

Review

The Unique Properties of Placental Mesenchymal Stromal Cells: A Novel Source of Therapy for Congenital and Acquired Spinal Cord Injury

Edwin S Kulubya ^{1,2}, Kaitlin Clark ^{1,3}, Dake Hao ^{1,3}, Sabrina Lazar ^{1,3} , Arash Ghaffari-Rafi ², Tejas Karnati ², Julius Okudu Ebinu ², Marike Zwienenberg ², Diana L Farmer ^{1,3} and Aijun Wang ^{1,3,4,*} 

¹ Department of Surgery, Davis School of Medicine, University of California, Sacramento, CA 95817, USA; ekulubya@ucdavis.edu (E.S.K.); kcclark@ucdavis.edu (K.C.); dkhao@ucdavis.edu (D.H.); lazars@amc.edu (S.L.); Dlfarmer@ucdavis.edu (D.L.F.)

² Department of Neurological Surgery, Davis School of Medicine, University of California, Sacramento, CA 95817, USA; aghaffarirafi@ucdavis.edu (A.G.-R.); tkarnati@ucdavis.edu (T.K.); joebinu@ucdavis.edu (J.O.E.); mzwien@ucdavis.edu (M.Z.)

³ Institute for Pediatric Regenerative Medicine, Shriners Hospitals for Children, Sacramento, CA 95817, USA

⁴ Department of Biomedical Engineering, UC Davis, Davis, CA 95616, USA

* Correspondence: aawang@ucdavis.edu



Citation: Kulubya, E.S.; Clark, K.; Hao, D.; Lazar, S.; Ghaffari-Rafi, A.; Karnati, T.; Ebinu, J.O.; Zwienenberg, M.; Farmer, D.L.; Wang, A. The Unique Properties of Placental Mesenchymal Stromal Cells: A Novel Source of Therapy for Congenital and Acquired Spinal Cord Injury. *Cells* **2021**, *10*, 2837. <https://doi.org/10.3390/cells10112837>

Academic Editor: Alexander E. Kalyuzhny

Received: 16 September 2021

Accepted: 19 October 2021

Published: 22 October 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Abstract: Spinal cord injury (SCI) is a devastating condition with no reliable treatment. Spina bifida is the most common cause of congenital SCI. Cell-based therapies using mesenchymal stem/stromal cells (MSCs) have been largely utilized in SCI. Several clinical trials for acquired SCI use adult tissue-derived MSC sources, including bone-marrow, adipose, and umbilical cord tissues. The first stem/stromal cell clinical trial for spina bifida is currently underway (NCT04652908). The trial uses early gestational placental-derived mesenchymal stem/stromal cells (PMSCs) during the fetal repair of myelomeningocele. PMSCs have been shown to exhibit unique neuroprotective, angiogenic, and antioxidant properties, all which are promising applications for SCI. This review will summarize the unique properties and current applications of PMSCs and discuss their therapeutic role for acquired SCI.

Keywords: mesenchymal stromal cells; extracellular vesicles; spinal cord injury; spina bifida; myelomeningocele

1. Introduction

Cell-based therapies for spinal cord injury (SCI) have been investigated in preclinical and clinical trials with limited success [1,2]. The majority of these investigations use mesenchymal stem/stromal cells (MSCs) derived from adult tissue, including bone marrow, adipose, and umbilical cord tissues [2]. Recently, placental early gestational chorionic villus-derived MSCs (PMSCs) have been applied to treat spina bifida in utero [3].

Spina bifida, a congenital form of SCI, results from the incomplete closure of the spinal canal during development. Due to this incomplete closure, the fetal spinal cord is subjected to physical and chemical trauma in utero, causing prenatal damage to the exposed spinal cord [4,5]. Children born with spina bifida are often paralyzed in their lower extremities and suffer from bowel and bladder incontinence [4]. Studying this congenital form of SCI could provide useful insights into developing an effective cellular therapy for acquired and adult SCI.

Placental tissues have been investigated for their potential for autologous treatment in fetal surgery. Fetal surgery for spina bifida showed improved motor outcomes in the landmark Management of Myelomeningocele Study (MOMS) [6]. Despite this success, there were still patients who could not walk or had bowel and bladder incontinence. Novel cellular therapy has the potential to improve those outcomes. The placenta, which

maintains fetal immunological tolerance, is known to contain unique MSCs which display immunomodulatory, neuroprotective, angiogenic, and antioxidant properties [7]. The current review will explore the unique properties and current applications of PMSCs and their potential for both congenital and acquired SCI treatment.

2. Spinal Cord Injury Pathogenesis

Prior to discussion of treatment for congenital and acquired SCI, a robust understanding of the pathogenesis underlying SCI is required. Historically, SCI has been stratified into two phases: primary and secondary injury [8,9]. Primary injury involves the immediate period (i.e., within 2 h) after direct mechanical forces are imparted onto the spinal cord [8,9]. Subsequently, secondary injury ensues, a chronic and progressive phase involving vasogenic and cytotoxic edema, free radical production, neurotransmitter-mediated excitotoxicity, vascular dysfunction (i.e., hemorrhage, ischemia, necrosis), oligodendrocyte death (demyelination), reactive astrocytosis, postponed apoptotic cell death, and protracted Wallerian degeneration extending past six months from injury [8–10].

Primary injury, which encompasses the first two hours after SCI, sets the precedent for SCI severity and outcome [8–12]. The initial mechanical force on the cord—including but not limited to shearing, laceration, compression, or sudden impact—directly damages neural substrate and blood vessels, triggering the cascade of spinal shock, via axon severing, grey matter hemorrhage and necrosis, microglial activation, and upregulation of proinflammatory cytokines (IL-1 β , IL-1 α , TNF α , and IL-6) [8–15]. Traumatic demyelination of damaged axons occurs at the lesion site [16]. At the onset of injury, spinal cord swelling presides first, with gray matter and then white matter hemorrhaging secondary to vascular disruption [17,18]. While such findings may be evident pathologically, magnetic resonance abnormalities can be absent within the first two hours of injury, notwithstanding major structural disruption [19,20]. Given primary injury rarely fully transects the spinal cord, there is often the persistence of spared dysmyelinated or demyelinated axons traversing the injured substrate [8,9,21–24]. Animal models have demonstrated that preservation of even 5% of the initial axons can yield significant neurofunctional sustenance [8,9,25,26]. Such observations could account for the observed benefits from immediate decompression of the spinal cord during primary injury in humans [8,9,27,28].

Secondary injury temporally follows the primary phase and can be categorized as early acute (within 48 h of injury), secondary subacute (within 14 days), intermediate (within 6 months), and chronic (past 6 months) [8,9]. During the early acute period (2–48 h), cord inflammation, edema, and hemorrhage continue to progress, yet are compounded by free radical mediated injury, loss of ionic homeostasis, glutamate-induced excitotoxicity, permeability of the blood–brain barrier, inflammatory cell infiltration, demyelination, and cell death [8,29–38]. Demyelination and Wallerian degeneration progress in both a rostral and caudal manner to the lesion in this secondary phase [16]. After, the subacute phase (2–14 days) ensues, which is marked by a maximal phagocyte response and initiation of reactive astrocytosis (astroglial scar formation) [8,31,39]. In the intermediate phase (2 weeks to 6 months), the astrocytic scar continues to mature, yet simultaneously corticospinal (3 weeks to 3 months) and reticulospinal tract (3 to 6 months) axons begin sprouting, highlighting the regenerative potential at even 6 months post-injury [8,40]. Finally, from 6 months and beyond, the chronic phase initiates, where the SCI lesion continues scarring with development of cysts and syrinxes [8,9]. At roughly 1–2 years post-injury, the lesion stabilizes and potential for neurologic recovery ceases; however, with syrinx formation, delayed neurofunctional deterioration may occur in an estimated 30% of patients as the syrinx expands, inducing ascending paralysis, brainstem symptoms, or neuropathic pain [8,9,41,42].

Studies involving animal models have recognized the subacute phase as the critical period to promote functional recovery via neural transplantation—cells transplanted prior or after the subacute phase often fail to stimulate functional recovery [43,44]. The optimal milieu for transplantation likely arises secondary to the significant macrophage

infiltration—which removes cell debris, including growth-inhibitory molecules—and astrocyte-mediated interventions (blood–brain barrier repair, edema resolution, ionic homeostasis reestablishment, and limitation of immune cell infiltration) [8,31,39,43,45].

In summary, while there may be potential for some neurofunctional recovery at 1–2 years post-injury, given the current understanding of SCI pathophysiology, earlier intervention (especially at the primary and sub-acute phases) likely imparts the greatest benefit for patients. Ideally, cellular treatments could coincide with the timing of surgery, which, when carried out within 24 h, improves outcomes and provide neuroprotection in the acute phase [28].

In terms of congenital SCI, myelomeningocele (MMC), the most severe form of spina bifida, is thought to derive from a “two-hit” hypothesis. The “first hit” is the failure of neural tube closure. The vertebral arches are spread wide, the dura is open and fused to the deep dermis of the skin, and the open pia mater is not covering neural tissue but rather connected to superficial dermis and epidermis [46,47]. The “second hit” is degeneration of the spinal cord in utero [48,49]. The developing spinal cord is not only exposed to physical trauma within the uterus but also the enzymatic activity of amniotic fluid [50]. Direct trauma can be visualized as focal hemorrhages and abrasions of the spinal cord at birth. In a study of MMC fetuses there were varying degrees of preserved neural tissue at the MMC defect [46]. This secondary injury is the rationale for fetal repair for spina bifida [51].

In a retinoic acid induced rat model of MMC, fetal spinal cords exposed to amniotic fluid showed astrogliosis, neuroinflammation and reactive microgliosis [52]. Elevated glial fibrillary acidic protein (GFAP) can also be seen in amniotic fluid, signifying neural tissue degeneration [53]. Significant cord edema is also present in animal models of MMC, similar to what is seen in acquired SCI pathology [52,54]. Studying the mechanisms of secondary injury in both types of SCI could inform targeted therapy to inhibit inflammation and support neuronal and glial cell survival and recovery.

3. Properties of Placental Mesenchymal Stem/Stromal Cells

3.1. Isolation and Culture

Placental stem/stromal cells (PMSCs) are typically harvested through an explant culture method from donated placentas or chorionic villus sampling. Lankford et al. described methods to isolate, expand, and bank early gestational PMSCs for use as stem cell therapy [55,56]. In brief, the chorionic villus tissue is carefully dissected from placental tissues then washed in a sterile solution of phosphate-buffered saline (PBS) containing 100 U/mL penicillin and 100 g/mL streptomycin, minced into <1 mm³ fragments and then cultured and maintained in stem cell culture media. These methods are extremely feasible and can generate cell populations on the order of 10⁹ cells in less than four weeks. PMSCs show higher plasticity compared with MSCs derived from adult tissue sources [7]. In a comparison study to bone marrow, umbilical cord, and adipose-derived MSCs, PMSCs had the highest proliferative capacity and could withstand longer periods of culture [57]. Barlow et al. demonstrated similar results showing superior proliferation capabilities at different seeding densities compared with more commonly sourced bone marrow MSCs [58].

