Neurospine 2022;19(4):961-975.
https://doi.org/10.14245/ns.2244624.312

Neurospine
pISSN 2586-6583 eISSN 2586-6591

Review Article

Therapeutic Approaches Targeting Vascular Repair After Experimental Spinal Cord Injury: A Systematic Review of the Literature

Corresponding Author
Peter Vajkoczy
https://orcid.org/0000-0003-4350-392X

Department of Neurosurgery, Charité - Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany
Email: peter.vajkoczy@charite.de

Received: July 23, 2022
Revised September 5, 2022
Accepted: September 16, 2022

Laurens Roolfs[1,*], Vanessa Hubertus[1,*], Jacob Spinnen[2], Lennard K. Shopperly[2], Michael G. Fehlings[3], Peter Vajkoczy[1]

[1]Department of Neurosurgery, Charité – Universitätsmedizin Berlin and Berlin Institute of Health, Berlin, Germany
[2]Tissue Engineering Laboratory, Charité – Universitätsmedizin Berlin and Berlin Institute of Health, Berlin, Germany
[3]Division of Neurosurgery and Krembil Neuroscience Centre, Toronto Western Hospital, University Health Network and University of Toronto, Toronto, Canada

*Laurens Roolfs and Vanessa Hubertus contributed equally to this study as co-first authors.

See the commentary on "Therapeutic Approaches Targeting Vascular Repair After Experimental Spinal Cord Injury: A Systematic Review of the Literature" via https://doi.org/10.14245/ns.2245022.511.

Traumatic spinal cord injury (SCI) disrupts the spinal cord vasculature resulting in ischemia, amplification of the secondary injury cascade and exacerbation of neural tissue loss. Restoring functional integrity of the microvasculature to prevent neural loss and to promote neural repair is an important challenge and opportunity in SCI research. Herein, we summarize the course of vascular injury and repair following SCI and give a comprehensive overview of current experimental therapeutic approaches targeting spinal cord microvasculature to diminish ischemia and thereby facilitate neural repair and regeneration. A systematic review of the published literature on therapeutic approaches to promote vascular repair after experimental SCI was performed using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards. The MEDLINE databases PubMed, Embase, and OVID MEDLINE were searched using the keywords "spinal cord injury," "angiogenesis," "angiogenesis inducing agents," "tissue engineering," and "rodent subjects." A total of 111 studies were identified through the search. Five main therapeutic approaches to diminish hypoxia-ischemia and promote vascular repair were identified as (1) the application of angiogenic factors, (2) genetic engineering, (3) physical stimulation, (4) cell transplantation, and (5) biomaterials carrying various factor delivery. There are different therapeutic approaches with the potential to diminish hypoxia-ischemia and promote vascular repair after experimental SCI. Of note, combinatorial approaches using implanted biomaterials and angiogenic factor delivery appear promising for clinical translation.

Keywords: Spinal cord injury, Blood-spinal cord barrier, Vascular injury, Spinal cord regeneration, Biocompatible materials, Therapeutics

INTRODUCTION

Traumatic spinal cord injury (SCI) is one of the leading causes of disability and a major burden for healthcare systems. Current therapeutic strategies are limited to acute medical and surgical management and rehabilitation, as there are no therapies available to promote spinal cord regeneration.[1]

SCI results from a primary mechanical injury which is amplified by a secondary injury cascade to result in loss or disruption of neural elements and vascular structures. The traumatic vascular disruption in the injured spinal cord plays a key role in modulating secondary injury development by promoting local blood-spinal cord barrier (BSCB) breakdown, inflammation, and neuronal cell death as well as creating a hypoxic-ischemic

environment which can spread to initially intact regions.[1] The characterization of endogenous vascular regeneration following SCI-induced vascular injury has been the goal of some recent experimental studies, conducted mostly in rodents. Results show that vascular regeneration occurs spontaneously after SCI, following a definite time schedule – this regeneration process is however deficient and, due to an increased BSCB-permeability, even potentially detrimental to preserved neural tissue.[2-6] But even if this new vasculature is only partially functional, it provides guidance for regenerating axons and is thereby crucial for neural regeneration.[7,8] To find a way to improve vascular repair after SCI and restore a functional blood supply, thereby supporting neural regeneration, is one of the major challenges in experimental SCI research.

A multitude of experimental therapeutic approaches have been applied to restore functional vascularization, consisting of (1) the application of angiogenic factors, (2) genetic engineering therapy, (3) physical stimulation, (4) cell transplantation, and (5) biomaterials carrying various factor delivery.[9-11]

The aim of this systematic review is to rigorously summarize and evaluate the present state of research in this emerging field. We first outline a focused overview of SCI pathophysiology with an emphasis on vascular injury and endogenous vascular repair and then shift to an examination of current experimental therapeutic approaches to promote vascular repair with the prospect of future translation of innovations into clinical patient care.

MATERIALS AND METHODS

1. Approach to the Systematic Literature Review

We performed a systematic, qualitative review of the literature, by screening the established MEDLINE databases PubMed, Embase, and OVID MEDLINE. The main search terms included "spinal cord injury," angiogenesis," "angiogenesis inducing agents," and "tissue engineering," in combination with "rodent subjects." The search included no time limit. Articles in English were included, meeting the following criteria: experimental research, original studies, rodent subjects, therapeutic intervention, and focus on vascular injury and repair. The systematic literature search was conducted by one researcher from June 2021 to July 2021 and from May 2022 to June 2022. Data analysis was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A total of 614 articles were selected for review, of which 475 were excluded after screening as a result of not meeting the inclusion criteria. An additional 30 articles were excluded due to not meeting the inclusion criteria after full-text assessment for eligibility. For qualitative synthesis 111 articles were assessed in detail and included in this publication (Fig. 1).

2. Relevant Experimental Therapeutic Approaches According to the Literature Search

According to the systematic literature search, 5 main categories of therapeutic approaches to promote vascular repair in experimental SCI research were identified: (1) angiogenic factors, (2) genetic engineering, (3) physical stimulation, (4) cell transplantation, and (5) biomaterials carrying various factor delivery (Table 1).

RESULTS

1. PART 1: Pathophysiology of Traumatic SCI With Emphasis on Vascular Injury And Repair

1) Pathophysiology and its progression following SCI

SCI is characterized as a sudden mechanical force impacting the spinal cord, e.g., following a fall, vehicle accident, or sports-related injury. It is commonly comprised of both contusion and compression injury causing direct cell death, axonal shearing, and disruption of the microvasculature with traumatic bleeding. This primary injury is not accessible to treatment[1,12] and is immediately followed by a sustained secondary injury cascade.[13] This secondary injury spreads to formerly unaffected regions, leading to further spinal cord damage with the consequences of demyelination and axonal dieback.[2,3,14] The developing secondary injury can be divided into acute (first 48 hours), subacute (48 hours–14 days), intermediate (14 days to 6 months) and chronic phases (>6 months)[2,12] (Fig. 2).

2) Time course of BSCB disruption and restitution following SCI

The BSCB protects the spinal cord, as part of the central nervous system (CNS), from the periphery and maintains a homeostatic environment. The BSCB, formed by endothelial cells (ECs), astrocytic foot processes and pericytes as well as a basal lamina together with adjoining neurons comprise the neurovascular unit (NVU) (Fig. 2A). The unique cell-cell-contacts between ECs containing CNS-specific tight junctions (TJs) provide an immune privilege to the spinal cord compared to the periphery, restricting the passage of neurotoxic molecules and inflammatory cells.[2,15]

Following the primary injury, a localized direct disruption of the NVU damages the microvasculature directly surrounding

 https://doi.org/10.14245/ns.2244624.312

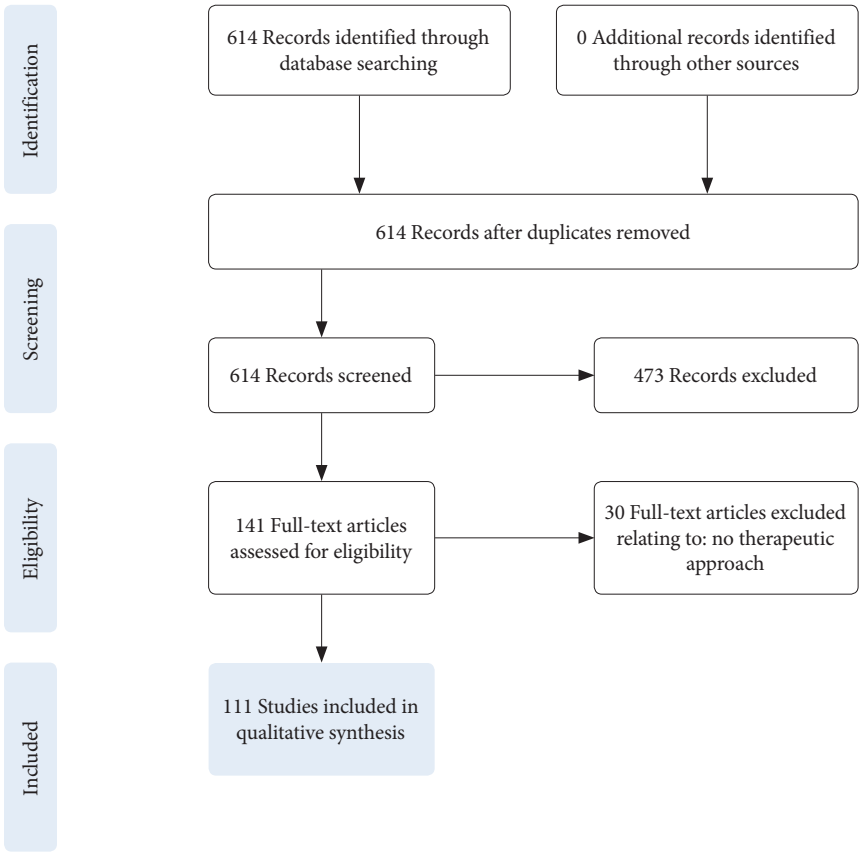


Fig. 1. Flow chart of the conducted literature review and the systematic synthesis according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for systematic reviews and meta-analyses.

