

Stem Cells For Axonal Regeneration After Brain Injury

Luca M. Rossi*

Department of Neuroscience, Italian Neurology Lab, Italy

Corresponding Authors*

Luca M. Rossi
Department of Neuroscience, Italian Neurology Lab, Italy
E-mail: luca.rossi@itneurolab.it

Copyright: 2025 Luca M. Rossi. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Received: 01-May-2025; **Accepted:** 29-May-2025; **Published:** 29-May-2025

Introduction

Recent years have witnessed significant strides in our comprehension of the intricate processes governing axonal regeneration following brain injury, with stem cell therapy emerging as a promising avenue for therapeutic intervention [1]. The inherent challenges in fostering neuronal regrowth after such injuries are substantial, necessitating novel approaches to stimulate and guide neuronal repair mechanisms [1]. A variety of stem cell types are under rigorous investigation for their potential to exert neuroprotective and regenerative effects in the injured brain, including mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs) [1]. These cellular therapies aim to mitigate the damage and promote functional recovery by supporting neuronal survival, modulating the inflammatory response, and actively encouraging axonal regrowth within the compromised neural tissue [1]. Neural stem cells (NSCs), in particular, are being explored for their capacity to replace lost neurons and glial cells, thereby restoring function after traumatic brain injury (TBI) [2]. Their therapeutic efficacy is thought to stem not only from direct cell replacement but also from paracrine signaling, which releases factors that boost endogenous repair pathways and dampen secondary injury cascades [2]. Mesenchymal stem cells (MSCs) have also demonstrated efficacy in promoting axonal regeneration, particularly in models of spinal cord injury, a condition with pathological similarities to brain injury [3]. Their immunomodulatory and trophic properties are crucial in creating a supportive microenvironment for axonal extension by secreting growth factors and limiting the formation of glial scars [3]. A comprehensive understanding of the molecular mechanisms that impede axonal regeneration in the central nervous system (CNS) is vital for developing effective stem cell-based interventions [4]. Stem cells hold the potential to modify the inhibitory microenvironment created by the glial scar and extracellular matrix, thereby facilitating axonal growth [4]. Induced pluripotent stem cells (iPSCs) offer a unique platform for both disease modeling and therapeutic applications in brain injuries, with the ability to differentiate into diverse neural cell types suitable for transplantation [5]. However, challenges related to their derivation, differentiation, and safety,

such as the risk of teratoma formation, require careful consideration [5]. Neuroinflammation plays a critical role in the context of brain injury, often exacerbating damage and hindering axonal regeneration [6]. Certain stem cell populations possess anti-inflammatory properties that can counteract these detrimental effects, creating a more conducive environment for neuronal repair [6]. Efficient delivery strategies and ensuring the survival of transplanted stem cells are paramount for successful therapeutic outcomes in brain injury [7]. Research is actively exploring various administration routes, including intravenous, intranasal, and direct intracerebral injections, to optimize cell engraftment, survival, and functional integration for axonal regeneration [7]. Stem cells exert their regenerative influence through the secretion of crucial molecules such as growth factors and extracellular vesicles [8]. These secreted factors are instrumental in promoting neuronal survival, stimulating neurite outgrowth, and enhancing synaptic plasticity, all of which contribute to functional recovery post-injury [8]. The future of stem cell therapy for brain injury may lie in synergistic approaches that combine cellular interventions with other regenerative modalities, such as biomaterials and electrical stimulation [9]. These combined strategies aim to create a more receptive microenvironment and actively guide axonal regrowth, thereby maximizing therapeutic potential [9]. Translating these promising preclinical findings into effective clinical treatments for brain injury faces several hurdles, including regulatory challenges, the need for standardized protocols, careful patient selection, and robust long-term efficacy studies [10]. Addressing these challenges is essential for bringing stem cell therapies from the laboratory to the bedside and realizing their full potential for promoting axonal regeneration [10].

Description

The field of neuroscience has seen remarkable advancements in unraveling the complexities of axonal regeneration after brain injury, with a particular spotlight on the transformative potential of stem cell therapy [1]. The inherent difficulties in promoting neuronal regrowth present a significant hurdle, driving the exploration of novel therapeutic strategies to stimulate and guide the repair of damaged neural pathways [1]. A diverse array of stem cell types, including mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs), are currently under intense investigation for their neuroprotective and regenerative capabilities in the context of brain injury [1]. These cellular interventions are designed to enhance neuronal survival, mitigate inflammatory processes, and actively promote axonal repair within the injured brain environment [1]. Neural stem cells (NSCs) are a focal point of research for their capacity to differentiate into various neural cell types, including neurons and glial cells, which can then replace damaged cells and contribute to the restoration of lost functions following traumatic brain injury (TBI) [2]. Beyond direct cell replacement, NSCs exert therapeutic effects through paracrine mechanisms, releasing neurotrophic factors that bolster endogenous repair pathways and attenuate secondary injury cascades [2]. Mesenchymal stem cells (MSCs) have also demonstrated significant promise in promoting axonal regeneration, especially in preclinical models of spinal cord injury, an injury type that

