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A review on properties of stem cells

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***Abstract*---**Stem cells are multipotent progenitors constituting a small proportion of the bone marrow and are present in both adult and fetal tissues including adipose tissue, umbilical cord blood, amniotic fluid, and fetal lung. They were first characterized by Friedenstein and colleagues more than 30 years ago and were described as fibroblast-like cells with the property of adhering to plastic when cultured. This property can be used to purify these cells and enables them to expand several-fold in vitro without losing their differentiation capacity. They can differentiate into both mesenchymal and non-mesenchymal cell lineages such as adipocytes, osteoblasts, chondrocytes, tenocytes, skeletal myocytes, neurons, and cells of the visceral mesoderm, both in vitro and in vivo.

***Keywords*---**Antibodies, Mesenchymal Stem Cells, Multipotent, Progenitors.

Introduction

Because a specific marker for human stem cells has not been identified, it is difficult to recognize these cells. The International Society for Cellular Therapy has recommended the following minimum criteria for defining multi-potent human MSCs: (i) adherence to plastic under standard culture conditions; (ii)

positive for expression of CD105, CD73, and CD90 and negative for expression of the hematopoietic cell surface markers CD34, CD45, CD11a, CD19 or CD79a, CD14 or CD11b and histocompatibility locus antigen (HLA)-DR; and (iii) under a specific stimulus, differentiation into osteocytes, adipocytes, and chondrocytes in vitro.[1]

Because of their unique regenerative potential, MSCs exhibit potential for use in tissue regeneration and repair for conditions such as cardiac anomalies or injury, bone disorders, and metabolic diseases. One of the most intriguing features of MSCs is that they escape immune recognition and can inhibit immune responses. In this review, we discuss the in vivo and in vitro immunomodulatory properties of MSCs, the possible mechanisms underlying the expression of these properties, and the potential clinical use of MSCs in vivo as modulators of immune responses.[2]

MSCs modulate T cell proliferation and function

Numerous studies have demonstrated that MSCs can suppress the T lymphocyte proliferation induced by alloantigens, mitogens, and anti-CD3 and anti-CD28 antibodies in vitro in humans, baboons, and mice. MSCs have a similar effect on memory and naive T cells, as well as CD4+ and CD8+ T cells, of a murine model. Also, this suppressive effect did not require major histocompatibility complex (MHC) restriction and could also be mediated by allogeneic MSCs. This effect may be attributed to the inhibition of cell division, which is evidenced by the accumulation of cells in the G0/G1 phase of the cell cycle. At the molecular level, cyclin D2 expression is down-regulated, whereas p27 expression is up-regulated; this may explain why T cell proliferation, rather than activation, and interferon (IFN)-g production are affected byMSCs. Inhibition of T cell proliferation by MSCs appears to be mediated by both cell–cell interaction and release of soluble factors such as IFN-g and interleukin (IL)-1b. Some studies have indicated that soluble factors are essential for enhancing the suppressive effect of human MSCs, while the effect of rodent MSCs is mediated by cell–cell contact. Transforming growth factor (TGF)-b1, hepatocyte growth factor (HGF), indoleamine 2,3-dioxygenase (IDO) and prostaglandin E2(PGE2) represent MSC-derived molecules that are believed to have immunomodulatory activity on T cell responses. Neutralizing antibodies against TGF-b and HGF can restore the MSC-induced suppression of T cell proliferation. Treatment with IFN-g causes MSCs to express the protein IDO and exhibit the functional activity of IDO, which in turn degrades essential tryptophan and results in kynurenine synthesis and thereby suppresses lymphocyte proliferation. Co-culturing T cells with MSCs resulted in elevated levels of PGE2, and treatment with inhibitors of PGE2 production mitigated the MSC-mediated immune modulation; however, the mechanism underlying the immunosuppressive effect of PGE2 is poorly understood. The production of nitric oxide (NO) by MSCs has also been implicated as a potential mechanism by which MSCs inhibit T cell proliferation. NO inhibits the proliferation of T cells by suppressing the phosphorylation of signal transducer and activator of transcription-5 (STAT5), a transcription factor crucial for T cell activation and proliferation.[3] The secretion of human leukocyte antigen-G5 (HLA-G5) by MSCs is reported to be essential for the following effects of MSCs: suppression of T cell and NK cell function, the shift of the allogeneic T cell response to a T helper type 2

