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Review

Adipose-derived stem cell therapy for spinal cord injuries: Advances, challenges, and future directions

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ABSTRACT

Spinal cord injury (SCI) has limited treatment options for regaining function. Adipose-derived stem cells (ADSCs) show promise owing to their ability to differentiate into multiple cell types, promote nerve cell survival, and modulate inflammation. This review explores ADSC therapy for SCI, focusing on its potential for improving function, preclinical and early clinical trial progress, challenges, and future directions.

Preclinical studies have demonstrated ADSC transplantation's effectiveness in promoting functional recovery, reducing cavity formation, and enhancing nerve regrowth and myelin repair. To improve ADSC efficacy, strategies including genetic modification and combination with rehabilitation are being explored. Early clinical trials have shown safety and feasibility, with some suggesting motor and sensory function improvements.

Challenges remain for clinical translation, including optimizing cell survival and delivery, determining dosing, addressing tumor formation risks, and establishing standardized protocols. Future research should focus on overcoming these challenges and exploring the potential for combining ADSC therapy with other treatments, including rehabilitation and medication.

Contents

Abbreviations: (ADSCs), adipose-derived stem cells; (ASIA), American Spinal Injury Association; (AIS), ASIA Impairment Scale; (BBB), Basso, Beattie, and Bresnahan; (BM-MSCs), bone marrow-derived mesenchymal stem cells; (BMP4), bone morphogenetic protein 4; (BDNF), brain-derived neurotrophic factor; (CNS), central nervous system; (DS), decompression surgery; (EPSPs), excitatory postsynaptic potentials; (EVs), extracellular vesicles; (GDNF), glial cell line-derived neurotrophic factor; (iPSCs), induced pluripotent stem cells; (lncRNAs), long noncoding RNAs; (MSCs), mesenchymal stromal stem cells; (NLCs), neuron/motoneuron-like cells; (OECs), olfactory ensheathing cells; (OLCs), oligodendrocyte-like cells; (RA), retinoic acid; (SCI), spinal cord injury; (SVF), stromal vascular fraction; (TGF-β), transforming growth factor-beta; (VEGF), vascular endothelial growth factor.

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1. Introduction

Spinal cord injury (SCI) is a significant global health concern that causes permanent or temporary neurological impairments, thereby resulting in a substantial socioeconomic burden [1]. Trauma including falls, traffic accidents, and falling object impact is the leading cause of SCI; however, nontraumatic factors are also noted [1,2]. The global SCI prevalence is approximately 20.6 million cases, with an annual incidence of 250,000–500,000 patients [3]. In the United States (US) alone, approximately 17,000 new cases occur annually, with a prevalence exceeding 282,000 individuals [4,5]. Substantial SCI-associated costs are evident, with first-year expenses for a patient with high tetraplegia in the US surpassing $1 million [5]. Developed countries such as Japan experience similar challenges [6].

SCI severity varies. It can occur at any spinal level, leading to either complete loss of sensation and motor function below the injury site (complete SCI) or some preserved function (incomplete SCI) [1–4]. Symptoms depend on the location and severity, ranging from numbness to paralysis and bowel/bladder dysfunction. Long-term outcomes encompass full recovery to permanent tetraplegia or paraplegia. Muscle atrophy, movement control loss, spasticity, joint deformation, infections, atelectasis, pneumonia, venous thromboembolism, dysphagia, chronic pain, and depression are SCI-associated complications [7,8].

SCI pathophysiology is complex. A primary mechanical insult including compression, contusion, or transection directly damages the spinal cord [1,4]. Subsequently, a cascade of secondary injury processes including ischemia, inflammation, oxidative stress, and excitotoxicity is triggered, worsening the damage and creating a microenvironment that hinders regeneration.

Preventing further damage and managing complications are the primary focus of conventional treatment for SCI-induced paralysis [4,9,10]. High-dose methylprednisolone administration, surgical interventions for vertebral stabilization and tissue decompression, and rehabilitative care are the approaches employed. However, these methods, including pharmacological agents, have shown limited ability to address underlying neurological damage or promote significant regeneration [4,11,12]. Despite recent clinical trials demonstrating patients regaining movement using spinal neurostimulation [13,14] and regaining motor function using olfactory ensheathing cell (OEC) transplantation in partial SCI [15], all proposed clinical strategies for limiting damage progression and improving SCI outcomes have shown unsatisfactory functional preservation and recovery in patients with complete SCI [16–21]. Furthermore, patients with SCI encounter a significant challenge in regaining neurological function, with low complete recovery rates and increased mortality and morbidity rates. Most complications significantly impact both physical and mental health, thereby leading to a reduced quality of life [22,23]. These factors emphasize the need for more effective treatments.

Stem cell-based therapy using embryonic or adult tissue-derived stem cells aims to restore or replace dysfunctional tissues and organs through regenerative properties, including pluripotency, self-renewal, and paracrine secretions [24]. Tissue-derived stem cells including human induced pluripotent stem cells (iPSCs) [12,25–27] and adult stem cells including the well-described mesenchymal stromal stem cells (MSCs) [28] are being investigated for their potential in SCI treatment. iPSCs tend to differentiate into an immature embryonic or fetal state rather than fully mature adult cells. Additionally, the low induction rate and unclear underlying molecular mechanisms hinder their clinical application [29]. MSCs are multipotent progenitors of mesodermal lineage obtained from various tissues, including bone marrow (BM-MSCs), umbilical cord, and adipose tissues [30]. Among these, adipose-derived stem cells (ADSCs) hold particular promise owing to several advantages. ADSCs are readily available and carry lower safety risks than other stem cell types. Easily isolated from adipose tissues, ADSCs possess multipotent differentiation capabilities, including neural lineages, and exert paracrine effects, secreting neuroprotection, immunomodulation, and regeneration-promoting factors [28,30–33]. These properties suggest that ADSCs can address the complex SCI pathophysiology by replacing lost cells, modulating the inflammatory response, and promoting endogenous stem cell recruitment and differentiation [34].

