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EDITORIAL

Regenerative medicine using dental pulp stem cells for liver diseases

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Abstract

Acute liver failure is a refractory disease and its prognosis, if not treated using liver transplantation, is extremely poor. It is a good candidate for regenerative medicine, where stem cell-based therapies play a central role. Mesenchymal stem cells (MSCs) are known to differentiate into multiple cell lineages including hepatocytes. Autologous cell transplant without any foreign gene induction is feasible using MSCs, thereby avoiding possible risks of tumorigenesis and immune rejection. Dental pulp also contains an MSC population that differentiates into hepatocytes. A point worthy of special mention is that dental pulp can be obtained from deciduous teeth during childhood and can be subsequently harvested when necessary after deposition in a tooth bank. MSCs have not only a regenerative capacity but also act in an anti-inflammatory manner *via* paracrine mechanisms. Promising efficacies and difficulties with the use of MSC derived from teeth are summarized in this review.

Key words: Dental pulp; Mesenchymal stem cell; Regenerative medicine; Liver disease; Tooth bank

Core tip: Dental pulp contains a mesenchymal stem cell population that has a similar gene expression pattern to that of the bone marrow and differentiates into cells of multi-cellular lineages. There have been several reports showing hepatic differentiation of this stem cell population in the presence of specific growth factors in serum-free culture medium. Their self-renewal and high proliferative capacities verify their stem-cell character and suggest that they are a promising cell source of regenerative medicine for refractory liver diseases. Currently, these cells are in the stage of animal studies to prove the efficacy and safety of dental pulp stem cell-

based medicine for liver diseases.

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INTRODUCTION

The liver has a remarkable regenerative capacity in both physiological and pathological situations. However, this regenerative capacity is still insufficient to compensate for the functions of end-stage liver cirrhosis and fulminant hepatic failure, and prognosis of these diseases is extremely poor. Orthotropic liver transplantation is currently the only way to save patients in these critical situations; however, chronic donor shortage, post-operative severe complications, cost-effectiveness, and ethical issues always limit its application[1].

There has always been a high expectancy that the remarkable regenerative capacities of stem cells will be used to treat intractable diseases and improve their prognosis. Currently, regenerative medicine using induced pluripotent stem cells (iPSCs) is attracting the most clinical attention[2]. The first clinical trial of a retina pigment epithelium cell transplant derived from iPSCs for the treatment of age-related macular degeneration was conducted in Japan in 2014[3]. In another study, Takebe *et al*[4] succeeded in creating artificial liver buds using iPS cells.

However, because iPS cells do not exist in nature and are obtained artificially by inducing foreign genes or proteins, unexpected tumorigenesis and immunological rejections are always clinical concerns when using these cells. It has also been suggested that the induced genes might affect the expression of cellular genes[5].

Mesenchymal stem cells (MSCs) are pluripotent cells that differentiate into variety of cell types. In particular, MSC from dental pulp (MSC-DP) has attracted clinical attention because they are easily obtained from extracted wisdom teeth or even from the deciduous teeth of children. This is in contrast to the collection of bone marrow MSCs for which a painful medical procedure is needed. MSC-DP have a marked proliferative capacity and can be passaged scores of times without losing their stem cell properties[6]. Thus, this cellular resource is considered to be a promising source of cells for regenerative medicine that could be applicable to a variety of impaired organs, including diseased livers[7]. In this review, recent experimental development of MSC-DP therapy for liver diseases is summarized.

MSCS AND THEIR APPLICATION TO REGENERATIVE MEDICINE

The recent developments in regenerative medicine using stem cells have been outstanding. Application of autologous tissue stem cells to treat injured organs is the ideal method of regenerative medicine because, unlike the use of iPS cells, these methods do not require the induction of foreign genes or proteins, which possibly decreases the risk of tumorigenesis. Additionally, it does not involve critical ethical issues such as those encountered with embryonic stem cell (ES cell) therapies. Organ stem cells reside in almost all tissues and have the abilities of self-renewal and multi-lineage differentiation. They include hematopoietic stem cells (HSCs), MSC, neural stem cells, and skin and gut stem cells. These cells are relatively easily obtained by low-invasive procedures such as bone marrow aspiration, by using operative material or even by re-using discarded tissues such as umbilical cord or teeth. In particular, it is expected that the tooth bank will be used as a practical source of cells for regenerative medicine in the near future[8,9].

MSCs have been most extensively studied using bone-marrow stem cells. Pittenger *et al*[10] reported the multilineage potential of monolayer-cultured MSCs derived from bone marrow. MSCs exist in the stromal cells of bone marrow where they represent only 0.001%-0.1% of the total population of nucleated cells[10,11]. They are adherent cells that show high proliferative potential in the presence of bFGF and hence, a homogeneous clone can be obtained by cell cloning[12]. MSCs were shown to differentiate into multiple lineages such as neurons, muscle, skin cells, and hepatocytes. They are positive for CD44, CD73, CD90, CD105, CD271, and STRO-1 and negative for hematopoietic cell markers such as CD34 and CD45[12].

