



STEM CELL APPLICATIONS IN ORAL LESIONS: RAPID REVIEW

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ABSTRACT With enormous potential to subside many diseases that currently have no effective therapy, during recent years stem cells have witnessed a drastic increase in literature in the research field. Stem cells have unique properties to differentiate and refurbish themselves into different cell types. They can be isolated and obtained from body fluids, peripheral blood and from human dental pulp. Advances have been seen for oro-facial regeneration but their use in oral lesion is still lagging behind. Stem cell therapy opens up exciting opportunities for treatment of oral sub mucous fibrosis where treatment options till now included use of antioxidants, steroids, surgery, chemotherapy and other palliative modalities.. This article revolves around the therapies involved under stem cells therapy in the treatment of Oral mucosal lesions.

KEYWORDS : Stem cell, oral lesions, Mesenchymal Stromal cells, stem cell therapy.

INTRODUCTION

We live in an Era where biological problems require biological solutions, Stem cell therapy; a biological boon is believed to change the face of human diseases. Stem cells have unique properties to differentiate and regenerate into various types of specialized cells [1]. Embryonic cells and Adult cells are the two type derived from stem cell. These various types of stem cells are derived from fertilized eggs, adult stem cells are found within tissues and organs but do not proliferate as much as embryonic cells. [1] Pluripotent stem cells on are genetically programmed cells which express stem cell markers and can generate characteristics of all three germ layers [2, 3]. There are characteristic feature which differentiate stem cells from normal cells

- **Cell Division:** By the process of cell division stem cells show enormous properties to refurbish them. [3] For Example, to repair and replace damaged and worn out cells, stem cells divide themselves consistently.
- **Cell Differentiation:** Under experimental and physiological conditions stem cells have capabilities to become organ or tissue specific cells. [3] For Example, in organs like pancreas and heart under specific conditions differentiation of stem cells is seen.

ISOLATION OF STEM CELLS

Receptors like Oct 4, TRA-1-60 present on the stem cell surface have made it possible to extract Stem cells from embryonic cells and from adult stem sources. [4] Regeneration of tissue Fibrin is made possible when sealants act as a matrix. [5, 6] The identification of embryonic stem cells (ESCs) is done by the presence of Nanog and Oct4 which act and help in as transcription factors. [7-9] the expression of Oct-4 and Nanog has been shown in human, during studies concerning breast cancer stem-like cells in humans, there are suggestions that transcription factors like Nanog and Oct4 are involved in self-renewal and tumorigenesis. [10-12]

KIND/SOURCES OF STEM CELLS

Embryonic Stem cells: Embryonic stem cells (ESCs) are found early (less than weeks) in the development of the embryo that can regenerate a developing fetus and ultimately a human body. [13, 14] ESCs are obtained from the inner cell mass of blastocyst and are pluripotent in nature. ECSs can be obtained through:

- Cloning
- In vitro fertilization
- Elective abortion

Adult Stem Cells: Adult Stem cells (ASCs) are also known as somatic stem cells have to ability to multiply when needed to repair adult organ and tissues, [15, 16] they have limited differential capacity yet are advantageous as they do not raise tissue rejection. [17] Several studies have demonstrated that transplantation of adult stem cells restores damaged organs in vivo. [18] These adult stem cells are:

- Oro-facial Region: Dental tissue, Buccalmucosa
- Bone Marrow Derived: Hemopoietic, Mesenchymal
- Other body tissues: Skin, Adipose Tissues etc. [19]

POTENCY OF STEM CELLS

The ability of any cell to differentiate into other cell types is called potency. Depending upon the descent and development potential, the stem cells are characterised under following four levels [3]:

