Stem Cells – A Scope For Regenerative Medicine

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Abstract

Stem cells are unspecialized cells that can regenerate themselves and give birth to specialized cells (toti-potent cells, pleuri-potent cells, multipotent cells and progenitor cells). Stem cells have the unique ability to differentiate into a variety of cells. When a stem cell divides, each new cell has the potential to either remain a stem cell or become another type of cell with a more specialized function - such as a muscle cell, a red blood cell or a nerve cell. In present day scenario stem cells have proven to be the mainstay of regenerative medicine. Recently dental tissues such as periodontal ligament, dental papilla and dental follicles have been identified as easily accessible sources of undifferentiated cells. This review article focuses on dental stem cells and their role in combating diseases.

INTRODUCTION

When an organ is degenerating, the cells are breaking down and losing their ability to function, regenerative therapies serve as amazing modern medical advancement that goes straight to the source of the problem ie damage at the cellular level. Stem cells are unspecialized cells that can regenerate themselves and give birth to specialized cells (totipotent cells ,pleuripotent cells, multipotent cells and progenitor cells). Stem cells have the unique ability to differentiate into a variety of cells. When a stem cell divides, each new cell has the potential to either remain a stem cell or become another type of cell with a more specialized function - such as a muscle cell, a red blood cell or a nerve cell. Stem cell therapy is a procedure by which damaged, diseased, or malfunctioning cells anywhere in the body are replaced by introducing healthy stem cells to that area of the body. Stem cell therapy is a promising treatment for all kinds of degenerative diseases because of the stem cells' regenerative abilities. Thereby offering the possibility of a renewable source of replacement cells and tissues - to treat diseases such as Parkinson's & Alzheimer's diseases, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis and rheumatoid arthritis

Given the right environment, stem cells can give rise to a number of tissues that constitute different organs. Stem cells also serve as a kind of repair system for the body, by dividing repeatedly and then differentiating and replenishing cells within the body. These unique characteristics make stem cells a breakthrough in regenerative medicine. Various Stem cells of dental origin include –bone marrow stem cells, dental pulp stem cells, periodontal ligament stem cells, cementoblast like cells, SHED (Stem cells of human exfoliated and deciduous teeth)and wisdom teeth stem cells. Human tissues harbor stem cells or precursor ,which are responsible for tissue development and repair. Recently dental tissues such as periodontal ligament, dental papilla or dental follicle have been identified as easily accessible sources of undifferentiated cells. Dental precursor cells (stem cells) are attractive for novel approaches such as treating periodontitis, dental caries or to improve dental pulp healing and for regeneration of craniofacial tissues and teeth.

HISTORICAL BACKGROUND

The history of stem cell research had a benign, embryonic beginning in the mid 1800's with the discovery that some cells could generate other cells. In the early 1900's real stem cells were discovered and it was found that some cells generate blood cells.

The history of stem cell research includes work with both animal and human stem cells. Stem cells can be classified into three broad categories, based on their ability to differentiate. Totipotent stem cells are found only in early embryos. Each cell can form a complete organism (e.g., identical twins). Pluripotent stem cells exist in the undifferentiated inner cell mass of the blastocyst and can form any of the over 200 different cell types found in the body. Multipotent stem cells are derived from fetal tissue, cord blood, and adult stem cells. Although their ability to differentiate is more limited than pluripotent stem cells, they

already have a track record of success in cell-based therapies.

A prominent application of stem cell research has been bone marrow transplants using adult stem cells. In the early 1900's physicians administered bone marrow by mouth to patients with anemia and leukemia. Although such therapy was unsuccessful, laboratory experiments eventually demonstrated that mice with defective marrow could be restored to health with infusions into the blood stream of marrow taken from other mice. This caused physicians to speculate whether it was feasible to transplant bone marrow from one human to another (allogeneic transplant). Among early attempts to do this were several transplants carried out in France following a radiation accident in the late 1950's. Performing marrow transplants in humans was not attempted on a larger scale until a French medical researcher made a critical medical discovery about the human immune system. In 1958 Jean Dausset identified the first of many human histocompatibility antigens. These proteins, found on the surface of most cells in the body, are called human leukocyte antigens, or HLA antigens. These HLA antigens give the body's immune system the ability to determine what belongs in the body and what does not belong. Whenever the body does not recognize the series of antigens on the cell walls, it creates antibodies and other substances to destroy the cell.