Table 1. Therapeutic approaches for vascular repair after experimental spinal cord injury

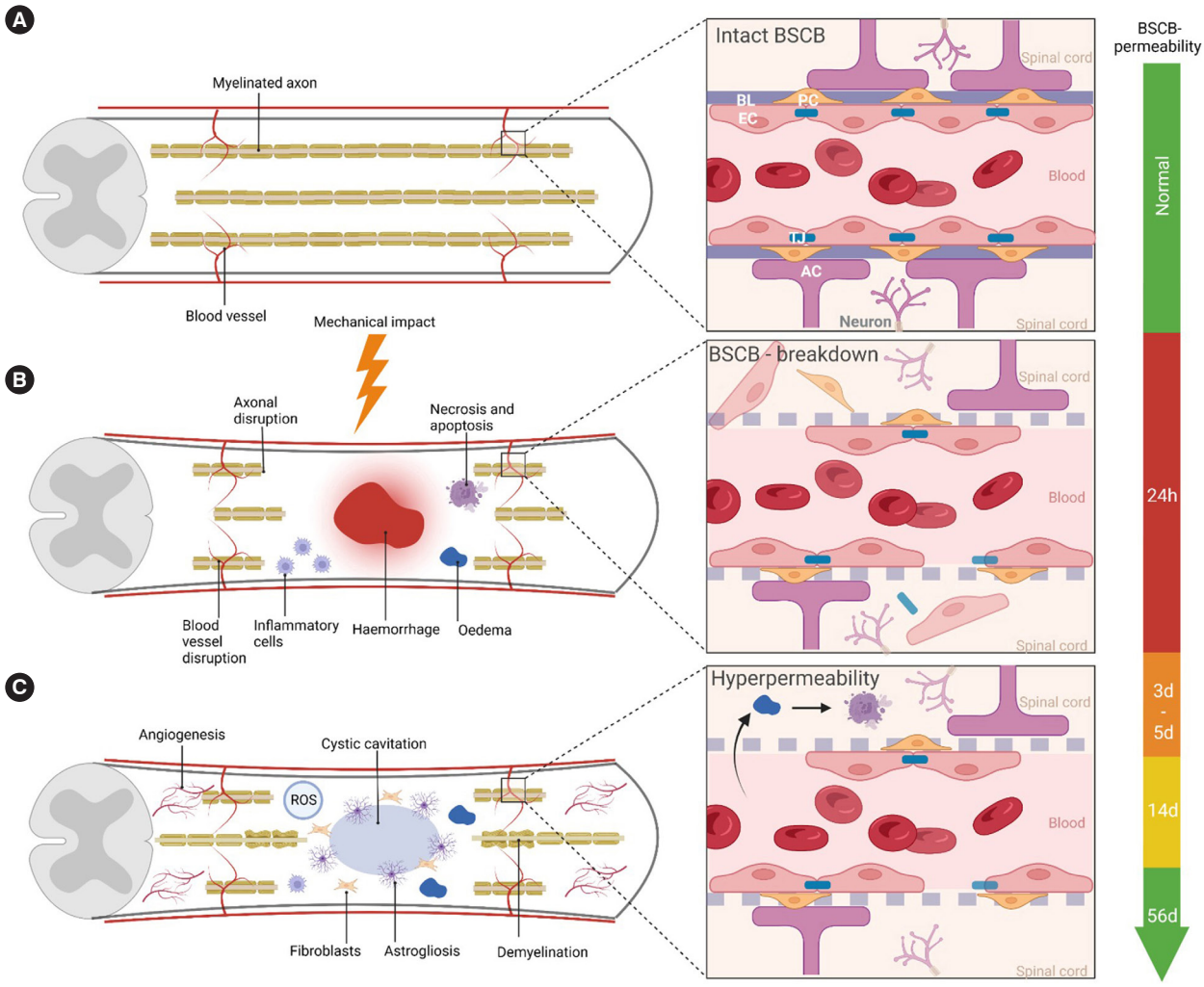
Therapeutic approaches	No. of included studies
1. Angiogenic factors	25
2. Genetic engineering	8
3. Physical stimulation	8
4. Cell transplantation	28
5. Biomaterial implantation	42

the injury site: Disruption of the protective cell-cell-contacts leads to altered cell permeabilization and consequent oedema formation, causing increased apoptotic and necrotic cell death[14,16,17] (Fig. 2B). These permeability changes not only lead to electrolyte influx and oedema, but to an influx of inflammatory cells (lymphocytes, macrophages, and neutrophils), as well as cytokines (tumor necrosis factor-α, interleukin [IL]-1β, IL-5) and vasoactive peptides. This immune response, commencing within the first minutes postinjury, leads to further oedema formation and thus tissue compression, resulting in further injury development spreading farther from the primary injury site.[2,15,18] These events further destabilize the BSCB and lead to a release of reactive oxygen species, resulting in the dysfunction of the NVU in formerly unharmed regions.[2,3,14] Correlating with these mechanisms, the first peak in BSCB-permeability in the penumbra zone is reached 24-hour postinjury, followed by a smaller peak after 3–5 days.[4,5]

Most of the BSCB function is believed to be reinstated after 14 days[4,19] (Fig. 2C). However, experimental studies show that the permeability for small molecules is increased up to the chronic phase of SCI, for as long as 56-day postinjury.[6]

3) Endogenous revascularization after SCI

The major form of vascular regeneration in the spinal cord is known to be angiogenesis, with a smaller part displayed by postnatal vasculogenesis. Angiogenesis is defined by the formation of blood vessels out of pre-existing vessels, whilst vasculogenesis describes the formation of new vessels.[20] The hypoxic milieu after SCI results in the release of angiogenic factors from the injury site. Endogenous revascularization following SCI is



Systemic effects: Hypotension, reduced cardiac output, neurogenic shock, infarction

A **Normal Spinal cord:** Spinal cord (SC) with an intact BSCB formed by endothelial cells (EC), astrocytic food processes (AC), pericytes (PC), a basal lamina (BL) and tight junctions (TJ)

B **Acute (0 - 48h):** Mechanical injury, Bleeding, Direct cell death, Microvascular disruption, Hypoxia, Ischemia
BSCB: High permeability due to disruption following the primary injury (minutes - 24h), Peek of permeability due to grave disruption following secondary injury (24h), High permeability due to prolonged cell death and increased endogenous angiogenesis (24h - 3d)

C **Subacute - Chronic (48h - >6m):** BSCB disruption with pathological permeability, Loss of electrolyte homeostasis, Influx of immune cells (Lymphocytes, Macrophages, Neutrophils), Activation of cytokines and vasoactive peptides, Apoptosis and necrosis resulting in the release of free radicals (ROS) and excitotoxity causing oedema formation, SC swelling and tissue compression, Loss of autoregulation, Progressive neural tissue loss, Formation of cystic cavities and glial scar, Wallerian degeneration
BSCB: Second peek through endogenous angiogenesis (3 - 5d), Moderate permeability due to restitution and stabilization (5 - 14d), Low permeability with complete restitution for bigger molecules (14 - 56d), Low permeability with altered function suspected (> 56d)

Fig. 2. (A-C) Pathophysiology of spinal cord injury and the neurovascular unit in health and its disruption. SC, spinal cord; BSCB, blood – spinal cord barrier; EC, endothelial cells; AC, astrocytic foot processes; PC, pericyte; BL, basal lamina; TJ, tight junction; ROS, reactive oxygen species; h, hours; d, days; w, weeks; m, months.

https://doi.org/10.14245/ns.2244624.312

expected to occur during the first week postinjury, and to disappear shortly afterwards.[21-24] Importantly, the second, smaller peak in BSCB-permeability correlates with the peak of endogenous revascularization after SCI. As new vessels form due to angiogenesis or vasculogenesis, this young vasculature does not necessarily possess a functional BSCB. As some parts of this newly formed vasculature gain a functional barrier and promote a functional NVU during its genesis, other parts never do.[4,15] This results in the increased extravasation of molecules and fluids causing oedematous swelling, inflammation, and necrotic and apoptotic cell death and thus exacerbating the secondary injury[2,3,5,25] (Fig. 2B).

4) Regenerative potential facilitated by vascular repair after SCI

As the spinal cord remains in a state of chronic hypoxia and ischemia postinjury, reinstatement of a steady tissue perfusion would be desirable. This was shown by previous research indicating that neovascularization is crucial for axon regeneration, as these were shown to grow along blood vessels. This suggests that the developing vasculature guides axonal sprouting after injury.[7,8] However, the increased permeability for molecules otherwise excluded from the selective CNS environment might provide a unique chance for therapeutic intervention, with a potential window of opportunity displayed over the first days postinjury.[4,26]

To address this multifaceted pathophysiology, several aspects of SCI must be taken into account to allow for tissue regeneration: Inhibition of the inflammatory response and sufficient perfusion might limit the secondary injury, while prevention of the glial scar formation could enable neural regeneration. Therefore, combinatorial approaches accounting for these mechanisms together in the adequate timespan might be promising for spinal cord repair.

2. PART 2: Experimental Therapeutic Approaches To Promote Vascular Repair

According to the systematic literature search, several experimental therapeutic approaches promising to diminish hypoxia and improve spinal cord microvasculature after SCI exist. In summary, 5 categories of experimental therapy were identified: (1) delivery of angiogenic factors, (2) genetic engineering, (3) physical stimulation, (4) cell transplantation, and (5) biomaterials carrying various factor delivery[9] (Fig. 3). In the following section of this study, we aim to provide a comprehensive overview of the literature in this field, comparing and discussing the most promising approaches for clinical translation.

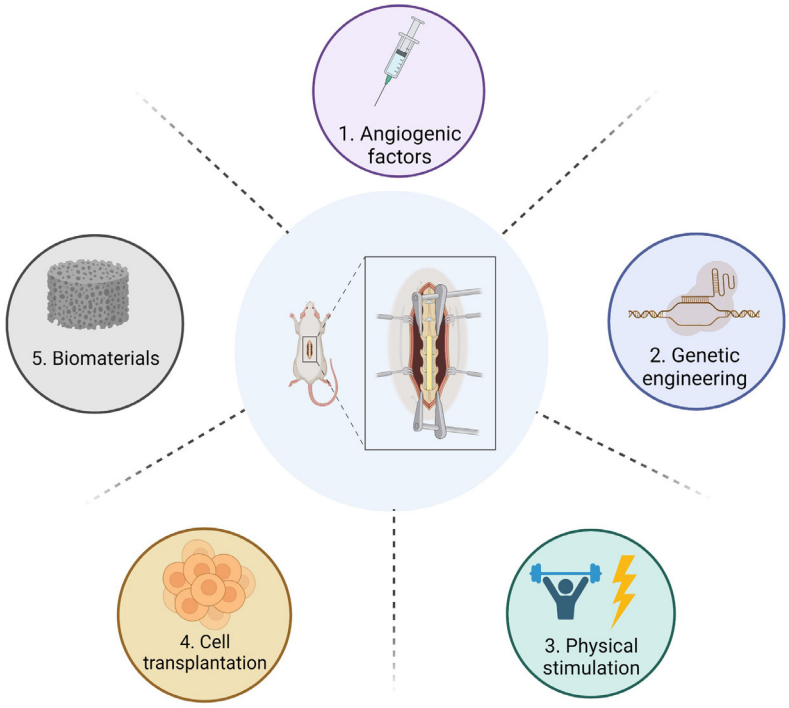


Fig. 3. Therapeutic approaches for vascular repair after experimental spinal cord injury: (1) angiogenic factors, (2) genetic engineering, (3) physical stimulation, (4) cell transplantation, and (5) biomaterials carrying various factor delivery.

1) Angiogenic factors

Many different therapeutic agents evoking an angiogenic answer, either directly or indirectly, have been investigated in experimental SCI models, often in combination with the implantation of biomaterials. In the following, we give an overview of different angiogenic factors and their previous experimental use in SCI research (Fig. 4A).

