Induced pluripotent stem cells in periodontal regeneration - Narrative review

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ABSTRACT

Purpose: Periodontal disease is a severe infection caused by inadequate oral hygiene, resulting in tooth loss due to the bone destruction that supports the teeth. “Induced pluripotent stem cells” (iPSCs or iPS cells) is a sort of pluripotent stem cell that can be acquired out of adult somatic cells like peripheral blood mononuclear cells (PBMCs) or skin fibroblasts through inducing genetic reprogramming genes (Klf4, Oct4, c-Myc, and Sox2).

Materials and Methods: This narrative review shows periodontal regeneration and bone regeneration using iPSCs and also highlights the drawbacks and challenges towards the future using iPSCs.

Results and Discussion: Recent studies have shown greater regeneration when combination of iPSCs and enamel matrix derivates (EMD™) inserted into treatment of periodontal and bone defects.

Conclusions: IPSC is a good alternative cell source in periodontal regeneration.

KEYWORDS

Stem cells, gingiva, periodontal regeneration, bone regeneration, induced pluripotent stem cells

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INTRODUCTION

Periodontal diseases affect considerable elimination of gingiva, alveolar bone, periodontal ligament (PDL), affecting root surfaces, and the other oral tissues. Loss of tooth is usually caused by over destruction of bone. Open Flap Debridement (OFD) or Scaling and Root Planning (SRP) are non-surgical procedures in periodontitis that utilize to decrease microbes, which enhances to reduce the pocket depth and to maintain oral hygiene. Periodontal regeneration is the propagation and re-establishment of the missing or damaged tooth-supporting tissues to revive the ruined anatomy's shape and performance. More preferably, regenerated periodontal ligament fibers are introduced within the immature cementum for bonding with alveolar bone and the surface of the root. Tissue engineering proposed a new technique based on cell biology and molecules for periodontal regeneration. Stem cells with the reproductive ability can be utilized by developing such sections within the three-dimensional (3D) manufacturers and then introducing it into the deficiencies.[1,2]

Periodontal tissue regeneration is evident by incorporating human PDL stem cells in unhealthy mice, which leads to the production of cementum or PDL like structures.[3] The predominantly employed cells in periodontal tissue engineering are mesenchymal stem cells (MSCs) and embryonic stem cells (ESCs), as well as bone marrow-derived MSCs (BMSCs), adipose-derived stem cells (ADSCs), periodontal ligament stem cells (PDLSCs).[4] However, induced pluripotent stem cells (iPSC), which evolves in recent times, are seeking attention nowadays.[5] This review will highlight iPSCs concerning their resources and significance and show their contest and expectation.

Stem cells

Each tissue and organ in the body and the periodontium develops from stem cells.[6] In increasing bone/periodontal regeneration, three sorts of stem cells, such as MSCs, ESCs, and induced pluripotent stem cells, were utilized based on the experiment. Han et al. have been exhaustively checked on for periodontal recovery in an assortment of creature models using the capability of PDLSCs, ADSCs, BMSCs, stem cells from exfoliated deciduous teeth (SCED), stem cells from apical papilla (SCAP), dental pulp stem cells (DPSCs), and also parental cells out of that dental follicles and gingiva[1], and later iPSCs by Yamanaka and his colleagues.

