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Stem Cell Therapy for Regeneration of Radiated Salivary Glands

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ABSTRACT

Radiation used in the treatment of head and neck cancer causes significant damage to the salivary glands and a loss of salivary function. Current therapies for radiation-induced salivary hypofunction aimed to stimulate residual functional salivary gland tissues and treat the symptoms of xerostomia without restoring the lost tissue. Several research strategies are emerging, aimed at regenerating salivary glands damaged by radiation via either gene therapy or by transplantation of stem cells. This concise review focuses on cell-based therapeutic strategies for regeneration of irradiated salivary gland (SG) tissues and discuss the possible regenerative potentials and applications of GMSCs in this context.

Keywords: Head and Neck Cancer; Gingival Mesenchymal Stem Cells; Radiotherapy; Salivary Glands; Transplantation; Xerostomia

Introduction

Head and neck cancer is one of the most common types of cancer worldwide, the current standard of care includes surgical resection of the tumor followed by chemotherapy and radiation [1]. Radiation causes significant damage to the salivary glands and a loss of salivary function [2]. Consequently, irradiated patients' quality of life decreases tremendously as a result of loss of saliva production, where they exhibit severe swallowing and speech disabilities, considerable pain and discomfort, mucosal infections, rampant formation of dental caries and severe accelerated periodontal disease resulting in loss of teeth [3].

Current Therapies for Radiation Induced Xerostomia

The objectives of the current therapies are to protect the salivary gland during radiotherapy, stimulate the remaining salivary gland function and treat the symptoms of xerostomia. Current and emerging therapies for radiation induced xerostomia are summarized in (Table 1) [4]. These protocols of treatment involve the administration of artificial saliva substitutes or sialagogues to increase the flow rate of saliva [5]. In addition, parasympathomimetic drugs such as pilocarpine and cevimeline, have been used to stimulate residual functional salivary gland tissues [6]. Unfortunately, those therapies

are short-lived and have multiple negative side effects of their own including nausea, diarrhea, and excessive sweating [7]. Therefore, novel therapeutic approaches to restore salivary gland function and the quality of life and to decrease the financial burden for these patients are required [8].

Table 1: Current and emerging solutions to address radiation-induced xerostomia [4].

Treatment Approaches		Available Treatment	Emerging Solutions
Prevention		• Intensity-modulated radiation therapy (IMRT). • Intensity-modulated proton radiation therapy. • Salivary gland transfer. • Radioprotective drugs (Amifostine).	• Radioprotective drugs (Tempol).
Treatment	Palliation	• Use of water. • Saliva substitutes, gels. • Hydration pack device.	
	Stimulation	• Cholinergic muscarinic. • receptor agonist drugs. • Chewing-gum and bitter • Substances. • Acupuncture.	• Electrical stimulation devices. • Gene therapy. • Growth factors. • Botulinum Toxin.
	Regeneration		• Stem cell transfer. • Artificial glands.

Tissue Engineering Approaches for Radiated Salivary Glands

Tissue engineering is a new area of science, its goal to unravel clinical and surgical problems associated with tissue loss and organ failure, by replacing or regenerating human cells, tissue or organs, to establish normal function [9]. Salivary gland regeneration has the potential to permanently restore salivary gland secretory function in patients with hyposalivation to improve their oral health and quality of life. The three main approaches that have been proposed are: Gene therapy, by using viral vectors, stem/progenitor cell-based therapy and replacement with a bioengineered gland [10].