The therapeutic effects of vascular endothelial growth factor (VEGF) in SCI have been variable. VEGF-A is used in many studies and is a promising growth factor that binds to the tyrosine kinase receptors (VEGFRs) 1 and 2, resulting in the proliferation of ECs and angiogenesis. VEGF-A may also have neurotrophic, neuroprotective, and neuroproliferative effects.[27] A common application of VEGF-A in experimental SCI is the direct injection into the lesion site which results in increased blood vessel density and blood vessel diameter.[28-29] This effect has been confirmed in studies of controlled release of VEGF from biomaterials, such as gel foam.[30] On the downside, increased BSCB-permeability was observed after application of VEGF-A indicating the growth of non- or only partially functional blood vessels. Changes in vessel architecture, resulting in tumor-like blood vessels, were described in human studies.[27,31]

To improve the angiogenic and neurotrophic effect through the application of VEGF, a release from biomaterials in combination with other growth factors such as fibroblast growth factor-2 (FGF2),[32] angiopoietin 1 and FGF2,[33] or brain-derived

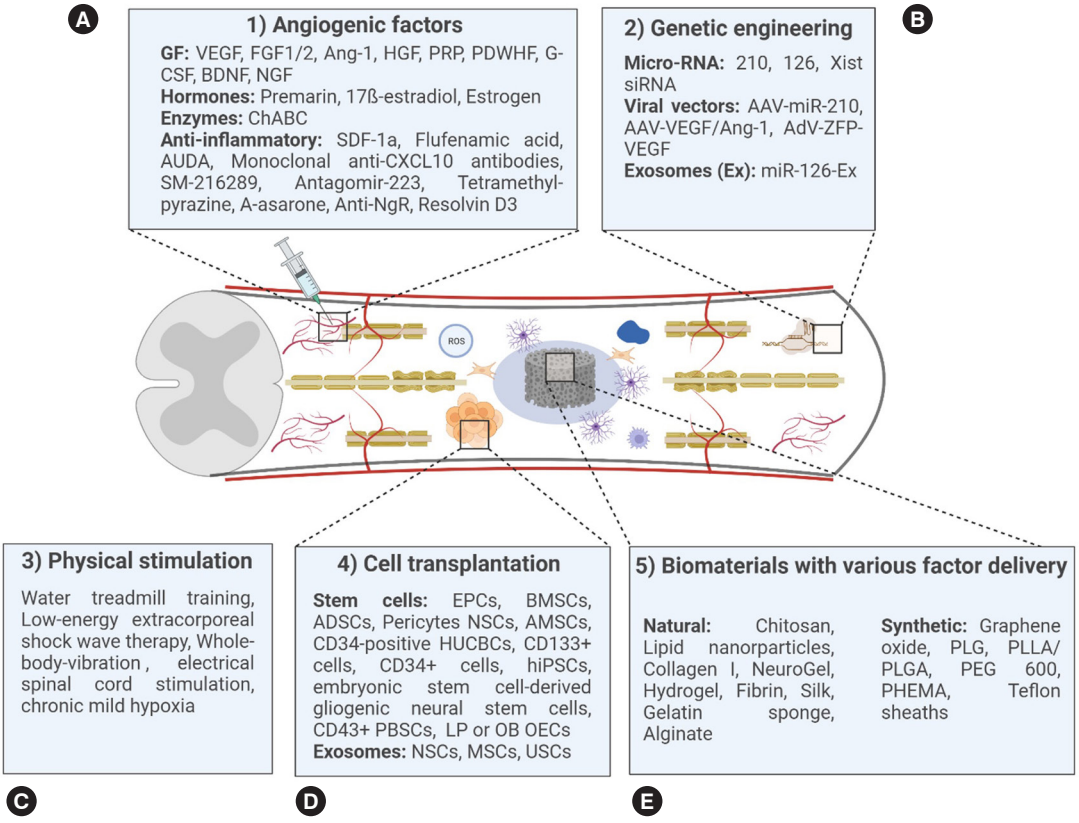


Fig. 4. (A-E) Overview of therapeutic approaches inducing spinal cord repair after experimental spinal cord injury. PLG(A), polylactide-co-glycolide (acid); PLLA, poly-l-lactic acid; PEG600, polyethylene glycol 600; PHEMA, poly(2-hydroxyethyl methacrylate); VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor; Ang-1, angiopoietin-1; HGF, hepatocyte growth factor; PRP, platelet-rich plasma; PDWHF, platelet-derived wound healing formula; G-CSF, granulocyte colony-stimulating factor; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor; ChABC, chondroitinase ABC; SDF-1a, stromal cell-derived factor-1 alpha; AUDA, soluble epoxide hydrolase inhibitor; Anti-NgR, anti-nogo receptor antibody; Xist, X-inactive specific transcript; AAV, adeno-associated virus; AdV-ZFP-VEGF, adenoviral vector with zinc-finger protein coding for VEGF; EPC, endothelial progenitor cell; BMSC, bone mesenchymal stem cell; ADSC, adipose-derived stem cell; HUCBC, human umbilical cord blood stem cell; NSC, neural stem cell; AMSC, amniotic mesenchymal stem cell; hiPSC, human-induced pluripotent stem cell; PBSC, peripheral blood stem cell; LP OEC, lamina propria-derived olfactory ensheathing cell; OB OEC, olfactory bulb-derived ensheathing cell; MSC, mesenchymal stem cell; USC, human urine stem cell.

https://doi.org/10.14245/ns.2244624.312

neurotrophic factor[34] was explored, also resulting in increased blood vessel density and associated localization of mature oligodendrocytes and axons.

FGF2 has also been frequently applied in experimental SCI. FGF2 was found to be highly overexpressed after SCI[35] and FGF2 is known to play a role in proliferation, differentiation and BSCB-integrity.[36,37] The application of FGF2 via biomaterials has been shown to increase the number of blood vessels,[38-40] whereas no significant vascular changes were observed when FGF2 was infused at the injury site.[41]

Further angiogenic factors that were previously tested for application in experimental SCI are hepatocyte growth factor (HGF) and the whole blood concentrates platelet-rich plasma (PRP) and platelet-derived wound healing formula (PDWHF). The number of blood vessels has been shown to increase after the application of activated PRP,[42] PDWHF alone, or PDWHF in combination with nerve growth factor and of HGF.[42-44]

Apart from these often-applied factors, other factors such as hormones, especially oestrogen,[45] enzymes,[46] and a multitude of anti-inflammatory substances[47] listed in (Fig. 4A) also showed potential to induce angiogenesis or to increase BSCB-integrity following SCI.

2) Genetic engineering

Genetic engineering is not widely used in experimental SCI but was shown to hold the potential to increase vascular repair and functional outcome after SCI[26,48-51] (Fig. 4B). Proofs-of-concept were brought forward in experiments using RNAs like micro-RNA-210,[48] micro-RNA-126 contained in exosomes[49] and X-inactive specific transcript-RNA.[50] The endogenous overexpression of VEGF using viral vectors also increased the number of blood vessels at the injury site.[26,51] The combination of VEGF165 and Ang-1 using an adeno-associated viral vector furthermore decreased the BSCB-permeability at the injury site.[51] Therefore, genetic engineering could become a promising approach to support vascular repair after experimental SCI.[51]

3) Physical stimulation

As the only noninvasive therapeutic approach, physical stimulation was also shown to increase angiogenesis and functional outcome after experimental SCI. Methods under investigation include water treadmill training,[52] low-energy extracorporeal shock wave therapy,[53] whole-body vibration,[54] chronic mild hypoxia,[55] and electric stimulation[56] (Fig. 4C). Especially water treadmill training seems to improve the regeneration of functional blood vessels and improve functional outcome after SCI.[52] Using low-energy extracorporeal shock wave therapy, not only increased vessel density but also enhanced functional outcomes suggesting that the regenerative potential is higher than the risk of further damage to the spinal cord. Electrical stimulation has made tremendous progress as experimental therapy in both preclinical and clinical studies, although only few studies focus on the evaluation of angiogenic effects. The application of transspinal direct current stimulation increases the blood temporarily and is able to stimulate cell proliferation and migration.[56] Another experimental therapeutic approach is the induction of chronic mild hypoxia after SCI. The induction of mild hypoxia results in vascular remodelling, with endothelial proliferation and vascular expansion being more pronounced in the white matter. Interestingly, newly formed blood vessels grow towards neurons and show the upregulation of TJ proteins, indicating the enhanced formation of functional blood vessels.[55] These results are promising to increase angiogenic repair after SCI, but further research needs to address the effect of these approaches in the intermediate and chronic injury phase.

4) Cell transplantation

Cell transplantation is widely used after experimental SCI. Stem cells of different origins can result in a significant increase in angiogenesis and have previously been injected, infused, or implanted following SCI with the result of potently increasing the angiogenic response and improving functional outcome (Fig. 4D). Endothelial progenitor cells (EPCs),[57] bone marrow mesenchymal stem cells,[58] adipose-derived stem cells,[59] human umbilical cord blood stem cells,[60] neural stem cells (NSCs),[61] amniotic mesenchymal stem cells,[62,63] human-induced pluripotent stem cells,[64,65] peripheral blood stem cells,[66] lamina propria-derived olfactory ensheathing cells, olfactory bulb-derived ensheathing cells,[67] and mesenchymal stem cells (MSCs)[68] increase angiogenesis when applied after SCI by expressing a wide range of growth factors and modulating the microenvironment. The effect of these cell types is shown in Table 2.

As not all implanted cells survive the hypoxic environment at and around the injury site, cell-based therapies to date can only unfold a fraction of their potential.[69] To overcome this limitation, other strategies rely on indirectly utilizing the therapeutic potential of stem cells. Especially the isolation of exosomes from different stem cells and their injection after experimental SCI showed similar results in terms of angiogenesis and functional outcome.[70-72] Exosomes derived from many different cell types result in increased angiogenesis after injection. Amongst

Table 2. Study overview of experimentally transplanted cells to promote vascular repair after experimental spinal cord injury (SCI)

Species	SCI model	Method	Outcome	References
Rat	T10 Contusion	EPCs	Increased axonal and blood vessel regeneration with functional improvement.	Wang et al.[57] (2018)
Rat	T10 Contusion	BMSCs overexpressing VEGF	Increased axonal and blood vessel regeneration with functional improvement. Increased VEGF protein expression.	Liu et al.[58] (2020)
Rat	T8, 9 Compression	ADSCs	Increased blood vessel regeneration, vascular branching, and axonal regeneration. Increased formation of functional blood vessels, which are associated with blood vessels. Functional improvement.	Menezes et al.[107] (2020)
Rat	T10 Contusion	HUCBCs	Increased blood vessel regeneration with functional improvement.	Ning et al.[60] (2013)
Rat	T8 – 10 Contusion	NSCs	Increased blood vessel regeneration, VEGF protein expression, and remyelination with functional improvement.	Li et al.[61] (2014)
Rat	T9 Contusion	AMSCs	Increased blood vessel regeneration, axonal regeneration, VEGF protein expression, and functional improvement. The BSCB – disruption was reduced at 7 days indicating the regeneration of functional vessels.	Zhou et al.[62,63] (2016, 2020)
Rat	T10 Contusion	hiPSCs	Increased blood vessel regeneration, myelination, and axonal regeneration with functional improvement. Transplanted cells differentiated into astrocytes, oligodendrocytes, and neurons which integrated with the host neural circuitry.	Nori et al.[64] (2011)
Mice	T9 Contusion	PBSCs	Increased blood vessel regeneration, myelination, and axonal regeneration with functional improvement.	Takahashi et al.[66] (2016)
Rat	C3, 4 Dorsolateral crush	LP and OB OECs	Increased axonal and blood vessel regeneration. The motor function was not assessed.	Richter et al.[67] (2005)
Rat	T8 Contusion	MSCs	Increased axonal and blood vessel regeneration with no functional improvement.	Kumagai et al.[68] (2013)

EPC, endothelial progenitor cell; BMSC, bone mesenchymal stem cell; VEGF, vascular endothelial growth factor; ADSC, adipose-derived stem cell; HUCBC, human umbilical cord blood stem cell; NSC, neural stem cell; AMSC, amniotic mesenchymal stem cell; hiPSC, human-induced pluripotent stem cell; PBSC, peripheral blood stem cell; LP OEC, lamina propria-derived olfactory ensheathing cell; OB OEC, olfactory bulb-derived ensheathing cell; MSC, mesenchymal stem cell.

these are NSC-derived exosomes,[70] exosomes derived from human placenta-derived MSCs,[71] and mesenchymal stromal cells-derived exosomes.[72]

Another promising strategy is the combinatorial release of stem cells via biomaterials to enhance cell survival at the injury site by modulating the environment and by providing guidance for the regenerating tissue.[69,73]

5) Biomaterials carrying various factor delivery

Biomaterials are materials engineered to interact with biological tissue and can be divided into natural materials sourced from plants or animals, synthetic materials and hybrid biomaterial combinations.[10] Many different biomaterials improve angiogenesis when implanted in combination with stem cells or angiogenic factors or even without concomitant application of other therapeutics. The implantation of biomaterials alone already holds the potential to support the ingrowth of blood vessels into the lesion site. This angiogenic potential was shown using many different biomaterials, such as a reduced graphene oxide scaffold,[74] an oxygen-generating hydrogel scaffold,[75,76] a nanofiber-hydrogel composite,[77] "NeuroGel,"[78] an aligned fibrin hydrogel,[79] and a collagen type I scaffold[80] (Fig. 4E). Biomaterials can be combined with other therapeutics at will, such as angiogenic factors and/or stem cells to potentiate their regenerative potential.

