

Stem Cell Therapy in Oral Mucosal Lesions

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Abstract

Stem cells are undifferentiated pluripotent cells that have capability of differentiating into diverse cellular phenotypes curing the disease. While the regeneration of a lost tissue is understood to mankind for several years, but it is only within the recent past that research on regenerative medicine/dentistry has gained momentum and eluded the dramatic yet scientific advancements within the field of molecular biology. The growing understanding of biological concepts within the regeneration of oral/dental tissues including experiments on stem cells is likely to result in a paradigm shift in the therapeutic armamentarium of dental and oral diseases culminating in an intense look for “biological solutions to biological problems.

At present, the adult mesenchymal stem cells are being used in the maxillofacial region for regeneration (including enamel, dentin, pulp and alveolar bone) and their use in the treatment of oral mucosal lesions. Moreover, there’s less literature available regarding role of stem cell therapy in the treatment of commonly seen oral mucosal lesions like oral submucous fibrosis, oral lichen planus, oral ulcers and oral mucositis. The present review will focus on the current knowledge about the role of stem cell therapies in oral mucosal lesions and could facilitate new advancements in this area.

Keywords: Adult Stem Cells, Embryonic Stem Cells, Lichen Planus, Mucositis, Oral Carcinoma, Oral Mucosal Lesions, Oral Sub Mucous Fibrosis, Pemphigus.

Introduction

It is to our knowledge that several tissues within the body are capable to trigger undifferentiated cells for restoration of damages caused by microorganism or infectious agent diseases or trauma in its completely different types. It is believed that stem cells enhance life, by giving the distinctive chance to interchange a damaged organ and regain health. Stem cells have recently been featured as a doable path to succeed in this objective, by scrutinizing their functions, evolution, development and possibilities; that embrace the potential to turn into cells the image of themselves or of differentiating into various cellular phenotypes.¹ Stem cells are being explored for the treatment of the many conditions, as well as neurodegenerative conditions like Parkinson's disease, cardiovascular disease, liver disease, diabetes, autoimmune disorders and for nerve regeneration and have shown a positive result with reduced suffering.^{2,3} Stem cell medical aid has additionally been tried for Orofacial including the periodontal and tooth regeneration, diarthrosis reconstruction, alveolar bone regeneration. Craniofacial stem cells as well as dental pulp derived stem cells have the potential to cure variety of diseases. Currently antioxidants, steroids, surgery, chemotherapy and different palliative treatment modalities are offered for oral mucosal lesions like ulcerative lesions, premalignancies and malignancies that were found to possess a brief result, were offered to the patients. Various studies have shown the successful role of stem cell therapies in the treatment of premalignant conditions, oral ulcers, wounds and mucositis.^{4,5} The recent idea of cancer stem cells (CSCs) has directed new field of research and doable potential treatment modalities for oral malignancy.⁵ This article discusses the role of stem cell applications in oral mucosal lesions.

Basic ideas of Stem cells

Stem cells are certain biological cells found in all multicellular organisms. They are in less portion in body mass, however will divide through mitosis and differentiate into various specialised cell sorts and may self-renew to provide a lot of stem cells. Differing kinds of stem cells vary in their degree of plasticity, or developmental versatility.⁶ Stem cells can be categorized into main 3 categories: embryonic, germinal, and somatic. Embryonic stem cells (ESCs) originate from the inner cell mass of the blastocyst. ESCs are omnipotent and have indefinite replicative life, that is due to their telomerase expression. Germinal stem cells are derived from primary germinal layers of embryo. They differentiate into antecedent cells to produce specific organ cells. Somatic/adult stem cells are antecedent cells as they are less totipotent i.e. less replicative life than ESCs. They exist in mature tissues like haematopoietic, neural, gastrointestinal and mesenchymal tissues. The foremost unremarkably used adult stem cells (ASCs) derived from bone marrow are hematopoietic stem cells (HSCs) and other primitive progenitor cells including mesenchymal stem cells (MSCs) and Induced Pluripotent stem cells (iPSCs).⁴ Pluripotent stem cells (iPSCs) are the adult cells that are reprogrammed genetically and helps to express genes and factors that are necessary for outlining the properties of the germ layers. These also can have a main role for drug development and in regenerative medicine.^{3,7}