3.2. PMSC Characterization

PMSCs have demonstrated multipotency and can differentiate into osteogenic, adipogenic, and chondrogenic phenotypes [55]. There have been reports of PMSC differentiating into neurons, oligodendrocytes, and glial cells [59–61]. PMSCs have also been shown to be positive for well-established MSC surface markers CD105, CD90, CD73, CD44, and CD29 [56]. Transcription factors Sox10 and Sox17 and intracellular stem cell-related proteins Nestin, S100 β , and neurofilament medium have been found in PMSCs [56]. Wang et al. cultured PMSCs in a collagen hydrogel and found they secreted a wide variety of growth factors in the first 24 h of culture. The highest were urokinase plasminogen activator (uPA), vascular endothelial growth factor (VEGF), TIMP-1, hepacyte growth factor (HGF), thrombospondin-1, monocyte chemoattractant protein 1 (MCP-1), interleukin (IL)-8,

serpin E1, serpin F1, and macrophage migratory inhibitory factor, all of which play key roles in angiogenesis, chemotaxis, extracellular matrix remodeling, and innate immune responses [62].

Similar to bone marrow-derived MSCs (BM-MSCs), PMSCs also express higher levels of alpha 4 beta 1 ($\alpha 4 \beta 1$), also known as very late antigen (VLA)-4 which facilitates endothelium adherence and helps MSCs home to sites of injury [63]. VLA-4 expression on MSCs can interact with inflammatory cell subsets, including circulating leukocytes and modulate infiltration of cell subsets into inflamed tissues. Therefore, expression of VLA-4 by PMSCs can modulate migration through binding the endothelium of the blood–brain barrier (BBB) into the central nervous system (CNS) [1,64].

3.3. PMSC-Secretome—Free Proteins

The efficacy of MSCs is understood to occur primarily through paracrine signaling effects rather than direct cell engraftment [1,65–68]. Cytokine arrays and single cell analysis have studied the secretome of PMSCs, which is key to understanding the differences between various MSCs. Early gestation PMSCs when compared with BM-MSCs secreted significantly higher levels of brain-derived neurotrophic factor (BDNF) and HGF [62]. BDNF has been shown to be an important regulator in neuronal differentiation [69]. BM-MSCs applied in stroke and SCI animal models correlated increased levels of BDNF with nerve growth factor and demonstrated improved motor function [70].

3.4. PMSC Secretome—Extracellular Vesicles (EVs)

The secretome of PMSCs also includes extracellular vesicles (EVs). EVs are membrane-bound nanovesicles containing proteins, DNA and RNA, and can be classified as apoptotic bodies, microvesicles, and exosomes [71]. EVs have the ability to reach sites of injury in the CNS by naturally crossing the BBB [72,73]. Nanosized exosomes could also more efficiently reach the target organ than larger MSCs [74]. Advantages of MSC-derived EVs over cellular therapy include safety, lack of tumorigenicity, and lower immunogenicity [73–75]. EVs also have the potential to be a readily available cell-free, off the shelf product as opposed to MSCs, which need to be thawed, cultured, and maintained before clinical applications.

EVs can be isolated through ultracentrifugation, precipitation, immunoaffinity size-exclusion chromatography, and ultrafiltration methods. Consistent isolation and purification at a large scale remains a limitation for all MSC-derived EVs [71]. Heterogeneity of EV preparations can make the mechanism of action studies challenging; however, this is an active area of research and new optimizations are constantly being developed. Standardization of intervention strategies will be key for translation applications using PMSCs or PMSC-EVs for the treatment of SCI.

4. Potential PMSC Therapeutic Mechanisms

4.1. Neuroprotection

Proteomic analysis of PMSC EVs revealed the presence of several proteins and RNAs involved in neuronal survival. As discussed, free proteins such as growth factors BDNF and HGF have neuroprotective properties. Conditioned medium (CM) and CM supplemented with HGF from bone marrow MSCs was shown to promote neural stem cell differentiation and neurite outgrowth in a rat model of SCI. [76]. Additionally, human BM-MSCs genetically modified to overexpress BDNF-preserved cortical neurons, and promoted axon sprouting, resulting in functional recovery in a rat model of acute SCI [77]. Additionally, galectin-1, an evolutionarily conserved β -galactoside-binding lectin, has been shown to have neuroprotective and immunomodulatory functions, is also highly expressed on PMSCs. [78] While PMSCs have been shown to have increased expression of several mediators including BDNF, HGF, and galectin-1, leading to superior neuroprotective effects, these mediators have multifaceted functional properties and can also be involved in the immunomodulatory and pro-angiogenic properties of PMSCs.

MSC-derived EVs can cross the blood–brain barrier, making them a promising courier for CNS targeting (Figure 1). PMSC-EVs have potent neuroprotective properties and contain proteins and RNAs which protect neurons from apoptosis induced by staurosporine [78]. Indirect coculture of PMSCs, PMSC EVs with apoptotic SH-SY5Y cells, showed the ability of PMSCs and PMSC EVs alone to protect dying neurons. Subsequent, neuron analysis showed an increased number of branching points, circuitry length, and tube length [78].

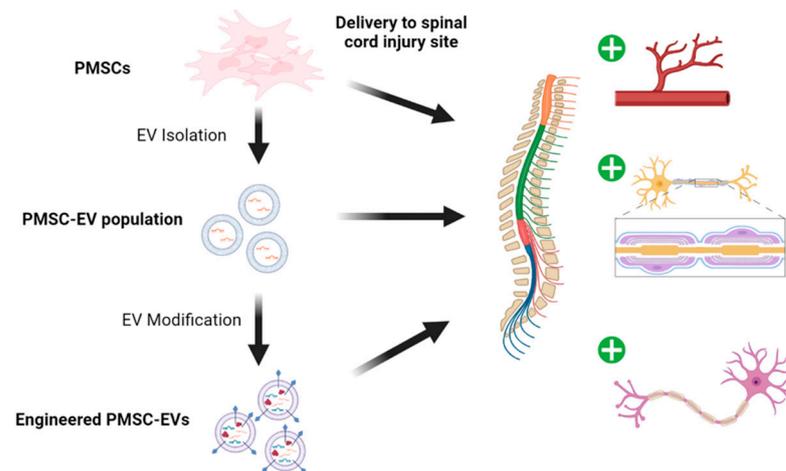


Figure 1. PMSCs, PMSC-EVs and engineered PMSC-EVs can each confer therapeutic effects in SCI by stimulating angiogenesis, remyelination, neuroprotection, and reducing inflammation.

4.2. Immunomodulation

The placenta, which helps maintain fetal tolerance, contains cells which display distinctive immunomodulatory properties [7]. Targeting the immune response in SCI has been studied with the testing of drugs such as minocycline and VX-210/BA-210 [15,79–81].

Following injury in the spinal cord, damage to resident oligodendroglia, axons, and neurons will occur due to mechanical injury, oxidative stress, and robust pro-inflammatory cytokines and chemokines. Modulation of pro-inflammatory responses including interleukin (IL)-1 β , IL-6, IL-8, MCP-1 and TNF α have been shown to attenuate symptoms associated with SCI [82–84]. Neuroinflammation and microglia activation are seen in several neurodegenerative diseases and contribute to chronic neurodegeneration after SCI [85]. Macrophages are essential for reconstruction of repaired tissue but can also damage neurons and glia. Macrophages in the spinal cord arise from activated resident microglia and blood-borne monocytes, the latter of which are believed to be effectors of secondary injury [86]. Within microglia, two phenotypes—M1 and M2—have been identified and play unique roles in SCI pathology; the M1 phenotype is pro-inflammatory and the M2 phenotype, by contrast, is anti-inflammatory [81]. MSC-derived EVs have been shown to modulate macrophage and microglia polarization by modulating M1 pro-inflammatory responses and driving an M2 anti-inflammatory phenotype [87]. Prolonged M1 responses can have detrimental effects in the context of SCI, and M2 phenotypes can promote axonal regeneration [84,88,89].

Several studies have reported that BM MSC-EVs improve SCI outcome by reducing microglia activation of neurotoxic reactive astrocytes [90]. BM-MSC EVs may also modulate activation of astrocytes by reducing NF- κ B signaling pathways and complement signaling activation [91]. Lee et al. demonstrated that PMSCs are more likely to have a stronger immunosuppressive function versus bone marrow- and adipose-derived MSCs due to increased expression of HLA-ABC and HLA g in PMSCs compared with others [92]. Similar results were seen by Chang et al. which showed decreased lymphocyte reactivity and increased numbers of regulatory T cells after mitogen or alloantigen stimulation [93]. PMSCs have also shown strong immunosuppressive effects in graft versus host disease

animal models [94,95]. MSCs from several tissue sources have been shown to reduce lymphocyte proliferation and reduce pro-inflammatory mediators in vitro [94,96]. In a canine model of inflammatory brain disease, PMSCs reduced TNF α -induced inflammatory responses in vitro by attenuating pro-inflammatory cytokines and inhibiting leukocyte proliferation by inducing apoptosis [97]. Additionally, canine PMSCs were shown to be more robustly immunosuppressive compared with ASCs, which were found to inhibit leukocyte proliferation causing cell cycle arrest [97]. These findings demonstrate that while MSCs from differing tissue sources are immunosuppressive the mechanism of action differs, suggesting therapeutic intervention strategies may need to be optimized for different disease targets.

MSC-mediated immunosuppression has been suggested to occur in part by the induction of regulatory T cells. The unique properties of PMSCs have been illustrated in T cell responses to mitogen and allogeneic cell simulations [93,98]. One mechanism for these properties is the expression of programmed death ligand (PD-L)1 and FasL immunomodulation mediated by PMSCs [99]. Promotion of a regulatory T cell subset has been shown in the experimental autoimmune encephalitis (EAE) model to promote oligodendrocyte differentiation and re-myelination [100]. The findings from this study demonstrate modulating the microenvironment and immune response in SCI, which can lead to downstream effects that preserve and promote regeneration of neural cell subsets including myelination oligodendrocytes.

4.3. Myelin Regeneration

Myelin regeneration is an attractive therapeutic target for SCI in the interest of regaining functional motor outcomes. Following injury, remyelination occurs as oligodendrocyte precursor cells home to damaged axons, a process which can be modulated by resident immune cells including astrocytes and microglia [101]. Environmental cues will promote differentiation of oligodendrocyte precursor cells (OPCs) to become mature myelinating oligodendrocytes. Therefore, intervention strategies for CNS disorders including SCI target the promotion of remyelination by altering the injured microenvironment to promote OPC maturation or replacing damaged or destroyed myelinating oligodendrocyte populations [101]. MSC-EVs have been studied for their potential to promote myelin regeneration. In an EAE model of multiple sclerosis (MS), PMSC EVs increased re-myelination by the maturation of oligodendrocyte precursor cells to mature oligodendrocytes [102]. HGF has been shown to play a role in remyelination through promoting development of oligodendrocytes and neurons in models of EAE [103]. The mechanism by which PMSC and PMSC-EVs promote remyelination is multifaceted. The ability of PMSCs and PMSC-EVs to modulate inflammatory responses may create a microenvironment that allows for superior OPC homing and maturation thus resulting in re-myelination. Additionally, these cells and nanoparticles can also interact directly with oligodendrocyte populations to promote re-myelination. Many studies have demonstrated MSC and MSC-EV promotion of myelination of chronic MS; however, the mechanism of action is not fully elucidated in the literature [104,105]. Therefore, further studies are warranted and in the context of SCI and acute injury.