Both natural and synthetic biomaterials were previously used successfully in animal studies to promote vascular repair after SCI with different advantages and disadvantages. Natural biomaterials are often intrinsically biodegradable and therefore

https://doi.org/10.14245/ns.2244624.312

Table 3. Study overview of experimentally used biomaterials to promote vascular repair after experimental spinal cord injury (SCI)

Species	SCI model	Method	Outcome	References
Natural biomaterials				
Rat	Lateral hemisection	NSCs, EPCs, hydrogel	NSCs and blood vessels infiltrate the hydrogel functional improvement	Marrotte et al.[87] (2021)
Rat	Lateral hemisection	AFG/fSAP hydrogel	Increased axonal regeneration with more myelinated axons, blood vessel regeneration at the lesion site with a larger diameter, increased vessel density, blood vessels and axons colocalized, functional improvement	Man et al.[101] (2021)
Rat	Compression injury	CORM-2-lipid nanoparticles	Increased formation of functional blood vessels and reduced BSCB-permeability at 1 day postinjury, functional improvement	Joshi et al.[76] (2020)
Synthetic biomaterials				
Rat	Lateral hemisection	rGO scaffold	Regeneration of functional blood vessels growing inside the scaffold, association with regenerating axons	López-Dolado et al.[74] (2016)
Rat	Transection	DPSCs PLLA/PLGA-scaffold	Increase in axonal regeneration with myelin sheaths and angiogenesis at the injury site, vessel density increased in the rubrospinal tract, spinothalamic tract, dorsal column, and spinocerebellar tract, but not in corticospinal tract, functional improvement	Guo et al.[84] (2020)
Rat	Contusion	VEGF, Ang-1, FGF2, PLGA-microspheres	Increased angiogenesis and neural regeneration with axons and mature oligodendrocytes mostly associated with blood vessels, functional improvement	Yu et al.[33] (2016)

NSC, neural stem cell; EPC, endothelial progenitor cell; AFG, aligned fibrin hydrogel; fSAP, functionalized self-assembling peptides derived from VEGF and brain-derived neurotrophic factor; CORM-2, carbon monoxide-releasing molecule-2; BSCB, blood-spinal cord barrier; rGO, reduced graphene oxide; DPSC, dental pulp stem cell; PLLA, poly-L-lactic acid; PLGA, polylactide-co-glycolide acid; VEGF, vascular endothelial growth factor; Ang-1, angiopoietin-1; FGF2, fibroblast growth factor 2.

useful to modify the delayed release of angiogenic factors or cells.[81] Synthetic biomaterials, unless modified accordingly, are nondegradable and guarantee more structural and long-lasting stability as well as reduced batch-to-batch variance. For implantation and combination with factor delivery, they can be sterilized and chemically modified to allow for an optimal release profile[10,81] (Table 3). Due to their high modifiability, both natural and synthetic biomaterials can be adapted to provide optimal release kinetics of incorporated factors at a defined location.[10] Release kinetics can be modified by using the intrinsic degradation rate of the biomaterial itself[82] or noncovalent interactions between the incorporated therapeutics and the biomaterial.[40]

After implantation or injection, biomaterials can occupy the space of a posttraumatic cavity and provide a cell-friendly environment with reduced infiltration of inflammatory cells.[77,81] Therefore, biomaterials are often used in combination with stem cells, which highly depend on such an environment.[83]

Exemplary, the number and density of blood vessels could be increased after implantation of an oligopolyethylene-glycol-fumarate-hydrogel combined with Rapamycin and Schwann-cells,[83] of a prevascularized poly-L-lactic acid (PLLA)–polylactide-co-glycolide acid (PLGA) scaffold containing dental pulp stem cells,[84] a fibrous porous silk scaffold containing human umbilical vein ECs,[85] a hydrogel PLGA-scaffold containing NSCs and ECs,[73] a gelatine sponge containing MSCs,[69] and a PLGA-scaffold containing human MSCs.[86] The implantation of a hydrogel containing NSCs and EPCs also increased the formation of blood vessels inside the scaffold.[87] These findings show the great potential of combinatorial approaches using biomaterials containing angiogenic factors and/or stem cells of different types.

The application of biomaterials to promote vascular repair after SCI varies in time, location, and mode of application in the analysed studies (Table 3, Supplementary Table 1). In nearly all studies showing vascular changes, biomaterials are applied directly after induction of the injury with monitoring for up to 8 months.[30,32-34,38-40,43,44,47,57,69,73-76,78,80,82-104] Only one study reports an increased blood vessel density after the implantation of a nanofiber-hydrogel composite 3 days after injury.[77] Biomateri-

als are mostly applied at the injury site as scaffolds replacing the lesion after implantation[32,34,38,40,43,44,47,69,73,74,78,80,83-90,92-94,96-105] or injection[33,75,77,82,95] with only a few hydrogels being implanted on top of the injured spinal cord[30,39,91] or injected systemically.[76]

POTENTIAL FOR CLINICAL IMPLEMENTATION

Taken together, all 5 experimental approaches discussed in this review show the potential to improve vascular repair and angiogenesis. The application of angiogenic factors (1) is a well-studied approach. Especially growth factors like VEGF have shown a promising potential to regenerate functional blood vessels. Genetic engineering (2) allows for direct activation of the endogenous expression of VEGF and other growth factors. Even if it is not applied as frequently as other approaches after SCI, it holds the potential to regenerate functional blood vessels. As physical stimulation techniques (3) also displayed the ability to induce vascular repair, they might be a useful supplementary therapy in a clinical setting as soon as intensive rehabilitation is possible. Cell transplantation (4) is another promising strategy to regenerate functional blood vessels after traumatic SCI, especially as they can be taken from a variety of sources. Their potential is inhibited by the toxic environment, which needs to be overcome to allow the cells to integrate at the injury site. The implantation of cells still poses a promising approach when combined with the implantation of biomaterials (5). These materials can be taken from many sources and are easily modifiable. Some have an inherent angiogenic potential and are biodegradable. As they can be modified to release incorporated therapeutics in the desired time frame at defined locations and provide guidance for regenerating axons, these combinatorial approaches seem promising for future research and potential clinical implementation. But before implementing promising biomaterials into clinical trials, several questions need to be addressed. For most biomaterials, especially when integrated in a combinatorial approach, the exact degradation time in SCI is neither known for humans nor for animals. As degradation byproducts might cause immunological reactions, biomaterials need to be actively characterized in preclinical and clinical studies.[106] Furthermore, most of the biomaterials summarized are solid materials filling a transection or hemisection injury, but contusion SCI is most common clinically. This and the overall limited comparability from controlled animal models into the individual human SCI makes it difficult to translate the results of preclinical studies into the design of clinical trials and shows the need for using clinically relevant SCI animal models with contusion or compression injuries.

Before applying these approaches in a clinical setting, future research needs to evaluate the ideal combinations to accurately address the multifaceted pathophysiology and the time course of BSCB de- and regeneration to allow for the regeneration of functional blood vessels as a basis for neural regeneration.

CONCLUSION

SCI is characterized by the injury of both neural and vascular components and results in extensive tissue loss. The disruption of the vasculature and its insufficient regeneration with a prolonged state of BSCB-permeability exacerbate the primary injury by amplification of secondary injury mechanisms. To restore a functional vasculature to prevent neural loss and to promote neural regeneration is one of the most important challenges in SCI research. Several therapeutic approaches show an improved vascularization after SCI, like the application of angiogenic factors, genetic engineering, physical stimulation, cell transplantation, and biomaterials carrying various factor delivery. Combinatorial approaches, like implanted biomaterials with the ability to release angiogenic factors or therapeutic cells in a temporally and spatially controlled manner seem most promising to restore functional vasculature and to be translatable into clinical patient care in the future.

NOTES

Supplementary Material: Supplementary Table 1 can be found via https://doi.org/10.14245/ns.2244290.145.

Supplementary Table 1. Complete list of studies using biomaterials to promote vascular repair after spinal cord injury identified by the systematic literature search.

Conflict of Interest: The authors have nothing to disclose.

Funding/Support: This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author Contribution: Conceptualization: LR, VH, MGF, PV; Data curation: LR, VH; Formal analysis: LR, VH; Project administration: VH, MGF; Visualization: LR; Writing - original draft: LR, VH; Writing - review & editing: VH, JS, LKS, MGF

Acknowledgments: Figures were created using BioRender.com.

ORCID

Laurens Roolfs: 0000-0002-7769-8844
Vanessa Hubertus: 0000-0002-2653-5818
Jacob Spinnen: 0000-0002-6726-2860
Lennard K. Shopperly: 0000-0001-7685-9223
Michael G. Fehlings: 0000-0002-5722-6364
Peter Vajkoczy: 0000-0003-4350-392X

REFERENCES

1. Ahuja CS, Nori S, Tetreault L, et al. Traumatic spinal cord injury-repair and regeneration. Neurosurgery 2017;80:S9-22.
2. Tator CH. Review of experimental spinal cord injury with emphasis on the local and systemic circulatory effects. Neurochirurgie 1991;37:291-302.
3. Tator CH. Update on the pathophysiology and pathology of acute spinal cord injury. Brain Pathol 1995;5:407-13.
4. Figley SA, Khosravi R, Legasto JM, et al. Characterization of vascular disruption and blood-spinal cord barrier permeability following traumatic spinal cord injury. J Neurotrauma 2014;31:541-52.
5. Ng MT, Stammers AT, Kwon BK. Vascular disruption and the role of angiogenic proteins after spinal cord injury. Transl Stroke Res 2011;2:474-91.
6. Sundberg LM, Herrera JJ, Narayana PA. In vivo longitudinal MRI and behavioral studies in experimental spinal cord injury. J Neurotrauma 2010;27:1753-67.
7. Bearden SE, Segal SS. Microvessels promote motor nerve survival and regeneration through local VEGF release following ectopic reattachment. Microcirculation 2004;11:633-44.
8. Ohab JJ, Fleming S, Blesch A, et al. A neurovascular niche for neurogenesis after stroke. J Neurosci 2006;26:13007-16.
9. Yao C, Cao X, Yu B. Revascularization after traumatic spinal cord injury. Front Physiol 2021;12:631500.
10. Harvey AR, Lovett SJ, Majda BT, et al. Neurotrophic factors for spinal cord repair: which, where, how and when to apply, and for what period of time? Brain Res 2015;1619:36-71.
11. Gadot R, Smith DN, Prablek M, et al. Established and emerging therapies in acute spinal cord injury. Neurospine 2022;19:283-96.
12. Ahuja CS, Wilson JR, Nori S, et al. Traumatic spinal cord injury. Nat Rev Dis Primers 2017;3:17018.
13. Allen AR. Surgery of experimental lesion of spinal cord equivalent to crush injury of fracture dislocation of spinal column: a preliminary report. JAMA 1911;LVII:878-80.
14. Tator CH, Koyanagi I. Vascular mechanisms in the pathophysiology of human spinal cord injury. J Neurosurg 1997;86:483-92.
15. Mautes AE, Weinzierl MR, Donovan F, et al. Vascular events after spinal cord injury: contribution to secondary pathogenesis. Phys Ther 2000;80:673-87.
16. Ling X, Bao F, Qian H, et al. The temporal and spatial profiles of cell loss following experimental spinal cord injury: effect of antioxidant therapy on cell death and functional recovery. BMC Neurosci 2013;14:146.
17. Lou J, Lenke LG, Ludwig FJ, et al. Apoptosis as a mechanism of neuronal cell death following acute experimental spinal cord injury. Spinal Cord 1998;36:683-90.
18. Sandler AN, Tator CH. Review of the effect of spinal cord trama on the vessels and blood flow in the spinal cord. J Neurosurg 1976;45:638-46.
19. Noble LJ, Wrathall JR. Distribution and time course of protein extravasation in the rat spinal cord after contusive injury. Brain Res 1989;482:57-66.
20. Risau W, Flamme I. Vasculogenesis. Annu Rev Cell Dev Biol 1995;11:73-91.
21. Casella GT, Marcillo A, Bunge MB, et al. New vascular tissue rapidly replaces neural parenchyma and vessels destroyed by a contusion injury to the rat spinal cord. Exp Neurol 2002;173:63-76.
22. Hagg T, Oudega M. Degenerative and spontaneous regenerative processes after spinal cord injury. J Neurotrauma 2006;23:264-80.
23. Loy DN, Crawford CH, Darnall JB, et al. Temporal progression of angiogenesis and basal lamina deposition after contusive spinal cord injury in the adult rat. J Comp Neurol 2002;445:308-24.
24. Ritz MF, Graumann U, Gutierrez B, et al. Traumatic spinal cord injury alters angiogenic factors and TGF-Beta1 that may affect vascular recovery. Curr Neurovasc Res 2010;7:301-10.
25. Yip PK, Malaspina A. Spinal cord trauma and the molecular point of no return. Mol Neurodegener 2012;7:6.
26. Figley SA, Liu Y, Karadimas SK, et al. Delayed administration of a bio-engineered zinc-finger VEGF-A gene therapy is neuroprotective and attenuates allodynia following traumatic spinal cord injury. PLoS One 2014;9:e96137.
27. Greenberg DA, Jin K. From angiogenesis to neuropathology. Nature 2005;438:954-9.