Stem Cell Approach for Regeneration of Radiated Salivary Glands

The clinical success of salivary gland regeneration using cell-based approach requires support of the stroma, nerves, vasculature, and immune system. For cell transplantation to be feasible, the transplanted cells have to attach and survive in the damaged region. Furthermore, transplanted cells should be integrated into the salivary gland and be able to differentiate into a salivary gland cell lineage [11]. Stem cells have received great interest as potential therapeutics for a range of chronic, debilitating diseases that don't have effective therapeutic options. A ''stem cell'' refers to a clonogenic, undifferentiated cell that's capable of self-renewal and multi-lineage differentiation [12]. Interactions among these stem cells initiate and regulate developmental processes, resulting in the formation of highly specialized functional tissues and organs, once the organism matures, the pluripotent embryonic stem cells evanesce and some multipotent adult stem cells remain in the developed tissue to sustain the homeostasis and repair injuries [13]. Stem cells origins and organogenesis are demonstrated in (Figure 1). Different types of stem cells have been used as a regenerative treatment modality to ameliorate radiation-induced salivary hypofunction as summarized in (Table 2) [14-25]. Despite all promising results from stem cell therapies there were limitations with their use as with bone marrow derived stem cells (BM-MSCs), [26-31] the process of isolating BM-MSCs from the bone marrow is expensive and invasive operation will be needed which is considered one of the great drawbacks of BM-MSCs isolated from the iliac crest [32]. Furthermore, the expansion capacity seems to be restricted, since cells tend to age and lose their properties with repeated passaging and culture time in their multi-differentiation potential [33].

