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SENSITIVITY OF SALIVARY GLANDS TO RADIATION- AN OVERVIEW

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Abstract:*Radiation therapy for head and neck cancer causes significant secondary side-effects in normal salivary glands, resulting in diminished quality of life for these individuals. Salivary glands are exquisitely sensitive to radiation and display acute and chronic responses to radiotherapy and the side effects including xerostomia, dysphagia, and malnutrition which are linked to significant reductions in patients' quality of life. This review will discuss clinical implications of radio sensitivity in normal salivary glands, compare animal models used to investigate radiation-induced salivary gland damage, address therapeutic advances, and project future directions in the field.*

Keywords:*Radiation, salivary gland dysfunction, salivary glands, animal models, therapy, xerostomia, dysphagia, therapeutic advances.*

1. INTRODUCTION

Salivary gland function plays an important role in oral health by aiding in food digestion, protecting oral mucosa, facilitating remineralization of dental hard tissues, and moistening the palate for articulation. Saliva is composed of water, electrolytes, proteins, and carbohydrates, which interact to accomplish multiple tasks in the oral cavity .[1] Moreover, the major salivary glands consists of parotid glands, submandibular gland and the sublingual glands . All of these salivary glands will work together with hundreds of the minor salivary glands located throughout the head and neck region. Each gland consists of a combination of mucous and serous acini cells in which the main functions are responsible for synthesizing protein components of saliva and transporting water and electrolytes.[2]Intensity-modulated radiation therapy (IMRT) is a type of radiotherapy used to spare normal tissues, like the salivary glands, in order to reduce the secondary side effects. IMRT has made improvements in salivary gland sparing; however, depending on tumor location and grade, radiation-induced damage to the salivary glands still occurs resulting in salivary gland dysfunction. The autonomic nervous system predominantly regulates salivary gland secretion and may have a role in glandular regeneration. Radiation-induced xerostomia is hypothesized to be multifactorial, involving damage to major and minor salivary glands. There are two stages of dysfunction of salivary glands which are acute and chronic.[3] Clinically, acute salivary gland dysfunction occurs within days and is characterized by loss of salivary flow, loss of acinar cells, glandular shrinkage, and changes in

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saliva composition. Chronic salivary gland dysfunction occurs months to years following radiotherapy and is characterized by reduced salivary flow and changes in saliva composition.[3,4] Affected patients suffer from xerostomia (dry mouth), oral mucositis, difficulty speaking, increased oral pathologies, difficulty chewing and swallowing food, as well as malnutrition due to loss of salivary flow. Due to the dysfunction of the salivary glands, patients must resort to temporary treatments for xerostomia to maintain adequate nutrition and hydration.

Overall, there is a significant reduction in quality of life for those undergoing treatment. Acute inflammatory processes largely fall into bacterial, viral, and autoimmune states. In chronic gland disorder, the symptoms are similar, although much less intense. There is usually swelling of the affected gland with a less intense discomfort and less overlying tenderness. The gland may fluctuate in size and discomfort with eating but usually not to the degree seen with acute infectious causes. In the inflammatory conditions, the gland is not so much a target of bacterial or viral processes but is inflamed by antibodies directed against salivary gland tissues.[5] Chronic salivary gland dysfunction occurs months to years following radiotherapy and is characterized by reduced salivary flow and changes in saliva composition . The mechanisms responsible for the elevated radiosensitivity of salivary glands are not well understood. Typically, radiosensitive tissues are relatively undifferentiated with a high level of proliferation. In contrast, salivary glands are highly differentiated tissues with very low levels of proliferation. Therefore, the response of salivary glands to radiation exposure could serve as a model for other normal differentiated tissues in close proximity to other cancers. In addition, radiosensitivity of normal tissues is highly dependent on the activity of wild type p53 and a number of tumors have mutated or altered p53 activity .[5,6] Theoretically this may provide an important therapeutic window, as the response of tumors that are highly proliferative with modulated p53 activity is likely to be quite different from differentiated normal tissues with unaltered p53 activity.

Clinical importance of induced salivary gland:

Worldwide, the problem is more significant, with head and neck cancer ranking as the 5th most common malignancy and not to forget in the United States about 50,000of cases related to the head and neck region are diagnosed each year.[7] Based on the diagnosis done , the patient will be given an option to undergo radiotherapy(radiation) and thus multiple secondary side effects can be seen in the patient such as xerostomia, change in taste and many more.

