

POLYLAMININ AND NERVOUS SYSTEM REGENERATION: A SYSTEMATIC REVIEW OF EXPERIMENTAL AND CLINICAL EVIDENCE

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ABSTRACT

Injuries to the central (CNS) and peripheral (PNS) nervous systems exhibit limited regenerative capacity, especially in the CNS, due to glial scar formation, persistent inflammation, and low neuronal plasticity. In this context, polylaminin (polyLM), a polymerized form of laminin with biomimetic organization of the extracellular matrix, emerges as a promising strategy in neural regenerative medicine. This systematic review evaluated the efficacy of polyLM in neural regeneration, functional recovery, and modulation of the tissue microenvironment after nervous system injuries. The review followed the PRISMA guidelines and the PICO strategy, with searches in the PubMed, Scopus, and SciELO databases. Experimental, observational, and clinical trials published in Portuguese or English, that investigated the use of polyLM in neural injuries were included. The outcomes analyzed included axonal regeneration, functional recovery, histological aspects, and modulation of the extracellular matrix. The results demonstrated high bioactivity of polyLM, promoting neuritogenesis, cell proliferation, and inflammatory modulation. In spinal cord injury models, axonal growth across the injury site, significant locomotor improvement, and a reduction in the early inflammatory response were observed. Translational evidence indicated functional improvement in dogs with chronic spinal cord injury and recovery of voluntary muscle contraction in patients with functionally complete spinal cord injury. Furthermore, its incorporation into biomaterials reduced fibrosis and macrophage activation, creating a microenvironment more favorable to regeneration. It is concluded that polylaminin is a bioactive biomaterial with potential in neural regeneration, acting on structural, cellular, and inflammatory mechanisms. However, its clinical consolidation requires controlled studies, therapeutic standardization, and long-term safety evaluation.

Keywords: Extracellular matrix, Laminin, Neurology, Nerve regeneration, Spinal cord injuries.

INTRODUCTION

Injuries to the central and peripheral nervous systems represent an important public health problem, affecting millions of people worldwide and being associated with permanent functional deficits and a significant impact on patients' quality of life. Neural regenerative capacity, particularly in the central nervous system, is extremely limited due to low intrinsic neuronal plasticity, the

presence of inhibitory molecules, and glial scar formation.^{1,2}

Polylaminin, the polymerized form of laminin, exhibits a biomimetic organization of the extracellular matrix and has been associated with positive effects on recovery from these injuries. Experimental studies have demonstrated its ability to promote axonal regeneration and functional improvement after spinal cord injury¹, as well as to modulate cellular pathways related to neuronal growth³. Recent evidence suggests potential translational applications, including functional improvement in animal models and preliminary results in humans.^{1,2}

Although experimental and translational studies have demonstrated promising results with polylaminin, the evidence remains scattered throughout the literature, and there is no consensus regarding its efficacy across different models of neural injury. In addition, the predominance of preclinical studies makes it difficult to extrapolate the findings to clinical practice. Therefore, a systematic analysis of the available evidence is needed to critically understand the effects of polylaminin on nervous system regeneration, identify its potential therapeutic applications, and highlight the main gaps that still limit its clinical applicability.

Given the limitations of current therapeutic approaches, increasing attention has been directed toward a deeper understanding of the role of the neural microenvironment in the regenerative process. In this context, the extracellular matrix emerges as a central element in the regulation of cell adhesion, axonal growth, and neuronal differentiation, with laminin being one of its main components and playing an important role in stimulating neuritogenesis.³

In this context, several strategies have been investigated with the aim of promoting axonal regeneration and functional recovery after nervous system injury, including cell therapies, growth factors, and biomaterials. However, the results remain limited and insufficient to promote significant recovery.

OBJECTIVES

The primary objective of this study is to evaluate, through a systematic literature review, the efficacy of polylaminin in axonal regeneration following nervous system injuries. As secondary objectives, it seeks to analyze the effects of polylaminin on functional recovery, investigate its role in modulating the extracellular matrix during the neural regeneration process, identify the main scientific evidence regarding its clinical applicability, and describe the existing gaps in the literature related to its therapeutic efficacy.

METHODS

This is a systematic review conducted in accordance with the PRISMA recommendations for systematic reviews.

