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Review Article

Adult Stem Cell- A Newer Dimension in Dentistry

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Abstract

A stem cell is essentially a 'blank' cell, capable of becoming another more differential cell type in the body, such as a skin cell, a muscle cell, or a nerve cell. Microscopic in size, stem cells are big news in medical science circle because they can be used to replace or even heal damaged tissues and cells in the body. It can play a leading role as it bears a unique property of differentiating into a required cell. Thus it can be a bank of cells which can be stimulated or triggered to get differentiated into any morphologically developed cell and function as so. This review, outlines the sources and the tremendous power these adult stem cell possess and ways of harnessing it for the benefit of humankind.

Keywords: Adult Stem Cell; Dimension

Introduction

A stem cell is essentially a 'blank' cell, capable of becoming another more differential cell type in the body, such as a skin cell, a muscle cell, or a nerve cell. Microscopic in size, stem cells are big news in medical science circle because they can be used to replace or even heal damaged tissues and cells in the body.

When called into action following an injury, a stem cell self-renews- undergoes cell division and gives rise to one daughter stem cell and one progenitor cell. A progenitor cell is an intermediate cell type formed before it achieves a fully differentiating along a particular cellular developmental pathway of stem cells:

Stem cell > Stem cell + Progenitor cell > Differentiated cell.

Based on their origin, stem cells are categorized either as embryonic stem cells (ESCs) or as postnatal stem cells/somatic stem cells/ adult stem cells (ASCs) Characteristics:

1. **Totipotency:** Generate all types of cells including germ cells (ESCs)
2. **Pluripotency:** Generate all types of cells except cells of the embryonic membrane.
3. **Multipotency:** Differentiate into more than one mature cell (MSC)
4. **Self renewal:** Divide without differentiation and create everlasting supply.
5. **Plasticity:** MSCs have plasticity and can undergo differentiation. The trigger for plasticity is stress or tissue injury which upregulates the stem cells and releases chemo-attractants and growth factors.

Among the types of differentiation are:

1. **Direct differentiation:** a specific type of cell in a special niche developed in a multistep unidirectional pathway (e.g. MSCs differentiating into osteoblasts/ fibroblasts)
2. **Transdifferentiation:** direct conversion of one cell type to another different cell type (e.g. blood cells into brain cells and vice versa)
3. **Dedifferentiation:** a unipotent stem cell becoming a multipotent one.

There are two types of stem cells:

1. Embryonic stem cells.
2. Adult stem cells.

Embryonic stem cells

These are derived from embryos that develop from eggs fertilised *in-vitro* in fertilisation clinics donated for research purpose with informed consent of the donors. The embryos from which human embryonic stem cells are derived are four to five days old and in 'blastocyst stage'. This blastocyst includes three structures: the trophoblast which is the layer of the cells that surrounds the blastocyst, the blastocoele, a hollow cavity inside the blastocyst, and the inner cell mass, which is a group of approximately 30 cells at one end of the blastocoele. Human embryonic stem cells are isolated by transferring the inner cell mass (ICM) into culture dish containing appropriate culture medium [1].

Embryonic cells are characterised as being pluripotent, that is, they have the potential to develop into many tissues in the body. As the embryo develops, embryonic stem cells begin down a path of differentiation and maturity, at which time they lose this potential.

Adult stem cells

An adult stem cells are defined as the undifferentiated cells that are found in a differentiated adult tissue, residing in a specific area of each tissue (called a 'stem cell niche') where they remain quiescent in the body until they are activated by epigenetic and/or environmental factors, such as mechanical forces, disease or trauma. The primary role of the adult stem cell is to maintain and repair the tissues in which they are primarily found. They are also called as 'Somatic stem cells' [2].

Adult stem cells have been identified in many organs and tissues, including brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin, teeth, heart, gut, liver, ovarian epithelium and testis. Sources of adult stem cells include the umbilical cord, amniotic fluid, bone marrow, adipose tissue, brain and teeth [3,4].

Adult stem cells come from

1. Umbilical cord blood stem cells (UCBSCs): Adult type stem cells can be served from various pregnancy related tissues. The greatest disadvantage of UCBSCs is that there is only one opportunity to harvest them from the umbilical cord at the time of birth. Similarly, amniotic stem cells can be sourced only from amniotic fluid and are therefore subject to time constraints [5].

2. Amniotic fluid-derived stem cells (AFSCs): These can be isolated from aspirated of amniocentesis during genetic screening. An increasing number of studies have demonstrated that AFSCs have the capacity for remarkable proliferation and differentiation into multiple lineages [3-9].

3. Bone-marrow derived stem cells (BMSCs) [10-11].

4. Adipose derived stem cells (ASCs) [12-17].

5. Dental stem cells (DSCs): restored in 2003, Dr. Songtao Shi at the National Institues of Health in Maryland discovered dental stem cells in his daughter's baby teeth (Shostak, 2006) [18].

