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Palliative Care for Salivary Gland Dysfunction Highlights the Need for Regenerative Therapies: A Review on Radiation and Salivary Gland Stem Cells

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Abstract

Radiotherapy remains the major course of treatment for Head and Neck cancer patients. A common consequence of radiation treatment is dysfunction of the salivary glands, which leads to a number of oral complications including xerostomia and dysphagia, for which there is no existent cure. Here, we briefly describe the current palliative treatments available for patients undergoing these conditions, such as oral lubricants, saliva substitutes, and saliva stimulants. None of these options achieves restoration of normal quality of life due to their limited effectiveness, and in some cases, adverse side effects of their own. Other therapies under development, such as acupuncture and electrostimulation have also yielded mixed results in clinical trials. Due to the ineffectiveness of palliative care to restore quality of life, it is reasonable to aim for the development of regenerative therapies that allow restoration of function of the salivary epithelium following radiation treatment. Adult stem cells are a necessary component of wound healing, and play important roles in preserving normal function of adult tissues. Thus, the present review mainly focuses on the effects of radiation on adult stem cells in a variety of tissues, which may be at play in the response of salivary glands to radiation treatment. This is of clinical importance because progenitor cells of the salivary glands have shown partial regenerative potential in mouse transplantation assays. Therefore, understanding how these progenitor cells are affected by radiation offers potential for development of new therapies for patients with xerostomia.

Keywords: Head and neck cancer; Xerostomia; Salivary gland dysfunction; Radiation; Stem cells

Introduction

The current standard treatment for head and neck cancer utilizes a multimodality approach, which includes surgery, in combination with radiotherapy and chemotherapy [1]. One of the most common side effects of radiotherapy treatment for head and neck cancer is dysfunction of the salivary glands [2]. The degree of dysfunction is dependent on the radiation dose and the amount of glandular tissue that is exposed in the radiation field [2,3]. Histopathological changes include loss of saliva-producing acinar cells, alteration in the epithelium of the ductal compartment, and fibrosis [4,5]. Ultimately, hypofunction of the salivary glands results in xerostomia, a condition characterized by patient reported severe oral dryness [3,4]. Reduction in saliva production and oral dryness can have a devastating effect on oral health that potentially leads to malnutrition and poorer quality of life [2,6,7]. In most cases, xerostomia develops into an irreversible life-long problem despite successful treatment of the cancer [8]. In addition, patients often need a feeding tube as they present with varying degrees of dysphagia, which predisposes to life-threatening pulmonary conditions [9]. Although palliative care exists to alleviate the symptoms of mouth dryness and difficulty swallowing, there are no definitive cures for xerostomia and dysphagia.

Palliative Care for Xerostomia and Dysphagia

The overall goal of palliative care for patients undergoing head and neck radiation is to improve the quality of life for these individuals and allow them to return to a "normal lifestyle" [10]. Common palliative therapies for xerostomia include oral lubricants, saliva substitutes, and saliva stimulants (gum, pilocarpine). Oral lubricants can include a variety of products such as mouthwashes, gels, and toothpastes that could protect the oral mucosa, while saliva substitutes attempt to incorporate all the natural functions of saliva. In general, these therapies are short-lived and have not consistently demonstrated the ability to relieve xerostomia symptoms [11]. Saliva stimulants rely on residual salivary gland function to provide protection to the oral cavity. Pilocarpine is the most commonly prescribed saliva stimulant; however due to a number of adverse side effects (excessive sweating, rhinorrhea, and frequent urination) and contraindications in patients with cardiovascular concerns, its utilization is limited [10,11]. Therapies currently under development include hyperbaric oxygen (HBO) therapy, acupuncture, and electrostimulation. In a retrospective pilot study where all patients underwent hyperbaric oxygen therapy, there were significant improvements in salivary secretions and a decrease in patient reported xerostomia [12]. While the long-term improvements in xerostomia following HBO are unknown, it is a promising treatment option for patients with long-term salivary dysfunction where other treatments have been ineffective [13]. The use of acupuncture for the treatment of xerostomia has had more mixed results [14]. A recent RCT across 7 oncology centers described reduced patient reported outcome measures related to dry mouth when compared to oral care education sessions [15].

Unfortunately the use of acupuncture in this study did not improve objective measurements of salivary output, which could be related to the long standing debate on the appropriate comparator group [14]. Overall a recent Cochrane review has determined that there is insufficient evidence that electrostimulation or acupuncture can consistently alleviate xerostomia [16].