4.4. Angiogenesis

SCI causes vasculature disruption and compromise of the blood–spinal cord barrier. The following ischemia and inflammation can also cause further damage and neurological deficits. Given these vascular changes after SCI, understanding the regulation of angiogenesis is key, as angiogenesis facilitates post-SCI recovery and plays an important role in SCI repair [106,107]. MSCs secrete proangiogenic factors such as VEGF, HGF, and BDNF [108]. Hao et al. demonstrated that early gestational PMSCs had high-level secretion of VEGF, HGF, and BDNF, indicating that early gestational PMSCs possess strong angiogenic properties [109]. In addition, MSC-derived EVs have recently been used for therapeutic angiogenesis in ischemic disease [110]. Hao et al. also demonstrated that

PMSC-EVs provided strong angiogenic properties via *in vitro* EC migration and *ex vivo* aortic ring sprouting assays [111].

5. PMSC and PMSC-EV Bioengineering

5.1. Delivery

Scaffolds and injectable hydrogels have been designed to enhance survival and support potential stem cell engraftment and differentiation of various cell types in injured tissue [2]. PMSCs have been seeded on collagen hydrogel and fibrin glue as well as nanofiber scaffolds made of synthetic polymers [56]. In contrast to injected cell therapies, bioscaffolds limit mass diffusion away into the vasculature, can be applied directly to injury sites, and allow for sustained release of therapeutic secretions. PMSCs have been shown to adhere well onto collagen and electrospun scaffolds, and in this 3D culture, can even differentiate into neuronal-like cells while attached to the scaffold [112]. This expands their potential and can be applied to areas of neuronal cell death, such as in SCI.

The viability of PMSCs on an SIS-ECM scaffold has been validated by Lankford et al., with an optimal seeding density between 3×10^5 and 5×10^5 cells/cm² [55]. MSCs seeded on SIS-ECM have also been shown to release more pro angiogenic factors, specifically VEGF and IL-8 [113]. MSC-derived EVs have also been shown to adhere well to both organic and synthetic bioscaffolds, and can still impart their therapeutic effects when implanted.

Hypoxic preconditioning can also be used to improve survival and engraftment of MSCs derived from different tissue. Hao et al. have demonstrated that hypoxic preconditioning significantly improved survival and angiogenic secretion of early gestational PMSCs [109,114,115].

5.2. Surface Modification

One limitation of EVs in treating CNS disorders is the issue of biodistribution after systemic administration. In some studies, EVs have been seen to accumulate in the spleen and liver and very few are detected in the CNS [116]. To address this limitation, ligand modification of EVs can improve longevity and cell- or tissue-specific targeting. It has been shown that EVs modified with a rabies virus glycoprotein (RVG) peptide cross the blood-brain barrier and deliver siRNA and miRNAs to injured brain tissue [117–119]. Another peptide, targeted axonal import (TAXI), can deliver protein cargo into spinal cord motor neurons by retrograde transport after intramuscular injection [120]. PMSC-EV plasma membranes can easily carry modified peptides and transmembrane proteins, and often carry “self” markers characteristic of their parent cell type [121]. Hao et al. developed an approach to utilize integrin $\alpha 4\beta 1$, highly expressed on surfaces of PMSCs and PMSC-EVs, to bind ligands with various capabilities on to the PMSC-EV surface [111,122]. The capability of EVs to retain desired surface modification and cross the BBB make EVs ideal for the targeted delivery of neuroprotective therapy.

5.3. Cargo Loading

EVs naturally contain small RNAs including microRNAs (miRNAs), which have numerous signaling and regulatory roles in the CNS, such as immunomodulation and spinal cord regeneration. EV contents can easily be modified to contain miRNAs and siRNAs for site-specific delivery [123]. For example, miR-210-loaded MSC EVs promoted angiogenesis and improved the survival rate of rats in a model of cerebral ischemia [124]. miR-124 is known to play a role in neurogenesis and brain homeostasis. miR-124-loaded EVs delivered intranasally in mice attenuated the activation of inflammatory microglia [125]. PMSCs EVs have the potential to be loaded with miRNA, proteins, or pharmaceuticals to treat SCI.

6. Applications of PMSCs in SCI

6.1. Congenital SCI

PMSCs are the first stem/stromal cells to be studied in a clinical trial for the fetal treatment of congenital SCI. Preclinical work involved ovine and rat models of myelomeningo-

cele. Fetal rats with MMC treated with PMSCs displayed less spinal cord compression and decreased apoptotic cell density in an ovine model; an MMC defect was surgically created in fetal sheep and then later repaired in utero [62,126,127]. In these studies, PMSCs seeded on an ECM were applied directly to the exposed spinal cord before repairing the open defect. Only lambs who received PMSC cell treatment were able to ambulate after birth. The density of large neurons was significantly greater in cell-treated lambs and correlated with motor score. There was no engraftment of GFP-labeled PMSCs in the spinal cords or tissues, suggesting a solely paracrine effect [62]. Although the mechanism is not fully elucidated, PMSCs in the fetal environment seem to augment healing and tissue regeneration.

6.2. Acquired SCI

A few groups have begun to investigate PMSCs in SCI. In a canine transection SCI model, PMSCs from discarded term placentas seeded on a linear ordered collagen scaffold promoted neuronal regeneration and functional motor recovery [128]. Histological analysis revealed decreased CSPG deposits, increased axon regeneration and remyelination, and increased ascending and descending sensory nerve fibers [128]. Zhou et al. demonstrated PMSC-EVs injected into a rat model of transectional SCI, PMSC-EVs alleviated neurogenic bladder function, promoted functional recovery by activating endogenous progenitor cell markers, stimulated neural stem cell proliferation, and were selectively taken up by neural stem cells [129]. Li et al. described an innovative implantation of PMSC-EVs that were immobilized in a peptide-modified adhesive hydrogel and delivered directly into injured nerve tissue in a rat long-span spinal cord transection model; the implantation demonstrated significant nerve recovery and urinary tissue preservation by effectively mitigating inflammation and oxidation [130].

In a mouse spinal cord contusion model, PMSC-EV application was associated with improved angiogenesis and tube formation via human umbilical cord vein epithelial cell (HUVEC) migration, and hindlimb sensory and locomotor responses [131]. The proangiogenic properties of PMSCs are beneficial as SCI causes local vascular damage, which can lead to ischemia and limit proper healing.

PMSCs and PMSC-EVs have also been applied to treat SCI caused by other reasons, such as multiple sclerosis [128]. Several other preclinical studies involving MSC-EVs have been conducted in recent years, proposing that MSC-EVs can induce angiogenesis, axon formation, regulate inflammation and the immune response, inhibit apoptosis, and maintain integrity of the blood–spinal cord barrier [132].

In a preliminary animal study, we applied our PMSCs and PMSC-EVs seeded on an extracellular matrix scaffold (SIS-ECM) to a rat C5 spinal cord hemicontusion model. As shown in Figure 2, C5 spinal cord hemicontusion was performed after hemilaminectomy (Figure 2a). PMSCs seeded on SIS-ECM were then directly placed onto the injured spinal cord after dura was opened (Figure 2b). The preliminary study showed that PMSCs seeded on SIS-ECM can be surgically applied to the local SCI site. Similar to the clinical trial for fetal repair of spina bifida, PMSCs seeded on a SIS-ECM scaffold can be placed directly on the injured spinal cord (Figure 2). Translationally, the SIS-ECM scaffold can serve as a dural graft, if a duroplasty is performed during the decompression of the spinal cord after SCI.

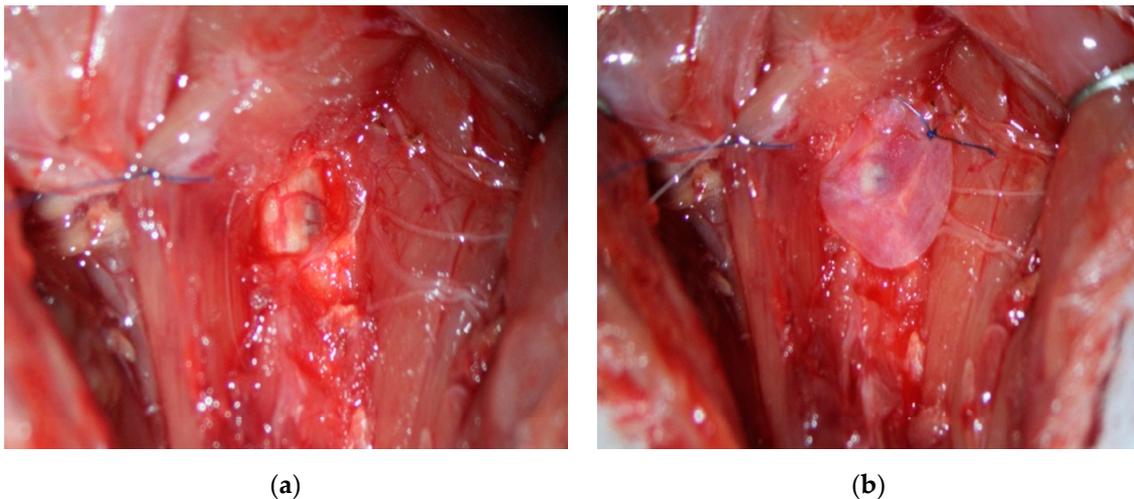


Figure 2. Surgical implantation of PMSCs seeded on an extracellular matrix scaffold (SIS-ECM) to a rat C5 spinal cord hemicontusion model. (a) Contused spinal cord visible after C5 hemilaminectomy and impact in an adult rat. (b) Placement of PMSCs seeded on SIS-ECM scaffold directly placed onto spinal cord after dura was opened.

7. MSCs and PMSCs in Clinical Trials

There are currently several active clinical trials utilizing MSCs in SCI; however, none use PMSCs as a source [133–135] (Table 1). Cells can be delivered intravenously, intrathecally, or intramedullary. The primary outcomes for most trials are improvement in motor function typically measured by the American Spinal Injury Association Impairment (ASIA) Scale (AIS) Score.

Table 1. Active clinical trials utilizing mesenchymal stem cells for spinal cord injury.

Trial Identifier	Name	Phase	Key Inclusion Criteria	Therapy
NCT03505034	Intrathecal Transplantation of UC-MSc in Patients with Late Stage of Chronic Spinal Cord Injury	2	Age 18–65 ASIA Scale A–D Injury more than 12 months	Intrathecal Transplantation of UC-MSCs, 10^6 cells/kg, once a month for 4 months
NCT03521336	Intrathecal Transplantation of UC-MSc in Patients with Sub-Acute Spinal Cord Injury	2	Age 18–65 ASIA Scale A–D Injury 2 weeks to 2 months	Intrathecal Transplantation of UC-MSCs, 10^6 cells/kg, once a month for 4 months
NCT03521323	Intrathecal Transplantation of UC-MSc in Patients with Early Stage of Chronic Spinal Cord Injury	2	Age 18–65 ASIA Scale A–D Injury 2 months to 12 months	Intrathecal Transplantation of UC-MSCs 10^6 cells/kg, once a month for 4 months
NCT02574585	Autologous Mesenchymal Stem Cells Transplantation in Thoracolumbar Chronic and Complete Spinal Cord Injury	2	Age 18–65 ASIA Scale A Injury T1–L2 with at least 12 months	Two percutaneous injections of MSCs, with a 3-month interval between the injections
NCT05018793	Safety of Cultured Autologous Adult Adipose-Derived Mesenchymal Stem Cell Intrathecal Injection for SCI	1	Diagnosis of Spinal Cord Injury	Single intrathecal injection of 100 million cells

Table 1. Cont.

