



RESEARCH ARTICLE

ROLE OF STEM CELL THERAPY IN ORAL PREMALIGNANT AND MALIGNANT LESIONS

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ABSTRACT

The growing field of Stem cells therapy has been proving its accurate results day by day due to the continuous researches. It is also found to be beneficial to various non-curable diseases that had no specific treatment earlier. These cells are the principal cells due to its unique and special property of capability to differentiate too many other cell types, its potency and its self-renewal. The stem cell therapy has been recently tried on the Orofacial region for the regeneration of various Soft and Hard tissues namely Enamel, Dentin, Pulp and Alveolar bone using the adult mesenchymal stem cells. Very few researches are conducted on the stem cell therapy for oral premalignant and malignant lesions like oral ulcers, leukoplakia, oral submucous fibrosis, lichen planus, oral cancer and others. Moreover, there is very less literature available on the functionality and efficacy of stem cell therapy application for these lesions and so the present review will enlighten about the functionality, efficacy and accurateness of the stem cell therapy for oral premalignant and malignant lesions. All the articles for the review were taken from the esteemed data bases like PubMed, Cochrane, EBSCO and more.

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INTRODUCTION

In the current scenario, the chemistry is totally been replaced by biomedical and biological solution for the biological problems. Amongst all these, regenerative medicines have evolved with a huge scope recently. Stem cells being one of its kind having a unique characteristic of potency and capability of self-differentiating in to other cells for curing the diseases. (Suma et al., 2015) Degenerative human diseases like Cardiovascular disease, Liver disease, Parkinson's disease, Temporomandibular disease, diabetes and soon have been explored with stem cell therapies and have also shown a positive result with reduced suffering. (Kim et al., 2012; Nadig, 2009) Stem cell therapy has also been tried for Orofacial region including the periodontal and tooth regeneration. Initially antioxidants, steroids, surgery, chemotherapy and other palliative treatment modalities which were found to have a

temporary effect were offered to the patients with oral pre malignant or malignant lesions. The current concept of Cancer stem cells (CSCs) have brought a new ray of hope for such patients and have also shown its efficacy on premalignant and malignant oral lesions. (Sagar et al., 2007; Devi et al., 2010) The present review will showcase and discuss the application of stem cell therapy in oral premalignant and malignant lesions.

Stem cells and its extraction

Human stem cell applications are more focused on the Mesenchymal stem cells (MSCs) which are found in the bone marrow stroma which can be easily isolated. (Patricia et al., 2002) These cells are also found to be precursor to the human tissues which are undifferentiated and have a self-potency to replicate by its own. (Robey, 2000) Amongst all types Induced Pluripotent stem cells (iPSCs) are the adult cells which are reprogrammed genetically and helps to express genes and factors that are important for defining the properties of the germ layers. (Stem Cell Basics, 2009) These can also have a prime role for drug development and in regenerative medicine.

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These cells can be obtained naturally from two major sources namely Embryonic stem cells and Adult stem cells. Further from embryonic cells it can be derived by in vitro fertilization, elective abortion, cloning or by somatic cell nuclear transfer. In adult stem cells, it can be derived from Orofacial region, Bone Marrow and other tissues like skin and adipose tissues. Bone marrow derived cells will be hemopoietic and mesenchymal. 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 be also derived in the laboratories; this is only possible due to its unique receptors Oct4, TRA -1-60 (called as stem cell markers). (Nagano *et al.*, 2008) These extracted cells are grown on a scaffold made up of bio friendly materials with growth factors that in acts temporary matrix during its regeneration process. (Gasparotto *et al.*, 2014; Horst *et al.*, 2012)