(Th2) cytokine profile and induction of CD4+ CD25highforkhead box P3 (FoxP3+) regulatory T cells (Tregs). MSCs do not express MHC class II and co-stimulatory molecules such as CD80, CD86, or CD40, and it is believed that T cell activity may result in anergy, which is reflected as immune tolerance. Le Blanc and co-workers reported that when MSCs are treated with IFN-g, which is up-regulated in inflammation, they express MHC class II. In an experimental arthritis model, MSCs decreased antigen-specific Th1/Th17 cell expansion and decreased the production of cytokines released by Th1/Th17 cells, such as IFN-g and IL-17, and caused the Th2 cells to increase production of IL-4 and IL-10 in lymph node joints [36]. T cell inhibition by MSCs is not due to the induction of apoptosis, but by the inhibition of cell division and probably by the production of soluble factors. However, a recent study reported that MSCs could induce apoptosis in activated T cells [CD3(+) and bromodeoxyuridine (BrdU)(+)], but not in the resting T cells [CD3(+) and BrdU(-)]; this leads to marked attenuation of delayed-type hypersensitivity (DTH) response in vivo by inducing NO production. Moreover, MSCs can inhibit the cytotoxic effects of antigen primed cytotoxic T cells (CTLs) by suppressing the proliferation of CTLs, rather than by direct inhibition of cytolytic activity. A recent study showed that the negative co-stimulatory molecule B7-H4 was involved in the immunosuppressive effect of MSCs on T cell activation and proliferation via induction of cell cycle arrest and inhibition of the nuclear translocation of nuclear factor (NF)-kappa B. Some studies revealed that the absence of T cell response in the presence of MSCs was transient and could be restored after the removal of MSCs; however, others reported that T cell tolerance was induced by MSCs in murine models. Although some of the mechanisms underlying the immunosuppressive effects of MSCs on T cells have been elucidated previously, the molecular mechanisms underlying this effect remain controversial. It is believed that the mechanisms underlying the suppressive effect of MSCs may differ by species. Ren and colleagues demonstrated that mouse MSCs and human MSCs utilize different effector molecules in suppressing immune reactions. Immunosuppression by human- or monkey-derived MSCs is mediated by IDO, whereas mouseMSCs exert their effect via NO under the same culture conditions. Immunosuppression by human MSCs was not intrinsic, but was induced by inflammatory cytokines and was chemokine-dependent, as it is in the mouse. The degree of the suppressive effect depends on the concentration of the MSCs. The high MSC/lymphocyte ratio is associated with the inhibitory effect of MSCs, while a low MSC/ lymphocyte ratio is often accompanied by enhanced proliferation. In this setting, MSCs may act synergistically with HLA-DR antigens upon mitogenic stimulation. However, the exact mechanisms need to be investigated further.[4]

MSCs modulate B cell proliferation and function

In murine models, MSCs have been shown to inhibit the proliferation of B cells when stimulated with anti-CD40L and IL-4 or pokeweed mitogen. Similarly, in humans, MSCs have also been shown to inhibit the proliferation of B cells activated with anti-immunoglobulin (Ig) antibodies, anti-CD40L antibody, and cytokines (IL-2 and IL-4). Also, the B cell functions of antibody production and secretion of the chemokine receptors CXCR4, CXCR5, and CCR7, which are responsible for chemotaxis to CXCL12 and CXCL13, were impaired by MSCs; however, the expression of B cell co-stimulatory molecules and cytokine

production were not affected by MSCs. MSCs inhibited the proliferation of B cells only in the presence of IFN-g, which probably implies that IFN-g causes MSCs to produce IDO, which in turn suppressed the proliferation of effector cells through the tryptophan pathway. The nature of the mechanism involved in this inhibitory effect of MSCs has not yet been elucidated completely.

