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Review

Frontier dental research on iPS cells

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ABSTRACT

New technologies are required to regenerate large defects in periodontal tissues and alveolar bone, and ultimately the lost tooth itself. Induced pluriopotent stem (iPS) cells can be differentiated into various cells in the body and can technically be produced from cells of human adult tissues. Accordingly, these cells have a high degree of availability for regenerative medicine in dentistry. In the field of iPS cell research, to solve many issues, researchers are carrying out various studies, in search for an effective technique for the generation of iPS cells, methods for the safe culture and transplantation of iPS cells, protocols for the induction from iPS cells to tissue-specific cells, and utilization as models of genetic diseases. In dental research, iPS cells would be applied for the regeneration of oral tissues and the development of clinical treatments for congenital diseases. In this review, we mention that dental tissue has higher availability for the production of iPS cells than other tissue types, and iPS cells have the capacity to differentiate into oral tissue cells including dental epithelial and mesenchymal cells. Therefore, iPS cell technology is expected to open new doors, especially for dental regenerative sciences, although many hurdles must still be overcome before iPS cells can fulfill their clinical promise.

Contents

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1. Production of iPS cells and their maintenance

1.1. Gingiva as an iPS cell source

Various tissue engineering technologies have been developed in recent years using stem cells as a source for missing tissues. Induced pluripotent stem (iPS) cells, which have similar potential to embryonic stem (ES) cells, can be generated through the reprogramming of somatic cells from different tissues by the forced expression of defined exogenous factors. These iPS cells can be efficiently generated from accessible tissues and have potential for use in various clinical applications [1].

The gingiva is an easily obtainable tissue for dentists, and cells can be isolated from patients with minimal discomfort. iPS cells can be easily generated from adult mouse or human gingival fibroblasts by the transduction of three factors (Oct3/4, Sox2 and Klf4) without the c-Myc oncogene, and omission of c-Myc transduction has actually been shown to result in more specific iPS cell generation (Fig. 1) [2]. In addition, gingival fibroblasts demonstrate higher reprogramming efficiency than the skin fibroblasts that have been conventionally used for the generation of iPS cells, possibly because of their high proliferative capacity [2].

The gingiva consists of highly vascularized connective tissue under a thin keratinocyte layer, and gingival fibroblasts, which are phenotypically different from other fibroblasts, are the main constituents of this connective tissue [3]. Clinical and experimental findings in patients and animal models have consistently demonstrated that oral mucosa, including gingival tissue, has enhanced wound healing capability relative to skin [4,5], even though both tissue types share similar healing processes and sequences. In particular, gingival fibroblasts are thought to contribute to enhanced wound healing in the oral mucosa through the expression of distinctive genes such as wit3.0 [6]. Additionally, gingival tissue has been recently demonstrated to contain a fibroblastic stem cell population [7]. These characteristics of gingival fibroblasts, i.e., high regenerative capacity and multipotent subpopulation, may represent a progenitor-like status that could enhance the iPS reprogramming efficiency of these cells relative to other cell types, because less developmental reversion, i.e., reprogramming, would be required to reach the desired pluripotent state. Furthermore, gingival fibroblasts spread and proliferate well on tissue culture plates under relatively simple culture conditions [8]; therefore, primary gingival fibroblast cultures can be easily established. These cells may thus be uniquely suited for iPS-related clinical applications because of their reprogramming efficiency combined with their accessibility and ease of culture.

1.2. Advantages of gingiva-derived iPS cells relative to other stem cell types

In addition to iPS cells, two other major sources of stem cells exist: ES cells and mesenchymal stem cells (MSCs) (Table 1). ES cells are of great interest to scientists and clinicians because of their developmental capacity to differentiate in vitro into cells of all somatic cell lineages, including germ cells. However, the use of ES cells always involves ethical issues, because early embryos have to be destroyed to obtain these cells. In addition, possible immune rejection following the implantation of non-autologous cells is another problem associated with ES cells.

MSCs, which are multipotent stem cells originally found in the bone marrow and subsequently isolated from many other adult tissues, are considered a promising stem cell source for tissue engineering. To date, strategies employing stem cell-based therapy using bone marrow aspirates have been successfully used in dentistry to regenerate jaw bone and periodontal tissue [1]. However, bone marrow aspiration from the iliac crest is not an easy procedure, and it is not commonly performed by dentists because of the limitations of the dental license and dental specialization. As an alternative, growing evidence has demonstrated that dental tissues are a rich source of MSCs found in the dental pulp, periodontal ligaments, and impacted third molars [7].

Although these dental tissue-derived MSCs harbor great potential for oral tissue engineering purposes, their actual applications may be limited. From the standpoint of accessibility, autologous isolation of dental stem cells is not as convenient as the harvesting

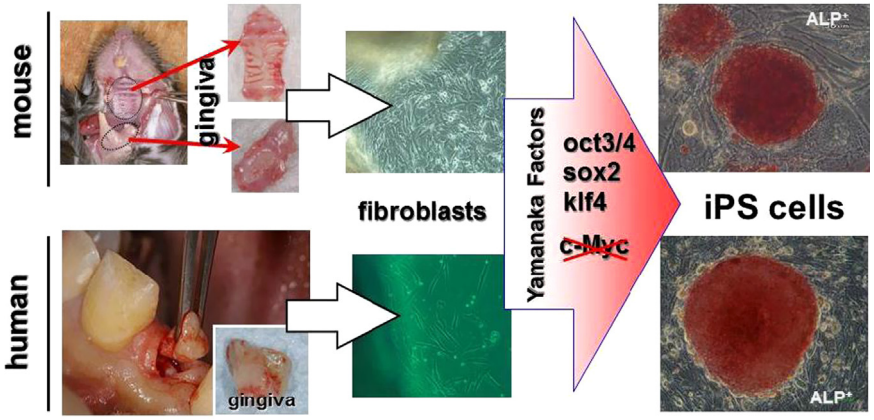

Fig. 1. Generation of iPS cells from gingiva. Gingival tissues from adult mice and patients (resected during dental implant surgery) can be used for iPS cell generation. Isolated gingival fibroblasts were easily reprogrammed by the transduction of three factors (Oct3/4, Sox2, and Klf4) without the c-Myc oncogene. Red iPS colonies in the figure show robust staining for alkaline phosphatase (ALP), which is associated with undifferentiated pluripotent stem cells. This figure is reproduced from the study by Egusa et al. [2] under open-access license policies.