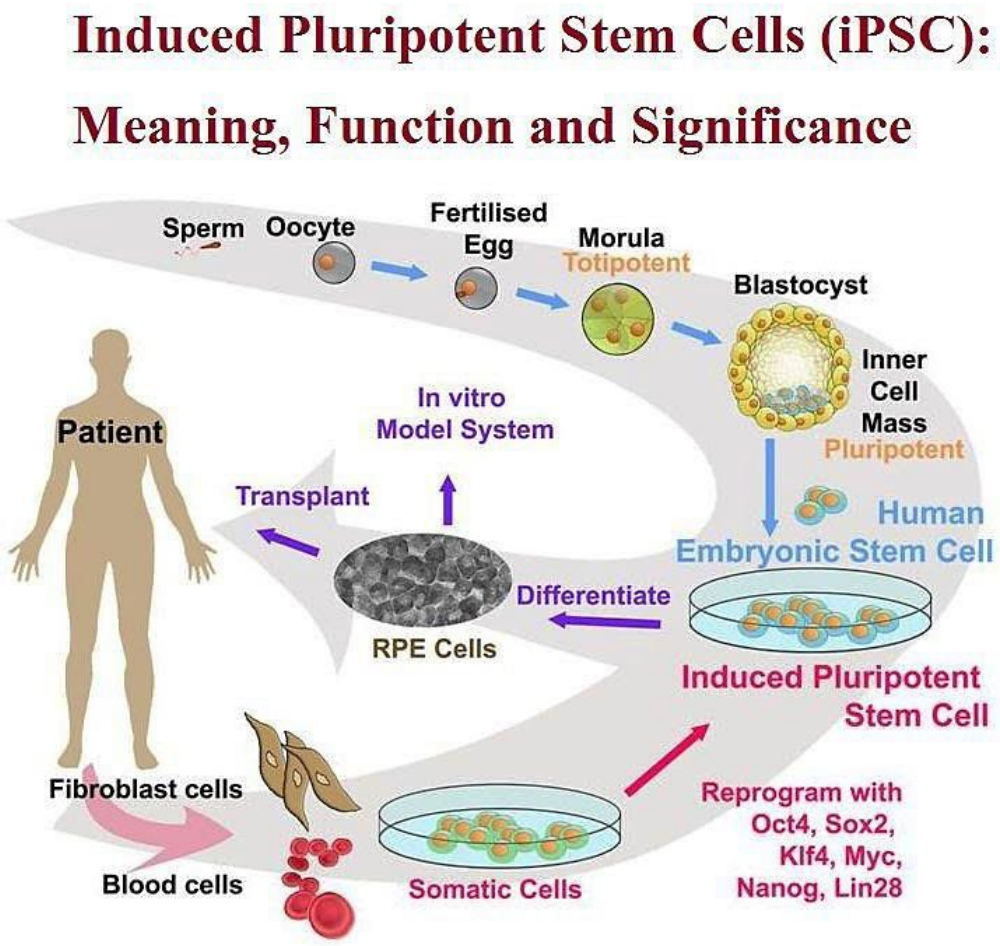
Induced pluripotent stem cells (iPSCs) and its appraisal

In 2006, Yamanaka and colleagues were first introduced Induced pluripotent stem cells (iPSC) by their innovative study. The combined usage of transcription factors, their performance published that somatic or terminally distinguished cells might restore into a pluripotent condition.[7] In 2012, the thorough stretch of Yamanaka's and Gurdon's performance was accepted by the Nobel Prize in Physiology or Medicine. The applied science of iPSC will advance our perception towards human illness by establishing genetic disorder models and a weapon for understanding biological development, discovering drugs, and the capability for genetic engineering applying regenerative therapies formulated on stem cells. iPSCs have a better future in regenerative procedures because of their increased proliferative property.

Table I. Shows the evolution of iPSCs

S.NO	AUTHOR AND YEAR	CELL SOURCE	TARGET OR MODEL USED	RESULTS
1.	TAKAHASHI AND YAMANAKA. (2006)	The retrovirus-mediated transfection of 4 transcription factors, such as Sox2, Oct3/4, Klf4, cMyc.	Mouse embryonic fibroblasts and adult mouse tail-tip fibroblasts.	Generated mouse induced pluripotent stem (iPS) cells.
2.	TAKAHASHI et al. (2007) YU et al. (2007).	From adult human somatic cells by optimizing retroviral transduction.	Human fibroblasts.	Generated human iPSCs.
3.	XUEJING DUAN. (2010)	Mouse iPS cells combined with Enamel matrix derivatives (EMD) or Emdogain gel (trademark).	Mouse iPS cells.	Enhance the restoration of mouse periodontal loss by promoting PDL development, alveolar bone, cementum.
4.	Hiroshi Egusa, Keisuke Okita. (2010)	Gingival fibroblasts from gingival tissues reprogrammed into iPS cells through 4 factors (Klf4, Sox2, Oct3/4, and cMyc; GF-iPS-4F cells) or 3 elements (which relates GF-iPS-4F cells, except cMyc oncogene; GF-iPS-3F cells) with no drug selection.	Adult wild-type mouse gingival fibroblasts (GFs).	Future application of these cells for investigation.