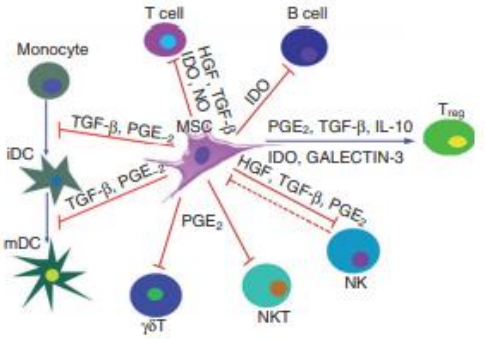

Figure 1: Effect of Stem cells on Immunocytes

Thus far, the major mechanism of B cell suppression by MSCs is attributed partly to the physical contact between MSCs and B cells and in part to the soluble factors released by MSCs; this leads to the blocking of B cell proliferation in the G0/G1 phase of the cell cycle with no apoptosis, unlike the case with T cells. Deng et al. reported that allogeneic MSCs inhibited the activation, proliferation, and IgG secretion of B cells in BXSB mouse models of human systemic lupus erythematosus (SLE).[5] Also, MSCs enhanced the CD40 expression and CD40 ligand ectopic hyperexpression on the B cells of BXSB mice (Figure 1).

MSCs modulate the functions of natural killer cells

It is seen that MSCs suppress NK cell proliferation and IFN-g production driven by IL-2 or IL-15, but only partially inhibit the proliferation of activated NK cells. Rasmusson et al. reported that MSCs did not inhibit the lysis of freshly isolated NK cells and that MSCs were not lysed by allogeneic NK cells. Conversely, Krampera et al. reported that NK cells cultured for 4–5 days with IL-2 in the presence of MSCs showed reduced cytolytic potential against K562 target cells and that this suppressive effect might be attributed to the IFN-g produced by NK cells. Exposure to IFN-g did not ablate MSCinduced inhibition of T cell proliferation but triggered the expression of HGF and TGF-b1 secreted by MSCs at concentrations that suppressed also responsiveness. Furthermore, a study indicated that MSCs suppressed NK cell cytotoxicity against HLA class I-positive cells more effectively than HLA class I-negative cells. Low HLA class I expression makes allogeneic as well as syngeneic MSCs more susceptible to lysis by activated NK cells. Incubation of MSCs with IFN-g decreased their susceptibility to NK cell-mediated lysis because of the up-regulation of HLA class I expression on MSCs. The mechanisms underlying the immunosuppressive effects of MSCs are still unclear and several different, sometimes contradictory, theories have been proposed. Soluble factors such as TGF-b1 and PGE2 are believed to play a role in the MSC-mediated suppression of NK cell proliferation.[6] The physiological

interactions between MSC and NK cells would be the reciprocal effects exerted by the two cell types, in particular the ability of activated NK cells to kill MSC. Some studies showed that IL-2-activated NK cells can effectively lyse MSCs because MSCs express ligands (ULBP, PVR, and nectin-2) that are recognized by activated NK receptors (NKp30, NKG2D, and DNAM-1), which in turn trigger NK cell alloreactivity. Recently, Prigione et al. found that the inhibitory effect of MSCs on the proliferation of invariant NK T (iNK T, Va24+ Vb11+) and gdT (Vd2+) cells in the peripheral blood is mediated by releasing PGE2, rather than IDO and TGF-b1; however, cytokine production and cytotoxic activity of the cells were only partially affected by MSCs.[7] Vd2+ cells also serve as professional antigen-presenting cells for naive CD4+ T cell response, and MSCs did not inhibit antigen processing/presentation by activated Vd2+ T cells to CD4+ T cells (Figure 2).

Interaction between MSCs and dendritic cells (DCs)

MSCs impaired the differentiation of monocytes or CD34+ hematopoietic stem cells into dendritic cells (DCs) by inhibiting the response of the former to maturation signals, reducing the expression of co-stimulatory molecules, and hampering the ability of the former to stimulate naive T cell proliferation and IL-12 secretion. Also, this inhibitory effect might be mediated via soluble factors and may be dose-dependent. Spaggiari et al. showed that MSCs strongly inhibited the maturation and functioning of monocyte-derived DCs by interfering selectively with the generation of immature via inhibitory mediator of MSC-derived PGE2, but not IL-6. However, the mechanism underlying the up-regulation of PGE2 in monocyte–MSC co-cultures remains unclear. Ramasamy et al. reported that the cell cycle in DCs was arrested in the G0/G1 phase upon interaction with MSCs. A recent study reported that MSCs isolated from human adipose tissue were more potent immunomodulators for the differentiation of human DCs than MSCs derived from the bone marrow.[8]