Trial Identifier	Name	Phase	Key Inclusion Criteria	Therapy
NCT02688049	NeuroRegen Scaffold™ Combined with Stem Cells for Chronic Spinal Cord Injury Repair	1, 2	Age 18–65 ASIA Scale A Injury C5-T12	Patients with chronic SCI (ASIA grade A) will receive NeuroRegen Scaffold with 10 million MSCs transplantation after localized scars cleared
NCT04520373	Autologous Adipose-Derived Mesenchymal Stem Cells for Spinal Cord Injury Patients	2	Age >18 ASIA Scale A, B	Patients will receive a single dose of autologous, adipose-derived MSCs one time
NCT03308565	Adipose Stem Cells for Traumatic Spinal Cord Injury (CELLTOP)	1	Age >18 ASIA Scale A, B Injury 2 weeks to 1 year	Patients will receive a single dose of 100 million autologous, adipose derived MSCs
NCT02917291	Safety and Preliminary Efficacy of FAB117-HC in Patients with Acute Traumatic Spinal Cord Injury	1, 2	Age 16–70 Phase 1—ASIA A, Injury 72–120 h prior Phase 2—ASIA A, B, Injury up to 96 h prior	Intramedullary administration of FAB117-HC (Adipose Derived Adult MSCs Expanded and Pulsed with H ₂ O ₂)
NCT04213131	Efficacy and Safety of hUC-MSCs and hUCB-MSCs in the Treatment of Chronic Spinal Cord Injury	n/a	Age 20–65 ASIA A-D with no change Injury over 1 year	Intravenous, lumbar, and local administration of hUC-MSCs/hUCB-MSCs

These current SCI clinical trials utilize MSCs derived from bone marrow, adipose, and umbilical cord. Umbilical cord MSCs (UC-MSCs) also derived from perinatal tissue and fetal origin are more like PMSCs than bone marrow or adipose cells [136]. UC-MSCs have been demonstrated to decrease astrogliosis in SCI, downregulate T-cell-mediated inflammation, and survive long after transplantation [137–139]. Adipose-derived MSCs have been associated with increased angiogenesis, axonal regeneration, and extracellular matrix formation [140,141]. PMSCs with their neuroprotective, angiogenic, and antioxidant are ready to be added to the milieu of MSC sources for spinal cord injury. Future research may seek to compare MSC sources to elucidate their individual effects and ability to treat specific diseases.

Cellular therapy for in utero repair of myelomeningocele – The CuRe Trial, is the first clinical trial utilizing MSCs for congenital SCI [142]. PMSCs used in the CuRE Trial and are also being investigated in other diseases. PMSCs due to their immunomodulatory effects have been effective in treating steroid refractory acute graft-versus-host disease; Ringden et al. showed a remarkable 73% survival rates in patients versus 6% in retrospective controls in a 1-year follow-up [143]. PMSCs have also been used to treat epidermolysis bullosa, a severe blistering skin disease that causes multiple cutaneous wounds from birth [144]. There are currently trials utilizing PMSCs in treating diabetic foot ulcer, COVID-19 pneumonia, and osteoarthritis [145–147].

8. Conclusions

The feasibility and safety of PMSCs and PMSC-EVs should encourage their use in more preclinical and clinical trials for SCI. Additionally, PMSCs and PMSC-EVs have shown promise in site-specific targeting and could be optimized for more precise targeting and specialized cargo delivery or downstream regenerative cell signaling cascades. PMSCs are easily isolated and can lend their immunomodulatory, antioxidant, angiogenic, and neuroprotective capabilities to SCI treatment. In summary, PMSCs and PMSC-EVs have

unique functional and therapeutic properties making them ideal targets for developing treatments for SCI.

Author Contributions: Conceptualization, E.S.K. and A.W.; writing—original draft preparation, E.S.K., K.C., D.H., S.L., A.G.-R., T.K.; writing—review and editing, E.S.K., K.C., D.H., S.L., A.G.-R., T.K., J.O.E., M.Z., D.L.F. and A.W. All authors have read and agreed to the published version of the manuscript.

Funding: Financial support for this study was provided by the Shriners Hospitals for Children Postdoctoral Fellowship (84705-NCA-19) and research grants (85108-NCA-19 and 85135-NCA-21), National Institutes of Health grants (5R01NS100761 and 1R01NS115860), Craig H. Neilsen Foundation grant (546558), and California Institute for Regenerative Medicine (CIRM) grants (PC1-08103, CLIN1-11404, CLIN2-12129). Kaitlin Clark was supported by the Willis W. and Ethel M. Clark Foundation Investment in Community Fellowship, the Lodric Maddox Graduate Fellowship, and the National Center for Advancing Translational Sciences, National Institutes of Health, through grant number UL1 TR001860 and linked award TL1 TR001861. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not Applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Cofano, F.; Boido, M.; Monticelli, M.; Zenga, F.; Ducati, A.; Vercelli, A.; Garbossa, D. Molecular Sciences Mesenchymal Stem Cells for Spinal Cord Injury: Current Options, Limitations, and Future of Cell Therapy. *Int. J. Mol. Sci.* **2019**, *20*, 2698. [CrossRef]
2. Jin, M.C.; Medress, Z.A.; Azad, T.D.; Doulames, V.M.; Veeravagu, A. Stem Cell Therapies for Acute Spinal Cord Injury in Humans: A Review. *Neurosurg. Focus* **2018**. [CrossRef] [PubMed]
3. Marketing, U.D.H. Public Affairs and First Stem Cell Clinical Trial for Spina Bifida Treatment Announced. Available online: <https://health.ucdavis.edu/health-news/newsroom/first-stem-cell-clinical-trial-for-spina-bifida-treatment-announced/2021/03> (accessed on 14 August 2021).
4. Mitchell, L.E.; Adzick, N.S.; Melchionne, J.; Pasquariello, P.S.; Sutton, L.N.; Whitehead, A.S. Spina Bifida. *Lancet* **2004**, *364*, 1885–1895. [CrossRef]
5. Dewan, M.C.; Wellons, J.C. Fetal Surgery for Spina Bifida: JNSPG 75th Anniversary Invited Review Article. *J. Neurosurg. Pediatr.* **2019**, *24*, 105–114. [CrossRef] [PubMed]
6. Adzick, N.S.; Thom, E.A.; Spong, C.Y.; Brock, J.W.; Burrows, P.K.; Johnson, M.P.; Howell, L.J.; Farrell, J.A.; Dabrowiak, M.E.; Sutton, L.N.; et al. A Randomized Trial of Prenatal versus Postnatal Repair of Myelomeningocele. *N. Engl. J. Med.* **2011**, *364*, 993–1004. [CrossRef] [PubMed]
7. Parolini, O.; Alviano, F.; Bagnara, G.P.; Bilic, G.; Bühring, H.-J.; Evangelista, M.; Hennerbichler, S.; Liu, B.; Magatti, M.; Mao, N.; et al. Concise Review: Isolation and Characterization of Cells from Human Term Placenta: Outcome of the First International Workshop on Placenta Derived Stem Cells. *Stem Cells* **2008**, *26*, 300–311. [CrossRef] [PubMed]
8. Rowland, J.W.; Hawryluk, G.W.J.; Kwon, B.; Fehlings, M.G. Current Status of Acute Spinal Cord Injury Pathophysiology and Emerging Therapies: Promise on the Horizon. *Neurosurg. Focus* **2008**, *25*, E2. [CrossRef] [PubMed]
9. Alizadeh, A.; Dyck, S.M.; Karimi-Abdolrezaee, S. Traumatic Spinal Cord Injury: An Overview of Pathophysiology, Models and Acute Injury Mechanisms. *Front. Neurol.* **2019**, *10*, 282. [CrossRef] [PubMed]
10. Venkatesh, K.; Ghosh, S.K.; Mullick, M.; Manivasagam, G.; Sen, D. Spinal Cord Injury: Pathophysiology, Treatment Strategies, Associated Challenges, and Future Implications. *Cell Tissue Res.* **2019**, *377*, 125–151. [CrossRef] [PubMed]
11. Essentials of Spinal Cord Injury. Available online: <https://www.thieme.com/books-main/neurosurgery/product/1390-essentials-of-spinal-cord-injury> (accessed on 5 September 2021).
12. Wilson, J.R.; Hashimoto, R.E.; Dettori, J.R.; Fehlings, M.G. Spinal Cord Injury and Quality of Life: A Systematic Review of Outcome Measures. *Evid. Based Spine Care J.* **2011**, *2*, 37–44. [CrossRef] [PubMed]
13. Figley, S.A.; Khosravi, R.; Legasto, J.M.; Tseng, Y.-F.; Fehlings, M.G. Characterization of Vascular Disruption and Blood-Spinal Cord Barrier Permeability Following Traumatic Spinal Cord Injury. *J. Neurotrauma* **2014**, *31*, 541–552. [CrossRef] [PubMed]
14. Pineau, I.; Lacroix, S. Proinflammatory Cytokine Synthesis in the Injured Mouse Spinal Cord: Multiphasic Expression Pattern and Identification of the Cell Types Involved. *J. Comp. Neurol.* **2007**, *500*, 267–285. [CrossRef] [PubMed]
15. David, S.; López-Vales, R.; Wee Yong, V. Harmful and Beneficial Effects of Inflammation after Spinal Cord Injury: Potential Therapeutic Implications. *Handb. Clin. Neurol.* **2012**, *109*, 485–502. [CrossRef] [PubMed]

