SYSTEMATIC REVIEW

Comparing natural hydrogels to self-assembling peptides in spinal cord injury treatment: a systematic review [version 1; peer review: awaiting peer review]

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Abstract

Background: In many cases, central nervous system (CNS) injury is unchanging due to the absence of neuronal regeneration and repair capabilities. In recent years, regenerative medicine, and especially hydrogels, has reached a significant amount of attention for their promising results for the treatment of spinal cord injury (SCI) currently considered permanent. Hydrogels are categorized based on their foundation: synthetic, natural, and combination. The objective of this study was to compare the properties and efficacy of commonly used hydrogels, like collagen, and other natural peptides with synthetic self-assembling peptide hydrogels in the treatment of SCI.

Open Peer Review

Approval Status AWAITING PEER REVIEW

Any reports and responses or comments on the article can be found at the end of the article.

Methods: Articles were searched in PubMed, Scopus, Web of Science, and Embase. All studies from 1985 until January 2020 were included in the primary search. Eligible articles were included based on the following criteria: administering hydrogels (both natural and synthetic) for SCI treatment, solely focusing on spinal cord injury treatment, and published in a peer-reviewed journal. Data on axonal regeneration, revascularization, elasticity, drug delivery efficacy, and porosity were extracted.

Results: A total of 24 articles were included for full-text review and data extraction. There was only one experimental study comparing collagen I (natural hydrogel) and polyethylene glycol (PEG) in an *in vitro* setting. The included study suggested the behavior of cells with PEG is more expectable in the injury site, which makes it a more reliable scaffold for neurites.

Conclusions: There is limited research comparing and evaluating both types of natural and self-assembling peptides (SAPs) in the same animal or *in vitro* study, despite its importance. Although we assume that the remodeling of natural scaffolds may lead to a stable hydrogel, there was not a definitive conclusion that synthetic hydrogels are more beneficial than natural hydrogels in neuronal regeneration.

Keywords

Hydrogels, Collagen, Peptides, Spinal cord Injuries, Systematic review

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Introduction

Injuries to the central nervous system (CNS) are challenging to rehabilitate. In the absence of neuronal regeneration and repair capabilities, the damage and resulting complications are permanent in many cases. There have not been any new treatments for spinal cord injury (SCI) in the past decade, and many studies in molecular medicine currently consider some spinal cord conditions as untreatable.¹

A permissive growth substrate is critical to promote regeneration at the injury site.² Many types of research have been conducted to advance and evaluate different natural and synthetic hydrogel systems,³ such as polysaccharides,^{4,5} synthetic polymers,⁶ proteins,⁷ peptides,⁸ and its derivatives.^{9–11}

Hydrogels are categorized as natural and synthetic structures with properties for extensive water absorption and resistance to dissolution.¹² We consider a perfect hydrogel to provide the following features: 1) high absorption capacity, 2) low soluble content and residue, 3) suitable biodegradability based on tissue type and the absence of toxic species formation, 4) local and sustained drug-release, 5) immunologically inert, and 6) substantial cost-benefit.^{12–14}

Both natural and synthetic hydrogels have different characteristics, and some of them are compatible with the features listed above.

Self-assembling peptides (SAPs) can spontaneously self-assemble in the aqueous solution to form highly organized structures, such as hydrogels. Due to their great water-holding capacity, outstanding biocompatibility,^{15–17} and similarities to the native extracellular matrix (ECM),¹⁸ these hydrogels have gained tremendous recognition in recent years. The advantages of these artificial hydrogels are their transmutative characteristics, such as porosity, elasticity, and drug delivery pace.¹⁹

For a previous project, we asked several distinguished companies in China, Denmark, Canada, and more to design and produce high concentration hydrogels. However, they could not produce SAPs with a desirable concentration percentage for cell culture purposes, which in some cases can be considered as a challenge of providing this type of scaffolds.

