurodegenerative disease, demonstrate enhanced recovery. This effect is explained by the observed axonal remyelination and regeneration, neuroplasticity through the formation of synapses between the exogenous and the endogenous cells, neurogenesis, neuroprotection, neuromodulation, modulation of the inflammatory process, and reduction of glial scar [17, 18]. In this approach, different exogenous cells can be used, *e.g.* embryonic [19], neural (NSC) [20] or mesenchymal stem cells (MSC) [21], mature somatic cells such as Schwann cells [22], astrocytes [23], olfactory ensheathing cells [24, 25], and oligodendrocyte precursor cells [13, 26]. The drawbacks of cells-based therapy are related to the

poor survival of transplanted cells, excessive proliferation, which can originate tumors (teratoma), out-of-target differentiation, migration from the delivery site and aberrant axonal growth [27]. Some of these issues can be solved by encapsulation of the exogenous cells in an artificial extracellular matrix (ECM), *i.e.*, in combination with the third approach. Using a biocompatible biomaterial with adequate morphology and mechanical properties to fill the injury lesion provides a suitable environment to be integrated into the native tissue and facilitates a long-distance axonal regeneration, which can result in the recovery of lost functionality. As ECM substitutes, a biomaterial scaffold should meet some requirements. First, the mechanical properties of the scaffolds are of utmost importance for neuronal regeneration and should match the tissue properties: an adult spinal cord has a compressive modulus of 8 kPa [15, 28] and a Young's modulus of 0.3-1.4 MPa [29], whereas the brain tissue has a compressive modulus between 0.47-1.6 kPa [30] and a Young's modulus in the range 40 Pa-20 kPa [31, 32], presenting a nonlinear viscoelastic behavior. Second, the scaffolds should possess adequate degradability, surface topography, porosity, and good cytocompatibility [33]. Finally, the scaffolds should adhere tightly and accommodate at the defect site, where they must promote healing/regeneration and avoid further damage [34]. The adhesiveness is a great advantage because often the CNS injuries are at difficult-to-reach areas, *e.g.* at the cervical spine, and the treatment must be provided by a single intervention that guarantees the therapeutic retainment, preventing it from displacing or migrating to other body areas. Biomaterials with self-healing characteristics are also advantageous as they support tissue integrity and functionality during the treatment and thus, can ensure long-term effectiveness of the therapy [35]. This is particularly important for spinal cord repair, for which the injury site undergo constant deformation due to the patients everyday activities, such as walking, sitting, and bending. The great promise of adhesive and self-healing materials for treatment of CNS diseases have motivated the development of different strategies towards such materials and more efficient therapies. Below, we provide an overview of most recent advances in this area.

2. Bioadhesive materials for CNS repair

The capacity of some synthetic or natural macromolecules to adhere to biological tissue is called "bioadhesion" [36, 37]. Bioadhesives have developed significantly in the last 30 years, being applied clinically mainly for wound closure to decrease the collateral tissue damage caused by conventional surgery techniques [38]. Tissue adhesives and sealants for medical use must provide high tissue bonding strength, especially in wet conditions, mechanical flexibility to accommodate wound contorts or sizes to ultimately lead to protection against external harm, minimal

inflammatory response and wound healing [39-41]. The American Society for Testing and Materials (ASTM) recommends several characterization methods to evaluate the adhesion capacity of a material: tensile test (ASTM F2258-05); lap shear test (ASTM F2255-05), peel test (ASTM F2256-05), wound closure (ASTM F2458-05) and bursting pressure (ASTM F2292-04) [42]. However, no reference values are established for bioadhesive materials [43].

Bioadhesives act via formation of chemical (covalen or non-covalent) bonds with the host tissue [44]. Four major adhesive mechanisms can be distinguished in a function of the formed bonds: 1. Weak non-covalent Van der Waals bonds: these intermolecular interactions can be further weaken in a wet tissue environment; 2. Covalent bonds: strong adhesion and long-term integration between the adhesive and the tissue; 3. Non-covalent electrostatic interactions based on opposite charges of the adhesive and the tissue; and 4. Mechanical interlocking resulting in the adhesive penetrating into the tissue microirregularities and interlocking with the tissue [45, 46]. The adhesive strength depends on different factors, including temperature, contact time, adhesive concentration, adhesive viscosity, and roughness of the defect [47]. Good bioadhesives are characterized by a balance between adhesive and cohesive strength. The adhesive strength refers to the intermolecular interactions between the tissue and the bioadhesive, whereas the cohesive strength depends on the intramolecular interactions within the bioadhesive [34] and is proportional to the elastic modulus of the adhesive [46]. A weak cohesive force is associated with damage of the adhesive when a repeated load under a dynamic tissue environment is applied, whereas an adhesive with a strong cohesive force can cause damage of neural tissue because of a mismatch in mechanical properties. The adhesive strength also depends on the tissue environment. For example, the pathological oxidative environment can accelerate the degradation of adhesive materials leading to a cohesive decrease that results in a loss of adhesive properties [41].

In SCI or TBI, adhesives can be applied either directly to join the two sides of the injury or indirectly, i.e. outside of the wound, to pull the tissue around and close the wound. The adhesives can be enhanced by immobilization of vehicles that deliver cells, growth factors, or pharmaceutical drugs.

Tissue adhesives can be classified into three main categories: 1) synthetic bioadhesive polymers such as cyanoacrylates; 2) bioadhesives based on natural polymers such as fibrin, albumin, and gelatin; and 3) biomimetic adhesives. Next, each of these distinct types of adhesives will be addressed in detail.

2.1. Synthetic bioadhesives

Synthetic bioadhesives (**Table 1**) have two main advantages when compared to natural ones: they are cost-effective and tunable, i.e. they can be modified to adjust the adhesion properties. On the other hand, they also have several drawbacks: low adherence to wet surfaces, low bioabsorption and high cytotoxicity. Below, we discuss the most common systems containing synthetic adhesives already used in CNS repair.

2.1.1. Cyanoacrylate adhesives

Cyanoacrylate adhesives were the first synthetic glue used in clinics, approved by Food and Drug Administration (FDA) for topical and internal use in 1998 and 2010, respectively [46]. They comprise acrylates monomers that upon exposure to aqueous environment **(Fig. 2B)** polymerize rapidly into flexible and waterproof adhesives. Several commercial cyanoacrylate-based tissue adhesives based on ethyl-, butyl-, or octyl- cyanoacrylates **(Fig. 2A)** are approved for medical use in topical applications (*e.g.* skin). Ethyl- and butyl- cyanoacrylates have been also studied for suture of peripheral nerves and showed a transient cytotoxicity effect in the human neuroblastoma cell line (SH-SY5Y) [48]. Cyanoacrylate adhesives have high adhesive strength (2.20 MPa) in a dry environment, but this value is significantly reduced in a wet environment due to their water-initiated curing [49]. Other disadvantages of these adhesives are their poor bioabsorbability, long degradation time, cytotoxic degradation products, and the heat (**Fig. 2B**) that is generated during the polymerization exothermic reaction [34, 50].

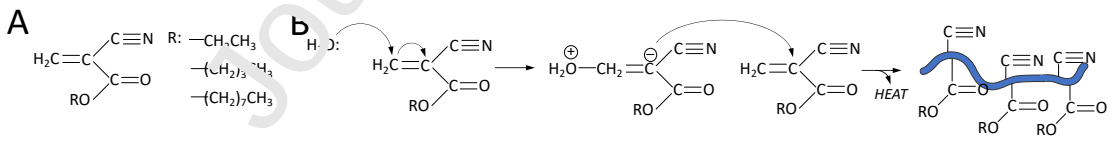


Figure 2. Cyanoacrylate adhesives: (A) Structure of cyanoacrylate monomers tested as CNS adhesives and (B) schematic presentation of the polymerization in the presence of water.

2.1.2. Polyethylene glycol (PEG) based adhesives

PEG is a hydrophilic and biocompatible synthetic polymer with excellent potential for treating SCI since it inhibits glial scar formation and reduces the inflammatory process. However, PEG itself is not adhesive, but can be chemically modified or combined with other polymers to attain bioadhesion. This strategy has been used in the development of different commercial products,

such as FocalSeal®, DuraSeal™ and CoSeal®. DuraSeal™ was one of the first PEG-based adhesives approved by FDA as a spine sealant to prevent cerebrospinal fluid leakage (CSF) after cranial or spinal surgery [51]. The hydrogel formulation involves two solutions: trilysine amine solution and a four-armed PEG functionalized with N-hydroxysuccinimide-esters (tetra-PEG-NHS). It has some disadvantages - low adhesive strength in a wet environment, less than 10 kPa for wet porcine skins [52], and high water uptake (87-558%), which can cause nerve pressure. Thus, DuraSeal™ is only applied after a primary suturing. An alternative sutureless approach involves the use of a four-armed PEG amine (tetra-PEG-NH_2) and the chemically complementary four-armed PEG succinimideactivated ester (tetra-PEG-SS) that form an adhesive *in situ* [53]. This system has an adhesive strength of 19.8 kPa (dura-mater of the ovine model), which is similar to the commercial fibrin glue. This PEG-based system has also been tested in durotomy site of a rabbit duraplasty model and showed a successful regeneration of dura-mater without any residual presence of the hydrogel. However, the motor and sensitivity recovery after implantation in *in vivo* studies was not evident. PEG-based injectable hydrogel can be designed as a therapeutic delivery platform. Recently, cetuximab (induces neuronal differentiation) and FTY720 (inhibiting glial scars) have been loaded within a PEG injectable hydrogel and combined with NSC for SCI treatment [54]. The injectable hydrogel was obtained through a hydrazone bond crosslinked tetra-PEG-$NHNH_2$ and an oxidized dextran. It had an adhesive strength of 4.2 kPa (glass substrate) and adhered to a rat spinal cord. Incorporating the two drugs into the injectable hydrogel in a SCI rat model, resulted in a significantly better motor functional recovery assessed by blood-brain barrier (BBB) score; however, the values were still far from normal scores. Furthermore, the injectable hydrogel increased neuronal differentiation and integration of exogenous NSC while inhibiting glial scar formation after transplant.

Different PEG and PEG-based materials and devices are already approved for clinical use, *e.g.* for treating rheumatoid arthritis or multiple sclerosis. However, PEG-based adhesives applied for TBI or SCI treatment require further optimization prior to clinical translation, especially in what concerns their high swelling degree.

Table 1. Synthetic bioadhesives for CNS regeneration

Material	**Adjuvant material**	***In vitro/ In vivo* studies**	**Shape form**	**Outcome**	**Ref**
Cyanoacrylate	-	SH-SY5Y cells	Solution	Transient cytotoxic	[48]

				effect.	
Modified PEG	-	Rabbit duraplasty model (Total laminectomy at L4-5	Injectable hydrogel	Good adhesive strength (20 kPa); Sealing of dural defects in a wet environment.	[53]
	Oxidized dextran	Sprague Dawley (SD) rats (SCI model)	Injectable hydrogel	Good adhesive strength (4.2 kPa); Reduced cystic cavity; Functional motor recovery.	[54]
	-	Female beagles (SCI model)	Membrane	Locomotion recovery; No pain syndrome over the long term; Re-establishment of anatomical axonal sprouting.	[55]

2.2. Natural bioadhesives

The main advantages of the adhesives based on natural polymers **(Table 2)** are their low cytotoxicity and biodegradability. On the other hand, the most significant limitation is related to their low cohesive and adhesive strength. In this section, we analyze representative examples of bioadhesives from proteins and polysaccharides that have been used to repair CNS.

Table 2. Bioadhesives for CNS regeneration

Adhesive	Adjuvant material	*In vitro/ In vivo* model	Shape form	Outcome	Ref
Fibrin	-	SD rats (SCI model)	Hydrogel	Adhesive strength 14kPa*; Reduced inflammation.	[56, 57]
	Collagen	SD rats (SCI model)	Hydrogel	Adhesive strength 3.5kPa**; Neuronal differentiation of endogenous neural stem/progenitor cells (NSPC); Functional motor recovery.	[58]
	Genipin	Human induced pluripotent stem cells (hiPSC)	Scaffold	Induced neurite outgrowth.	[59]
Gelatin	-	C57BL/6 mice (SCI and TBI model)	Hydrogel	Adhesive strength: 23kPa* and 77kPa**; Functional motor recovery; Neurogenesis; Reduced inflammation; Apoptosis inhibition.	[60-62]
	Polycaprolactone (PCL)	Pheochromocytoma 12 (PC12) cells	Membrane	Neurite outgrowth; Improved cell	[63, 64]

				adhesion.	
	PCL	SD rats (SCI model)	Scaffold	Adhesive strength: 352kPa*; Healing the spinal cord; Control of the secondary injury.	[65, 66]
	Agarose/ Polypyrrole (PPy)	NSC SD rats (SCI model)	Injectable hydrogel	Adhered tightly to the rat spinal cord tissue and glass; Reduced cystic cavity; Neuronal differentiation; Functional motor recovery.	[67]
Chitosan	Fibrin glue	SD rats (SCI model)	Scaffold	Reduced glial scar; Increased NSC proliferation.	[68]
	Gelatin	PC12 cells	Film	Neurite outgrowth; Increased cell adhesion.	[69]
	-	Wistar rats (Alzheimer disease (AD) model)	Nanoparticles	Apoptosis inhibition; Reduced inflammation.	[70, 71]
	-	Swiss Albino mice (AD model)	Nanoparticles	Mucoadhesive (mucin-particle method);	[72]

				Improved acquisition of short and long-term spatial memory; Decreased level of Aβ aggregation.	
	-	C6 glioma cells	Nanoemulsion	Decreased viability of glioma cells.	[73]
Chondroitin sulfate	-	SD rats (SCI model)	Injectable hydrogel	Tight adhesion to the rat spinal cord tissue and glass; Reduced cavity; Increased neurogenesis; Locomotion recovery.	[74]

Lap shear test, Test substrate: * Porcine mucin;** Egg Membrane

2.2.1 Fibrin adhesives

Fibrin is the first approved material for clinical use in hemostatic, sealant and adhesive applications [75]. Fibrin-based adhesives are commercially available and contain two main active compounds - fibrinogen and thrombin that form a clot when mixed [76]. Thrombin is usually isolated from human plasma and thus, the probability of virus transmission or anaphylactic reaction is relatively high [75]. Several studies reported that fibrin glue can be used on the spinal cord and CNS tissues [57], showing support for neurite outgrowth and increased neural cells proliferation at the injury site. In general, it performs better than synthetic glues that cause spinal cord inflammation and degeneration (**Fig. 3**).