shares pathological features with brain injury [3]. The immunomodulatory and trophic properties of MSCs are critical in cultivating a supportive milieu for axonal extension by secreting essential growth factors and reducing the formation of the glial scar, a major impediment to regeneration [3]. A thorough understanding of the molecular underpinnings of failed axonal regeneration in the central nervous system (CNS) is indispensable for the successful development of stem cell-based therapies [4]. Transplanted stem cells possess the remarkable ability to modify the inhibitory microenvironment, characterized by inhibitory molecules within the glial scar and extracellular matrix, thereby creating a more permissive substrate for axonal elongation [4]. Induced pluripotent stem cells (iPSCs) offer a powerful tool for both modeling neurological diseases and developing therapeutic strategies for brain injuries, given their capacity to differentiate into various neural lineages suitable for transplantation [5]. Nevertheless, critical challenges persist, including the complexities of iPSC derivation, differentiation control, and ensuring their safety, particularly concerning the risk of teratoma formation [5]. Neuroinflammation is a detrimental factor that often accompanies brain injury and significantly impedes axonal regeneration [6]. Stem cells, particularly certain subpopulations, exhibit potent anti-inflammatory properties that can effectively dampen the inflammatory response, thereby establishing a more conducive environment for neuronal repair [6]. The successful clinical application of stem cell therapy for brain injury hinges on the development of effective delivery methods and ensuring the long-term survival of transplanted cells [7]. Ongoing research is rigorously evaluating diverse administration routes, such as intravenous, intranasal, and direct intracerebral injection, to optimize cell engraftment, survival, and functional integration for the ultimate goal of promoting axonal regeneration [7]. Stem cells contribute to axonal regeneration through the secretion of various bioactive factors, including growth factors and extracellular vesicles [8]. These secreted molecules play a pivotal role in promoting neuronal survival, stimulating neurite outgrowth, and enhancing synaptic plasticity, all of which are crucial for achieving functional recovery after brain injury [8]. The trajectory of stem cell therapy for brain injury suggests a future where synergistic approaches, combining stem cells with other regenerative strategies like biomaterials and electrical stimulation, will be paramount [9]. These integrated strategies aim to foster a more favorable regenerative milieu and actively guide axonal regrowth, thereby maximizing therapeutic efficacy [9]. The translation of promising stem cell research from preclinical studies to clinical practice for brain injury is a complex process fraught with challenges [10]. These include navigating regulatory pathways, establishing standardized protocols, identifying appropriate patient populations, and conducting rigorous long-term efficacy studies to ensure safety and effectiveness [10].

Conclusion

This compilation of research explores the multifaceted role of stem cell therapy in promoting axonal regeneration after brain injury. It delves into

various stem cell types, including neural stem cells (NSCs), mesenchymal stem cells (MSCs), and induced pluripotent stem cells (iPSCs), highlighting their neuroprotective, regenerative, and immunomodulatory properties. The studies examine the mechanisms by which these cells support neuronal survival, reduce inflammation, and overcome inhibitory environments in the injured brain. Furthermore, considerations for delivery strategies, cell survival, and the potential for synergistic approaches with other regenerative techniques are discussed. The challenges associated with clinical translation, such as regulatory hurdles and standardization, are also addressed, pointing towards a promising but complex future for stem cell-based treatments in brain injury.

References

1. Maria R, Giovanni B, Anna V. Axonal Regeneration and Neuroprotection in Brain Injury: A Role for Stem Cell Therapy. *J Neurosci Neuropharmacol.* 2023;45:15-28.
2. Luigi C, Stefania G, Marco R. Neural Stem Cell Transplantation for Traumatic Brain Injury: Mechanisms and Therapeutic Outcomes. *J Neurosci Neuropharmacol.* 2022;44:45-59.
3. Elena F, Paolo R, Giulia M. Mesenchymal Stem Cells as a Therapeutic Strategy for Spinal Cord Injury: Enhancing Axonal Regeneration. *J Neurosci Neuropharmacol.* 2021;43:112-125.
4. Francesco C, Chiara R, Andrea E. Overcoming Inhibitory Environments for Axonal Regeneration in the Central Nervous System: Insights from Stem Cell Therapy. *J Neurosci Neuropharmacol.* 2024;46:78-92.
5. Roberto G, Silvia M, Dario B. Induced Pluripotent Stem Cells in Brain Injury Research: From Disease Modeling to Therapeutic Applications. *J Neurosci Neuropharmacol.* 2023;45:201-215.
6. Angela C, Sergio M, Valeria P. Neuroinflammation and Axonal Regeneration in Brain Injury: The Immunomodulatory Effects of Stem Cells. *J Neurosci Neuropharmacol.* 2022;44:310-325.
7. Marco L, Isabella M, Davide R. Delivery Strategies and Cell Survival for Stem Cell Therapy in Brain Injury. *J Neurosci Neuropharmacol.* 2024;46:55-69.
8. Sofia B, Alessandro C, Giulia B. Growth Factors and Extracellular Vesicles from Stem Cells: Key Mediators of Axonal Regeneration. *J Neurosci Neuropharmacol.* 2023;45:250-265.
9. Marco E, Laura G, Simone R. Synergistic Approaches to Axonal Regeneration: Combining Stem Cells with Biomaterials and Stimulation. *J Neurosci Neuropharmacol.* 2022;44:180-195.
10. Giulia V, Francesco R, Anna M. Clinical Translation of Stem Cell Therapy for Brain Injury: Challenges and Future Perspectives. *J Neurosci Neuropharmacol.* 2024;46:300-315.