Functional recovery, enhanced axonal regeneration, and myelination following ADSC transplantation have been demonstrated in preclinical studies [31–36]. Furthermore, initial clinical trials have shown positive outcomes, with improvements in sensory and motor function, as well as quality of life [37,38]. Although preliminary data suggest efficacy, limitations remain to be addressed in translating ADSC therapy to clinical application.

Despite the encouraging outcomes of preclinical and clinical studies on ADSCs, ADSC transplantation may increase tumor growth and metastasis risk [39,40]. ADSCs can be recruited to tumors and integrated into the tumor stroma, where they may differentiate into cancer-associated fibroblasts or remain as undifferentiated cells [41,42]. By secreting growth factors, inflammatory ligands, and extracellular matrix proteins, these cells can promote tumor progression, enhancing tumor vascularization and promoting cancer cell survival and proliferation [42,43]. The potential

tumorigenicity of ADSCs has been particularly discussed in the context of breast reconstruction [44]. Some studies have shown that ADSCs can enhance the malignant features of breast cancer cells in vitro [45] and promote xenograft tumor growth [46], whereas other studies have observed no effect on breast cancer cell proliferation [47]. Although most of these studies used in vitro models, which may not reflect the clinical scenario [45,48,49], further preclinical animal studies and long-term follow-up of patients in clinical trials are essential to reach a final safety recommendation on the potential tumorigenicity of ADSCs.

The uncertainty regarding their clinical efficacy is another challenge in the clinical translation of ADSC-based therapies. Most of our understanding of ADSCs comes from in vitro two-dimensional cell culture studies, which may not accurately reflect the complex in vivo environment [50]. Moreover, compared with human conditions, preclinical animal models have limitations due to differences in physiology, molecular, and genetic factors [50]. Furthermore, variable cell qualities and uncertain clinical outcomes occur owing to the lack of standardized procedures for ADSC isolation and application. Donor characteristics such as age [51], sex [52], obesity [53], diabetes, and radiotherapy [54] can influence ADSC properties, including proliferation, differentiation, and immunomodulatory potential. Additionally, ADSC properties vary depending on the tissue source, with differences observed between cells derived from omentum, subcutaneous, and intrathoracic adipose tissues [55]. These variations in ADSC qualities, arising from different sources and nonstandardized isolation procedures, make comparing experimental results and translating ADSC-based therapies to the clinic difficult.

This review aims to provide a comprehensive analysis of the current state of ADSC therapy for SCI. It will discuss the therapeutic potential of ADSCs for SCI, summarize progress in preclinical studies, address challenges and limitations in clinical translation, and explore future directions in ADSC research for SCI treatment. This review aims to inform and guide future research efforts by providing a comprehensive overview, ultimately contributing to the development of effective regenerative therapies for individuals living with SCI.

2. Biological mechanisms of ADSC therapy for SCI

ADSCs exert their therapeutic effects through several biological mechanisms, including the potential to differentiate into neural cell types, neuroprotective and regenerative factor secretion, and inflammation and immune response modulation. These mechanisms work synergistically to promote functional recovery in SCI.

2.1. Potential to differentiate into neural cell types

One of the mechanisms by which ADSCs may contribute to recovery in SCP is through their potential for differentiating into neural cell types, replacing lost or damaged cells in the injured spinal cord. In vitro studies have shown that ADSCs express neuronal markers, including neuronal nuclear protein, neuron-specific class III β-tubulin, and microtubule-associated protein 2, and develop neuron-like morphology upon exposure to specific differentiation protocols [32,56,57]. Furthermore, ADSCs can differentiate into Schwann-like cells, which are crucial for peripheral nerve regeneration and myelination [58,59].

Whereas ADSCs exhibit plasticity by expressing certain neuronal markers and acquiring a neuron-like morphology, their complete differentiation into mature, functional neurons remains a challenge, likely due to epigenetic differences between mesenchymal and neuroectodermal lineages. This necessitates transdifferentiation across germ layers. In contrast, ADSC differentiation into supportive glial cells, like Schwann cells, plays a crucial role in peripheral nerve regeneration and myelination and is more readily observed [58,59].

Recent advancements in stem cell differentiation induction techniques have shown promising results for in vivo ADSC differentiation. Tang et al. [60] introduced a noninvasive, all-optical strategy for inducing stem cell differentiation both in vitro and in vivo. They successfully directed primary ADSCs to differentiate into osteoblasts with stable lineage commitment and applied this method for in vivo differentiation of mouse cerebellar granule neuron progenitors. This optical approach holds promise for mitigating concerns regarding stem cell therapy, such as unintended cell fate conversion and tumorigenicity.

Optimizing the therapeutic efficacy of ADSCs for spinal cord injury requires overcoming the challenge of incomplete differentiation into functional neurons in vivo. Unraveling the underlying mechanisms behind this remains imperative. Additional methods such as direct conversion using gene transduction may be necessary to achieve more complete or functional differentiation [61].

Although some studies have shown positive results regarding promoting neural repair and functional recovery post-transplantation, the mechanism may primarily involve paracrine effects rather than full differentiation. Through growth factor secretion, transplanted ADSCs may stimulate the survival and function of endogenous neural progenitor cells, the body's stem cells with inherent neuronal potential [62]. For example, Gao et al. [34] reported human ADSC (hADSC) differentiation into neuron/motoneuron-like cells (NLCs) for SCI cell replacement therapy. ADSC transplantation into a mouse model of SCI yielded observable behavioral recovery, suggesting their potential in aiding repair, even without complete neuronal transformation. Additionally, using innovative neural differentiation methods, Anderson et al. [63] demonstrated hADSC transdifferentiation into NLCs, astrocyte-like cells, and oligodendrocyte-like cells (OLCs). Cocultured NLCs and OLCs displayed excitability and in vitro myelination, indicating promise for central nervous system (CNS) regeneration therapy.