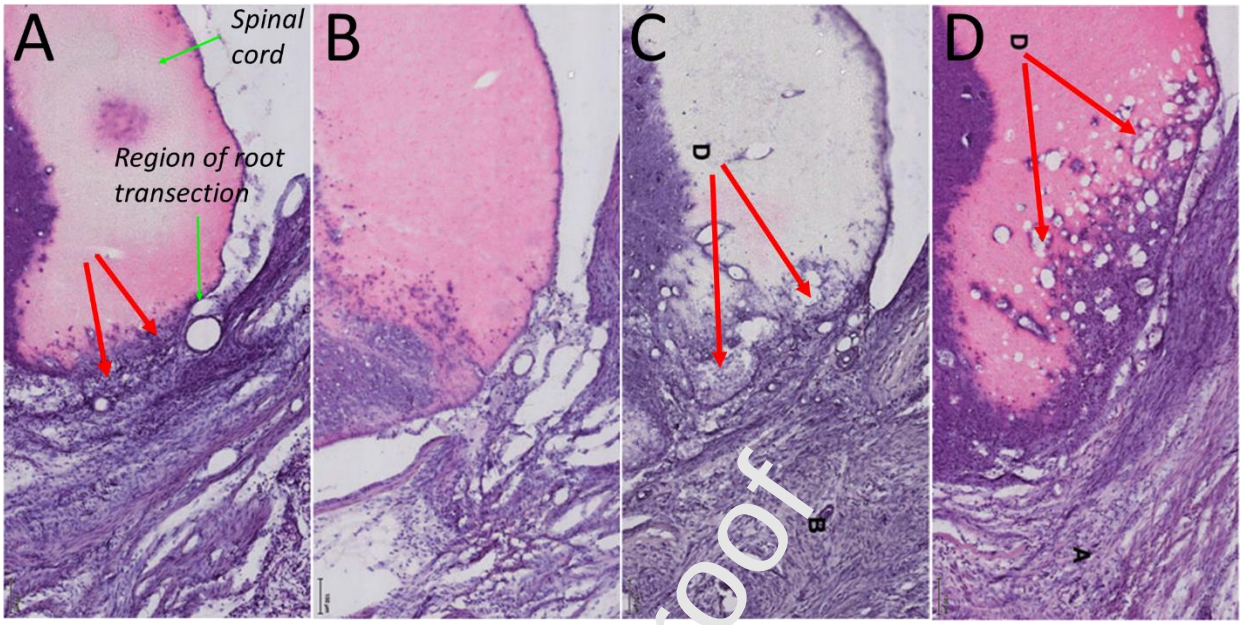


Figure 3. Haematoxylin & Eosin stained sections of spinal cord at day 28 after the application of different adhesives. (A) Control group: the region of transection of the dorsal rootand the spinal cord are shown with green arrows; the black arrows show a focal inflammatory infiltrate on the surface of the spinal cord. (B) Lesion treated with fibrin-based adhesive (Tisseel®): the Tisseel® has been absorbed, only a mild inflammatory infiltrate in the cord is visible with no evidence of spinal cord degeneration. (C) Lesion treated with albumin-based adhesive (BioGlue®): the adhesive material is not broken down by day 28 and a spinal cord degeneration is visible (red arrows). (D) Lesion treated with synthetic PEG-based adhesive (Adherus®): the sealant compresses the spinal cord and an area of spinal cord degeneration (red arrows) is visible with a eosinophilic chronic inflammatory infiltrate in the cord. Reproduced with permission from [57]

The most common use of fibrin sealants in CNS is for treating and preventing CSF leakage. The adhesive strength of the fibrin glue is around 13.54 ± 3.07 kPa to the porcine skin, however, it depends on many parameters such as the substrate, method of fibrin preparation, or the presence of water or collagen [56]. Moreover, the mechanical properties of fibrin glue can be tunable to match human spinal cord tissue [77]. Fibrin glue has been combined with collagen, presenting a higher elongation at break, higher adhesive strength, and a lower Young's modulus, *i.e.*, softer material than pristine collagen hydrogel [58]. The application of this hydrogel to deliver a stromal cell-derived factor-1α and paclitaxel in a SCI rat model promoted neuronal differentiation of endogenous NSPC, leading a motor recovery.

Genipin-crosslinked fibrin scaffolds have also been investigated for their use in neural tissue engineering (TE) applications. Genipin, a plant-derived crosslinking agent, form strong and stable bonds between fibrin chain, thus increasing the mechanical properties [78], adhesion [79], and stability of fibrin [59]. Recent work has demonstrated that a genipin-crosslinked fibrin scaffold promoted neural differentiation of hiPSC and had neuroprotective properties, *i.e.*, it has a potential to be used in neural tissue repair [59].

2.2.2. Gelatin adhesives

Gelatin is a widely used biomaterial obtained from animal collagen by thermal or chemical denaturation. It is less antigenic than the native protein [2, 69]. In general, the gelatin adhesiveness is low, although it depends on the content of phenol groups and is, thus, directly related to the content of the tyrosine amino acids. To increase the adhesive strength of gelatin, different chemical crosslinkers can be used, such as N-ethyl-N'-(3-(dimethylamino)propylcarbodiimide/N-hydroxysuccinimide (EDC/NHS) [60] **(Fig. 4)**, glutaraldehyde, resorcinol-formaldehyde, but their application is limited due to the associated cytotoxicity.

The combination with other polymers, namely PCL, polylactic acid or poly(lactic-*co*-glycolic acid) (PLGA), is also a desirable way to increase the adhesive properties of gelatin [80]. For instance, gelatin can be used as an adhesive coating: gelatin-coated PCL nanopatterns have a good adhesion strength (352.3 kPa) which improves the MSC attachment and proliferation compared to the non-coated PCL nanopattern surface [66]. Electrospunned PCL membranes combined with gelatin were tested *in vitro* with hMSC and PC12 cells and showed to support neurite outgrowth, enhance cell adhesion and promote nerve repair [63, 64]. The neurite was longer when the cells were seeded on aligned fibers. These promising results are also supported by *in vivo* studies: PCL/gelatin scaffolds with co-cultures human endometrial stem cells and human Schwann cells were transplanted into SCI rat model. The results showed that these scaffolds enhanced the healing of the injured spinal cord and controlled secondary injury [65].

At human body temperature, a reversible gel-sol transition can occur, which limits the application of gelatin-based adhesives. Other polymers can be added to control this drawback: a combination of polymers with adhesive and conductive properties is favorable for SCI repair. As an example, a new bioadhesive was obtained by combining agarose, gelatin and PPy in the presence of $FeCl_3$ as a crosslinker. This gelatin-based adhesive can re-connect damaged spinal cord tissue [67]. The conductivity of the adhesive hydrogel was 0.2 S/m, and given that the conductivity of nerve tissue

is between 0.08-1.3 S/m [81], materials with a similar or higher conductivity may transfer electrical signals between the neurons. The *in vivo* studies showed that this adhesive significantly reduced injured cavity space and inhibited glial scar formation [67].

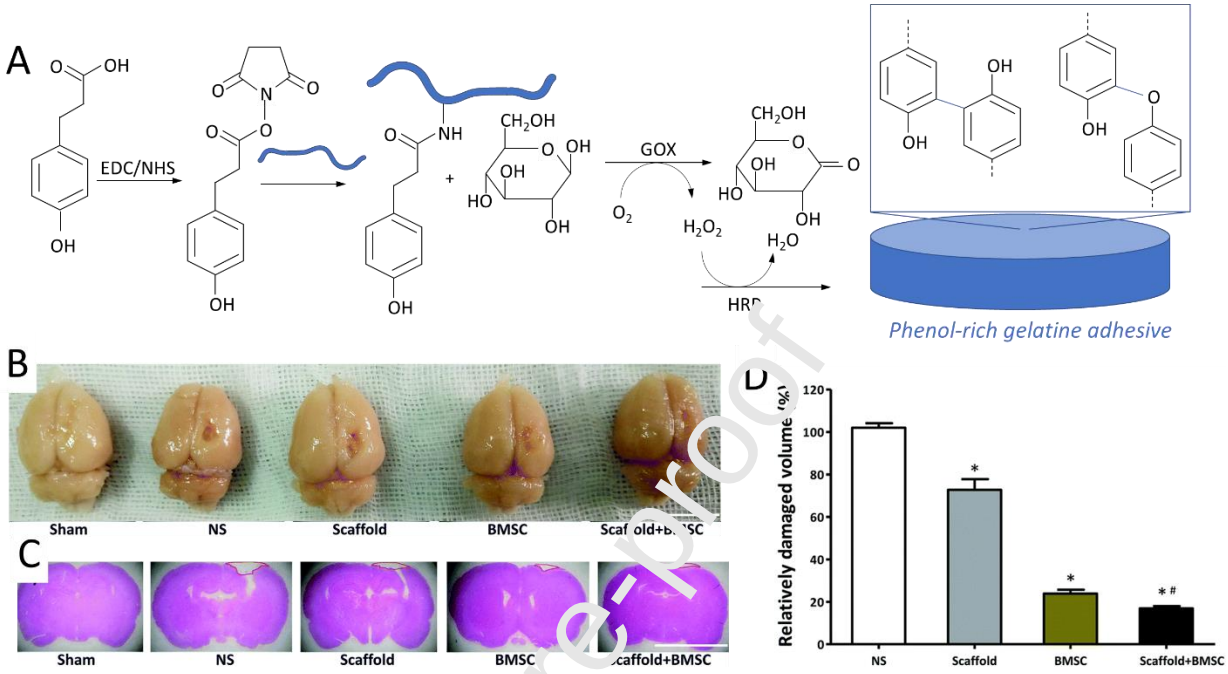


Figure 4. Effect of an injectable gelatin adhesive loaded with stem cells on neurological function recovery of TBI in rats. (A) Synthetic route to obtain phenol-rich adhesive by in situ crosslinking with glucose oxidase (GOX) and horseradish peroxidase (HRP). (B) Macroscopic images, (C) histological staining, and (D) respective relative quantitative analysis of the damaged areas in the rat brains of different transplanted groups (NS – treated with saline, bone marrow stem cells (BMSC)) 28 days after the injury. Scale bar is 1 cm. Statistics: *$p < 0.05$ compared with NS and #$p < 0.05$ compared with the BMSC control, mean ± standard deviation. Adapted with permission from [60]

2.2.3. Chitosan adhesives

Chitosan is a linear polysaccharide composed of β-(1-4) linked D-glucosamine and N-acetyl-D-glucosamine residues. It is obtained after a deacetylation of chitin, found in the cell walls of fungi, insects or crustaceans [82, 83]. Chitosan can be used for a wound closure due to its positive charge, which can attract negatively charged red blood cells and facilitate rapid blood clotting without coagulation. Additionally, the positive charge imparts antibacterial properties: chitosan can inhibit bacterial infections after surgery [84]. Surgical adhesive films from chitosan with an adhesive strength of 12.5 ± 2.6 kPa [85] are commercially available under the trade name SurgiLux® and

assayed for peripheral nerve reconstruction [86], tibial nerve wound closure in a rodent model [85], and corneal wounds in the bovine model [87].

Chitosan belongs to the so-called mucoadhesive polymers, *i.e.*, polymers that can adhere to a mucosal membrane. The interest in these polymers has increased in the last years due to their application in developing drug delivery systems [88]. They are particularly relevant to CNS therapies, for which crossing the BBB is crucial. Intranasal (nose-to-brain) delivery can prolong the therapeutical window and the bioavailability of the drug and reduces systemic side effects. Due to its mucoadhesive properties, chitosan has been used for treating neurodegenerative, anxiety disorders and brain tumors [89-91]. However, the number of approved pharmaceutical drugs using chitosan as an excipient is still limited.

Chitosan can be modified at the hydroxyl or amine groups to obtain enhanced bioadhesives. One of the possible modifications is thiolation, where the amine group of chitosan is reacted with a coupling agent containing a thiol group, likely cysteine, or thiobutylamidine, increasing the permeation, mucoadhesion, solubility and *in situ* gelling properties [92]. A hydrogel based on thiolated chitosan was produced for intranasal delivery of liposomal donepezil HCL, one of the FDA-approved cholinesterase inhibitors developed for AD treatment [93]. The mucoadhesion strength of the hydrogels was measured against a nasal mucosa using an Instron machine with a load cell of 5 kN. After 10 min, the detachment force between a chitosan hydrogel and nasal mucosa was 10 N, whereas for the thiolated chitosan was 20.6 N. This intranasal delivery system increased (107 %) the drug delivery to the brain compared with oral delivery tablets.

Haque and colleagues prepared a delivery system for the antidepressant drug venlafaxine hydrochloride (VH) by ionic gelation of chitosan with sodium tripolyphosphate [71]. The generated nanoparticles were administrated intravenously (the traditional way) or by intranasal route. The levels of intravenous and intranasal delivery of VH in the brain tissues were 0.0293 ± 0.0033 ng/ml and 0.1612 ± 0.062 ng/ml, respectively, after 30 min, *i.e.*, a significant increase of VH bioavailability in the brain when delivered through an intranasal course was observed (**Fig. 5**). In a similar approach, Elnaggar and colleagues developed mucoadhesive chitosan nanoparticles for delivery of piperine, a phytopharmaceutical with potential in AD. These nanoparticles showed a significant decrease in neural apoptosis and neural inflammation assessed through caspase-3 and TNF-α, respectively, on AD model of adult male Wistar rats [70].

Luteolin (LUT) is also a good candidate for AD therapy due to its antioxidant and anti-inflammatory properties. LUT reduces the AD symptoms in *in vivo* models but has a major limitation: it has low solubility in water and thus poor oral bioavailability. To overcome this

drawback, LUT has been incorporated in chitosan nanoparticles. LUT-loaded in chitosan nanoparticles (chitosomes) have a good mucoadhesion, as shown by changes in zeta potential [72]. The initial zeta potential of chitosomes was between +28.0 and + 37.4, and after mixing with mucin solution at pH 6.5 the zeta potential decreased to -6.42 and -5.44, indicating a high affinity of chitosomes to mucin particles. *In vivo* studies in AD mice model showed that 21 days of intranasal administration of chitosomes increased neuronal survival rate and reduced the amyloid plaques. Furthermore, behavior studies revealed an improvement in the acquisition of short-term memory. Altogether, the results showed that these chitosomes attenuated the pathological changes of AD in a safe and non-invasive way.