- **Totipotent Stem Cells:** These cells can give rise to an entire organism e.g., spores and zygote are Totipotent cells. The capability of a single cell to divide and produce all cell types is called Totipotency. [20]
- **Pluripotent Stem Cells:** These are cell that derive from totipotent cells. They can give rise to most but not all cells which are necessary for foetal development. They can be isolated from early embryos. Also known as embryonic stem cells, [21]
- **Multipotent Stem Cells:** They are formed after further differentiation of Pluripotent cells; they can give rise to only limited number of cell types. [22] These cells have been found in adipose tissues, cardiac cells and Mesenchymal Stem Cells (MSCs) which are expected to be found in the third molar. [23]
- **Oligopotent Stem Cells:** Oligopotent Stem Cells are capable to form two or more lineages within a specific tissue and to differentiate only into specialised cells. [24]
- **Unipotent Stem Cells:** These cells are formed from further differentiation of multipotent cells, they give rise to single specific cell type. [24] Along a single lineage these cells result in giving rise to their own type.

Stem Cell Therapy in Oral Mucosal Lesions

Oral cavity marks the gateway for mucosal diseases mostly caused by local, systemic, drug related reactions or unhealthy habits during lifetime. [25] The oral mucosal lesions include:

Ulcerative Lesions

- Oral mucositis,
- Oral ulcers and wounds,
- Pemphigus Vulgaris

Premalignant Lesions

- Oral lichen Planus (OLP)
- Oral Submucous fibrosis (OSMF),

Malignant Lesions

- Oral carcinomas.

Stem Cell Therapy: Ulcerative Lesions

In the oral cavity the list of ulcerative lesions is quite elaborate, the focus here will be on the ones who have gained some advances in stem cell therapy and need extensive research in their field. [25]

Oral Ulcer and wound healing

Being one of the most common complaints of oral mucosa, oral ulcers are simply a loss or a break in the continuation of surface epithelium or mucous membrane that extends in lamina propria. [26] Due to its diversity in etiology and presentation, it's challenging to diagnose the right cause and more than that it's challenging to provide proper

treatment and management, because ulcers not only lose or break the surface epithelium they leave behind unacceptable scars and strictures. [19] Proper healing is considered one where no scars are left behind, it requires complex molecular and biological events involving cell migration and proliferation, deposition of extracellular matrix, angiogenesis and remodeling in an integrated manner. [26]

During recent years, the emerging treatment modalities have been promised by the stem cell therapy, having the ability to restore the tissue into a state before injury took place that is a pre injured state. [27] Precisely, Mesenchymal Stem Cells (MSC) has shown recent advancements in wound healing and promoting angiogenesis. [28, 29] Evidences from past researches have shown effective advances in the quality and the rate of healing during delivery of stem cells, particularly Mesenchymal Stromal cells. [19]

Oral Mucositis

The single most debilitating complication of hematopoietic cell transplantation undoubtedly remains Oral Mucositis; Patients who are receiving high dose chemotherapy are often subjected to oral mucositis and often cases are reported for the same. [30] During periods of profound immune suppression, life threatening systemic sepsis is most usual to be caused during oral mucositis. [30] With direct effects on a patients' survival rate it is considered as a dose limiting toxicity of cancer chemotherapy. [31] Due to intense pain perceived by these patients, gastrostomy tube or intravenous lines are used to provide nutrition. [32] Prophylaxis against infection sometimes do cause unplanned breaks in radiation therapy and add considerably to the total cost involved in the care. [33]

In allogeneic Hematopoietic Stem Cell Transplantation (HSCT), grafting remains a major cause of morbidity and mortality. [34] There are many challenges faced like the graft must contain immunologically competent cells (T-Cells) otherwise rejection with further complications is observed. [35] These complications can be overcome if the graft contains immunologically similar cell makeup having immunomodulatory, anti-inflammatory functions as well as regenerative properties, easily achieved in case of stem cell therapy. [36]

Pemphigus Vulgaris

Pemphigus Vulgaris a fatal disease is seen in patients above 50 years of age. [37] Though uncommon it still remains a potentially fatal autoimmune disease where auto-antibodies are directed against the calcium dependent cadherins desmoglein 3 and sometimes desmoglein 2. [37] Flaccid bullae, the primary lesions are characterised by intra-epidermal blisters and extensive erosions. [36] They may allow diseases such as septicaemia or advanced tuberculosis to reach an advanced stage before diagnosis. [37] Bone marrow suppression has been reported in patients receiving immune suppressants, an increased incidence of leukaemia and lymphoma is reported in patients receiving prolonged immune suppressors. [38]

