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Review Article

Dental Pulp Stem Cells for Stroke Therapy - A Review

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Abstract

Background: Stroke is second leading cause of death and third leading cause of disability worldwide with limited restorative treatments. People with high blood pressure, high cholesterol, diabetes and those who smoke are at higher risk. Current treatment regimens are holding limitations, hence alternative approaches are being developed. One such approach is transplantation of Dental Pulp Stem Cells. Dental pulp stem cells (DPSC's) are the mesenchymal cells derived from a cranial neural crest which have a multipotent differentiation and self-renewal ability. Other than dental diseases, they are also useful for systemic diseases. DPSC's have significant benefits like strong proliferation ability and can be cryopreserved without losing their differentiation capacity, easy to isolate with a less invasive procedure and also there will be no immune rejection. Due to these unique properties DPSC's are an ideal source for Ischemic stroke. This review outlines the isolation and potential use of DPSC's.

Keywords: Stem Cells; Mesenchymal Cells; Dental Pulp Stem Cells; Ischemic Stroke

Introduction

Stroke also called as Cerebrovascular accident, occurs when the blood supply to brain gets interrupted due to blockage of blood vessel that carries oxygen and nutrients to brain.

Types of strokes

- **Ischemic stroke:** This occurs due to blood clot that prevents oxygen and nutrients to brain.
- **Haemorrhagic stroke:** This occurs when blood vessel ruptures.
- **Transient Ischemic Attack (TIA):** Blockage of blood to brain for a brief period of time.

The currently available therapeutic strategies for stroke are Recanalization, Thrombectomy, Thrombolysis but very less number of patients are qualifying for recanalization [1,2].

Thrombectomy is effective when performed within 24 hours post – stroke [3]. Thrombolysis is performed by intravenously administered plasminogen activator which is applicable within short time frame of 4.5hours from symptomatic onset [4].

As neurological injury due to ischemic is largely irreversible, it is necessary to develop novel approaches to restore the neurological functions by regeneration of neurons [5]. Cell based therapies

shows a therapeutic effect in patients affected by stroke and other neurological diseases. Extensive studies have suggested that DPSC's are promising therapeutic option for ischemic stroke due to their strong proliferation ability [6].

Dental pulp stem cells

DPSC's are stem cells present in dental pulp derived from a cranial neural crest lineage. They have 30% higher re-generative potential than bone marrow-derived mesenchymal stem cells [7,8]. Worldwide many new protocols were evaluated for isolation of DPSC's for therapeutic purposes [9]. Granthos., *et al.* were the first to isolate DPSC's in 2000 [10].

Figure 1: Isolation and culture of dental pulp mesenchymal stem cells [11].

Properties of DPSC's

- Multipotency
- Self-renewal capacity.
- *In vivo* tissue regeneration capacity.
- High proliferation activity.
- Immunomodulation
- Expression of cell -surface markers.

Isolation of DPSC's

Materials

Culture medium: - Alpha - minimum essential medium supplemented with 10% Foetal Bovine Serum, 100 U/ml Penicillin - G, 100mg/ml Streptomycin, 0.25 mg/ml Fungizone. Phosphate -Buffered saline [PBS], Collagenase Type - 1 = 3 mg/ ml, + Dispase - 4 mg/ml, Tissue culture dishes/flasks, 70 µM cell strainer, Sterilized dental fissure bar on a high-speed hand piece, Forceps, Tweezer, Scalpel handle and a Blade.

Procedure

The isolation procedure is done under sterile condition, working with a biosafety laminar flow hood. The freshly extracted tooth is cleaned with PBS.

The surface debris and periodontal ligament were removed using a scalpel blade. The tooth is slowly cut at the Cemento-Enamel junction using a sterile fissure bur to reveal the pulp chamber.

The contact point of the bur needs to be constantly irrigated with PBS to prevent over heating of Dental tissue. Pulp tissue is tenderly isolated from the crown and root and cut into little pieces with the guide of Scalpel cutting edge.

The small pieces of pulp tissue are transferred into enzyme solution and digested for 1 hr at 37°C then the cells are passed through 70 µM strainer to obtain single cell suspensions.

Single cell suspensions are centrifuged at 1200 rpm for 5 min at room temperature. Supernatants are carefully pipetted off and the pellet is re-suspended in 1 ml medium.

The residual enzyme solution is washed out by Centrifuging and removing the supernatant.

Single cell suspension of DPSC's are seeded on to 25 cm^2 culture flask with culture medium and then incubated at 37°C in 5% CO_2. The culture medium is changed every 3 days and cells are sub-cultured at 70% confluence.

Colonies of DPSC's can be seen after 10 to 14 days. After isolation, the cells need to be examined for their sternness.

This is done by confirming the expression of mesenchymal Phenotypic markers such as STRO -1, CD 73, CD90 and CD 105 and negative expression of hematopoietic markers such as CD45.

Further multipotent differentiation ability of cells needs to be confirmed by Adipogenic, Osteogenic and Neurogenic induction [12,13].

Figure 2

Intra cerebral transplant of DPSC's

Several studies have provided evidence that dental pulp stem cell transplantation have therapeutic effect in stroke [14]. Recent study has demonstrated that transplantation of $CD31^{-}/CD146^{-}$ Side population stem cells promote vasculogenesis and neurogenesis in an induced peri-infarct area and accelerated the functional recovery after transient middle cerebral artery occlusion [TMLAO] in adult male Sprague-Dawley rats [15].