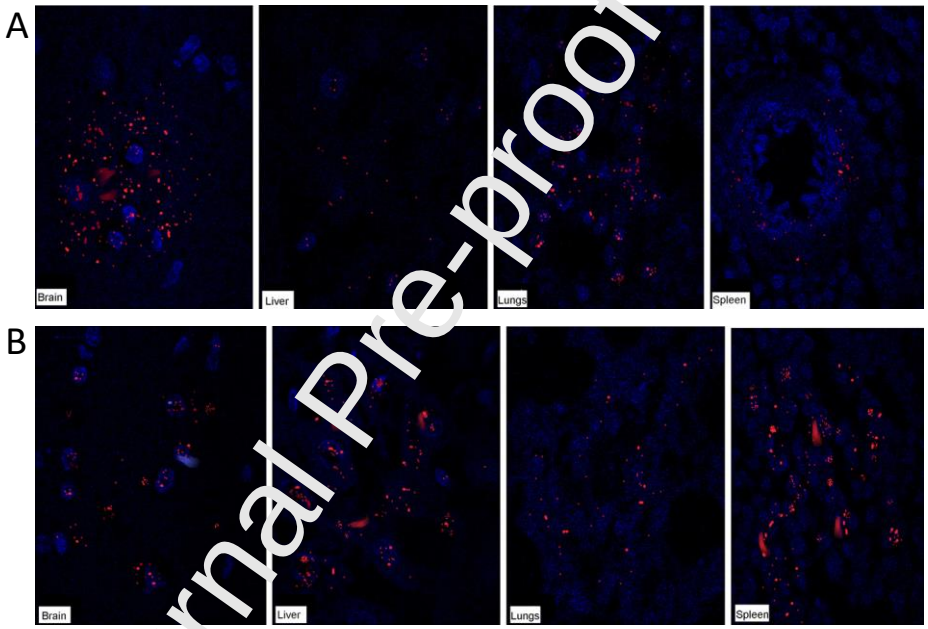


Figure 5. Confocal laser scanning microscopy images of brain, lungs, liver and spleen of adult Wistar strain rats at 120 min after administration of chitosan nanoparticles loaded with VH (red): (A) intranasal and (B) intravenous administration. Reproduced with permission from [71].

Chitosan has also been used as a component of nanoemulsions to enhance their mucoadhesive properties. Nanoemulsions exhibit unique characteristics, including good solubilization of lipophilic drugs and thermodynamic stability. The kaempferol loaded in chitosan nanoemulsion has enhanced antitumor activity against glioma cells [73]. The composition was administrated via an intranasal route and chitosan extended the residence time of the nanoemulsion in the nasal cavity that together with the close contact with the nasal epithelium provided a better drug absorption [73].

Chitosan-based bioadhesives are versatile and can be processed as different devices such as hydrogels, scaffolds, (nano)fibers, sponges, liposomes, beads, membranes, films, nanoemulsions and (nano)particles. Such versatility renders diverse applications of chitosan bioadhesives, *e.g.* wound dressing, hemostatic and drug delivery to CNS. So far, most chitosan-based mucoadhesion nanosystems have shown promising results without signals of toxicity. However, long-term studies of the potential risks are lacking. Such studies are imperative before any clinical tests keeping in mind the low degradation rate of chitosan *in vivo* and the absence of lysozyme in the CNS. Overall, the major limitation of chitosan-based bioadhesives is the variation of properties, such as purity, molecular weight and deacetylation degree, and the required time-consuming processing and high manufacturing cost, which makes its commercialization difficult.

2.2.4. Chondroitin sulfate adhesives

Chondroitin sulfate (CS) is a sulfated glycosaminoglycan that is linked to a different core protein to form chondroitin sulfate proteoglycans. These proteoglycans are abundant in the ECM of the CNS (representing about 20% of its total volume) [38, 94] and have a dual role: on the one hand, they have an essential role in neurogenesis [95]; and on the other hand, they are upregulated in the glial scar after CNS injury, where inhibit the synapse formation and consequently neuroplasticity [96]. CS can be chemically modified to enhance its adhesive properties. For example, the functionalization of its carboxyl groups with NHS allows binding to substrates with -NH_2 groups via formation of new amide bonds (**Fig. 6**) [97]: a reaction between CS-NHS and PEG-$(NH_2)_6$ results in a hydrogel ten folds stronger than fibrin glue, while the interaction between CS-NHS and primary amine groups of the ECM molecules result in high adhesion between tissues and CS.

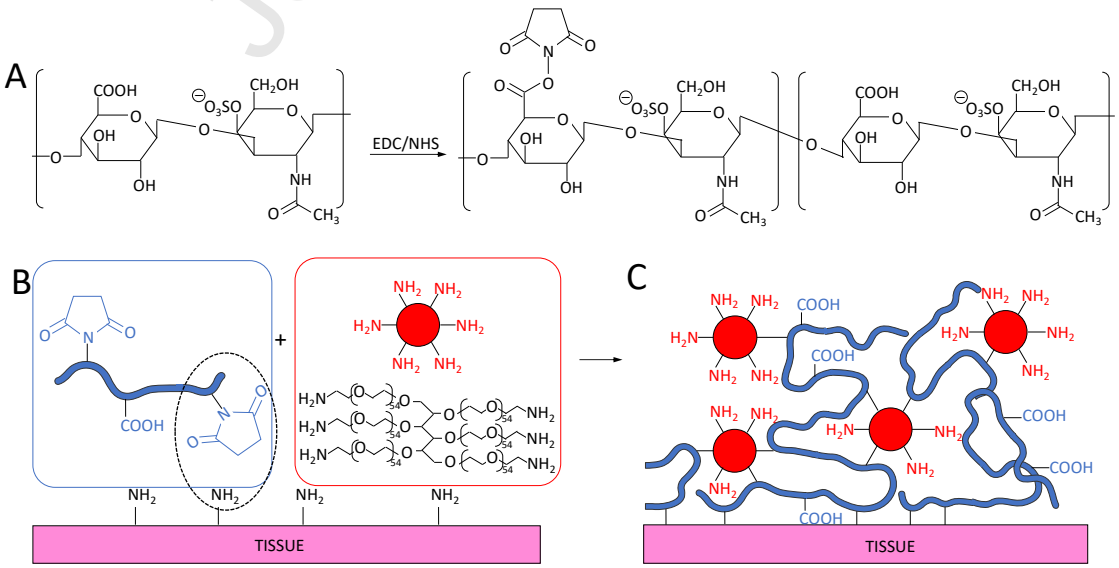


Figure 6. The adhesive properties of chondroitin sulfate (CS) can be enhanced by functionalization with NHS. (A) Reaction scheme used for the CS modification. (B) The NHS activated carboxyl groups of CS (blue) react with the primary amines of PEG–$(NH_2)_6$ (red) and the primary amines of proteins in tissue (black, reactive groups circled) to (C) form new chemical bonds (amide bonds, black). Adapted with permission from [97].

Methacrylation is another approach to increase the adhesive properties of CS. Gels prepared from methacrylated CS have Young's modulus of 660 ± 25 Pa and good adhesion to withstand the force of gravity of the spinal cord of rats [74], *i.e.*, it is a good material for the treatment of SCI/TBI. NSC can be encapsulated in these gels and when applied in SCI rats model, a functional recovery, a reduction of cavity space, and an increase of neurogenesis was observed [74].

2.3. Biomimetic adhesives

Marine resources have inspired the development of different types of biomimetic adhesives. For example, mussels naturally produce adhesive substances to attach to all types of surfaces, including metals, rocks, and polymers under different environmental conditions **(Fig. 7A**) [34]. Mussel adhesive proteins are rich in the amino acid 3,4-dihydroxyphenyl-L-alanine (L-DOPA, **Fig. 7B**), which contains catechol groups responsible for the strong adhesion [45, 98]. DOPA can bind through reversible interactions (hydrogen bonding; metal complexation and π-π stacking) and covalent chemical bonds (between catechol/quinone group and thiol/amine groups) [99]. The adhesive strength of catechol compounds is pH-dependent **(Fig. 7C)**: at acidic pH, catechol groups are in their reduced form and have high adhesive strength, while at basic pH semiquinone and quinone are formed, thus, reducing the adhesive strength [100]. Furthermore, the addition of oxidants such as chelate ions (Fe^{2+}, Cu^{2+}, Zn^{2+}or Mn^{2+}) enhances the cohesive force for adhesives (**Fig. 7D**), facilitating the formation of hydrogels [49, 100, 101].

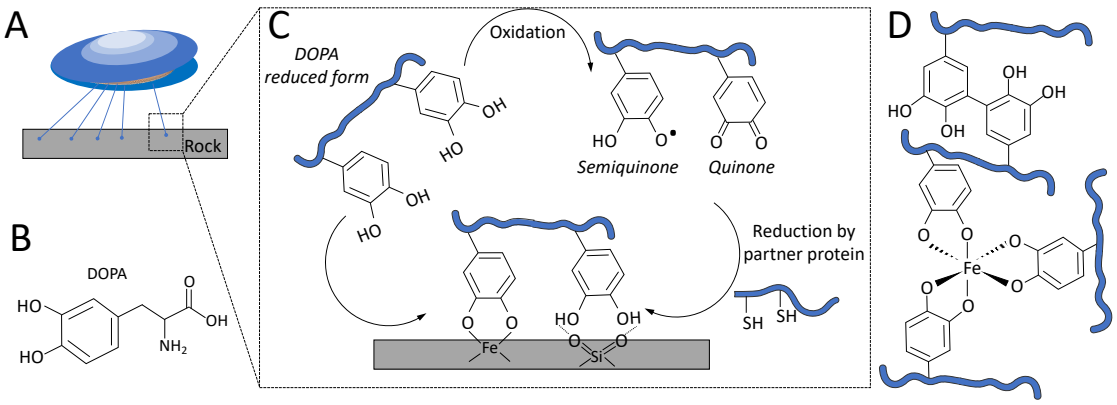


Figure 7. (A) Mussels adhere to rock surfaces via proteins that are rich of (B) 3,4-dihydroxyphenyl-L-alanine DOPA. (C) The adhesion mechanism involves different forms of DOPA [102]. (D) The cohesion strength is enhanced in the presence of chelate ions such as Fe^{2+}.

Various adhesives have been developed by the functionalization of different polymers, e.g. hyaluronic acid (HA) [103] or silk fibroin [104], with catechol groups. HA is a promising candidate for the treatment of CNS injury, since HA is one of the main backbones of the ECM in the brain and spinal cord. To produce an injectable hydrogel, HA was modified with dopamine and combined with germanium phosphide modified with polydopamine (GeP@PDA), using horseradish peroxidase/ hydrogen peroxide (HRP/H_2O_2) as an initiator system to crosslink the hydrogel via oxidative coupling of catechol groups [105]. The hydrogels were produced with different percentages of GeP@PDA. The gelation time was around 7 min at 37ºC, offering excellent conditions for injectable applications. The adhesiveness was calculated through a lap-shear test showing an adhesive strength of around 7.9 kPa. GeP enhanced the conductivity of the biohybrid hydrogel to 0.4 S/m without compromising their biocompatibility. The hydrogels increased the *in vitro* differentiation of NSC into neurons. When implanted in SD rats (SCI model), the hydrogels activated the endogenous NSC neurogenesis in the lesion area and improved the motor function in rat model after 6 post-surgery evaluated by BBB score [105].

Silk fibroin has been modified with dopamine via Schiff base reaction ([dopamine] < 2mg/mL) to introduce adhesive characteristics [104]. This new conjugate was used to prepare an injectable hydrogel to culture L929 fibroblastic cells and primary hippocampal neurons. The hippocampal neurons showed a higher viability and cell density when compared to cultures on pristine silk fibroin hydrogel, demonstrating the potential for spinal cord regeneration **(Fig. 8)**.

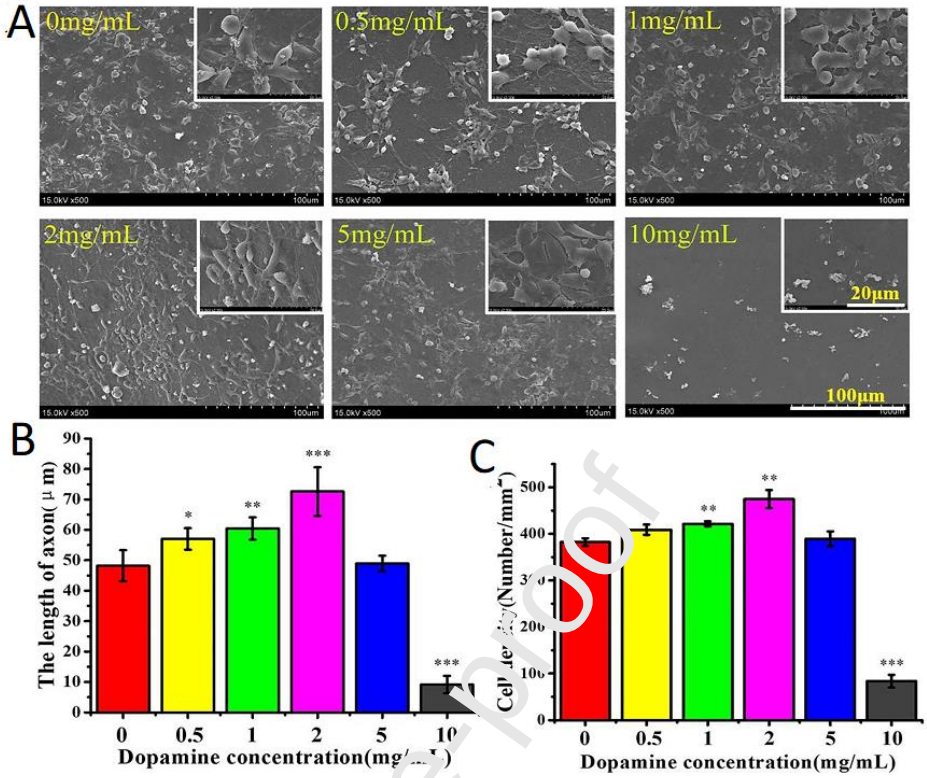


Figure 8. Effect of dopamine concentration on in vitro cell culture of hippocampal neurons. (A) SEM images, (B) axon length, and (C) density of the hippocampal neurons in the presence of different amount of dopamine, $*p < 0.05$, $**p < 0.01$ and $***p < 0.001$ by one-way ANOVA test. Reproduced with permissions from [104].

The functionalization with catechol groups can also prevent contaminations related to surgical procedures [98, 106], quench reactive radical species (ROS) [106, 107] and inhibit lipid peroxidation [108]. Furthermore, catechol-functionalized hydrogels also have anti-inflammatory activity that is exerted through the inhibition of three enzymes: elastase, collagenase and peroxidase, which are overexpressed in chronic wounds [109]. Recently, Puertas-Bartolomé and colleagues have developed a hydrogel of chitosan, oxidized HA and a catechol terpolymer that forms an interpenetrated polymer network in the presence of ferric cation Fe^{3+} [107]. This material has high adhesive strength (18 ± 6.1 kPa), reduces intracellular ROS formation (H_2O_2 treated hBMSC), and decreases the IL-1β release, i.e. reduces the inflammatory response. On the other hand, a generation of H_2O_2 has been detected in a dopamine-modified hydrogel when its catechol site chain was oxidized to quinone [110]. Therefore, the release of H_2O_2 needs to be carefully controlled, *i.e.*, a low concentration is related to angiogenesis and tissue regeneration, whereas elevated levels of H_2O_2 destroy healthy tissues, resulting in the formation of chronic wounds [111].

Zhang and co-workers described a PLGA coated with DOPA-IGF1, a small pentapeptide tag composed by DOPA-Lys-DOPA-Lys-DOPA residues, to improve the proliferation and adhesion of cultured human umbilical cord mesenchymal stem cells (hUCMSC) [112]. This modification enhanced the release of neurotrophic factors, especially for nerve growth factor (NGF) from the hUCMSC and promoted neuritogenesis behavior (neurite outgrowth) of PC12 cells. PLGA coated with DOPA was also used as a strategy to immobilize poly-l-lysine (PLL) and fibronectin (FN) to enhance NSC adhesion and promote their differentiation in neurons and glial cells, permitting a complete restoration of the damaged neural tissue by enhancing neurogenesis and axonal regrowth **(Fig. 9)** [4].