Tregs induced by MSCs

MSCs may also modulate immune responses via the induction of Tregs. MSC can induce the generation of CD4+ CD25+ cells displaying a regulatory phenotype (FoxP3+) in mitogen-stimulated cultures of peripheral blood mononuclear cells, although the functional properties of these cells have not yet been elucidated. For example, depletion of CD4+ CD25+ Tregs did not affect the inhibition of T cell proliferation by MSCs. However, a recent study reported that MSCs could induce kidney allograft tolerance by inducing the generation of CD4+ CD25+ FoxP3+ Tregs in vivo. Additionally, MSCs have been reported to induce the formation of CD8+ Tregs that are responsible for the inhibition of allogeneic lymphocyte proliferation. In a recent study, Ghannam et al. found that under inflammatory conditions, MSCs prevented the differentiation of naive CD4+ T cells into Th17 cells and inhibited the function of Th17 cells in vitro by secreting PGE2. Moreover, MSCs could induce the Treg phenotype in Th17 cells, which can inhibit the proliferative responses of activated CD4+ T cells in vitro. Tipnis et al. reported that umbilical cord-derived MSCs (UC-MSCs) constitutively express B7-H1, which is a negative regulator of T cell activation. Also, B7-H1 expression was increased and IDO expression was induced in UC-MSCs after IFN-g treatment. Furthermore, UC-MSCs inhibited the differentiation and maturation of monocyte-

derived DCs and augmented the generation of Tregs. These immunosuppressive effects of UC-MSCs are mediated largely by cell–cell contact. The induction of Tregs by MSCs involves not only involves direct contact between MSCs and CD4+ cells, but also the secretion of soluble factors such as PGE2 and TGF-b1. Human gingiva-derived MSCs (GMSCs) can induce IL-10, IDO, inducible NO synthase (iNOS), and cyclooxygenase 2 (COX-2) and thereby serve as immunomodulatory components in the treatment of experimental inflammatory diseases.[7]