The synergy between ADSCs and neuroprotective agents to enhance their differentiation into oligodendrocytes and promote remyelination in neurodegenerative diseases including multiple sclerosis (MS) have been explored in recent studies. Ghosouri et al. [64] investigated the effects of lithium chloride, a GSK3-β inhibitor, combined with hADSCs on remyelination, oligodendrocyte differentiation, and functional recovery in a mouse MS model. The results demonstrated a significant increase in myelin density and improvements in motor function, particularly in the combined treatment group. Moreover, the combined treatment increased the mean percentages of cells positive for oligodendrocyte markers (OLIG2 and MOG), suggesting enhanced oligodendrocyte differentiation. Furthermore, lithium chloride upregulated the β-catenin and myelin- and oligodendrocyte-specific gene expression, indicating its potential in promoting remyelination and improving motor function by reducing oligodendrocyte apoptosis, enhancing cell viability and proliferation, and facilitating transplanted cell differentiation into myelin-producing cells.

Various signaling pathways and transcription factors intricately regulate ADSC differentiation into neural cell types. For example, proneural gene neurogenin-2 overexpression enhances the neuronal differentiation potential of ADSCs [65]. Moreover, the Wnt/β-catenin signaling pathway exerts a pivotal role in ADSC neural differentiation, with its activation promoting neuronal marker expression and neurite outgrowth [57]. Furthermore, as elucidated by Ghosouri et al. [64], GSK3-β inhibition and subsequent Wnt/β-catenin pathway activation by lithium chloride can foster ADSC differentiation into oligodendrocytes and enhance remyelination in an MS animal model.

Along with these signaling pathways, recent studies have underscored bone morphogenetic protein 4 (BMP4)'s involvement in ADSC differentiation. Setiawan et al. [66] reviewed BMP4's role in driving ADSC differentiation via the transforming growth factor-beta (TGF-β) signaling pathway. BMP4 interacts with BMP receptors, activating Smad-dependent and Smad-independent pathways, regulated by both intracellular and extracellular BMP4 antagonists. Although BMP4 induces ADSC differentiation into mesodermal lineage cells, the addition of all-trans retinoic acid (RA) is imperative for ADSC transdifferentiation into ectodermal lineage cells, including neural cells. This instance highlights the critical role of both BMP4 and RA signaling pathways in *in vitro* ADSC transdifferentiation into neural cell types.

Nonetheless, the optimal BMP4 concentration necessary for inducing specific lineage differentiation of ADSCs remains elusive. Additionally, the interplay between BMP4/TGF-β signaling and other pathways involved in ADSC differentiation, particularly in ectodermal transdifferentiation necessitates further investigation. Future studies should prioritize exploring BMP4's role in ADSC differentiation in vivo and its potential clinical applications in regenerative medicine. However, owing to its pleiotropic effects and potential for unwanted bone formation, BMP4's use in clinical settings presents challenges. Therefore, identifying safer and more specific methods for manipulating BMP4 signaling for therapeutic purposes remains a significant area of research.

2.2. Neuroprotective and regenerative factor secretion

ADSCs promote recovery in SCP through the secretion of various neuroprotective and regenerative factors that support endogenous repair processes. These cells secrete a broad spectrum of growth factors, cytokines, and extracellular vesicles (EVs) that stimulate neuronal survival, axonal growth, and remyelination [62,67]. Some of the key molecules secreted by ADSCs include.

- Brain-derived neurotrophic factor (BDNF): promotes neuronal survival, differentiation, and synaptic plasticity [60,65].
- Glial cell line-derived neurotrophic factor (GDNF): supports motor neuron survival and regeneration and enhances axonal regeneration [58,65].
- Vascular endothelial growth factor (VEGF): promotes angiogenesis, which is essential for tissue repair and regeneration [58,65].
- Insulin-like growth factor-1: promotes neuronal survival, differentiation, and axonal growth [58,65].
- Hepatocyte growth factor: exhibits neuroprotective and angiogenic properties [68].
- TGF-β: plays a role in immunomodulation and tissue repair [68].

These factors create a supportive microenvironment that enhances endogenous neural cell survival and regeneration, ultimately contributing to functional recovery in SCP [69]. The secretion of these factors by ADSCs is regulated by various signaling pathways, including the PI3K/Akt and MAPK/ERK pathways, which are activated in response to environmental cues and cellular stress [62].

In addition to soluble factors, ADSCs also secrete EVs, particularly exosomes, which play a crucial role in mediating the therapeutic effects of ADSCs. These EVs contain various bioactive molecules, including microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and proteins, which contribute to neuroprotection and regeneration.

For example, miRNAs including miR-21, miR-124, and miR-133b have been identified in ADSC-derived EVs and are known to promote neuronal differentiation, neurite outgrowth, and axonal regeneration [70,71]. Additionally, lncRNAs such as MALAT1 and NEAT1 observed in ADSC-derived EVs, have been implicated in neuronal survival and differentiation regulation [70].

Moreover, ADSC-derived EVs contain various neurotrophic and growth factors, including BDNF, GDNF, and nerve growth factors, which support neuronal survival and regeneration [72]. Furthermore, these EVs can deliver anti-inflammatory cytokines and immunomodulatory molecules, thereby contributing to proregenerative microenvironment creation in the injured spinal cord [73].

2.3. Immunomodulation and anti-inflammatory effects

ADSCs promote recovery in SCP by modulating inflammation and immune responses to create a proregenerative microenvironment. SCI triggers a complex inflammatory cascade involving resident microglia activation and peripheral immune cell infiltration, which can lead to secondary damage and hinder the regenerative process [74]. ADSCs possess potent immunomodulatory and anti-inflammatory properties that can help mitigate the detrimental effects of inflammation in the injured spinal cord [75,76].

ADSCs can secrete various immunomodulatory factors, including interleukin-10, TGF-β, and prostaglandin E2, which suppress the activation and proliferation of inflammatory cells, including T cells and macrophages [77,78]. Additionally, these factors promote macrophage polarization toward an anti-inflammatory M2 phenotype, which is associated with tissue repair and regeneration [79].

Several signaling pathways including the Notch and JAK/STAT pathways mediate the immunomodulatory effects of ADSCs. Notch signaling pathway activation in ADSCs enhances their immunosuppressive properties and promotes the expansion of regulatory T cells, which play a key role in immune homeostasis maintenance [67]. Moreover, the JAK/STAT pathway is involved in the immunomodulatory effects of ADSCs, with STAT3 activation being associated with anti-inflammatory cytokine production and T cell proliferation suppression [80].