It was not until the 1960's that physicians knew enough about HLA compatibility to perform transplants between siblings who were not identical twins. The 1990's saw rapid expansion and success of the bone marrow program with more than 16,000 transplants to date for the treatment of immunodeficiencies and leukemia. Adult stem cells also have shown great promise in other areas. These cells have shown the potential to form many different kinds of cell types and tissues, including functional hepatocyte-like (liver) cells. Such cells might be useful in repairing organs ravaged by diseases.
In 1998, James Thompson (University of Wisconsin - Madison) isolated cells from the inner cell mass of early embryos, and developed the first embryonic stem cell lines. In the same year, John Gearhart (Johns Hopkins University) derived germ cells from cells in fetal gonadal tissue (primordial germ cells). Pluripotent stem cell “lines” were developed from both sources. Ongoing researches are now focused on transplanting stem cells of non-self origin.

HUMAN BODY - RESERVOIR OF STEM CELLS

a) Bone Marrow - Of all adult tissues, the bone marrow is an extremely rich source of somatic stem cells. Drawn from the spongy tissue, found in the center of bones, the main function of these stem cells is to make blood cells that circulate in our bodies and fight infection. In stem cell therapy, bone marrow was the earliest source of stem cells due to its rich supply.[1]

b) Umbilical Cord - The other rich source of stem cells is the blood left over in the umbilical cord and placenta of a newborn child. Till recently, this blood was (and continues to be) often discarded as medical waste. However, umbilical cord blood is known to be a rich source of stem cells thus more parents are choosing to bank these cells for its potential future use. Exciting new research on a new type of stem cell called “mesenchymal stem cell” has now enhanced the scope of diseases that can potentially be treated with stem cell therapy. .[2]

c) Embryonic (Or Fetal) Germ Cells (EGCS)

These pluripotent stem cells are derived from primordial germ cells, which give rise to the gametes (sperm & eggs) in adults. They are found in a 5 to 9 week old embryo/fetus in the area that is destined to become either the testicles or the ovaries. Deriving stem cells through this process is controversial since the embryo or the fetuses from which the germ cells are obtained are destroyed. The embryo or the fetuses, even though not fully formed, are considered 'human' in many cultures and hence their destruction leads to ethical dilemmas. Such a dilemma exists even if the embryonic germ cells are derived from a fetus that is obtained as a result of a miscarriage or abortion.[1,2]

d) Menstrual Blood-

Menstrual fluid contains self-renewing stem cells. A woman's menstrual blood includes tissue shed from the endometrial lining of the uterus which potentially contains hundreds of millions of rich and abundant stem cells which could possibly serve as a source for a wide range of regenerative therapies. These menstrual stem cells are unique because they have many properties and characteristics similar to both bone marrow and embryonic stem cells; they multiply rapidly and can differentiate into many other types of stem cells such as neural, cardiac, bone, fat, cartilage and possibly others; demonstrating great promise for future use in clinical regenerative medical therapies.[10]

e) Peripheral Blood-

Stem cells, in limited quantities, can also be found in the peripheral blood circulation. Peripheral blood stem cells are easier to obtain than bone marrow as they can be drawn from blood. Some studies have shown that these stem cells engraft faster than bone marrow stem cells.[1,2,10]

STEM CELLS IN DENTISTRY

There are two major categories of stem cells, which are discussed for dentistry: (1) Embryonic stem cells; (2) Somatic or adult stem cells. Isolation and use of human embryonic stem cells is ethically controversial. Somatic stem cells have a limitation in their potentials of differentiation. However, somatic or adult stem cells are a better option for dentistry, as these cells are easily accessible, and their use does not bring up ethical concerns. Embryonic (Or Fetal) Germ Cells (EGCS) are pluripotent stem cells derived from primordial germ cells, which give rise to the gametes (sperm & eggs) in adults. They are found in a 5 to 9 week old embryo/fetus in the area that is destined to become either the testicles or the ovaries. Deriving stem cells through this process is controversial since the embryo or the fetuses from which the germ cells are obtained are destroyed.

The main differentiation potential of dental stem cells lies within the formation of dentin or periodontium-associated tissues, whether these cells are derived from pulp, PDL or dental follicle. It is obvious that dental ectomesenchymal stem cells can be classified in two different groups with respect to their major differentiation potential. The first group is associated with the dental pulp, consisting of DPSCs, SHEDs and SCAPs; the second group contains PDL stem cells and dental follicle progenitor cells and is related to the periodontium. periodontal ligament stem cells (PDLSCs) and dental follicle progenitor cells (DFPCs).