Pemphigus has been seen along with proper treatment. [37] Successful treatment for Pemphigus Vulgaris with stem cell therapy requires proper establishment and to become a procedure of choice it requires a lot of successful clinical trials. [38]

Stem Cell Therapy For Premalignant And Malignant Lesions

Characterized by formation of fibrous bands in the buccal mucosa, oropharynx and sometimes in the upper third of the oesophagus, Oral Submucous Fibrosis (OSMF) is a chronic disorder. [39] On clinical examination OSMF presents characteristic features of loss of tissue mobility and blanching. It has a positive correlation with the consumption of areca nuts. [39] Spices, genetic and immunological factors may also cause OSMF [39]. Sujatha D et al in 2012 found that submucous fibrosis has a malignant potential of 7.6% [40]. There is an exciting possibility with stem cell therapy where such insidious diseases are treated permanently even in their terminal stages. [40] The therapy causes cytokine release and certain growth factors. In oral submucous there is blanching of tissues [41], stem cell therapy helps in neoangiogenesis which removes aging/ dead cells by supplying scavenger cells and the state of hypoxia from the affected area can be reversed [42].

Oral lichen Planus

Evidences propose that OLP is brought about by CD-8 cell mediated damage to the basal keratinocytes leading to apoptosis [43]. The antigen inciting the cytotoxic T cells could be any of the previously mentioned factors including stress, chronic liver disease, HCV virus,

dental restorative materials and/or drugs. [43, 44] Langerhans which are recruited by increased production of cytokines cells produce interferon -alpha (IFN - α) in increased amounts, which further activates cytotoxic cell mediated apoptosis, via the keratinocyte caspase cascade [45, 46]. Mesenchymal cells can be obtained through both in vitro and in vivo methods. [47]

Oral Submucous Fibrosis

Oral submucous fibrosis (OSMF) is chronic disease, its onset is insidious. OSMF affects the sub-mucosal layer featuring the deposition of fibrosis tissues in the oral cavity causing stiffness of the oral mucosa, causing trismus. [48] The condition leads to the inability to eat sometimes also involving the pharynx with epithelial atrophy. [48] OSMF has a high rate of morbidity because it causes progressive inability to open the mouth producing scars, tissue fibrosis, and precancerous lesions the main cause of OSF is Chewing betel nut. [49] Currently, Oral submucous fibrosis complications include side effects of treatment and chances of healing is always less. [50] With the recent approaches the treatment for Oral submucous fibrosis can also be done successfully. [51]

Oral Carcinoma

Shankarnarayanan et al in 2005 reported that oral cancer affected 17% men and 20% women [52] Stepanov I et al in 2005 found that the incidence of oral cancer can be as high as 10.8 per 100000 cases [53]. Boffeta in 2008 found that the major aetiological factor in oral cancer was smokeless tobacco [54]. Multipotent in nature, Cancer stem cells have the ability to regenerate also their rate of proliferation is very high. Targeting these cancer cells will ensure that the therapeutic efficacy is increased and tumour recurrence is prevented [55].

FACTORS INFLUENCING STEM CELL THERAPY

In the treatment of cancers a critical role is played by the route through which the therapy of stem cells is delivered [56]. The treatment methodology must consider the kind of pathology, treatment goals and patient risk-benefit profile. [57]

The outcome of the treatment also depends on the number of cells transplanted and its timing. [58] If a large number of cells are transplanted there is a risk of teratoma formation or ectopic engraftment. Thus for providing successful treatment the number of cells must be optimal. [59]

CONCLUSION

Treatments with effective results are now possible for many incurable diseases with the emergence and advancements in the field of stem cell therapy. Stem cell therapy the paradigm for future medicine has opened up new possibilities of treatment of oral lesions. Advances in Mesenchymal stem cell mediated tissue regeneration suggest clinical advances in near future.

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