Along with their direct immunomodulatory effects, ADSCs can also indirectly modulate the inflammatory response by influencing the function of other cell types in the injured spinal cord. For example, ADSCs can promote the survival and proliferation of endogenous neural stem cells and oligodendrocyte precursor cells, which have immunomodulatory properties and can contribute to tissue repair and regeneration [81,82].

2.4. Synergistic mechanisms of ADSC therapy in SCI

The therapeutic potential of ADSCs in SCI stems from their multifaceted actions, working in concert to promote recovery. Here, we explore three key mechanisms:

Neurodifferentiation: In vitro studies suggest ADSCs possess the ability to differentiate into various central nervous system (CNS) cell types, including neurons, astrocytes, and oligodendrocytes, under specific culture conditions [40]. This neurogenic potential raises the possibility of ADSCs replacing damaged cells within the injured spinal cord. This could theoretically facilitate functional circuit reconstruction by supporting axonal regrowth and remyelination.

Supportive Microenvironment: Beyond potential cell replacement, ADSCs secrete a complex mixture of neurotrophic and regenerative factors. These factors create a supportive microenvironment that promotes the survival and regeneration of endogenous neural cells, further aiding functional recovery [40]. Notably, ADSC-derived exosomes, small membrane-bound vesicles, have been implicated in enhancing neural differentiation. These exosomes may modulate inflammatory responses and promote cell

survival and proliferation [40]. Additionally, they might influence the transplanted ADSCs to differentiate into neural cell types, potentially through paracrine or autocrine signaling pathways. However, this mechanism requires further investigation.

Immunomodulation and Anti-inflammatory Effects: ADSCs possess immunomodulatory and anti-inflammatory properties that help mitigate the detrimental effects of the inflammatory response triggered by SCI. By suppressing inflammatory cell activation and promoting macrophage polarization toward a pro-regenerative phenotype, ADSCs create a more favorable environment for neural repair and regeneration.

The synergistic action of these mechanisms could lead to significant improvements in functional recovery following SCI. This multifaceted approach highlights the potential of ADSC therapy as a comprehensive treatment strategy for SCI, targeting multiple aspects of the injury and repair process.

While the mechanisms discussed above are specific to ADSCs, it is worth noting that other MSCs, such as BM-MSCs, may share similar therapeutic properties. Preclinical studies using intravenous administration of BM-MSCs in animal models of SCI have provided valuable insights into potential therapeutic mechanisms, such as modulation of gene expression patterns in the brain [83], blood-spinal cord barrier stabilization, axonal regeneration/sprouting, and remyelination [84]. Given the shared characteristics between ADSCs and BM-MSCs, it is reasonable to hypothesize that similar mechanisms may contribute to the benefits observed with ADSC therapy. However, further research is warranted to directly investigate the specific genetic and molecular pathways influenced by ADSC transplantation in the context of SCI.

3. Preclinical evidence for ADSC therapy in SCI

The efficacy of ADSC transplantation in improving functional outcomes following SCI in animal models has been explored in several studies. These studies have provided valuable insights into the therapeutic potential of ADSCs and investigated various strategies to optimize their regenerative capacity for SCI repair. However, of note, these preclinical studies have limitations and potential biases that should be considered when interpreting their findings. A summary of key findings from these preclinical studies is presented in Table 1.

3.1. Functional benefits of ADSC transplantation in SCI models

Multiple animal studies investigating SCI demonstrate the potential of ADSC transplantation to promote functional recovery (Table 1). For instance, Bonnet et al. [85] assessed the efficacy of transplanting mechanically stimulated lipoaspirate tissue, rich in ADSCs, in a rat model of acute thoracic spinal cord contusion. Their findings revealed a reduction in post-SCI inflammatory response, evidenced by decreased levels of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) 14 days after injury. Additionally, the transplanted activated adipose tissue significantly improved sensorimotor recovery, as measured by weekly monitoring for 12 weeks and gait and electrophysiological analyses at the end of the observation period. The authors further reported that the transplanted tissue restored the segmental sensorimotor loop and communication between supraspinal and sublesional spinal cord regions.

Chen et al. [86] reported that ADSC sheet transplantation in a rat model of complete spinal cord transection at T10 led to an increase in β-tubulin III-positive axons and the formation of new tissues at the injury site, accompanied by a decrease in cavity area, atrophy, and GFAP expression compared to the control SCI group.

Ertlen et al. [87] investigated the therapeutic efficacy of the adipose-derived stromal vascular fraction (SVF) on sensorimotor recovery following acute thoracic spinal cord contusion in adult rats. Compared to untreated animals, SVF administration mitigated endogenous inflammation and enhanced behavioral recovery. Additionally, H-reflex depression and ventilatory adjustments to muscle fatigue were similar between the sham and SVF groups,

Table 1
Summary of preclinical studies investigating ADSC therapy for SCI.

Study	Animal model	ADSC type and dose	Transplantation method and timing	Main findings
Bonnet et al. [85]	Rat, acute spinal cord contusion	Mechanically stimulated human lipoaspirate	Transplantation into the injury site	Reduced inflammation and enhanced sensorimotor recovery
Chen et al. [86]	Rat, complete spinal cord transection at T10	ADSC sheets	Implantation at the injury site	Increased β-tubulin III-positive axons, reduced cavity area, and improved bladder function
Ertlen et al. [87]	Rat, acute thoracic spinal cord contusion	SVF	Transplantation at the injury site	Reduced inflammation and improved behavioral recovery
Emiliano et al. [88]	Rat, experimental SCI	Human ADSCs; one or two infusions	Systemic infusion	Reduced neuronal loss
Rosado et al. [89]	Rat, spinal cord compression at T8–9	Allogeneic ADSCs; 1×10^6 cells	Intravenous injection 3 h post-injury	Improved BBB score
Zaminy et al. [90]	Rat, spinal cord transection at T9–10	Rat ADSC-derived Schwann cells, 20×10^4 cells	Intralesional injection immediately following injury	Improved BBB score and tail flick test
Kolar et al. [99]	Rat, cervical (C3–4) spinal cord hemisection	Human ADSCs	Transplantation into lateral funiculus 1-mm rostral and caudal to the injury site	Stimulated ingrowth of 5HT-positive raphaespinal axons, modified glial scar, and reduced microglial reactivity
Kim et al. [100]	Dog, acute thoracolumbar intervertebral disc disease	ADSCs	Transplantation into the injured spinal cord parenchyma	Better recovery than decompression surgery (DS) alone
Menezes et al. [101]	Rat, spinal cord compression injury	Human ADSCs; 1×10^6 cells	Direct injection into the spinal parenchyma immediately following injury	Promoted functional recovery, tissue preservation, axonal regeneration, laminin deposition, and neural precursor cell clusters
Sarveazad et al. [102]	Rat, spinal cord contusion	Human ADSCs; 1×10^6 cells, combined with chondroitinase ABC	Intraspinal injection	Reduced cavity formation, increased cell density, and improved motor function recovery
Mukhamedshina et al. [103]	Rat, spinal cord contusion	Rat ADSCs combined with fibrin matrix	Application at the injury site during the subacute period	Improved functional recovery, reduced cavity area, decreased astroglial activation, and modulated inflammatory response

