Angiogenesis in Spinal Cord Injury: Progress and Treatment

Konstantinos Tsivelekas 1, Dimitrios Stergios Evangelopoulos 2, Dimitrios Pallis 1, Ioannis S. Benetos 2, Stamatis A. Papadakis 1, John Vlamis 2, Spyros G. Pneumaticos 2

1. Second Department of Orthopaedics, KAT General Hospital, Athens, GRC. 2. Third Department of Orthopaedics, National and Kapodistrian University of Athens School of Medicine, KAT General Hospital, Athens, GRC.

Corresponding author: Konstantinos Tsivelekas, tsivelekaskonstantinos@gmail.com

Abstract

Traumatic spinal cord injury (SCI) provokes the onset of an intricate pathological process. Initial primary injury ruptures local micro-neuro-vascular complex triggering the commencement of multi-factorial secondary sequences which exert significant influence on neurological deterioration progress. Stimulating by local ischemia, neovascularization pathways emerge to provide neuroprotection and improve functional recovery. Although angiogenetic processes are prompted, newly formed vascular system is frequently inadequate to distribute sufficient blood supply and improve axonal recovery. Several treatment interventions have been endeavored to achieve the optimal conditions in SCI microenvironment, enhancing angiogenesis and improve functional recovery. In this study we review the revascularization pathogenesis and importance within the secondary processes and condense the proangiogenic influence of several angiogenetic-targeted treatment interventions.

Categories: Orthopedics, Trauma

Keywords: spinal cord regeneration, angiogenetic factor, angiogenesis, revascularization, spinal cord injury

Introduction And Background

Spinal cord injuries (SCI) account for a worldwide incidence estimated from 250,000 to 500,000 per year, while they mostly occur during high energy injuries such as vehicle accidents, falls from height, gunshots, etc. [1]. Frequently followed by significant lesions, including compressions, ruptures, and fractures, spinal cord injuries result in a range of neurological symptoms depending on the level and severity of the injury. The neurological deficit is generally determined within 72 h after SCI, while post-traumatic processes can be divided into acute, subacute, intermediate, and chronic (Table 1) [2,3]. Almost half of the patients will not regain their everyday functionality, whereas the majority of them experience chronic types of pain [2,4].

| Stage of Spinal cord injury | Time elapsed since precipitation |
|-----------------------------|---------------------------------|
| Acute                       | < 48 hours                      |
| Sub-acute                   | 2 days – 2 weeks                |
| Intermediate                | 2 weeks – 3 months              |
| Chronic                     | >3 months                       |

TABLE 1: Post-traumatic progress time distribution

Primary mechanical injury triggers the onset of a secondary multifactorial process [2]. Over the last decades, extensive research has been performed regarding the progressive damage on the lesion site, including vascular disorders, inflammatory process, demyelination, and cell apoptosis, resulting in glial scar and cavity formation and having a significant impact on axon regeneration and functional recovery [5]. Vascular integrity and adequacy are determining, providing a propitious regeneration microenvironment on the lesion site.

Although endogenous angiogenesis is triggered by SCI and the ensuing ischemia, the local vascular response is usually insufficient [6]. Hence, the meticulous comprehension of the SCI microenvironment is significant, in achieving the optimal conditions for axonal and functional recovery. Several pieces of research and various pre-clinical approaches have focused on regulating the vascular response following SCI, obstructing secondary processes, and contributing to the development of an organized and properly functional vascular system. Angiogenetic factors administration, gene modulation, and multiple treatment interventions
stimulate revascularization on the injury site, providing promising results in SCI management [7].

In this study, a review of the literature determined the crucial role of the secondary vascular process within SCI providing an overview of vascular impairment within SCI, angiogenetic response on the lesion site, and conceivable proangiogenic interventions, promoting local angiogenesis and functional recovery.

**Review**

**Injury classification**

Several classification algorithms have been proposed to ensure the most optimal conditions and the proper management of SCI, considering predominantly anatomical (skeletal level of injury) as well as functional-neurological points of criteria [8,9]. In order to determine the accurate level of spinal cord lesion, regarding the neurological level of SCI, the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) developed the American Spinal Injuries Association (ASIA) score. Since 1982, ASIA defined the "key muscles and dermatomes", aiming to the particular assessment and documentation of SCI through the ASIA motor-sensory-impairment scale. ASIA or AIS scale is able to provide an integrated evaluation of the significance of the neurological distinction (complete to incomplete), providing essential management documentation while often assembling crucial prognostic details [10].