Radiation-Induced Injury in Salivary Glands

It is clear that current palliative care fails to offer a decent quality of life to patients undergoing xerostomia, and better approaches need to be developed. In order to improve current treatments and develop regenerative therapies, it is necessary to better understand the mechanisms behind radiation-induced salivary dysfunction. In general, it is known that ionizing radiation induces DNA damage, either indirectly through the generation of reactive oxygen species (ROS), or directly through the breakage of the DNA double strand, which results in the acquisition of mutations or cell death [17]. Previous studies in animal models have shown that therapeutically relevant doses of targeted radiation to the head and neck induce cell death in the salivary glands [18,19], and chronically decrease the saliva output [4,5,20]. Depending on the cause of injury, cell type, and cellular response, cell death can be mediated by apoptosis and necrosis, while autophagy seems to play a protective role [21,22]. It is likely that all three pathways interact to determine the overall response of the salivary epithelium to radiation damage [21,23]. Findings from our lab demonstrated an early apoptotic response of acinar cells following radiation treatment, which is mediated by induction of p53 [18]. Similar findings were found in cells that are highly radiosensitive, such as thymocytes, lymphocytes, and the small intestine [24-26]. This early apoptotic response seems to be crucial for chronic salivary dysfunction, as several animal studies have achieved radioprotective effects and preservation of salivary function by inhibiting apoptosis [27,28]. Additional mechanisms have been proposed to contribute to salivary hypofunction following radiation, such as activation of the calcium permeable channel TRPM2 (transient potential melastatin-like 2) [29], and a possible loss of salivary progenitors [30].

Even though salivary glands are a slowly proliferative, fully differentiated tissue, work utilizing the ductal ligation technique has shown that salivary glands have some capacity to regenerate following an injury event [31-34]. Osailan et al. [31,34] demonstrated that by ligating the rat submandibular gland with a metal clip, cellular atrophy follows with major loss of acinar cells. When the parasympathetic ganglion (chorda lingual nerve) is excluded from the ligation clip, acinar cell atrophy occurs albeit the extent of atrophy is less severe. However, once the metal clip was removed, the glands underwent a regenerative process leading to restored glandular weight, histological structure and secretory output [31]. While de-ligated salivary glands appear completely restored structurally, a few defects in some enzymatic processes remain. In contrast with ductal ligation, ionizing radiation leads to persistent loss of salivary gland function despite cessation of the radiotherapy treatment [1,2,6]. This clearly indicates that radiation targets a major aspect of glandular regeneration and wound healing, potentially stem or progenitor cells. Nonetheless, restoration of salivary gland function has been achieved by administrating Insulin-like growth factor 1 (IGF-1) to irradiated mice [20]. This resulted in a normal salivary flow and amylase composition of the glands as early as 30 days after treatment [20]. While therapeutic administration of IGF-1 would not be clinically feasible in cancer patients, this study shows that the salivary glands have the capacity to regenerate following irradiation upon administration of the right stimuli. Interestingly, concurrent administration of IGF-1 and radiation to mice bearing head and neck cancer cell xenografts partially modulated tumor growth rates, but when IGF-1 was administered as a post-therapy following radiation, comparable tumor growth delays were observed as in the radiation group [35]. The mechanism by which IGF-1 aids in restoration of function in salivary glands following radiation is not well understood, highlighting the need to deepen our studies in the wound healing processes of the salivary glands.

Effects of Radiation on Adult Stem Cells

Adult stem cells are a necessary component of wound healing [36-39] and thus it is of great importance to understand the effects radiation treatment has upon these cells, particularly in tissues such as salivary glands, in which radiation-induced damage leads to a progressive and permanent loss of function, and regeneration does not naturally occur [20,40,41]. In the past few years, several studies have uncovered some of the mechanisms by which radiation directly and indirectly affects stem cells in a number of tissues (Figure 1). While such mechanisms cannot be generalized, they may serve as clues for what might happen in other tissues where the interaction between stem cells and radiation is not well understood. This section focuses on how the wound healing response is altered following radiation treatment, such that it allows for regeneration in tissues like the intestine, but fails to regain function in salivary glands or hair follicles.

