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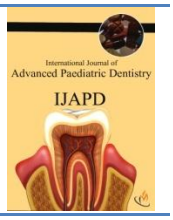

STEM CELLS AND ITS RELEVANCE IN ORAL CAVITY: A REVIEW OF LITERATURE

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ABSTRACT

Stem cells represent only a small percentage of cells that constitute each tissue but are the only cells with self-renewal capacity, ability to grow in vitro, in a laboratory, under a given environment, and to produce different cell types. These properties have led many researchers to come up with regenerative medicine to replace the lost tissue structure, with a mad rush to isolate the stem cells. Oral cavity is found to be one such place to harbor plenty of stem cells with ease of isolation and has attracted lot of clinical and research interest. This short review is to brief the stem cells in general and its relevance in oral cavity.

INTRODUCTION

Stem cells are the precursors of the body tissue. They are defined as immature or undifferentiated cells that are capable of generating daughter cells identical to themselves or of differentiating into diverse cellular phenotypes [1]. By the conventional definition, these cells can renew themselves indefinitely through ‘‘self-renewal’’ and they vary in terms of their location in the body and the type of cells that they can produce [2] and gives rise to more differentiated populations, called the progenitor cells [3].

The story of regeneration goes 100s of years ago in Greek through story of Prometheus, the mortal who stole the secret of fire from Zeus and introduced it to humans. Prometheus was then punished by having his liver plucked out by an eagle daily. His liver regenerated overnight, thus providing the eagle with eternal food and Prometheus with eternal torture. This phenomenon was later recognized in medicine, and it was probably first introduced into scientific literature in the 1800s in several German reports [4]. The evidence of stem cells existence was first detailed during 1960s, in bone marrow [5,6]. Since then numerous discoveries have been made like Embryonic Stem(ES) cells in mouse blastocyst and human embryos, pluripotent cells from human embryonic and foetal gonads [7-9] and ES-like cells, called “induced pluripotent stem (iPS) cells” [10-12].

STEM CELLS:

Stem cells differ from other cells in the body due to their unique properties like; are undifferentiated and unspecialized, have ability of Self-renewal, that is the ability to go through numerous cycles of cell division while maintaining their undifferentiated state, are capable of differentiating into specialized cells of a particular tissue, have the ability to grow in vitro, in a laboratory, under a given environment, [13] possess relatively long

telomeres compared to more differentiated somatic cells, are usually quiescent or proliferate more slowly than their differentiated progeny, have increased longevity, [14] with morphological features like small size, poor differentiation and primitive cytoplasm and they can be serially transplanted [15].

An adult is formed from a single egg cell after fertilization of an ovule by a spermatozoid. Egg fertilization results in creation of totipotent stem cells which will further gives rise to cells with diverse degrees of differentiation potential like pluripotent, multipotent, unipotent and nullipotent [12]. Thus stem cells can be divided into totipotent, pluripotent, multipotent, unipotent and nullipotent cells on the basis of differentiation.

Totipotent stem cells are present in the fertilized egg cell or zygote, and can generate all cell and tissue types present in an organism [7]. Approximately four days after fertilization, these totipotent stem cells undergo several mitotic divisions to form identical cells, and after this point, they tend to lose their high proliferative potential and begin to specialize by becoming pluripotent stem cells, these cells, are the precursor cells of all tissues of embryo, yolk sac, amniotic sac, allantois, and embryonic portion of placenta [12,16]. The totipotency in human zygote is seen until the 8 cells morula stage [17].

Pluripotent cells are stem cells with the ability to differentiate into cells of every lineage in the body. These cells are embryonic stem cells present in the inner cell mass or gonads. Pluripotent stem cells form most of the tissues necessary for the embryo formation, these cells then mature into a more specialized stem cell called progenitor cells or multipotent stem cells [12,18].

