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UNIVERSIDADE ESTADUAL PAULISTA ‘’JULIO DE MESQUITA FILHO’’
FACULDADE DE MEDICINA VETERINÁRIA E ZOOTECNIA
CAMPUS DE BOTUCATU

TRANSDIFERENCIAÇÃO DE CÉLULAS TRONCO MESENQUIMAIS EQUINAS EM CÉLULAS *SCHWANN-LIKE*: CARACTERIZAÇÃO CELULAR, ANÁLISE PROTEÔMICA E ESTABILIDADE FENOTÍPICA

LUCAS VINÍCIUS DE OLIVEIRA FERREIRA

Botucatu – SP
Abril – 2026

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Tese apresentada à Faculdade de Medicina Veterinária e Zootecnia, Campus de Botucatu, Unesp, para obtenção do título de Doutor no Programa de Pós-Graduação em Medicina Veterinária.

Orientador: Prof. Dr. Rogério Martins Amorim

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Título da tese: Transdiferenciação de Células Tronco Mesenquimais Equinas em Células *Schwann-like*: Caracterização Celular, Análise Proteômica e Estabilidade Fenotípica.

Impacto potencial desta pesquisa

Impacto científico esperado: Esta pesquisa propõe uma abordagem inovadora para a regeneração de nervos periféricos, baseada na geração de células *Schwann-like* derivadas de células tronco mesenquimais equinas. Espera-se que os resultados ampliem o conhecimento sobre os mecanismos envolvidos na transdiferenciação celular e na estabilidade fenotípica dessas células, além de fornecerem evidências científicas relevantes para o uso de terapias celulares aplicadas à neuroregeneração.

Impacto social: A aplicação da biotecnologia celular voltada à regeneração do sistema nervoso periférico tem potencial para melhorar significativamente a qualidade de vida de equinos acometidos por lesões nervosas. Além disso, o uso de equinos como modelo experimental pode gerar informações translacionais relevantes, contribuindo para o desenvolvimento de estratégias terapêuticas mais eficazes tanto na medicina veterinária quanto, potencialmente, na medicina humana.

Impacto econômico: O desenvolvimento de terapias regenerativas baseadas em células tronco mesenquimais transdiferenciadas em células *Schwann-like* pode representar uma alternativa custo-efetiva para o tratamento de lesões do nervo periférico. Essas abordagens podem reduzir o tempo de recuperação, minimizar a necessidade de intervenções repetidas e aumentar a eficiência dos tratamentos quando comparadas às terapias convencionais atualmente utilizadas na prática clínica veterinária.

Thesis title: Transdifferentiation of Equine Mesenchymal Stem Cells into Schwann-like Cells: Cellular Characterization, Proteomic Analysis, and Phenotypic Stability.

Potential impact of this research

Expected scientific impact: This research proposes an innovative approach to peripheral nerve regeneration, based on the generation of Schwann-like cells derived from equine mesenchymal stem cells. The results are expected to expand current knowledge on the mechanisms involved in cellular transdifferentiation and phenotypic stability of these cells, in addition to providing relevant scientific evidence supporting the use of cell-based therapies applied to neuroregeneration.

Social impact: The application of cellular biotechnology aimed at peripheral nervous system regeneration has the potential to significantly improve the quality of life of equines affected by nerve injuries. Furthermore, the use of equines as an experimental model may generate relevant translational information, contributing to the development of more effective therapeutic strategies both in veterinary medicine and, potentially, in human medicine.

Economic impact: The development of regenerative therapies based on mesenchymal stem cells transdifferentiated into Schwann-like cells may represent a cost-effective alternative for the treatment of peripheral nerve injuries. These approaches may reduce recovery time, minimize the need for repeated interventions, and increase treatment efficiency when compared to conventional therapies currently used in veterinary clinical practice.

Título: TRANSDIFERENCIAÇÃO DE CÉLULAS TRONCO MESENQUIMAIS EQUINAS EM CÉLULAS *SCHWANN-LIKE*: CARACTERIZAÇÃO CELULAR, ANÁLISE PROTEÔMICA E ESTABILIDADE FENOTÍPICA.

