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MINIREVIEWS

Dental pulp cell bank as a possible future source of individual hepatocytes

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Abstract

Mesenchymal stem cells (MSCs) as a source for regenerative medicine are now the subject of much clinical attention. There are high expectations due to their safety, low tumorigenic risk, and low ethical concerns. MSC therapy has been approved for acute graft-versus host diseases since 2015. Tooth-derived MSCs are known to have a great potential in their proliferation and differentiation capacities, even when compared with bone-marrow-derived MSCs. In particular, stem cells from human exfoliated deciduous teeth (SHEDs) are the best candidates for personal cell banking (dental pulp cell bank), because they can be obtained less invasively in the natural process of individual growth. SHEDs are known to differentiate into hepatocytes. There have been several studies showing the effectiveness of SHEDs on the treatment of liver failure in animal models. They may exert their effects either by repopulation of cells in injured liver or by paracrine mechanisms due to their immune-regulatory functions. Moreover, it may be possible to use each individuals' dental pulp cells as a future source of tailor-made differentiated hepatocytes in the context of a bioartificial liver or liver-on-a-chip to screen for drug toxicity.

Key words: Mesenchymal stem cells; Stem cells from

human exfoliating teeth; Hepatocytes; Dental pulp cell bank; Liver diseases

Core tip: Dental pulp-origin mesenchymal stem cells have a remarkable potential for regenerative medicine in both differentiation and proliferation capacity. Dental pulp cell banks are currently under operation in several institutions in Japan, as they can be obtained easily and less invasively in the personal growth process. Recent findings that they can differentiate into hepatocytes suggest that they can be applied to refractory liver diseases as either auto or allogenic cell therapies. These hepatocytes can be used as tailor-made components for a bioartificial liver or liver-on-a-chip to screen for drug toxicities in preparation for future use.

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INTRODUCTION

Mesenchymal stem cells (MSCs), which reside in a variety of tissues, are able to differentiate into many cell types. They have a low risk of tumorigenesis because they do not need the introduction of foreign genes to differentiate, unlike induced pluripotent stem (iPS) cells. They also have a low risk of immune rejection. They can be obtained in a minimally invasive manner such as umbilical cord blood, providing a promising cell source for regenerative medicine. Application of MSCs in the treatment of refractory liver diseases is currently under great clinical scrutiny[1-3].

It was first reported in 2000 that MSCs were present in dental pulp tissues within the teeth[4]. Dental pulp-derived MSCs (DP-MSCs) are known to differentiate into many cell types like other MSCs, such as osteoblasts, adipocytes and neural cells[5]. DP-MSCs also have good potential for proliferation and differentiation similarly to other types of MSC. In particular, MSCs derived from exfoliated deciduous teeth (SHED) in childhood have been reported to have a pronounced potential of proliferation[6,7]. Because these are normally discarded in the process of personal growth, they are perfectly suited for cell banking in a manner similar to umbilical cord blood[8]. The dental pulp cell bank is a best fit for future tailor-made medicine, where people deposit their own tooth-derived MSCs, preparing for their future medical needs. In this review, we concisely review the current and future status of DP-MSCs, including SHED-based regenerative medicines, particularly focusing on their application for liver diseases and for the construction of bio-assay systems that are suitable for drug side-effect testing, with the aim of achieving tailor-made medicine.

Cells from teeth for regenerative medicine

Recent progress in regenerative medicine has been outstanding; it is now possible to remove one's own cells or tissues, differentiate them into many cell types, and use these to repair dysfunctional organs. The development of iPS cells has contributed greatly to this movement. In Japan, a clinical study for age-related macular degeneration using iPS cells started in 2014[9]. However, there remain some clinical concerns regarding iPS cell-based regenerative medicine. For instance, because autologous transplantation of self-iPS cells is costly, heterologous cells must be used in practical situations. Establishment of cell panels to cover all HLA types remains costly and laborious. In addition, because they are prepared with transfection by foreign genes, the risk of tumorigenesis cannot be ignored[10].