Multipotent stem cells can generate a limited number of cell and tissue types, usually dependent on their germ layer of origin [7]. These Stem cells are restricted to one lineage (ectoderm, mesoderm or endoderm). They are committed to generate specific cell groups that have distinct functions, such as haematopoietic stem cells, which produce erythrocytes, white blood cells and platelets. Multipotent cells are needed in the adult organism in order to maintain the number of differentiated cells in constant levels, by replacing the cells that die under normal or stress conditions [19-21]. Furthermore, multipotent stem cells become more specialized and give rise to precursor committed cells or unipotent stem cells, which are able to differentiate into only one cell lineage. The unipotent stem cells function is to act as cell reservoirs for different tissues. Certain unipotent cells, such as adult hepatocytes, may even have long-term repopulating functions. Finally, from unipotent stem cells originate the nullipotent cells which are terminally differentiated and have lost their self-renewal capabilities [12].

Further according to developmental status, stem cells can be classified as embryonic or adult stem cells [22].

Embryonic stem cells or pluripotent cells; harvested from fertilized egg or blastocyst, have an extraordinary ability to form many cell types [18]. In 1981 the first ES cells were isolated from mouse blastocysts [7,23] and in 1998, the first human ES cells were collected from fresh or frozen embryos. Since then, numerous researchers have obtained ESC lines from both mice and humans [8]. The ES cells are considered to be pluripotent cells due their ability to differentiate into cells of every lineage in the body and are present in the inner cell mass or the gonads. Moreover, ES cells can undergo cell divisions without differentiation through symmetrical divisions [18].

The advance in the ESC research has limitation due to involvement of destruction of human embryos which has caused huge religious and ethical problems.[12] To overcome these issues in 2006 the adult cells were genetically reprogrammed to an embryonic stem cell-like state called “induced pluripotent stem” cells (iPSCs), by being forced to express genes and factors important for maintaining the defining properties of embryonic stem cells. They are capable of generating cells characteristic of all three germ layers and may prove to be useful tool for drug development and modeling of diseases and in transplantation medicine [24].

Adult SCs or somatic SCs; are SCs from fully developed tissues and organs. These cells are committed to producing a more restricted repertoire of cells and adult SCs are multipotent, are undifferentiated cells with more limited self renewal and a differentiation potential that is more restricted to cell types of the tissue from where they are found and play a major role in tissue homeostasis and regeneration [17,20,25-31] and most of them have self-renewal capacity throughout the entire lifetime of an organism; in addition, they can give rise to other adult tissue-specific stem cells and precursor cells that can produce mature differentiated cells by asymmetric division [32].

Adult tissue-specific stem cells represent a small percentage of total cellularity and are found deep within organs and tissues, spread diffusely throughout and have restricted ability to proliferate, [6] they are usually quiescent or proliferate more slowly than their differentiated progeny, and they have increased longevity; for this reason, they are exposed to more damaging agents than more differentiated cells over time. Thus, they accumulate mutations that are then transmitted to the rapidly proliferating progeny [14]. They are slow cyclers that normally remain dormant until they receive a stimulating signal when their activity is needed, as during wound healing [33]. They respond to injury by increasing proliferation and by reducing differentiation until the cellular content of the tissue has been restored [34,35]. Some stem cells, such as hematopoietic stem cells, continue relatively rapid division, to maintain the massive number of lymphocytes and red blood cells needed by the body. Other stem cells, such as those in the skin and colon, undergo a slow but constant growth, replenishing the tissue, whereas other tissue stem cells can remain quiescent to become activated when stimulated by tissue damage or

hormone exposure. It becomes obvious then that the proliferation of all the different types of stem cells in the adult requires exquisite control and that aberrant regulation could be hazardous [15]. It is believed that SCs divide extremely rarely in order to preserve the integrity of DNA by minimizing accumulation of mutations by cell division [12].