These post-natal populations have mesenchymal- stem-cell-like (MSC) qualities, including the capacity for self-renewal and multilineage differentiation potential. MSCs derived from bone marrow (BMMSCs) are capable of giving rise to various lineages of cells, such as osteogenic, chondrogenic, adipogenic, myogenic, and neurogenic cells. The dental-tissue-derived stem cells are isolated from specialized tissue with potent capacities to differentiate into odontogenic cells. Among stem cells of mesenchymal origin, BMMSCs or BM-derived stromal stem cells (BMSSCs) are the most studied stromal stem cell populations (Caplan, 1991; Prockop, 1997; Pittenger et al., 1999).[20]

DENTAL MSCS

Dental tissues are specialized tissues that do not undergo continuous remodeling as shown in bony tissue therefore, dental-tissue derived stem/progenitor cells may be more committed or restricted in their differentiation potency in comparison with BMMSCs. Additionally, dental mesenchyme is termed ‘ectomesenchyme’ due to its earlier interaction with the neural crest. From this perspective, ectomesenchyme-derived dental stem cells may possess different characteristics akin to those of neural crest cells.[5,6]

DENTAL PULP STEM CELLS (DPSCS)

One important feature of pulp cells is their odontoblastic differentiation potential. Human pulp cells can be induced in vitro to differentiate into cells of odontoblastic phenotype, characterized by polarized cell bodies and accumulation of mineralized nodules (Tsukamoto et al., 1992; About et al., 2000; Couble et al., 2000). In addition to their dentinogenic potential, subpopulations of hDPSCs also possess adipogenic and neurogenic differentiation capacities by exhibiting adipocyte- and neuronal-like cell morphologies and expressing respective gene markers (Gronthos et al., 2002). More recently, DPSCs were also found to undergo osteogenic, chondrogenic and myogenic differentiation in vitro (summarized in Table 1) (Laino et al., 2005; Zhang et al., 2006; d’Aquino et al., 2007).[9,11,12,13]

PDL STEM CELLS

A further class of dental ectomesenchymal stem cells are PDL stem cells, which were isolated from the root surface of extracted teeth. These cells could be isolated as plastic-adherent, colony-forming cells, but display a low potential for osteogenic differentiation under in vitro conditions. PDL stem cells differentiate into cells or tissues very similar to the periodontium[27]. Moreover, PDL stem cells transplanted into immunocompromised mice and rats demonstrated the capacity for tissue regeneration and periodontal repair. Recently, PDL stem cells were also isolated from sheep and pigs[22]. It has been shown that a functional periodontium could successfully be established using PDL stem cells .

DENTAL FOLLICLE PRECURSOR CELLS

The human dental follicle is a tissue of the tooth germ, which can easily be isolated after wisdom tooth extraction. Likewise, bovine dental follicles, cells of the human dental sac develop into the mature periodontium consisting of alveolar bone, the PDL and cementum . The dental follicle contains ectomesenchymal cells which are derived from the neural crest. DFPCs, like BMSCs, are plastic adherent and

colony forming cells, and they can differentiate into osteoblast like cells under in vitro conditions. Similar to PDL stem cells, DFPCs can also differentiate, form robust connective tissues and produce clusters of mineralized tissue.[25]

STEM CELLS FROM APICAL PAPILLA

A new class of dental stem cells was isolated from the dental papilla of wisdom teeth or incisors of 4 month old mini-pigs (SCAP, stem cells from apical papilla). The dental papilla is an embryonic-like tissue that becomes dental pulp during maturation and formation of the crown. Therefore, SCAPs can only be isolated at a certain stage of tooth development. However, SCAPs have a greater capacity for dentin regeneration than DPSCs because the dental papilla contains a higher number of adult stem cells compared to the mature dental pulp.[23,27]

STEM CELLS OF HUMAN EXFOLIATED DECIDUOUS TEETH (SHED

Furthermore, ectomesenchymal stem cells of human exfoliated deciduous teeth (SHEDs) were isolated from the dental pulp of exfoliated incisors[24].These cells could be cultivated either as fibroblast-like, adherent cells, or like neural stem cells as neurospheres. SHEDs are capable of differentiation into odontoblast, adipocytes and neural cells . They induced bone formation and produced dentin under in vivo conditions; and they were able to survive and migrate in murine brain after transplantation into immunocompromised animals[24].