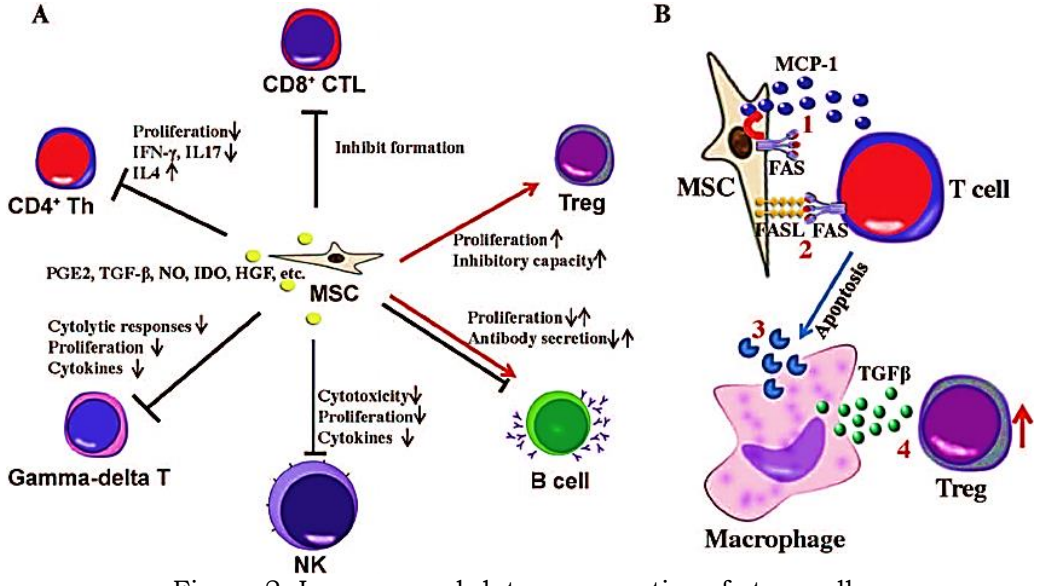

Figure 2: Immunomodulatory properties of stem cells

Clinical application of MSCs for immune-mediated diseases

Over the past 3 decades, numerous efforts have been made to explore the therapeutic applicability of MSCs. In pathological conditions, MSCs migrate preferentially into lymphoid organs, allografts, injured and/or inflammatory tissue sites after systemic transfusion, where MSCs interact with the activated immune cells and modulate their function. The in vivo immunomodulatory properties of MSCs were first described in a baboon model of skin transplantation. The therapeutic potential of MSCs in immunomodulation is being explored currently in several Phase I, II, and III clinical trials, many of which have recently been completed or are underway, as reported in the clinical trials website of the United States sponsored by the National Institutes of Health (http://clinicaltrials.gov).[8] Because of their immunosuppressive properties, MSCs are believed to play a role in the maintenance of peripheral tolerance and the induction of transplantation tolerance, and they are considered potential candidates in cellular therapy for graft-versus-host disease (GVHD) and autoimmune diseases and in protecting solid-organ grafts from being rejected. Recently, Le Blanc et al. reported that MSCs obtained from HLA-identical sibling donors, haploidentical donors and third-party HLA-mismatched donors infused in 55 patients with steroid-refractory acute GVHD elicited a response in more than half the patients; the study showed that MSCs exerted their therapeutic effect in the case of both HLAmatched and HLA-unmatched donors. However, for GVHD,

the use of MSCs is a double-edged sword, because the prevention of GVHD was associated with a high incidence of leukemia relapse, which is the result of the non-specific immunosuppressive effect of MSCs on graft-versus-leukemia. Liang et al. reported that allogeneic MSC transplantation in patients with refractory SLE resulted in the amelioration of disease activity, improvement in the levels of serological markers, and stabilization of renal function without the occurrence of serious adverse events.[9]

For solid organ transplantation, the beneficial effect of MSC-based immunosuppressive therapy is debatable. The application of calcineurin inhibitors (CNIs) would abrogate the immunosuppressive effect of MSC therapy. Also, CNIs cause renal failure, hypertension, and hyperglycemia and increase the risk of malignancy; therefore, efforts have been made to minimize the use of CNIs treatment in organ transplantation protocols. Consequently, it may be worthwhile to compare the usefulness of combining CNI treatment and MSC therapy in organ transplantation. Conversely, non-selective immunosuppression would have affected patients' antiviral immunity equally.

Stem cells are unspecialized cells that have the property of differentiating into specific specialized cell types. They also have a self-renewal property. Stem cells are identified in various human adult tissues including adipose tissue, skin, blood, bone marrow, hair follicles, and dental pulp (1). Stem cell research has undergone rapid development owing to its usefulness in regenerative therapies for various neurological and genetic disorders. Previous studies have shown that the dental pulp tissue can also be used to derive mesenchymal stem cells (MSCs) when tissue is grown in culture (2). These MSCs can differentiate into several cell types. It is proposed that dental pulp stem cells (DPSCs) can develop Induced Pluripotent Stem Cells (iPSCs) which can be used for therapies of various diseases.[10]

Odontogeny of dental pulp stem cells:

The development of teeth involves continuous interactions between the oral ectodermal epithelial cells that give rise to Enamel, Dental Papilla, and follicles and the mesenchymal cells that give rise to Dentin, Pulp, Cementum, and Periodontal Ligament.

Five subtypes of mesenchymal stem cells have been described; these are dental pulp stem cells (DPSC), periodontal ligament stem cells (PDLSC), stem cells from apical papilla (SCAP), dental follicle stem cells (DFSC), and gingival mesenchymal stem cells (GMSC). Teeth are therefore an excellent source of stem cells for therapeutic procedures in the future and can be easily harvested following tooth extraction or natural shedding of deciduous teeth.

Dental Pulp Stem Cells (DPSC) was first isolated from third molars. These cells are found to have high clonogenicity and formed highly calcified colonies. DPSC has also been confirmed as mesenchymal stem cells by demonstrating their ability to form adipocytes, osteoblasts, odontoblasts, chondrocytes, neural ectodermal cells, and myoblasts. From a developmental viewpoint, the dental pulp is derived from ectomesenchyme arising in the periphery of the neural tube

which migrates to the oral region where the cells differentiate into mesenchymal cells (Figure 3).