16. Huntmer-Silveira, A.; Patil, N.; Brickner, M.A.; Parr, A.M. Strategies for Oligodendrocyte and Myelin Repair in Traumatic CNS Injury. *Front. Cell. Neurosci.* **2021**, *14*, 458. [[CrossRef](#)] [[PubMed](#)]
17. Kakulas, B.A. Neuropathology: The Foundation for New Treatments in Spinal Cord Injury. *Spinal Cord* **2004**, *42*, 549–563. [[CrossRef](#)] [[PubMed](#)]
18. Tator, C.H.; Koyanagi, I. Vascular Mechanisms in the Pathophysiology of Human Spinal Cord Injury. *J. Neurosurg.* **1997**, *86*, 483–492. [[CrossRef](#)] [[PubMed](#)]
19. Aoyama, T.; Hida, K.; Akino, M.; Yano, S.; Iwasaki, Y.; Saito, H. Ultra-Early MRI Showing No Abnormality in a Fall Victim Presenting with Tetraparesis. *Spinal Cord* **2007**, *45*, 695–699. [[CrossRef](#)] [[PubMed](#)]
20. Norenberg, M.D.; Smith, J.; Marcillo, A. The Pathology of Human Spinal Cord Injury: Defining the Problems. *J. Neurotrauma* **2004**, *21*, 429–440. [[CrossRef](#)] [[PubMed](#)]
21. Bunge, R.P.; Puckett, W.R.; Becerra, J.L.; Marcillo, A.; Quencer, R.M. Observations on the Pathology of Human Spinal Cord Injury. A Review and Classification of 22 New Cases with Details from a Case of Chronic Cord Compression with Extensive Focal Demyelination. *Adv. Neurol.* **1993**, *59*, 75–89. [[PubMed](#)]
22. McDonald, J.W.; Belegu, V. Demyelination and Remyelination after Spinal Cord Injury. *J. Neurotrauma* **2006**, *23*, 345–359. [[CrossRef](#)] [[PubMed](#)]
23. Nashmi, R.; Fehlings, M.G. Changes in Axonal Physiology and Morphology after Chronic Compressive Injury of the Rat Thoracic Spinal Cord. *Neuroscience* **2001**, *104*, 235–251. [[CrossRef](#)]
24. Radojicic, M.; Reier, P.J.; Steward, O.; Keirstead, H.S. Septations in Chronic Spinal Cord Injury Cavities Contain Axons. *Exp. Neurol.* **2005**, *196*, 339–341. [[CrossRef](#)] [[PubMed](#)]
25. Fehlings, M.G.; Tator, C.H. The Relationships among the Severity of Spinal Cord Injury, Residual Neurological Function, Axon Counts, and Counts of Retrogradely Labeled Neurons after Experimental Spinal Cord Injury. *Exp. Neurol.* **1995**, *132*, 220–228. [[CrossRef](#)]
26. Lu, P.; Jones, L.L.; Snyder, E.Y.; Tuszynski, M.H. Neural Stem Cells Constitutively Secrete Neurotrophic Factors and Promote Extensive Host Axonal Growth after Spinal Cord Injury. *Exp. Neurol.* **2003**, *181*, 115–129. [[CrossRef](#)]
27. Wilson, J.R.; Tetreault, L.A.; Kwon, B.K.; Arnold, P.M.; Mroz, T.E.; Shaffrey, C.; Harrop, J.S.; Chapman, J.R.; Casha, S.; Skelly, A.C.; et al. Timing of Decompression in Patients with Acute Spinal Cord Injury: A Systematic Review. *Glob. Spine J.* **2017**, *7*, 95S–115S. [[CrossRef](#)] [[PubMed](#)]
28. Fehlings, M.G.; Vaccaro, A.; Wilson, J.R.; Singh, A.; W Cadotte, D.; Harrop, J.S.; Aarabi, B.; Shaffrey, C.; Dvorak, M.; Fisher, C.; et al. Early versus Delayed Decompression for Traumatic Cervical Spinal Cord Injury: Results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS). *PLoS ONE* **2012**, *7*, e32037. [[CrossRef](#)] [[PubMed](#)]
29. Schanne, F.A.; Kane, A.B.; Young, E.E.; Farber, J.L. Calcium Dependence of Toxic Cell Death: A Final Common Pathway. *Science* **1979**, *206*, 700–702. [[CrossRef](#)] [[PubMed](#)]
30. Lipton, S.A.; Rosenberg, P.A. Excitatory Amino Acids as a Final Common Pathway for Neurologic Disorders. *N. Engl. J. Med.* **1994**, *330*, 613–622. [[CrossRef](#)] [[PubMed](#)]
31. Donnelly, D.J.; Popovich, P.G. Inflammation and Its Role in Neuroprotection, Axonal Regeneration and Functional Recovery after Spinal Cord Injury. *Exp. Neurol.* **2008**, *209*, 378–388. [[CrossRef](#)] [[PubMed](#)]
32. Xiong, Y.; Rabchevsky, A.G.; Hall, E.D. Role of Peroxynitrite in Secondary Oxidative Damage after Spinal Cord Injury. *J. Neurochem.* **2007**, *100*, 639–649. [[CrossRef](#)] [[PubMed](#)]
33. Noble, L.J.; Wrathall, J.R. Distribution and Time Course of Protein Extravasation in the Rat Spinal Cord after Contusive Injury. *Brain Res.* **1989**, *482*, 57–66. [[CrossRef](#)]
34. Fleming, J.C.; Norenberg, M.D.; Ramsay, D.A.; Dekaban, G.A.; Marcillo, A.E.; Saenz, A.D.; Pasquale-Styles, M.; Dietrich, W.D.; Weaver, L.C. The Cellular Inflammatory Response in Human Spinal Cords after Injury. *Brain* **2006**, *129*, 3249–3269. [[CrossRef](#)] [[PubMed](#)]
35. Popovich, P.G.; Wei, P.; Stokes, B.T. Cellular Inflammatory Response after Spinal Cord Injury in Sprague-Dawley and Lewis Rats. *J. Comp. Neurol.* **1997**, *377*, 443–464. [[CrossRef](#)]
36. Beattie, M.S.; Hermann, G.E.; Rogers, R.C.; Bresnahan, J.C. Cell Death in Models of Spinal Cord Injury. *Prog. Brain Res.* **2002**, *137*, 37–47. [[CrossRef](#)] [[PubMed](#)]
37. Emery, E.; Aldana, P.; Bunge, M.B.; Puckett, W.; Srinivasan, A.; Keane, R.W.; Bethea, J.; Levi, A.D. Apoptosis after Traumatic Human Spinal Cord Injury. *J. Neurosurg.* **1998**, *89*, 911–920. [[CrossRef](#)] [[PubMed](#)]
38. Keane, R.W.; Kraydieh, S.; Lotocki, G.; Bethea, J.R.; Krajewski, S.; Reed, J.C.; Dietrich, W.D. Apoptotic and Anti-Apoptotic Mechanisms Following Spinal Cord Injury. *J. Neuropathol. Exp. Neurol.* **2001**, *60*, 422–429. [[CrossRef](#)] [[PubMed](#)]
39. Herrmann, J.E.; Imura, T.; Song, B.; Qi, J.; Ao, Y.; Nguyen, T.K.; Korsak, R.A.; Takeda, K.; Akira, S.; Sofroniew, M.V. STAT3 Is a Critical Regulator of Astroglial Scar Formation after Spinal Cord Injury. *J. Neurosci.* **2008**, *28*, 7231–7243. [[CrossRef](#)] [[PubMed](#)]
40. Hill, C.E.; Beattie, M.S.; Bresnahan, J.C. Degeneration and Sprouting of Identified Descending Supraspinal Axons after Contusive Spinal Cord Injury in the Rat. *Exp. Neurol.* **2001**, *171*, 153–169. [[CrossRef](#)] [[PubMed](#)]
41. Stoodley, M.A. Pathophysiology of Syringomyelia. *J. Neurosurg.* **2000**, *92*, 1069–1073.
42. McDonald, J.W.; Becker, D.; Sadowsky, C.L.; Jane, J.A.; Conturo, T.E.; Schultz, L.M. Late Recovery Following Spinal Cord Injury. Case Report and Review of the Literature. *J. Neurosurg.* **2002**, *97*, 252–265. [[CrossRef](#)] [[PubMed](#)]

43. Karimi-Abdolrezaee, S.; Eftekharpour, E.; Wang, J.; Morshead, C.M.; Fehlings, M.G. Delayed Transplantation of Adult Neural Precursor Cells Promotes Remyelination and Functional Neurological Recovery after Spinal Cord Injury. *J. Neurosci.* **2006**, *26*, 3377–3389. [[CrossRef](#)] [[PubMed](#)]
44. Keirstead, H.S.; Nistor, G.; Bernal, G.; Totoiu, M.; Cloutier, F.; Sharp, K.; Steward, O. Human Embryonic Stem Cell-Derived Oligodendrocyte Progenitor Cell Transplants Remyelinate and Restore Locomotion after Spinal Cord Injury. *J. Neurosci.* **2005**, *25*, 4694–4705. [[CrossRef](#)] [[PubMed](#)]
45. Hagg, T.; Oudega, M. Degenerative and Spontaneous Regenerative Processes after Spinal Cord Injury. *J. Neurotrauma* **2006**, *23*, 264–280. [[CrossRef](#)] [[PubMed](#)]
46. Meuli, M.; Meuli-Simmen, C.; Hutchins, G.M.; Seller, M.J.; Harrison, M.R.; Adzick, N.S. The Spinal Cord Lesion in Human Fetuses with Myelomeningocele: Implications for Fetal Surgery. *J. Pediatr. Surg.* **1997**, *32*, 448–452. [[CrossRef](#)]
47. Hutchins, G.M.; Meuli, M.; Meuli-Simmen, C.; Jordan, M.A.; Heffez, D.S.; Blakemore, K.J. Acquired Spinal Cord Injury in Human Fetuses with Myelomeningocele. *Pediatr. Pathol. Lab. Med.* **1996**, *16*, 701–712. [[CrossRef](#)] [[PubMed](#)]
48. Stiefel, D.; Copp, A.J.; Meuli, M. Fetal Spina Bifida: Loss of Neural Function in utero. *J. Neurosurg.* **2007**, *106*, 213–221. [[CrossRef](#)] [[PubMed](#)]
49. Heffez, D.S.; Aryanpur, J.; Hutchins, G.M.; Freeman, J.M. The Paralysis Associated with Myelomeningocele: Clinical and Experimental Data Implicating a Preventable Spinal Cord Injury. *Neurosurgery* **1990**, *26*, 987–992. [[CrossRef](#)] [[PubMed](#)]
50. Copp, A.J.; Stanier, P.; Greene, N.D.E. Neural Tube Defects—Recent Advances, Unsolved Questions and Controversies. *Lancet Neurol.* **2013**, *12*, 799–810. [[CrossRef](#)]
51. Adzick, N.S. Fetal Surgery for Myelomeningocele: Trials and Tribulations. Isabella Forshall Lecture. *J. Pediatr. Surg.* **2012**, *47*, 273–281. [[CrossRef](#)] [[PubMed](#)]
52. Oria, M.; Figueira, R.L.; Scorletti, F.; Sbragia, L.; Owens, K.; Li, Z.; Pathak, B.; Corona, M.U.; Marotta, M.; Encinas, J.L.; et al. CD200-CD200R Imbalance Correlates with Microglia and pro-Inflammatory Activation in Rat Spinal Cords Exposed to Amniotic Fluid in Retinoic Acid-Induced Spina Bifida. *Sci. Rep.* **2018**, *8*, 1–12. [[CrossRef](#)] [[PubMed](#)]
53. Danzer, E.; Zhang, L.; Radu, A.; Bebbington, M.W.; Liechty, K.W.; Adzick, N.S.; Flake, A.W. Amniotic Fluid Levels of Glial Fibrillary Acidic Protein in Fetal Rats with Retinoic Acid Induced Myelomeningocele: A Potential Marker for Spinal Cord Injury. *Am. J. Obs. Gynecol.* **2011**, *204*, 178.e1-11. [[CrossRef](#)] [[PubMed](#)]
54. Tomko, P.; Farkaš, D.; Čížková, D.; Vanický, I. Longitudinal Enlargement of the Lesion after Spinal Cord Injury in the Rat: A Consequence of Malignant Edema? *Spinal Cord* **2017**, *55*, 255–263. [[CrossRef](#)] [[PubMed](#)]
55. Lankford, L.; Chen, Y.J.; Saenz, Z.; Kumar, P.; Long, C.; Farmer, D.; Wang, A. Manufacture and Preparation of Human Placenta-Derived Mesenchymal Stromal Cells for Local Tissue Delivery. *Cytotherapy* **2017**, *19*, 680–688. [[CrossRef](#)] [[PubMed](#)]
56. Lankford, L. Early Gestation Chorionic Villi-Derived Stromal Cells for Fetal Tissue Engineering. *World J. Stem Cells* **2015**, *7*, 195–207. [[CrossRef](#)] [[PubMed](#)]
57. Heo, J.S.; Choi, Y.; Kim, H.-S.; Kim, H.O. Comparison of Molecular Profiles of Human Mesenchymal Stem Cells Derived from Bone Marrow, Umbilical Cord Blood, Placenta and Adipose Tissue. *Int. J. Mol. Med.* **2016**, *37*, 115–125. [[CrossRef](#)] [[PubMed](#)]
58. Barlow, S.; Brooke, G.; Chatterjee, K.; Price, G.; Pelekanos, R.; Rossetti, T.; Doody, M.; Venter, D.; Pain, S.; Gilshenan, K.; et al. Comparison of Human Placenta- and Bone Marrow-Derived Multipotent Mesenchymal Stem Cells. *Stem Cells Dev.* **2008**, *17*, 1095–1108. [[CrossRef](#)] [[PubMed](#)]
59. Portmann-Lanz, C.B.; Schoeberlein, A.; Portmann, R.; Mohr, S.; Rollini, P.; Sager, R.; Surbek, D.V. Turning Placenta into Brain: Placental Mesenchymal Stem Cells Differentiate into Neurons and Oligodendrocytes. *Am. J. Obs. Gynecol.* **2010**, *202*. [[CrossRef](#)] [[PubMed](#)]
60. Martini, M.M.; da S. Jeremias, T.; Kohler, M.C.; Marostica, L.L.; Trentin, A.G.; Alvarez-Silva, M. Human Placenta-Derived Mesenchymal Stem Cells Acquire Neural Phenotype Under the Appropriate Niche Conditions. *DNA Cell Biol.* **2013**, *32*, 58–65. [[CrossRef](#)] [[PubMed](#)]
61. Chen, L.; He, D.-M.; Zhang, Y. The Differentiation of Human Placenta-Derived Mesenchymal Stem Cells into Dopaminergic Cells in Vitro. *Cell Mol. Biol. Lett.* **2009**, *14*, 528–536. [[CrossRef](#)] [[PubMed](#)]
62. Wang, A.; Brown, E.G.; Lankford, L.; Keller, B.A.; Pivetti, C.D.; Sitkin, N.A.; Beattie, M.S.; Bresnahan, J.C.; Farmer, D.L. Placental Mesenchymal Stromal Cells Rescue Ambulation in Ovine Myelomeningocele. *Stem Cells Transl. Med.* **2015**, *4*, 659–669. [[CrossRef](#)] [[PubMed](#)]
63. Karlsson, H.; Erkers, T.; Nava, S.; Ruhm, S.; Westgren, M.; Ringdén, O. Stromal Cells from Term Fetal Membrane Are Highly Suppressive in Allogeneic Settings in Vitro. *Clin. Exp. Immunol.* **2012**, *167*, 543–555. [[CrossRef](#)] [[PubMed](#)]
64. Lee, J.-R.; Kyung, J.W.; Kumar, H.; Kwon, S.P.; Song, S.Y.; Han, I.-B.; Kim, B.-S. Targeted Delivery of Mesenchymal Stem Cell-Derived Nanovesicles for Spinal Cord Injury Treatment. *Int. J. Mol. Sci.* **2020**, *21*, 4185. [[CrossRef](#)] [[PubMed](#)]
65. Park, W.S.; Ahn, S.Y.; Sung, S.I.; Ahn, J.-Y.; Chang, Y.S. Strategies to Enhance Paracrine Potency of Transplanted Mesenchymal Stem Cells in Intractable Neonatal Disorders. *Pediatr. Res.* **2018**, *83*, 214–222. [[CrossRef](#)] [[PubMed](#)]
66. Cížková, D.; Rosocha, J.; Vanický, I.; Jergová, S.; Cízek, M. Transplants of Human Mesenchymal Stem Cells Improve Functional Recovery after Spinal Cord Injury in the Rat. *Cell Mol. Neurobiol.* **2006**, *26*, 1167–1180. [[CrossRef](#)] [[PubMed](#)]
67. Kim, H.J.; Park, J.-S. Usage of Human Mesenchymal Stem Cells in Cell-Based Therapy: Advantages and Disadvantages. *Dev. Reprod* **2017**, *21*, 1–10. [[CrossRef](#)] [[PubMed](#)]

