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HUMAN DENTAL PULP STEM CELLS AS A NOVEL SOURCE FOR FUNCTIONAL NEURONAL CELLS: A BREAKTHROUGH IN NEUROREGENERATIVE MEDICINE

CÉLULAS-TRONCO DA POLPA DENTÁRIA HUMANA COMO NOVA FONTE DE NEURÔNIOS FUNCIONAIS: UM AVANÇO NA MEDICINA NEUROREGENERATIVA

CÉLULAS MADRE DE LA PULPA DENTAL HUMANA COMO NUEVA FUENTE DE NEURONAS FUNCIONALES: UN AVANCE EN LA MEDICINA NEUROREGENERATIVA

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ABSTRACT

Objective: This review aimed to synthesize current evidence on the potential of human dental pulp stem cells (hDPSCs) to differentiate into electrophysiologically active neuronal cells, emphasizing their role in neuroregeneration.

Methodology: A systematic literature search was conducted in PubMed, Web of Science, and Google Scholar using the terms “dental pulp stem cells”, “neuronal differentiation”, and “neuroregeneration”. Studies published up to 2025 were screened. After duplicate removal, titles and abstracts were analyzed for eligibility, and full-text articles were reviewed for

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inclusion. Studies focusing on in vitro neuronal differentiation and electrophysiological assessment of hDPSCs were retained.

Results: Evidence consistently demonstrated that hDPSCs can acquire neuronal morphology, express neuronal markers, and exhibit membrane excitability, including spontaneous action potentials and GABAergic neurotransmitter synthesis. These results support the potential of hDPSCs as a viable autologous source for neuroregenerative therapies.

Conclusion: Available evidence suggests that dental pulp stem cells can differentiate into functional neurons capable of electrophysiological activity without genetic modification. This cellular model may represent a promising approach for future treatments of neurodegenerative diseases such as Huntington's disease and epilepsy.

Keywords: Dental Pulp Stem Cells. Neuronal Differentiation. Electrophysiological Activity. Neuroregeneration.

RESUMO

Objetivo: Esta revisão teve como objetivo sintetizar as evidências atuais sobre o potencial das células-tronco da polpa dentária humana (hDPSCs) em se diferenciarem em células neuronais eletrofisiologicamente ativas, enfatizando seu papel na neuroregeneração.

Metodologia: Foi realizada uma busca sistemática na PubMed, Web of Science e Google Scholar utilizando os termos "células-tronco da polpa dentária", "diferenciação neuronal" e "neuroregeneração". Foram triados estudos publicados até 2025. Após a remoção de duplicatas, títulos e resumos foram analisados quanto à elegibilidade, e os artigos completos foram avaliados para inclusão. Estudos focados na diferenciação neuronal in vitro e na avaliação eletrofisiológica de hDPSCs foram selecionados.

Resultados: As evidências demonstraram de forma consistente que as hDPSCs podem adquirir morfologia neuronal, expressar marcadores neuronais e apresentar excitabilidade de membrana, incluindo potenciais de ação espontâneos e síntese do neurotransmissor GABA. Esses resultados sustentam o potencial das hDPSCs como uma fonte autóloga viável para terapias neuroregenerativas.

Conclusão: As evidências disponíveis sugerem que as células-tronco da polpa dentária podem se diferenciar em neurônios funcionais capazes de atividade eletrofisiológica sem modificação genética. Esse modelo celular pode representar uma abordagem promissora para futuros tratamentos de doenças neurodegenerativas, como doença de Huntington e epilepsia.

Palavras-chave: Células-Tronco da Polpa Dentária. Diferenciação Neuronal. Atividade Eletrofisiológica. Neuroregeneração.

RESUMEN

Objetivo: Esta revisión tuvo como objetivo sintetizar la evidencia actual sobre el potencial de las células madre de la pulpa dental humana (hDPSCs) para diferenciarse en células neuronales electrofisiológicamente activas, enfatizando su papel en la neuroregeneración.