28. Widenfalk J, Lipson A, Jubran M, et al. Vascular endothelial growth factor improves functional outcome and decreases secondary degeneration in experimental spinal cord contusion injury. Neuroscience 2003;120:951-60.
29. van Neerven S, Joosten EA, Brook GA, et al. Repetitive intrathecal VEGF(165) treatment has limited therapeutic effects after spinal cord injury in the rat. J Neurotrauma 2010;27:1781-91.
30. Patel CB, Cohen DM, Ahobila-Vajjula P, et al. Effect of VEGF treatment on the blood-spinal cord barrier permeability in experimental spinal cord injury: dynamic contrast-enhanced magnetic resonance imaging. J Neurotrauma 2009;26:1005-16.
31. Benton RL, Whittemore SR. VEGF165 therapy exacerbates secondary damage following spinal cord injury. Neurochem Res 2003;28:1693-703.
32. De Laporte L, des Rieux A, Tuinstra HM, et al. Vascular endothelial growth factor and fibroblast growth factor 2 delivery from spinal cord bridges to enhance angiogenesis following injury. J Biomed Mater Res A 2011;98:372-82.
33. Yu S, Yao S, Wen Y, et al. Angiogenic microspheres promote neural regeneration and motor function recovery after spinal cord injury in rats. Sci Rep 2016;6:33428.
34. Wen Y, Yu S, Wu Y, et al. Spinal cord injury repair by implantation of structured hyaluronic acid scaffold with PLGA microspheres in the rat. Cell Tissue Res 2016;364:17-28.
35. Zai LJ, Yoo S, Wrathall JR. Increased growth factor expression and cell proliferation after contusive spinal cord injury. Brain Res 2005;1052:147-55.
36. Zhu H, Yang A, Du J, et al. Basic fibroblast growth factor is a key factor that induces bone marrow mesenchymal stem cells towards cells with Schwann cell phenotype. Neurosci Lett 2014;559:82-7.
37. Ye LB, Yu XC, Xia QH, et al. Regulation of caveolin-1 and junction proteins by bFGF contributes to the integrity of blood-spinal cord barrier and functional recovery. Neurotherapeutics 2016;13:844-58.
38. Patist CM, Mulder MB, Gautier SE, et al. Freeze-dried poly(D,L-lactic acid) macroporous guidance scaffolds impregnated with brain-derived neurotrophic factor in the transected adult rat thoracic spinal cord. Biomaterials 2004;25:1569-82.
39. Kang CE, Baumann MD, Tator CH, et al. Localized and sustained delivery of fibroblast growth factor-2 from a nanoparticle-hydrogel composite for treatment of spinal cord injury. Cells Tissues Organs 2013;197:55-63.
40. Shang J, Qiao H, Hao P, et al. bFGF-sodium hyaluronate collagen scaffolds enable the formation of nascent neural networks after adult spinal cord injury. J Biomed Nanotechnol 2019;15:703-16.
41. Baffour R, Achanta K, Kaufman J, et al. Synergistic effect of basic fibroblast growth factor and methylprednisolone on neurological function after experimental spinal cord injury. J Neurosurg 1995;83:105-10.
42. Chen NF, Sung CS, Wen ZH, et al. Therapeutic effect of platelet-rich plasma in rat spinal cord injuries. Front Neurosci 2018;12:252.
43. Hiraizumi Y, Fujimaki E, Transfeldt EE, et al. The effect of the platelet derived wound healing formula and the nerve growth factor on the experimentally injured spinal cord. Spinal Cord 1996;34:394-402.
44. Hiraizumi Y, Transfeldt EE, Kawahara N, et al. In vivo angiogenesis by platelet-derived wound-healing formula in injured spinal cord. Brain Res Bull 1993;30:353-7.
45. Ni S, Cao Y, Jiang L, et al. Synchrotron radiation imaging reveals the role of estrogen in promoting angiogenesis after acute spinal cord injury in rats. Spine (Phila Pa 1976) 2018;43:1241-9.
46. Milbreta U, von Boxberg Y, Mailly P, et al. Astrocytic and vascular remodeling in the injured adult rat spinal cord after chondroitinase ABC treatment. J Neurotrauma 2014;31:803-18.
47. Yao Y, Xu J, Yu T, et al. Flufenamic acid inhibits secondary hemorrhage and BSCB disruption after spinal cord injury. Theranostics 2018;8:4181-98.
48. Ujigo S, Kamei N, Hadoush H, et al. Administration of microRNA-210 promotes spinal cord regeneration in mice. Spine (Phila Pa 1976) 2014;39:1099-107.
49. Huang JH, Xu Y, Yin XM, et al. Exosomes derived from miR-126-modified MSCs promote angiogenesis and neurogenesis and attenuate apoptosis after spinal cord injury in rats. Neuroscience 2020;424:133-45.
50. Cheng X, Xu J, Yu Z, et al. LncRNA xist contributes to endogenous neurological repair after chronic compressive spinal cord injury by promoting angiogenesis through the miR-32-5p/notch-1 axis. Front Cell Dev Biol 2020;8:744.
51. Herrera JJ, Sundberg LM, Zentilin L, et al. Sustained expression of vascular endothelial growth factor and angiopoietin-1 improves blood-spinal cord barrier integrity and functional recovery after spinal cord injury. J Neurotrauma 2010;27:2067-76.

 https://doi.org/10.14245/ns.2244624.312

52. Shin HY, Kim H, Kwon MJ, et al. Molecular and cellular changes in the lumbar spinal cord following thoracic injury: regulation by treadmill locomotor training. PLoS One 2014;9:e88215.
53. Yahata K, Kanno H, Ozawa H, et al. Low-energy extracorporeal shock wave therapy for promotion of vascular endothelial growth factor expression and angiogenesis and improvement of locomotor and sensory functions after spinal cord injury. J Neurosurg Spine 2016;25:745-55.
54. Manthou M, Nohroudi K, Moscarino S, et al. Functional recovery after experimental spinal cord compression and whole body vibration therapy requires a balanced revascularization of the injured site. Restor Neurol Neurosci 2015;33:233-49.
55. Halder SK, Kant R, Milner R. Chronic mild hypoxia promotes profound vascular remodeling in spinal cord blood vessels, preferentially in white matter, via an α5β1 integrin-mediated mechanism. Angiogenesis 2018;21:251-66.
56. Samaddar S, Vazquez K, Ponkia D, et al. Transspinal direct current stimulation modulates migration and proliferation of adult newly born spinal cells in mice. J Appl Physiol (1985) 2017;122:339-53.
57. Wang T, Fang X, Yin ZS. Endothelial progenitor cell-conditioned medium promotes angiogenesis and is neuroprotective after spinal cord injury. Neural Regen Res 2018;13:887-95.
58. Liu X, Xu W, Zhang Z, et al. Vascular endothelial growth factor-transfected bone marrow mesenchymal stem cells improve the recovery of motor and sensory functions of rats with spinal cord injury. Spine (Phila Pa 1976) 2020;45:E364-72.
59. Oh JS, Park IS, Kim KN, et al. Transplantation of an adipose stem cell cluster in a spinal cord injury. Neuroreport 2012;23:277-82.
60. Ning G, Tang L, Wu Q, et al. Human umbilical cord blood stem cells for spinal cord injury: early transplantation results in better local angiogenesis. Regen Med 2013;8:271-81.
61. Li Z, Guo GH, Wang GS, et al. Influence of neural stem cell transplantation on angiogenesis in rats with spinal cord injury. Genet Mol Res 2014;13:6083-92.
62. Zhou HL, Fang H, Luo HT, et al. Intravenous administration of human amniotic mesenchymal stem cells improves outcomes in rats with acute traumatic spinal cord injury. Neuroreport 2020;31:730-6.
63. Zhou HL, Zhang XJ, Zhang MY, et al. Transplantation of human amniotic mesenchymal stem cells promotes functional recovery in a rat model of traumatic spinal cord injury. Neurochem Res 2016;41:2708-18.
64. Nori S, Okada Y, Yasuda A, et al. Grafted human-induced pluripotent stem-cell-derived neurospheres promote motor functional recovery after spinal cord injury in mice. Proc Natl Acad Sci U S A 2011;108:16825-30.
65. Kobayashi Y, Okada Y, Itakura G, et al. Pre-evaluated safe human iPSC-derived neural stem cells promote functional recovery after spinal cord injury in common marmoset without tumorigenicity. PLoS One 2012;7:e52787.
66. Takahashi H, Koda M, Hashimoto M, et al. Transplanted peripheral blood stem cells mobilized by granulocyte colony-stimulating factor promoted hindlimb functional recovery after spinal cord injury in mice. Cell Transplant 2016;25:283-92.
67. Richter MW, Fletcher PA, Liu J, et al. Lamina propria and olfactory bulb ensheathing cells exhibit differential integration and migration and promote differential axon sprouting in the lesioned spinal cord. J Neurosci 2005;25:10700-11.
68. Kumagai G, Tsoulfas P, Toh S, et al. Genetically modified mesenchymal stem cells (MSCs) promote axonal regeneration and prevent hypersensitivity after spinal cord injury. Exp Neurol 2013;248:369-80.
69. Zeng X, Zeng YS, Ma YH, et al. Bone marrow mesenchymal stem cells in a three-dimensional gelatin sponge scaffold attenuate inflammation, promote angiogenesis, and reduce cavity formation in experimental spinal cord injury. Cell Transplant 2011;20:1881-99.
70. Zhong D, Cao Y, Li CJ, et al. Neural stem cell-derived exosomes facilitate spinal cord functional recovery after injury by promoting angiogenesis. Exp Biol Med (Maywood) 2020;245:54-65.
71. Zhang C, Zhang C, Xu Y, et al. Exosomes derived from human placenta-derived mesenchymal stem cells improve neurologic function by promoting angiogenesis after spinal cord injury. Neurosci Lett 2020;739:135399.
72. Huang JH, Yin XM, Xu Y, et al. Systemic administration of exosomes released from mesenchymal stromal cells attenuates apoptosis, inflammation, and promotes angiogenesis after spinal cord injury in rats. J Neurotrauma 2017;34:3388-96.
73. Rauch MF, Hynes SR, Bertram J, et al. Engineering angiogenesis following spinal cord injury: a coculture of neural progenitor and endothelial cells in a degradable polymer