Extraction of stem cells

Embryonic stem cells

Embryonic stem cells (ESCs) a derived from embryos that are 2–11 days old known as blastocysts that are totipotent in nature. ESCs have the very best potential to regenerate and repair morbid tissue and organs within the body.⁷ However, ESCs are raising ethical and moral considerations because it is believed that the method of

extraction of stem cells from an embryo destroys the embryo itself and a few read this as taking life. As, it is troublesome to regulate the growth and differentiation of the embryonic stem cell, they possess the danger of tumorigenicity and teratoma formation.⁶

Adult stem cells

Adult stem cells(ASCs) are found in most adult tissues. They are multipotent – capable of differentiating into quite one cell sort however not all cell sorts. ASCs can be classified as hemopoetic stem cells (HSCs) and mesenchymal stem cells (MSCs) according to their origin. HSCs are obtained either from cord blood or peripheral blood. MSCs are those that originate from the mesodermal layer of the foetus and within the adult reside in various forms of tissues like the bone marrow stem cells (BMSCc), limbal stem cells, hepatic stem cells, dermal stem cells, fatty tissue, orofacial region etc. From Orofacial region, stem cells can be derived from dental tissues like pulp, periodontal ligament, dental follicle, deciduous pulp cells, apical papilla, buccal mucosa, gingiva and alveolar bone. Stem cells can additionally be derived within the laboratories; this can be solely possible due to its distinctive receptors Oct4, TRA -1-60 (called as stem cell markers). These extracted cells are grown on a scaffold created of bio friendly materials with growth factors that in acts temporary matrix throughout its regeneration method.^{5,8,9}

Applications of stem cell in Orofacial Region

Mesenchymal stem cells derived from dental and nondental sources have been employed in orofacial region. These cells can be used for revascularization of root canal system, regeneration of pulp and pulp implantation. The employment of growth and differentiation factors for regenerating periodontal tissue is the favoured tissue engineering approach. Stem cells are employed in the tissue engineering of a human-shaped temporomandibular

joint, for the repair of craniofacial bone and even the replacement or regeneration of oral tissues.¹⁰ However, the employment of stem cell treatment for oral mucosal lesions may be a new idea, that has to be reviewed to promote the research further in the field. This review presently focuses on the oral lesions shown in Table 1.⁵

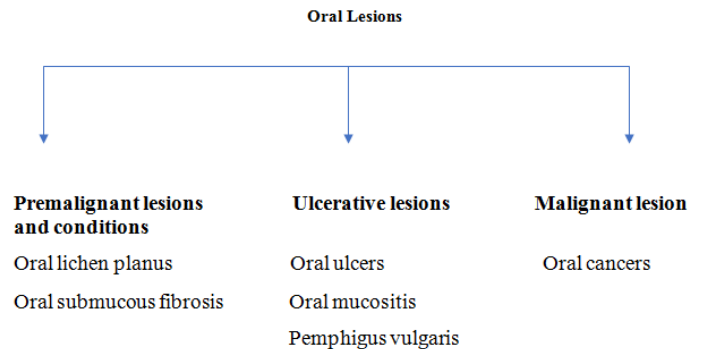


Figure 1: Oral mucosal lesions

Premalignant lesions and conditions

Oral lichen planus

Oral lichen planus (OLP) is a common and chronic mucocutaneous disease with multifactorial etiopathogenesis and potentially leads to cancer. It is generally accepted that the onset of OLP is a T cell-mediated immune damage course, and is associated with autoimmunity.¹¹ The nonspecific mechanisms like mast cell degranulation and matrix metalloproteinase activation. Due to this it disrupts the basal membrane.^{5,11}