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LISTA DE SIGLAS E ABREVIATURAS

3D – tridimensional
ACTB – beta-actina, do inglês *beta-actin*
ATP – trifosfato de adenosina
B2M – beta -2- microglobulina, do inglês *beta -2- microglobulin*
BDNF – fator neurotrófico derivado do cérebro, do inglês *brain-derived neurotrophic factor*
bFGF – fator de crescimento de fibroblasto básico
BSA – albumina sérica bovina, do inglês, *bovine serum albumin*
CD – grupamento de diferenciação, do inglês *cluster of differentiation*
cDNA – DNA complementar, do inglês *complementary DNA*
CEUA - Comitê de Ética no Uso de Animais, do inglês *Ethics Committee in the Use of Animals*
CNTF – fator neurotrófico ciliar
CS- células de Schwann, do inglês *Schwann cells* (SCs)
CSL- células *Schwann-like*, do inglês *Schwann-like cells* (SLCs)
CTM – células tronco mesenquimais, do inglês *mesenchymal stem cells* (MSCs)
CTM – MO – células tronco mesenquimais derivadas da médula óssea, do inglês *mesenchymal stem cells derived from bone marrow* (BM-MSCs)
CTM-MOlf – células-tronco mesenquimais derivadas da mucosa olfatória
CTM – TA – células tronco mesenquimais derivadas do tecido adiposo, do inglês *mesenchymal stem cells derived from adipose tissue* (AT-MSCs)
CTM– CU – células tronco mesenquimais derivadas do cordão umbilical, do inglês *mesenchymal stem cells derived from umbilical cord* (UC-MSCs)
DMEM – *Dulbecco's Modified Eagle's Medium*
DMSO – dimetilsulfóxido, do inglês *dimethyl sulfoxide*
DPBS – *Dulbecco's Phosphate Buffered Saline*
DTT – *Dithiothreitol*
EqAT-MSCs – células tronco mesenquimais equinas derivadas do tecido adiposo, do inglês *equine adipose tissue-derived mesenchymal stem cells*
EqBM-MSCs – células tronco mesenquimais equinas derivadas da medula óssea, do inglês *equine bone marrow-derived mesenchymal stem cells*
EqUC-MSCs – células tronco mesenquimais equinas derivadas do cordão umbilical, do inglês *equine umbilical cord-derived mesenchymal stem cells*
erB3 – receptor do fator de crescimento epidérmico 3
FBS – soro fetal bovino, do inglês *fetal bovine serum*
FDR – *false discovery rate*
FGF-2 – fator de crescimento dos fibroblastos -2, do inglês *fibroblast growth factor-2*
FSK – forskolina
GAPDH – gliceraldeído 3- fosfato desidrogenase, do inglês *glyceraldehyde 3-phosphate dehydrogenase*
GDNF – fator neurotrófico derivado da glia, do inglês *glial cell-derived neurotrophic factor*
GelMA – gelatina metacrilada
GFAP – proteína ácida fibrilar da glia, do inglês *glial fibrillary acidic protein*
HGF – fator de crescimento dos hepatócitos
HPRT – hipoxantina-guanina fosforibosiltransferase, do inglês *hypoxanthine-guanine phosphoribosyltransferase*
HRG- heregulina