The neurological functional improvement was observed in rodents at 3 and 4 weeks after induced stroke in which DPSC's are transplanted intracerebrally. 2.3% of originally transplanted DPSC's had survived in rodent brain. These surviving DPSC's were differentiated into astrocytes and neurons in post ischemic brain [16].

This targeted migration of transplanted cells towards the ischemic border zone is mediated by SDF1 gradient [17]. These studies provided the first pre-clinical support for the use of DPSC's in stroke therapy.

Other studies have suggested that due to the capacity of DPSC's to release neurotropic factor (Sugiyama., *et al*.) and anti - inflammatory molecule (Yamagata., *et al*.), they show neuro-protective effect.

Possible mechanisms

DPSC's have the potential in enhancing neurogenesis. Previous studies have suggested that the integration of neuronally pre-differentiated Human Dental Pulp Stem cells in to brain [18,19].

Similarly, studies showed the migration of grafted DPSC's to infarct boundary zones and their differentiation to neurons and astrocytes in rat. DPSC's also have been shown to exert immunemodulatory properties by inhibition of T-lymphocyte proliferation [20].

Limitations

Though DPSC's have higher proliferation rate, to acquire enough cells from isolation it takes months [21]. In spite of the fact that these pre-clinical examinations have demonstrated with respect to restorative capacities of DPSC's, constrained clinical preliminaries have been distributed. Therefore, to verify the therapeutic ability of DPSC's, large-scale clinical trials should be conducted.

Conclusion

As shown in this review, previous studies have indicated that DPSC's are useful in promoting neurological functional improvement in Ischemic stroke and is very powerful tool in regenerative medicine. However, to understand the significance of DPSC's markedly and mechanisms underlying the therapeutic effects of DPSC's it requires further research.

Bibliography

1. T Brandt., *et al*. "Thrombolytic Therapy of Acute Basilar Artery Occlusion. Variables Affecting Recanalization and Outcome". *Stroke* 27 (1996): 875-881.

2. Mayank Goyal MD., *et al.* "Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke". *The New England Journal of Medicine* 371 (2015): 1019-1030.

3. Raul G Nogueira., *et al*. "Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct January 4, 2018". *The New England Journal of Medicine* 378 (2018): 11-21.

4. Maarten G Lansberg., *et al*. "Efficacy and Safety of Tissue Plasminogen Activator 3 to 4.5 Hours After Acute Ischemic Stroke: A Metaanalysis (2009).

5. Koji Abe., *et al.* "Kawahara Stem Cell Therapy for Cerebral Ischemia: From Basic Science to Clinical Applications.

6. Wai Khay Leong., *et al*. "Human Adult Dental Pulp Stem Cells Enhance Poststroke Functional Recovery Through Non-Neural Replacement Mechanisms (2012).

7. Marco Tatullo., *et al.* "Dental Pulp Stem Cells: Function, Isolation and Applications in Regenerative Medicine (1899).

8. S Shia., *et al*. "Comparison of human dental pulp and bone marrow stromal stem cells by cDNA μ array analysis". *Bone* 29.6 (2001): 532-539.

9. Maryam Raoof., *et al.* "A modified efficient method for dental pulp stem cell isolation". *Dental Research Journal* 11.2 (2014): 244-250.

10. Gronthos S., *et al.* "Postnatal human dental pulp stem cells [DPSCs] in vitro and in vivo". *Proceedings of the National Academy of Sciences of the United States of America* 97.25 (2000): 13625-13630.

11. Isolation and culture of dental pulp mesenchymal stem cells.

12. P Hilkens., *et al*. "Effect of isolation methodology on stem cell properties and multilineage differentiation potential of human dental pulp stem cells". *Cell and Tissue Research* 353 (2013): 65-78.

13. Jakub Suchánek., *et al*. "Human Dental Pulp Stem Cells – Isolation And Long Term Cultivation". *Acta Medica* 50.3 (2007): 195-201.

14. Terry C Burns., *et al*. "Stem Cells for Ischemic Brain Injury: A Critical Review". *The Journal of Comparative Neurology* 15.1 (2009): 125-144.

15. Masahiko Sugiyama., *et al*. "Dental Pulp-Derived $CD31^{-}$/$CD146^{-}$ Side Population Stem/Progenitor Cells Enhance Recovery of Focal Cerebral Ischemia in Rats 17-9-10 (2011): 1303-1311.

16. Wai khay leong., *et al*. "Human Adult Dental Pulp Stem Cells Enhance Poststroke Functional Recovery Through Non-Neural Replacement Mechanisms". *Stem Cells Translational Medicine* 1 (2012): 177-187.

17. Maria R Gancheva., *et al*. "Using Dental Pulp Stem Cells for Stroke Therapy". *Frontiers in Neurology* 10 (2019): 422.

18. Király M., *et al*. "Integration of neuronally predifferentiated human dental pulp stem cells into rat brain in vivo". *Neurochemistry International* 59.3 (2011): 371-381.

19. Nosrat IV., *et al.* "Dental pulp cells provide neurotrophic support for dopaminergic neurons and differentiate into neurons in vitro; implications for tissue engineering and repair in the nervous system". *The European Journal of Neuroscience* 19.9 (2004): 2388-2398.

20. Laura Pierdomenico., *et al.* "Multipotent Mesenchymal Stem Cells with Immunosuppressive Activity Can Be Easily Isolated from Dental Pulp". *Transplantation* 80.6 (2005): 836-842.

21. Qing Dong., *et al*. "Dental Pulp Stem Cells: Isolation, Characterization, Expansion, and Odontoblast Differentiation for Tissue Engineering Methods". *Journal of Molecular Biology* 1922 (2019): 91-101.