The research question was structured according to the PICO strategy: P (Population): patients (humans or animal models) with central or peripheral nervous system injury; I (Intervention): treatment with polylaminin (or polymerized laminin); C (Comparison): no treatment, placebo, or other regenerative treatments; O (Outcome): axonal regeneration, functional recovery (motor/sensory), modulation of the extracellular matrix, and cytological/histological aspects.

The literature search was conducted in March 2026 in the PubMed, Scopus, and SciELO databases, considering publications in English or Portuguese available in full text for analysis. No eligible studies were identified in the SciELO database. Due to the scarcity of publications on polylaminin, a broad search strategy based on the terms “polylaminin” and “polymerized laminin” was used, followed by the

application of eligibility criteria. A total of 30 records were identified in the databases searched (15 in PubMed and 15 in Scopus). After removal of duplicates, 15 studies remained for screening. Of these, 5 were excluded after title and abstract screening because they did not address neural regeneration or did not meet the eligibility criteria. In the end, 10 studies were included in the systematic review.

Experimental *in vitro* studies, animal model studies, observational studies, and clinical trials investigating the use of polylaminin as the main intervention in central or peripheral nervous system injuries and reporting outcomes related to neural regeneration, functional recovery, histological changes, or modulation of the extracellular matrix were included. Duplicate studies, studies without full-text access, letters to the editor, editorials, literature reviews, as well as studies that did not use polylaminin as the main intervention or did not assess outcomes related to neural regeneration, were excluded.

Study screening was performed independently by two reviewers, with initial analysis of titles and abstracts followed by full-text reading of potentially eligible articles, without the use of automation tools. Data extraction was performed by four independent reviewers using a standardized form. Information was collected on the author, year of publication, country, study design, sample size, population characteristics, study objective, and main outcomes. Disagreements were resolved by consensus between the two editors in both cases.

Considering the heterogeneity of the designs of the included studies and the small number of available publications, a qualitative assessment of methodological quality was performed, considering study design, presence of a control group, sample size, and clarity of outcomes. The data were organized with the aid of the Mendeley platform.

RESULTS AND DISCUSSIONS

The analysis of the selected articles demonstrated a multifaceted role of polylaminin (polyLM) in nervous system regeneration, encompassing structural, cellular, and functional aspects. Consistently, the studies demonstrated its ability to promote neuritogenesis, modulate the extracellular matrix, attenuate inflammation, and favor functional recovery in different experimental models, including preliminary evidence in humans.

Ten studies were included in this systematic review, comprising biophysical analyses, *in vitro* studies, animal models of central and peripheral nervous system injury, translational studies in dogs, and one pilot study in humans. The studies evaluated different aspects of polylaminin, including its structural properties, ability to promote neuritogenesis, axonal regeneration, functional recovery, inflammatory modulation, and applications in biomaterials. The main characteristics of the included studies are summarized in Table 1.

Reference	Model	Main outcome
Franchi et al. (2014)	Biophysical analysis	Identification of fractal characteristics and increased surface area.
Menezes et al. (2010/2020)	Rats / In vitro	Axonal regeneration in SCI and organization of collagen IV.
Siqueira-Santos (2013)	Retinal cells	Significant increase in neuritogenesis and cell adhesion.
Spanevello et al. (2019)	Sciatic nerve (rats)	Improved regeneration in PCL filaments.
Gadelha et al. (2025)	Dogs (chronic SCI)	Clinical safety and efficacy in a large-animal model.
Menezes et al. (2024)	Humans (SCI)	Recovery of voluntary motor contraction in complete injuries.
Ullah et al. (2022)	iPSCs	Stem cell expansion with a low protein dose.
Jatuviriyapornchai (2019)	Microcapsules	Reduced inflammation and fibrosis in implants.