On the other hand, because MSCs do not need transfection of genes, they may have a lower risk of tumorigenesis. In addition, they induce immune tolerance in general, so rejection of cells is unlikely. MSCs might also increase the acceptance of regenerative medicine because they do not undergo any gene manipulation.

In the dental field, starting with their acquisition from wisdom and deciduous teeth, MSCs from dental pulp, periodontal ligament, apical papilla, and dental follicle have been reported[11-13]. These dental stem cells have variety of differentiation and active proliferation capacities. These are obtained in a less-invasive manner, and the concept of "waste material re-utilization" is the main rationale to promote a system of dental pulp cell banking.

Gronthos *et al*[4] first reported that dental pulp-derived cells from adults were clonogenic, rapidly-progressive and produced dentin/pulp-like complex under specific conditions. This study opened the way for the application of DP-MSCs to regenerative medicine. Subsequently, it was shown that DP-MSCs could differentiate into cells that were irrelevant to teeth, such as adipocytes or neural cells[5] and are known to be osteogenic, odontogenic, dentinogenic, cementogenic, adipogenic, chondrogenic and neurogenic[11,14]. Miura *et al*[6] showed that SHEDs had a higher potential of proliferation and differentiation, and would therefore be a hopeful source for regenerative medicine. This may be the beginning of the concept of dental bank reusing the exfoliated juvenile teeth that would be discarded otherwise. MSCs from an early age may be expected to be more capable of regeneration and differentiation, as was shown by study finding that SHEDs were more proliferative than other DP-MSCs[7]. There was also a report showing a superior differentiation capacity for SHED when compared with stem cells from adult dental pulp[15].

It is known that stem cells from bone marrow or blood are able to differentiate into cells like hepatocytes[16-18]. Ishkitiev *et al*[19] first reported that DP-MSCs

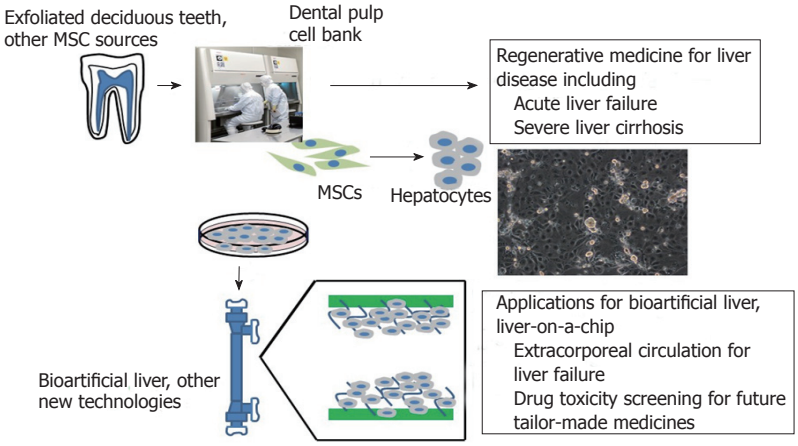

Figure 1 Schematic representation of processes that utilize dental pulp cell bank for future use as hepatocytes. They may be used as cellular sources for cytotherapies to treat refractory liver diseases or as a component of bioartificial liver aiming at tailor-made applications such as future drug-toxicity screening. A hepatocyte-like cell induced from dental pulp-derived-mesenchymal stem cells in our laboratory is shown (unpublished data).

could differentiate into hepatocytes. They cultured cells from deciduous teeth in medium containing HGF, Insulin-Transferrin-Selenium-X, and oncostatin M, and found that they differentiated into cells with an appearance of hepatocytes and produced albumin. These hepatocytes were able to metabolize ammonia to urea, suggesting the presence of a urea cycle. Purification of the cell fractions positive for CD117 enabled efficient induction of hepatocytes[20]. The level of hepatic differentiation in SHED when compared with bone marrow-derived MSC (BM-MSC)s was the same or higher[21]. A recent report also showed a higher expression of hepatocyte-markers in DP-MSCs than in BM-MSCs at both the genetic and protein levels[22]. We also succeeded in differentiating DP-MSC into cells with hepatocyte-morphology, by culturing them first under the presence of activin A, Na-butylate and fibroblast growth factor, and then insulin, dexamethasone, and hepatocyte growth factor (unpublished results, Figure 1).