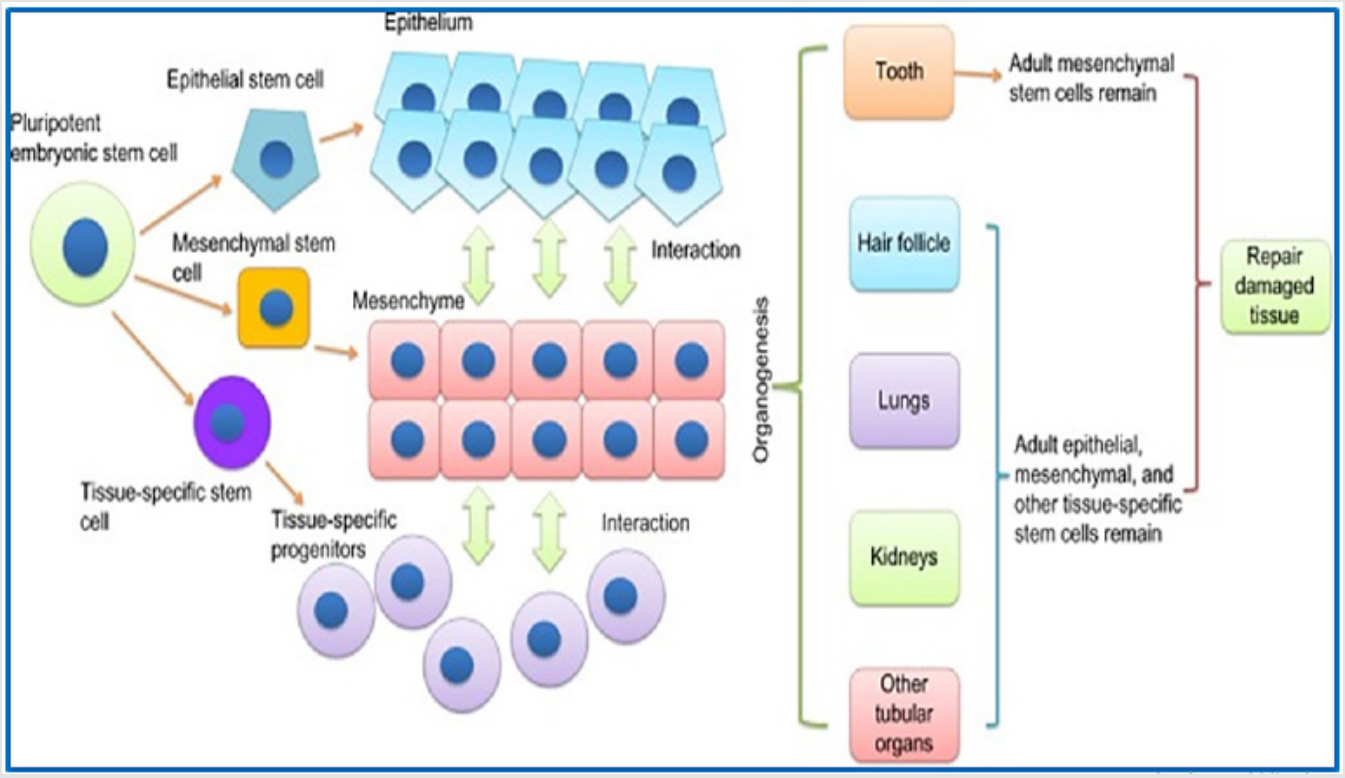

Figure 1: The embryonic stem cells undergo differentiation into multipotent stem cells. Interactions among these stem cells initiate and regulate developmental processes, resulting in the formation of highly specialized functional tissues and organs. Once the organism matures, the pluripotent embryonic stem cells evanesce and some multipotent adult stem cells remain in the developed tissue to sustain the homeostasis and repair injuries.

Table 2: A review of researches demonstrated regenerative potential of different types of stem cells in managing radiation-induced salivary hyposalivation.

Type of Stem cells	Researches Findings
Bone Marrow-Mesenchymal Stem Cells (BM-MSCs)	Schwarz, et al. [14] reported positive migration of intravenous injected BM-MSCs to ligated and non-ligated rat submandibular salivary gland.
	Sumita, et al. [15] showed that: • BM-MSCs had increased saliva production, greater weights of irradiated mice submandibular and parotid glands, more areas of acinar cells, higher levels of tissue regenerative activity in the glands. • Salivary compositions of irradiated mice transplanted with BM-MSCs were of comparable quality as the non-irradiated group.
	Lin, et al. [16] found that subcutaneously transplanted BM-MSCs and acinar-like cells in mice irradiated submandibular salivary glands were found to be integrated into the salivary gland and transdifferentiated into acinar-like cells.
	Lim, et al. [17] investigated the effects of intraglandular transplanted BM-MSCs into irradiated submandibular salivary gland of mice and showed significant increase in saliva flow rate and improvement in salivary gland weight, fewer apoptotic cells, higher numbers of functional acinar cells and an increase in blood micro vessel density compared to irradiated control mice.
	Tran, et al. [18] reported that bone marrow stem cells-treated mice had their salivary flow rate restored to normal levels when compared with the irradiated mice without treatment.

Adipose Stem Cells (ASCs)	Kojima, et al. [19] investigated the administration of ASCs to the submandibular glands of irradiated mice and showed that the salivary flow rate was significantly recovered, more acinar cells were found, blood endothelial cell recovery and alleviation of the severe inflammatory infiltration, as well as significant increase in angiogenesis enzymes and growth factors critical to salivary gland regeneration.
	Lim, et al. [20] investigated the effects of adipose-derived MSCs on radiation damaged salivary gland in mice and found that ASCs significantly increased salivary flow rate, promoted regeneration of salivary gland cells, and provided protection against radiation damage to cells.
	Xiong, et al. [21] reported that subcutaneously injected human adipose stem cells in irradiated submandibular salivary gland of rats had resulted in a significant increase in salivary flow rate compared with the untreated irradiated gland at 24 weeks post-irradiation.
	Lee, et al. [22] successfully differentiated mouse adipose-derived stromal cells into acinar cells when these cells were co-cultured with mouse acinar cells.
	An, et al. [23] and Lia, et al. [24] demonstrated that the ASCs strongly induced proliferation of salivary gland epithelial cells and led to a significant decrease in cell death *in vivo* and *in vitro* 256, as well as increased gland weight, and improved salivary flow rate.
	Grønhøj, et al. [25] intraglandular injection of adipose stem cells in human submandibular salivary gland following neck radiotherapy, resulted in significant increase of unstimulated salivary flow rate by 33% at 4 weeks and 50% at 16 weeks which was also higher than that observed in placebo group.

Oral derived tissues as sources of stem cell therapy for radiated salivary glands have also been investigated as documented in (Table 2). But major limitation for salivary gland regeneration in treating radiation-induced hyposalivation is the difficulty in isolating autologous stem cells from a severely injured gland [34]. Restriction in handling salivary gland stem cells due to their relatively short life span during in vitro cultivation resulted in narrowing the time window for implantation [35].