indicating the efficacy of SVF and its potential to improve sensorimotor function after a traumatic contusion.

Emiliano et al. [88] evaluated the efficacy of human ADSC (hADSC) infusion for mitigating neuronal loss following experimental SCI in rats. Isolated and characterized hADSCs from bariatric surgery were infused in Wistar rats with SCI. One group received a single infusion, while the other received two (days 0 and 7 post-SCI). The control groups received culture medium. Compared with controls, ADSC infusion significantly reduced neuronal loss but did not affect the myelin or astrocyte area. Notably, one versus two infusions showed no difference, suggesting that distal ADSC infusion is a safe and effective approach for SCI treatment.

Several studies report significant improvements in motor function recovery, as assessed by the Basso, Beattie, and Bresnahan (BBB) locomotor rating scale, following ADSC transplantation [89,90]. Rosado et al. [91] observed that intravenous injection of allogeneic, cryopreserved ADSCs 3 h post-injury improved the BBB scores in a rat model of spinal cord compression at T8–9. Similarly, Zaminy et al. [90] demonstrated that the intralesional injection of Schwann cells differentiated from rat ADSCs immediately following injury improved the BBB scores and tail flick test results in a rat spinal cord transection model at T9–10.

It is crucial to acknowledge that many of these studies have small sample sizes, potentially limiting their statistical power and the generalizability of their results. Additionally, significant heterogeneity exists in the SCI models employed (e.g., contusion, transection, and compression) and treatment protocols (e.g., ADSC source, dose, timing, and route of administration). This heterogeneity makes direct comparisons across studies challenging and may contribute to inconsistencies in the reported outcomes. Furthermore, the need for further replication and validation of these results in larger, well-controlled studies is evident. Several of the preclinical studies have been conducted by a limited number of research groups, and independent replication by other laboratories would strengthen the evidence base for ADSC therapy in SCI.

While the precise mechanisms underlying the functional improvements observed in these preclinical studies remain to be fully elucidated, it is believed that ADSC differentiation into supportive cells, such as Schwann cells, may play a significant role in promoting functional recovery [59,61].

3.2. Strategies for enhancing the regenerative potential of ADSCs

Recent studies have explored various strategies for improving the regenerative potential of ADSCs for SCI repair. These strategies include.

- Genetically modified ADSCs that overexpress neurotrophic factors [91,92].
- ADSC-derived EVs, which are membrane vesicles containing proteins, nucleic acids, and lipids that reflect the biological functions of their donor cells [93–95].
- Injectable hydrogels for the targeted delivery of ADSCs and their derived EVs to the injured spinal cord [3,94,95,96].
- ADSC sheet technology, which offers advantages including improved cell survival and retention at the injury site, and extracellular matrix preservation [86,97].
- SVF, which has demonstrated efficacy in reducing inflammation and improving behavioral recovery [87].

Although these strategies show promise in enhancing the therapeutic potential of ADSCs, most of these studies have been conducted in preclinical models, and their translation to human clinical trials may face additional challenges. As these approaches move toward clinical application, factors including scalability, safety, and regulatory considerations should be carefully addressed.

A systematic review by Shang et al. [98] analyzed 15 types of stem cells in animal models of SCI and observed that ADSCs had the greatest therapeutic potential for promoting locomotor recovery, particularly at later stages post-injury (3, 5, and 8 weeks). Additionally, Mallappa et al. [99] investigated the effects of ADSCs in both the peripheral nerve and SCI models, providing valuable insights into their therapeutic mechanisms, including stimulating the ingrowth of serotonergic (5HT-positive) raphaespinal axons, modifying the glial scar, and reducing microglial reactivity.

In summary, preclinical studies have provided encouraging evidence for the therapeutic potential of ADSC therapy in SCI. However, critically evaluating the limitations and biases of these studies such as small sample sizes, variability in injury models and treatment protocols, and the need for independent replication and validation is imperative. Future studies should address these limitations by conducting larger well-controlled studies using standardized methodologies, while also exploring strategies for enhancing the regenerative capacity of ADSCs. As the field advances, a more comprehensive understanding of the mechanisms underlying ADSC-mediated neural regeneration and the optimal strategies for enhancing their therapeutic efficacy will be essential for successful translation to clinical application.

4. Clinical trials of ADSC therapy for SCI

Building upon the promising results from studies of ADSC therapy in SCI animal models, researchers are currently actively translating this promise into clinical applications. This section explores the ongoing clinical trials investigating the safety, feasibility, and potential benefits of ADSC therapy for patients with SCI, as summarized in Table 2. These trials represent a crucial step in determining whether the regenerative potential observed in preclinical models can be effectively harnessed to improve functional outcomes in humans.

4.1. Design and objectives of ADSC therapy trials

To determine the safety and efficacy of ADSC therapy for SCI, completed and ongoing clinical trials are investigating its potential in this patient population. These mostly early phase trials represent a significant step toward establishing ADSC therapy as a viable clinical treatment.

Assessing the safety and feasibility of ADSC transplantation in patients with SCI is the primary goal of these trials. To minimize the risk of immune rejection, researchers primarily use autologous ADSCs, that is, cells are derived from the patient's fat tissues [104]. The trials aim to determine the safety profile of ADSC transplantation, identify the most effective dosage and delivery method, and evaluate initial efficacy in terms of functional recovery and improved quality of life [37,38].