Normal somatic stem cells may undergo either symmetrical cell division or asymmetrical cell division.[36] The main feature of SCs, self renewal is sustained by the asymmetric divisions in which one SC produces a copy of itself and another more committed transit amplifying cell (TAC), which enters limited rounds of rapid cell division that increase their number, [37] following the differentiation pathway. SCs can also undergo symmetric division and produce either two SCs or two differentiated cells when there is a need to expand the SCs pool or the progenitors pool respectively [17,20,31,38-40]. Further division and differentiation of TA cells follow up into specialized cells that maintain the tissue and finally get slough off from the epithelial surface [40].

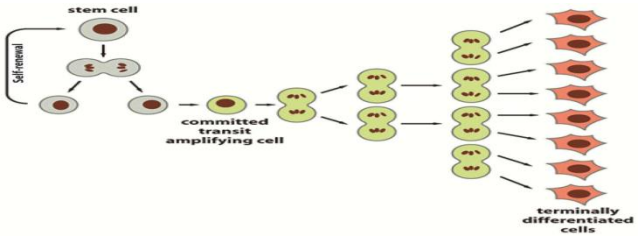

Figure 1: Asymmetrical division of stem cells resulting in one daughter stem cell and a committed transit amplifying cell. Source: ALBERTS B, JOHNSON A, LEWIS J et al [33]

It is not yet clear what underlies the choice between self-renewal and differentiation: in some systems cell-intrinsic mechanisms, such as differential distribution of stem cell factors as the cell divides, are important and in others the position of newly formed cells in relation to local environment factors may determine cell fate [37,41,42]. In normal epithelial tissues, localized areas, referred to as 'stem cell niches' influence the distribution, number and behavior of stem cells and appear to have special abilities to support their survival [43].

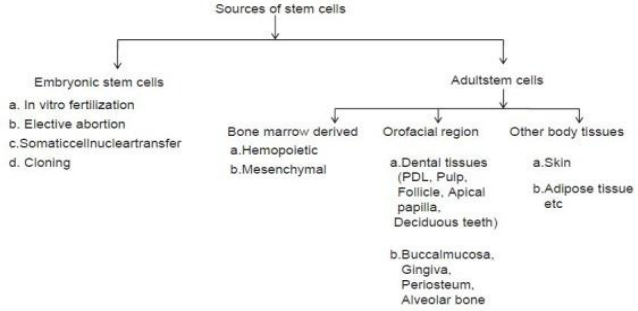

Figure 2: Sources of stem cells. Source: G. N. Suma, Madhu Pruthi Arora, and Manisha Lakhanpal [18]

O RAL CAVITY THE DOMAIN OF STEM CELLS:

The oral cavity offers an opportunity to collect stem cells as it harbor plenty of stem cell resources, can nearly always be easily obtained and in comparatively large quantities. Numerous studies proposes that the cells derived from the oral cavity might be important sources of cellular therapeutics [44].

The oral cavity is endowed with multiple rich sources of stem cells, including the stem cells from mucosal soft tissues, [44-46] Dental pulp stem cells (DPSCs), Stem Cells from Exfoliated Deciduous Teeth (SHED), [47] Periodontal Ligament Stem Cells (PDLSCs), Stem Cells from Apical Papilla (SCAP), [48] Stem cells from third molars [49]. The dental follicle stem cells (DFSCs) and both the epithelial and connective tissue compartments of gingiva [50].

As compared to skin, oral mucosa is well described to be more highly proliferative, and the concept that oral epithelium has a higher turnover rate than that of skin is well accepted. The limited adnexal appendages in oral mucosa suggest that oral mucosa may undergo repair using a more restricted source of progenitors than what has been described in skin [44,51], the basal epithelial layer of oral mucosa has also been shown to contain an epithelial progenitor population [51]. The number of progenitors in oral mucosa is sufficient to easily grow oral keratinocytes in culture, Epithelial sheets produced in vitro from keratinocytes derived from the oral mucosa have been transplanted into patients to successfully replace the damaged corneal epithelium and provide long-term improvement in visual acuity [52].