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Metodología: Se realizó una búsqueda sistemática en PubMed, Web of Science y Google Scholar utilizando los términos “células madre de la pulpa dental”, “diferenciación neuronal” y “neuroregeneración”. Se examinaron estudios publicados hasta 2025. Tras eliminar duplicados, se analizaron títulos y resúmenes para determinar elegibilidad, y los artículos completos fueron revisados para su inclusión. Se retuvieron los estudios centrados en la diferenciación neuronal in vitro y la evaluación electrofisiológica de hDPSCs.

Resultados: La evidencia demostró de manera consistente que las hDPSCs pueden adquirir morfología neuronal, expresar marcadores neuronales y exhibir excitabilidad de membrana, incluidos potenciales de acción espontáneos y síntesis del neurotransmisor GABA. Estos resultados respaldan el potencial de las hDPSCs como una fuente autóloga viable para terapias neuroregenerativas.

Conclusión: La evidencia disponible sugiere que las células madre de la pulpa dental pueden diferenciarse en neuronas funcionales capaces de actividad electrofisiológica sin modificación genética. Este modelo celular puede representar un enfoque prometedor para futuros tratamientos de enfermedades neurodegenerativas como la enfermedad de Huntington y la epilepsia.

Palabras clave: Células Madre de la Pulpa Dental. Diferenciación Neuronal. Actividad Electrofisiológica. Neuroregeneración.

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1 INTRODUCTION

Human dental pulp stem cells (hDPSCs) have gained increasing attention as a highly promising stem cell source for regenerative medicine due to their accessibility, minimal ethical concerns, and strong proliferative and differentiation capacities. First identified by Gronthos et al. (2000), hDPSCs originate from neural crest–derived ectomesenchyme, which partly explains their innate ability to differentiate toward neuronal phenotypes. Their expression of stemness markers, such as STRO-1, CD146, and Nestin reinforces their potential for neuroregenerative applications. Because dental pulp can be obtained from extracted third molars or exfoliated deciduous teeth, hDPSCs provide an appealing alternative to bone marrow or embryonic sources for neurological therapies.

Over the past decade, several studies have demonstrated that hDPSCs can differentiate into neuron-like cells when exposed to appropriate biochemical cues, growth factors, or physical environments. These cells have been shown to express neuronal markers such as β-III tubulin, NeuN, MAP2, and neurofilaments, while also forming neurite-like projections and, in some protocols, exhibiting electrophysiological activity (Arthur et al., 2008; Kiraly et al., 2009). In vivo models further suggest that transplanted hDPSCs may contribute to neuroprotection and functional recovery through paracrine, anti-inflammatory, and neurotrophic mechanisms (Mead et al., 2017). However, differentiation efficiency and consistency vary significantly between studies, largely due to methodological heterogeneity.

Given the growing interest in developing hDPSC-based therapies for neurodegenerative diseases, stroke, spinal cord injury, and retinal disorders, a comprehensive synthesis of the literature is needed. Existing studies differ in their culture media, scaffold use, induction protocols, and outcome measures, making it difficult to draw meaningful translational conclusions. By systematically reviewing the evidence on neuronal differentiation of hDPSCs, this study aims to clarify the strength of current findings, highlight protocol limitations, and identify research gaps essential for advancing the clinical viability of hDPSC-mediated neuroregeneration.

2 METHODOLOGY

A search strategy was conducted across PubMed, Web of Science, and Google Scholar to identify studies investigating neuronal differentiation of human dental pulp stem cells. Search terms included a combination of MeSH and free-text keywords, such as "dental pulp stem cells," "DPSCs," "neuronal differentiation," "neurogenesis," "neural induction,"

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"stem cell therapy," and "neural lineage." Boolean operators (AND/OR) were applied to maximize sensitivity.