Application of Stem Cell therapy for Oral Premalignant and Malignant Lesion

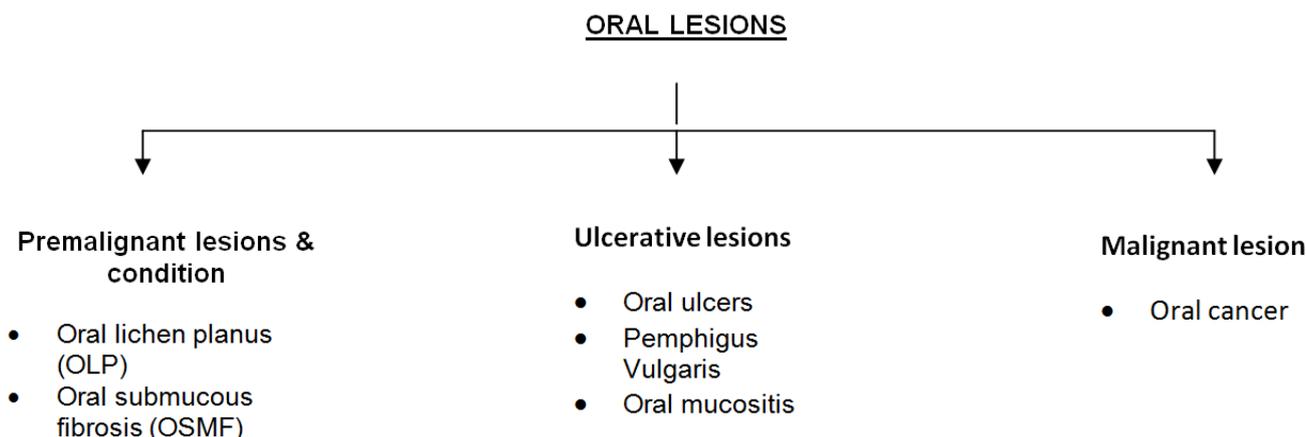
This review currently focuses on the oral lesions shown in Table 1.

have capacity ability to regenerate and modulate immune response. This self-modulated immune response of mesenchymal cells suppress the function of major immune cells including B cells and T cells. (Ding *et al.*, 2011)

Oral submucous Fibrosis (OSMF)

It is a chronic, debilitating potentially malignant lesion of the oral cavity, associated with areca nut habits, characterized by reduced mouth opening and has maximum chance of getting converted into malignancy.* These habits leads to increased cytokine production and releases oxygen that results in more collagen synthesis, reduces break down of collagen that in turns leads to reduction of vascularity and increase in the tissue stress due to oxygen liberation that results in OSMF. (Sudarshan *et al.*, 2012) There are various treatment modalities for OSMF but are not found to be successful at every stages. The recent stem cell therapy for OSMF has given a new ray of hope for patients, which is principally aimed at neoangiogenesis by cytokine release and growth factors; it is also called ad paracrine effect. This results in more free radical scavenging. Neoangiogenesis can also remove senescent cells from the affected area by supplying increased number of

Table 1. Oral lesions



Stem cell therapy for Premalignant Lesions and condition

Premalignant lesions and conditions is a disease or finding that if not treated leads to cancer. The term was coined by Victor Babes, a Romanian physician in 1875. These lesions are commonly occurring with statistics of 2.5% from the total population. (Sunitha Carnelio *et al.*, 2011) Amongst all the lesions and condition, Oral lichen planus and Oral submucous fibrosis are the most common ones. So the underneath is the stem cell therapy for these lesions.

Oral lichen planus (OLP)

It is a chronic mucocutaneous disease with multifactorial etiopathogenesis. The factor causing this disease occurs by antigen specific mechanisms by activating cytotoxic T-cells and nonspecific mechanisms like mast cell degranulation and matrix metalloproteinase activation. Due to this it disrupts the basal membrane. (Srinivas *et al.*, 2011) The conventional treatment for this lesion are not proved to be satisfactory and so a new method of treatment has been proposed to treat oral lichen planus using T cell immune modulations using mesenchymal cells. These mesenchymal cells can be isolated using various methods both in vivo and in vitro. These cells

scavenging defense cell and reverses the state of hypoxia from the affected area. Stem cell therapy may induce the new fibroblast formation in the affected area which can be beneficial in discarding the altered collagen fibers. (Sankaranarayanan *et al.*, 2007) There are studies conducted demonstrating the efficacy and effectiveness of stem cell therapy in OSMF patients. By injecting 0.5 to 1 ml of stem cells derived from marrow in to patients' buccal mucosa and tongue under the control of local anesthesia, positive results were found stating reduced blanching and decreased burning sensation on spicy food consumption with increased mouth opening within 5 to 6 months of therapy. (Sankaranarayanan *et al.*, 2013)