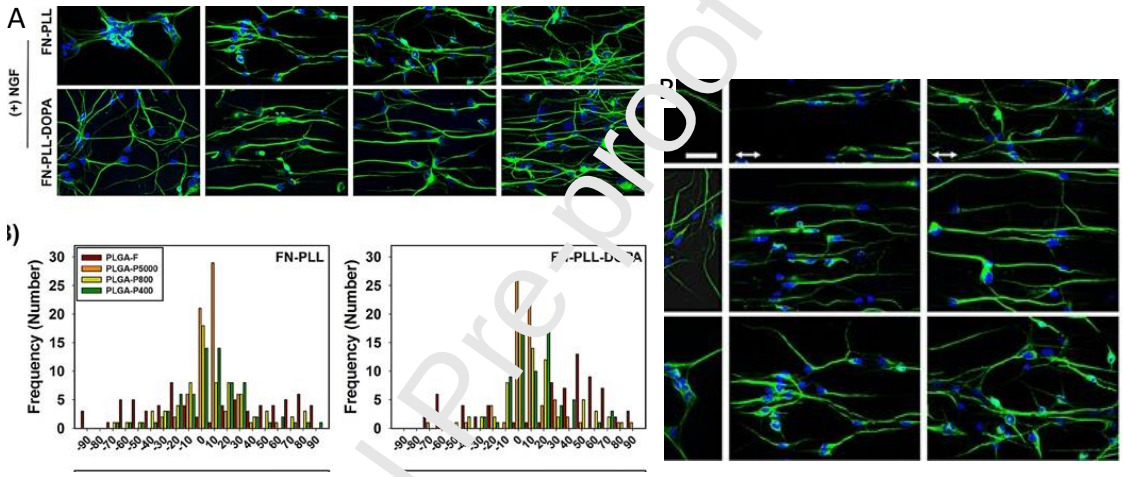


Figure 9. Enhanced neuronal differentiation and directed neurite extension of NSC on PLGA nanopatterned substrates by a combination of DOPA-mediated FN and PLL immobilization and NGF. (A) Immunofluorescent neuronal marker (Tuj1) staining of NSC differentiated on substrates with and without NGF addition to the medium after 4 days in culture. Scale bar = 50 μm. Arrows indicate the direction of the groove-patterned structures on the substrates. (B) Quantification of neurite length (n = 42–82) in Tuj1-positive NSC (**$p < 0.01$ vs. no NGF treatment groups, ##$p < 0.01$ vs. PLGA-F without DOPA coating and NGF treatment group, ++$p < 0.01$ versus PLGA-F without DOPA coating but with NGF treatment group, ||$p < 0.01$ vs. PLGA-F with DOPA coating but without NGF treatment group). Reproduced with permission from [4].

Tunicate is a marine organism with good adhesion properties in wet environments related to the presence of 3,4,5- trihydroxyphenylalanine, which contains a pyrogallol (or gallol group) - a benzene ring with three adjacent hydroxyl groups [113]. Due to the presence of one additional OH group, gallol group-based adhesives have superior adhesion properties than catechol-based adhesives [113]. An electrostatic complexation of gallol-conjugated HA and aminated PCL fibers results in a pastable, adhesive, injectable, nanofibrous, and tunable (PAINT) matrix. The adhesion

of the PAINT matrix to the porcine heart surface and bovine eyeball was studied and showed that the material can fit in any cavity with irregular morphologies and maintained its adhesion to the tissue surface. The PAINT matrix was also used for delivering hNSC to treat rat SCI model and showed a functional and sensory recovery after 4 weeks post-implantation [114].

Tannic acid (TA) is composed of five pyrogallol and five catechol groups, which result in a strong adherence to various substrates. TA was combined with conductive PPy in the presence of Fe^{3+} to obtain a soft conducting hydrogel with adhesive properties. Fe^{3+} is an oxidant and ionic crosslinker for the gelation process thus, had an essential role in the hydrogel formation. The obtained hydrogel showed a high adhesion capability to adhere to mouse spinal cord tissue for 6 weeks, which confirmed the potential of this construct for SCI therapy [115]. Furthermore, the hydrogel matched the mechanical properties of the target tissue and exhibited a high conductivity, which allowed the differentiation of endogenous NSC in the lesion area. The implantation of this bioadhesive hydrogel increased the motor recovery in the mice SCI model after 6 weeks post-implantation and significantly decreased the cavity area compared to the control group. Another strategy was to combine the TA with pluronic F127 (PF127) to produce a gel through the hydrogen bonding between -OH groups and oxygen atoms present in the poly(ethylene oxide) (PEO) chain of PF127 [116]. The prepared TA-PF127 gel exhibited an adhesive strength of ~7.8kPa and a sealing effect of preventing a postoperative cerebral spinal fluid leakage in rabbit brain dura-mater. Moreover, the adhesive hydrogel was implanted in a mice SCI model, showing decreased lesion size after 2 weeks post-implantation and thus, the potential to treat TBI and SCI in clinical neurosurgical procedures.

The biomimetic adhesives join the advantages of natural and synthetic adhesives. Their simple composition and biocompatible properties potentiate their use for simultaneous wound closing and neural TE in SCI/TBI treatment in clinical neurosurgical procedures **(Table 3)**. Nevertheless, it should be remarked that most *in vivo* studies are performed during the acute lesion, *i.e.*, they do not consider the glial scar formation and development. Keeping that in mind, applying new models that consider these processes will be essential in further studies.

Table 3. Biomimetic adhesives for CNS regeneration

Material	**Adjuvant material**	***In vitro/ In vivo* studies**	**Shape form**	**Outcome**	**Ref**
Dopamine	HA, PLL	Umbilical	Hydrogel	Good adhesion	[103]

		vein endothelial cell line		strength: HA-dopamine (21 kPa) and HA-dopamine/ PLL (28 kPa)*; Improved adhesion and cell viability.	
	Silk Fibroin	L929 cells and primary hippocampal neuron	Injectable Hydrogel	Promoted the growth of hippocampal neurons; Enhanced axon length, cell density and viability.	[104]
	HA,GeP@PDA	NSC; SD rats (SCI model)	Hydrogel	Good adhesion strength HA-DA (6.3 kPa), and HA-DA/GeP@PDA (7.9 kPa)*; Improved neural differentiation of NSC; Enhanced motor recovery of rat SCI model.	[105]
	PLGA	PC12 cells	Film	Neural regeneration; Neurite outgrowth.	[112]
L-DOPA	PLGA, PLL	hNSC	Nanopatterned membrane	Promoted the neurogenesis of hNSC through enhanced contact	[4]

				guidance, focal adhesion, and cytoskeletal alignment.	
Poly(norepine-phrine)	PCL/PEO	PC12 cells	3D macroporous microfibrous scaffold	Enhanced PC12 cell differentiation.	[117]
Gallol groups (5-hydroxydopa-mine hydrochloride)	HA, PCL	SD rats (SCI model)	Hydrogel	Adhesive to the porcine heart surface after 15 min at RT; Promoted locomotive and sensory recovery.	[114]
Tannic acid	PPy	NSC and C57BL/6 mice (SCI model)	Hydrogel	Adhesive to the Mice spinal cord tissue *in vitro*; The hydrogel remained attached for 6 weeks to the spinal cord; Improved the differentiation of NSC into neurons; Enhanced motor recovery of rat SCI model.	[115]
	PF127	C57BL/6 mice (SCI model)	Hydrogel	Good adhesion strength : ~7.8 kPa**;	[116]

				Promoted antioxidant and anti-inflammatory effect; Inhibited neural cells apoptosis; Promoted glial scar formation and decreased the lesion zone.	

Lap shear test, Test substrate: *Porcine skin; **Porcine Dura-Matter

3. Self-healing materials for CNS repair

The capacity of some biomaterials to recover to their original morphology and mechanical performance after a crack or damage is called self-healing [118, 119]. Self-healing functionality could be implemented in an adhesive material to preserve its stability under a dynamic tissue environment. The development of self-healing materials has been inspired by the capacity of some tissues to heal and restore their mechanical properties after damage [120, 121]. The self-healing materials are characterized by the formation of reversible covalent (e.g. disulfide, oxime, imine) or non-covalent bonds (e.g. metal-ligand coordination, hydrogen bonds, and electrostatic interaction) (**Fig.10**) [118]. Upon a fissure, the bonds are cleaved but their reversible nature allows reformation [69]. Different strategies have been suggested for the design of biomaterials that have both adhesive and self-healing properties [99, 122].

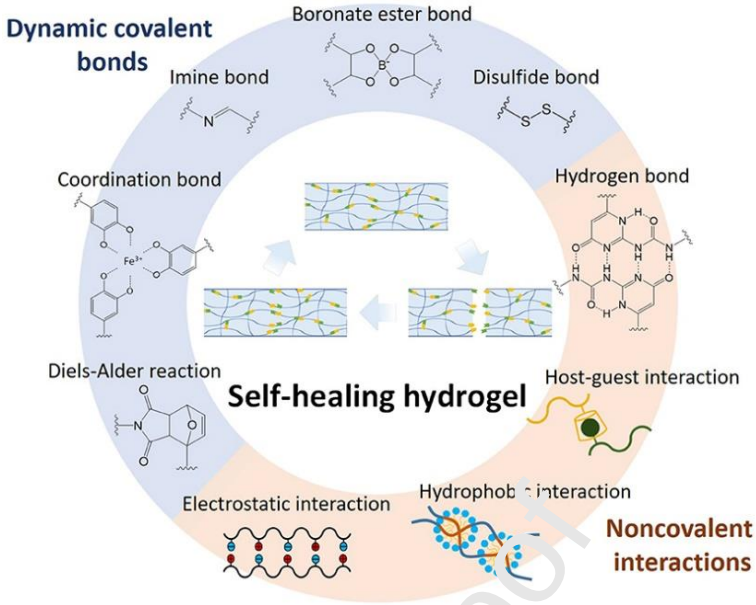


Figure 10. Different self-healing mechanisms: dynamic covalent bonds and non-covalent interactions. Reproduced with permission from [118].

The self-healing capacity is usually assessed by a tear-heal test, in which the material is broken and the crosshead is moved to bring the two broken pieces into contact again (**Fig. 11**) [123]. Dynamic rheological or dynamic cyclic strain tests can also be used to quantify the self-healing capacity [124, 125]. A high strain amplitude (γ=100%) is used to break the material, and then a low strain amplitude (γ=0.01%) and low frequency (ω=1 Hz) are applied to allow its recovery. If the storage modulus (G') of the recovered material is close to the initial value, the material is considered self-healable [123]. The self-healing efficiency depends on the time [126], the mechanical properties [127], the number of damaged/healing cycles [120], temperature and pH [128]. The time between the damage of material and rejoining of different parts is crucial for self-healing capacity. Long periods reduce the self-healing capacity because the hydrophobic molecules migrate to the damaged surface and decrease surface energy, reducing the binding sites onto the damaged area [129]. The viscoelastic behavior of materials allows us to evaluate the deformation frequency as a function of time and thus can be used as an indicator for the self-healing process [122, 129].

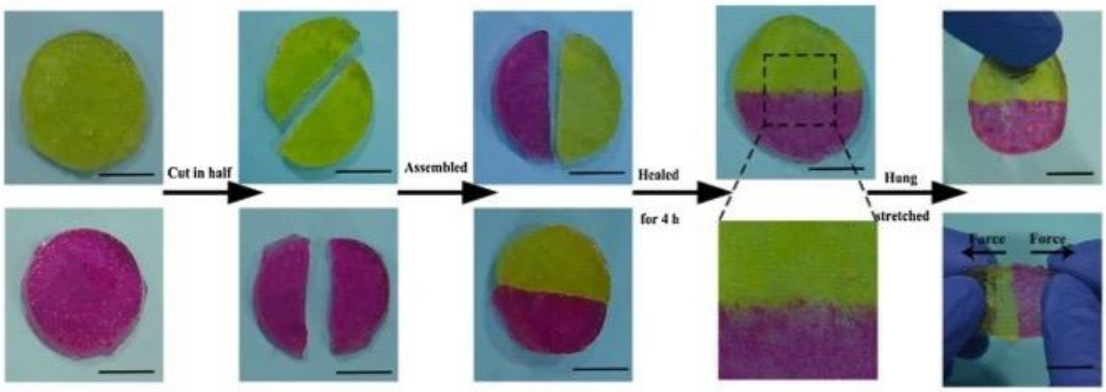


Figure 11. Macroscopic self-healing test. Reproduced with permissions from [123].

Self-healing hydrogels with injectability characteristics can be briefly fluidized under shear stress and recover their original shape and mechanical properties after release, which means that such injectable hydrogels can be administered in a minimally invasive way at the target tissue with high spatial control and molded into patient-specific tissue defects [130].

Because of their remarkable properties and ability to bridge gaps, self-healing materials can be extremely useful in SCI/TBI treatment [130] (**Table 4**). As an example, a self-healable hydrogel based on PEG and glycol chitosan (GC) (**Fig. 12A**) was developed with an appropriate stiffness (~1.5 kPa) for CNS repair [28]. The self-healing ability of PEG-GC hydrogels was demonstrated by rheology measurements (**Fig. 12B**) and is due to the dynamic uncoupling and recoupling of the imine linkages created between amine groups on GC and benzaldehyde groups of PEG chain ends. In addition, these hydrogels revealed an excellent functional recovery in a zebrafish-impaired model (**Fig. 12C-E**) [28]. In a similar approach, Liu and co-workers developed self-healing hydrogels using 3% of GC and 2% of PEG with 4-formylbenzoic acid via carbodiimide chemistry (DF-PEG) containing different concentrations of HA (0.1; 0.3 and 0.5%) [131]. These hydrogels were tested in the zebrafish TBI and intracerebral hemorrhage rat models, demonstrating the potential for CNS repair.

