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EXAME DE PROFICIÊNCIA EM LEITURA EM LÍNGUA INGLESA
GRANDE ÁREA: CIÊNCIAS BIOLÓGICAS E CIÊNCIAS DA SAÚDE

Polylaminin, a polymeric form of laminin, promotes regeneration after spinal cord injury

Adapted from: MENEZES, Karla et al. Polylaminin, a polymeric form of laminin, promotes regeneration after spinal cord injury. *The FASEB Journal*, 2010.

INTRODUCTION

[1] Spinal cord injury (SCI) leads to devastating and often permanent neurological deficits due to both the primary mechanical damage and a secondary wave of degeneration largely driven by inflammation. Although several therapeutic strategies have aimed to reduce inflammation or stimulate regeneration, effective clinical treatments remain limited. In this study, Menezes et al. (2010) investigate whether a polymerized form of laminin—termed polylaminin (polyLM)—can promote neuroprotection and regeneration after SCI in rats.

BACKGROUND AND RATIONALE

[2]Laminin is a major extracellular matrix glycoprotein that plays a critical role in neural development, axonal growth, cell migration, differentiation, and survival. In the peripheral nervous system, laminin is well established as a promoter of regeneration. In the central nervous system (CNS), laminin expression increases after injury; however, endogenous production is insufficient to induce significant regeneration. Surprisingly, previous attempts to use exogenous full-length laminin in SCI models had failed to demonstrate functional recovery, although certain laminin-derived peptides showed modest benefits.

[3]Importantly, laminin naturally exists in polymeric forms within basement membranes, and its biological activity depends on its supramolecular organization. The authors previously demonstrated that laminin can self-polymerize under acidic conditions (pH 4), forming a stable biomimetic polymer similar to naturally occurring laminin networks. This polymeric form, termed polylaminin (polyLM), enhances neurite outgrowth in vitro. Based on these findings, the authors hypothesized that the polymeric structure of laminin, rather than the monomeric protein, may be critical for therapeutic efficacy in SCI.

EXPERIMENTAL DESIGN

[4] Adult female Sprague-Dawley rats were subjected to three different SCI models of increasing severity:

1. Compression injury
2. Partial dorsal transection
3. Complete transection

[5] Animals received a single acute local injection of either:

- Polylaminin (polyLM; laminin polymerized in acidic buffer),
- Non-polymerized laminin (LM; neutral pH), or
- Vehicle buffer control.

[6] Motor recovery was assessed weekly for up to 8 weeks using the Basso, Beattie, Bresnahan (BBB) locomotor scale. Histological, immunohistochemical, and retrograde tracing analyses were performed to evaluate tissue preservation, inflammation, axonal growth, and neuronal connectivity.

FUNCTIONAL RECOVERY

[7]In the compression model, all animals exhibited partial spontaneous recovery. However, polyLM-treated rats showed significantly faster and more complete recovery compared to controls. By week 6, polyLM-treated animals reached normal locomotor scores (BBB = 21), whereas animals treated with non-polymerized laminin showed no improvement beyond vehicle-treated controls. This demonstrates that polymerization is essential for therapeutic efficacy.

[8]In the partial transection model, polyLM treatment significantly improved motor function throughout the 8-week period, enhancing final BBB scores by approximately 50% compared to controls.

[9]Most notably, in the complete transection model—where spinal cord stumps were physically separated—polyLM-treated animals showed substantial recovery. BBB scores increased from approximately 4 in controls to nearly 9 in polyLM-treated rats at 8 weeks, effectively doubling functional performance. Comparable results were obtained using polymerized laminin derived either from murine tumor sources (laminin 111) or from human placenta (primarily laminin 211), suggesting that the regenerative effect depends on polymerization rather than on specific laminin isoforms.

NEUROPROTECTION AND TISSUE PRESERVATION

[10] Histological analyses revealed that polyLM treatment significantly reduced cavity formation and tissue degeneration. In compression injuries, polyLM decreased cystic cavity size and reduced expression of glial fibrillary acidic protein (GFAP), a marker of glial scar formation. Tissue architecture—including gray and white matter organization—was better preserved.