The lamina propria, which is the connective tissue layer of oral mucosa, harbors a unique stem cell population called Mesenchymal stem cells (MSCs)/ human Oral mesenchymal stem cells (hOMSC), that show extraordinary plasticity with the characteristic of retaining their multilineage potential when expanded into groups of cells designated as colonies. They are able to differentiate into a number of different mesodermal cells such as chondrocytes, adipocytes or osteocytes, can give rise to lineages of embryonic layers [53-55] and have a primitive neural crest-like phenotype [56].

Oral gingival-derived mesenchymal stem cells (GMSCs), derived from gingival connective tissue when systemically infused led to enhanced wound repair in a mouse model which could be via the modulation of the inflammatory response, as GMSCs have been proposed to promote polarization of macrophages toward a regenerative phenotype [57]. GMSCs proliferate faster than BMSCs, display a stable morphology and do not lose their MSC characteristics with extended passaging [58].

DPSCs and SHED possess definitive stem cell properties, such as multi-differentiation and self-renewal capacity, [56,59,60] ability to regenerate the dentin–pulp complex when transplanted into immunocompromised mice. SHED can specifically induce the formation of a bone-like matrix with a lamellar structure by recruiting host cells [56,61]. Periodontal ligament stem cells

(PDLSCs) can regenerate periodontal tissues (cementum, periodontal ligament and alveolar bone) in experimental animal models
[62,63].

DFSCs have the ability to regenerate periodontal tissues [64]. The dental mesenchyme of the third molar tooth germ (tooth germ progenitor cells: TGPCs) at the late bell stage have high proliferation activity and the capability to differentiate in vitro into lineages of the three germ layers including osteoblasts, neural cells and hepatocytes [65,66]. The ‘‘developing’’ dental tissues may provide a better source for immature stem cells than ‘‘developed’’ dental tissues.

Stem cell-based therapies are being investigated for the treatment of many conditions, including neurodegenerative conditions such as Parkinson's disease, cardiovascular disease, liver disease, diabetes, autoimmune diseases and for nerve regeneration. [18,67] In orofacial region stem cells are being used for tooth and periodontal regeneration, temporomandibular joint reconstruction, alveolar bone regeneration, regeneration of salivary gland, repair of cleft lip and palate and craniofacial regeneration, [68] in the treatment of precancerous conditions, oral ulcers, wounds, mucositis, [69] Pemphigus vulgaris, Oral submucous fibrosis, Oral lichen planus and Oral carcinomas [18].

SCs possess the ability to engraft at the site of injury and promote tissue regeneration and wound healing through synergistic downregulation of proinflammatory cytokines and increased production of soluble factors with antioxidant, antiapoptotic, and proangiogenic properties [70]. SC also act by increasing re-epithelialization, cellularity, intracellular matrix formation and neoangiogenesis [71]. Thus SC help in healing by their immunomodulatory, antiinflammatory and regenerative properties [70]. SC in turn increases free radical scavenging by antioxidants and facilitate the removal of senescent cells from the lesions by supplying more number of scavenging defense cells, reversal of hypoxia in the diseased tissue and by stimulating resident tissue stem cells to transform into new fibroblasts [72,73]. Recently Stem cells are being used as cell-based carriers and delivery vehicles that may target the desired site in treatment of cancer [74].

Though we saw plenty of advantages of stem cells, it has disadvantage that they could be likely the target of mutation leading to the formation of CSCs for they already possess active self-renewal pathways [75] leading to tumorigenesis, progression and metastasis of tumor.

CONCLUSION

The field of stem cell have evolved through a lot of hurdles since 100s of years to give certain fruitful results like regeneration of tissues and reconstruction, and treating certain diseases. Obtaining stem cells from oral cavity has many advantages like less ethical issues, ease of isolation, clinical abundance and rapid ex vivo expansion, are possibly more prone to forming neurons than other stem cells and is the good source for potential clinical applications. Though many studies have confirmed the effectiveness of stem cell therapy in certain diseases and in regenerative medicine, the research is mainly confined to animal models and more human research trials are needed to ascertain the role of stem cells in their management.

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