implant leads to an increase in vessel density and formation of the blood-spinal cord barrier. Eur J Neurosci 2009; 29:132-45.
74. López-Dolado E, Gonzalez-Mayorga A, Gutierrez MC, et al. Immunomodulatory and angiogenic responses induced by graphene oxide scaffolds in chronic spinal hemisected rats. Biomaterials 2016;99:72-81.
75. Liu L, Wan J, Dai M, et al. Effects of oxygen generating scaffolds on cell survival and functional recovery following acute spinal cord injury in rats. J Mater Sci Mater Med 2020; 31:115.
76. Joshi HP, Kumar H, Choi UY, et al. CORM-2-solid lipid nanoparticles maintain integrity of blood-spinal cord barrier after spinal cord injury in rats. Mol Neurobiol 2020;57:2671-89.
77. Li X, Zhang C, Haggerty AE, et al. The effect of a nanofiber-hydrogel composite on neural tissue repair and regeneration in the contused spinal cord. Biomaterials 2020;245: 119978.
78. Woerly S, Doan VD, Sosa N, et al. Prevention of gliotic scar formation by NeuroGel allows partial endogenous repair of transected cat spinal cord. J Neurosci Res 2004;75:262-72.
79. Yao S, Yu S, Cao Z, et al. Hierarchically aligned fibrin nanofiber hydrogel accelerated axonal regrowth and locomotor function recovery in rat spinal cord injury. Int J Nanomedicine 2018;13:2883-95.
80. Altinova H, Hammes S, Palm M, et al. Dense fibroadhesive scarring and poor blood vessel-maturation hamper the integration of implanted collagen scaffolds in an experimental model of spinal cord injury. Biomed Mater 2020;15: 015012.
81. Haggerty AE, Maldonado-Lasuncion I, Oudega M. Biomaterials for revascularization and immunomodulation after spinal cord injury. Biomed Mater 2018;13:044105.
82. des Rieux A, De Berdt P, Ansorena E, et al. Vascular endothelial growth factor-loaded injectable hydrogel enhances plasticity in the injured spinal cord. J Biomed Mater Res A 2014;102:2345-55.
83. Siddiqui AM, Oswald D, Papamichalopoulos S, et al. Defining spatial relationships between spinal cord axons and blood vessels in hydrogel scaffolds. Tissue Eng Part A 2021; 27:648-64.
84. Guo S, Redenski I, Landau S, et al. Prevascularized scaffolds bearing human dental pulp stem cells for treating complete spinal cord injury. Adv Healthc Mater 2020;9: e2000974.
85. Zhong J, Xu J, Lu S, et al. A prevascularization strategy using novel fibrous porous silk scaffolds for tissue regeneration in mice with spinal cord injury. Stem Cells Dev 2020; 29:615-24.
86. Ropper AE, Thakor DK, Han I, et al. Defining recovery neurobiology of injured spinal cord by synthetic matrix-assisted hMSC implantation. Proc Natl Acad Sci U S A 2017; 114:E820-9.
87. Marrotte EJ, Johnson K, Schweller RM, et al. Induction of neurogenesis and angiogenesis in a rat hemisection spinal cord injury model with combined neural stem cell, endothelial progenitor cell, and biomimetic hydrogel matrix therapy. Crit Care Explor 2021;3:e0436.
88. Brazda N, Estrada V, Voss C, et al. Experimental strategies to bridge large tissue gaps in the injured spinal cord after acute and chronic lesion. J Vis Exp 2016;(110):e53331.
89. Liu D, Shen H, Shen Y, et al. Dual-cues laden scaffold facilitates neurovascular regeneration and motor functional recovery after complete spinal cord injury. Adv Healthc Mater 2021;10:e2100089.
90. Xi K, Gu Y, Tang J, et al. Microenvironment-responsive immunoregulatory electrospun fibers for promoting nerve function recovery. Nat Commun 2020;11:4504.
91. Lutton C, Young YW, Williams R, et al. Combined VEGF and PDGF treatment reduces secondary degeneration after spinal cord injury. J Neurotrauma 2012;29:957-70.
92. Xu ZX, Zhang LQ, Zhou YN, et al. Histological and functional outcomes in a rat model of hemisected spinal cord with sustained VEGF/NT-3 release from tissue-engineered grafts. Artif Cells Nanomed Biotechnol 2020;48:362-76.
93. Bakshi A, Fisher O, Dagci T, et al. Mechanically engineered hydrogel scaffolds for axonal growth and angiogenesis after transplantation in spinal cord injury. J Neurosurg Spine 2004;1:322-9.
94. Colello RJ, Chow WN, Bigbee JW, et al. The incorporation of growth factor and chondroitinase ABC into an electrospun scaffold to promote axon regrowth following spinal cord injury. J Tissue Eng Regen Med 2016;10:656-68.
95. Gwak SJ, Yun Y, Yoon DH, et al. Therapeutic use of 3beta-[N-(N',N'-Dimethylaminoethane) Carbamoyl] cholesterol-modified PLGA nanospheres as gene delivery vehicles for spinal cord injury. PLoS One 2016;11:e0147389.
96. Wei YT, He Y, Xu CL, et al. Hyaluronic acid hydrogel modified with nogo-66 receptor antibody and poly-L-lysine to promote axon regrowth after spinal cord injury. J Biomed

 https://doi.org/10.14245/ns.2244624.312

Mater Res B Appl Biomater 2010;95:110-7.
97. Xu ZX, Zhang LQ, Wang CS, et al. Acellular spinal cord scaffold implantation promotes vascular remodeling with sustained delivery of VEGF in a rat spinal cord hemisection model. Curr Neurovasc Res 2017;14:274-89.
98. Woerly S, Pinet E, de Robertis L, et al. Spinal cord repair with PHPMA hydrogel containing RGD peptides (NeuroGel). Biomaterials 2001;22:1095-111.
99. Yang B, Wang PB, Mu N, et al. Graphene oxide-composited chitosan scaffold contributes to functional recovery of injured spinal cord in rats. Neural Regen Res 2021;16:1829-35.
100. Woerly S, Petrov P, Sykova E, et al. Neural tissue formation within porous hydrogels implanted in brain and spinal cord lesions: ultrastructural, immunohistochemical, and diffusion studies. Tissue Eng 1999;5:467-88.
101. Man W, Yang S, Cao Z, et al. A multi-modal delivery strategy for spinal cord regeneration using a composite hydrogel presenting biophysical and biochemical cues synergistically. Biomaterials 2021;276:120971.
102. Hakim JS, Rodysill BR, Chen BK, et al. Combinatorial tissue engineering partially restores function after spinal cord injury. J Tissue Eng Regen Med 2019;13:857-73.
103. Li G, Che MT, Zeng X, et al. Neurotrophin-3 released from implant of tissue-engineered fibroin scaffolds inhibits inflammation, enhances nerve fiber regeneration, and improves motor function in canine spinal cord injury. J Biomed Mater Res A 2018;106:2158-70.
104. Facchiano F, Fernandez E, Mancarella S, et al. Promotion of regeneration of corticospinal tract axons in rats with recombinant vascular endothelial growth factor alone and combined with adenovirus coding for this factor. J Neurosurg 2002;97:161-8.
105. Wang L, Shi Q, Dai J, et al. Increased vascularization promotes functional recovery in the transected spinal cord rats by implanted vascular endothelial growth factor-targeting collagen scaffold. J Orthop Res 2018;36:1024-34.
106. Jarrah R, Sammak SE, Onyedimma C, et al. The role of alginate hydrogels as a potential treatment modality for spinal cord injury: a comprehensive review of the literature. Neurospine 2022;19:272-80.
107. Menezes K, Rosa BG, Freitas C, et al. Human mesenchymal stromal/stem cells recruit resident pericytes and induce blood vessels maturation to repair experimental spinal cord injury in rats. Sci Rep 2020;10:19604.

Supplementary Table 1. Complete list of studies using biomaterials to promote vascular repair after spinal cord injury identified by the systematic literature search

Species	SCI model	Method	Time & duration (day)	Outcome	References
Rat, Wistar, M	C6 Lateral hemisection (2×2×2 mm)	rGO scaffold	Acute (0)	*Morphology*: Functional blood vessels were observed in inner parts of the scaffold at 30 days; blood vessels were identified in close relation with regenerated axons inside the scaffold at 30 days; no significant alterations indicating toxicity *Function*: / *Survival*: 10, 30 days	López-Dolado et al.[74] (2016)
Rat, Wistar, F	T8, 9 Transection	Ployethylene glycol (PEG 600), mechanical microconnector system (mMS)	Acute (0) and chronic (5)	*Morphology*: After acute implantation of mMS blood vessels in close proximity with axonal structures could be detected in the mMS lumen at 5 wk; after scar resection and PEG 600 implantation the injury site was invaded by endothelial cells *Function*: Significant improvement at 10 and 30 days with mMS (BBB) and with PEG (mBBB) *Survival*: 30 days (mMS), 39 wk (PEG)	Brazda et al.[88] (2016)
Rat, Long Evans, F	T9, 10 Lateral hemisection (4 mm long)	VEGF165, FGF2 (in microspheres) PLGA multiple channel bridge	Acute (0)	*Morphology*: VEGF-levels at injury site were significantly (20-fold) greater than without VEGF-treatment at 1 week; significantly more blood vessels inside bridges with 2-μg VEGF and 1-μg FGF2 at 6 wk; the number of blood vessels was significantly increased; neurite growth was 1,7-fold greater at 6 wk in bridges with VEGF and FGF2 *Function*: / *Survival*: 1, 6 wk	De Laporte et al.[32] (2011)
Rat, Sprague-Dawley, F	T10 Transection	DPSCs PLLA/PLGA-scaffold	Acute (0)	*Morphology*: Angiogenesis was significantly abundant at the injury site in rats treated with prevascularized scaffolds compared to DPSC-scaffolds, empty scaffolds and untreated rats; the mean diffusivity (indicator of molecular diffusion rate and demyelination) was significantly lower in prevascularized scaffolds at 8 wk, total vessel volume and vessel density in the lesion site were significantly higher in prevascularized scaffolds (increased vessel density in the rubrospinal tract, spinothalamic tract, dorsal column and spinocerebellar tract, but not in corticospinal tract) *Function*: Significant improvement at 2 and 4 wk (BBB) *Survival*: 8 wk	Guo et al.[84] (2020)
Rat, Wistar, F	T7 Transection, (5 mm long)	FGF2 Hyaluronate collagen scaffold (CRS)	Acute (0)	*Morphology*: The number of blood vessels was significantly increased caudal, rostral and at the injury site in the FGF2-CRS and CRS groups compared to the control group at 12 wk as well as the FGF2-CRS group compared to the CRS group *Function*: Significant improvement after 4 wk (BBB) *Survival*: 12 wk	Shang et al.[40] (2019)
Mice, C57BL/6, M	T9 Hemisection	HUVECs Fibrous porous silk scaffold (FPSS)	Acute (0)	*Morphology*: Microvessel density and microvessel count in the FPSS-cells group were significantly higher at 28 days; significantly more regenerating axons formed along the blood vessels in the white matter at the injury site at 4 wk *Function*: Significant improvement after 4 wk (BBB) *Survival*: 4 wk	Zhong et al.[85] (2020)
Rat, Sprague-Dawley, F	T9, 10 Transection (4 mm long)	Oxygen-generating scaffold (CPO/PLGA-microspheres in hydrogel)	Acute (0)	*Morphology*: Oxygen-generating scaffolds had a significantly oxygen level up to 21 days than hydrogel; blood vessels were observed in the scaffold and neovascularization was significantly greater than in control groups *Function*: Significant improvement after 2 wk (BBB) *Survival*: 12 wk	Liu et al.[75] (2020)
Rat, Fischer, F	T9 Transection (2 mm long)	OPF+ hydrogel scaffold SCs, SCs + RAPA (PLGA-microspheres)	Acute (0)	*Morphology*: Mean length density (Lv) of blood vessels was lowest in RAPA channels; blood vessel surface area was significantly larger in SC group; significantly larger mean vessel volumes in the SC group; mean diameter of blood vessels in SC channels was significantly greater; mean cross-sectional area per blood vessel in SC channels was significantly larger; number of axons regenerating had positive correlations to the surface and volume area densities of vessels and to the diameter of blood vessels; for SC channels significant negative correlations were shown between peak axonal density of total axon amplitudes and vessel cross-sectional area for total axons → SCs in hydrogel channels supported neurovascular bundle regeneration significantly in axon and vessel density and in physiologic parameters of vessel diameter and radial diffusion distances *Function*: / *Survival*: 6 wk	Siddiqui et al.[83] (2021)
Rat, Sprague-Dawley, F	T8 Transection (2 mm long)	Hydrogel scaffold with CBD-SDF1a + Taxol liposomes	Acute (0)	*Morphology*: The number of blood vessels was significantly higher in the full treatment group at 10 days; axonal fibers with a regenerative length longer than 1 mm at the lesion site were always close to regenerated blood vessels *Function*: Significant improvement after 3 wk (BBB) *Survival*: 5, 10 days, 6 wk	Liu et al.[89] (2021)