Table 4. Self-healing materials for CNS regeneration

Material	**Adjuvant material**	***In vitro/ In vivo* studies**	**Shape form**	**Outcome**	**Self-healing**	**Ref**

GC	DF-PEG	Zebrafish brain injury	Injectable hydrogel	Moderate recovery rate (38%); In combination with NSC spheroids: high recovery rate (81%).	After 12 h	[28, 132]
	DF-PEG/ HA	Zebrafish (TBI model) and SD rats	Injectable hydrogel	High functional recovery; The hydrogel created an ideal microenvironment for axonal growth on brain lesion cavity.	After 20 min at RT	[131]
	DF-PEG/ Cellulose	Zebrafish brain injury (Cerebellar level)	Injectable hydrogel	CNS functional recovery.	After 9 h	[133]
Carboxy-methyl chitosan	Gold nanoparticles	Wister rats (Parkinson's disease (PD) model)	Injectable hydrogel	Functional and locomotor recovery; Reduced the inflammatory response; Decresed astrocyte's response.	After 6 h	[134]
CS/gelatin	PPy	NSC and SD rats	Injectable	Good adhesion to the spinal cord of	After 1 h at	[135]

		(SCI model)	hydrogel	rat; Increase neuronal and oligodendrocyte differentiation; Promote axonal regeneration and remyelination; Locomotor recovery.	37ºC	
Polycitrate-PEG-polyethyleneimine (PCE)/ PF127	Extracellular vesicle	Rats (SCI model)	Injectable hydrogel	Good adhesion to the spinal cord and skin; Locomotor recovery and decrease of lesion cavity; Reduction of inflammatory process and promotion of axonal regeneration and remyelination.	After 1 h	[136]

Hsieh and colleagues used a similar approach to deliver NSC to CNS impaired zebrafish model [132]. The hydrogel was obtained using bacteriorhodopsin plasmid and after excitation with green light, the NSC differentiated into neurons, improving neuronal functions. Cheng and colleagues reported the GC–cellulose nanofiber hydrogels with tunable self-healing properties [133]. These hydrogels showed a 50% improvement in neural regeneration effect compared with the pristine chitosan hydrogel in the zebrafish brain injury model. The damage-healing cycles were used to prove the self-healing capacity of the novel hydrogels. Moreover, NSC were embedded in these

hydrogels and injected into adult zebrafish after a CNS injury. The results showed an improvement in the recovery of zebras fish's swimming activity [133].

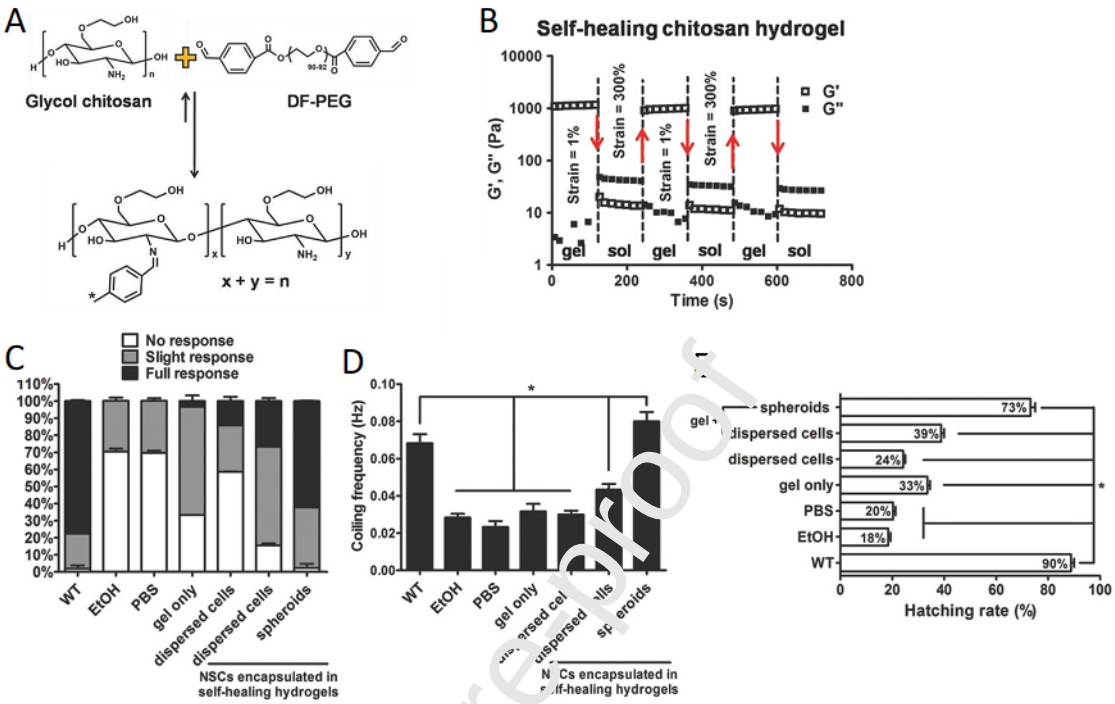


Figure 12. (A) Schematic presentation of the reaction used to obtain self-healing chitosan-based gels. (B) The damage-healing property of the hydrogel was demonstrated by the continuous step strain (1% strain→300% strain→1% strain) measurements at 37 °C (C-E). Functional assays for CNS rescue in zebrafish by the self-healing hydrogel: (C) the spontaneous contraction of zebrafish embryos examined at 18 somite stage; (D) total coiling contractions within 2 min counted at 24 hpf. (E) the hatching rate of the embryos was evaluated at 48 hpf, which serves as the index for the rescue of the nervous function. WT represents wild-type blank control. EtOH represents the untreated damaged group. *$p < 0.05$, among the indicated groups. Reproduced with permission from [28].

After a SCI/TBI, the cystic cavities and glial fibrosis interrupt the electrical signals between the neurons affecting axons regeneration [35]. The incorporation of conductive materials within adhesive hydrogels mimics the physiological environment of electroactive tissue and, thus, is advantageous for CNS regeneration after injury or disease. In fact, such combination facilitates neuron to neuron signal transmittance and also communication between neurons and other adjacent cells, therefore, enhancing neurite outgrowth and cell adhesion. As an example, hydrogels made from CS and gelatin combined with PPy were used to bridge a cavity space after a SCI. Besides

self-healing and conductive ability of 0.4 S/m, similar to the natural spinal cord tissue (**Fig.13 A-B**), the hydrogels exhibited excellent adhesive properties due to aldehyde groups present in CS, that can react with the tissue surface amine groups. The hydrogels were applied to connect the spinal cord to resist the force of gravity (**Fig.13 C**) [135]. The *in vitro* differentiation of NSC on the hydrogel displayed a large amount of Tuj1-positive neurons and MBP-positive oligodendrocytes and a low number of GFAP-positive astrocytes. Moreover, when applied in a SCI rat model, the hydrogel showed significant locomotor function restoration and a reduction of the lesion cavity (**Fig.13 D- G**).

PCE was combined with PF127 to create a thermosensitive, injectable, self-healing and adhesive hydrogel for stable delivery of MSC extracellular vesicle for treating SCI [136]. This hydrogel was prepared through a dynamic hydrogen bond between PF127 and PCE polymers. Then, self-healing characteristics were assessed through rheological tests and macroscopic analysis, where the two pieces of hydrogel were able to heal together after 1 hour. In addition, the hydrogel showed adhesive abilities when adhering without falling to the two spinal cord (one on each side of the hydrogel) or skin tissue. These two characteristics had an added value when these hydrogels were applied in a SCI rat model, showing an improvement of the functional motor score through BBB test, a reduction of cavity lesion, and promotion of remyelination and axonal regeneration.

Besides SCI/TBI, self-healing injectable hydrogels are also being used to deliver neuroprotective therapeutic, including anti-inflammatory agents, to counteract neurodegenerative diseases such as PD [134]. These hydrogels are particularly beneficial for the administration to sites that are otherwise difficult or dangerous to access, including CNS.

Therefore, we anticipate the widespread use of self-healing adhesives mixed with healing conductivity properties to provide a long-term candidate for clinical treatment in different CNS diseases and injuries.

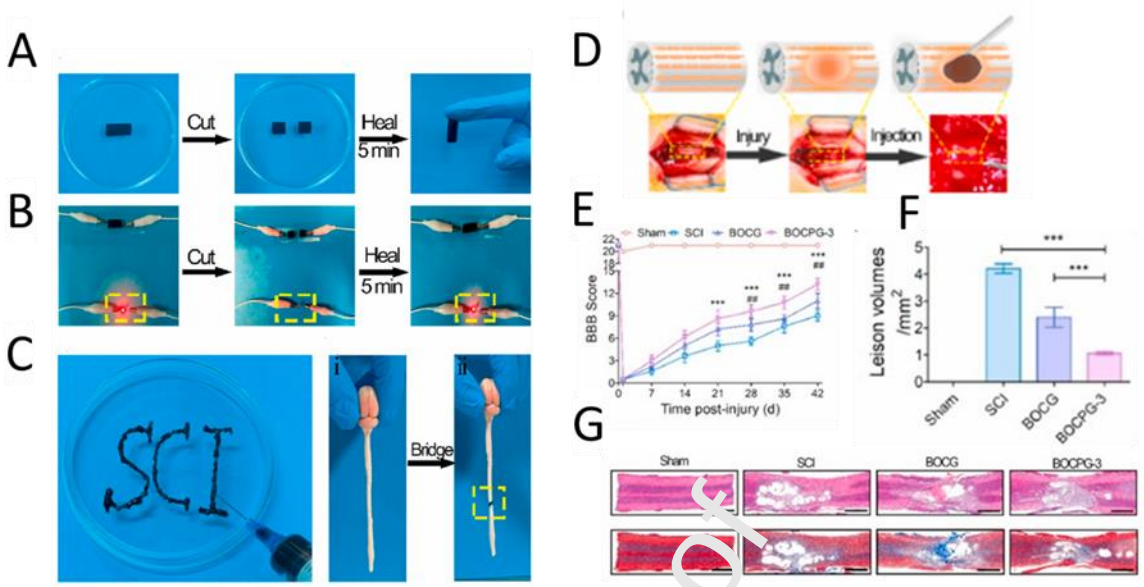


Figure 13. Properties of self-healing and electroconductive hydrogels: (A) Self-healing ability of hydrogels obtained from BOCPG-3 combined with CS, gelatin, and PPy (B) Electroconductive properties (C) The injections of BOCPG-3 hydrogels through a syringe; (i) spinal cord of rat; (ii) The adhesive properties of hydrogels were demonstrated by cutting the rat's spinal cord in the middle and placing the hydrogel to bind it. Injection of BOCPG-3 hydrogel improves functional recovery and reduces the lesion cavity in SCI rat model: (D) illustration of traumatic SCI and hydrogel injections; (E) Locomotor recovery of SCI model rat was assessed by BBB score on an open field. The rats treated with the BOCPG-3 hydrogel showed an enhanced locomotor recovery 3 weeks after injury relative to the SCI group ***$p < 0.001$; (F) illustration of lesion volume area ***$p < 0.001$ (n=3); (G) Images of haematoxylin-eosin staining and Masson's trichrome staining show the morphology of the spinal cord in different groups. Reproduced with permission from [135].

4. Conclusions and future perspectives

The pathophysiology of CNS after an injury or disease is complex and the traditional surgical treatments and drug therapies are not sufficiently efficient to restore the functionality of the damaged tissue. The use of bioadhesives for fixing such lesions has grown in the last decade. These materials can be used under different approaches for CNS repair: as simple fillers at the defect site, as functional glues that promote cell attachment, as delivery systems for bioactive agents or cells, as bioactive components that control inflammatory free radicals.

The use of bioinspired materials is much promising: natural materials have been optimized *via* an evolutionary process and, thus, have advantages over traditional adhesives, namely strong adhesion

in wet environments, low toxicity, and antibacterial, anti-inflammatory, antioxidant properties and self-healing ability.

To prolong the lifespan and efficiency of bioadhesives-based therapies, the self-healing concept has been explored. Self-repair after mechanical damage is beneficial for long-term *in vivo* applications in a complex physiological environment and stress induced by body movements. The addition of an electroconductive material to these systems promote further neural tissue repair and motor function recovery.

So far, the experience has shown that the complexity of CNS pathologies requires a combination of strategies targeting different mechanisms to provide complementary effects and improve the therapeutic effect. Integration between self-healing bioadhesives and cell transplantation offers several advantages over traditional cell transplantation methods: bioadhesives not only provide mechanical support to the transplanted stem cells, protect them from damage, and improve their survival rate but can additionally increase the precision and control of cell transplantation. Of note, functional bioadhesives must be specifically designed for each disease/tissue to address the affected downstream signaling, electro- and mechanotransduction.

Besides the tremendous progress made during the last decade, more efforts are needed to explore the full potential of these functional bioadhesives. Assessment of the adhesive strength to neural tissue and not to models, *e.g.* skin tissue, is imperative. The translational studies on the biocompatibility of the functional bioadhesive are another issue that must be addressed before clinical trials. An example of the urgency of such studies is the application of one of the most widely studied biomimetic adhesives, DOPA-based materials. In fact, DOPA has been recently reported to generate H_2O_2 as a byproduct during crosslinking reactions. The biocompatibility of the adhesives is in most cases studied under physiological but not pathological conditions. The injured tissue environment can influence the effectiveness of the adhesive and thus, a better understanding of bioadhesion under specific pathological conditions is also essential.

New technologies that hold great promise for CNS repair are emerging and can be combined with adhesive and self-healing materials. These include patient specific 3D bioprinted scaffolds and spinal cord-like spheroids/organoids, among others. However, further studies are needed to refine these approaches and to translate them into safe and efficient therapies.

Author Contributions

All authors have approved the final version of the manuscript.

Acknowledgments

The authors acknowledge the Portuguese Foundation for Science and Technology (FCT) and the European program FEDER/FEEI for the financial support through project PTDC/BTM-MAT/28123/2017. FCT is also acknowledged for the PhD scholarship SFRH/BD/143209/2019 granted to Cátia Correia.

References

[1] World Health Organization, Neurological disorders: Public health challenges, in: WHO (Ed.), Geneva, 2006, p. 217.
[2] R. Boni, A. Ali, A. Shavandi, A.N. Clarkson, Current and novel polymeric biomaterials for neural tissue engineering, J. Biomed. Sci. 25 (2018) 90. https://doi.org/10.1186/s12929-018-0491-8.
[3] J. Chedly, S. Soares, A. Montembault, Y. von Boxberg, M. Veron-Ravaille, C. Mouffle, M.N. Benassy, J. Taxi, L. David, F. Nothias, Physical chitosan microhydrogels as scaffolds for spinal cord injury restoration and axon regeneration, Biomaterials 138 (2017) 91-107. https://doi.org/10.1016/j.biomaterials.2017.05.024.
[4] K. Yang, E. Park, J.S. Lee, I.S. Kim, K. Hong, K.I. Park, S.W. Cho, H.S. Yang, Biodegradable Nanotopography Combined with Neurotrophic Signals Enhances Contact Guidance and Neuronal Differentiation of Human Neural Stem Cells, Macromol. Biosci. 15 (2015) 1348-1356. https://doi.org/10.1002/mabi.201500080.
[5] A.E. Haggerty, I. Maldonado-Lasuncion, M. Oudega, Biomaterials for revascularization and immunomodulation after spinal cord injury, Biomed. Mater. 13 (2018) 044105. https://doi.org/10.1088/1748-605X/aaa9d8.
[6] D.W. Simon, M.J. McGeachy, H. Bayir, R.S. Clark, D.J. Loane, P.M. Kochanek, The far-reaching scope of neuroinflammation after traumatic brain injury, Nat. Rev. Neurol. 13 (2017) 171-191. https://doi.org/10.1038/nrneurol.2017.13.
[7] B. Niemczyk, P. Sajkiewicz, D. Kolbuk, Injectable hydrogels as novel materials for central nervous system regeneration, J. Neural Eng. 15 (2018) 051002. https://doi.org/10.1088/1741-2552/aacbab.
[8] O.A. Carballo-Molina, I. Velasco, Hydrogels as scaffolds and delivery systems to enhance axonal regeneration after injuries, Front. Cell Neurosci. 9 (2015) 1-12. https://doi.org/10.3389/fncel.2015.00013.
[9] R. Shechter, M. Schwartz, CNS sterile injury: just another wound healing?, Trends Mol. Med. 19 (2013) 135-43. https://doi.org/10.1016/j.molmed.2012.11.007.
[10] S.S. Rao, J.O. Winter, Adhesion molecule-modified biomaterials for neural tissue engineering, Front. Neuroeng. 2 (2009) 1-14. https://doi.org/10.3389/neuro.16.006.2009.
[11] C. Gumera, B. Rauck, Y. Wang, Materials for central nervous system regeneration: bioactive cues, J. Mater. Chem. 21 (2011) 7033-7051. https://doi.org/10.1039/c0jm04335d.
[12] M.G. Fehlings, L.A. Tetreault, J.R. Wilson, B.K. Kwon, A.S. Burns, A.R. Martin, G. Hawryluk, J.S. Harrop, A Clinical Practice Guideline for the Management of Acute Spinal Cord Injury: Introduction, Rationale, and Scope, Global Spine J. 7 (2017) 84S-94S. https://doi.org/10.1177/2192568217703387.