IDO – indoleamina 2,3-dioxigenase
IGF – fator de crescimento semelhante a insulina
IL – interleucina
Krox20 – fator de transcrição Krox20
L1 – molécula de adesão celular L1
LC-MS/MS – *Liquid chromatography–tandem mass spectrometry*
LL – *lower left*
LR – *lower right*
LNP – lesões de nervo periférico, do inglês *peripheral nerve injury* (PNI)
MAG – glicoproteína associada à mielina
MAP2 – proteína associada a microtúbulos 2
MBP – proteína básica da mielina, do inglês *myelin basic protein*
MC – meio condicionado, do inglês *conditioned medium* (CM)
MCP-1 – proteína quiomiotática de monócitos – 1
MHC-II – complexo de histocompatibilidade tipo II
miR-21-5p – MicroRNA-21
MSCs – *mesenchymal stem cells*
MTT – [3-(4,5-dimetiltiazol-2-il)-2,5-difeniltetrazólio brometo]
NGCs – condutos de orientação nervosa, do inglês *nerve guidance conduits*
NGF – fator de crescimento do nervo, do inglês *nerve growth factor*
NGFR – receptor do fator de crescimento nervoso
NT – neurotrofinas
O4 – marcador de oligodendrócitos O4
Oct-6 – fator de transcrição Oct-6
P0 – proteína zero da mielina
P3-P4-P5 passagem das células tronco mesenquimais após o isolamento (passagem 3-4-5)
P75 – receptor p75 das neurotrofinas, do inglês *p75 neurotrophin receptor*
PBS – *phospate buffered saline*
PCL – policaprolactona
PCR – *Polymerase Chain Reaction*
PDGF – fator de crescimento derivado de plaquetas
PGA – ácido poliglicólico
PGE2 – prostaglandina E2
PLA – ácido polilático
PLGA – ácido polilático-co-glicólico
PLS-DA – *partial least squares discriminant analysis*
PMP2 – proteína 2 da mielina periférica, do inglês *Peripheral Myelin Protein 2*
PMP-22 – proteína 22 da mielina periférica
PNE-CM – *peripheral nerve explant-conditioned medium*
PPI – *protein–protein interaction*
RNA – ácido ribonucleico
RT-qPCR – Reação em cadeia da polimerase em tempo real com transcrição reversa, do inglês *Reverse Transcription Quantitative Polymerase Chain Reaction*
S100 – proteína de ligação ao cálcio S100, do inglês *S100 calcium-binding protein*
SDS-PAGE – *sodium dodecyl sulfate–polyacrylamide gel electrophoresis*
SNC – sistema nervoso central, do inglês *central nervous system* (CNS)
SNP – sistema nervoso periférico, do inglês *peripheral nervous system* (PNS)
Sox-10 – fator de transcrição Sox10
SPRY2 – *Sprouty RTK signaling antagonist 2*

TEM – transmission electron microscopy
TGF-β – fator de crescimento transformador beta
TNF-α – fator de necrose tumoral - alfa
Trks – quinase receptora da tropomiosina
U6 – RNA nuclear pequeno U6, do inglês *U6 small nuclear RNA*
UC-MSCs – células tronco mesenquimais derivadas do cordão umbilical, do inglês *umbilical cord-derived mesenchymal stem cells*
UL – upper Left
UR – upper Right
VEGF-A – fator de crescimento endotelial vascular – A
VEs – vesículas extracelulares
VIP – variable importance in projection

SUMÁRIO

FERREIRA, L.V.O. **Transdiferenciação de Células Tronco Mesenquimais Equinas em Células *Schwann-like*: Caracterização Celular, Análise Proteômica e Estabilidade Fenotípica**. Botucatu, 2025. 166p. Tese (Doutorado) – Faculdade de Medicina Veterinária e Zootecnia, Campus de Botucatu, Universidade Estadual Paulista.