(*Continued*)

https://doi.org/10.14245/ns.2244624.312

Supplementary Table 1. Complete list of studies using biomaterials to promote vascular repair after spinal cord injury identified by the systematic literature search (Continued)

Species	SCI model	Method	Time & duration (day)	Outcome	References
Rat, Sprague-Dawley, F	T9 Contusion, (175 kDyne)	Nanofiber-hydrogel composite (NHC) (Injection into injury site)	Subacute (3)	*Morphology*: The blood vessel density increased in time in the injury with NHC or HA but decreased in the control group; the blood vessel density was significantly higher at 28 days *Function*: No significant improvement (BBB) *Survival*: 3, 7, 28, 56 days	Li et al.[61] (2020)
Rat, Sprague-Dawley, F	T9 Lateral hemisection (3 mm long)	Microsol electrospun oriented fiber scaffold pDNA/aLiposome (NGF) + IL-4	Acute (0)	*Morphology*: The number of blood vessels was significantly higher; neovascularization was significantly higher at 4 and 8 wk → polarized M2 subtypes possibly secreted VEGF which promotes blood vessel formation *Function*: Significant improvement after 3 wk (BBB) and 4 wk (Inclined Plane Test) *Survival*: 4, 8 wk	Xi et al.[90] (2020)
Rat, Wistar, M	T10 Lateral hemisection	VEGF/PDGF Hydrogel patch Mini-pump At injury site	Acute (0) For 2 days (patch)/7 days (pump)	*Morphology*: The blood vessel density 200 μm from the lesion cavity was not significantly affected by VEGF/PDGF treatment *Function*: No significant improvement (BBB) *Survival*: 1, 3 mo	Lutton et al.[91] (2012)
Rat, Sprague-Dawley, F	T9–11 Lateral hemisection	VEGF, NT-3, BMSCs PLGA-nanoparticles with acellular spinal cord scaffold (ASCS)	Acute (0)	*Morphology*: The levels of VEGF and NT-3 were significantly increased at the injury site 1 and 4 wk in the VEGF/NT-3-ASCS- and BMSC-treatment groups; the blood vessel density was significantly higher; more intensive blood vessels are ordinarily accompanied with lower infiltration of macrophages and vice versa at the lesion site *Function*: Significant improvement at all timepoints (BBB) *Survival*: 1, 4, 8 wk	Xu et al.[92] (2020)
Rat, Sprague-Dawley, F	T9 Contusion injury	VEGF, Ang-1, FGF2 PLGA-microspheres Injection into injury site	Acute (0)	*Morphology*: The levels of VEGF, Ang-1 and FGF2 were significantly higher at the injury site at 2, 4, and 8 wk in animals treated with angiogenic microspheres; the numbers of blood vessels at the injury site at 4 and 8 wk were significantly higher; the numbers of cells positive for nestin or ßIII-tubulin (marker of neural precursor recruitment) at the injury site were significantly higher and mostly associated with blood vessels; the density of neurofilament (NF)-positive fibers was significantly greater at the injury site at 8 wk in treated animals often aligned with blood vessels; serotonergic (5-HT) fibers were associated with blood vessels and significantly longer in treated rats; the numbers of MBP-positive mature oligodendrocytes were significantly higher in treated rats and aggregated around blood vessels in the white matter region; most axons in treated animals were myelinated and followed blood vessels at 12 wk *Function*: Significant improvement after 14d (BBB) *Survival*: 2, 4, 8, 12 wk	Yu et al.[33] (2016)
Rat, Sprague-Dawley, F	T9, 10 Lateral hemisection (4 mm long)	NPCs, ECs Hydrogel + PLGA-scaffold	Acute (0)	*Morphology*: Significantly more vessels in the implant + NPCs/ECs treated rats in the lesion epicenter at 8 wk; only implant + NPCs/ECs treated rats had EBA-positive vessels (marker of functional BSCB) at the injury epicenter; the vessel density was significantly increased at the injury epicenter *Function*: / *Survival*: 3, 8 wk	Rauch et al.[73] (2009)
Rat, Fischer F344, F	T9, 10 Lateral hemisection	NSCs, EPCs Hydrogel	Acute (0)	*Morphology*: Infiltration of native NSCs into lesion area and formation of blood vessels appeared in NSC/EPC hydrogel group, the acellular hydrogel group and in the control group with connective tissue formation *Function*: significant improvement after 2 wk (BBB) *Survival*: 4 wk	Marrotte et al.[54] (2021)
Rat, Sprague-Dawley, F	T2 Clip compression (26 g for 60 s)	FGF2 HAMC, PLGA-nanoparticles, (Intrathecal injection)	Acute (0)	*Morphology*: The number of blood vessels was significantly higher 300 μm rostral and caudal to the lesion site at 4 wk in HAMC/PLGA/FGF2-treated rats in the dorsal horn *Function*: No significant improvement (BBB) *Survival*: 4 wk	Kang et al.[39] (2013)
Rat	Cervical hemisection	BDNF PHEMA-scaffold	Acute (0)	*Morphology*: Blood vessels grew into the entire PHEMA-scaffold within 2 wk and persisted until 4 wk *Function*: / *Survival*: 1, 2, 4 wk	Bakshi et al.[93] (2004)
Rat, Sprague-Dawley, F	T9, 10 Dorsal hemisection, (3 mm × 1,5 mm)	VEGF, BDNF PLGA-microspheres, HA-antiNgR -scaffold	Acute (0)	*Morphology*: The number of blood vessels and axonal fibers were significantly higher in HA + PLGA scaffolds treated rats at 8 wk; more myelinated axons were found in HA + PLGA scaffolds at 14 wk compared to HA scaffolds and they often had contact with blood vessels *Function*: Significant improvement after 2 wk (BBB, CatWalk) *Survival*: 4, 8, 14 wk	Wen et al.[34] (2016)

(*Continued*)

Supplementary Table 1. Complete list of studies using biomaterials to promote vascular repair after spinal cord injury identified by the systematic literature search (Continued)

Species	SCI model	Method	Time & duration (day)	Outcome	References
Rat, Sprague-Dawley, F	T9, 10 Transection, (4 mm long)	NGF, ChABC Alginate beads, electrospun PDS scaffold	Acute (0)	*Morphology*: Many parallel-aligned blood vessels in contact with regenerating axons were present in the implant; some endothelial cells were in close association with electrospun monofilaments at 7 days, after 2–3 wk blood cells were observed in this lumen *Function*: Significant improvement at 21 days (BBB) *Survival*: 7, 21 days	Colello et al.[94] (2016)
Rat, Sprague-Dawley, F	T10 Transection, (1,5 mm long)	MSCs PLGA, GS-scaffold	Acute (0)	*Morphology*: The number of blood vessels was significantly increased in GS+MSCs treated rats at the injury site at 1 wk; only MSCs surrounding blood vessels expressed VEGF *Function*: / *Survival*: 1, 8 wk	Zeng et al.[69] (2011)
Rat, Sprague-Dawley, M	T9 Clip compression	pSV-VEGF PLGA/DC-Chol-nanospheres Injection into injury site	Acute (0)	*Morphology*: Arteriole density was significantly higher in VEGF-loaded PLGA/DC-Chol nanosphere treated rats at 4 wk *Function*: Significant improvement after 2 wk (BBB) *Survival*: 2, 4, 6 wk	Gwak et al.[95] (2016)
Rat, Sprague-Dawley, F	T8, 9 Lateral hemisection, (3 mm long) antiNgR HA-PLL hydrogel	Acute (0)	Acute (0)	*Morphology*: antiNgR was detectable for 8 wk; some blood vessels and axons were seen in the edge and epicenter of HA-PLL/antiNgR and HA-PLL treated rats at 8 wk *Function*: / *Survival*: 2, 4, 8, 12 wk	Wei et al.[96] (2010)
Rat, Wistar, F	T12 Transection, (3 mm long)	PDWHF, NGF Collagen-I	Acute (0)	*Morphology*: Axonal regrowth and number of blood vessels were significantly greater in PDWHF and NGF groups; the number of vessels was significantly greater in PDWHF group compared to NGF group *Function*: No significant improvement observed *Survival*: 4, 8, 12 wk	Hiraizumi et al.[43] (1996)
Rat, Sprague-Dawley, M	T9–11 Lateral hemisection, (3 mm long)	VEGF165 PLGA-nanospheres, ASCS	Acute (0)	*Morphology*: Vessel branches increased significantly at 1 wk in V-ASCS group compared with control and B-ASCS groups but in the following weeks the density of vessel branches decreased in B-and V-ASCS groups, vessel volume/tissue volume (VV)/(TV) were significantly increased in B-and V-ASCS groups at 1wk and VV/TV were significantly greater in V-ASCS compared with B-ASCS; VV/TV was not significantly different between V-ASCS and B-ASCS groups at 8 wk and data in V-ASCS group was significantly lower than in Sham group; vessel density (VDn) was significantly highest in V-ASCS group, higher in B-ASCS group and the lowest in control group at 1wk; VDn was significantly higher in V-ASCS group compared with B-ASCS at 8 wk; average vessel diameter was significantly greater in V-ASCS and B-ASCS groups compared with control group at 1wk but there was no significant difference at 4 and 8 wk, density of vessel branches (VBDn) was significantly higher in V-ASCS group compared with control group and B-ASCS groups at 1, 4 and 8 wk *Function*: Significant improvement after 3d (BBB) *Survival*: 1, 4, 8 wk	Xu et al.[97] (2017)
Cat	L2 Incomplete cord injury (5 mm longitundinal insertion of teflon scheaths)	PDWHF Hydron (coated on Teflon catheter sheaths)	Acute (0)	*Morphology*: The number of vessels was significantly greater in PDWHF-treated animals and the number of vessels appeared significantly more 1 mm from the lesion site *Function*: No significant improvement observed *Survival*: 3 wk	Hiraizumi et al.[44] (1993)
Rat, Sprague-Dawley, M	T9 Transection, (3 mm long)	VEGF Collagen scaffold (CS)	Acute (0)	*Morphology*: The microvessel density and microvessel count in the CS/VEGF group were significantly higher at 12 wk *Function*: Significant improvement after 7 wk *Survival*: 4, 10, 12 wk	Wang et al.[105] (2018)
Rat, Long Evans, F	T9, 10 Lateral hemisection, (4 mm long)	VEGF164 Alginate/fibrinogen-hydrogel, chitosan-nanoparticles	Acute (0)	*Morphology*: Endothelial, ß-III tubulin and growing neurites staining intensity were significantly greater in rats treated with VEGF-loaded hydrogels at 4 wk *Function*: No significant improvement (CatWalk) *Survival*: 4 wk	des Rieux et al.[82] (2014)
Rat, Sprague-Dawley, F	T5, Transection, (3 mm long)	NeuroGel (PHPMA)-hydrogel	Acute (0)	*Morphology*: Vascular response with proliferating capillary sprouts into the hydrogel at 7 days as well as glial cells; extensive ingrowth of sinusoidal capillaries *Function*: Significant improvement observed after 2 wk *Survival*: 2, 4 mo	Woerly et al.[98] (2001)
Rat, Fischer, F	T9, 10 Transection, (4 mm long)	BDNF, FGF1 PLA-foam scaffold, fibrin glue	Acute (0)	*Morphology*: The number of blood vessels was significantly higher in fibrin only group at 2, 4, and 8 wk and in BDNF + foam group at 8 wk *Function*: No significant improvement (BBB) *Survival*: 2, 4, 8 wk	Patist et al.[38] (2004)