**Spinal cord injury pathophysiology**

*Primary Injury*

Direct or persistent compression forces exerted among the canal seem to mostly insult spinal cord integrity. The primary stage of SCI consists of mechanical forces, shrill damage, and strain to the spinal cord and the surrounded neurovascular complex through fracture fragments, dislocations, strain, compression, and/or torsion forces (Figure 1) [11]. Accompanied hematomas constitute a presumable compression threat of the spinal cord, as bleeding erupts shortly after SCI, followed by local ischemic infraction and hypoxia [12]. Primary lesion harmfully affects gray matter, neurons, and oligodendrocytes, which essentially mediate neuronal transmission, whereas vascular damage, including blood spinal cord barrier (BSCB), augments inflammatory cell infiltration [13]. Furthermore, edema and macrophage accumulation on the lesion site aggravates distortion in neuronal transmission. Initial injury triggers a consequent secondary “cascade” contributing to further deterioration of the damaged spinal cord and consequent neurological impairment [14].

![FIGURE 1: Sagittal views of the cervical spine fracture](image)

A) Sagittal T1 view of cervical spine fracture  B) Sagittal T2 view of the cervical spine fracture. The red arrow is showing the C6 vertebrae fracture. The green arrow reveals the concomitant compression of the spinal cord.

*Secondary Injury*

The secondary injury was firstly described by Allen in 1911 while studying SCI in dogs [15]. Secondary injury onsets shortly after SCI and is able to last for a week to months, concerning a multifaceted pathological self-destruction process of the spinal cord at cellular, biochemical and molecular levels [5]. Divided into acute, sub-acute, and chronic secondary mechanisms of injury, encompass a handful of perturbations containing vascular damage, ionic imbalance, excitotoxicity (neurotransmitter accumulation), free radical
development, calcium inundation, inflammatory processes, edema, and necrotic cell death [16].
Progressively, apoptosis, axial demyelination, Wallerian deterioration/degeneration, matrix remodeling, and
glial scar formation on the injury site consist of the sub-acute stage, until the lastly developed axonal
dieback, cystic cavity accretion, and glial scar maturation on the chronic phase [17,18].

Vascular Response After SCI

The vascular system consists of a well-architected and organized structure providing a supportive
environment to the nervous system [19]. Initial spinal cord injury results in local vascular impairment and
BSCB deterioration, intensifying vascular permeability, while the secondary injury progress demonstrates
deterrent conditions for regeneration and functional recovery [20]. Mechanical trauma consequences on
disruption of perivascular basement membrane (BM) and detachment of extracellular matrix (ECM), leading to
a huge loss of endothelial cells (EC) and EC apoptosis, instigated by the ensuing ischemia [21,22].
Disorders in BM structure intensify the inflammatory response outspread, impairing cell death in the
subacute stage, while the accompanied hemorrhage aggravates axonal breakdown [23]. In addition,
mechanical shear induces disruption of BSCB, occurring in the very first hours of the injury. Pro-
inflammatory cytokines (interleukin (IL)-1β, tumor necrosis factor (TNF)α), metalloproteinase (MMPS), and
vasoactive agents exacerbate vascular permeability, contributing to inflammatory infiltrate and secondary
injury process on the injury site [6,24,25].

Endogenous Angiogenesis

Angiogenesis consists of the fundamental form of vessel evolvement in the injury site after SCI, prompted by
local hypoxia and proangiogenic substances, and includes chiefly three formation mechanisms:
vasculogenesis, splitting angiogenesis, and sprouting angiogenesis [26,27]. Vasculogenesis concerns the "de
novo" vessel formation from precursor endothelial cells or angioblasts, generating predominantly among
embryogenesis [28]. Regarding SCI, new vessels proceed through the pre-existing vascular system
(angiogenesis), separated into two main processes: firstly, sprouting angiogenesis where ECM restructures
and reorganizes providing a propitious microenvironment for EC migration, escalation, tube formation, and
lastly configuration of new sprouts and intussusception (or splitting angiogenesis), accomplished by old-
vessel splitting [27,29].

Angiogenesis and EC remodeling and regeneration are stimulated by local ischemia and augmented by
miscellaneous molecules through various signaling pathways [30,31]. Endothelial cell augmentation is
provided by several transcription agents including Sox17, Foxo1, FoxM1, Atf3, and HIF-1α, exerting influence
on the sprouting angiogenesis process, which is additionally affected by Mef2 factors/agents [32,33].
Vascular endothelial growth factor (VEGF), one of the most identified angiogenic components in blood
vessel formation and regeneration, engages angiogenic pathways in both regular and pathological
circumstances [34]. Expression of HIF-1α is increased through PI3K-Akt signaling set-off and induces VEGF
production, contributing to the angiogenetic process, whereas prevention of the PI3K-Akt and mTOR
signaling pathways prompt Foxo1 expression and instigate EC curvature [35,36]. Notch signaling conduces
to sprouting and splitting procedure management through Dll4 expression in tip cells [37].