On the other hand, many studies have applied natural hydrogels like collagen-based hydrogel designed based on the Nature Protocols²⁰ for drug delivery in spinal cord injuries in animals, and the results have been somewhat promising. Due to their soft tissue-like formation characteristics, agarose, alginate, and collagen hydrogels have been acknowledged as likely scaffolds in the CNS and the peripheral nervous system (PNS).^{21–23} Therefore, we performed this review to determine how these two very different, yet very promising, scaffolds would perform in similar conditions.

Method

Ethical considerations

The Ethics Committee of Tehran University of Medical Sciences, approved the study with reference number 99-1-101-388. This systematic review has been conducted according to the PRISMA 2020 Checklist.^{24,25}

Eligibility criteria

In the review, articles had to meet the following inclusion criteria: 1) administering hydrogels (both natural and synthetic) for SCI treatment, 2) specifically focused on spinal cord injury, and 3) original articles published in a peer-reviewed journal. Exclusion criteria included: 1) studies on injuries other than SCI, 2) studies focusing on only tissue-engineered self-assembling peptides, 3) studies focused only on natural hydrogels.

There was no limitation of language for included studies.

Electronic searches

We performed this systematic review to evaluate axonal regeneration, revascularization, porosity, elasticity, and drug delivery efficacy of natural and synthetic hydrogels. Our search strategy in different databases utilized Medical Subject Headings (MeSH, from PubMed), Excerpta Medica Tree (Emtree, from Embase), keywords of related articles and reviews, and experts' opinions. A systematic search of the literature was performed on PubMed, Scopus, Web of Science, and Embase for published articles from 1985 until January 2020. The detailed search syntax is presented in the *Extended data*.²⁴ We also manually checked the references of primarily included studies and relevant reviews to identify additional relevant articles. After removing duplicate articles, the remaining articles were transferred to an EndNote file (version X9, Thomson Reuters, USA).

Selection and data collection process

After eliminating duplicates, the records were divided into two groups. Each group was reviewed by two independent reviewers (in two teams) based on the keywords, and 24 papers were selected eligible for full-text review. The resulting records were then divided again and each full text was reviewed by two independent reviewers (in two teams) for data extraction. Differences of opinion between two reviewers of each team was solved by consultation with the corresponding author.

Data items

We designed a data collection sheet, and the items below were collected to compare natural and self-assembling hydrogels:

- Axonal regeneration: The axon (proximal fragment) regrowth from the injury site toward its target following the original pathway.
- Revascularization: restoration of the flow of blood to a previously ischemic tissue after a traumatic injury.
- Porosity: a fraction of the volume of voids over the total volume. Hydrogel porosity is critical for local angiogenesis and has a substantial effect on the mechanical properties
- Elasticity: the ability of a hydrogel to resume its standard shape after implantation.
- Invasion/Elongation of astrocytes, fibroblasts, endothelial or Schwann cells
- Efficacy of drug delivery

Results

Out of a total number of 2742 identified articles, 2718 records were excluded based on title and abstract screening, and the full text of the remaining 24 records were investigated by the same four reviewers as two review groups. In total, 23 were excluded at this stage and only one record was selected for full-text review (Figure 1). Of the 23 articles excluded, 18 were because they did not evaluate a natural hydrogel in their study,^{26–43} and five because they had not administrated a SAP in the study.^{44–48}

According to the single record included (Table 1), axonal regeneration of the administrated scaffolds was reported individually based on the type and the combination of scaffolds.

In this study, with the addition of fibronectin (FN) at various concentrations to PEG gels, and collagen I in various concentrations and stiffness, cell behavior and axonal regeneration were investigated in an *in vitro* environment shown in Table 2. The article found that adding FN to collagen has a biphasic response due to specific interactions in collagen and the growing neurites, contrary to PEG, which has a more expectable behavior regarding the FN addition within the graft.

PEG gels were examined at 3%, 4%, and 5% concentration with 0, 1, 10, 100 µg/ml FN added; 3% PEG+ 100 µg/ml FN presented the most significant neurite length growth by 145 µm. It is also worth remarking that adding any concentrations of FN to PEG gels had a positive effect on axonal regeneration than PEG gels with no FN added.