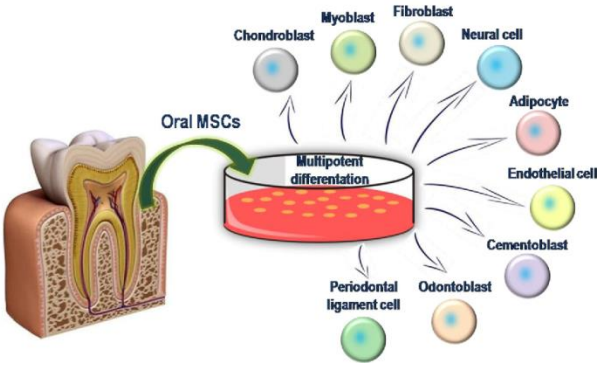

Figure 3: Human dental pulp stem cells

In normal physiology, the dental pulp cells maintain and repair the periodontal tissue and respond to damage. Deep caries results in the dental pulp cells migrating to the damaged area and the creation of odontoblasts and dentine in an attempt to repair the damaged tooth. These observations led to the proposal that dental pulp stem cells could be active during reparative dentinogenesis.

Laboratory processing of dental pulp stem cells

There are many approaches to dental pulp stem cell collection and processing, the key is to ensure the quality and safety of the end product. The most common use done is described below: once exfoliated, or extracted, teeth are sent to the processing laboratory within 72 hours of exfoliation or extraction. The tooth is transported in sterile phosphate-buffered saline with calcium and magnesium inside a validated and monitored collection kit which keeps the tooth between 4 and 26 °C. On arrival at the laboratory, the tooth is opened in a Grade A cleanroom environment using a medical circular saw, the pulp exposed to 10% DMSO, and the whole tooth is then frozen in a controlled rate freezer and stored in the vapor phase of liquid nitrogen. When the dental pulp stem cells are required then the tooth is thawed rapidly in a 37 °C water bath and then processed using either one of two standard techniques: the explant method and the enzymatic digestion method. In the explant method, the dental pulp is dissected from the tooth in a Grade A cleanroom environment and the cells are then grown in vitro from these tissue fragments. In the enzymatic method, the dental pulp tissue is digested in collagenase and dispase, in a Grade A cleanroom environment, and the resultant cells are then grown in vitro. Both of these processing technologies yield good numbers of viable DPSC and future research will no doubt optimize these technologies to develop a gold standard.[10]

Immunocytochemical identification of dental pulp mesenchymal stem cells

The International Society for Cellular Therapy (ISCT) state that mesenchymal stem cells express the following surface antigens: CD105 (endoglin: a putative novel endothelial cell specification gene), CD73 (5' ectonucleotidase: an enzyme which metabolizes nucleotides to nucleosides), and CD90/Thy-1

(glycosylphosphatidylinositol-anchored glycoprotein) and a negative for CD11b, CD14, CD19, CD34, CD45, CD79a surface antigens, and HLA-DR. These are assessed by the use of flow cytometry. Other workers propose that mesenchymal stem cells express STRO-1 (stromal precursor antigen 1), VCAM-1 (vascular cell adhesion molecule 1), SH2 (Src homology 2), SH3/SH4, CD271, GD2 (ganglioside 2), and SSEA-4 (stage-specific embryonic antigen-4). Some workers even suggest that DPSC may have a different immunophenotype to those traditionally thought to be MSC. This variation in surface antigen expression may reflect the proliferative potential of DPSC. STRO-1 positive DPSC has been shown to have odontoosteogenic characteristics whereas CD34+, CD117+, and CD45- DPSC have a greater capacity for cell renewal and osteogenic differentiation. Other authors have referred to DPSC MSC expressing CD29+, CD44+, and CD73+. The expression of transcription factor genes Oct-4 and Nanog have also been used to identify DPSC MSC. The identification of DPSC mesenchymal stem cells is a developing science that will no doubt be refined in the future to clearly describe each subpopulation of DPSC. The fact that DPSC has low expression of Class II HLA-DR (MHC) molecules means that they are immunologically privileged and it may be possible to transplant these cells from one person to another without the need for tissue matching. This raises the possibility of a public DPSC bank, perhaps in collaboration with key dental hospitals, providing DPSC to anyone in need. Such donated DPSC could be extremely useful when using artificial bone to provide new bone for dental implants where the artificial bone could be used along with donated DPSC to enhance bone formation.[11]