68. Liang, X.; Ding, Y.; Zhang, Y.; Tse, H.-F.; Lian, Q. Paracrine Mechanisms of Mesenchymal Stem Cell-Based Therapy: Current Status and Perspectives. *Cell Transplant.* **2014**, *23*, 1045–1059. [[CrossRef](#)] [[PubMed](#)]
69. Liu, F.; Xuan, A.; Chen, Y.; Zhang, J.; Xu, L.; Yan, Q.; Long, D. Combined Effect of Nerve Growth Factor and Brain-derived Neurotrophic Factor on Neuronal Differentiation of Neural Stem Cells and the Potential Molecular Mechanisms. *Mol. Med. Rep.* **2014**, *10*, 1739–1745. [[CrossRef](#)] [[PubMed](#)]
70. Li, Y.; Chen, J.; Chen, X.G.; Wang, L.; Gautam, S.C.; Xu, Y.X.; Katakowski, M.; Zhang, L.J.; Lu, M.; Janakiraman, N.; et al. Human Marrow Stromal Cell Therapy for Stroke in Rat: Neurotrophins and Functional Recovery. *Neurology* **2002**, *59*, 514–523. [[CrossRef](#)] [[PubMed](#)]
71. Phan, J.; Kumar, P.; Hao, D.; Gao, K.; Farmer, D.; Wang, A. Engineering Mesenchymal Stem Cells to Improve Their Exosome Efficacy and Yield for Cell-Free Therapy. *J. Extracell. Vesicles* **2018**, *7*, 1522236. [[CrossRef](#)] [[PubMed](#)]
72. Luarte, A.; Bátiz, L.F.; Wyneken, U.; Lafourcade, C. Potential Therapies by Stem Cell-Derived Exosomes in CNS Diseases: Focusing on the Neurogenic Niche. *Stem Cells Int.* **2016**, *2016*, 5736059. [[CrossRef](#)] [[PubMed](#)]
73. Gorabi, A.M.; Kiaie, N.; Barreto, G.E.; Read, M.I.; Tafti, H.A.; Sahebkar, A. The Therapeutic Potential of Mesenchymal Stem Cell-Derived Exosomes in Treatment of Neurodegenerative Diseases. *Mol. Neurobiol.* **2019**, *56*, 8157–8167. [[CrossRef](#)] [[PubMed](#)]
74. Mendt, M.; Rezvani, K.; Shpall, E. Mesenchymal Stem Cell-Derived Exosomes for Clinical Use. *Bone Marrow Transplant.* **2019**, *54*, 789–792. [[CrossRef](#)] [[PubMed](#)]
75. Wong, R.S.Y. Mesenchymal Stem Cells: Angels or Demons? *J. Biomed. Biotechnol.* **2011**, *2011*, 459510. [[CrossRef](#)] [[PubMed](#)]
76. Song, P.; Han, T.; Xiang, X.; Wang, Y.; Fang, H.; Niu, Y.; Shen, C. The Role of Hepatocyte Growth Factor in Mesenchymal Stem Cell-Induced Recovery in Spinal Cord Injured Rats. *Stem Cell Res. Ther.* **2020**, *11*, 178. [[CrossRef](#)] [[PubMed](#)]
77. Sasaki, M.; Radtke, C.; Tan, A.M.; Zhao, P.; Hamada, H.; Houkin, K.; Honmou, O.; Kocsis, J.D. BDNF-Hypersecreting Human Mesenchymal Stem Cells Promote Functional Recovery, Axonal Sprouting, and Protection of Corticospinal Neurons after Spinal Cord Injury. *J. Neurosci.* **2009**, *29*, 14932–14941. [[CrossRef](#)] [[PubMed](#)]
78. Kumar, P.; Becker, J.C.; Gao, K.; Carney, R.P.; Lankford, L.; Keller, B.A.; Herout, K.; Lam, K.S.; Farmer, D.L.; Wang, A. Neuroprotective Effect of Placenta-Derived Mesenchymal Stromal Cells: Role of Exosomes. *FASEB J.* **2019**, *33*, 5836–5849. [[CrossRef](#)] [[PubMed](#)]
79. Casha, S.; Zygun, D.; McGowan, M.D.; Bains, I.; Yong, V.W.; John Hurlbert, R. Results of a Phase II Placebo-Controlled Randomized Trial of Minocycline in Acute Spinal Cord Injury. *Brain* **2012**, *135*, 1224–1236. [[CrossRef](#)] [[PubMed](#)]
80. Fehlings, M.G.; Theodore, N.; Harrop, J.; Maurais, G.; Kuntz, C.; Shaffrey, C.I.; Kwon, B.K.; Chapman, J.; Yee, A.; Tighe, A.; et al. A Phase I/IIa Clinical Trial of a Recombinant Rho Protein Antagonist in Acute Spinal Cord Injury. *J. Neurotrauma* **2011**, *28*, 787–796. [[CrossRef](#)] [[PubMed](#)]
81. Papa, S.; Caron, I.; Erba, E.; Panini, N.; De Paola, M.; Mariani, A.; Colombo, C.; Ferrari, R.; Pozzer, D.; Zanier, E.R.; et al. Early Modulation of Pro-Inflammatory Microglia by Minocycline Loaded Nanoparticles Confers Long Lasting Protection after Spinal Cord Injury. *Biomaterials* **2016**, *75*, 13–24. [[CrossRef](#)] [[PubMed](#)]
82. Biglari, B.; Swing, T.; Child, C.; Büchler, A.; Westhauser, F.; Bruckner, T.; Ferbert, T.; Jürgen Gerner, H.; Moghaddam, A. A Pilot Study on Temporal Changes in IL-1 β and TNF- α Serum Levels after Spinal Cord Injury: The Serum Level of TNF- α in Acute SCI Patients as a Possible Marker for Neurological Remission. *Spinal Cord* **2015**, *53*, 510–514. [[CrossRef](#)] [[PubMed](#)]
83. Kwon, B.K.; Streijger, F.; Fallah, N.; Noonan, V.K.; Bélanger, L.M.; Ritchie, L.; Paquette, S.J.; Ailon, T.; Boyd, M.C.; Street, J.; et al. Cerebrospinal Fluid Biomarkers To Stratify Injury Severity and Predict Outcome in Human Traumatic Spinal Cord Injury. *J. Neurotrauma* **2017**, *34*, 567–580. [[CrossRef](#)] [[PubMed](#)]
84. Liu, W.; Ma, Z.; Li, J.; Kang, X. Mesenchymal Stem Cell-Derived Exosomes: Therapeutic Opportunities and Challenges for Spinal Cord Injury. *Stem Cell Res. Ther.* **2021**, *12*, 102. [[CrossRef](#)] [[PubMed](#)]
85. Colton, C.A. Heterogeneity of Microglial Activation in the Innate Immune Response in the Brain. *J. Neuroimmune Pharm.* **2009**, *4*, 399–418. [[CrossRef](#)] [[PubMed](#)]
86. Popovich, P.G.; Guan, Z.; Wei, P.; Huitinga, I.; van Rooijen, N.; Stokes, B.T. Depletion of Hematogenous Macrophages Promotes Partial Hindlimb Recovery and Neuroanatomical Repair after Experimental Spinal Cord Injury. *Exp. Neurol.* **1999**, *158*, 351–365. [[CrossRef](#)] [[PubMed](#)]
87. Romanelli, P.; Bieler, L.; Scharler, C.; Pachler, K.; Kreutzer, C.; Zaunmair, P.; Jakubecova, D.; Mrowetz, H.; Benedetti, B.; Rivera, F.J.; et al. Extracellular Vesicles Can Deliver Anti-Inflammatory and Anti-Scarring Activities of Mesenchymal Stromal Cells After Spinal Cord Injury. *Front. Neurol.* **2019**, *10*, 1225. [[CrossRef](#)] [[PubMed](#)]
88. David, S.; Kroner, A. Repertoire of Microglial and Macrophage Responses after Spinal Cord Injury. *Nat. Rev. Neurosci.* **2011**, *12*, 388–399. [[CrossRef](#)] [[PubMed](#)]
89. Kigerl, K.A.; Gensel, J.C.; Ankeny, D.P.; Alexander, J.K.; Donnelly, D.J.; Popovich, P.G. Identification of Two Distinct Macrophage Subsets with Divergent Effects Causing Either Neurotoxicity or Regeneration in the Injured Mouse Spinal Cord. *J. Neurosci.* **2009**, *29*, 13435–13444. [[CrossRef](#)] [[PubMed](#)]
90. Liu, W.; Wang, Y.; Gong, F.; Rong, Y.; Luo, Y.; Tang, P.; Zhou, Z.; Zhou, Z.; Xu, T.; Jiang, T.; et al. Exosomes Derived from Bone Mesenchymal Stem Cells Repair Traumatic Spinal Cord Injury by Suppressing the Activation of A1 Neurotoxic Reactive Astrocytes. *J. Neurotrauma* **2019**, *36*, 469–484. [[CrossRef](#)] [[PubMed](#)]