Induced pluripotent stem (iPS) cells had been recently accepted by incorporating human somatic cells and mouse with transcription factors c-Myc, Oct3/4, Klf4, Sox2 or SOX2, NANOG, OCT3/4 and LIN28.[7,8] The features of ES cells could adapt to 3 germ layers and also had the ability for self-healing and pluripotential, which will be preserved by induced pluripotent stem cells.[7] In addition to the favour of these biological characteristics, iPS cells with the combination of gene therapy are often efficient to cure genetic diseases and degenerative syndromes, as well as ischemia, stroke, cardiovascular malfunction, Parkinson's disease, and Alzheimer's disease[16,7,15] including periodontal regeneration.



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Cell origins for deriving iPSCs

iPSCs were obtained from various species, viz humans, rabbits, mice, rats, rhesus monkeys, marmosets, and pigs. iPSCs had been entirely derived among different dental and non-dental tissues and keratinocytes, periodontal ligament fibroblasts, melanocyte blood cells, adipose cells, bone marrow cells, fibroblasts, tissue-resident progenitor cells, gingival fibroblasts.[9-12] And these cells had been associated with the transduction of Sox2, Klf4, and Oct3/4.[13,14] iPSCs obtained from gingival fibroblasts (GF) were observed as superior over dermal fibroblasts (DF), while GF could get readily accepted at the time of the usual dental procedure, and these were modified into iPSCs.[13] For iPSCs generation, the most prevalent parental somatic cell varieties among others where the fibroblasts. In 2010, Yan et al. stated that dental derived tissues had high reprogramming property efficiency compared to the human fibroblast cells.[17]

Approaches

Transgene and chemical reprogramming are the two techniques for factor reprogramming. Transgene reprogramming is often indexed into three categories: DNA based, RNA based & protein transduction (direct cell transduction). Synthetic RNA, modified RNA, and micro RNA are RNA-based reprogramming methods.[18] While the most used process is DNA based, which includes the utilization of plasmids and viruses. Retroviral distribution of 4 transcription factors (Myc, Oct4, Klf4, and Sox2) was the actual first method for cell reprogramming. Apart from it get easily simulated at the character of recombinant proteins, several researchers found that direct protein transduction might enhance its inducing efficiency in 2009.[19-21] The combination of reprogramming elements within the genome through lentiviral or retroviral transduction was the systematic and most straightforward technique at present amidst the obtainable reprogramming techniques.[22,23]

iPSC in periodontal regeneration

In the department of tissue engineering, iPSCs issues a new perspective. Below mentioned features show the motives of involving iPSCs in periodontal regeneration:

- iPSCs were often acquired among dental obtained cells, like periodontal ligament and gingival fibroblasts.
- iPSCs could be modified into osteogenic cells following provoked through definite factors.
- iPSCs could also help restore artificial periodontal bone

imperfection and formation of fresh periodontal tissues such as periodontal ligament, cementum, and alveolar bone, using with or without the scaffolds.

In 2011, the first study of iPSC in the regeneration of periodontium was done by Duan et al. This study was conducted by incorporating iPSC in periodontal fenestration defects in mice, which was surgically made. Along with iPSC, Emdogain gel (EMD™), which consists of enamel matrix derivatives, shown to reinforce the periodontal regeneration. A higher periodontal regeneration was seen with EMD™ by stimulating the proliferation of various MSC types and improves the expression of tissue-specific maturation markers.[27-31] A remarkably higher regeneration of bone tissue was seen when a combination of miPSC and EMD™ inserted into the periodontium defects, rather than treating the defects with EMD™ alone.[24]

Likewise, Yang et al. illustrated with the result that rat iPSCs can be influenced to distinguished into MSCs, and topical and intravenous application of those cells which had been transfected with tumour necrosis factor "alpha-stimulated gene-6" (TSG-6) that has a powerful anti-inflammatory reaction was able to reduce swelling and suppress the resorption of alveolar bone in periodontitis of rat experiment.[26]