Sources and characteristics of dental pulp stem cells (DPSC) and stem cells from human exfoliated deciduous teeth (SHED)

DPSC has been isolated from exfoliated deciduous teeth (SHED: stem cells from human exfoliated deciduous teeth), from permanent secondary dentition, from teeth extracted due to impaction or periodontitis, and from inflamed pulp tissue. SHED cells have been shown to have a high proliferative rate and are capable of producing osteoblasts, adipocytes, neuronal cells, and odontoblasts. Some workers suggest that SHED cells have a greater proliferative capacity than DPSC obtained from adult third molars, incisors, or supernumerary teeth on the basis that SHED cells represent a more immature type of stem cell. It has been shown that the properties of DPSC are directly related to the physical age of the tooth from which they are obtained. It is interesting to note that in terms of cell cycle 69.8% of SHED cells were found to be in the S and G2 stage, but only 56% of the DPSC were in those phases indicating the increased proliferative capacity in SHED cells. The surface antigen expression of SHED cells also differs from that seen in DPSC. This is reflected in the fact that proliferation-related and extracellular matrix (ECM) formation genes, for example, genes encoding transforming growth factor (TGF) and fibroblast growth factor 2 (FGF), are expressed in SHED cells. Genes coding for collagen I and collagen III and pluripotency markers, such as Pou5f1, Oct3/Oct4, Sox2, and Nanog are also expressed higher in SHED cells. The expression of Nestin (a marker of neuroepithelial stem cells) is reduced in SHED resulting in their reduced ability to form neurospheres in comparison to DPSC. Permanent teeth impacted third molars and supernumerary teeth are an excellent source of DPSC which have the following mesenchymal stem cell surface antigens: CD90+, CD146+, CD105+,

and CD45−; and also express Oct4 and Nanog but lower expression than that seen in SHED cells. Both DPSC and SHED cells are an excellent source of mesenchymal stem cells for regenerative medicine procedures, also, SHED cells have recently been proposed as potential immunomodulators in the treatment of autoimmune encephalomyelitis and other autoimmune pathologies of the central nervous system.[12]

Clinical applications of DPSC in regenerative medicine
Bone formation

In a recent study, few researchers attempted cell-based therapy for bone regeneration using stem cells from deciduous teeth, dental pulp, and bone marrow. The results obtained from their study demonstrated that stem cells from deciduous teeth, dental pulp, and bone marrow with platelet-rich plasma can form bone. Bone formation with Deciduous and adult Tooth Stem Cells may possess the ability to generate a graft between a child and parent. This preclinical study could lay the path for stem cell therapy in orthopedics and oral and maxillofacial reconstruction for clinical application. In studies involving human beings Dental Pulp Stem Cells have been transplanted along with some sort of framework or porous biomaterial to permit the cells to mature to enable osteogenesis. The dental pulp stem cells have the capability of repairing skin lesions, ischemic tissue, bone damage, periodontal tissue, liver, skeletal muscle tissue, neuronal tissue, and blood vessels. For these reasons, dental pulp seems like a reliable and easy to obtain a source of mesenchymal stem cells which can be used in regenerative medicine (Figure 4).