91. Zhao, C.; Zhou, X.; Qiu, J.; Xin, D.; Li, T.; Chu, X.; Yuan, H.; Wang, H.; Wang, Z.; Wang, D. Exosomes Derived From Bone Marrow Mesenchymal Stem Cells Inhibit Complement Activation In Rats With Spinal Cord Injury. *Drug Des. Dev.* **2019**, *13*, 3693–3704. [[CrossRef](#)] [[PubMed](#)]
92. Lee, J.M.; Jung, J.; Lee, H.-J.; Jeong, S.J.; Cho, K.J.; Hwang, S.-G.; Kim, G.J. Comparison of Immunomodulatory Effects of Placenta Mesenchymal Stem Cells with Bone Marrow and Adipose Mesenchymal Stem Cells. *Int. Immunopharmacol.* **2012**, *13*, 219–224. [[CrossRef](#)] [[PubMed](#)]
93. Chang, C.-J.; Yen, M.-L.; Chen, Y.-C.; Chien, C.-C.; Huang, H.-I.; Bai, C.-H.; Yen, B.L. Placenta-Derived Multipotent Cells Exhibit Immunosuppressive Properties That Are Enhanced in the Presence of Interferon-Gamma. *Stem Cells* **2006**, *24*, 2466–2477. [[CrossRef](#)] [[PubMed](#)]
94. Abumaree, M.H.; Abomaray, F.M.; Alshabibi, M.A.; AlAskar, A.S.; Kalionis, B. Immunomodulatory Properties of Human Placental Mesenchymal Stem/Stromal Cells. *Placenta* **2017**, *59*, 87–95. [[CrossRef](#)] [[PubMed](#)]
95. Jang, M.J.; Kim, H.-S.; Lee, H.-G.; Kim, G.J.; Jeon, H.G.; Shin, H.-S.; Chang, S.-K.; Hur, G.-H.; Chong, S.Y.; Oh, D.; et al. Placenta-Derived Mesenchymal Stem Cells Have an Immunomodulatory Effect That Can Control Acute Graft-versus-Host Disease in Mice. *Acta Haematol.* **2013**, *129*, 197–206. [[CrossRef](#)] [[PubMed](#)]
96. Duffy, M.M.; Ritter, T.; Ceredig, R.; Griffin, M.D. Mesenchymal Stem Cell Effects on T-Cell Effector Pathways. *Stem Cell Res.* **2011**, *2*, 34. [[CrossRef](#)] [[PubMed](#)]
97. Amorim, R.M.; Clark, K.C.; Walker, N.J.; Kumar, P.; Herout, K.; Borjesson, D.L.; Wang, A. Placenta-Derived Multipotent Mesenchymal Stromal Cells: A Promising Potential Cell-Based Therapy for Canine Inflammatory Brain Disease. *Stem Cell Res. Ther.* **2020**, *11*, 304. [[CrossRef](#)] [[PubMed](#)]
98. Li, C.; Zhang, W.; Jiang, X.; Mao, N. Human-Placenta-Derived Mesenchymal Stem Cells Inhibit Proliferation and Function of Allogeneic Immune Cells. *Cell Tissue Res.* **2007**, *330*, 437–446. [[CrossRef](#)] [[PubMed](#)]
99. Gu, Y.; Xue, Q.; Chen, Y.; Yu, G.-H.; Qing, M.; Shen, Y.; Wang, M.; Shi, Q.; Zhang, X.-G. Different Roles of PD-L1 and FasL in Immunomodulation Mediated by Human Placenta-Derived Mesenchymal Stem Cells. *Hum. Immunol.* **2013**, *74*, 267–276. [[CrossRef](#)] [[PubMed](#)]
100. Dombrowski, Y.; O'Hagan, T.; Dittmer, M.; Penalva, R.; Mayoral, S.R.; Bankhead, P.; Fleville, S.; Eleftheriadis, G.; Zhao, C.; Naughton, M.; et al. Regulatory T Cells Promote Myelin Regeneration in the Central Nervous System. *Nat. Neurosci.* **2017**, *20*, 674–680. [[CrossRef](#)] [[PubMed](#)]
101. Franklin, R.J.M.; Ffrench-Constant, C. Remyelination in the CNS: From Biology to Therapy. *Nat. Rev. Neurosci.* **2008**, *9*, 839–855. [[CrossRef](#)] [[PubMed](#)]
102. Clark, K.; Zhang, S.; Barthe, S.; Kumar, P.; Pivetti, C.; Kreutzberg, N.; Reed, C.; Wang, Y.; Paxton, Z.; Farmer, D.; et al. Placental Mesenchymal Stem Cell-Derived Extracellular Vesicles Promote Myelin Regeneration in an Animal Model of Multiple Sclerosis. *Cells* **2019**, *8*, 1497. [[CrossRef](#)] [[PubMed](#)]
103. Bai, L.; Lennon, D.P.; Caplan, A.I.; DeChant, A.; Hecker, J.; Krasno, J.; Zaremba, A.; Miller, R.H. Hepatocyte Growth Factor Mediates Mesenchymal Stem Cell-Induced Recovery in Multiple Sclerosis Models. *Nat. Neurosci.* **2012**, *15*, 862–870. [[CrossRef](#)] [[PubMed](#)]
104. Giunti, D.; Marini, C.; Parodi, B.; Usai, C.; Milanese, M.; Bonanno, G.; Kerlero de Rosbo, N.; Uccelli, A. Role of MiRNAs Shuttled by Mesenchymal Stem Cell-Derived Small Extracellular Vesicles in Modulating Neuroinflammation. *Sci. Rep.* **2021**, *11*, 1740. [[CrossRef](#)] [[PubMed](#)]
105. Osorio-Querejeta, I.; Alberro, A.; Muñoz-Culla, M.; Mäger, I.; Otaegui, D. Therapeutic Potential of Extracellular Vesicles for Demyelinating Diseases; Challenges and Opportunities. *Front. Mol. Neurosci.* **2018**, *11*, 434. [[CrossRef](#)] [[PubMed](#)]
106. Ng, M.T.; Stammers, A.T.; Kwon, B.K. Vascular Disruption and the Role of Angiogenic Proteins after Spinal Cord Injury. *Transl. Stroke Res.* **2011**, *2*, 474–491. [[CrossRef](#)] [[PubMed](#)]
107. Rauch, M.F.; Hynes, S.R.; Bertram, J.; Redmond, A.; Robinson, R.; Williams, C.; Xu, H.; Madri, J.A.; Lavik, E.B. 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*, 132–145. [[CrossRef](#)] [[PubMed](#)]
108. Hofer, H.R.; Tuan, R.S. Secreted Trophic Factors of Mesenchymal Stem Cells Support Neurovascular and Musculoskeletal Therapies. *Stem Cell Res.* **2016**, *7*, 131. [[CrossRef](#)] [[PubMed](#)]
109. Hao, D.; He, C.; Ma, B.; Lankford, L.; Reynaga, L.; Farmer, D.L.; Guo, F.; Wang, A. Hypoxic Preconditioning Enhances Survival and Proangiogenic Capacity of Human First Trimester Chorionic Villus-Derived Mesenchymal Stem Cells for Fetal Tissue Engineering. *Stem Cells Int.* **2019**, *2019*, 9695239. [[CrossRef](#)] [[PubMed](#)]
110. Bian, X.; Ma, K.; Zhang, C.; Fu, X. Therapeutic Angiogenesis Using Stem Cell-Derived Extracellular Vesicles: An Emerging Approach for Treatment of Ischemic Diseases. *Stem Cell Res. Ther.* **2019**, *10*, 158. [[CrossRef](#)] [[PubMed](#)]
111. Hao, D.; Swindell, H.S.; Ramasubramanian, L.; Liu, R.; Lam, K.S.; Farmer, D.L.; Wang, A. Extracellular Matrix Mimicking Nanofibrous Scaffolds Modified with Mesenchymal Stem Cell-Derived Extracellular Vesicles for Improved Vascularization. *Front. Bioeng. Biotechnol.* **2020**, *8*. [[CrossRef](#)] [[PubMed](#)]
112. Rahimi-Sherbaf, F.; Nadri, S.; Rahmani, A.; Dabiri Oskoei, A. Placenta Mesenchymal Stem Cells Differentiation toward Neuronal-like Cells on Nanofibrous Scaffold. *Bioimpacts* **2020**, *10*, 117–122. [[CrossRef](#)] [[PubMed](#)]