The secondary injury process accelerates rapidly following SCI, hence endogenous angiogenesis is
frequently inadequate to confront the progressive local ischemia and cell death. New vessels ephemeral
enhance within two weeks after SCI providing an early-novel scaffold for axonal renascence and remodeling,
however, accompanied BSCB disruption often lays in peril vessel vulnerability [37]. Additionally, the
development of the recently formed vessels into a well-structured and functional vascular system usually
falls due to their anatomic features and lack of connections with local neurons, vascular mural, and glial
cells, resulting in poor branching germination [6,23].

Several studies have proved the beneficial role of sufficient capillary blood flow, angiogenesis, and BSCB
probitry to ensure the distinguished conditions for tissue survival and functional regeneration [38,39].
Significant interaction among vessel regrowth and nerve reconnection has been demonstrated concerning
both salutary and repellent evidence, including Slits, Nogo, Semaphorins, Ephrins, VEGF, neurotrophins
(NGF, NT-3), vascular cell types (vSMCs), astrocytes, microglia, and oligodendrocytes [19,40–42]. By and
large, revascularization is crucial in SCI rehabilitation. Interventions targeting the harmed vascular system
by providing blood supply adequacy, triggering angiogenesis, and ensuring BSCB integrity and vascular
decency, are capable of potentially diminishing secondary progression and promoting axonal guidance and
functional recovery following SCI.

Revascularization treatment interventions following SCI

Development of vascular response and augmentation of the angiogenetic process within SCI conducts the
delivery of proangiogenic factors, gene regulation, and several vascular interventions. However, modulation
of adjustable and controlled angiogenesis prevails the vast research confrontation. Increased microvascular
permeability carries the risk of spreading the lesion through leukocyte infiltration, while immoderate VEGF
expression has been implicated in tumor formation [43].
(i) Proangiogenic factor administration: Blood vessel formation, as well as, ECs migration and proliferation is significantly affected by vascular endothelial growth factor (VEGF) [34]. Isolated or combined VEGF administration and its isoform (VEGF-A165, 121, 189) provided significant post-traumatic enhancing recovery and neuroprotection in numerous studies [44,45]. Delivery of modified zinc protein transcription factor (ZFP) activates all isoforms of VEGF-A, whereas a combination of VEGF with platelet-derived growth factor (PDGF)/fibroblast growth factor-2 (FGF2)/Angiopoietin (ANG1) improved blood vessel density, abated BSCB permeability and enhance blood supply [46-48].

Several hormones, enzymes, or substances such as melatonin and estrogen, have been shown to detect an angiogenetic influence in SCI management [49]. Chondroitinase ABC (ChABC) provides axonal remodeling and regeneration by triggering revascularization. Studies have presented the shrinking of extracellular chondroitin sulfate proteoglycans (CSPG) by ChABC, stimulating neoangiogenesis and protecting vessel BM [50,51]. Additionally, MMPs, flufenamic acid (FFA) or MMP-8 inhibitor (MMP-81), and granulocyte colony-stimulating factor (G-CSF), provide a permissive environment for local revascularization and BSCB disruption deterrence [52,53].

(ii) Gene modulation: Neuroprotection and functional recovery through several genetic pathways has been observed in assorted experimental studies, concerning the reciprocal of genetic perturbation in proangiogenic factors expression [54]. Kumar et al. assessed the transient potential channel protein (TRPV4) fluctuation and increase following SCI, providing the statement of the detrimental repercussion of TRPV4 activation in endothelial cell damage, inflammation progress, and rehabilitation/functional recovery [55]. Diminution of UTX (Ubiquitously Transcribed tetratricopeptide repeat on chromosome X), a histone H3K27 demethylase, which is significantly increased after SCI, augments EC migration and tubule/tube formation/generation and enhances epigenetically the vascular remodeling and functional retrieval through miR-24pathway [56]. Blocking in proangiogenic microRNAs expression outcomes in inflammatory impediment and proceeds vascular growth. Knockdown of PTP1B and EFNA3 through miR-210 delivery, as well as SPPREDI AND PIK3R2 crash prompted by Agomir-126/miR-126 administration, operated in revascularization and functional recovery [57,58].