Figure 1A summarizes the results of DNA damage as a direct mechanism of radiation-induced injury upon stem cells. Unrepaired DNA damage in stem cells is thought to be the cause of mutations that leads to carcinogenesis [38,39]. Additionally, radiation has been shown to modify gene expression in stem cells, altering cell fate decisions and differentiation pathways [38,42-44], which can lead to inappropriate proliferative responses or an abnormal state of quiescence [36,42]. All these changes have the potential to disrupt wound healing; however, stem cells have different ways of coping with DNA damage, and some will be more efficient at repairing it. In the intestinal epithelium, the Lgr5+ crypt base columnar (CBC) stem cells have been shown to be somewhat radioresistant in spite of being actively dividing cells [45]. Following radiation, CBCs undergo cell death due to extensive DNA damage, but their capacity to repair DNA more effectively through homologous recombination (HR), rather than the more inaccurate mechanism of non-homologous end joining (NHEJ), allows for a subset of CBCs to survive [45]. These surviving CBCs are responsible for regenerating the intestinal epithelium. In skin, Keratinocyte stem cells (KSC) and Melanocyte stem cells (MSC) work together to maintain the integrity of epidermis and hair follicles. Upon radiation exposure, KSC are more resilient to radiation-induced apoptosis but become largely quiescent and have reduced colony-forming activity [46]. MSCs, in contrast, are induced to exit their niche, initiate proliferation and subsequently differentiate into melanocytes, which likely depletes the pool of MSCs [42,46,47].

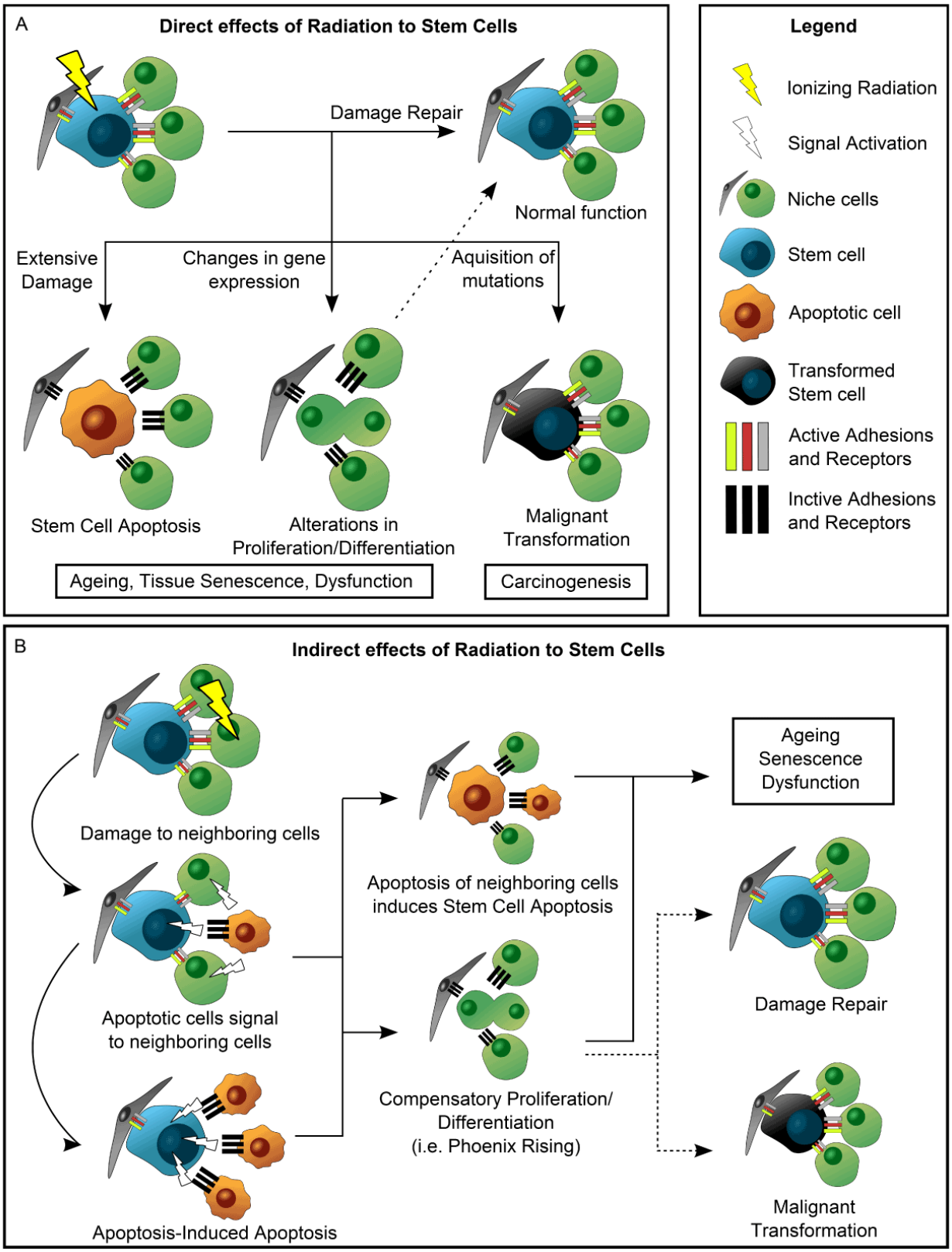

Figure 1: Direct and Indirect effects of Radiation to stem cells.