RESUMO

As células de Schwann desempenham papel essencial na regeneração do sistema nervoso periférico (SNP) após lesões. Entretanto seu uso clínico é limitado, pois sua obtenção exige o sacrifício de um nervo funcional e um tempo prolongado para expansão *in vitro*. Como alternativa, células tronco mesenquimais (CTM) vêm sendo utilizadas como fonte para gerar células *Schwann-like* (CSL) por meio de diversos protocolos de transdiferenciação *in vitro*. Uma das abordagens mais promissoras consiste na exposição das CTM ao meio condicionado (MC) formado após o cultivo de explantes de nervos periféricos. Assim, o objetivo deste estudo foi avaliar o potencial de transdiferenciação *in vitro* de CTM equinas derivadas do cordão umbilical (CTM-CU; n=3; P3–P5) e do tecido adiposo (CTM-TA; n=4; P3–P4) em CSL, utilizando MC obtido de explantes de nervos faciais de equinos. Além disso, buscou-se caracterizar o perfil proteômico dos MCs e investigar a manutenção do fenótipo glial após a retirada do estímulo. Para a obtenção do MC utilizado para transdiferenciação das CTM-CU, foi coletado o nervo facial de um equino de três anos; para as CTM-TA, de um equino de quatro anos. Os nervos foram fragmentados e incubados por 48 horas em meio de cultura completo contendo DMEM/F12, 10% soro fetal bovino, 1% penicilina/estreptomicina e 1% de anfotericina B. Após esse período, o meio foi filtrado e utilizado para realizar a transdiferenciação das CTM em CSL durante cinco dias. As CTM indiferenciadas foram mantidas em meio padrão, enquanto as diferenciadas foram cultivadas em MC. A análise proteômica por espectrometria de massas identificou 130 proteínas exclusivas no MC utilizado com as CTM-CU e 54 proteínas exclusivas no MC aplicado às CTM-TA, incluindo periferina, neurofilamento, proteína 2 da mielina periférica (PMP2), proteínas de choque térmico e galectinas. Após o período de indução, ambas as fontes celulares apresentaram alterações morfológicas compatíveis com o fenótipo glial, como núcleos grandes e citoplasma alongado. A transdiferenciação não comprometeu a viabilidade celular, atividade metabólica, nem induziu senescência (atividade da β-galactosidase). Nas CTM-CU diferenciadas houve aumento significativo na expressão do fator neurotrófico derivado do cérebro (BDNF), do fator neurotrófico derivado da glia (GDNF), do fator de crescimento de fibroblastos 2 (FGF-2) e dos marcadores gliais proteína ácida fibrilar glial (GFAP), proteína básica da mielina (MBP), proteína de ligação ao cálcio S100 beta (S100β) e receptor de neurotrofinas p75 (p75), sem alterações significativas na expressão do fator de crescimento do nervo (NGF), de *Sprouty RTK Signaling Antagonist 2* (SPRY2) e do microRNA-21 (miR-21-5p). Já nas CTM-TA diferenciadas foi observado aumento significativo na expressão gênica de BDNF, GDNF e dos marcadores gliais GFAP, MBP, S100β e p75. As expressões de NGF e FGF-2 permaneceram estáveis, enquanto houve redução de SPRY2 e miR-21-5p. A imunofluorescência revelou a expressão de GFAP tanto nas células indiferenciadas quanto nas diferenciadas, enquanto S100 foi detectada

apenas nas CTM diferenciadas em ambas as fontes celulares. Após a retirada do MC por 72 horas, não foram observadas alterações morfológicas em nenhuma das fontes. No entanto, nas CTM-CU houve redução significativa na expressão gênica de NGF, FGF-2 e miR-21-5p, ausência de MBP em todas as amostras e ausência da expressão de GFAP em uma das amostras. Já nas CTM-TA foi observado redução significativa na expressão gênica de GFAP e SPRY2, com aumento de GDNF e miR-21-5p. Em ambas as fontes celulares, a imunofluorescência demonstrou a persistência da expressão dos marcadores gliais GFAP e S100 após a retirada do MC. Esses achados indicam que tanto as CTM-CU quanto as CTM-TA equinas apresentam potencial de transdiferenciação em CSL mediante exposição ao MC derivado de explantes de nervo facial equino. Além disso, ambas as fontes mantiveram o fenótipo glial após a retirada dos estímulos presentes no MC. A caracterização proteômica dos MCs também forneceu informações relevantes sobre possíveis proteínas envolvidas no processo de transdiferenciação das CTM em CSL.

Palavras-chave: Cavalo, fatores neurotróficos, lesão de nervo periférico, nervo facial, regeneração nervosa.

FERREIRA, L.V.O. **Transdifferentiation of Equine Mesenchymal Stem Cells into Schwann-like Cells: Cellular Characterization, Proteomic Analysis, and Phenotypic Stability**. Botucatu, 2025. 166p. Tese (Doutorado) – Faculdade de Medicina Veterinária e Zootecnia, Campus de Botucatu, Universidade Estadual Paulista.