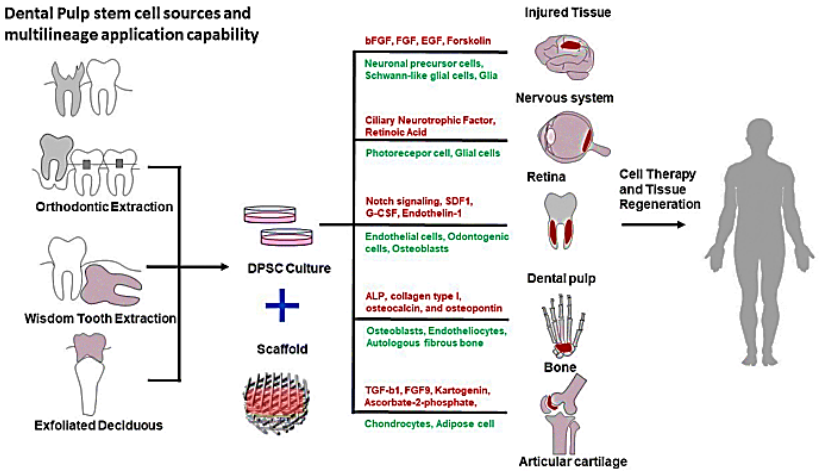

Figure 4: Human dental pulp stem cells regenerative capacity

Tooth reconstruction

Rebirth of entire new teeth from scratch for the substitution of missing or lost teeth is the most ambitious goal in dentistry and necessitates the use and recombination of dental pulp stem cells. Dental Mesenchymal Stem Cells can form all mesenchymal components of the tooth organ and the surrounding tissues such as dentin, cementum, and alveolar bone, while Dental enamel Stem

Cells are crucial for the generation of enamel. Since most of the dental epithelial cell populations disappear shortly after tooth eruption and Dental Stem Cells are limited in human adult teeth, current knowledge on Dental Stem Cells has been obtained mainly from rodents, where they contribute to the renewal of the enamel and other tooth structures in the continuously growing incisors. Although encouraging, this methodology also needs further research and investigation, as effective protocols for the differentiation of human Dental Stem Cells from inducible pluripotent stem cells are not available yet.

Pulp and dentin regeneration

To produce functional pulp for clinical application, several concerns must be considered: first of all the regenerated pulp tissue must have sufficient vascularity, even though the blood supply occurs only from the apical foramen, second of all newly differentiated odontoblasts should form new dentin on the existing dentin wall of the root canal and finally, new dentin must be produced by the differentiated odontoblasts from the stem cells on the existing dentin. Regeneration of dentin relies on having pulp vitality, however, regeneration of pulp tissue has been challenging as the tissue is covered by dentin without a guaranteed blood supply except for the apical foramen at the root end. With the dawn of modern tissue engineering concepts and the unearthing of dental stem cells, regeneration of pulp and dentin is still under testing.

Liver regeneration

Stem Cell therapy as a treatment for liver disease requires operative stem cell-derived hepatocyte cells. Dental Pulp Stem Cells have been differentiated to produce Hepatocyte-Like Cells (HLCs) with hepatocyte-like functions that have been acquired, such as glycogen storage and urea production.

Neurology

In a recent study, Dental pulp cells were transplanted into collagen gels and infused within a silicon tube, which was positioned within a 7 mm gap in the buccal branch of the rat facial nerve. The dental pulp cells formed blood vessels and myelinating tissue and contributed to the promotion of normal nerve regeneration. Considering the results, dental pulp stem cells could be used to treat nerve injury and neurological disorders. DPSC has been used as a graft into hemisected spinal cords in animal models resulting in an increased number of surviving motor neurons illustrating the promise of this technology in future clinical trials.[9,13]

Ophthalmology

DPSC has also been shown to promote neurogenesis when co-cultured with rat retinal cells, this is thought to be related to the ability of DPSC to induce the expression of neurotrophins (neurotrophins are a family of proteins that induce the survival, development, and function of neurons). The ultimate application in ophthalmology is to develop cell-based regenerative technology which could repair or replace a damaged retina and therefore restore sight, This raises the possibility

that DPSC could differentiate into functional photoreceptors which could, in turn, be used to restore sight in patients suffering from a damaged retina.
Stem cells hold great promise to solve a variety of health problems, diseases, and disorders both inside the oral cavity and outside it. Although there are a variety of sources from which stem cells can be isolated, the dental pulp is a very reliable and easy to obtain source. Dental pulp stem cells can be collected, processed, and cryogenically stored each time a deciduous tooth is exfoliated or a healthy adult tooth is extracted.[14] In recent days the applications of the dental pulp stem cells have escalated, due to this the amount of study on their regenerative property has also increased. Nevertheless, it is still a fairly recent discovery and therefore requires further research on its biological capability, regenerative property, etc until it is introduced into everyday medical practices.

Conclusion

In the future, well-designed preclinical trials should be conducted to explore the clinical applicability of MSCs. Thereafter, randomized trials comparing treatment with infusions of MSCs and conventional drug-based therapies should be undertaken to confirm the therapeutic potential of these cells, as it is important not to overestimate the potential therapeutic effects of MSCs. Information gathered over such studies would help to develop innovative cell-based therapies for the treatment of diseases characterized by exaggerated immune responses.

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