Collagen I was examined at 0.4-2 mg/ml concentrations with 0, 1, 10, 100 µg/ml FN added; As mentioned above, the addition of FN had a biphasic response in collagen, with reducing neurite growth length in lower concentrations (0.4-0.6 mg/ml) compared to collagens with no FN, while increasing neurites length in mid and high collagen concentrations (1.0-2.0 mg/ml).

While the addition of FN impacted the overall growth within the different gels, there were no differences noted in viability with increasing FN concentrations. No differences were found between PEG gel concentrations. Moreover, cells within collagen gels had higher viability overall.

Discussion

We believe biomaterials and natural hydrogels are expected to not dissolve quickly and remain for a long time when injected into the injured spinal cord whilst directly delivering drugs into it, and render a sufficient environment for axonal

Figure 1. Flowchart of the article screening process following identification of studies via database search.

Table 1. General information of the only one included study.

Title	First author	Year of Study	Country	Study Characteristics	Type of Study
Comparison of neurite growth in three dimensional natural and synthetic hydrogels	Wenda Zhou	Aug 2012	United States	Experimental	<i>In Vitro</i>

regeneration and revascularization of the damaged tissues. Also, these scaffolds help with the need for a physical matrix to which neurons and endogenous repairing cells can adhere.⁴⁹

In this regard, designing a hydrogel must meet some fundamental principles, such as biocompatibility, so it does not trigger an immune response from the host⁴⁹; specifically designed mechanical and physicochemical characteristics allow both spinal cord stabilization and cell adherence and growth.²⁶

The biodegradability of these materials must be considered, and the biomaterial degrades as new tissue grows, mimicking the natural mechanisms of breakdown and synthesis of ECM in the natural tissue.^{50–54}

In a previous study, Merchand et al. used collagen as scaffolds to fill the gap transected in the spinal cord of Sprague-Dawley rats, and extended the stability of collagen (2-3 months) by adding a cross-linking agent to the gel which helped axonal regrowth over a six months' timeline.⁵⁶

Table 2. Axonal regeneration and elasticity of scaffold.