In addition to these direct mechanisms in which stem cell homeostasis is disturbed, radiation can also indirectly impair or induce their ability to regenerate their homing tissue (Figure 1B). Stem cells are highly dependent on their interaction with the cellular niche in order to function properly. They maintain adhesions with their surrounding cells, which are in part responsible for the transmission of signals that regulate stem cell fate decisions [48]. When these neighboring cells are damaged by external factors, signaling changes occur that will dictate stem cell behavior. Li F. et al. [49] described a process called Phoenix Rising, in which the apoptotic cells signal to the neighboring stem cells to begin proliferation and tissue repair. In their study, Caspase 3 and Caspase 7 from apoptotic cells activated calcium-independent Phospholipase A2, which in turn increased the synthesis of arachidonic acid, a precursor of prostaglandin E2 (PGE2). The latter is a known inducer of stem cell proliferation and was found to increase in response to radiation of MEF cells in a Caspase-dependent fashion [49]. In contrast to this study, it was recently reported that apoptotic cells in Drosophila are capable of emitting long-range signals through the JNK pathway to induce apoptosis in distal sites (apoptosis-induced apoptosis) [50]. Whether any of these mechanisms contribute to radiation-induced salivary gland dysfunction remains to be determined.

Regenerative Potential of Salivary gland Stem Cells

In salivary glands, therapeutic doses of radiation are sufficient to induce an apoptotic response in the secretory acinar cells [18]. In turn, increased levels of proliferation take place shortly after apoptosis, and are sustained chronically [28]. Thus, it is feasible that the events depicted in Figure 1 and described above could explain why radiation treatment causes permanent damage to salivary glands. For example, as explained in the previous sections, it is possible that radiation treatment directly targets salivary progenitors, impairing their ability for self-renewal and differentiation; alternatively, it is also possible that radiation causes a disruption in cell-cell interactions, which are required for proper function of stem cells. In fact, it was recently reported that Keratin 5 (K5) progenitors in submandibular gland explants from mice embryos survive after radiation treatment, but epithelial regeneration is greatly impaired nonetheless [51]. In this case, stimulation of the parasympathetic ganglion with neurturin promoted glandular regeneration, suggesting that an interaction between parasympathetic nerves and salivary progenitors must occur in order to restore homeostasis in the salivary glands.

It has been proposed that stem cell therapies have great potential for regeneration of the salivary glands after radiation injury [52]; therefore, it is of clinical importance to determine whether the mechanisms shown in Figure 1 take place in the salivary epithelium. It has been hypothesized that radiation-induced dysfunction of the salivary glands is due to the induction of cell death in salivary gland stem cells [30,53,54], but no scientific evidence exists to support this theory. Nevertheless, a study showed that transplantation of c-kit+ putative salivary gland progenitors to the submandibular gland of irradiated animals allows for partial restoration of function, demonstrating the therapeutic potential of salivary gland stem cells [54]. A major problem that remains in the field is the poor characterization of adult salivary gland stem cells, which does not allow for improvement in transplantation and regeneration therapies. Some markers have been found in salivary gland progenitors, such as Ascl3 [55], Keratin 5 [56], Keratin 14 [57], and c-kit [54], which have important functions in development. However, the relative importance of these individual progenitors in adult salivary glands, as well as their collective role in glandular homeostasis remains elusive. Further studies aimed at the mechanisms that prevent salivary gland progenitors from restoring homeostasis following radiation, will greatly facilitate the development of new therapies for patients with salivary hypofunction.

Conclusion

Radiation-induced salivary gland dysfunction is a common problem in head and neck cancer patients, which leads to adverse conditions such as dysphagia and xerostomia, for which there is no cure. Given the lack of effectiveness of the current palliative care for head and neck cancer patients undergoing radiotherapy, it is crucial that regenerative therapies are further developed, in order to increase quality of life of these patients. It is vital for this purpose that studies are aimed to better characterize salivary gland stem cells to facilitate future mechanistic studies. Regeneration of the salivary glands has been achieved in animal models, but the mechanisms for regeneration are mostly unknown. The use of salivary gland stem cells remains a promising field for developing regenerative therapies, and thus it is of major clinical importance to characterize this population and their involvement in radiation-induced injury to the salivary epithelium.

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