3.1. Structural Properties and Interaction with the Extracellular Matrix

Poly laminin is characterized by a unique structure, consisting of an acid-induced, non-covalent nano- and microstructured laminin polymer⁴. Morphologically, it appears as a loose, homogeneous, flocculated network, in contrast to the dense aggregates of conventional laminin. This supramolecular organization has a fractal nature, suggesting a relevant role in the organization of basement membranes in neurogenic niches of the central nervous system.¹

Additionally, polyLM demonstrates the ability to organize other components of the extracellular matrix. Type IV collagen has been observed to conform to its structure, indicating that polymerized laminin may guide basement membrane assembly⁵. This biomimetic behavior reinforces its role as a structural template for the formation of artificial basement membranes. Its chemical nature, based on the self-association of heterotrimeric laminin under specific electrostatic conditions, favors molecular recognition and anchoring of different cellular substrates.⁶

3.2. Effects on Neuritogenesis and Cell Proliferation

Poly laminin has consistently demonstrated the ability to stimulate neuritogenesis and cell proliferation. In *in vitro* studies, it promotes neuritogenesis at levels higher than those observed with non-polymerized laminin.⁴

Retinal cells distinguish polyLM from conventional laminin, showing greater adhesion and greater neurite extension when cultured on the polymerized form³. Thus, active polymerized laminin exerts a positive influence on both neuritogenesis and cell proliferation, demonstrating greater bioactivity and efficiency as a substrate for neuronal growth.³

In addition, poly laminin-521 has been shown to be a viable substrate for the expansion of human induced pluripotent stem cells, allowing large-scale expansion with high viability and maintenance of pluripotency even at low concentrations.⁷ Its organization mimics the native basement membrane, favoring more stable cell-matrix interactions and appropriate integrin recruitment.

3.3. Axonal Regeneration and Functional Recovery

The application of poly laminin has demonstrated promising results in axonal regeneration and functional recovery. In rat models of spinal cord injury, local administration resulted in axonal growth across the injury site, associated with significant functional improvement.¹ Increased locomotor scores and evidence of neural reconnection were observed, indicating regeneration of nerve fibers.

Furthermore, poly laminin exhibited an anti-inflammatory effect, contributing to the early onset of functional improvement, which was already observed during the first week after treatment.¹

On the other hand, in peripheral nerve injury models, the results were heterogeneous. Although poly laminin showed benefits at the cellular level, non-polymerized laminin associated with poly- ϵ -caprolactone (PCL) filaments demonstrated better motor functional recovery and a greater number of motor endplates, suggesting that its effects may vary according to the experimental context.⁸

3.4. Clinical Applications and Translational Evidence

Translational studies reinforce the therapeutic potential of poly laminin. In animal models, such as dogs with chronic spinal cord injury, the administration of polyLM associated with neurotrophic factors was shown to be safe and promoted significant improvement in motor function.²

In humans, a pilot study demonstrated the recovery of voluntary muscle contraction after functionally complete spinal cord injury, with recovery confirmed by clinical and electrophysiological methods⁹. Although preliminary, these findings indicate a potentially relevant regenerative effect of poly laminin.

3.5. Modulation of the Inflammatory Response and Biomaterials

Poly laminin also plays a relevant role in modulating the inflammatory response. Its incorporation into biomaterials, such as alginate microcapsules, resulted in reduced macrophage activation, decreased pericapsular fibrosis, and lower production of pro-inflammatory cytokines¹⁰.

In addition, improved integration with host tissue and preservation of the function of encapsulated cells were observed, indicating that polyLM contributes to the creation of a microenvironment more favorable to tissue regeneration.

The findings of this systematic review suggest a promising role for poly laminin (polyLM) as a bioactive biomaterial in nervous system regeneration, particularly because it acts simultaneously on multiple aspects of the regenerative process, including extracellular matrix organization, neuritogenesis, inflammatory

modulation, and functional recovery. This multifactorial action is particularly relevant given the complexity of neural injuries, especially in the central nervous system, where spontaneous regeneration is limited.

From a structural perspective, the supramolecular organization of polylaminin emerges as one of the main determinants of its bioactivity. Unlike conventional laminin, which tends to form irregular aggregates, polyLM exhibits a homogeneous three-dimensional network with fractal characteristics, capable of mimicking the architecture of the native basement membrane.³ This organization favors more efficient cell-matrix interactions, promoting greater cell adhesion, axonal guidance, and organization of the regenerative microenvironment. In addition, evidence indicates that this structure results from the non-covalent self-association of laminin under specific pH conditions and in the presence of Ca^{2+} , reinforcing its biomimetic and functional nature.⁶ In this context, polylaminin acts not only as structural support but also as an active modulator of tissue regeneration.