[13] K. Venkatesh, S.K. Ghosh, M. Mullick, G. Manivasagam, D. Sen, Spinal cord injury: pathophysiology, treatment strategies, associated challenges, and future implications, Cell Tissue Res. 377 (2019) 125-151. https://doi.org/10.1007/s00441-019-03039-1.
[14] J.R. Bago, K.T. Sheets, S.D. Hingtgen, Neural stem cell therapy for cancer, Methods 99 (2016) 37-43. https://doi.org/10.1016/j.ymeth.2015.08.013.
[15] A. Higuchi, S. Suresh Kumar, G. Benelli, Q.-D. Ling, H.-F. Li, A.A. Alarfaj, M.A. Munusamy, T.-C. Sung, Y. Chang, K. Murugan, Biomaterials used in stem cell therapy for spinal cord injury, Prog. Mater. Sci. 103 (2019) 374-424. https://doi.org/10.1016/j.pmatsci.2019.02.002.
[16] F. Duraes, M. Pinto, E. Sousa, Old Drugs as New Treatments for Neurodegenerative Diseases, Pharmaceuticals 11 (2018) 44-65. https://doi.org/10.3390/ph11020044.
[17] H. Huang, W. Young, S. Skaper, L. Chen, G. Moviglia, H. Saberi, Z. Al-Zoubi, H.S. Sharma, D. Muresanu, A. Sharma, W. El Masry, S. Feng, N. International Association of, N. The Chinese Association of, Clinical Neurorestorative Therapeutic Guidelines for Spinal Cord Injury (IANR/CANR version 2019), J. Orthop. Translat. 20 (2020) 14-24. https://doi.org/10.1016/j.jot.2019.10.006.
[18] A. Platt, B.T. David, A.R.G. Fessler, Stem Cell Clinical Trials in Spinal Cord Injury: A Brief Review of Studies in the United States, Medicines (Basel) 7 (2020) 27. https://doi.org/10.3390/medicines7050027.
[19] S. Vadivelu, T.J. Stewart, Y. Qu, K. Horn, S. Liu, Q. Li, J. Silver, J.W. McDonald, NG2+ progenitors derived from embryonic stem cells penetrate glial scar and promote axonal outgrowth into white matter after spinal cord injury, Stem Cells Transl. Med. 4 (2015) 401-11. https://doi.org/10.5966/sctm.2014-0107.
[20] I.M. Pereira, A. Marote, A.J. Salgado, N.A. Silva, Filling the Gap: Neural Stem Cells as A Promising Therapy for Spinal Cord Injury, Pharmaceuticals (Basel) 12 (2019). https://doi.org/10.3390/ph12020065.
[21] L.L. Liau, Q.H. Looi, W.C. Chia, T. Subramaniam, M.H. Ng, J.X. Law, Treatment of spinal cord injury with mesenchymal stem cells, Cell Biosci. 10 (2020) 112-129. https://doi.org/10.1186/s13578-020-00475-3.
[22] M. Mousavi, A. Hedayatpour, K. Mortezaee, Y. Mohamadi, F. Abolhassani, G. Hassanzadeh, Schwann cell transplantation exerts neuroprotective roles in rat model of spinal cord injury by combating inflammasome activation and improving motor recovery and remyelination, Metab. Brain. Dis. 34 (2019) 1117-1130. https://doi.org/10.1007/s11011-019-00433-0.
[23] X. Zheng, W. Wang, Astrocyte transplantation for repairing the injured spinal cord, J. Biomed. Res. 36 (2022) 312-320. https://doi.org/10.7555/JBR.36.20220012.
[24] R. Yao, M. Mukaza, J.T. Velasquez, M. Todorovic, A. Rayfield, J. Ekberg, M. Barton, J. St John, Olfactory Ensheathing Cells for Spinal Cord Injury: Sniffing Out the Issues, Cell Transplant 27 (2018) 879-889. https://doi.org/10.1177/0963689718779353.
[25] R. Reshamwala, M. Shah, J. St John, J. Ekberg, The link between olfactory ensheathing cell survival and spinal cord injury repair: a commentary on common limitations of contemporary research, Neural Regen. Res. 15 (2020) 1848-1849. https://doi.org/10.4103/1673-5374.280310.
[26] P. Assinck, G.J. Duncan, J.R. Plemel, M.J. Lee, J.A. Stratton, S.B. Manesh, J. Liu, L.M. Ramer, S.H. Kang, D.E. Bergles, J. Biernaskie, W. Tetzlaff, Myelinogenic Plasticity of Oligodendrocyte Precursor Cells following Spinal Cord Contusion Injury, J. Neurosci. 37 (2017) 8635-8654. https://doi.org/10.1523/JNEUROSCI.2409-16.2017.
[27] N. Ashammakhi, H.J. Kim, A. Ehsanipour, R.D. Bierman, O. Kaarela, C. Xue, A. Khademhosseini, S.K. Seidlits, Regenerative Therapies for Spinal Cord Injury, Tissue Eng. Part B Rev. 25 (2019) 471-491. https://doi.org/10.1089/ten.TEB.2019.0182.
[28] T.C. Tseng, L. Tao, F.Y. Hsieh, Y. Wei, I.M. Chiu, S.H. Hsu, An Injectable, Self-Healing Hydrogel to Repair the Central Nervous System, Adv. Mater. 27 (2015) 3518-24. https://doi.org/10.1002/adma.201500762.

[29] I. Levental, P.C. Georges, P.A. Janmey, Soft biological materials and their impact on cell function, Soft Matter 3 (2007) 299-306. https://doi.org/10.1039/b610522j.
[30] S. Budday, G. Sommer, C. Birkl, C. Langkammer, J. Haybaeck, J. Kohnert, M. Bauer, F. Paulsen, P. Steinmann, E. Kuhl, G.A. Holzapfel, Mechanical characterization of human brain tissue, Acta Biomater. 48 (2017) 319-340. https://doi.org/10.1016/j.actbio.2016.10.036.
[31] C.L.S. Pettikiriarachchi J.T.S.; Parish, M.,S.; Forsythe, J.S.; Nisbet, D.R., Biomaterials for brain tissue engineering, Aust. J. Chem. 63 (2010) 1143–1154.
[32] K. Franze, P.A. Janmey, J. Guck, Mechanics in neuronal development and repair, Annu. Rev. Biomed. Eng. 15 (2013) 227-251. https://doi.org/10.1146/annurev-bioeng-071811-150045.
[33] S. Liu, Y.Y. Xie, B. Wang, Role and prospects of regenerative biomaterials in the repair of spinal cord injury, Neural Regen. Res. 14 (2019) 1352-1363. https://doi.org/10.4103/1673-5374.253512.
[34] A. Bal-Ozturk, B. Cecen, M. Avci-Adali, S.N. Topkaya, E. Alarcin, G. Yasayan, Y.C. Ethan, B. Bulkurcuoglu, A. Akpek, H. Avci, K. Shi, S.R. Shin, S. Hassan, Tissue Adhesives: From Research to Clinical Translation, Nano Today 36 (2021) 101049. https://doi.org/10.1016/j.nantod.2020.101049.
[35] Q. Yu, S. Jin, S. Wang, H. Xiao, Y. Zhao, Injectable, adhesive, self-healing and conductive hydrogels based on MXene nanosheets for spinal cord injury repair, Chem. Eng. J. 452 (2023). https://doi.org/10.1016/j.cej.2022.139252.
[36] N.A. Peppas, P.A. Buri, Surface, interfacial and molecular aspects of polymer bioadhesion, J. Control. Release 2 (1985) 257-275. https://doi.org/10.1016/0168-3659(85)90050-1.
[37] S.A. Mortazavi, B.G. Carpenter, J.D. Smart, An investigation of the rheological behaviour Int. J. Pharm. 83 (1992) 221-225. https://doi.org/10.1016/0378-5173(82)90025-4.
[38] L. Ge, S. Chen, Recent Advances in Tissue Adhesives for Clinical Medicine, Polymers (Basel) 12 (2020) 939. https://doi.org/10.3390/polym12040939.
[39] Z. Bao, M. Gao, Y. Sun, R. Nian, M. Xian, The recent progress of tissue adhesives in design strategies, adhesive mechanism and applications, Mater. Sci. Eng. C 111 (2020) 110796. https://doi.org/10.1016/j.msec.2020.110796.
[40] M. Rahimnejad, W. Zhong, Mussel-inspired hydrogel tissue adhesives for wound closure, RSC Adv. 7 (2017) 47380-47396. https://doi.org/10.1039/c7ra06743g.
[41] G.M. Taboada, K. Yang, M.J.N. Pereira, S.S. Liu, Y. Hu, J.M. Karp, N. Artzi, Y. Lee, Overcoming the translational barriers of tissue adhesives, Nat. Rev. Mater. 5 (2020) 310-329. https://doi.org/10.1038/s41578-019-0171-7.
[42] Y. Bu, A. Pandit, Cohesion mechanisms for bioadhesives, Bioact. Mater. 13 (2022) 105-118. https://doi.org/10.1016/j.bioactmat.2021.11.008.
[43] J. Feng, X.A. Tong, S. Zhao, J.I. Paez, A. Del Campo, Mechanically Reinforced Catechol-Containing Hydrogels with Improved Tissue Gluing Performance, Biomimetics (Basel) 2 (2017) 23. https://doi.org/10.3390/biomimetics2040023.
[44] F. Sun, Y. Bu, Y. Chen, F. Yang, J. Yu, D. Wu, An Injectable and Instant Self-Healing Medical Adhesive for Wound Sealing, ACS Appl. Mater. Interfaces 12 (2020) 9132-9140. https://doi.org/10.1021/acsami.0c01022.
[45] N. Pandey, L.F. Soto-Garcia, J. Liao, Z. Philippe, K.T. Nguyen, Y. Hong, Mussel-inspired bioadhesives in healthcare: design parameters, current trends, and future perspectives, Biomater. Sci. 8 (2020) 1240-1255. https://doi.org/10.1039/c9bm01848d.
[46] J. Park, Y. Kim, B. Chun, J. Seo, Rational engineering and applications of functional bioadhesives in biomedical engineering, Biotechnol. J. 16 (2021) 2100231. https://doi.org/10.1002/biot.202100231.
[47] C.R. Matos-Perez, J.D. White, J.J. Wilker, Polymer composition and substrate influences on the adhesive bonding of a biomimetic, cross-linking polymer, J. Am. Chem. Soc. 134 (2012) 9498-505. https://doi.org/10.1021/ja303369p.

[48] T. Landegren, M. Risling, J.K. Persson, A. Sonden, Cyanoacrylate in nerve repair: transient cytotoxic effect, Int. J. Oral Maxillofac. Surg. 39 (2010) 705-12. https://doi.org/10.1016/j.ijom.2010.03.008.
[49] W. Wang, Y. Xu, A. Li, T. Li, M. Liu, R. von Klitzing, C.K. Ober, A.B. Kayitmazer, L. Li, X. Guo, Zinc induced polyelectrolyte coacervate bioadhesive and its transition to a self-healing hydrogel, RSC Adv. 5 (2015) 66871-66878. https://doi.org/10.1039/c5ra11915d.
[50] M. Brennan, Fibrin Glue, Blood Reviews 5 (1991) 240-244.
[51] K.D. Kim, N.M. Wright, Polyethylene glycol hydrogel spinal sealant (DuraSeal Spinal Sealant) as an adjunct to sutured dural repair in the spine: results of a prospective, multicenter, randomized controlled study, Spine (Phila Pa 1976) 36 (2011) 1906-12. https://doi.org/10.1097/BRS.0b013e3181fdb4db.
[52] H. Yuk, C.E. Varela, C.S. Nabzdyk, X. Mao, R.F. Padera, E.T. Roche, X. Zhao, Dry double-sided tape for adhesion of wet tissues and devices, Nature 575 (2019) 169-174. https://doi.org/10.1038/s41586-019-1710-5.
[53] T. Zhu, H. Wang, Z. Jing, D. Fan, Z. Liu, X. Wang, Y. Tian, High efficacy of tetra-PEG hydrogel sealants for sutureless dural closure, Bioact. Mater. 8 (2022) 12-19. https://doi.org/10.1016/j.bioactmat.2021.06.022.
[54] Z. Qi, T. Zhang, W. Kong, C. Fu, Y. Chang, H. Li, X. Yang, S. Pan, A dual-drug enhanced injectable hydrogel incorporated with neural stem cells for combination therapy in spinal cord injury, Chem. Eng. J. 427 (2022) 130906. https://doi.org/10.1016/j.cej.2021.130906.
[55] S. Ren, Z. Liu, C.Y. Kim, K. Fu, Q. Wu, L. Hou, L. Sun, J. Zhang, Q. Miao, J. Kim, V. Bonicalzi, X. Guan, M. Zhang, W. Zhang, J. Xu, S. Canavero, X. Ren, Reconstruction of the spinal cord of spinal transected dogs with polyethylene glycol, Surg. Neurol. Int. 10 (2019) 50. https://doi.org/10.25259/SNI-73-2019.
[56] V. Bhagat, M.L. Becker, Degradable Adhesives for Surgery and Tissue Engineering, Biomacromolecules 18 (2017) 3009-3039. https://doi.org/10.1021/acs.biomac.7b00969.
[57] P. Kalsi, M. Thom, D. Choi, Histological effects of fibrin glue and synthetic tissue glues on the spinal cord: are they safe to use?, Br. J. Neurosurg. 31 (2017) 695-700. https://doi.org/10.1080/02688697.2017.1359491.
[58] Z. Chen, H. Zhang, C. Fan, Y. Zhuang, W. Yang, Y. Chen, H. Shen, Z. Xiao, Y. Zhao, X. Li, J. Dai, Adhesive, Stretchable, and Spatiotemporal Delivery Fibrous Hydrogels Harness Endogenous Neural Stem/Progenitor Cells for Spinal Cord Injury Repair, ACS Nano 16 (2022) 1986-1998. https://doi.org/10.1021/acsnano.1c06892.
[59] M. Robinson, S. Douglas, S. Michelle Willerth, Mechanically stable fibrin scaffolds promote viability and induce neurite outgrowth in neural aggregates derived from human induced pluripotent stem cells, Sci. Rep. 7 (2017) 6250. https://doi.org/10.1038/s41598-017-06570-9.
[60] M. Yao, F. Gao, R. Xu, J. Zhang, Y. Chen, F. Guan, A dual-enzymatically cross-linked injectable gelatin hydrogel loaded with BMSC improves neurological function recovery of traumatic brain injury in rats, Biomater. Sci. 7 (2019) 4088-4098. https://doi.org/10.1039/c9bm00749k.
[61] P. Le Thi, Y. Lee, D.H. Nguyen, K.D. Park, In situ forming gelatin hydrogels by dual-enzymatic cross-linking for enhanced tissue adhesiveness, J. Mater. Chem. B 5 (2017) 757-764. https://doi.org/10.1039/c6tb02179d.
[62] Y. Liu, S. Cheong Ng, J. Yu, W.-B. Tsai, Modification and crosslinking of gelatin-based biomaterials as tissue adhesives, Colloids Surf. B 174 (2019) 316-323. https://doi.org/10.1016/j.colsurfb.2018.10.077.
[63] M.A. Alvarez-Perez, V. Guarino, V. Círillo, L. Ambrosio, Influence of Gelatin Cues in PCL Electrospun Membranes on Nerve Outgrowth, Biomacromolecules 11 (2010) 2238-2246. https://doi.org/10.1021/bm100221h.