[11] In transected cords, polyLM-treated animals displayed improved structural continuity between stumps, reduced fibrosis, and preservation of central canal structure. These findings indicate strong neuroprotective effects.

ANTI-INFLAMMATORY EFFECTS

[12] A major finding of the study is the anti-inflammatory action of polyLM. Immunostaining for ED1 (a marker of activated macrophages and microglia) showed that in control animals, inflammatory cells were diffusely distributed throughout white matter. In contrast, polyLM treatment restricted macrophage distribution primarily to lesion margins.

[13] Quantitative analysis demonstrated a significant reduction in macrophage infiltration in white matter. Furthermore, serum levels of C-reactive protein (CRP)—a systemic inflammatory marker—were elevated after SCI but were markedly suppressed in polyLM-treated animals.

[14] Importantly, functional improvement was observed as early as the first week post-injury, suggesting that polyLM exerts early neuroprotective effects by modulating inflammation. The authors propose that polyLM may influence inflammatory signaling pathways, potentially involving cAMP/PKA-mediated mechanisms.

AXONAL REGENERATION

[15]Beyond neuroprotection, polyLM promoted axonal growth. Increased expression of GAP-43, a marker of axonal regeneration, was observed in treated animals. In the transection model, serotonergic (5-HT-positive) descending fibers were detected crossing the lesion site only in polyLM-treated rats.

[16]To confirm functional reconnection, the authors performed retrograde tracing with fluorogold injected below the lesion. Significantly more labeled neurons were detected in the spinal cord and brainstem of polyLM-treated animals compared to controls. This demonstrates regeneration of both short propriospinal and long descending fibers across a complete transection.

MECHANISTIC CONSIDERATIONS

[17] The study suggests that polyLM has dual actions:

1. Neuroprotection through anti-inflammatory effects
2. Direct stimulation of axonal regeneration

[18] The fact that delayed polyLM treatment (after the inflammatory phase) enhanced axonal labeling without reducing tissue degeneration supports the idea that neuroprotection and regeneration may be partially independent mechanisms.

[19] The findings also emphasize that laminin's supramolecular organization is critical for biological activity. Non-polymerized laminin was ineffective, underscoring the importance of extracellular matrix architecture in therapeutic design.

SIGNIFICANCE AND TRANSLATIONAL POTENTIAL

[20] This study presents several advances:

- Demonstration of strong functional recovery, including in complete transection.

- Validation across three SCI models.
- Efficacy with a single acute dose.
- Use of human-derived laminin polymers.
- Identification of both anti-inflammatory and regenerative mechanisms.

[21] Given that laminin is an endogenous protein that can be purified from human placenta or produced recombinantly, polyLM represents a promising candidate for translational application in human SCI therapy.

CONCLUSION

[22] Menezes et al. demonstrate that polylaminin—a polymerized, biomimetic form of laminin—significantly promotes functional recovery after spinal cord injury in rats. Its therapeutic effect depends on polymerization and involves both suppression of inflammation and stimulation of axonal regeneration.

[23] The findings reposition laminin as a viable candidate for SCI treatment when delivered in its appropriate supramolecular form and highlight the importance of extracellular matrix architecture in CNS repair strategies.

I. RESPONDA ÀS PERGUNTAS DE 1 A 3 EM PORTUGUÊS, DE ACORDO COM AS INFORMAÇÕES VEICULADAS NO TEXTO:

1. Considere os Parágrafos [1 e 2]. Por que as estratégias terapêuticas atuais para lesão da medula espinhal ainda são consideradas limitadas, e qual é o papel da laminina nesse contexto? *(1,5 pontos)*

As estratégias terapêuticas atuais para lesão da medula espinhal são consideradas limitadas porque não conseguem promover uma recuperação funcional efetiva, mesmo quando reduzem a inflamação ou tentam estimular a regeneração.
A laminina é uma glicoproteína importante da matriz extracelular, pois participa do crescimento axonal, da migração celular e da sobrevivência dos neurônios. Após a lesão, sua produção no sistema nervoso central aumenta. No entanto, essa quantidade produzida naturalmente não é suficiente para promover uma regeneração significativa.