(iii) Cell-based therapeutic strategies: Stem cell transplantation erupted as a persuasive path in both degenerative and traumatic disorders owing to their immanent differentiation diversity and providing auspicious treatment options [59]. Mesenchymal stem cells (MSCs) originating from the umbilical cord, adipose tissue, amnion, and bone marrow have been observed to promote BSCB restoration and enhance revascularization on the lesion site [60,61]. Exosomes or extracellular vesicles originating from MSC include secreted or paracrine-secreted proangiogenic factors, emulating MSCs' endeavor in revascularization [40].

Neutral stem/progenitor cells (NS/PCs) or neural stem cells' potential differentiation into neurons, astrocytes, and oligodendrocytes provided an augmented angiogenetic impact on the damaged spinal cord [62,63]. Stimulated by VEGF secretion, NSCs transplantation or co-implantation with ECs offers a prosperous microenvironment for ministrant vascular regrowth and BSCB maintenance/conservation, whereas the astrocytic module of NCS can also merge with endogenous astrocytes through migration providing further BSCB integrity [64-66]. Additionally, numerous cells including HUVECs, pericytes, and CD133+ blood cells have been assessed due to their proangiogenic effect on SCI [67,68].

(iv) Other angiogenetic administrators: Natural or synthetic biomaterials, including hyaluronic acid (HA), collagen, fibrin, Poly-L-lactic acid (PLLA), poly-lactic-co-glycolic (PLGA) have been observed due to their proangiogenic effect on SCI [69,70].

An abundance of treatment interventions has been endeavored, utilizing their angiogenetic influence on lesion sites as illustrated in Table 2.

| Author           | Method                              | Results                                                   |
|------------------|-------------------------------------|------------------------------------------------------------|
| Kitamura et al. 2007 | Delivery of HGF gene                | Increased neural survival, promoted angiogenesis and functional recovery |
| Kumagai et al. 2009   | Transplantation of NS/PCs            | Stimulated angiogenesis, axonal volume and remyelination, promoted locomotor recovery |
| Rauch et al. 2009        | Administration of a co-culture of ECs and NPCs | Induced angiogenesis                                         |
| Sasaki et al. 2009      | Administration of CD133+ cells       | Increased VEGF expression, promoted angiogenesis, axonal regeneration, functional recovery |
| Kang et al. 2010         | Delivery of FGF2                    | Increased spinal cord blood flow, improved vessel density   |
| Herrera et al. 2010     | Co-delivery of VEGF and Ang-1       | Vascular stabilization, improved locomotor function         |
| Wei et al. 2010         | Administration of HA-based hydrogels modified with PLL and antiNgR | Increased angiogenesis and prevented glial scar formation    |
**TABLE 2: Angiogenesis enhance administrators.**

| Method                                                                 | Effect                                                                                     |
|------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Co-delivery of VEGF, ang-1 and bFGF                                      | Increased expression of angiogenic factors, promoted angiogenesis and neurogenesis, improved neurologic function. |
| Co-delivery of CS targeted with CS-B-VEGF                               | Promoted angiogenesis, axonal regeneration, enhanced the microenvironment                  |
| Delivery of FFA                                                         | Prevented capillary fragmentation, induced angiogenesis, reduced hemorrhage and BSCB disruption |
| Knockdown of UTX                                                       | Increased vascular regeneration and promoted neurological recovery                          |
| Delivery of TRPV4 agonist                                              | Decreased inflammation, preserved BSCB, reduced scarring, improved functional outcome       |
| Administration of cocultured FPSS with ADAMTS13 overexpressing HUVECs   | Promoted neovascularization, microvascular formation and functional recovery                |

bFGF = basic fibroblast growth factor, Ang-1 = angiopoietin, FGF2 = fibroblast growth factor 2, CHABC = chondroitinase ABC, FFA = flufenamic acid, MMP-8 = Matrix Metalloproteinase-8, G-CSF = Granulocyte colony-stimulating factor, HGF = hepatocyte growth factor, TRPV4 = transient receptor potential vanilloid type 4, UTX = Ubiquitously Transcribed tetratricopeptide repeat on chromosome X, mR-210 = micro-RNA 210, mR-126 = MicroRNA-126, HADSCs = Human Adipose Tissue-derived Mesenchymal Stem Cells, NADSCs = human adipose tissue-derived mesenchymal stromal cells, NSPCs = neural stem/progenitor cells, hiPSCs = human-induced pluripotent stem cells, ECSs = endothelial cells, NPCs = neural progenitor cells, FPSS = fibrous porous silk scaffold, HUVECs = human umbilical vein endothelial cells, ADAMTS13 = ADAM Metalloproteinase with thrombospondin type 1 motif 13, AFG = aligned fibrin hydrogel, HA = hyaluronic acid, PLL= poly-L-lysine, antiNgR = nogo-66 receptor antibody, CS = collagen scaffold, CBD-VEGF = constructed protein, collagen-binding VEGF