113. Lin, X.; Robinson, M.; Petrie, T.; Spandler, V.; Boyd, W.D.; Sondergaard, C.S. Small Intestinal Submucosa-Derived Extracellular Matrix Bioscaffold Significantly Enhances Angiogenic Factor Secretion from Human Mesenchymal Stromal Cells. *Stem Cell Res.* **2015**, *6*, 164. [[CrossRef](#)] [[PubMed](#)]
114. Jaussaud, J.; Biais, M.; Calderon, J.; Chevaleyre, J.; Duchez, P.; Ivanovic, Z.; Couffignal, T.; Barandon, L. Hypoxia-Preconditioned Mesenchymal Stromal Cells Improve Cardiac Function in a Swine Model of Chronic Myocardial Ischaemia. *Eur. J. Cardiothorac. Surg.* **2013**, *43*, 1050–1057. [[CrossRef](#)] [[PubMed](#)]
115. Kim, Y.S.; Noh, M.Y.; Cho, K.A.; Kim, H.; Kwon, M.-S.; Kim, K.S.; Kim, J.; Koh, S.-H.; Kim, S.H. Hypoxia/Reoxygenation-Preconditioned Human Bone Marrow-Derived Mesenchymal Stromal Cells Rescue Ischemic Rat Cortical Neurons by Enhancing Trophic Factor Release. *Mol. Neurobiol.* **2015**, *52*, 792–803. [[CrossRef](#)] [[PubMed](#)]
116. Wiklander, O.P.B.; Nordin, J.Z.; O’Loughlin, A.; Gustafsson, Y.; Corso, G.; Mäger, I.; Vader, P.; Lee, Y.; Sork, H.; Seow, Y.; et al. Extracellular Vesicle in Vivo Biodistribution Is Determined by Cell Source, Route of Administration and Targeting. *J. Extracell. Vesicles* **2015**, *4*, 26316. [[CrossRef](#)] [[PubMed](#)]
117. Gao, Y.; Wang, Z.Y.; Zhang, J.; Zhang, Y.; Huo, H.; Wang, T.; Jiang, T.; Wang, S. RVG-Peptide-Linked Trimethylated Chitosan for Delivery of siRNA to the Brain. *Biomacromolecules* **2014**, *15*, 1010–1018. [[CrossRef](#)] [[PubMed](#)]
118. Yang, J.; Zhang, X.; Chen, X.; Wang, L.; Yang, G. Exosome Mediated Delivery of MiR-124 Promotes Neurogenesis after Ischemia. *Mol. Ther. -Nucleic Acids* **2017**, *7*, 278–287. [[CrossRef](#)] [[PubMed](#)]
119. Alvarez-Erviti, L.; Seow, Y.; Yin, H.; Betts, C.; Lakkhal, S.; Wood, M.J.A. Delivery of siRNA to the Mouse Brain by Systemic Injection of Targeted Exosomes. *Nat. Biotechnol.* **2011**, *29*, 341–345. [[CrossRef](#)] [[PubMed](#)]
120. Sellers, D.L.; Bergen, J.M.; Johnson, R.N.; Back, H.; Ravits, J.M.; Horner, P.J.; Pun, S.H. Targeted Axonal Import (TAXI) Peptide Delivers Functional Proteins into Spinal Cord Motor Neurons after Peripheral Administration. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, 2514–2519. [[CrossRef](#)] [[PubMed](#)]
121. Song, Z.; Xu, Y.; Deng, W.; Zhang, L.; Zhu, H.; Yu, P.; Qu, Y.; Zhao, W.; Han, Y.; Qin, C. Brain Derived Exosomes Are a Double-Edged Sword in Alzheimer’s Disease. *Front. Mol. Neurosci.* **2020**, *13*, 79. [[CrossRef](#)] [[PubMed](#)]
122. Hao, D.; Ma, B.; He, C.; Liu, R.; Farmer, D.L.; Lam, K.S.; Wang, A. Surface Modification of Polymeric Electrospun Scaffolds via a Potent and High-Affinity Integrin A4β1 Ligand Improved the Adhesion, Spreading and Survival of Human Chorionic Villus-Derived Mesenchymal Stem Cells: A New Insight for Fetal Tissue Engineering. *J. Mater. Chem. B* **2020**, *8*, 1649–1659. [[CrossRef](#)] [[PubMed](#)]
123. Reza-Zaldivar, E.E.; Hernández-Sapiéns, M.A.; Minjarez, B.; Gutiérrez-Mercado, Y.K.; Márquez-Aguirre, A.L.; Canales-Aguirre, A.A. Potential Effects of MSC-Derived Exosomes in Neuroplasticity in Alzheimer’s Disease. *Front. Cell Neurosci.* **2018**, *12*, 317. [[CrossRef](#)] [[PubMed](#)]
124. Zhang, H.; Wu, J.; Wu, J.; Fan, Q.; Zhou, J.; Wu, J.; Liu, S.; Zang, J.; Ye, J.; Xiao, M.; et al. Exosome-Mediated Targeted Delivery of MiR-210 for Angiogenic Therapy after Cerebral Ischemia in Mice. *J. Nanobiotechnol.* **2019**, *17*, 29. [[CrossRef](#)] [[PubMed](#)]
125. Chivero, E.T.; Liao, K.; Niu, F.; Tripathi, A.; Tian, C.; Buch, S.; Hu, G. Engineered Extracellular Vesicles Loaded With MiR-124 Attenuate Cocaine-Mediated Activation of Microglia. *Front. Cell Dev. Biol.* **2020**, *0*. [[CrossRef](#)] [[PubMed](#)]
126. Vanover, M.; Pivetti, C.; Lankford, L.; Kumar, P.; Galganski, L.; Kabagambe, S.; Keller, B.; Becker, J.; Chen, Y.J.; Chung, K.; et al. High Density Placental Mesenchymal Stromal Cells Provide Neuronal Preservation and Improve Motor Function Following In utero Treatment of Ovine Myelomeningocele. *J. Pediatr. Surg.* **2019**, *54*, 75–79. [[CrossRef](#)] [[PubMed](#)]
127. Kabagambe, S.; Keller, B.; Becker, J.; Goodman, L.; Pivetti, C.; Lankford, L.; Chung, K.; Lee, C.; Chen, Y.J.; Kumar, P.; et al. Placental Mesenchymal Stromal Cells Seeded on Clinical Grade Extracellular Matrix Improve Ambulation in Ovine Myelomeningocele. *J. Pediatr. Surg.* **2017**, *53*, 178–182. [[CrossRef](#)] [[PubMed](#)]
128. Han, S.; Xiao, Z.; Li, X.; Zhao, H.; Wang, B.; Qiu, Z.; Li, Z.; Mei, X.; Xu, B.; Fan, C.; et al. Human Placenta-Derived Mesenchymal Stem Cells Loaded on Linear Ordered Collagen Scaffold Improves Functional Recovery after Completely Transected Spinal Cord Injury in Canine. *Sci. China Life Sci.* **2018**, *61*, 2–13. [[CrossRef](#)] [[PubMed](#)]
129. Zhou, W.; Silva, M.; Feng, C.; Zhao, S.; Liu, L.; Li, S.; Zhong, J.; Zheng, W. Exosomes Derived from Human Placental Mesenchymal Stem Cells Enhanced the Recovery of Spinal Cord Injury by Activating Endogenous Neurogenesis. *Stem Cell Res. Ther.* **2021**, *12*, 174. [[CrossRef](#)] [[PubMed](#)]
130. Li, L.; Zhang, Y.; Mu, J.; Chen, J.; Zhang, C.; Cao, H.; Gao, J. Transplantation of Human Mesenchymal Stem-Cell-Derived Exosomes Immobilized in an Adhesive Hydrogel for Effective Treatment of Spinal Cord Injury. *Nano Lett.* **2020**, *20*, 4298–4305. [[CrossRef](#)] [[PubMed](#)]
131. Zhang, C.; Zhang, C.; Xu, Y.; Li, C.; Cao, Y.; Li, P. Exosomes Derived from Human Placenta-Derived Mesenchymal Stem Cells Improve Neurologic Function by Promoting Angiogenesis after Spinal Cord Injury. *Neurosci. Lett.* **2020**, *739*, 135399. [[CrossRef](#)] [[PubMed](#)]
132. Ren, Z.; Qi, Y.; Sun, S.; Tao, Y.; Shi, R. Mesenchymal Stem Cell-Derived Exosomes: Hope for Spinal Cord Injury Repair. *Stem Cells Dev.* **2020**, *29*, 1467–1478. [[CrossRef](#)] [[PubMed](#)]
133. Bydon, M. CELLTOP Part. II: A Phase II Clinical Trial of Autologous Adipose Derived Mesenchymal Stem Cells in the Treatment of Paralysis Due to Traumatic Spinal Cord Injury. Available online: <http://www.clinicaltrials.gov> (accessed on 10 September 2021).

134. Santos, R.R. dos Randomized Clinical Trial for the Evaluation of Autologous Mesenchymal Stem Cells Transplantation in Thoracolumbar Chronic and Complete Spinal Cord Injury. Available online: <http://www.clinicaltrials.gov> (accessed on 10 September 2021).
135. The Foundation for Orthopaedics and Regenerative Medicine Safety of Cultured Autologous Adult Adipose Derived Mesenchymal Stem Cell Intrathecal Injection for the Treatment of Spinal Cord Injury. Available online: <https://clinicaltrials.gov/ct2/show/NCT05018793> (accessed on 10 September 2021).
136. Wu, M.; Zhang, R.; Zou, Q.; Chen, Y.; Zhou, M.; Li, X.; Ran, R.; Chen, Q. Comparison of the Biological Characteristics of Mesenchymal Stem Cells Derived from the Human Placenta and Umbilical Cord. *Sci. Rep.* **2018**, *8*, 5014. [[CrossRef](#)] [[PubMed](#)]
137. Moinuddin, F.M.; Yolcu, Y.U.; Wahood, W.; Siddiqui, A.M.; Chen, B.K.; Alvi, M.A.; Goyal, A.; Nesbitt, J.J.; Windebank, A.J.; Yeh, J.; et al. Early and Sustained Improvements in Motor Function in Rats after Infusion of Allogeneic Umbilical Cord-Derived Mesenchymal Stem Cells Following Spinal Cord Injury. *Spinal Cord* **2021**, *59*, 319–327. [[CrossRef](#)] [[PubMed](#)]
138. Mebarki, M.; Abadie, C.; Larghero, J.; Cras, A. Human Umbilical Cord-Derived Mesenchymal Stem/Stromal Cells: A Promising Candidate for the Development of Advanced Therapy Medicinal Products. *Stem Cell Res. Ther.* **2021**, *12*, 152. [[CrossRef](#)] [[PubMed](#)]
139. Xiao, X.; Li, W.; Rong, D.; Xu, Z.; Zhang, Z.; Ye, H.; Xie, L.; Wu, Y.; Zhang, Y.; Wang, X. Human Umbilical Cord Mesenchymal Stem Cells-Derived Extracellular Vesicles Facilitate the Repair of Spinal Cord Injury via the MiR-29b-3p/PTEN/Akt/MTOR Axis. *Cell Death Discov.* **2021**, *7*, 1–10. [[CrossRef](#)] [[PubMed](#)]
140. Huang, L.; Fu, C.; Xiong, F.; He, C.; Wei, Q. Stem Cell Therapy for Spinal Cord Injury. *Cell Transplant.* **2021**, *30*. [[CrossRef](#)] [[PubMed](#)]
141. Li, F.; Liu, H.; Zhang, K.; Xiao, D.-J.; Wang, C.; Wang, Y.-S. Adipose-Derived Stromal Cells Improve Functional Recovery after Spinal Cord Injury through TGF-B1/Smad3/PLOD2 Pathway Activation. *Aging* **2021**, *13*, 4370–4387. [[CrossRef](#)] [[PubMed](#)]
142. Farmer, D.L. Phase 1/2a Trial of Placental Mesenchymal Stem Cells for Repair of Fetal Myelomeningocele. Available online: <http://www.clinicaltrials.gov> (accessed on 10 September 2021).
143. Ringden, O.; Baygan, A.; Remberger, M.; Gustafsson, B.; Winiarski, J.; Khoein, B.; Moll, G.; Klingspor, L.; Westgren, M.; Sadeghi, B. Placenta-Derived Decidua Stromal Cells for Treatment of Severe Acute Graft-Versus-Host Disease. *Stem Cells Transl. Med.* **2018**, *7*, 325–331. [[CrossRef](#)] [[PubMed](#)]
144. Nevala-Plagemann, C.; Lee, C.; Tolar, J. Placenta-Based Therapies for the Treatment of Epidermolysis Bullosa. *Cytotherapy* **2015**, *17*, 786–795. [[CrossRef](#)] [[PubMed](#)]
145. Institute of Cell Therapy Treatment of Coronavirus COVID-19 Pneumonia (Pathogen SARS-CoV-2) with Cryopreserved Allogeneic Multipotent Mesenchymal Stem Cells of the Placenta and Umbilical Cord. Available online: <http://www.clinicaltrials.gov> (accessed on 10 September 2021).
146. Beijing Tongren Hospital Phase I Clinical Trials of Human Placental Mesenchymal Stem Cells Treatment on Diabetic Foot Ulcer. Available online: <http://www.clinicaltrials.gov> (accessed on 10 September 2021).
147. Institute of Cell Therapy Efficacy of Bone-Marrow-Derived and Placenta-Derived Multipotent Mesenchymal Stem/Stromal Cells for Osteoarthritis. Available online: <http://www.clinicaltrials.gov> (accessed on 10 September 2021).