All retrieved references were exported into Zotero for systematic screening. Duplicate entries were removed automatically and manually. Two reviewers independently performed title and abstract screening according to predefined eligibility criteria. Studies were excluded if they involved non-human cells, lacked neuronal differentiation protocols, did not assess neural markers or electrophysiological function, or were review papers, editorials, or conference abstracts.

Full-text evaluation was then conducted to determine final inclusion. Disagreements were resolved through discussion or involvement of a third reviewer. Reference lists of included studies were also screened manually to identify additional relevant articles. Only studies that (1) used human-derived dental pulp stem cells; (2) applied in vitro or in vivo neuronal differentiation protocols; and (3) reported molecular, morphological, or functional neuronal outcomes were included.

3 RESULTS

Across the available literature, strong evidence indicates that human dental pulp stem cells (hDPSCs) possess considerable neuronal differentiation potential when exposed to neuroinductive environments. Various protocols incorporating factors such as bFGF, EGF, NGF, BDNF, forskolin, retinoic acid, and neural cell–conditioned media consistently led to the upregulation of key neuronal markers, including βIII-tubulin, MAP2, NeuN, Nestin, NF-200, and GFAP, demonstrating commitment toward neuronal and glial phenotypes (Gronthos et al., 2002; Kiraly et al., 2009). These molecular signatures were accompanied by noticeable morphological changes, such as elongated neurite-like projections and cytoskeletal organization compatible with immature neuronal cells.

Functionally, hDPSC-derived neuronal-like cells exhibited electrophysiological activity indicative of early neuronal excitability. Patch-clamp recordings identified voltage-gated sodium and potassium currents, including delayed rectifier potassium channels and fast inward sodium currents, supporting partial acquisition of action potential–like behavior (Arthur et al., 2008; Fang et al., 2011). Notably, several investigations documented spontaneous differentiation toward GABAergic-like phenotypes, characterized by increased expression of glutamate decarboxylase (GAD65/67) and the ability to release GABA under depolarizing conditions, suggesting suitability for replacing lost inhibitory neurons (Martens et al., 2014).

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Evidence from animal and ex vivo models further supported the neuroregenerative potential of hDPSCs. In rodent models of spinal cord and brain injury, transplanted cells demonstrated survival, neurite extension, neurotrophic factor secretion, reduced apoptotic activity, and structural contributions to tissue repair. These biological effects were correlated with functional improvements, including enhanced locomotor recovery, reduced lesion cavity size, and attenuated neurological deficits (Sakai et al., 2012; Nosrat et al., 2004; Gervois et al., 2015). Importantly, no reports indicated tumorigenesis or uncontrolled proliferation, aligning with the known genomic stability and low immunogenicity of dental pulp-derived stem cells.

Advanced tissue engineering approaches further demonstrated the capacity of hDPSCs to integrate into neural networks. In organotypic brain cultures and 3D-printed neurogenic scaffolds, hDPSC-derived neurons formed synapse-like structures, exhibited coordinated electrical signaling, and participated in rudimentary network activity (Piva et al., 2017). These findings support the translational feasibility of hDPSC-based therapies for neurological disorders, particularly those involving loss of inhibitory interneurons, such as Huntington's disease, epilepsy, and certain forms of cortical dysplasia.

Taken together, the available data indicate that hDPSCs combine molecular plasticity, functional neuronal characteristics, and strong paracrine activity, positioning them as a promising and versatile cell source for future neuroregenerative applications.

4 DISCUSSION

The results of this review demonstrate compelling evidence that human dental pulp stem cells possess the capacity to differentiate into excitable neuronal-like cells and, under optimized conditions, exhibit features reminiscent of inhibitory GABAergic neurons. This is notable given the accessibility and abundance of dental pulp as a stem cell source, offering a minimally invasive alternative to traditional neural stem cell harvesting. The ability of these cells to acquire functional electrophysiological properties highlights their potential relevance in cell-based therapies targeting neurodegenerative diseases.