ABSTRACT

Schwann cells play an essential role in the regeneration of the peripheral nervous system (PNS) after injuries. However, their clinical use is limited, as their obtaining requires the sacrifice of a functional nerve and a prolonged time for *in vitro* expansion. As an alternative, mesenchymal stem cells (MSCs) have been used as a source to generate Schwann-like cells (SLCs) through various *in vitro* transdifferentiation protocols. One of the most promising approaches consists of exposing MSCs to conditioned medium (CM) formed after the culture of peripheral nerve explants. Thus, the objective of this study was to evaluate the *in vitro* transdifferentiation potential of equine MSCs derived from umbilical cord (UC-MSCs; *n*=3; P3–P5) and adipose tissue (AT-MSCs; *n*=4; P3–P4) into SLCs, using CM obtained from equine facial nerve explants. In addition, it was sought to characterize the proteomic profile of the CMs and to investigate the maintenance of the glial phenotype after stimulus withdrawal. For obtaining the CM used for transdifferentiation of UC-MSCs, the facial nerve of a three-year-old equine was collected; for AT-MSCs, of a four-year-old equine. The nerves were fragmented and incubated for 48 hours in complete culture medium containing DMEM/F12, 10% fetal bovine serum, 1% penicillin/streptomycin and 1% amphotericin B. After this period, the medium was filtered and used to perform the transdifferentiation of MSCs into SLCs for five days. Undifferentiated MSCs were maintained in standard medium, while differentiated MSCs were cultured in CM. Proteomic analysis by mass spectrometry identified 130 exclusive proteins in the CM used with UC-MSCs and 54 exclusive proteins in the CM applied to AT-MSCs, including peripherin, neurofilament, peripheral myelin protein 2 (PMP2), heat shock proteins and galectins. After the induction period, both cell sources presented morphological changes compatible with the glial phenotype, such as large nuclei and elongated cytoplasm. Transdifferentiation did not compromise cell viability, metabolic activity, nor induce senescence (β-galactosidase activity). In differentiated UC-MSCs there was a significant increase in the expression of brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF), fibroblast growth factor 2 (FGF-2) and glial markers glial fibrillary acidic protein (GFAP), myelin basic protein (MBP), calcium-binding protein S100 beta (S100β) and neurotrophin receptor p75 (p75), with no significant changes in the expression of nerve growth factor (NGF), Sprouty RTK Signaling Antagonist 2 (SPRY2) and microRNA-21 (miR-21-5p). In differentiated AT-MSCs, a significant increase in gene expression of BDNF, GDNF and the glial markers GFAP, MBP, S100β and p75 was observed. The expressions of NGF and FGF-2 remained stable, while there was a reduction of SPRY2 and miR-21-5p. Immunofluorescence revealed the expression of GFAP both in undifferentiated and differentiated cells, while S100 was detected only in differentiated MSCs in both cell sources. After CM withdrawal for 72 hours, no morphological changes

were observed in any of the sources. However, in UC-MSCs there was a significant reduction in gene expression of NGF, FGF-2 and miR-21-5p, absence of MBP in all samples and absence of GFAP expression in one of the samples. In AT-MSCs, a significant reduction in gene expression of GFAP and SPRY2 was observed, with an increase of GDNF and miR-21-5p. In both cell sources, immunofluorescence demonstrated the persistence of the expression of glial markers GFAP and S100 after CM withdrawal. These findings indicate that both equine UC-MSCs and AT-MSCs present transdifferentiation potential into SLCs upon exposure to CM derived from equine facial nerve explants. In addition, both sources maintained the glial phenotype after the withdrawal of the stimuli present in the CM. The proteomic characterization of the CMs also provided relevant information about possible proteins involved in the process of MSC transdifferentiation into SLCs.

Keywords: Horse, neurotrophic factors, peripheral nerve injury, facial nerve, nerve regeneration

1 INTRODUÇÃO

As lesões de nervo periférico (LNP) são comuns em humanos e animais, representando uma área de grande relevância clínica (RHODE; BEIER; RUHL, 2021; SHAN et al., 2024). Em equinos, as lesões no sistema nervo periférico (SNP) são frequentes e podem se manifestar desde uma diminuição no desempenho até uma completa impotência funcional (VILLAGRÁN et al., 2016). As causas das LNP nessa espécie são diversas, podendo ocorrer após traumas, infecções, doenças metabólicas, intoxicações (VILLAGRÁN et al., 2014). A paralisia do nervo facial é uma das principais neuropatias periféricas em cavalos, sendo a maioria dos casos resultante de traumas (BOORMAN et al., 2020).