Several studies have investigated the use of ADSCs in patients with SCI. Ra et al. [104] intravenously administered human ADSCs to eight male patients with chronic SCI, whereas Hur et al. [37] observed sensory and motor function improvements in 14 patients with SCI treated with intrathecal ADSCs. Bydon et al. [38] reported motor and sensory score improvements in a patient with SCI following autologous ADSC therapy. Thakkar et al. [105] intrathecally coadministered autologous ADSCs, differentiated into neuronal and hematopoietic stem cells, in 10 patients with post-traumatic paraplegia.

More recently, Tien et al. [106] conducted a phase 1/2 clinical trial in Vietnam comparing patients receiving decompression surgery (DS) alone and patients receiving DS followed by intrathecal

Table 2
Summary of clinical studies investigating ADSC therapy for SCI.

Study	Study patient description	ADSC type and dose	Transplantation method and timing	Main findings
Ra et al. [104]	8 male patients with chronic SCI	Autologous ADSCs; dose not specified	Intravenous injection	No serious adverse events during the 3-month follow-up
Hur et al. [37]	14 patients with SCI (AIS A–D)	Autologous ADSCs; 9×10^7 ADMSCs per patient	Intrathecal injection	Sensory and motor function improvements in some patients; no serious adverse events
Bydon et al. [38]	1 patient with SCI (AIS A)	Autologous ADSCs; 100 million cells	Intrathecal injection, 11 months post-injury	Improvements in ASIA motor and sensory scores and quality of life
Thakkar et al. [105]	10 patients with posttraumatic paraplegia	Autologous ADSCs differentiated into neuronal and hematopoietic stem cells; mean 4.5×10^4 cells/μL	Intrathecal injection	Variable improvements in Hauser's index and ASIA scores; no adverse effects
Tien et al. [106]	47 patients with acute and subacute SCI	Autologous ADSCs; escalating doses (30×10^6 cells/8 mL–100×10^6 cells/10 mL)	Intrathecal injection; combined with DS	Improvements in all measures at 3 and 6 months; almost double the AIS improvement compared with surgery alone
NCT03308565 [107]	10 patients with chronic SCI (AIS A–B)	Autologous ADSCs; dose not specified	Intrathecal injection	Ongoing study; estimated completion in 2023
NCT04520373 [107]	Patients with severe traumatic SCI	Autologous ADSCs; dose not specified	Intrathecal injection; compared with physical therapy alone	Ongoing study; estimated completion in 2024

autologous ADSC injection. Patients who received ADSCs showed improvements in all measures at 3- and 6-month follow-ups, and ADSC transplantation with DS resulted in almost double the AIS improvement compared with patients who received DS alone (NCT02034669).

Ongoing trials include a phase 1 study evaluating the safety and efficacy of autologous ADSC intrathecal delivery in patients with traumatic SCI (NCT03308565) and a phase 2 trial comparing a single autologous ADSC intrathecal injection to physical therapy alone in patients with severe traumatic SCI (NCT04520373) [107].

Trial designs vary, with some involving a single ADSC injection and others employing multiple injections over time. The most common method is intrathecal injection [106]; however, some trials explore intravenous or intralesional injections. To assess safety and efficacy, stringent patient selection criteria, standardized ADSC isolation and preparation protocols, and comprehensive outcome measures are employed [37,38].

4.2. Early findings on safety, feasibility, and efficacy

Current data from completed clinical trials suggest that ADSC transplantation appears to be generally safe and well-tolerated in patients with SCI [37,104]. No reports of major adverse events or complications have been documented, indicating the potential feasibility and safety of ADSC therapy in a clinical setting [38,105]. However, long-term safety data are limited, and further studies with extended follow-up periods are required to fully establish the safety profile of ADSC therapy [107].

Regarding efficacy, some clinical trials have yielded promising results, demonstrating improvements in sensory and motor function, as well as overall patient quality of life [37,106]. In a study by Hur et al. [37], 5 out of 14 patients (35.7%) experienced improvements on the American Spinal Injury Association (ASIA) Impairment Scale (AIS) grade. Specifically, 2 patients improved from AIS A to B, 2 patients from AIS B to C, and 1 patient from AIS A to C. Additionally, 6 patients (42.9%) showed increased ASIA motor scores, with an average increase of 11.6 points (ranging from 2 to 28 points). Furthermore, sensory improvements were observed in 8 patients (57.1%), with a mean increase of 14.4 points (ranging from 2 to 36 points) in ASIA sensory scores.

Another study by Tien et al. [106] reported that patients who received ADSC transplantation along with DS demonstrated significantly greater improvements in ASIA motor and sensory scores at the 6-month follow-up compared to those who received DS alone. The mean improvement in ASIA motor scores was 28.2 points (ranging from 12 to 45 points) for the ADSC + DS group compared to 15.6 points (ranging from 5 to 30 points) for the DS alone group. Similarly, the mean improvement in ASIA sensory scores was 36.4 points (ranging from 15 to 60 points) for the ADSC + DS group compared to 18.3 points (ranging from 5 to 35 points) for the DS alone group.

While this review focuses on ADSC therapy for SCI, it is important to consider the broader context of stem cell therapy in this field. BM-MSCs offer a relevant example, with clinical investigations in Japan exploring their use for SCI treatment [108]. Although BM-MSCs originate from a different tissue source and exhibit distinct characteristics compared to ADSCs [28], studies on BM-MSC transplantation provide valuable insights into the general application of stem cell therapy for SCI. Notably, these studies highlight the importance of investigating the fate of transplanted cells after transplantation.

By and large, these findings suggest the potential efficacy of ADSC therapy for SCI; however, the magnitude of improvement varies among patients, and the relatively small sample sizes of these trials limit the ability to draw definitive conclusions about treatment efficacy [107]. Additionally, the lack of control groups in some studies makes it challenging to definitively attribute observed improvements solely to ADSC therapy, as spontaneous recovery and other factors may also play a role [109]. To definitively determine the therapeutic potential of ADSCs for SCI treatment, larger, well-controlled clinical trials with standardized outcome measures are necessary [109].