Although hepatocytes have previously been considered to differentiate from endodermal cells, they have now been found to differentiate even from non-endodermal cells. Research involving the differentiation of MSCs into hepatocytes has mainly used MSCs from bone marrow. Lagasse *et al*[13] transplanted HSCs into a model mouse of tyrosinemia and found that they engrafted in liver and improved of liver function. Krause *et al*[14] showed that a single HSC clone not only reconstituted bone marrow but also differentiated into lung, skin, liver, and gut cells. Schwartz *et al*[15] reported the culture of MSC derived from bone marrow in the presence of FGF-4 and HGF and showed that these MSCs developed the capacity to produce albumin and urea, which indicated the presence of progenitor cells of hepatocytes.

Subsequently, it was shown that such features were not limited to MSCs from bone marrow; MSCs from adipose tissue and placenta were also shown to differentiate into hepatocytes[16,17].

LIVER REGENERATION STUDIES USING STEM CELLS

Terai *et al*[18] administered bone marrow cells derived

from GFP-labelled mice to carbon tetrachloride-induced liver injury model mice and found that these bone-marrow cells engrafted in the injured liver, resulting in the absorption of fibrosis and the improvement of prognosis. Based on these experimental results, clinical trials of autologous bone marrow cells for end-stage liver cirrhosis patients started in November, 2011, in Japan[19]. Many other clinical trials of regenerative treatment for end-stage liver cirrhosis using HSCs have also been reported. Pai *et al*[20] reported the improvement in the liver function of alcoholic cirrhotic patients who were administered CD34-positive cells that were induced by G-CSF treatment.

While general anesthesia is needed to obtain a sufficient number of bone marrow cells for treatment, MSCs can be expanded from a small volume of bone marrow fluid because of their high proliferative capacity under simple culture conditions. MSCs have also been applied to the treatment of ischemic heart disease, cerebral infarction, and neurological or autoimmune disorders *via* the production of growth factors and cytokines, which stimulate the repair of injured tissues[21]. Several clinical trials using MSCs for decompensated liver cirrhosis have also been reported since 2007[22]. However, not all of these clinical trials showed efficacy of this treatment[23].

MSCS DERIVED FROM DENTAL PULP

Dental pulp is surrounded by dentin and is located in an enclosed space that connects with the external space through the apical foramen. Dental pulp has a strong capacity for repairing worn-down or carious teeth by producing dentin. Bone tissues are occasionally produced in the healing process of dental pulp. Dental pulp polyps are formed as granuloma tissues when squamous epithelium is formed that covers nerves that are exposed due to dental caries. These phenomena suggest that dental pulp has the capacity to develop into cells of multiple lineages, forming both bone and squamous epithelium.

Dental pulp is a mesenchymal tissue derived from dental papillae. Dental pulp cells have been reported to express bone markers similar to those expressed by osteoblasts[24]. Gronthos *et al*[25] were the first to report the presence of MSC-DP. They showed that dental pulp cells from adult teeth became clonogenic and rapidly proliferated under culture conditions. The cells formed densely calcified nodules under osteo-inductive culture conditions and also formed dentin/pulp-like complexes when conjugated with hydroxyapatite/tricalcium phosphate, which revealed their stem cell characters. They further showed that MSC-DP also displayed a multi-lineage capacity, differentiating into adipocytes and neural cells, which seemed to be irrelevant to tooth function[26]. The gene expression profiles of MSC-DP were shown to be similar to those of osteoblasts or bone marrow stromal stem cells[27].

Because MSC-DP are positive for STRO-1 and most STRO-1-positive MSC-DP are positive for pericyte-associated antigen, MSC-DP are considered to have originated from perivascular cell populations[28]. Although the first MSCs were obtained from adult teeth, MSCs have also been derived from human exfoliated deciduous teeth (SHED), periodontal ligament[29], apical papillae of immature permanent teeth[30], or periapical cysts[31]. In particular, SHED have a distinct capacity by virtue of higher proliferative potential than adult teeth with a multi-lineage differentiation capacity[32]. SHED are easily applicable to a cell banking source such as that used for umbilical cord because of the low ethical hurdles and the fact that the concept of the re-use of discarded tissues is easily acceptable to the general public[33]. Recent studies have shown that MSC-DP might induce immune regulatory mechanism of the host and have indicated the possibility of the application of MSC-DP to clinical practice[34,35].

