Journal of Dentistry and Oral Biology

Short Communication
Published: 20 Sep, 2017

Prospects for the Application of Neural Crest Cells for the Periodontal Therapy

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Abstract

Periodontal tissues are predominantly formed by ecto-mesenchymal cells derived from the neural crest during embryonic development. Neural Crest Cells (NCCs), a transient multipotent stem cell population that plays crucial roles in the tissue development, have been regarded as highly promising candidates for the periodontal tissue regeneration. Our previous study demonstrated the establishment of a multipotent clonal Periodontal Ligament (PDL) cell line termed cell line 1-17 that showed NCCs phenotypes. In addition, our studies also reported the generation of Neural Crest-Like Cells (NCLCs) from human PDL-derived Induced Pluripotent Stem Cells (iPSCs). This article discusses the application of cell line 1-17 and human PDL iPSC-derived NCLCs for the study of clinical periodontal therapy.

Introduction

Periodontitis, a chronic inflammatory condition in the periodontal tissues caused by bacterial infections, leads to common clinical symptoms including extensive connective tissue destruction and alveolar bone loss. Therefore, severely advanced periodontitis eventually results in tooth loss. The ultimate goal of periodontal therapy is to regenerate the healthy and functional periodontal tissues destructed by periodontitis. Stem cell population has been considered essential for the tissue development and regeneration because of their special properties: self-renewal and multipotency. Neural crest cells (NCCs), a transient stem cell population that derives from the neural crest, contribute to the formation of diverse cell lineages and structures in periodontal tissues; they differentiate into ecto-mesenchymal cells and give rise to various tissues including alveolar bone, cementum, and periodontal ligament (PDL). Given the principal role NCCs have in periodontal tissue development, they are a highly promising candidate for the application to the periodontal therapy. NCCs are present in the human embryo and in several adult tissues, however their number is extremely small. The rarity of human NCCs prevents their application for the study of regenerative medicine. Therefore, we aimed to establish human cell line that possesses NCCs phenotypes and generate neural crest-like cells (NCLCs) from human PDL-derived induced pluripotent stem cells (iPSCs).

Establishment of Human Multipotent Periodontal Ligament Cell Line with Neural Crest Cell Phenotypes

Human PDL cells isolated from the healthy a third molar of 20-year-old female were immortalized by using by using simian virus40 T-antigen and human telomerase reverse transcriptase transfection [1]. Following the limiting dilution, we obtained 20 clonal PDL cell lines and investigated the characteristics of one line termed cell line 1-17. This line showed the potential to differentiate into osteoblasts, chondrocytes, adipocytes, and neurocytes [2]. It also revealed the high expression of mesenchymal stem cell-related cell surface markers including CD13, CD29, CD44, CD71, CD90, CD105, and CD166, and pluripotency genes *OCT4* and *Nanog* [3]. These results suggested the stem cell phenotypes of cell line 1-17. This line also exhibited NCCs phenotypes; it highly expressed neural crest marker genes *SLUG*, *SOX10*, *NESTIN*, *p75NTR*, and *CD45d* [3]. In addition, the conditioned medium from cell line 1-17 promoted neural differentiation of neural progenitors. This result is consistent with the previous study reporting the ability of conditioned medium from NCCs to induce neurite outgrowth of neural cells [4]. Therefore, cell line 1-17 would provide an innovative tool to clarify the behavior of NCCs during healing processes of periodontal ligament tissues.

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Received Date: *31 Jul 2017*
Accepted Date: *13 Sep 2017*
Published Date: *20 Sep 2017*

Citation:
Tomokiyo A, Hamano S, Hasegawa D, Sugii H, Yoshida S, Maeda H. Prospects for the Application of Neural Crest Cells for the Periodontal Therapy. J Dent Oral Biol. 2017; 2(15): 1091.

ISSN: 2475-5680

Generation of Neural Crest-Like Cells from Human Induced Pluripotent Stem Cells

Induced pluripotent stem cells (iPSCs) are one of the most promising stem cells for regenerative therapy because they are generated from somatic cells and show high multipotency and self-renewal capabilities [5]. However, iPSCs have the risk of tumor formation because of the insertion of a tumorigenic gene. A previous study reported the successful generation of iPSC-derived NCLCs that did not formed any tumors after their transplantation [6]. This result suggested that neural crest lineage-committed iPSCs had no tumorigenic potential *in vivo*. Moreover, we tried to generate NCLCs that closely resembled the phenotypic and functional hallmarks of NCCs. iPSCs derived from human PDL (PDL iPSCs) was used for our study because PDL was originated with a neural crest and epigenetic memories for the somatic tissue persisted in iPSCs. We sorted the HNK-1 positive population from PDL iPSCs-derived NCLCs because HNK-1 expression was identified in premigratory and migrating NCCs [7]. These cells revealed a higher expression of NCCs marker genes and a greater capacity to differentiate into neural crest lineage cells than HNK-1 negative population from PDL iPSC-derived NCLCs as well as NCLCs generated from non-neural crest tissue-derived iPSCs [8]. This result suggested the HNK-1 positive population from PDL iPSCs-derived NCLCs was enriched with a population that has characteristics of NCCs and could help to establish a new periodontal therapy based on NCCs transplantation.

Conclusion

Cell line 1-17 and/or HNK-1 positive population from PDL iPSCs-derived NCLCs would overcome the rarity of human NCCs and may be used as a valuable and unlimited cell source for the study of regenerative medicine. Further analyses based on a molecular biological approach are required to establish a new NCC-based periodontal therapy.

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