Radiosensitivity:

The leakage of granules and subsequent lysis of acinar cells was suggested to be responsible for the acute radiation-induced function loss of the salivary glands. The main problem with these hypotheses is that recently performed assays show no cell loss during the first days after irradiation, while saliva flow is dramatically diminished. The water secretion is selectively hampered during the first days after single-dose irradiation.[7,8] Literature is discussed that shows that the compromised cells suffer selective radiation damage to the plasma membrane, disturbing signal transduction primarily affecting watery secretion. Although the cellular composition of the submandibular gland and the parotid gland are different, the damage response is very alike. The acute radiation-induced function loss in both salivary glands can be ameliorated by prophylactic treatment with specific receptor agonists. selective radiation damage to the plasma membrane of the secretory cells, disturbing muscarinic receptor stimulated watery secretion.[8] Later damage is mainly due to classical mitotic cell death of progenitor cells, leading to a hampered replacement capacity of the gland for secretory cells, but is also caused by damage to the extracellular environment, preventing proper cell functioning.[9]

Models of Radiation induced salivary glands damage:

- Acute and chronic physiological response following the single dose'sirradiation.
- Radiation targeting
- Fractionated radiation

Mechanisms of the sensitivity of radiation:

- Cellular attrition
- Signaling pathways involved in apoptosis of salivary mucous and serous acinar cells.
- Other signaling pathways which are involved in radiation of mucous and serous acinar cells.

Symptoms for xerostomia:

Mass with nasopharyngeal carcinoma, bad breath, sore tongue, painless ulcer or sores in the mouth that do not heal, white, red or dark patches in the mouth that will not go away, ear ache, unusual bleeding or numbness in the mouth, lump in the lip, mouth or gums enlarged lymph glands in the neck, slurring of speech (if the cancer is affecting the tongue),hoarse voice which persists for more than six weeks, sore throat which persists for more than six weeks, difficulty swallowing food and change in diet. [10]

Treatment for induced radiation- xerostomia:

- Protective therapies
- Growth factors
- Palliative therapies
- Restorative therapies which include gene transfer, artificial salivary gland and stem cell transplantation.

2. Diagnosis

Very dry, erythematous oral mucosal tissues with areas of erosion extending through the epithelial layers. Especially affected is the tongue, which is also fissured and atrophic with loss of papillae covered with a thin white coating.[11] The gingiva and periodontium are quiet except for some erythema all around the marginal gingiva and difficulty eating and swallowing and not to forget loss of sense for taste.

3. Treatment

For example, the treatment was first experimented on mices. Mice were treated with radiation, intraperitoneal injections of Roscovitine, or a combination of the two. R-roscovitine . For irradiation treatments, mice were anesthetized with intramuscular injections of ketamine/xylazine (50 mg/kg/10 mg/m). Once anesthetized, mice were placed individually in a holding device, allowing exposure of the head and neck region to radiation while the rest of the body was shielded. [12] Whereas for humans, the current palliative therapies for relieving the side effects of salivary gland dysfunction are short lived and often are accompanied by their own unwanted side effects. In this study we focused on the use of Roscovitine, a

cyclin-dependent kinase inhibitor, as a possible preventative therapy for salivary gland dysfunction. We found that Roscovitine improved salivary flow rates in irradiated mice at both early and late time points.[13] Importantly, these improvements were not statistically different from unirradiated controls suggesting a complete preservation of normal

tissue function. This preservation of salivary physiology by Roscovitine is similar to previous work utilizing IGF-1 pretreatment.

4. Summary

Salivary glands are exquisitely sensitive to radiation and display acute and chronic responses to radiotherapy. Maximum cumulative exposure to the parotid and sub mandibular glands in affected individuals.[13] While several pathways may be involved in the radio sensitivity of salivary glands, studies suggest that p53 expression plays a major role in acute and chronic salivary gland dysfunction following irradiation. Some of the most exciting advances in therapeutic options involve preventive measures to preserve salivary function and restore function to previously damaged glands.[14,15] Future directions in molecular mechanisms and stem cell biology might lead to new therapeutic interventions to improve the quality of life for persons undergoing radiation therapy for head and neck malignancies.

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