CELL TRANSPLANTATION THERAPY WITH SHEDS FOR LIVER DISEASES

The effects of MSC-based therapy consist of two major mechanisms. The first is that MSCs transdifferentiate into the cells of damaged-tissues and compensate for organ dysfunction. The second is that, responding to cytokines from the inflamed tissues, MSCs exert paracrine functions including immunomodulation and tissue repair[23]. MSCs produce a variety of cytokines, chemokines and growth factors. The immunomodulatory effects may be one of the main mechanisms of MSC treatment for acute graft versus host disease that has been approved[24].

To date, about half of the papers describing cytotherapies with MSCs were those using bone-marrow-derived MSCs, followed by umbilical cord blood and adipose tissues, and very few were on DP-MSCs[23], despite their promising capabilities. This may partly be due to difficulties of collaboration between dental and medical departments.

Cytotherapies with MSCs have been applied for refractory liver diseases with severe dysfunctions and fibrosis[3]. Transdifferentiation of MSCs into hepatocytes and paracrine mechanisms have been considered to be the main effects. Shi *et al*[25] reported that 13/15 pigs with acute liver failure that were administered bone-marrow derived MSCs survived, while none of the controls did. They showed that 4.5% of cells in surviving liver were repopulated by MSC-derived hepatocytes, concluding that MSC paracrine mechanisms as well as repopulation of hepatocytes by transdifferentiated MSCs contributed to the effects of MSC treatment.

Paracrine mechanisms, including immunomodulation, have attracted the most clinical attention[26]. As the immune effects of MSCs are most likely caused by soluble factors, restriction by HLA in donor selection can be ignored[27]. Moreover, DP-MSCs might induce stronger immune tolerance than bone-marrow derived MSCs[28].

There have been several experimental reports that showed the application of DP-MSCs for liver diseases. Ishikiev *et al*[29] reported that transplantation of hepatocytes induced by SHEDs into the spleen of rats with acute and chronic liver failure improved hepatic functions *via* transdifferentiation and repopulation of the cells. Yamaza *et al*[30] also reported that trans-spleen administration of SHEDs into CCL4-induced cirrhotic mice significantly improved liver function, inflammation, and fibrosis. Both studies attributed the effects to the direct implantation of cells through their differentiation into hepatocytes. Ito *et al*[31] reported that only conditioned medium (CM) from SHEDs resulted in significant survival effects in rats with acute liver failure due to D-galactosamine. They reported that the survival effect of CM on liver failure was induced by anti-inflammatory M2 macrophages that suppressed hepatocyte apoptosis, and promoted hepatocyte proliferation. It is important

Table 1 Comparison of benefits and disadvantages among 3 types of cell sources, mesenchymal stem cells, induced pluripotent stem and embryogenic stem cells

	MSC	iPS cells	ES cells
Proliferation	Low	High	High
Differentiation	Limited	Pluripotent	Pluripotent
Gene transfer	No	Yes	No
Cancer risk	Low	Not neglected	Not neglected
Immune rejection	Low	Possible	High
Paracrine mechanism	Yes	Unknown	Unknown
Banking	Easy	Easy	Possible
Ethical hurdle	Low	Low	High

MSC: Mesenchymal stem cells; iPS: Induced pluripotent stem; ES: Embryogenic stem.

to know that only soluble factors, not the use of cells, induce significant clinical outcomes. Moreover, exosomes secreted by MSCs have been reported to be effective in the improvement of liver function and fibrosis[32,33]. Future studies should verify the effects of no-cell-therapy with conditioned medium or intracellular vesicles on liver diseases.

ESTABLISHMENT AND OPERATION OF DENTAL PULP CELL BANK

Three cellular resources, embryonic stem (ES) cells, iPS cells and MSCs, are currently the major candidates for the clinical application of regenerative medicine. A comparison of the benefits and disadvantages among these cellular resources is shown in Table 1. MSCs do not have higher potential of proliferation or differentiation than ES cells or iPS cells, some consider them to be a primary source for regenerative medicine because of the low possibility of tumorigenesis and the lack of ethical concerns.