**Conclusions**

Spinal cord injuries signify the onset of inherent pathological complex process. There is peremptory necessity for an extensive knowledge of all the intrinsic procedure occurring within the initial injury, so that the optimal conditions for the proper treatment and recovery will be ensured. Vascular disruption, following SCI, comes up with a dominant consistency, regarding the progression of the injury. Improved technological methods and multiple studies have been developed to ensure an adequate blood supply at the site of injury and develop well-functioned vascular system providing promising outcomes, however many aspects of both pathophysiological and angiogenic processes remain unspecified. Presumably, integration of proangiogenic strategies could provide braced outcomes, although further research is essential.
Disclosures

Conflicts of Interest: In compliance with the ICJIE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Jazayeri SB, Breyi S, Shokranee H, Hagen EM, Rahimi-Movaghar V: Incidence of traumatic spinal cord injury worldwide: a systematic review. Eur Spine J. 2015, 24:905-18. 10.1007/s00586-014-3524-6
2. Alizadeh A, Dyck SM, Karimi-Abdolrezae S: Traumatic spinal cord injury: an overview of pathophysiology, models and acute injury mechanisms. Front Neurol. 2019, 10:282. 10.3389/fneur.2019.00282
3. Masri R, Keller A: Chronic pain following spinal cord injury . Adv Exp Med Biol. 2012, 760:74-88. 10.1007/978-1-4614-4090-1_5
4. Austin JW, Aflar M, Fehlings MG: The relationship between localized subarachnoid inflammation and perechymal pathophysiology after spinal cord injury. J Neurotrauma. 2012, 29:1838-49. 10.1089/neu.2012.2534
5. Oyinbo CA: Secondary injury mechanisms in traumatic spinal cord injury: a nugget of this multiply cascade . Acta Neurobiol Exp (Wars). 2011, 71:281-99.
6. 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. 10.1007/s12975-011-0099-x
7. Haggerty AE, Maldonado-Lasuncion J, Oudega M: Biomaterials in neural repair. J. Neurotrauma. 2012, 29:1838-49. 10.1089/neu.2012.2534
8. Divi SN, Schroder GD, Oner FC, et al.: AOSpine-Spine Trauma Classification System: the value of modifiers: a narrative review with commentary on evolving descriptive principles. Global Spine J. 2019, 9:775-885. 10.1177/2192568219827260
9. Vaccaro AR, Lehman RA Jr, Hurbert RI, et al.: A new classification of thoracolumbar injuries: the importance of injury morphology, the integrity of the posterior ligamentous complex, and neurologic status. Spine (Phila Pa 1976). 2005, 30:2522-33. 10.1097/01.brs.0000182986.43545.ch
10. Roberts TT, Leonard GR, Celapa DJ: Classifications in brief: American Spinal Injury Association (ASIA) Impairment Scale. Clin Orthop Relat Res. 2017, 475:1499-504. 10.1199/1199-016-5135-4
11. Wasner G, Naleshinski D, Baron R: A role for peripheral afferents in the pathophysiology and treatment of at-level neuropathic pain in spinal cord injury? A case report. Pain. 2007, 131:219-25. 10.1016/j.pain.2007.05.005
12. Yeziereki RP: Pain following spinal cord injury: pathophysiology and central mechanisms . Prog Brain Res. 2000, 129:429-49. 10.1016/S0079-6123(00)29053-X
13. Nickel M, Gu C: Regulation of central nervous system myelination in higher brain functions . Neural Plast. 2018, 2018:6456453. 10.1155/2018/6456453
14. Fehlings MG, Agrawal S: Role of sodium in the pathophysiology of secondary spinal cord injury . Spine (Phila Pa 1976). 1995, 20:2187-91. 10.1097/00007632-199510001-00002
15. Allen AF: Surgery of experimental lesion of spinal cord equivalent to crush injury of fracture dislocation of spinal column. JAMA. 1911, LVII:878-80. 10.1001/jama.1911.0246090100008
16. von Leden RE, Vauger YJ, Khayrullina G, Byrnes KR: Immunomodulation after spinal cord injury: a narrative review with commentary on evolving descriptive principles. Global Spine J. 2019, 9:775-885. 10.1177/2192568219827260
17. Tran AP, Warren PM, Silver J: The biology of regeneration failure and success after spinal cord injury . J Neurotrauma. 2018, 35:1645-56. 10.1089/neu.2016.4486
18. Alizadeh A, Karimi-Abdolrezae S: Microenvironmental regulation of oligodendrocyte replacement and remyelination in spinal cord injury. J Physiol. 2016, 594:5359-52. 10.1113/JP270895
19. Serini G, Bussolino F: Common cues in vascular and axon guidance . Physiology (Bethesda). 2004, 19:548-54. 10.1152/physiol.00002.2004
20. Yao C, Cao X, Yu B: Revascularization after traumatic spinal cord injury . Front Physiol. 2021, 12:631500. 10.3389/fphys.2021.631500
21. Takigawa T, Vonezawa T, Yoshitaka T, et al.: Separation of the perivascular basement membrane provides a conduit for inflammatory cells in a mouse spinal cord injury model. J Neurotrauma. 2010, 27:739-51. 10.1089/neu.2009.1111
22. Oudega M: Molecular and cellular mechanisms underlying the role of blood vessels in spinal cord injury and repair. Cell Tissue Res. 2012, 349:269-88. 10.1007/s00441-012-1440-6
23. Losey P, Young C, Kimholdt E, Bordet R, Anthony DC.: The role of hemorrhage following spinal-cord injury . Brain Res. 2014, 1569:9-18. 10.1016/j.brainres.2014.04.053
24. Jin LY, Li J, Wang KF, et al.: Blood-spinal cord barrier in spinal cord injury: a review . J Neurotrauma. 2021, 38:2025-24. 10.1089/neu.2020.7415
25. Donnelly DJ, Popovich PG: Inflammation and its role in neuroprotection, axonal regeneration and functional recovery after spinal cord injury. Exp Neurol. 2008, 209:578-88. 10.1016/j.expneuro.2007.06.009
26. Carmeliet P: Angiogenesis in health and disease . Nat Med. 2003, 9:653-60. 10.1038/rmm0306-653
27. Adams RH, Etchmann A: Axon guidance molecules in vascular patterning . Cold Spring Harb Perspect Biol. 2010, 2:a001875. 10.1101/cshperspect.a001875
28. Flamme I, Frölich T, Riasu W: Molecular mechanisms of vasculogenesis and embryonic angiogenesis . J Cell Physiol. 1997, 175:206-10. 10.1002/sjcp.10997175206
29. Gianni-Barrera R, Butschkau A, Uccelli A, et al.: PDGF-BB regulates splitting angiogenesis in skeletal muscle by limiting VEGF-induced endothelial proliferation. Angiogenesis. 2018, 21:883-900. 10.1007/s10456-018-
intravenous infusion of bone marrow mesenchymal stem cells