At the cellular level, the results demonstrate that polylaminin is consistently superior to non-polymerized laminin in inducing neuritogenesis and cell proliferation. In *in vitro* models, polyLM promotes greater neurite extension, increased cell adhesion and proliferation, as well as activation of intracellular pathways related to neuronal differentiation, such as PKA and PKC³. These effects are attributed to its spatial organization, which favors recognition by cellular receptors such as integrins, promoting more efficient intracellular signaling. Additionally, its use in pluripotent stem cell culture demonstrates the ability to maintain viability, genetic stability, and pluripotency even at low concentrations, reinforcing its translational potential in regenerative medicine.⁹

Regarding axonal regeneration and functional recovery, the data indicate that polylaminin has significant effects, particularly in spinal cord injury models. Experimental studies demonstrate functional improvement associated with axonal growth, with evidence of neural reconnection and increased locomotor scores after injury.⁸ These effects appear to be related not only to direct stimulation of axonal growth but also to modulation of the inflammatory response, with a reduction in secondary inflammation, a crucial factor in the progression of neural injury. In fact, inflammation is one of the main mechanisms of secondary degeneration after spinal cord injury, and its early modulation is a determining factor for functional prognosis.

However, the results are not uniform across all experimental contexts. In peripheral nerve injury models, although polylaminin demonstrates a greater ability to induce neuritogenesis *in vitro*, non-polymerized laminin associated with biomaterials, such as poly- ϵ -caprolactone filaments, showed better motor functional outcomes *in vivo*.⁴ This finding suggests that the efficacy of polylaminin may depend on the microenvironment and its interaction with other biomaterials, indicating that its isolated application may not be ideal in all settings. Thus, combined strategies may be more effective in enhancing its effects.

From a translational perspective, the available data are particularly relevant. Studies in large-animal models, such as dogs with chronic spinal cord injury, demonstrate significant improvement in locomotor function after the use of polylaminin associated with neurotrophic factors, without relevant adverse events.² In addition, preliminary evidence in humans indicates recovery of voluntary muscle contraction in patients with complete spinal cord injury, a notable finding considering the low rate of spontaneous recovery in these cases.⁹ These results suggest that polylaminin may overcome classical limitations of clinical translation by acting as a multitarget therapeutic strategy.

Another relevant aspect observed is the ability of polylaminin to modulate the inflammatory response and improve integration with biomaterials. Its incorporation into systems such as alginate microcapsules reduces macrophage activation and fibrosis formation, favoring a microenvironment more permissive to regeneration. This effect is particularly important because glial scar formation and exacerbated inflammation

represent critical barriers to regeneration in the central nervous system.

Despite the promising results, this review highlights important limitations. Most studies are based on experimental models, with substantial methodological heterogeneity, including variations in injury models, doses, routes of administration, and evaluated outcomes. In addition, clinical studies remain preliminary, with small samples and the absence of robust control groups, limiting the generalizability of the findings. Furthermore, there is a scarcity of investigations addressing long-term safety and potential adverse effects of polyaminin, which are essential aspects for its clinical validation.

CONCLUSION

Thus, although polyaminin appears to be a highly promising strategy for neural regeneration, its clinical application still requires validation through randomized controlled clinical trials, as well as the standardization of therapeutic protocols. Future studies should explore combined therapeutic approaches, including the use of growth factors, enzymes that modulate glial scarring, and biomaterials, in order to enhance its effects. Furthermore, a deeper understanding of the molecular mechanisms involved in the interaction between polyaminin and the neural microenvironment, particularly with regard to integrin-mediated signaling, inflammatory modulation, and extracellular matrix organization, will be essential to optimize its therapeutic application.

The findings of this review indicate that polyaminin acts not only as structural support but also as a bioactive biomaterial capable of integrating multiple regenerative processes, representing a potentially multitarget approach to the treatment of nervous system injuries. Despite methodological limitations and the predominance of preclinical evidence, the results point to a promising scenario in which polyaminin may represent an advance in neural regenerative medicine.

Therefore, it can be concluded that polyaminin has relevant potential for promoting axonal regeneration and functional recovery, particularly in central nervous system injuries. However, its consolidation in clinical practice will depend on the robustness of future evidence, the reproducibility of the results, and the establishment of safe, effective, and scalable therapeutic protocols.

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