Stem cell therapy for Ulcerative lesions

Oral ulcers

The proper healing of the oral ulcer requires a good combination of complex molecular and biological events of cell migrations, proliferation, matrix depositing, and angiogenesis till the last stage till it arises remodeling. The mesenchymal cells derived from bone marrow have capability to 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 leads towards healing. This happens through the summative effect of increased production of soluble factors with proangiogenic, antioxidant and antiapoptotic properties and thus can be useful in oral ulcer healing proving a promising results. (Zhang *et al.*, 2012; Wu *et al.*, 2007)

Pemphigus Vulgaris

This disease occurs in the 5th decay of life, principally affecting the mucous membranes characterized by autoantibodies formation against desmosomal glycoprotein that appears on the surface of the keratinocyte which leads to formation of intraepithelial bullae and ulcerations on mucosa, thus makes it as a life threatening disease. The current key treatment of this disease is corticosteroids which has a derogatory complication on human body. (Kanwar and De, 2011) As the stem cell has a property of self-immunomodulation and anti inflammation properties, it can be a boon for the pemphigus vulgaris patients. Stem cell therapy will not only promises the results but will also bring a long shift towards discarding steroidal therapy for autoimmune diseases. As literature shows lack of evident efficacy of stem cells over this disease, more clinical trials and studies are required to get exact application for such lesions.

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. (Zhang *et al.*, 2012) In the study performed by Zhang *et al.*, injections of spheroid gingiva derived mesenchymal cells (GMSCs) were given to mice with mucositis induced due to chemo therapy. The results found in this study were found to be positive with decreased ulceration and severity of the inflammation in comparison to the controlled group having mucositis. These GMSCs shows the best grafting at the affected site and does conduct trans-differentiation in to epithelial cells and helps to reduce its hypoxic state. Thus it can be said that GMSCs can be a choice of treatment at the time of chemotherapy to prevent mucositis.

Stem cell therapy for Oral Malignant lesions

There are various treatment modalities for the oral cancer. Surgical intervention, chemo therapy and radiation therapy are the most common choice of treatment. Despite of these modalities, the recurrence and failure have continued its path without any significant decrease. There are studies conducted with CSCs, which have a unique characteristic of self-renewal and ability to initiate tumorigenesis and hold the growth of tumor. (Rastogi, 2012; Routray and Mohanty, 2014) In past stem cells are used for replenishing the blood and immune system that gets damaged post chemo therapy and radiotherapy. (Beccheroni *et al.*, 2003) The stem cells not only support the immune reconstruction but also provide regeneration and differentiation. Stem cells are also used as delivery vehicles during the cancer therapy, this function brings

out the fact that the tumors leach out chemo attractants, especially VEGF to promote mesenchymal cell for the formation of supporting stroma of the tumor. (Gao *et al.*, 2013; Studeny *et al.*, 2004) In brief, stem cells work at the neoangiogenesis, tissue regeneration, increases vascularity and cellularity and immunomodulation, leading it to being novel and non-interventional modality of treatment.

Conclusion

As in the current scenario conservative and the effective treatments are taken in to the consideration for life threatening diseases. With the evolution and new applications of stem cell therapy, it has brought a new ray of hope for these diseases. Though many studies have been carried out on stem cell therapy, majorly are still at the animal model level. Thus more clinical trials and extensive researches are needed on human models to confirm its effectiveness of the oral premalignant and malignant lesions like Lichen planus, Oral submucous fibrosis, oral ulcers, mucositis, pemphigus vulgaris and oral malignancy.

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