Matsushita T, Lankford KL, Arroyo EJ, Sasaki M, Neyazi M, Radtke C, Kocsis JD: Mice contusion spinal cord injury in rats regulating vascular regeneration

Ni S, Luo Z, Jiang L, et al.: functional recovery after spinal cord injury

Kumar H, Jo MJ, Choi H, et al.: 10.1089/neu.2013.3143 adult rat spinal cord after chondroitinase ABC treatment

Milbreta U, von Boxberg Y, Mailly P, Nothias F, Soares S: Appl Neurobiol. 2011, 37:585-99. after spinal cord transection: effects of peripheral nerve graft and fibroblast growth factor 1

Disruption of blood spinal cord barrier in mice

Wu Q, Jing Y, Yuan X, et al.: 10.1089/neu.2010.1423 Lutton C, Young YW, Williams R, Meedeniya AC, Mackay-Sim A, Goss B: in injury and stroke using an engineered zinc finger protein that upregulates VEGF-A

D’Onofrio PM, Thayapararajah M, Lysko MD, et al.: cord injury

Herrera JJ, Nesic O, Narayana PA: injury improves functional outcome and decreases secondary degeneration in experimental spinal cord contusion

Widenfalk J, Lipson A, Jubran M, Hofstetter C, Ebendal T, Cao Y, Olson L: heart by controlling nerve growth factor expression

Oh JS, An SS, Gwak SJ, Pennant WA, Kim KN, Yoon DH, Ha Y: Hypoxia-specific VEGF-expressing neural stem cells in spinal cord injury model. Neuroreport. 2012, 23:174-8. 10.1097/WNR.0b013e32834f4e5a

Ieda M, Fukuda K, Hisaka Y, et al.: Endothelin-1 regulates cardiac sympathetic innervation in the rodent heart by controlling nerve growth factor expression. J Clin Invest. 2004, 113:876-84. 10.1172/JCI19480

Wardenfalk I, Lipson A, Juhan, Mofsetter C, Ebbatal, Cao Y, Olson L: Vascular endothelial growth factor improves functional outcome and decreases secondary degeneration in experimental spinal cord contusion injury. Neuroscience. 2005, 120:951-60. 10.1016/j.neuroscience.2005.03.009