Type of Scaffold	Results	Elasticity
3% PEG + 0 µg/ml FN, 90	≈ 90 µm	10 ^{^2} Pa>
3% PEG + 1 µg/ml FN, 95	≈ 95 µm	10 ^{^2} Pa>
3% PEG + 10 µg/ml FN, 130	≈ 130 µm	10 ^{^2} Pa>
3% PEG + 100 µg/ml FN, 145	≈ 145 µm	10 ^{^2} Pa>
4% PEG + 0 µg/ml FN, 80	≈ 80 µm	10 ^{^3} Pa>
4% PEG + 1 µg/ml FN, 110	≈ 110 µm	10 ^{^3} Pa>
4% PEG + 10 µg/ml FN, 130	≈ 130 µm	10 ^{^3} Pa>
4% PEG + 100 µg/ml FN, 135	≈ 135 µm	10 ^{^3} Pa>
5% PEG + 0 µg/ml FN, 85	≈ 85 µm	≈ 10 ^{^3} Pa
5% PEG + 1 µg/ml FN, 90	≈ 90 µm	≈ 10 ^{^3} Pa
5% PEG + 10 µg/ml FN, 100	≈ 100 µm	≈ 10 ^{^3} Pa
5% PEG + 100 µg/ml FN, 125	≈ 125 µm	≈ 10 ^{^3} Pa
0.4 mg/ml Col. + 0 µg/ml FN,	≈ 187 µm	10 Pa>
0.4 mg/ml Col. + 1 µg/ml FN,	≈ 160 µm	10 Pa>
0.4 mg/ml Col. + 10 µg/ml FN,	≈ 165 µm	10 Pa>
0.4 mg/ml Col. + 100 µg/ml FN	≈ 155 µm	10 Pa>
0.6 mg/ml Col. + 0 µg/ml FN,	≈ 200 µm	10 Pa>
0.6 mg/ml Col. + 1 µg/ml FN,	≈ 187 µm	10 Pa>
0.6 mg/ml Col. + 10 µg/ml FN,	≈ 185 µm	10 Pa>
0.6 mg/ml Col. + 100 µg/ml FN	≈ 155 µm	10 Pa>
0.8 mg/ml Col. + 0 µg/ml FN,	≈ 168 µm	10 Pa>
0.8 mg/ml Col. + 1 µg/ml FN,	≈ 180 µm	10 Pa>
0.8 mg/ml Col. + 10 µg/ml FN,	≈ 190 µm	10 Pa>
0.8 mg/ml Col. + 100 µg/ml FN	≈ 165 µm	10 Pa>
1 mg/ml Col. + 0 µg/ml FN,	≈ 160 µm	10 Pa>
1 mg/ml Col. + 1 µg/ml FN,	≈ 168 µm	10 Pa>
1 mg/ml Col. + 10 µg/ml FN,	≈ 195 µm	10 Pa>
1 mg/ml Col. + 100 µg/ml FN,	≈ 185 µm	10 Pa>
1.25 mg/ml Col. + 0 µg/ml FN,	≈ 160 µm	≈ 10 Pa
1.25 mg/ml Col. + 1 µg/ml FN,	≈ 185 µm	10 Pa>
1.25 mg/ml Col. + 10 µg/ml FN,	≈ 178 µm	10 Pa>
1.25 mg/ml Col. + 100 µg/ml FN,	≈ 180 µm	10 Pa>
1.5 mg/ml Col. + 0 µg/ml FN,	≈ 180 µm	10 ^{^2} Pa>
1.5 mg/ml Col. + 1 µg/ml FN,	≈ 188 µm	10 ^{^2} Pa>
1.5 mg/ml Col. + 10 µg/ml FN,	≈ 185 µm	10 ^{^2} Pa>
1.5 mg/ml Col. + 100 µg/ml FN,	≈ 188 µm	10 ^{^2} Pa>
2 mg/ml Col. + 0 µg/ml FN,	≈ 155 µm	10 ^{^2} Pa>
2 mg/ml Col. + 1 µg/ml FN,	≈ 175 µm	10 ^{^2} Pa>
2 mg/ml Col. + 10 µg/ml FN,	≈ 175 µm	10 ^{^2} Pa>
2 mg/ml Col. + 100 µg/ml FN,	≈ 158 µm	10 ^{^2} Pa>

The biocompatibility characteristics of natural hydrogels allow for cell adhesion and migration.⁵⁷ Moreover, not only can natural hydrogels be used to bridge the gap in the lesion site for cell regeneration, but they are also considered for sustained drug delivery.⁵⁸

However, synthetic hydrogels, such as poly (hydroxyethyl methacrylate) (PHEMA) based hydrogels, are favorites for the treatment of SCI and drug delivery to the lesion site due to their ability to be mass produced and their ability to have their properties modified.⁵⁹

Our study indeed had some limitations. Regenerative studies for SCI primarily focus on different characteristics of one specific type of hydrogel and, comparing different features of these types of hydrogels were completely overlooked, or if these two types of hydrogels are used together in a study, it is in the form of a new combinatorial hydrogel scaffold.

There are no definitive findings regarding synthetic hydrogels' advantage over natural hydrogels in SCI treatment in animals or humans. Still, there might be some inadequate shreds of evidence to report that one of these types has an advantage over the other. However, more studies with the specific objective to compare synthetic and natural hydrogels is necessary to find their advantages and disadvantages in a mutual condition. Until then, both synthetic and natural scaffolds are in the race for the ultimate scaffolds.

This study sheds light on a notable absence of evaluation following our objectives and intentions performing this review.