Gingival Mesenchymal Stem Cells for Salivary Glands Regeneration

Gingival mesenchymal stem cells (GMSCs) exhibit clonogenicity, self-renewal, and multipotent differentiation capacity, and these cells possess both stem cell-like and immuno-modulatory properties as compared to BM-MSCs, GMSCs show a faster proliferation rate [36]. Unlike BM-MSCs, which demonstrate abnormalities of cellular aging at 8–10 passages, GMSCs retain a stable morphology, maintain normal karyotype, do not lose MSCs' characteristics at higher passages, and are not tumorigenic. Besides the well-established self-renewal, multipotent differentiation, and tissue regeneration capabilities, GMSCs possess outstanding immunomodulatory properties, which could be of great therapeutic interest. This allows GMSCs to ameliorate inflammatory diseases therapeutically, through their influence on the local microenvironment [37]. Zhang, et al. [38] demonstrated the value of treating wounds with GMSCs through their systemic infusion for wound repair and reported that besides their local enrichment in multipotent and self-renewing at the wound site, one of the mechanisms by which GMSCs were assumed to improve repair is via their modulation of the local inflammatory response. The therapeutic effect of GMSCs was thought to be mediated through the suppression of inflammatory infiltrates and inflammatory cytokines/mediators, the increased infiltration of regulatory T-cells, and the expression of anti-inflammatory cytokine IL-10 at the injured sites [36].

Table 3: Researches demonstrated regenerative potential of oral tissues derived stem cells in managing radiation-induced salivary hyposalivation.

Type of Stem cells	Researches Findings
Dental Pulp Stem Cells (DPSCs)	Janebodin, et al. [26] demonstrated that *in vitro* differentiation DPSCs co-cultured with human salivary gland cell line (HSG) differentiated into mature acinar-like structures. *In vivo* subcutaneous co-transplantation of HSG and DPSCs demonstrated higher expression of mature human salivary gland differentiation marker, higher expression of endothelial, and angiogenic markers.
	Yamamura, et al. [27] observed that the average salivary flow rate in mice treated with DPSCs was significantly higher than that observed in untreated group. .
	Aurrekoetxea, et al. [28] reported that *in vitro* recombination of embryonic mouse salivary epithelia and dissociated human DPSCs performed in 3D laminin or other extracellular matrix scaffolds, resulted in binding of DPSCs and interaction with the salivary epithelia.
Salivary gland-Derived Stem Cells (SGSCs)	Nanduri, et al. [29] reported that transplantation of salisphere derived c-Kit+ cells in irradiated submandibular glands of mice improved saliva production. Moreover, ductal stem cell marker expression such as c-Kit, CD133, CD24 and CD49f identified after transplantation, indicates long-term functional maintenance potential of the gland.
	Jeong, et al. [30] demonstrated that transplantation of human submandibular salivary gland to radiation-damaged rat salivary glands rescued hyposalivation and body weight loss, restored acinar and duct cell structure, and decreased the number of apoptotic cells.
	Pringle, et al. [31] showed that intraglandular injection of human submandibular gland stem cells, human salisphere, resulting in increase of salivary flow in irradiated mice.

Gingival-derived mesenchymal stem cells (GMSCs) have shown remarkable tissue regenerative potential, noteworthy immunomodulatory properties and promising primary experimental therapeutic applications [39]. An interesting study was demonstrated by Abd El-Latif, et al. [40] who studied the regenerative potential of GMSCs in partially dissected rats' submandibular salivary gland, they reported that GMSCs combined with fibrin glue at the surgically created defect site have resulted in restoration of the gland architecture showing deeply stained serous acini, reduction in granulation tissue, multiple blood vessels formed around well-defined ducts. Unfortunately, there is a lack of knowledge in the regenerative potential of GMSCs in treating salivary hypofunction secondary to irradiation (Table 3).

Future Prospects

Research in the regenerative potential of GMSCs, as well as preclinical studies to investigate optimum concentration and suitable route for transplanted cells seem to be critical for clinical translation of this cell-based therapy for restoring the structure and function of irradiated salivary glands.

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Conflict of Interest

None declared.

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