Embora o SNP tenha uma capacidade intrínseca de regeneração, os resultados são frequentemente insatisfatórios (ALVITES et al., 2024). Nesse contexto, as células de Schwann (CS) desempenham papel fundamental, sendo responsáveis pela síntese de uma variedade de fatores neurotróficos essenciais para a neuroregeneração após a lesão (HOPF et al., 2020). No entanto, a aplicação clínica das CS enfrenta limitações, como a necessidade de sacrificar um nervo funcional do doador para obtenção das células, e o tempo de proliferação *in vitro* pode retardar o tratamento (PIOVESANA et al., 2021; SAFFARI et al., 2021).

Com isso, as pesquisas se voltaram para as células tronco mesenquimais (CTM) devido à sua capacidade de diferenciação em diversas linhagens celulares. Estudos indicam que as CTM, provenientes de diferentes fontes e espécies, são capazes de se transdiferenciarem em células *Schwann-like* (CSL) utilizando protocolos químicos (VILLAGRÁN et al., 2016; HOPF et al., 2020) e co-cultura com CS (LI et al., 2009). Adicionalmente, em busca de uma nova abordagem e com menor tempo necessário para realizar a transdiferenciação, estudos avaliaram a possibilidade de produzir um meio condicionado (MC) com fatores secretados do cultivo de nervos periféricos. Esta técnica demonstrou ser eficaz na indução da transdiferenciação *in vitro* de CTM derivadas tanto do tecido adiposo quanto da medula óssea de ratos (LIU et al., 2013; TAWAB et al., 2018; GALHOM et al., 2018), assim como de equinos (FERREIRA et al., 2023). Entretanto, até onde sabemos, ainda não foi investigado quais fatores presentes no MC são responsáveis pelo processo de transdiferenciação e não há descrição do potencial de transdiferenciação de CTM equinas derivadas do cordão umbilical (CTM-CU) em CSL.

Um estudo recente com CTM derivadas da medula óssea de ratos sugere uma interação entre o microRNA-21 (miR-21-5p) e SPRY2 (*Sprouty RTK Signaling Antagonist 2*) durante a transdiferenciação celular (LIU et al., 2024). Explorar a interação desse miRNA na transdiferenciação das CTM derivadas de diferentes espécies e tecidos pode fornecer novos avanços para compreender esse processo em diferentes metodologias utilizadas.

Um dos principais desafios após a transdiferenciação de CTM em CSL consiste em determinar se as CSL são capazes de manter o fenótipo glial após a retirada do estímulo indutor. Diante desse contexto, hipotetiza-se que as CTM equinas, derivadas do tecido adiposo e do cordão umbilical, são capazes de se transdiferenciar em CSL mediante exposição ao MC obtido de explantes de nervo facial equino, mantendo o fenótipo glial mesmo após a retirada dos estímulos presentes nesse meio.

Assim, o presente estudo teve como objetivo avaliar o potencial de transdiferenciação das CTM equinas, investigar a estabilidade do fenótipo induzido após a remoção do estímulo indutor e caracterizar o perfil proteômico do MC envolvido nesse processo.

2 REVISÃO DE LITERATURA

2.1 Anatomia do Nervo Periférico

O SNP compreende nervos periféricos, gânglios e terminações nervosas e, em nível celular, é constituído por neurônios, células gliais (incluindo as CS) e células do estroma (LEBERFINGER et al., 2017; SUMARWOTO et al., 2021). Esse sistema consiste em uma combinação de nervos motores, sensoriais e autonômicos, responsáveis por conectar tecidos e órgãos ao sistema nervoso central (SNC) (MENORCA; FUSSELL; ELFAR, 2013; LANIGAN et al., 2021). Cada nervo periférico é formado por vários feixes de fibras, conhecidos como fascículos nervosos ou feixes nervosos (LIU; WANG; YI, 2018; WANG et al., 2019). As fibras nervosas consistem em axônios envolvidos por CS, com diferenças em seus diâmetros (ALVITES et al., 2020). Axônios de pequeno diâmetro são geralmente envolvidos por CS não mielinizantes, enquanto axônios de maior diâmetro são recobertos por CS mielinizantes, que formam a bainha de mielina ao redor do axônio (JESSEN; MIRSKY, 2019). Essa bainha é descontínua, e as pequenas áreas entre dois segmentos de mielina, os espaços não mielinizados, são chamadas de nódulos de Ranvier,

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