4.3. Challenges in translating preclinical findings to clinical trials

Despite promising preclinical data on ADSC therapy, significant hurdles exist in translating these findings into effective clinical applications. A major challenge lies in the limited generalizability of results from rodent models to humans. The CNS exhibits substantial interspecies differences in motor function networks, neural plasticity, and structural variations. These disparities must be carefully considered when interpreting preclinical data.

For example, unlike humans, rats lack monosynaptic corticomotoneuronal excitatory postsynaptic potentials (EPSPs). Instead,

their system relies on disynaptic EPSPs mediated via reticulospinal neurons and polysynaptic EPSPs mediated by segmental interneurons [110]. Conversely, disynaptic pyramidal excitation in forelimb motoneurons of Macaca fuscata (long-tailed macaque) is mediated by C3-C4 propriospinal neurons and exhibits stronger inhibitory control compared to the feline system [110]. Additionally, functional recovery of stepping in neonatally spinal cord-transected rats is not due to axonal regrowth across the lesion site, but rather due to adaptations within the lumbosacral neural circuitry. This highlights the significant interspecies variations in neural plasticity [111]. These structural and functional discrepancies emphasize the critical need to consider interspecies differences when translating preclinical findings for human application.

To improve the evaluation of ADSC therapy's potential therapeutic effects in humans, conducting experiments in larger mammals with a CNS structure and function closer to humans (e.g., Dogs, pigs, and monkeys) is crucial [98,111]. Such studies can provide valuable insights into safety, feasibility, and efficacy in larger mammals, bridging the gap between preclinical findings and human trials.

Patient heterogeneity in terms of injury location, severity, and chronicity presents another significant challenge [107]. This variability makes it difficult to standardize treatment protocols and assess the efficacy of ADSC therapy across different patient subgroups [109].

Determining the optimal dosage, timing, and delivery route of ADSCs in human trials remains another challenge [6]. Preclinical studies have employed diverse doses and administration strategies, necessitating the identification of the most effective approach for clinical translation [112]. Additionally, a complete understanding of the long-term survival, integration, and safety of transplanted ADSCs within the human spinal cord is lacking and requires further investigation [107].

Finally, regulatory and ethical considerations surrounding human stem cell therapy pose additional challenges [107]. Ensuring the quality, safety, and consistency of ADSC preparations, along with obtaining regulatory approval for clinical trials, necessitates significant time and resources [109]. Addressing these challenges is essential for successfully translating ADSC therapy into routine clinical practice for spinal cord injury treatment.

5. Limitations and future directions of ADSC therapy for SCI

ADSC therapy offers a promising avenue for SCI treatment and associated paralysis through regenerative medicine. However, its seamless translation into clinical practice is hindered by several challenges.

The hostile environment of the injured spinal cord is the primary challenge. This environment is characterized by inflammation and nutrient deprivation, which significantly reduces transplanted ADSC survival and integration [40,113,114]. Preconditioning ADSCs with hypoxia, growth factors, or small molecules to enhance their regenerative potential are strategies addressing this hurdle [40,115]. Additionally, genetic modification can overexpress pro-survival and neurotrophic factors, such as Bcl-2, GDNF, or VEGF, improving cell viability and function [40,115]. Cotransplantation with supportive cells including Schwann cells or OECs alongside biomaterial scaffolds aims to create a more favorable environment for ADSC survival and function [40,113].

Furthermore, the inherent variability of ADSCs due to tissue source and donor characteristics poses a significant challenge [40,52,115]. This variability can significantly impact the therapeutic efficacy of ADSC therapy, necessitating further investigation into optimization strategies [40]. Determining the most effective delivery route, establishing the optimal cell dose, and identifying the ideal timing of intervention following SCI are the optimization efforts [113,114].

Safety considerations remain paramount, particularly the potential risks of ADSC therapy-associated tumorigenicity [40,113,114]. Although the authors briefly mentioned this concern, a more in-depth discussion is warranted. Current evidence suggests that ADSCs can promote tumor growth and metastasis through various mechanisms, including differentiation into cancer-associated fibroblasts, growth factor and cytokine secretion that support tumor progression, and tumor microenvironment modulation [39–43]. However, most of these studies have been conducted in vitro or using animal models, and the clinical relevance of these findings remains unclear [45,48,49].

Several strategies are employed to mitigate the risks of tumorigenicity. Thorough characterization and quality control of ADSCs to ensure the absence of transformed or genetically unstable cells, the use of suicide genes or other safety switches to eliminate transplanted cells if necessary, and the development of targeted delivery methods to minimize off-target effects are the strategies employed [40,113,114]. Furthermore, to detect any potential tumorigenic events and promptly address them, long-term safety monitoring is crucial in clinical trials. This monitoring should include regular imaging studies, including magnetic resonance imaging or positron emission tomography, to track the fate and distribution of transplanted ADSCs, as well as long-term follow-up of patients to assess the incidence of any neoplastic complications [114].

Standardized protocols, large-scale controlled trials, and combinatorial approaches integrating rehabilitation strategies are essential to advance ADSC therapy for robust clinical applications [113–115]. To ensure reproducibility and facilitate comparisons across studies, standardized protocols for ADSC isolation, expansion, characterization, and transplantation are crucial [40,113,114].

5.1. Potential synergies with other emerging therapeutic approaches

Although ADSC therapy has shown promise in promoting functional recovery following SCI, combining it with other emerging therapeutic approaches may yield synergistic effects and enhance overall outcomes. The most promising complementary approaches to ADSC therapy include rehabilitation strategies, neural interface technologies, and pharmacological interventions.

Rehabilitation strategies including locomotor training and functional electrical stimulation promote neuroplasticity and improve functional outcomes in patients with SCI [116,117]. Combining ADSC transplantation with targeted rehabilitation protocols may enhance transplanted cell integration and functionality and promote endogenous neural circuit regeneration [118]. For example, a study by Gollihue et al. [119] demonstrated that the combination of Schwann cell transplantation and locomotor training improved hind limb function and promoted tissue sparing in a rat model of SCI compared with either treatment alone.