DIFFERENTIATION OF DP-MSC INTO HEPATOCYTES AND REGENERATIVE MEDICINE

The above information suggested that MSC-DP may be a promising cell resource for regenerative medicine for various organs. Ishkitiev *et al*[36] were the first to report that MSC-DP differentiated into hepatocyte-like cells. They cultured SHED in the presence of HGF, dexamethasone, and oncostatin, and found that they transformed into a hepatocyte-like shape and produced IGF-1 and albumin. They also identified the presence of urea in the culture medium, which suggested the possibility that the urea cycle was functioning in these cells. They purified CD117-positive cells from MSC-DP using magnetic cell sorting and succeeded in inducing hepatic differentiation of these cells in serum-free medium with a high efficacy[37]. Since these cells still maintained stem cell markers such as embryonic (nanog), mesenchymal (CD44H), endodermal (nestin, CK19), ectodermal (p63), and mesodermal (SPARC, alkaline phosphatase, STRO-1) even after 70 passages, they may be applicable as a solid cell resource for regenerative medicine that can be obtained in sufficient cell numbers[37]. The efficacy of MSC-DP in differentiating into hepatocytes was as high as that of bone marrow-MSC[38]. When incubated with hydrogen sulphide, MSC-DP acquired more characteristic features of hepatocytes, showing a higher urea metabolism and glycogen synthesis[39]. Hepatocytes that were differentiated from MSC-DP repopulated the cirrhotic livers of rats and were shown to improve liver function and survival of the animals[7]. Yamaza *et al*[40] reported that transplanted SHED ameliorated liver dysfunction and improved inflammation and fibrosis in carbon tetrachloride - induced liver fibrosis model mice.

TOOTH BANK FOR REGENERATIVE MEDICINE

There is emerging interest in using MSC-DP as a clinical resource of cells for regenerative medicine for myocardial infarction[41], rheumatoid arthritis[42], diabetes mellitus[43], Parkinsonism[44], Alzheimer diseases[45], and refractory muscle diseases[46]. SHED derived from primary teeth are immature and have higher potential stem cell characteristics than adult-derived cells in terms of their proliferative capacity[32]. The benefits of SHED cell banking are as follows:

Minimum immunological rejection since the cells are derived from an autologous source: Cell banking is possible at a very young age, long before illness manifests; the cells are obtained painlessly; low cost compared to umbilical cord cells; low ethical hurdles.

SHED are suitable for obtaining cells of multiple lineages such as cells of connective tissue, teeth, nerve, liver, and pancreas, while umbilical cord MSCs are suitable for obtaining HSCs.

A large number of SHED cells can be obtained because of their high proliferative capacity and cloning of cells derived from a single MSC clone is possible.

MSC-DP is covered by enamel tissue and has little exposure to external radiation, which is related to a lowered risk of carcinogenesis of the graft.

A tooth bank for the storage of MSC-DP from deciduous teeth has been established by public-private collaboration[33]. However, many practical problems remain to be solved such as cost-benefit issues based on the balance of the risk of suffering diseases with the cost of long-term storage and harvest of cells, safety, and ethical concerns.

FUTURE DIRECTIONS

It has been reported that engrafted MSC do not actually transdifferentiate into specific cell lineages, but instead fuse with host cells using their plasticity[47,48]. MSCs are less potent than ES cells. In addition, MSC-DP, similar to MSCs in general, not only contribute to tissue repair as an actual source of regeneration, but they also elaborate immunomodulatory or anti-inflammatory functions that may affect the local environment of transplanted tissues[34,35,49]. There have been studies that showed that the conditioned medium of MSC cultures exerted immunomodulatory effects through paracrine mechanisms, that were mediated by extracellular vesicles such as exosomes produced by these cultured cells[50-52]. Moreover, MSCs were reported to improve the levels of liver injury and attenuate fibrosis in animal models[53,54]. These tissue repair effects of MSC-DP that occur through MSC-DP mediated paracrine mechanisms should be elucidated in parallel with studies to clarify the capacity of MSC-DP-derived hepatocytes as a substantial source of repopulating hepatocytes for fatal liver diseases.

Takebe *et al*[4] recently proposed the concept of "organ buds" instead of organ and cell transplantation. They obtained a liver bud by co-culturing hepatocytes derived from iPS cells with MSCs and vascular endothelial cells. That study indicated the possibility that MSC might not be a central player in regenerative medicine, providing a substantial hepatic function, but might instead be a supporting player in the development of regenerating organ. Based on this concept, these researchers recently showed that MSCs contributed the formation of an organ bud by providing MSC-dependent cytoskeletal contraction force[55].

These effects of MSC-DP on promotion of damaged-liver tissue repair through a paracrine mechanism or by an auxiliary force, should be elucidated in future studies.

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