[64] V. Cirillo, V. Guarino, M.A. Alvarez-Perez, M. Marrese, L. Ambrosio, Optimization of fully aligned bioactive electrospun fibers for "in vitro" nerve guidance, J. Mater. Sci. Mater. Med. 25 (2014) 2323-32. https://doi.org/10.1007/s10856-014-5214-4.
[65] H. Babaloo, S. Ebrahimi-Barough, M.A. Derakhshan, M. Yazdankhah, N. Lotfibakhshaiesh, M. Soleimani, M.T. Joghataei, J. Ai, PCL/gelatin nanofibrous scaffolds with human endometrial stem cells/Schwann cells facilitate axon regeneration in spinal cord injury, J. Cell Physiol. 234 (2019) 11060-11069. https://doi.org/10.1002/jcp.27936.
[66] S. Kim, Y. Gwon, S. Park, W. Kim, Y. Jeon, T. Han, H.E. Jeong, J. Kim, Synergistic effects of gelatin and nanotopographical patterns on biomedical PCL patches for enhanced mechanical and adhesion properties, J. Mech. Behav. Biomed. Mater. 114 (2020) 104167. https://doi.org/10.1016/j.jmbbm.2020.104167.
[67] B. Yang, C. Liang, D. Chen, F. Cheng, Y. Zhang, S. Wang, J. Shu, X. Huang, J. Wang, K. Xia, L. Ying, K. Shi, C. Wang, X. Wang, F. Li, Q. Zhao, Q. Chen, A conductive supramolecular hydrogel creates ideal endogenous niches to promote spinal cord injury repair, Bioact. Mater. 15 (2022) 103-119. https://doi.org/10.1016/j.bioactmat.2021.11.032.
[68] W. Yang, Z. Wang, J. Zhang, K. Yang, C. Lu, X. Cui, H. Lu, S. Cao, Q. Chen, X. Lu, N. He, L. Wu, Fibrin scaffolds embedded with sonic hedgehog/chitosan microspheres for recovery of spinal cord injury in rats, Mater. Express 10 (2020) 437-445. https://doi.org/10.1166/mex.2020.1654.
[69] M. Cheng, J. Deng, F. Yang, Y. Gong, N. Zhao, X. Zhang, Study on physical properties and nerve cell affinity of composite films from chitosan and gelatin solutions, Biomaterials 24 (2003) 2871-2880. https://doi.org/10.1016/s0142-9612(03)00117-0.
[70] Y.S.R. Elnaggar, S.M. Etman, D.A. Abdelmonsif, O.Y. Abdallah, Intranasal Piperine-Loaded Chitosan Nanoparticles as Brain-Targeted Therapy in Alzheimer's Disease: Optimization, Biological Efficacy, and Potential Toxicity, J. Pharm. Sci. 104 (2015) 3544-3556. https://doi.org/10.1002/jps.24557.
[71] S. Haque, S. Md, M. Fazil, M. Kumar, J.K. Sahni, J. Ali, S. Baboota, Venlafaxine loaded chitosan NPs for brain targeting: pharmacokinetic and pharmacodynamic evaluation, Carbohydr. Polym. 89 (2012) 72-9. https://doi.org/10.1016/j.carbpol.2012.02.051.
[72] H. Abbas, N.S.E. Sayed, N. Youssef, M.E.G. P, M.R. Mousa, A.M. Fayez, M.A. Elsheikh, Novel Luteolin-Loaded Chitosan Decorated Nanoparticles for Brain-Targeting Delivery in a Sporadic Alzheimer's Disease Mouse Model: Focus on Antioxidant, Anti-Inflammatory, and Amyloidogenic Pathways, Pharmaceutics 14 (2022) 1003 https://doi.org/10.3390/pharmaceutics14051003.
[73] M. Colombo, F. Figueiró, A. de Fraga Dias, H.F. Teixeira, A.M.O. Battastini, L.S. Koester, Kaempferol-loaded mucoadhesive nanoemulsion for intranasal administration reduces glioma growth in vitro, Int. J. Pharm. 543 (2018) 214-223. https://doi.org/10.1016/j.ijpharm.2018.03.055.
[74] C. Liu, L. Fan, J. Xing, Q. Wang, C. Lin, C. Liu, X. Deng, C. Ning, L. Zhou, L. Rong, B. Liu, Inhibition of astrocytic differentiation of transplanted neural stem cells by chondroitin sulfate methacrylate hydrogels for the repair of injured spinal cord, Biomater. Sci. 7 (2019) 1995-2008. https://doi.org/10.1039/c8bm01363b.
[75] W.D. Spotnitz, Fibrin Sealant: The Only Approved Hemostat, Sealant, and Adhesive-a Laboratory and Clinical Perspective, ISRN Surg. 2014 (2014) 203943. https://doi.org/10.1155/2014/203943.
[76] F. Esposito, F.F. Angileri, P. Kruse, L.M. Cavallo, D. Solari, V. Esposito, F. Tomasello, P. Cappabianca, Fibrin Sealants in Dura Sealing: A Systematic Literature Review, PLoS One 11 (2016) e0151533. https://doi.org/10.1371/journal.pone.0151533.
[77] Z. Yu, H. Li, P. Xia, W. Kong, Y. Chang, C. Fu, K. Wang, X. Yang, Z. Qi, Application of fibrin-based hydrogels for nerve protection and regeneration after spinal cord injury, J. Biol. Eng. 14 (2020) 22. https://doi.org/10.1186/s13036-020-00244-3.

[78] C.J. Panebianco, S. Rao, W.W. Hom, J.H. Meyers, T.Y. Lim, D.M. Laudier, A.C. Hecht, M.D. Weir, J.R. Weiser, J.C. Iatridis, Genipin-crosslinked fibrin seeded with oxidized alginate microbeads as a novel composite biomaterial strategy for intervertebral disc cell therapy, Biomaterials 287 (2022) 121641. https://doi.org/10.1016/j.biomaterials.2022.121641.
[79] M.A. Cruz, S. McAnany, N. Gupta, R.G. Long, P. Nasser, D. Eglin, A.C. Hecht, S. Illien-Junger, J.C. Iatridis, Structural and Chemical Modification to Improve Adhesive and Material Properties of Fibrin-Genipin for Repair of Annulus Fibrosus Defects in Intervertebral Disks, J. Biomech. Eng. 139 (2017) 0845011-7. https://doi.org/10.1115/1.4036623.
[80] A. Ahmady, N.H. Abu Samah, A review: Gelatine as a bioadhesive material for medical and pharmaceutical applications, Int. J. Pharm. 608 (2021) 121037. https://doi.org/10.1016/j.ijpharm.2021.121037.
[81] P. Zarrintaj, S. Manouchehri, Z. Ahmadi, M.R. Saeb, A.M. Urbanska, D.L. Kaplan, M. Mozafari, Agarose-based biomaterials for tissue engineering, Carbohydr. Polym. 187 (2018) 66-84. https://doi.org/10.1016/j.carbpol.2018.01.060.
[82] M.M. Islam, M. Shahruzzaman, S. Biswas, M. Nurus Sakib, T.U. Rashid, Chitosan based bioactive materials in tissue engineering applications-A review, Bioact. Mater. 5 (2020) 164-183. https://doi.org/10.1016/j.bioactmat.2020.01.012.
[83] K. You, H. Chang, F. Zhang, Y. Shen, Y. Zhang, F. Cai, L. Liu, X. Liu, Cell-seeded porous silk fibroin scaffolds promotes axonal regeneration and myelination in spinal cord injury rats, Biochem. Biophys. Res. Commun. 514 (2019) 273-279. https://doi.org/10.1016/j.bbrc.2019.04.137.
[84] S. Mahira, A. Jain, W. Khan, A.J. Domb, Chapter 1. Antimicrobial Materials—An Overview, Antimicrobial Materials for Biomedical Applications 2019, pp. 1-37.
[85] A. Lauto, L.J. Foster, A. Avolio, D. Sampson, C. Raston, M. Sarris, G. McKenzie, M. Stoodley, Sutureless nerve repair with laser-activated chitosan adhesive: a pilot in vivo study, Photomed. Laser Surg. 26 (2008) 227-34. https://doi.org/10.1089/pho.2007.2131.
[86] S. Gnavi, C. Barwig, T. Freier, K. Haastert-Talini, C. Grothe, S. Geuna, The use of chitosan-based scaffolds to enhance regeneration in the nervous system, Int. Rev. Neurobiol. 109 (2013) 1-62. https://doi.org/10.1016/B978-0-12-420045-6.00001-8.
[87] J. Tan, L.J.R. Foster, S.L. Watson, Application of a Novel Film Sealant Technology for Penetrating Corneal Wounds: An Ex-Vivo Study, Appl. Sci. 10 (2020) 3193. https://doi.org/10.3390/app10093193.
[88] J. Xu, G.M. Soliman, L. Barralet, M. Cerruti, Mollusk glue inspired mucoadhesives for biomedical applications, Langmuir 28 (2012) 14010-7. https://doi.org/10.1021/la3025414.
[89] B.A. Aderibigbe, T. Naki, Chitosan-Based Nanocarriers for Nose to Brain Delivery, Appl. Sci. 9 (2019) 2219. https://doi.org/10.3390/app9112219.
[90] P. Mura, F. Maestrelli, M. Cirri, N. Mennini, Multiple Roles of Chitosan in Mucosal Drug Delivery: An Updated Review, Mar. Drugs 20 (2022) 335. https://doi.org/10.3390/md20050335.
[91] D.D. Ojeda-Hernandez, A.A. Canales-Aguirre, J. Matias-Guiu, U. Gomez-Pinedo, J.C. Mateos-Diaz, Potential of Chitosan and Its Derivatives for Biomedical Applications in the Central Nervous System, Front. Bioeng. Biotechnol. 8 (2020) 389. https://doi.org/10.3389/fbioe.2020.00389.
[92] Y. Wang, H. Tan, X. Hui, Biomaterial Scaffolds in Regenerative Therapy of the Central Nervous System, Biomed Res. Int. 2018 (2018) 7848901. https://doi.org/10.1155/2018/7848901.
[93] S. Al Harthi, S.E. Alavi, M.A. Radwan, M.M. El Khatib, I.A. AlSarra, Nasal delivery of donepezil HCl-loaded hydrogels for the treatment of Alzheimer's disease, Sci. Rep. 9 (2019) 9563. https://doi.org/10.1038/s41598-019-46032-y.
[94] L. Djerbal, H. Lortat-Jacob, J. Kwok, Chondroitin sulfates and their binding molecules in the central nervous system, Glycoconj. J. 34 (2017) 363-376. https://doi.org/10.1007/s10719-017-9761-z.