Tumorigenicity related to iPSC was ruled out when MSC, like cells extracted from iPSC, serves as a promising somatic cell used in regenerative medicine.[32-36] Thus, iPSC-MSC-like cells are the regularly available stem cells resource, which would be utilized in the regeneration of tissue approaches toward periodontal defects 25 and probably other diseases, including the lost dental tissues.

iPSC in bone regeneration

In 2012, an article published by Li and Niyibizi et al., it had been stated that, with the assistance of BMP-2, TGF-beta family or bFGF; can distinguish murine iPSC-obtained cells into osteoblasts.[37] Duan et al. and his group found that iPSCS could differentiate into osteogenic cells using EMD gel. When a combination of iPSCs and EMD is stimulated, an essential reproduction factor appeared throughout the differentiation of osteogenic cells, which is the mRNA aspect of Runt-related transcription factor 2 (Runx2), significantly elevated EMD-stimulated method.[24]

An autogenous bone graft is said to be the benchmark for remodelling of bone deformities[38], but it has the disadvantage of resorption in bone and infection of the donor site. Hence the adequate quality of the graft may not always be accessible.[39] An alternative for autogenous grafting is iPSC technology, in which the bone tissue engineering is carried out with the patient's somatic cells that are being inducted into bone-forming cells that are packed on the suitable scaffold combined with appropriate bioactive molecules.[40] Isolation either combination, as well as vitamin C, vitamin D3, osteogenic media, dexamethasone, b-glycerophosphate, bone morphogenetic proteins (BMP), are different types of factors that were suggested to get differentiation of osteogenic cells of iPSCs.[41-44] The differentiation of osteogenic cell accompanies accurate picturization of acquired bone cells by osteogenesis-related genes such as collagen type I (COL1A1), RUNX2, osterix (OSX), osteocalcin (OCN), and osteopontin (OPN)[45-47] additionally, evaluation of mineralization in the laboratory, and activity of alkaline phosphatase (ALP).[49,50]

The prospective of osteogenic cells in human iPSCs was revealed upon polymer-based nano-fibrous polyethersulfone (PES) scaffold from up-regulated expression genes related to osteogenic cells and alkaline activity phosphatase in the laboratory.[46-50] In transgenic mice, ES cells and iPSCs were developed, and it produces rat 2.3 kb type I collagen promoter-driven green fluorescent protein (Col2.3GFP), which distinguished into osteoblast lineage cells that produce Col2.3GFP in the laboratory.[51]

Drawbacks of iPSCs

The main disadvantage of using iPSCs in humans involves their unstable genome and their tendency to form tumours because of its integrating viral vectors. Before including the iPSCs in dentistry for treatment modalities, it is necessary to notice safety issues related to iPSCs that required being concerned.[52-54] As there are many drawbacks associated with iPSCs, it requires further research to minimize the risk of iPSCs before it has been incorporated in the treatment of multiple disorders.

Obstacles and future perspective about IPSCs

The application of iPSCs in clinical medicine was still a challenge for examiners. The critical limitations were biological safety, the efficiency of reprogramming, large-scale expansion, and directed differentiation. Regardless of the reprogramming methods used, naturally subsided efficiency of complete reprogramming is one of the obstacles in reprogramming iPSCs.[55] Finally, whether iPSCs possess an immunoregulatory property, which is considered a crucial feature of the process of MSCs, have never been examined, and question also remains to mark the most potent combo of iPSCs, growth factors, and biomaterials for the several clinical circumstances.

CONCLUSION

Even though research on the utilization of iPSCs in favour of regeneration of periodontium was in their initial phases, iPSCs-related treatment schemes would be a stable background and the fair prospect for periodontal regeneration's clinically available treatment modalities. Therefore, their efforts should consolidate the reprogramming performance, maximize the strategies of widespread expansion, ensure biological safety, and guided specializations.

CONFLICT OF INTEREST

The authors declared that there is no conflict of interest.

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