Conclusion

We assume that remodeling natural scaffolds may lead to sensible axonal regeneration, progress such as reducing the scar tissue, and a stable graft at the injury site; however, there was not a definite evidence regarding the benefits of neuronal regeneration in synthetic hydrogels compared to natural hydrogels.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Extended data

Zenodo: Comparing natural hydrogels to self-assembling peptides in spinal cord injury treatment: a systematic review. <https://doi.org/10.5281/zenodo.5759312>.²⁵

This project contains the following extended data:

- search strategy.docx

Reporting guidelines

Zenodo: PRISMA checklist for 'Comparing natural hydrogels to self-assembling peptides in spinal cord injury treatment: a systematic review'. <https://doi.org/10.5281/zenodo.5759312>.²⁵

Data are available under the terms of the Data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

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References

1. Gazdic M, et al.: **Stem Cells Therapy for Spinal Cord Injury**. *Int. J. Mol. Sci.* 30 Mar. 2018; **19**(4): 1039. [PubMed Abstract](#) | [Publisher Full Text](#)
2. Jain A, et al.: **In situ gelling hydrogels for conformal repair of spinal cord defects, and local delivery of BDNF after spinal cord**
3. Huang R, et al.: **Self-assembling peptide-polysaccharide hybrid hydrogel as a potential carrier for drug delivery**. *Soft Matter*. 2006; **27**(3): 497–504. [Publisher Full Text](#)

