

Stem Cells in Management of Xerostomia

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Abstract

Xerostomia is a subjective symptom of dry mouth due to lack of saliva. It occurs due to multiple etiologic factors including systemic diseases and drug intake. Radiotherapy is commonly used in the management of head and neck cancers. One of the side effects of radiotherapy is xerostomia which causes debilitating symptoms such as pain, ulcers, infections, difficulty in speaking, chewing and swallowing food; and in wearing dentures, often resulting in stoppage of radiotherapy in these patients. Review of current literature points out the fact that available treatment to manage xerostomia is unsatisfactory. Stem cell therapy is gaining tremendous importance in recent years. Protecting, maintaining and transplanting the salivary gland stem cells appears to be an exciting option to prevent the occurrence of xerostomia and also to cure it. The current article aims to give insight into the probable uses of stem cells in the managing and treating xerostomia.

Keywords: Xerostomia; Adipose stem cells; Bone marrow stem cells; Dental pulp stem cells; Mesenchymal stem cells; Radiotherapy; Salivary glands; Stem cells.

Introduction

Radiotherapy is commonly used in the management of head and neck cancers. One of the common debilitating undesired consequences of radiotherapy is irreversible damage to salivary glands leading to xerostomia. Xerostomia is subjective feeling of dry mouth. Etiology is attributed to wide variety of causative factors including radiotherapy, drugs, Sjogren's syndrome, etc. Xerostomia in turn makes the patient susceptible to dental caries, oral infections, ulceration, and difficulty in wearing complete denture, difficulty in speaking, chewing and swallowing food. Unfortunately currently there is no effective curative treatment modality for xerostomia. So, a prompt thorough research on the role of stem cells in the treatment of xerostomia may hold a promising future.

Stem cells in Management of Xerostomia

The focus of recent researches in medical field has been increasingly on regenerative therapy using stem cells. Stem cells are cells capable of self renewal, differentiation into all lineages of an organ and are useful in regenerating tissues. They have inherent capacity to migrate to injured tissue. Stem cells in salivary gland are responsible for regeneration of the damaged glands. In irradiation, the stem cell population of salivary glands is destroyed. So it would be a good idea to replace these destroyed stem cells with new stem cells, thereby regenerating the Salivary Gland Epithelial Cells (SGEC) and protecting the gland [1]. Xerostomia resulting from destruction of salivary gland from various causative factors can perhaps be prevented, decreased or managed with regenerative medicine. Stem cells can be of potent help in regeneration of damaged salivary gland and those of the damaged vasculature supplying the salivary glands.

Systemic administration of Human Adipose Derived Mesenchymal Stem Cells (hADSCs) in mice has been found to reduce the radiation induced salivary gland damage. Decreased damage and atrophy of acinar cells, higher mucin and amylase production, increased salivary flow rates are observed in the hADSCs treated irradiated mice when compared to untreated irradiated ones. The hADSCs when administered immediately after the radiation and thereafter once a week for three consecutive weeks differentiates into SGEC. The hADSCs in addition to offering

protection against the radiation induced cell damage, also promotes the regeneration of SGEC. Also hADSCs are found to be nontoxic, non-tumorigenic and immune-privileged. The advantage of adipose derived mesenchymal stem cells is that the method to obtain them is minimally invasive and readily accessible and is unaffected by donors age. Also density of mesenchymal stem cells in adipose tissue is higher when compared to bone marrow stem cells [2]. hADSCs increase salivary flow rate, expression of vascular endothelial growth factor, hepatocyte growth factor, cyclooxygenase-2, matrix metalloproteinase-2, when administered immediately after irradiation. Also angiogenesis, anti-apoptosis, anti-fibrosis and differentiation of hADSCs into acinar and ductal cells are observed [1]. MSCs derived from Bone Marrow (BSC) are observed to migrate to healthy and damaged salivary glands following intra glandular and intravenous injections in a rodent model [3]. However it is to be noted that obtaining BSCs is a painful procedure with low yield rate. Also proliferation rates are low for BSCs [1].

Human salivary glands contain stem cells expressing c-kit which are capable of *in vitro* differentiation and self renewal, indicating their potential to future applications in managing the irradiation induced salivary gland damage. These stem cells are usually located in the excretory ducts. It should be noted that the ducts are essential for the engraftment of the stem cells. Also, irradiated salivary glands histologically exhibit intact excretory ducts, indicating the availability of stem cells for potential therapeutic purposes. However similar characteristics *in vivo* remains to be researched [4].

An advantage of MSCs is that they decrease immune mediated destruction of salivary gland [5]. MSC does not increase the incidence of cancer [6]. Lin⁻CD24⁺c-Kit⁺Sca1⁺ salivary stem cells have the ability to form larger and higher number of salispheres with more proliferative capabilities *in vitro*. They have capacity to increase the acinar cell numbers and salivary secretion in pre-irradiated submandibular salivary glands *in vivo*. These stem cells express high amounts of glial cell line-derived neurotrophic factor (*Gdnf*) which promotes their survival. It is observed that administration of GDNF before or after radiation therapy increases salivary output in submandibular glands of mice without increasing the

head and neck cancer growth [7]. *In vitro* cultivation of salivary gland stem cells expressing high amounts of CD 24 and CD 29 has applications to efficiently restore the loss of function that occur due to radiation induced salivary gland damage [8].

Stem cells reside in ductal compartment. Transplantation of ductal derived c-kit⁺ stem cells in mice rescues the salivary glands from irradiation damage. Stem cells can be identified in the submandibular gland of mice by their virtue of expression of stem cell markers like CD133, CD24, CD29 and CD 49f in excretory ducts. Salispheres cultured from dispersed mouse submandibular gland express the stem cell marker c-Kit, and are able to differentiate and self-renew *in vitro*. c-kit⁺ expressing cells exhibit more stem cell properties than the cells exhibiting other stem cell markers. As salispheres may contain different subpopulation, efficiency of salivary gland regeneration following irradiation is increased by combining c-kit⁺ cells with CD133⁺ or CD49f⁺ progenitor like cells [9]. Also salisphere derived c-kit⁺ cell transplantation improves the tissue homeostasis of irradiated salivary gland, which is of importance in terms of long term tissue maintenance [10]. Functional restoration of irreversibly damaged irradiated mouse submandibular salivary gland is possible on intraglandular injection of *in vitro* cultured c-kit⁺ salivary gland stem cells [11]. Cytokines like epidermal growth factor, insulin growth factor, and basic fibroblast growth factor appear to enhance proliferation and inhibit apoptosis of stem cells. Keratinocyte growth factor appears to increase proliferation of salivary gland stem cells, thus having potential applications to enhance regeneration following radiation treatment to the salivary gland [12].

Dental Pulp Endothelial Cells (DPEC) differentiated from dental pulp stem cells, isolated from green fluorescent protein-expressing mice is observed to partially regress the salivary gland hypofunction due to radiation therapy. DPECs express Nanog, Rex1, Klf4, Sox2 and Sca-1. They also form structures resembling tubes after plating on Matrigel [13].

Conclusions

Stem cell therapy is of great importance in preventing or managing radiation induced hyposalivation/ xerostomia. Adipose stem cells appear to be more attractive option with the potential to cure and protect the patient from xerostomia. More research successfully translating the positive findings in animal experiments to clinical setting can be of high importance.

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