(*Continued*)

https://doi.org/10.14245/ns.2244624.312

Supplementary Table 1. Complete list of studies using biomaterials to promote vascular repair after spinal cord injury identified by the systematic literature search (Continued)

Species	SCI model	Method	Time & duration (day)	Outcome	References
Cat	T6, 7 Transection, (3 mm long)	NeuroGel	Acute (0)	*Morphology*: At 17 months large capillaries crossed the injury site and a profuse network of blood vessels in proximity of the spinal stumps were seen *Function*: Improvement observed (treadmill test) *Survival*: 6, 9, 17 mo	Woerly et al.[78] (2004)
Rat, Sprague-Dawley, F	T9 Transection, (2 mm long)	Chitosan – graphene oxide (CS/GO) scaffold	Acute (0)	*Morphology*: Regenerating neurons and erythrocytes were seen inside the GS/GO scaffold *Function*: Significant improvement after 7 wk (BBB) and 10 wk (SSEP) *Survival*: 10 wk	Yang et al.[99] (2021)
Rat, Sprague-Dawley, F	T9 Transection, (2 mm long)	NeuroGel (PHPMA hydrogel)	Acute (0)	*Morphology*: Blood vessels, processes of astrocytes and myelinated and unmyelinated axons were observed arranged inside the porous hydrogel implant at 5 mo *Function*: / *Survival*: 5 months	Woerly et al.[100] (1999)
Rat, Sprague-Dawley, F	T9, 10 Lateral hemisection, (5 mm long)	AFG/fSAP hydrogel (aligned fibrin hydrogel/functionalized self-assembling peptide nanofiber hydrogel)	Acute (0)	*Morphology*: Blood vessels were found in the lesion site in AFG/fSAP-treated rats with larger diameter compared with AFG-treated rats at 12 wk; the microvessel density was significantly greater in AFG/fSAP-treated rats at the lesion site compared with AFG-treated rats and control group at 12 wk; regenerating blood vessels and axons showed colocalization *Function*: Significant improvement after 3 wk (BBB) and at 12 wk (Catwalk, MEP) *Survival*: 1, 8, 12 wk	Man et al.[101] (2021)
Rat, Fischer, F	T9 Transection, (2 mm long)	SC, RAPA OPF+ hydrogel (MG), PLGA-microspheres (MS)	Acute (0)	*Morphology*: Vessel length and vessel surface area were significantly greater in SC + Empty-MS treated rats compared with MG + Empty-MS at 6 wk but not different to SC + Low or medium RAPA-MS; vessel length and surface area in SC-loaded scaffolds with high doses RAPA was not different from MG-only scaffolds without RAPA; the mean blood vessel diameter in SC + Empty-MS was greater than in MG-only scaffolds; the number of vessels with Pericytes (PC)/ Endothelial cells (EC) was greatest in SC + Empty-MS treated rats; PC/EC decreased with increasing RAPA concentration and was significantly lower in MG + Empty-MS treated rats; the number of blood vessels with normal PC/EC ratio was highest in SC + Low RAPA-MS treated rats; surface area of functionals was significantly higher in RAPA treated rats compared to MG + Empty-MS group indicating an improved vascular connectivity to the systemic circulation *Function*: Significant improvement after 4 wk (BBB) *Survival*: 6 wk	Hakim et al.[102] (2019)
Rat, Sprague-Dawley, F	C3, 4 Lateral funiculotomy, (2 mm long)	Collagen-I scaffold	Acute (0)	*Morphology*: At 10 wk blood vessels were seen inside the scaffold but most of them were not associated with ZO-1-immunoreactive tight junctions, ZO-1-immunoreactivity was intensive at the transition zones, density of blood vessels was significantly greater at the transition zone of the scaffold compared to the contralateral non-lesioned white matter but staining within the scaffold was not significantly greater than that of the contralateral white matter; the number of functional vessels was significantly lower within the scaffold at 10 wk than the total number of vessels and most functional vessels within the scaffold were not positive for ZO-1 tight junction → delayed or slowed maturation *Function*: / *Survival*: 10 wk	Altinova et al.[80] (2020)
Rat, Sprague-Dawley, F	T9, 10 Dorsal hemisection, (4 mm long)	Aligned fibrin hydrogel (AFG)	Acute (0)	*Morphology*: The number of blood vessels was significantly greater in AFG-treated rats at 2 and 4 wk *Function*: Significant improvement after 2 wk (BBB) *Survival*: 1, 2, 4, 8 wk	Yao et al.[79] (2018)
Canine, Beagle, F	T10 Lateral hemisection, (4 mm long)	Gelatin sponge (GS), NT-3/fibroin particles (NF)	Acute (0)	*Morphology*: Blood vessels or capillaries were identified only in the NF-GS group at 4 wk *Function*: Significant improvement after 3 wk (Olby score test) and at 4 wk *Survival*: 4 wk	Li et al.[103] (2018)
Rat, Sprague-Dawley, F	T9, 10 Lateral hemisection, (4 mm long)	MSCs, PLGA-scaffold	Acute (0)	*Morphology*: The umber of blood vessels was significantly increased around the lesion site at 6 wk in the transplant group *Function*: Significant improvement after 7d (BBB), 2 wk (inclined plane downward, righting reflex) and 4 wk (at level allodynia) *Survival*: 6 wk	Ropper et al.[86] (2017)
Rat, Sprague-Dawley, F	T10 Compression injury, (35 g, 5 min)	CORM-2-SLNs (Carbon monoxide-releasing molecule-2 solid lipid nanoparticle) (i.p. injection)	Acute (0) For 8 days	*Morphology*: The fluorescence intensity of Evan´s Blue dye was significantly lower in the treatment group at the injury site at 1d indicating reduced BSCB permeability; the number of blood vessels was significantly greater in the treatment group at 21 days *Function*: Significant improvement after 7d (BBB, withdrawal test) *Survival*: 1, 3, 14, 21 days	Joshi et al.[76] (2020)

(*Continued*)

Supplementary Table 1. Complete list of studies using biomaterials to promote vascular repair after spinal cord injury identified by the systematic literature search (Continued)

Species	SCI model	Method	Time & duration (day)	Outcome	References
Rat, Wistar, F	T8 Complete transection of CST	VEGF165, Ad.CMV. VEGF165 (Injection in lesion site, controlled release via Matrigel)	Acute (0) For 30 days	*Morphology*: The number of vessels in VEGF-treated rats was significantly higher (ca. 300%), retrograde axonal degeneration was significantly reduced in VEGF-treated rats, regenerating CST axons (HRP-labeled) where located mostly in the ventral gray matter *Function*: / *Survival*: 0, 3, 7, 10, 16, 18, 30 days	Facchiano et al.[104] (2002)
Rat, Sprague-Dawley, M	T7 Contusion injury	VEGF165 Gelfoam placed on injury site	Acute (0)	*Morphology*: Significant increase in BSCB permeability after VEGF-treatment in non-enhancing-areas (magnetic resonance imaging) in the epicenter in the subacute (7–14 days) and chronic (28–56 days) periods *Function*: Significant improvement at 28 days, but not at 56 days (BBB) *Survival*: 56 days	Patel et al.[30] (2009)

/, not assessed; AFG, aligned fibrin hydrogel; fSAP, functionalized self-assembling peptides; CORM-2, carbon monoxide-releasing molecule-2; rGO, reduced graphene oxide; DPSCs, dental pulp stem cells; PLGA, polylactide-co-glycolide acid; PLLA, poly-L-lactic acid; PEG 600 - polyethylene glycol, PLG(A) - polylactide-co-glycolide (acid), PLLA - poly-l-lactic acid; mMS, mechanical microconnector system; BBB, Basso, Beattie and Bresnahan score; VEGF, vascular endothelial growth factor; FGF2, fibroblast growth factor 2; DPSCs, dental pulp stem cells; CRS, hyaluronate collagen scaffold; HUVECs, human umbilical vein endothelial cells; FPSS, fibrous porous silk scaffold; CPO, calcium peroxide; OPF, oligopolyethylene-glycol-fumarate; SCs, Schwann cells; RAPA, rapamycin; CBD-SDF-1a, collagen-binding domain-stromal cell-derived factor-1a; NHC, nanofiber-hydrogel composite; MSaP-aL/p, microsol electrospun fiber scaffold with pDNA-loaded liposomes; NGF, nerve growth factor; IL-4, interleukin-4; PDGF, platelet-derived growth factor; NT-3, neurotrophin-3; BMSCs, bone mesenchymal stem cells; ASCS, acellular spinal cord scaffold; Ang-1, angiopoietin-1; NPCs, neural progenitor cells; EPCs, endothelial progenitor cells; HAMC, biopolymer blend of hyaluronan and methylcellulose; BDNF, brain derived neurotrophic factor; PHEMA, poly-2-hydroxyethylmethacrylate hydrogel; HA, hyaluronic acid; AntiNgR, anti-Nogo receptor antibody; ChABC, chondroitinase ABC; PDS, polydioxinone; MSCs, bone marrow-derived mesenchymal stem cells; pSV-VEG, encapsulated plasmid DNA of VEGF; DC-Chol, 3à-[N-(N0,N0- dimethylaminoethane) carbamoyl] cholesterol; PDWHF, platelet-derived wound healing formula; PHPMA, Poly [iV-(2-hydroxypropyl) methacrylamide]; GS, gelatin sponge; BSCB, blood-spinal cord barrier; CST, corticospinal tract; Ad.CMV.VEGF, replication-defective adenovirus coding for VEGF.

https://doi.org/10.14245/ns.2244624.312