- 2011; **7**(13): 6222–6230.
[Publisher Full Text](#)
4. Tan H, *et al.*: **Injectable in situ forming biodegradable chitosan-hyaluronic acid-based hydrogels for cartilage tissue engineering.** *Biomaterials*. 2009; **30**(13): 2499–2506.
[PubMed Abstract](#) | [Publisher Full Text](#)
 5. Jin R, Teixeira LSM, Dijkstra PJ, *et al.*: **Injectable chitosan-based hydrogels for cartilage tissue engineering.** *Biomaterials*. 2009; **30**: 2544–2551.
[PubMed Abstract](#) | [Publisher Full Text](#)
 6. Choi J, *et al.*: **Controlled drug release from multilayered phospholipid polymer hydrogel on titanium alloy surface.** *Biomaterials*. 2009; **30**(28): 5201–5208.
[Publisher Full Text](#)
 7. Yan H, *et al.*: **Thermo-reversible protein fibrillar hydrogels as cell scaffolds.** *Faraday Discuss*. 2008; **139**: 71–84.
[PubMed Abstract](#) | [Publisher Full Text](#)
 8. Koutsopoulos S, *et al.*: **Controlled release of functional proteins through designer self-assembling peptide nanofiber hydrogel scaffold.** *Proc. Natl. Acad. Sci.* 2009; **106**(12): 4623–4628.
[PubMed Abstract](#) | [Publisher Full Text](#)
 9. Cui H, Webber MJ, Stupp SI: **Self-assembly of peptide amphiphiles: From molecules to nanostructures to biomaterials.** *Peptide Science: Original Research on Biomolecules*. 2010; **94**(1): 1–18.
[PubMed Abstract](#) | [Publisher Full Text](#)
 10. Sui Z, King WJ, Murphy WL: **Protein-Based Hydrogels with Tunable Dynamic Responses.** *Adv. Funct. Mater.* 2008; **18**(12): 1824–1831.
[Publisher Full Text](#)
 11. Bhattacharya S, Ghanashyam Acharya SN: **Impressive Gelation in Organic Solvents by Synthetic, Low Molecular Mass, Self-Organizing Urethane Amides of L-Phenylalanine.** *Chem. Mater.* 1999; **11**(11): 3121–3132.
[Publisher Full Text](#)
 12. Ahmed EM: **Hydrogel: Preparation, characterization, and applications: A review.** *J. Adv. Res.* 2015; **6**(2): 105–121.
[Publisher Full Text](#)
 13. Baumann MD, *et al.*: **Intrathecal delivery of a polymeric nanocomposite hydrogel after spinal cord injury.** *Biomaterials*. 2010; **31**(30): 7631–7639.
[Publisher Full Text](#)
 14. Hejčl A, *et al.*: **Biocompatible hydrogels in spinal cord injury repair.** *Physiol. Res.* 2008; **57**(3): S121–S132.
[Publisher Full Text](#)
 15. Guiseppi-Elie A: **Electroconductive hydrogels: synthesis, characterization and biomedical applications.** *Biomaterials*. 2010; **31**(10): 2701–2716.
[PubMed Abstract](#) | [Publisher Full Text](#)
 16. Hoffman AS: **Hydrogels for biomedical applications.** *Adv. Drug Deliv. Rev.* 2002; **54**(1): 3–12.
[Publisher Full Text](#)
 17. Tomme V, Sophie R, *et al.*: **In situ gelling hydrogels for pharmaceutical and biomedical applications.** *Int. J. Pharm.* 2008; **355**(1–2): 1–18.
[Publisher Full Text](#)
 18. Annabi N, *et al.*: **Controlling the porosity and microarchitecture of hydrogels for tissue engineering.** *Tissue Eng. Part B Rev.* 2010; **16**(4): 371–383.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 19. Perle G, *et al.*: **Hydrogels in spinal cord injury repair strategies.** *ACS Chem. Neurosci.* 2011; **2**(7): 336–345.
[PubMed Abstract](#) | [Publisher Full Text](#)
 20. Rajan N, Habermehl J, Cote M-F, *et al.*: **Preparation of ready-to-use, storable and reconstituted type I collagen from rat tail tendon fortissue engineering applications.** *Nat. Protoc.* 2006; **1**: 2753–2758.
[PubMed Abstract](#) | [Publisher Full Text](#)
 21. Kataoka K, *et al.*: **Alginate enhances elongation of early regenerating axons in spinal cord of young rats.** *Tissue Eng.* 2004; **10**(3–4): 493–504.
[PubMed Abstract](#) | [Publisher Full Text](#)
 22. Houweling DA, *et al.*: **Collagen containing neurotrophin-3 (NT-3) attracts regrowing injured corticospinal axons in the adult rat spinal cord and promotes partial functional recovery.** *Exp. Neurol.* 1998; **153**(1): 49–59.
[PubMed Abstract](#) | [Publisher Full Text](#)
 23. Labrador RO, *et al.*: **Influence of collagen and laminin gels concentration on nerve regeneration after resection and tube repair.** *Exp. Neurol.* 1998; **149**(1): 243–252.
[PubMed Abstract](#) | [Publisher Full Text](#)
 24. Moher D, Liberati A, Tetzlaff J, *et al.*: **Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.** *PLoS Med.* 2009; **6**: e1000097.
[PubMed Abstract](#) | [Publisher Full Text](#)
 25. Kurosh M: **Comparing natural hydrogels to self-assembling peptides in spinal cord injury treatment: a systematic review [Data set].** *Zenodo*. 2021.