The conventional treatment for this lesion are not proved to be satisfactory and a new therapy employing T-cell immune modulation using MSCs have been proposed to treat OLP. MSCs can be easily isolated and expanded in vitro and in vivo and can be utilized via systemic infusion or local application to the lesion site. In addition to their regenerative capacities, culture-expanded MSCs possess the unique ability to modulate immune responses (both in vitro and in vivo) and may function as immunomodulators in the maintenance of peripheral tolerance, transplantation tolerance and autoimmunity. Making use of multiple

pathways, MSCs suppress the function of a broad range of immune cells, including T-cells and B-cells.^{3,12,13}

Oral submucous fibrosis

Oral submucous fibrosis is a chronic, insidious disease associated with both significant morbidity (including pain, reduced oral opening) and an increased risk of malignancy. Various agents like Areca nut, gutkha, spices etc., are known to cause insult to oral mucosa by increasing cytokine production and release of reactive oxygen species; which in turn results in increased synthesis of collagen, decreased collagen breakdown, compromised vascularity and increased tissue oxidative stress, ultimately resulting in clinical OSMF.¹⁴ A variety of medicinal, as well as surgical treatment modalities, have been tried to intervene the disease process at different levels, but with limited success. Stem cell-based therapy is evolving as a promising new treatment approach in this direction.

Stem cell therapy primarily aims at neoangiogenesis by releasing cytokines and growth factors. This may result in increased free radical scavenging by antioxidants (either naturally occurring or extraneous). Neoangiogenesis may also facilitate the removal of dead cells from the lesions by supplying more number of scavenging defence cells and reversal of hypoxia in the diseased tissue.

Stem cell therapy may help to stimulate resident tissue stem cells to transform into new fibroblasts, which may help in the removal of disintegrated biochemically and morphologically altered collagen fibres.

Sankaranarayanan et al. have demonstrated the effectiveness of stem cell treatment in 7 OSMF patients by injecting 0.5–1 ml of marrow-derived stem cell concentrate into labial and buccal mucosa and tongue under local anesthesia. The results showed reduction in blanching, improved suppleness of the mucosa, decrease in the burning sensation while consuming spicy food,

significant increase in the mouth opening and the results were found to be sustained in the follow-up period from 6 months to 5 years.^{3,15}

Ulcerative lesions

Oral ulcers

Various diseases affecting oral cavity presents as ulcerative lesions. Included are acute and chronic processes, benign and malignant diseases, generalized and systemic diseases. Trauma is the most common cause of ulceration of the oral mucous membranes. Ulcer healing goes through a genetically programmed repair process, including inflammation, cell proliferation, re-epithelialization, formation of granulation tissue, angiogenesis, interactions between various cells, and matrix and tissue remodeling, all resulting in scar formation.¹⁶ The mesenchymal cells which are derived from bone marrow get differentiated in different types of cells namely adipocytes, osteoblasts and chondrocytes. These cells can be grafted at the affected site and can promote the tissues regeneration which in turn heads towards healing. This occurs due to combine effect of increased production of soluble factors with proangiogenic, antioxidant and antiapoptotic properties and thus can be useful in oral ulcer healing.^{5,17,18}

In a study by El-Menoufy et al. he submucosally injected autologous BM-MSCs suspended in phosphate buffered saline around formocresol induced oral ulcers in dogs. There was increased expression of both collagen and VEGF (vascular endothelial growth factor) genes in MSCs-treated ulcers compared with controls.¹⁶ One more study showed similar results by Aziz Aly et al. on formocresol induced oral ulcers in dogs using BM and adipose-derived stem cells.¹⁶ Hence concluded MSCs transplantation may help accelerate the healing of oral ulcers.³

Oral mucositis

Mucositis is one of the most common occurring conditions, especially as a side effect of post radiotherapy and chemo therapy. There are various treatment modalities for oral mucositis. The recent application of mesenchymal cells has showcased its best results due to its regenerative, self immunomodulatory and anti-inflammatory properties. The efficacy of the stem cell therapy can increase further either with the help of transgenic approach or by preconditioning them with specific factors.