Herreza JL, Nesis O, Narayana PA: Reduced vascular endothelial growth factor expression in contusive spinal cord injury. J Neurotrauma. 2009, 26:995-1005. 10.1089/neu.2008.0779

D’Onofrio PM, Thayapararajah M, Lyso MD, et al.: Gene therapy for traumatic central nervous system injury and stroke using an engineered zinc finger protein that upregulates VEGF-A. J Neurotrauma. 2011, 28:1863-79. 10.1089/neu.2011.1896

Lutton C, Young YW, Williams R, Meedeniya AC, Mackay-Sim A, Goss B: Combined VEGF and PDGF treatment reduces secondary degeneration after spinal cord injury. J Neurotrauma. 2012, 29:957-70. 10.1089/neu.2010.1423

Wu Q, Jing Y, Yuan X, et al.: Melatonin treatment protects against acute spinal cord injury-induced disruption of blood spinal cord barrier in mice. J Mol Neurosci. 2014, 54:714-22. 10.1007/s12035-014-0430-4

Lee Mj, Chen CJ, Huang WC, et al.: Regulation of chondroitin sulphate proteoglycan and reactive gliosis after spinal cord transaction: effects of peripheral nerve graft and fibroblast growth factor. 1. Neuropharmacol. 2011, 57:585-99. 10.1111/j.1476-5381.2011.01183.x

Milbreta U, von Boxberg Y, Mailly P, Nothias F, Soares S: Astrocytic and vascular remodeling in the injured adult rat spinal cord after chondroitinase ABC treatment. J Neurotrauma. 2014, 31:803-18. 10.1089/neu.2013.3145

Kawabe J, Koda M, Hashimoto M, et al.: Neuroprotective effects of granulocyte colony-stimulating factor and relationship to promotion of angiogenesis after spinal cord injury in rats: laboratory investigation. J Neurosurg Spine. 2011, 15:414-21. 10.3171/2011.5.SPINE10421

Kumar H, Jo MJ, Choi H, et al.: Matrix metalloproteinase-8 inhibition prevents disruption of blood-spinal cord barrier and attenuates inflammation in rat model of spinal cord injury. Mol Neurobiol. 2018, 55:2577-90. 10.1007/s12035-017-0509-3

Kitamura K, Iwamari A, Nakamura M, et al.: Hepatocyte growth factor promotes endogenous repair and functional recovery after spinal cord injury. J Neurosci Res. 2007, 85:2532-42. 10.1002/jn.151732

Kumar H, Lino CS, Choi H, et al.: Elevated TRPV4 levels contribute to endothelial damage and scarring in experimental spinal cord injury. J Neurosci. 2020, 40:1945-51. 10.1523/JNEUROSCI.0520-2020

Ni S, Luo Z, Jiang L, et al.: UTX/KDM6A deletion promotes recovery of spinal cord injury by epigenetically regulating vascular modulation. Mol Ther. 2019, 27:2134-46. 10.1038/s41397-018-0099-0

Hu J, Zeng L, Huang I, Wang G, Lu H: miR-126 promotes angiogenesis and attenuates inflammation after contusion spinal cord injury in rats. Brain Res. 2015, 1608:191-202. 10.1016/j.brainres.2015.02.056

Ujigo S, Kamet N, Hadouh H, et al.: Administration of microRNA-210 promotes spinal cord regeneration in mice. Spine (Phila Pa 1976). 2016, 41:1099-107. 10.1097/BRS.0000000000001055

Baraniak PR, McDevitt TC: Stem cell paracrine actions and tissue regeneration. Regen Med. 2010, 5:121-43. 10.2217/rems.09.74