[Publisher Full Text](#)
 26. Nomura H, *et al.*: **Complete spinal cord transection treated by implantation of a reinforced synthetic hydrogel channel results in syringomyelia and caudal migration of the rostral stump.** *Neurosurgery*. 2006; **59**(1): 183–192; discussion 183–92.
[PubMed Abstract](#) | [Publisher Full Text](#)
 27. Tsai EC, *et al.*: **Matrix inclusion within synthetic hydrogel guidance channels improves specific supraspinal and local axonal regeneration after complete spinal cord transection.** *Biomaterials*. 2006; **27**(3): 519–533.
[PubMed Abstract](#) | [Publisher Full Text](#)
 28. Wang Q, *et al.*: **Novel multi-drug delivery hydrogel using scar-homing liposomes improves spinal cord injury repair.** *Theranostics*. 8(16): 4429–4446. 7 Aug.
[PubMed Abstract](#) | [Publisher Full Text](#)
 29. Woerly S, *et al.*: **Heterogeneous PHPMA hydrogels for tissue repair and axonal regeneration in the injured spinal cord.** *J. Biomater. Sci. Polym. Ed.* 1998; **9**(7): 681–711.
[PubMed Abstract](#) | [Publisher Full Text](#)
 30. Woerly S, *et al.*: **Spinal cord repair with PHPMA hydrogel containing RGD peptides (NeuroGel).** *Biomaterials*. 2001; **22**(10): 1095–1111.
[PubMed Abstract](#) | [Publisher Full Text](#)
 31. Baumann MD, *et al.*: **Intrathecal delivery of a polymeric nanocomposite hydrogel after spinal cord injury.** *Biomaterials*. 2010; **31**(30): 7631–7639.
[PubMed Abstract](#) | [Publisher Full Text](#)
 32. Chen BK, *et al.*: **Comparison of polymer scaffolds in rat spinal cord: a step toward quantitative assessment of combinatorial approaches to spinal cord repair.** *Biomaterials*. 2011; **32**(32): 8077–8086.
[PubMed Abstract](#) | [Publisher Full Text](#)
 33. Cigognini D, *et al.*: **Evaluation of mechanical properties and therapeutic effect of injectable self-assembling hydrogels for spinal cord injury.** *J. Biomed. Nanotechnol.* 2014; **10**(2): 309–323.
[PubMed Abstract](#) | [Publisher Full Text](#)
 34. Conova L, *et al.*: **A pilot study of poly(N-isopropylacrylamide)-g-polyethylene glycol and poly(N-isopropylacrylamide)-g-methylcellulose branched copolymers as injectable scaffolds for local delivery of neurotrophins and cellular transplants into the injured spinal cord.** *J. Neurosurg. Spine*. 2011; **15**(6): 594–604.
[PubMed Abstract](#) | [Publisher Full Text](#)
 35. Hejčl A, Růžicka J, Kekulová K, *et al.*: **Modified Methacrylate Hydrogels Improve Tissue Repair after Spinal Cord Injury.** *Int. J. Mol. Sci.* 2018; **19**(9): 2481.
[PubMed Abstract](#) | [Publisher Full Text](#)
 36. Kang CE, *et al.*: **Poly (ethylene glycol) modification enhances penetration of fibroblast growth factor 2 to injured spinal cord tissue from an intrathecal delivery system.** *J. Control. Release*. 2010; **144**(1): 25–31.
[PubMed Abstract](#) | [Publisher Full Text](#)
 37. Madigan NN, *et al.*: **Comparison of cellular architecture, axonal growth, and blood vessel formation through cell-loaded polymer scaffolds in the transected rat spinal cord.** *Tissue Eng. A*. 2014; **20**(21–22): 2985–2997.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 38. Kubinová Š, *et al.*: **SIKVAV-modified highly superporous PHEMA scaffolds with oriented pores for spinal cord injury repair.** *J. Tissue Eng. Regen. Med.* 2015; **9**(11): 1298–1309.
[PubMed Abstract](#) | [Publisher Full Text](#)
 39. Lee J, *et al.*: **Formulation of thrombin-inhibiting hydrogels via self-assembly of ionic peptides with peptide-modified polymers.** *Soft Matter*. 2020; **16**(15): 3762–3768.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 40. Siddiqui AM, *et al.*: **Defining Spatial Relationships Between Spinal Cord Axons and Blood Vessels in Hydrogel Scaffolds.** *Tissue Eng. Part A*. 2021; **27**(11–12): 648–664.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 41. Kubinova S, Tukmachev D, Forostyak S, *et al.*: **Comparison of synthetic versus biologic hydrogel scaffolds in spinal cord injury treatment.** *J. Tissue Eng. Regen. Med.* 2014; **8**: 43–43.
 42. Austin JW, *et al.*: **The effects of intrathecal injection of a hyaluronan-based hydrogel on inflammation, scarring and neurobehavioural outcomes in a rat model of severe spinal cord injury associated with arachnoiditis.** *Biomaterials*. 2012; **33**(18): 4555–4564.
[PubMed Abstract](#) | [Publisher Full Text](#)