A study by Zhang et al. in mice with chemotherapy-induced oral mucositis were injected with spheroid gingiva-derived mesenchymal stem cells (GMSCs) showed that treatment with GMSCs decreased the severity and incidence of ulceration and restored the papillae structure, the lining, and thickness of the epithelial layer as compared with those of untreated disease group. In this study they have demonstrated that the therapeutic efficacy for the treatment of oral mucositis is due to their enhanced multipotency, homing, survival and transdifferentiation capacities.^{5,18}

Pemphigus vulgaris

Pemphigus vulgaris may be a life threatening malady that happens within the fifth decade of life, primarily affecting the mucous membranes characterised by autoantibodies formation against desmosomal glycoproteins (dsg1, dsg3) that seems on the surface of the keratinocyte that ends up in formation of intraepithelial bullae and ulcerations on mucous membrane. The current key treatment of this malady is corticosteroids that features a derogatory complication on human body. For autoimmune diseases, haemopoietic stem cell transplantation (HSCT) has been advised as a promising therapeutic strategy for autoimmune diseases. Vanikar et al. did a prospective, single-center trial between month 2001 and Oct 2002 in eleven (M:F=5:6) patients with mean age 33.5 years and

mean length of malady 22.8 months, having painful pruritic blisters and ulcers were immune to corticosteroids to evaluate the consequences of high-dose unfractionated HSCT into thymus, bone marrow and peripheral circulation on central and peripheral arms of self-tolerance, and were treated with cytokine-stimulated allogeneic HSCT (mean dose: 21.8×10^8 cells/kg BW) from blood group-matched related donors. BM with mean CD34+ count 1.1% was inoculated into thymus, marrow and periphery, followed by 2 peripheral blood stem cell (PBSC) infusions found that recovery began within 24 hours of HSCT and new lesions stopped when 6 months. No graft versus host disease (GvHD)/adverse result was ascertained in any patient/donor. Over a mean follow-up of 8.02 years no recurrence/new lesions were reported.¹⁹ Hence stem cell therapy in pemphigus not solely has shown promises in treatment however conjointly brings a shift towards nonsteroidal approach in autoimmune diseases.

Oral carcinomas

Oral Cancer is the foremost cause of morbidity and mortality. Surgical intervention, chemotherapy, radiotherapy or combination of above have been the mainstay of treatment for head and neck carcinomas. Despite the recent improvement in treatment modalities, the cancer recurrence and treatment failures still occur in an exceedingly vital proportion of patients.⁴ Stem cells here play a pivotal role not solely in carcinogenesis however conjointly within the development of attainable new cancer treatment options in future. For past so many years stem cells are employed in the replenishment of blood and immune system damage during the treatment of cancer by chemotherapy or radiotherapy. Apart from their use within the immuno-reconstitution, stem cells from haematopoietic tissues appears to own extraordinary abilities to produce or switch between haematogenic and nonhaematopoietic lineages, exhibiting an unpredictable

degree of developmental or differentiation potential. Stem cells are also used as delivery vehicles throughout the cancer treatment, this function brings out the very fact that the tumors leach out chemo attractants, particularly VEGF to promote mesenchymal cell for the formation of supporting stroma of the tumor.^{5,20} To summarize, oral

mucosal lesions primarily aims at neoangiogenesis, tissue regeneration increased cellularity, modulation of collagen gene expression and immunomodulation, thereby creating noninterventional and innovative treatment modality. Table1.³

	Increased Cellularity	Neoangiogenesis	Tissue Regeneration	Modulation of collagen gene expression	Immuno-modulation
Wound healing & oral ulcers	√	√	√	√	
Oral mucositis			√		√
Pemphigus vulgaris			√		√
OSMF	√	√	√	√	
Oral lichen planus			√		√
Oral carcinoma		√	√		√

Table1: Summarization of biology of stem cells in oral mucosal lesions

Conclusion

The presently accessible conservative treatment of serious and disfiguring diseases is the treatment of choice. With the evolution and new applications of stem cell therapy, the treatment of incurable diseases has become reality. Though few studies have confirmed the effectiveness of stem cell therapy in oral mucosal disorders like OSMF, for diseases like oral ulcers and mucositis, the research is very confined to animal models and additional human trials area required to work out the role of stem cells in their management. There is the requirement of comprehensive research and evolution of ways to form it a promising tool in such conditions.

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