Various stem cells along with their differentiation potential have been studied by J. Huang, S. Gronthos et al,which is tabulated below

Figure 1

Cell Type	*vitro* Analysis (Multipotentiality)	*In vivo* Analysis (Ectopic tissue formation)
DPSCs	Osteo/Dentinogenic,Adipogenic Chondrogenic,Myogenic,Neurogenic	Dentin-pulp-like complex Odontoblast-like cells,Bone-like tissue
SHED	Dentinogenic,Adipogenic,Chondrogenic Myogenic,Neurogenic,Osteo-inductive	Dentin-pulp-like tissue,Odontoblast-like cells No dentin-pulp complex formation Bone formation
SCAP	Dentinogenic,Adipogenic,Chondrogenic Myogenic,Neurogenic	Dentin-pulp-like complex Odontoblast-like cells
PDLSCs	Osteo/Cementogenic,Adipogenic Chondrogenic,Myogenic Neurogenic	Cementum-like PDL-like formation
DFPCs	Cementogenic,Odontogenic Adipogenic-Chondrogenic,Myogenic Neurogenic	PDL-like formation Cementum matrix formation

(J. Huang, S. Gronthos et al)

Stem cells can be employed for varied functions in dentistry eg : for development of new tooth, management of periodontal diseases, dentofacial orthopaedics corrective methods, Geno-dental interrelations.[11,12,13]

Stem cells of dental origin can be used for regeneration of entire tooth ,for cleft palate treatment ,regeneration of nerve cells in parkinsons disease etc. Management of periodontal diseases employ use of stem cells. Studies indicate use of periodontium injectible gel(mixture of ex-vivo cultured osteoblast like cells differentiated from mesenchymal stem cells and scaffold to be useful in the effective treatment of new periodontal diseases through guided tissue and bone regeneration techniques.[3,4]

Moreover geno-dental interrelations, stem cells in cervical loop of incisors of mouse shows that their maintenance and differentiation depends on genetic signal pathways(FGF – fibroblast growth factor and ectoplastin) that are used to correct defects caused by ectodermal dysplasia.[15,16,17]

STEM CELLS IN SUCCESSFULLY TREATING HUMAN DISEASES

Scientists have been able to do experiments with human embryonic stem cells (hESC) only since 1998, when a group led by Dr. James Thomson at the University of Wisconsin developed a technique to isolate and grow the cells. Although hESCs are thought to offer potential cures and therapies for many devastating diseases, research using them

is still in its early stages.

The NIH funded its first basic research study on hESCs in 2002. Since that time, biotechnology companies have built upon those basic foundations to begin developing stem cell-based human therapies. In July, 2010, the FDA notified the biotechnology company Geron that could begin enrolling patients in the first clinical trial of a hESC-derived therapy. This trial has been designed to test the safety of using hESCs to achieve restoration of spinal cord function: oligodendrocyte progenitor cells derived from hESCs will be injected directly into the lesion site of the patient's injured spinal cord. [11,15,19]

Stem cell therapy promises to treat diseases such as Parkinson's & Alzheimer's diseases, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis and rheumatoid arthritis. In dental application regeneration of dental pulp is right around the corner. Very soon periodontal ligament repair and regeneration will be possible preventing loss of tooth. Stem cell therapy will also aid in implant treatment for bone defects or compromised residual ridges. Dentistry is about to change with the possible implications of stem cell therapy.

FUTURE SCOPE AND PERSPECTIVE

There will be continuous advancement in stem cell research and dental cells applied to clinical therapies. U.S.A and Japan are major countries carrying out these researches. In Japan scientists have been able to form entire tooth from stem cells in mice. Stem cells are being applied to dental implants and they have shown ligamentous attachment between implant surface and bone. Regeneration or regrowing pulp tissue is all set to reform the specialty of endodontics within next five years. Dental stem cells and other stem cells from craniofacial origin develop from material that is created during development of nervous system. These stem cells can therefore help in regeneration of cells of orofacial origin.

Mesenchymal stem cells ,found in dental pulp these cells have been helpful in treating diseases such as Parkinson’s disease, heart disease, diabetes, management of spinal cord and brain injuries,cranial bone repair and root formation.

The research is relatively new therefore it is yet not been proven that stem cells can be used for other people different from donors .however in future these cells can be matched without the risk of rejection.[14,18]

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