43. Ando K, *et al.*: **Self-assembling Peptide Reduces Glial Scarring, Attenuates Posttraumatic Inflammation, and Promotes Neurite Outgrowth of Spinal Motor Neurons.** *Spine.* 2016; **41**(20): E1201–E1207.
[PubMed Abstract](#) | [Publisher Full Text](#)
44. Estrada V, *et al.*: **Long-lasting significant functional improvement in chronic severe spinal cord injury following scar resection and polyethylene glycol implantation.** *Neurobiol. Dis.* 2014; **67**: 165–179.
[PubMed Abstract](#) | [Publisher Full Text](#)
45. Marchand R, Woerly S: **Transected spinal cords grafted with in situ self-assembled collagen matrices.** *Neuroscience.* 1990; **36**(1): 45–60.
[PubMed Abstract](#) | [Publisher Full Text](#)
46. Shoichet MS, *et al.*: **Intrathecal drug delivery strategy is safe and efficacious for localized delivery to the spinal cord.** *Prog. Brain Res.* 2007; **161**: 385–392.
[PubMed Abstract](#) | [Publisher Full Text](#)
47. Wang Q, *et al.*: **A Thermosensitive Heparin-Poloxamer Hydrogel Bridges aFGF to Treat Spinal Cord Injury.** *ACS Appl. Mater. Interfaces.* 2017; **9**(8): 6725–6745.
[PubMed Abstract](#) | [Publisher Full Text](#)
48. Abu-Rub MT, *et al.*: **Nano-textured self-assembled aligned collagen hydrogels promote directional neurite guidance and overcome inhibition by myelin associated glycoprotein.** *Soft Matter.* 2011; **7**(6): 2770–2781.
[Publisher Full Text](#)
49. Page MJ, McKenzie JE, Bossuyt PM, *et al.*: **The PRISMA 2020 statement: an updated guideline for reporting systematic reviews.** *BMJ.* 2021; **372**: n71.
[Publisher Full Text](#)
50. Rahimi-Movaghar V, *et al.*: **Epidemiology of traumatic spinal cord injury in developing countries: a systematic review.** *Neuroepidemiology.* 2013; **41**(2): 65–85.
[PubMed Abstract](#) | [Publisher Full Text](#)
51. Zhou W, Blewitt M, Hobgood A, *et al.*: **Comparison of neurite growth in three dimensional natural and synthetic hydrogels.** *J. Biomater. Sci. Polym. Ed.* 2013; **24**(3): 301–314.
[PubMed Abstract](#) | [Publisher Full Text](#)
52. Assunção-Silva RC, *et al.*: **Hydrogels and cell-based therapies in spinal cord injury regeneration.** *Stem Cells Int.* 2015; **2015**: 1–24.
[PubMed Abstract](#) | [Publisher Full Text](#)
53. Xing H, Yin H, Sun C, *et al.*: **Preparation of an acellular spinal cord scaffold to improve its biological properties.** *Mol. Med. Rep.* 2019; **20**(2): 1075–1084.
[PubMed Abstract](#) | [Publisher Full Text](#)
54. Zhang N, Yan H, Wen X: **Tissue-engineering approaches for axonal guidance.** *Brain Res. Rev.* 2005; **49**(1): 48–64.
[PubMed Abstract](#) | [Publisher Full Text](#)
55. Little L, Healy KE, Schaffer D: **Engineering biomaterials for synthetic neural stem cell microenvironments.** *Chem. Rev.* 2008; **108**(5): 1787–1796.
[PubMed Abstract](#) | [Publisher Full Text](#)
56. Marchand R, *et al.*: **Evaluation of two cross-linked collagen gels implanted in the transected spinal cord.** *Brain Res. Bull.* 1993; **30**(3-4): 415–422.
[PubMed Abstract](#) | [Publisher Full Text](#)
57. Malafaya PB, Silva GA, Reis RL: **Natural-origin polymers as carriers and scaffolds for biomolecules and cell delivery in tissue engineering applications.** *Adv. Drug Deliv. Rev.* 2007; **59**(4-5): 207–233.
[Publisher Full Text](#)
58. Han Q, Sun W, Lin H, *et al.*: **Linear Ordered Collagen Scaffolds Loaded with Collagen-Binding Brain-Derived Neurotrophic Factor Improve the Recovery of Spinal Cord Injury in Rats.** *Tissue Eng. Part A.* Oct 2009; **15**: 2927–2935.
[PubMed Abstract](#) | [Publisher Full Text](#)
59. Shoichet MS: **Polymer scaffolds for biomaterials applications.** *Macromolecules.* 2010; **43**(2): 581–591.
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