6. Body tissues: In adults and children, from the moment we are born, stem cells are present within virtually all tissues and organ systems.

7. Cadavers: Neural stem cells have been removed from specific areas in postmortem human brains as late as 20 hours following death.

Cell- based therapy

Adult stem cells have been used in pilot studies as potential cell based therapy for various diseases. The following stem cell characteristics make them good candidates for cell-based therapy [19].

1. Potential to be harvested from patients

2. High capacity of cell proliferation in culture.

3. Ease of manipulation to replace existing nonfunctional genes via gene splicing method.

4. Ability to migrate to host target tissues (homing)

5. Ability to integrate into host tissues and interact with the surrounding tissues.

Types of stem cells	May differentiate into
Embryonic	Any type of cells
Amniotic fluid derived stem cells	Cartilage cells, Fat cells, Bone cells, Muscle cells, Endothelial cells, Neuron-like cells, Liver cells
Umbilical cord derived stem cells	Liver cells, skeletal muscle cells, Neural tissue, Immune cells
Bone marrow derived stem cells	Cartilage cells, Muscle cells, Fat cells, Neuron-like cells, Pancreatic islet beta cells
Tooth derived stem cells	Neural cells lineages, Bone cells, Cartilage cells, Muscle cells, Fat cells, Pancreatic islet beta cells

Table 1: Types of Stem cells.

Normal differentiation pathways of adult stem cells

In a living animal, adult stem cells are available to divide, when needed, and can give rise to mature cell types that have characteristic shapes and specialised structures and functions of a particular tissue. The following are examples of differentiation pathways of adult stem cells (Figure 2) that have been demonstrated *in vitro* or *in vivo.*

Hematopoietic stem cells give rise to all the types of blood cells: red blood cells, B lymphocytes, T lymphocytes, natural killer cells, neutrophils, basophils, eosinophils, monocytes and macrophages.

Mesenchymal stem cells give rise to a variety of cell types: bone cells (osteocytes), cartilage cells (chondrocytes), fat cells (adipocytes) and other kinds of connective tissue cells such as those in tendons.

Neural stem cells in the brain give rise to three major cell types: nerve cells (neuron), and two categories of non-neuronal cells -astroctyes and oligodendrocytes.

Epithelial stem cells in the lining of the digestive tract occur in deep crypts and give rise to several cell types: absorptive cells, goblet cells, panted cells and enteroendocrine cells.

Skin stem cells occur in the basal layer of the epidermis and at the base of hair follicles. The epidermal stem cells give rise to keratinocytes, which migrate to the surface of the skin and form a protective layer. The follicular stem cells can give rise to both the hair follicle and to the epidermis.

Potential applications of adult stem cells in dentistry.

The regenerative potential of adult stem cells obtained from various sources including dental tissues have been of interest for clinicians over the past years and most research is directed toward achieving the following:

Human dental stem/progenitor cells collectively termed dental stem cells (DSCs) that have been isolated and characterised include dental pulp stem cells, stem cells from exfoliated deciduous teeth, stem cells from apical papilla, periodontal ligament stem cells and dental follicle progenitor cells. Common characteristics of these cell populations are the capacity for self-renewal and the ability to differentiate into multiple lineages. *In vitro* and animal studies have shown that DSCs can differentiate into osseous, odontogenic, adipose, endothelial and neural like tissues. The potential of dental MSC for tooth regeneration and repair has been extensively studied in the last years.

Stem cells from human exfoliated deciduous teeth (SHED). The isolation of post-natal stem cells from an easily accessible source is indispensable for tissue engineering and clinical applications. Recent findings demonstrated the isolation of mesenchymal progenitors from the pulp of human deciduous incisors (Miura., *et al.* 2003). These cells were named SHED (Stem cells from Human Exfoliated Deciduous teeth) and exhibited a high plasticity since they could differentiate into neurons, adipocytes, osteoblasts, and odontoblasts (Miura., *et al.* 2003). *In vivo* SHED cells can induce bone or dentin formation [20].

Adult dental pulp stem cells (DPSC). After a dental injury, dental pulp is involved in a process called regenerative dentinogenesis, where cells elaborate and deposit a new dentin matrix for the repair of the injured site. (Mitsiadis and Rahiotis 2004). It has been shown that adult dental pulp contains precursors capable of forming odontoblasts under appropriate signals. (About., *et al.* 2000; About and Mitsiadis 2001; Alliot-Lichdt., *et al.* 2005; Growths., *et al.* 2000, 2002; Miura., *et al*. 2003; Tecles., *et al.* 2005) [21].