2. Considere o Parágrafo [3]. Explique por que a forma polimérica da laminina (polylaminin) pode ser mais eficaz do que a forma não polimerizada no processo de regeneração neural. *(2 pontos)*

A forma polimérica da laminina (polylaminin) é mais eficaz porque sua atividade biológica depende de sua organização supramolecular. Quando polimerizada, a laminina forma uma

estrutura semelhante às redes naturais da matriz extracelular, o que potencializa seus efeitos biológicos, como o crescimento de neuritos.
Já a forma não polimerizada (monomérica) não reproduz essa organização estrutural, sendo menos eficaz no estímulo à regeneração neural.

3 Considere os Parágrafos [10 a 14]. Explique como o polylaminin contribui para a neuroproteção após a lesão medular, destacando seus efeitos sobre a inflamação e a preservação do tecido. *(2 pontos)*

A polylaminin promove neuroproteção ao reduzir a inflamação e preservar o tecido lesionado. Ele diminui a formação de cavidades e a degeneração tecidual, além de reduzir a expressão de GFAP, indicando menor formação de cicatriz glial.
Além disso, restringe a infiltração de macrófagos às margens da lesão e reduz os níveis de proteína C-reativa (CRP), evidenciando efeito anti-inflamatório. Esses efeitos contribuem para a preservação da arquitetura do tecido nervoso e favorecem a recuperação funcional.

II. NAS QUESTÕES de 4-7 ASSINALE A ALTERNATIVA CORRETA DE ACORDO COM AS INFORMAÇÕES VEICULADAS NO TEXTO.

4. Considere os Parágrafo [4] (0,5 ponto)

Sobre os modelos experimentais utilizados no estudo, é correto afirmar que:	
A	Apenas lesões leves foram utilizadas para avaliar a eficácia do tratamento.
B	Foram utilizados três modelos de lesão medular com diferentes níveis de severidade.
C	O estudo foi realizado exclusivamente com modelos de lesão parcial.
D	Apenas modelos de regeneração espontânea foram analisados.

5. Considere o parágrafo [7] (0,5 ponto)

No modelo de compressão, o tratamento com polylaminin resultou em:	
A	Nenhuma diferença em relação ao grupo controle.
B	Recuperação mais lenta, porém mais estável.
C	Recuperação mais rápida e completa da função motora.
D	Redução da inflamação sem impacto funcional.

6. Considere o parágrafo [12 e 13] (0,5 pontos)

O efeito anti-inflamatório do polylaminin é evidenciado por:

A	Aumento da infiltração de macrófagos no tecido lesionado.
B	Distribuição uniforme das células inflamatórias na substância branca.
C	Redução da infiltração de macrófagos e diminuição dos níveis de proteína C-reativa.
D	Estímulo à produção de marcadores inflamatórios sistêmicos.

7. **Considere o parágrafo [15 e 16]** (0,5 ponto)

A regeneração axonal promovida pelo polylaminin foi confirmada por:	
A	Redução da expressão de proteínas associadas ao crescimento neural.
B	Ausência de fibras nervosas no local da lesão.
C	Presença de fibras descendentes atravessando a lesão e aumento de neurônios marcados.
D	Exclusiva regeneração de fibras periféricas.

III. CONSIDERE OS PARÁGRAFOS E JULGUE CADA SENTENÇA ABAIXO COMO VERDADEIRA OU FALSA DE ACORDO COM AS INFORMAÇÕES VEICULADAS NO TEXTO. (0,5 PONTO CADA QUESTÃO)

	Sentenças	Verdadeira	Falsa
a.	**[Parágrafo 3]** A atividade biológica da laminina depende de sua organização estrutural, sendo a forma polimérica mais funcional.	X	
b.	**[Parágrafos 7-9]** A laminina não polimerizada apresentou os mesmos efeitos terapêuticos que o polylaminin.		X
c.	**[Parágrafos 10-11]** A polylaminin contribui para a preservação da estrutura do tecido e reduz a formação de cavidades após a lesão.	X	
d.	**[Parágrafo 18]** Os efeitos de neuroproteção e regeneração dependem exclusivamente do mesmo mecanismo biológico.		X
e.	**[Parágrafos 20-21]** A polylaminin apresenta potencial translacional, podendo futuramente ser aplicado em terapias humanas.	X	