[95] C.P. Mencio, R.K. Hussein, P. Yu, H.M. Geller, The Role of Chondroitin Sulfate Proteoglycans in Nervous System Development, J. Histochem. Cytochem. 69 (2020) 61-80. https://doi.org/10.1369/0022155420959147.
[96] T. Fuhrmann, P.N. Anandakumaran, M.S. Shoichet, Combinatorial Therapies After Spinal Cord Injury: How Can Biomaterials Help?, Adv. Healthc. Mater. 6 (2017) 1601130. https://doi.org/10.1002/adhm.201601130.
[97] I. Strehin, Z. Nahas, K. Arora, T. Nguyen, J. Elisseeff, A versatile pH sensitive chondroitin sulfate-PEG tissue adhesive and hydrogel, Biomaterials 31 (2010) 2788-97. https://doi.org/10.1016/j.biomaterials.2009.12.033.
[98] C. Zhang, B. Wu, Y. Zhou, F. Zhou, W. Liu, Z. Wang, Mussel-inspired hydrogels: from design principles to promising applications, Chem. Soc. Rev. 49 (2020) 3605-3637. https://doi.org/10.1039/c9cs00849g.
[99] X. Wei, K. Ma, Y. Cheng, L. Sun, D. Chen, X. Zhao, H. Lu, B. Song, K. Yang, P. Jia, Adhesive, Conductive, Self-Healing, and Antibacterial Hydrogel Based on Chitosan–Polyoxometalate Complexes for Wearable Strain Sensor, ACS Appl. Polym. Mater. 2 (2020) 2541-2549. https://doi.org/10.1021/acsapm.0c00150.
[100] P. Kord Forooshani, B.P. Lee, Recent approaches in designing bioadhesive materials inspired by mussel adhesive protein, J. Polym. Sci. A Polym. Chem. 55 (2017) 9-33. https://doi.org/10.1002/pola.28368.
[101] C. Xie, X. Wang, H. He, Y. Ding, X. Lu, Mussel-Inspired Hydrogels for Self-Adhesive Bioelectronics, Adv. Funct. Mater. 30 (2020) 1909954. https://doi.org/10.1002/adfm.201909954.
[102] J.J. Wilker, Biomaterials: Redox and adhesion on the rocks, Nat. Chem. Biol. 7 (2011) 579-80. https://doi.org/10.1038/nchembio.639.
[103] Y. Zhou, L. Kang, Z. Yue, X. Liu, G.G. Wallace, Composite Tissue Adhesive Containing Catechol-Modified Hyaluronic Acid and Poly-l-lysine, ACS Appl. Bio. Mater. 3 (2019) 628-638. https://doi.org/10.1021/acsabm.9b01003.
[104] S. Chen, S. Liu, L. Zhang, Q. Han, H. Liu, J. Shen, G. Li, L. Zhang, Y. Yang, Construction of injectable silk fibroin/polydopamine hydrogel for treatment of spinal cord injury, Chem. Eng. J. 399 (2020) 125795. https://doi.org/10.1016/j.cej.2020.125795.
[105] C. Xu, Y. Chang, P. Wu, K. Liu, X. Dong, A. Nie, C. Mu, Z. Liu, H. Dai, Z. Luo, Two-Dimensional-Germanium Phosphide-Reinforced Conductive and Biodegradable Hydrogel Scaffolds Enhance Spinal Cord Injury Repair, Adv. Funct. Mater. 31 (2021) 2104440. https://doi.org/10.1002/adfm.202104440.
[106] M. Puertas-Bartolome, B. Vazquez-Lasa, J. San Roman, Bioactive and Bioadhesive Catechol Conjugated Polymers for Tissue Regeneration, Polymers (Basel) 10 (2018) 768. https://doi.org/10.3390/polym10070768.
[107] M. Puertas-Bartolome, L. Benito-Garzon, S. Fung, J. Kohn, B. Vazquez-Lasa, J. San Roman, Bioadhesive functional hydrogels: Controlled release of catechol species with antioxidant and antiinflammatory behavior, Mater. Sci. Eng. C 105 (2019) 110040. https://doi.org/10.1016/j.msec.2019.110040.
[108] N. Schweigert, A.J.B. Zehnder, R.I.L. Eggen, Chemical properties of catechols and their molecular modes of toxic action in cells, from microorganisms to mammals, Environ. Microbiol. 3 (2001) 81-91. https://doi.org/10.1046/j.1462-2920.2001.00176.x.
[109] D. Huber, A. Grzelak, M. Baumann, N. Borth, G. Schleining, G.S. Nyanhongo, G.M. Guebitz, Anti-inflammatory and anti-oxidant properties of laccase-synthesized phenolic-O-carboxymethyl chitosan hydrogels, N. Biotechnol. 40 (2018) 236-244. https://doi.org/10.1016/j.nbt.2017.09.004.
[110] H. Meng, Y. Li, M. Faust, S. Konst, B.P. Lee, Hydrogen peroxide generation and biocompatibility of hydrogel-bound mussel adhesive moiety, Acta Biomater. 17 (2015) 160-9. https://doi.org/10.1016/j.actbio.2015.02.002.

[111] H. Meng, Y. Liu, B.P. Lee, Model polymer system for investigating the generation of hydrogen peroxide and its biological responses during the crosslinking of mussel adhesive moiety, Acta Biomater. 48 (2017) 144-156. https://doi.org/10.1016/j.actbio.2016.10.016.
[112] Y. Zhang, Z. Wang, Y. Wang, L. Li, Z. Wu, Y. Ito, X. Yang, P. Zhang, A Novel Approach via Surface Modification of Degradable Polymers With Adhesive DOPA-IGF-1 for Neural Tissue Engineering, J. Pharm. Sci. 108 (2019) 551-562. https://doi.org/10.1016/j.xphs.2018.10.008.
[113] S.Y. Lee, J.N. Lee, K. Chathuranga, J.S. Lee, W.H. Park, Tunicate-inspired polyallylamine-based hydrogels for wet adhesion: A comparative study of catechol- and gallol-functionalities, J. Colloid Interface Sci. 601 (2021) 143-155. https://doi.org/10.1016/j.jcis.2021.05.101.
[114] S.H. Kim, K. Hwang, H.A. Lee, J. Kim, M. Cho, M. Kim, J.E. Shin, H. Lee, K.I. Park, J.H. Jang, Pastable, Adhesive, Injectable, Nanofibrous, and Tunable (PAINT) Biphasic Hybrid Matrices as Versatile Therapeutic Carriers, ACS Appl. Mater. Interfaces 13 (2021) 42429-42441. https://doi.org/10.1021/acsami.1c10818.
[115] L. Zhou, L. Fan, X. Yi, Z. Zhou, C. Liu, R. Fu, C. Dai, Z. Wang, X. Chen, P. Yu, D. Chen, G. Tan, Q. Wang, C. Ning, Soft Conducting Polymer Hydrogels Cross-Linked and Doped by Tannic Acid for Spinal Cord Injury Repair, ACS Nano 12 (2018) 10957-10967. https://doi.org/10.1021/acsnano.8b04609.
[116] Y. Wang, C. Xie, P. Wang, X. Wang, C. Wang, X. Xun, C. Lin, Z. Huang, Y. Cheng, L. Li, H. Teng, An elastic gel consisting of natural polyphenol and pluronic for simultaneous dura sealing and treatment of spinal cord injury, J. Control. Release 323 (2020) 613-623. https://doi.org/10.1016/j.jconrel.2020.04.042.
[117] Y. Chen, M.B. Taskin, Z. Zhang, Y. Su, X. Han, M. Chen, Bioadhesive anisotropic nanogrooved microfibers directing three-dimensional neurite extension, Biomater. Sci. 7 (2019) 2165-2173. https://doi.org/10.1039/c8bm01603h.
[118] Y. Liu, S.H. Hsu, Synthesis and Biomedical Applications of Self-healing Hydrogels, Front. Chem. 6 (2018) 449. https://doi.org/10.3389/fchem.2018.00449.
[119] Y. Tu, N. Chen, C. Li, H. Liu, R. Zhu, S. Chen, Q. Xiao, J. Liu, S. Ramakrishna, L. He, Advances in injectable self-healing biomedical hydrogels, Acta Biomater. 90 (2019) 1-20. https://doi.org/10.1016/j.actbio.2019.03.057.
[120] H. Zhang, H. Xia, Y. Zhao, Poly(vinyl alcohol) Hydrogel Can Autonomously Self-Heal, ACS Macro Letters 1 (2012) 1233-1236. https://doi.org/10.1021/mz300451r.
[121] O. Speck, T. Speck, An Overview of Bioinspired and Biomimetic Self-Repairing Materials, Biomimetics (Basel) 4 (2019) 26-60. https://doi.org/10.3390/biomimetics4010026.
[122] L. Han, L. Yan, K. Wang, L. Fang, H. Zhang, Y. Tang, Y. Ding, L.-T. Weng, J. Xu, J. Weng, Y. Liu, F. Ren, X. Lu, Tough, self-healable and tissue-adhesive hydrogel with tunable multifunctionality, NPG Asia Mater. 9 (2017) e372. https://doi.org/10.1038/am.2017.33.
[123] H. Chen, J. Cheng, L. Ran, K. Yu, B. Lu, G. Lan, F. Dai, F. Lu, An injectable self-healing hydrogel with adhesive and antibacterial properties effectively promotes wound healing, Carbohydr. Polym. 201 (2018) 522-531. https://doi.org/10.1016/j.carbpol.2018.08.090.
[124] J. Karvinen, M. Kellomäki, Characterization of self-healing hydrogels for biomedical applications, Eur. Polym. J. 181 (2022) 111641. https://doi.org/10.1016/j.eurpolymj.2022.111641.
[125] B. Gyarmati, B.Á. Szilágyi, A. Szilágyi, Reversible interactions in self-healing and shape memory hydrogels, Eur. Polym. J. 93 (2017) 642-669. https://doi.org/10.1016/j.eurpolymj.2017.05.020.
[126] A. Phadke, C. Zhang, B. Arman, C.C. Hsu, R.A. Mashelkar, A.K. Lele, M.J. Tauber, G. Arya, S. Varghese, Rapid self-healing hydrogels, Pro.c Natl. Acad. Sci. U.S.A. 109 (2012) 4383-8. https://doi.org/10.1073/pnas.1201122109.
[127] S. Maiz-Fernandez, L. Perez-Alvarez, L. Ruiz-Rubio, J.L. Vilas-Vilela, S. Lanceros-Mendez, Polysaccharide-Based In Situ Self-Healing Hydrogels for Tissue Engineering Applications, Polymers (Basel) 12 (2020) 2261. https://doi.org/10.3390/polym12102261.

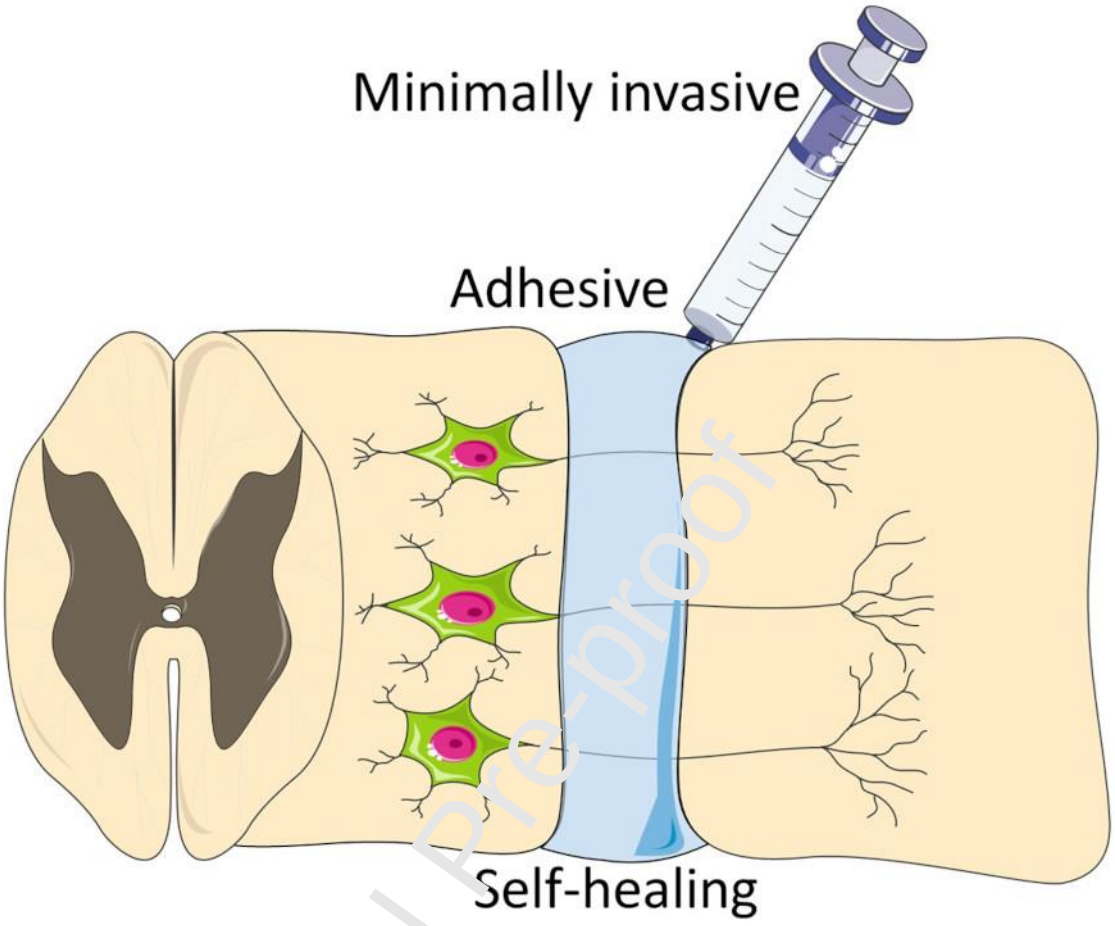
[128] W. Wang, L. Xiang, L. Gong, W. Hu, W. Huang, Y. Chen, A.B. Asha, S. Srinivas, L. Chen, R. Narain, H. Zeng, Injectable, Self-Healing Hydrogel with Tunable Optical, Mechanical, and Antimicrobial Properties, Chem. Mater. 31 (2019) 2366-2376. https://doi.org/10.1021/acs.chemmater.8b04803.
[129] G. Deng, W.-T. Wong, M. Huang, R. Wu, W.-F. Lai, Self-healing properties of hydrogels based on natural polymers, in: Y. Chen (Ed.), Hydrogels Based on Natural Polymers 2020, pp. 223-245.
[130] P. Bertsch, M. Diba, D.J. Mooney, S.C.G. Leeuwenburgh, Self-Healing Injectable Hydrogels for Tissue Regeneration, Chem. Rev. 123 (2022) 834-873. https://doi.org/10.1021/acs.chemrev.2c00179.
[131] Y. Liu, Y.H. Hsu, A.P. Huang, S.H. Hsu, Semi-Interpenetrating Polymer Network of Hyaluronan and Chitosan Self-Healing Hydrogels for Central Nervous System Repair, ACS Appl. Mater. Interfaces 12 (2020) 40108-40120. https://doi.org/10.1021/acsami.0c11433.
[132] F.Y. Hsieh, H.W. Han, X.R. Chen, C.S. Yang, Y. Wei, S.H. Hsu, Non-viral delivery of an optogenetic tool into cells with self-healing hydrogel, Biomaterials 174 (2018) 31-40. https://doi.org/10.1016/j.biomaterials.2018.05.014.
[133] K.-C. Cheng, C.-F. Huang, Y. Wei, S.-h. Hsu, Novel chitosan–cellulose nanofiber self-healing hydrogels to correlate self-healing properties of hydrogels with neural regeneration effects, NPG Asia Mater. 11 (2019) 25. https://doi.org/10.1038/s41427-019-0124-z.
[134] J. Xu, C.-H. Tai, T.-Y. Chen, S.-h. Hsu, An anti-inflammatory electroconductive hydrogel with self-healing property for the treatment of Parkinson's disease, Chem. Eng. J. 446 (2022) 137180. https://doi.org/10.1016/j.cej.2022.137180.
[135] Y. Luo, L. Fan, C. Liu, H. Wen, S. Wang, P. Guan, D. Chen, C. Ning, L. Zhou, G. Tan, An injectable, self-healing, electroconductive extracellular matrix-based hydrogel for enhancing tissue repair after traumatic spinal cord injury, Bioact. Mater. 7 (2021) 98-111. https://doi.org/10.1016/j.bioactmat.2021.05.039.
[136] C. Wang, M. Wang, K. Xia, J. Wang, F. Cheng, K. Shi, L. Ying, C. Yu, H. Xu, S. Xiao, C. Liang, F. Li, B. Lei, Q. Chen, A bioactive injectable self-healing anti-inflammatory hydrogel with ultralong extracellular vesicles release synergistically enhances motor functional recovery of spinal cord injury, Bioact. Mater. 6 (2021) 2523-2534. https://doi.org/10.1016/j.bioactmat.2021.01.029.

Declaration of interests

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

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Graphical abstract



Highlights

- Central nervous system (CNS) has a limited self-regeneration ability
- Bioadhesives and self-healing materials are promising alternatives to the current clinical treatments
- They restore CNS function by bridging gaps and delivering therapeutic agents/cells to the injured site in a minimally invasive way