Stem cells from the apical part of the papilla (SCAP): Stem cells from the apical part of the human dental papilla (SCAP) have been isolated and their potential to differentiate into odontoblasts was compared to that of the periodontal ligament stem cells (PDLSC) (Sonoyama., *et al*. 2006). SCAP exhibit a higher proliferative rate and appears more effective than PDLSC for tooth formation. Importantly, SCAP are easily accessible since they can be isolated from human third molars [22].

Stem cells from the dental follicle (DFSC): DFSC have been isolated from follicle of human third molars and express the stem cell markers Notch 1, STRO-1 and nesting (Morsczeck., *et al.* 2005). These cells can be maintained in culture for at least 15 passages. STRO-1 positive DFSC can differentiate into cementoblasts in vitro (Kemoun., *et al*. 2007) and are able to form cementum in vivo (Handa., *et al*. 2002). Immortalised dental follicle cells are able to re-create a new periodontal ligament (PDL) after in vivo implantation (Yokoi., *et al.* 2007) [23-24].

Periodontal ligament stem cells (PDLSCs): The PDL is a specialised tissue located between the cementum and the alveolar bone and has a role in the maintenance and support of the teeth. Its continuous regeneration is thought to involve mesenchymal progenitors arising from the dental follicle. PDL contains STRO-1 positive cells that maintain certain plasticity since they can adopt adipogenic, osteogenic and chondrogenic phenotypes *in vitro* (Gay., *et al.* 2007) [25]. It is thus obvious that PDL itself contain progenitors, which can be activated to self-renew and regenerate other tissues such as cementum and alveolar bone (Seo., *et al.* 2004) [26].

Dental pulp stem cells (DPSCs) represent a kind of adult cell colony which has the potent capacity of self-renewing and multilineage differentiation. The exact origin of DPSCs has not been fully determined and these stem cells seem to be the source of odontoblasts that contribute to the formation of dentin-pulp complex. Recently, achievements obtained from stem cell biology and tooth regeneration has enabled us to contemplate the potential application of DPSCs. Some studies have proved that DPSCs are capable of producing dental tissues in vivo including dentin, pulp and crown like structures. Whereas other investigations have shown that these stem cells can bring about the formation of bone like tissues [27]. Theoretically, a bio-tooth made from autogenous DPSCs should be the best choice for clinical tooth reconstruction.

Isolation approaches of DPSCs

So far, no stable model has been set up to isolate and purify DPSCs of the lack of specific cell surface markers. The identification of DPSCs mainly depends on the biological characteristics, including small cell volume, vigorous proliferative ability, potent clonogenecity, self-renewal and multi-differentiation potential [1,12,14]. Various methods have been developed to isolate stem cells from dental pulp, below are the conventional ones.

- Self - sieved isolation
- Fluorescence Activated Cell Sorting
- Magnetic Activated Cell Sorting
- Stem Cell Colony Cultivation.

Future prospects of stem cells in dentistry

Stem cells derived from all sources hold immense medical promises. Stem cell therapies have virtually unlimited medical and dental applications. Although there is great excitement in scientific community about stem cells and regenerative medicine, it is yet to be known about the clinical applications of stem cells. While there are several barriers that need to be broken down before this novel therapy can be translated from lab to clinics, it is certain that the future is going to be exciting for all of us. Taken together these recent findings clearly indicate that the control of morphogenesis and cyto-differentiation is a challenge that necessitates a thorough understanding of the cellular and molecular events involved in development, repair and regeneration of teeth. We have moved on from the surgical model of care to the medical model and are likely to move onto the biological model of care. The need of the hour is high quality research coupled with collaboration between basic scientist and the clinicians. A team effort engaging the expertise of the molecular biologists, immunologists, biomaterial scientists, cell biologists, matrix biologists and practicing dental surgeons is crucial in attaining the desired goals. Stem cell therapy is no longer science fiction. Recent developments in the technique of stem cell isolation and expansion together with advances in growth factor biology and biodegradable polymer constructs have set a stage for successful tissue engineering of tooth/tooth-related tissues.

Conclusion

A stem cell is essentially a 'blank' cell, capable of becoming another more differential cell type in the body, when called into action following an injury, a stem cell self-renews- undergoes cell division and gives rise to one daughter stem cell and one progenitor cell. Stem cells derived from all sources hold immense medical promises. Stem cell therapies have virtually unlimited medical and dental applications. Stem cell therapy is no longer science fiction. It holds a great potentiality in expanding the horizon known to us. Although there is great excitement in scientific community about stem cells and regenerative medicine, it is yet to be known about the clinical applications of stem cells. A team effort engaging the expertise of the molecular biologists, immunologists, biomaterial scientists, cell biologists, matrix biologists and practicing dental surgeons is crucial in attaining the desired goals. Stem cell therapy holds the possibility of changing the major aspect of medical and dental practice.

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