Matsushita T, Lankford KL, Arroyo EJ, Sasaki M, Neyazi M, Radtke C, Kocsis JD: Diffuse and persistent blood-spinal cord barrier disruption after contusive spinal cord injury rapidly recovers following intravenous infusion of bone marrow mesenchymal stem cells. Exp Neurol. 2015, 267:152-64. 10.1016/j.expneurol.2015.03.001
61. Zhou HL, Zhang XJ, Zhang MY, Yan ZJ, Xu ZM, Xu RX: 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. 10.1007/s11064-016-1987-9
62. Zhou Z, Chen Y, Zhang H, Min S, Yu B, He B, Jin A: Comparison of mesenchymal stromal cells from human bone marrow and adipose tissue for the treatment of spinal cord injury. Cytotherapy. 2013, 15:453-48. 10.1016/j.jcyt.2012.11.015
63. 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. Pro Natl Acad Sci U S A. 2011, 108:16825-30. 10.1073/pnas.110677108
64. Kumagai G, Okada Y, Yamane J, et al.: Roles of ES cell-derived gliogenic neural stem/progenitor cells in functional recovery after spinal cord injury. PLoS One. 2009, 4:e7706. 10.1371/journal.pone.0007706
65. 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. 10.1111/j.1460-9568.2008.06567.x
66. Lien BV, Tuszyński MH, Lu P: Astrocytes migrate from human neural stem cell grafts and functionally integrate into the injured rat spinal cord. Exp Neurol. 2019, 314:46-57. 10.1016/j.expneurol.2019.01.006
67. Badner A, Vawda R, Lahilherte A, et al.: Early intravenous delivery of human brain stem cells modulates systemic inflammation and leads to vasoprotection in traumatic spinal cord injury. Stem Cells Transl Med. 2016, 5:991-1003. 10.5966/stemcells.2015-0295
68. Fujioka Y, Tanaka N, Nakanishi K, et al.: Magnetic field-based delivery of human CD133+ cells promotes functional recovery after rat spinal cord injury. Spine (Phila Pa 1976). 2012, 37:8768-77. 10.1097/BRS.0b013e318224edf7a
69. Ying X, Xie Q, Yu X, et al.: Water treadmill training protects the integrity of the blood-spinal cord barrier following SCI via the BDNF/TrkB-CREB signalling pathway. Neurochem Int. 2021, 145:104945. 10.1016/j.neuint.2020.104945
70. 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. 10.1007/s10456-017-9593-2
71. Sasaki H, Ishikawa M, Tanaka N, Nakanishi K, Kamei N, Asahara T, Ochi M: Administration of human peripheral blood-derived CD133+ cells accelerates functional recovery in a rat spinal cord injury model. Spine (Phila Pa 1976). 2009, 34:249-54. 10.1097/BRS.0b013e318181913cde
72. Kang CE, Clarkson T, Tator CH, Yeung IW, Shoichet MS: Spinal cord blood flow and blood vessel permeability measured by dynamic computed tomography imaging in rats after localized delivery of fibroblast growth factor. Exp Neurol. 2019, 314:46-57. 10.1016/j.expneurol.2019.01.006
73. Ying X, Xie Q, Yu X, et al.: Water treadmill training protects the integrity of the blood-spinal cord barrier following SCI via the BDNF/TrkB-CREB signalling pathway. Neurochem Int. 2021, 145:104945. 10.1016/j.neuint.2020.104945
74. 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. 10.1007/s10456-017-9593-2
75. Sasaki H, Ishikawa M, Tanaka N, Nakanishi K, Kamei N, Asahara T, Ochi M: Administration of human peripheral blood-derived CD133+ cells accelerates functional recovery in a rat spinal cord injury model. Spine (Phila Pa 1976). 2009, 34:249-54. 10.1097/BRS.0b013e318181913cde
76. Kang CE, Clarkson T, Tator CH, Yeung IW, Shoichet MS: Spinal cord blood flow and blood vessel permeability measured by dynamic computed tomography imaging in rats after localized delivery of fibroblast growth factor. Exp Neurol. 2019, 314:46-57. 10.1016/j.expneurol.2019.01.006
77. Ying X, Xie Q, Yu X, et al.: Water treadmill training protects the integrity of the blood-spinal cord barrier following SCI via the BDNF/TrkB-CREB signalling pathway. Neurochem Int. 2021, 145:104945. 10.1016/j.neuint.2020.104945
78. Samantaray S, Das A, Matzelle DC, et al.: Administration of low dose estrogen attenuates persistent inflammation, promotes angiogenesis, and improves locomotor function following chronic spinal cord injury in rats. J Neurochem. 2016, 137:604-17. 10.1111/jnc.13641
79. Yu S, Yao S, Wen Y, Wang Y, Wang H, Xu Q: Angiogenic microspheres promote neural regeneration and motor function recovery after spinal cord injury in rats. Sci Rep. 2016, 6:33428. 10.1038/srep33428
80. Ying X, Bai F, Chen H, Dong H: Melatonin prevents blood vessel loss and neurological impairment induced by spinal cord injury in rats. J Spinal Cord Med. 2017, 40:222-3. 10.1089/jnc.2016.1227912
81. 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. 10.2147/IJN.S159356
82. Wang L, Shi Q, Dai J, Gu Y, Feng Y, Chen L: 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. 10.1002/jor.23678
83. Yao S, Xu J, Yu T, et al.: Flufenamic acid inhibits secondary hemorrhage and BSCB disruption after spinal cord injury. Theranostics. 2018, 8:4181-98. 10.7150/thno.25707
84. 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, 29:15-24. 10.1089/scd.2019.0199