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ScienceDirect

Journal of the Chinese Medical Association 77 (2014) 605–607

www.jcma-online.com

Editorial

Teeth and dental pulp tissue: The origin for generating induced pluripotent stem cells?

We read the article by Yun-Ching Chang et al[1] with great interest, and would like to supplement their discussion briefly with additional information and observations associated with the imperative research topic of dental pulp-derived induced pluripotent stem cells (iPSCs).

Stem cells

Stem cells can be categorized into three different types based on their respective ability to differentiate. The first type is totipotent stem cells, which can be implanted in the uterus of a living animal and subsequently give rise to a full organism. The second type of stem cell is the pluripotent stem cell, such as embryonic stem cells and iPSCs. These cells can give rise to every cell of an organism except extra-embryonic tissues. The last type of stem cell is the multipotent stem cell, associated with adult stem cells that can only generate specific lineages of cells in the differentiation processing. Adult stem cells (also known as somatic stem cells) are undifferentiated cells that can differentiate to some or all of the major specialized cell types of the tissue or organ in the living body. In the past 2 decades, scientists have been focusing on developing stem cell therapy, searching for various sources for stem cells, and applying stem cell treatments for diseases such as osteoarthritis, neurodegenerative disorders and heart infarction.

Dental stem cells

In vivo, dental pulp stem cells (DPSCs) are able to produce ectopic dentin and related pulp tissues. Since DPSCs were discovered originating from wisdom teeth in 2000,[2] the search for suitable stem cell sources has been focused on dental tissues, such as human gingival stem cells, periodontal ligament stem cells, stem cells of apical papilla, dental follicle progenitor stem cells, stem cells of exfoliated deciduous teeth, and adult permanent teeth. These stem cells are considered as undifferentiated mesenchymal cells that are characterized by their unlimited self-renewal, colony forming capacity, and multipotent differentiation.

Dental stem cells are now known to be neural crest-derived and mesenchymal in origin and are therefore considered to share a common lineage derived from neural crest cells.[3] The normal morphogenesis of tooth depends on mutual signal interaction between mesenchymal stem cells and epithelial/endothelial cells. The DPSC niche was traditionally regarded as being located in the cell-rich zone of the four cell layers (odontoblastic zone, cell free zone, cell rich zone, and pulp core) within dental pulp and in the perivascular area. From the viewpoint of embryonic development, the cranial neural crest gives birth to most dental tissue, including dental pulp and DPSCs. Additionally, DPSCs have been shown to contain primitive stem cell subpopulations of neural crest origin, and also express several neural crest cell markers.[4] Recently, Kaukua et al[5] pointed out that the location of the DPSC's niche may originate from peripheral nerve-associated glia cells identified by the clonal color-coding technique.

A variety of stem cell sources in dental tissues have been studied. However, harvesting DPSCs remains the preferable choice due to its several apparent advantages. First, it is relatively easy to have surgical access to and collect somatic cells with low morbidity after extraction of dental pulp. Second, autologous DPSCs could be efficiently isolated and amplified from an impacted molar or exfoliated deciduous tooth. Third, DPSCs could be safely cryopreserved as a bank of stem cells and be fabricated with many scaffolds to be later utilized for a variety of purposes. Last but not least, DPSCs have shown immune-privilege, anti-inflammatory abilities and immune-modulating properties.[6] When focusing on regenerative medicine, the ability to maintain self-renewal and multilineage differentiating potential after implantation is vital and strongly associated with the types of stem cells that are being selected.

iPSCs

Other than adult stem cells, iPSCs have been successfully generated from mouse embryonic fibroblasts and human skin fibroblasts using retroviral transfection of the four Yamanaka factors (Oct-4/Sox2/Klf4/c-Myc) since 2007.[7] The capacity for *in vivo* teratoma formation has often been used as a landmark for evaluating the pluripotency of iPSCs.[8] However, possible tumorigenesis from iPSCs is a major concern if the

http://dx.doi.org/10.1016/j.jcma.2014.09.008
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c-Myc oncogene is used to overstimulate cell growth and metabolism with possible genomic instability. Dysregulated expression of c-Myc occurs in a wide range of human cancers and is often associated with poor prognosis of disease, indicating a key role of this oncogene in tumor progression.[9] Further studies have successfully generated iPSCs from mouse and human fibroblasts using only three transcription factors: Oct-4/Sox2/Klf4 (without c-Myc). In that research, cells derived from these iPSCs without c-Myc did not develop tumors during reprogramming.[10] In this intriguing research article by Chang et al,[1] the authors showed the results they obtained by developing DPSC-derived iPSCs without c-Myc for the purpose of describing a safer way to undertake stem cell therapy. Despite the fact that DPSCs remain a popular stem cell source due to several advantages over other cell sources, there currently exists only limited evidence and studies associated with DPSC-derived iPSCs.

Differentiation of dental pulp-derived iPSCs

Although there are several types of dental tissues that can serve as stem cell sources, differences among these tissues still exist and it is vital to know these differences before more purposefully pursuing stem cell-based regeneration medicine. For example, stem cells of exfoliated deciduous teeth (SHEDs) have been found to have a high proliferative and osteogenic capacity. Also, periodontal ligament-derived stem cells were shown to possess the best regeneration capacity of the periodontal ligament, alveolar bone, and cementum in periodontal defect animal models.[11] *In vitro*, periodontal ligament-derived stem cell culture has been shown to sustain for 25 passages and present qualities of cryopreservation, immunosuppresive ability, and presentation of mesenchymal stem cell markers. DPSCs also disclosed better osteogenic and odontogenic capacity and are currently viewed as a promising cell type for bone tissue engineering. Besides their osteogenic capacity, DPSCs have been viewed as a promising therapeutic tool since an earlier study showed that DPSCs could promote the proliferation and differentiation of the neural cell in mouse hippocampus.[12]

The therapeutic application of stem cells remains a popular topic in iPSC technology, particularly through the expression of certain transcription factors in somatic cells to potentially manipulate pathological mechanisms of diseases. This is an exciting and groundbreaking scientific undertaking, which could conceivably open a new window for regenerative medicine. For example, patient-specific iPSCs could be differentiated into neural crest precursors, motor neurons, mature hepatocytes, and retinal pigment epithelium.[13−15] These experimental results demonstrated that human iPSCs could be applied to simulate the specific pathogenesis of a genetically inherited disease, to screen drug candidates, and to facilitate the design of cell replacement therapy.

In conclusion, the work of Chang et al[1] has made a notable contribution, not only to providing a safer procedural avenue for generating DPSCs-derived iPSCs, but also to the differentiation of DPSCs-derived iPSCs into neuron-like cells. Ultimately, this research may prove to be of substantial value in assisting future investigations in the field of neuroregenerative medicine.

Conflicts of interest

The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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Ke-Hung Chien
Department of Ophthalmology, Tri-Service General Hospital and National Defense Medical Center, Taipei, Taiwan, ROC

Institute of Pharmacology, National Yang-Ming University, Taipei, Taiwan, ROC

Shih-Hwa Chiou*
National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC

Department of Ophthalmology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC

Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan, ROC

Department of Medical Research and Education, Taipei Veterans General Hospital, Taipei, Taiwan, ROC

*Corresponding author. Dr. Shih-Hwa Chiou, Department of Medical Research and Education, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, ROC.
E-mail address: shchiou@vghtpe.gov.tw (S.-H. Chiou)