Neural interface technologies including brain–computer interfaces and spinal cord stimulation have emerged as promising tools for restoring motor and sensory functions in patients with SCI [120,121]. Integrating ADSC therapy with these technologies may provide a more comprehensive approach to SCI treatment, targeting both damaged neural tissue regeneration and functional connectivity restoration [122]. For example, a study by Capogrosso et al. [123] showed that epidural electrical stimulation of the spinal cord, combined with intraspinal neural stem cell transplantation, promoted long-term functional recovery in a nonhuman primate model of SCI.

Pharmacological interventions including neuroprotective agents, anti-inflammatory drugs, and growth factors have also

shown potential in mitigating secondary injury processes and promoting neural regeneration following SCI [18,124]. Combining ADSC therapy with these pharmacological approaches may create a more favorable microenvironment for cell survival and regeneration, thereby enhancing the overall therapeutic efficacy [125]. A study by Saini et al. [126] demonstrated that methylprednisolone and bone marrow-derived mesenchymal stem cell coadministration improved functional recovery and reduced inflammation in a rat model of SCI compared with either treatment alone.

As research in these complementary fields is advancing, exploring the optimal ways to integrate ADSC therapy with these emerging approaches will be crucial. Preclinical studies investigating the safety and efficacy of combinatorial strategies will be essential for guiding the design of future clinical trials and maximizing the therapeutic potential of ADSC therapy for SCI.

Future research directions encompass high-throughput screening of the ADSC secretome to identify factors promoting nerve regeneration and protection [114,115]. Bioengineering approaches aim to optimize the ADSC niche within the body [40,115], whereas the development of predictive biomarkers will improve treatment selection [40,113,115]. The integration of advanced technologies including CRISPR-Cas9 gene editing tools, organoid technologies, bioengineered spinal cord tissue models, and computational modeling approaches offer promising avenues for developing personalized medicine strategies for SCI treatment [114,115].

Overall, although ADSC therapy for SCI holds significant promise, addressing challenges related to cell survival, transplantation parameter optimization, safety considerations, and variability in study designs is crucial. Particularly, for the safe and successful translation of this therapy into clinical practice, a more thorough understanding of the tumorigenic potential of ADSCs and the development of effective strategies to mitigate these risks are essential. Exploring the synergistic potential of ADSC therapy with other emerging therapeutic approaches including rehabilitation strategies, neural interface technologies, and pharmacological interventions will be crucial in developing comprehensive and effective treatments for SCI. To realize the full potential of ADSC therapy in regenerative medicine for SCI, continued interdisciplinary research efforts, alongside advancements in technology and methodology, are essential.

6. Conclusion and future directions

Owing to ADSCs' multilineage differentiation potential, neurotrophic factor secretion, and immunomodulatory properties, they have emerged as a promising cell population for SCI treatment. Preclinical studies in animal models of SCI have yielded compelling evidence for the therapeutic potential of ADSCs, demonstrating their capacity to promote functional recovery, reduce cystic cavity formation within the injured spinal cord, and enhance axonal regeneration and myelination [84,87,88,97,99–101]. These findings underscore the importance of considering interspecies differences in CNS structure and function when translating preclinical results to human applications. Early clinical trials have provided initial evidence for safety and feasibility, with some studies suggesting potential improvements in motor and sensory function [37,38,104,106]. However, the magnitude of improvement varies among patients, and the relatively small sample sizes of these trials limit the ability to draw definitive conclusions about ADSC therapy efficacy.

To optimize and translate ADSC therapy into a standard clinical intervention for SCI, several key challenges should be addressed. These challenges encompass enhancing cell survival and engraftment post-transplantation, determining the most effective delivery methods and dosing regimens, mitigating potential risks such as tumorigenesis, and establishing standardized protocols for large-scale clinical trials [40,113–115]. Further research is also needed to directly investigate the specific genetic and molecular pathways influenced by ADSC transplantation in the context of SCI. Augmenting the therapeutic potential of ADSCs by exploring strategies such as genetic modification, preconditioning techniques, and combinatorial approaches that integrate biomaterials and rehabilitation therapies are the focus of future research endeavors [113–115].

The following are the most promising avenues for future research in ADSC therapy for SCI: (1) developing innovative strategies to enhance the survival, engraftment, and regenerative capacity of transplanted ADSCs; (2) conducting larger well-controlled clinical trials to definitively establish the safety and efficacy of ADSC therapy; (3) investigating potential synergies between ADSC therapy and other emerging therapeutic approaches, including rehabilitation strategies, neural interface technologies, and pharmacological interventions; and (4) exploring the use of advanced technologies, including gene editing, organoid models, and computational approaches, to optimize and personalize ADSC therapy for SCI [114,115]. Studies on BM-MSC transplantation in SCI provide valuable insights into the broader field of stem cell therapy and highlight the importance of investigating the fate and mechanisms of action of transplanted cells [83,84].

A multidisciplinary approach fostering close collaboration among basic scientists, clinical researchers, clinicians, and patients is needed for the successful development and clinical implementation of ADSC therapy for SCI. Basic scientists play a critical role in elucidating the mechanisms underlying ADSC-mediated neural regeneration and identifying novel therapeutic targets. Clinical researchers design and conduct well-controlled clinical trials to definitively establish the safety and efficacy of ADSC therapy. Clinicians particularly those specializing in rehabilitation medicine are essential in integrating ADSC therapy with established rehabilitation strategies to maximize functional recovery in patients with SCI. Importantly, to ensure that ADSC therapy development aligns with patients' needs and priorities, their participation and engagement in research and advocacy efforts are vital.

In conclusion, ADSC therapy offers significant promise as a regenerative approach for SCI treatment. Although substantial progress has been made in understanding the potential of ADSCs and developing therapeutic strategies, further research is necessary to optimize and translate this promising therapy into a safe, effective, and clinically viable treatment option. Overcoming current challenges will require a concerted effort from the scientific community, clinicians, and patients. By fostering collaborative research, investing in innovative approaches, and maintaining a patient-centric focus, the full potential of ADSC therapy for SCI can be realized, ultimately offering new hope and improved quality of life for individuals with SCI.

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Ethics approval and consent to participate

Not applicable.

Declaration of competing interest

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

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