SHEDs are an ideal resource in regenerative medicine because of their high capacity, low ethical concerns and cost, and re-use concept[8]. In addition, dental pulp is viable 5 d after extraction[34]. Not only could they be used as a low immunogenic source for allogenic transplantation therapy, but they can also be applied as a tailor-made self-source preparing for future needs[35].

Aiming at the future progress of regenerative medicine from ethical and technical aspects, new legislation was introduced in Japan in 2014. Regenerative medicine using tissue stem cells including MSCs is classified as medium risk, while those using iPS or ES cells are classified as high risk.

The dental pulp cell bank should be officially approved under investigation by the regenerative medicine committee, on the premise of acquisition of informed consent and act of protection of personal information. It must fulfill the requirement of Pharmaceuticals and Medical Devices Agency (PMDA). In Japan, two dental banks are currently under operation, including the Dental Cell Bank™ of The Nippon Dental University which started in 2016 after obtaining permission to operate as a cell processing facility (CPF) from the Japanese Government. Extracted teeth from registered dental clinics are stored in preservation solution and are sent to the Dental Cell Bank™. Dental pulp cells are propagated in culture and stored.

The merits of using dental pulp cells for regenerative medicines, in addition to the general benefits of MSC (Table 1), are follows: the stock cells are obtained when in good health and in a minimally-invasive manner, low cost, and low external radiation exposure because of their confinement in the enamel.

Although some difficulties remain to be overcome in order to achieve successful dental cell bank operations including cost barriers, restrictions imposed by current preservation technology, and the limitation of operation method, the promising capabilities of SHEDs and other tooth-derived sources are supporting the development of the dental pulp cell banking system.

APPLICATION OF HEPATOCYTES FROM DENTAL PULP CELL BANK TO TAILOR-MADE MEDICINE TO MEET FUTURE NEEDS

Fulminant hepatic failure is an aggressive disease that has an extremely poor prognosis. Liver transplantation may be the only medical method to rescue most patients. Because the keys of the success of liver transplantation depend on the acquisition of donor liver, medical bridging therapies while waiting for the appearance of donor liver are critical for life-saving. Extra-corporeal circulation using bioartificial livers that have hepatocytes in the column to reduce toxic substances such as ammonia that can affect consciousness levels have been developed[36]. Although primary hepatocytes or highly differentiated hepatoma cell lines were used for the column, significant survival elongation using bioartificial livers have not yet been confirmed. Recently, development of artificial livers using iPS cells has been reported. Takebe *et al*[37] cultured iPS cells with vascular endothelial cells and macrophages, and succeeded in the creation of an organ bud or mini-liver. Because DP-MSC-derived hepatocytes had high proliferation activity, express hepatocyte nuclear factor 4a (HNF-4a), and metabolize ammonia to urea (unpublished observation), they are expected to bear the function of bioartificial livers.

On the other hand, the liver is an organ involved in drug metabolism. In the era of new medicine development, there will certainly be a need to predict the adverse effects of drugs in a tailor-made manner. Because drug metabolism varies from individual to individual, it is necessary to use self-hepatocytes to screen for drug toxicity. Hepatocytes derived from dental pulp cell bank may suit this purpose. Cells lose differentiation levels in two dimension or spheroid cultures where diffusion of materials is the only way to feed the cells. Recently, microenvironments of the cells in tissues have been

simulated in the organ-on-a-chip system that reproduces the dynamic environments of real tissues[38]. Nakao *et al*[39] reported liver-on-a-chip that reproduced the cord-like structures of hepatocytes with bile -duct canalicular formations. Vernetti *et al*[40], succeeded in drug toxicity screening with construction of a culture system that had hepatocytes, vascular endothelial cells, immune and stellate cells. Hepatocytes derived from a dental pulp cell bank may be a good cellular source of such a three-dimensional culture system and may enable people who deposit their teeth to meet the future use of hepatocytes, such as in drug screening, while providing an allo-auto cellular source to cure liver diseases (Figure 1).

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