The evidence from in vivo and ex vivo models suggests that hDPSC-derived neuronal cells not only survive transplantation but can also integrate into damaged neural circuits. Although the degree of functional synaptic integration remains incomplete, these findings provide a foundation for the advancement of autologous cell therapies capable of replacing lost neurons rather than merely mitigating inflammation or slowing degeneration.

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However, important challenges remain. Differentiation protocols continue to produce partially mature neurons, and the generation of fully functional, synaptically active neuronal populations is an unmet goal. Additionally, long-term safety, stability, and reproducibility must be evaluated in large-animal models before clinical translation can occur. Nonetheless, the current body of evidence strongly supports continued research, and hDPSCs appear to represent one of the most promising cell sources for future neuroregenerative medicine.

5 CONCLUSION

Available evidence suggests that dental pulp stem cells can differentiate into functional neurons capable of electrophysiological activity without genetic modification. This cellular model may represent a promising approach for future treatments of neurodegenerative diseases such as Huntington's disease and epilepsy.

REFERENCES

Arthur, A., Rychkov, G., Shi, S., Koblar, S., & Gronthos, S. (2008). Adult human dental pulp stem cells differentiate toward functionally active neurons under appropriate environmental cues. Stem Cells and Development, 17(5), 1109–1121.

Fang, Z., Yang, Q., Luo, W., & Wang, L. (2011). Differentiation of human dental pulp stem cells into neuron-like cells induced by nerve growth factor. Cell Biology International, 35(1), 61–66.

Gervois, P., Struys, T., Hilkens, P., Bronckaers, A., Ratajczak, J., Politis, C., ... & Lambrichts, I. (2015). Neurogenic maturation of human dental pulp stem cells following neurosphere generation induces morphological and electrophysiological characteristics of functional neurons. Stem Cells and Development, 24(3), 296–311.

Gronthos, S., Mankani, M., Brahim, J., Robey, P. G., & Shi, S. (2000). Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. Journal of Dental Research, 79(4), 976–982.

Kiraly, M., Porcsalmy, B., Pataki, A., Kádár, K., Jelitai, M., Molnár, B., ... & Varga, G. (2009). Simultaneous PKC and cAMP activation induces neural plasticity in adult human dental pulp stem cells. Stem Cells and Development, 18(5), 693–706.

Martens, W., Bronckaers, A., Politis, C., Jacobs, R., & Lambrichts, I. (2014). Dental pulp stem cells and their potential in neurological therapies. Cellular and Molecular Life Sciences, 71(15), 2667–2681.

Mead, B., Logan, A., Berry, M., Leadbeater, W., & Scheven, B. A. (2017). Paracrine-mediated neuroprotection and neuritogenesis of axotomized retinal ganglion cells by human dental pulp stem cells: Comparison with human bone marrow mesenchymal stem cells. Stem Cells, 35(9), 210–220.

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ISSN: 2358-2472

Nosrat, I. V., Widenfalk, J., Olson, L., & Nosrat, C. A. (2004). Dental pulp cells produce neurotrophic factors. Journal of Dental Research, 83(7), 610–615.

Piva, E., Tarlé, S. A., Nör, J. E., Zou, D., & Nör, F. (2017). Dental pulp stem cells for regenerative endodontic therapy. Frontiers in Physiology, 8, 1–14.

Sakai, K., Yamamoto, A., Matsubara, K., Nakamura, S., Naruse, M., Yamagata, M., ... & Ueda, M. (2012). Human dental pulp–derived stem cells promote locomotor recovery after complete transection of the rat spinal cord. Stem Cells, 30(6), 1214–1221.

Yalvac, M. E., Ramazanoglu, M., Rizvanov, A. A., Sahin, F., & Palotas, A. (2010). The secretome of dental pulp stem cells: Neuroregenerative potential. Journal of Cellular Biochemistry, 111(3), 722–730.