

## Current approaches of salivary glands regeneration for management of xerostomia and hyposalivation: A narrative review

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### ABSTRACT

**Background:** The salivary glands are the organs that produce saliva and have a role keeping the oral cavity moist and lubricated. Salivary glands regeneration is important for developing treatments on management of xerostomia and hyposalivation because of the irreversible damage of salivary glands. Common causes include aging, polypharmacy, autoimmune disease, including Sjogren's syndrome, and head and neck radiation, in which xerostomia and hyposalivation having a substantial impact on patient health and wellbeing. **Purpose:** To describe current approach of salivary glands regeneration for management of xerostomia and hyposalivation through narrative review. **Review:** A literature search using Science Direct and PubMed yielded results between 1973 and 2022, and the results were evaluated to identify the most promising approaches and for future research. The keywords of the search strategy were "salivary gland regeneration" and "xerostomia" or "hyposalivation". Current studies have revealed potential targets in the development of salivary gland regeneration for the management of xerostomia and hyposalivation. Stem cells therapy aims to repair damaged at the cellular level, especially stimulating acini cells, multiplying and differentiating to replace dead or damaged acini cells. Bioengineering is through isolated acini cells cultured on many modified cell line and administration of bioactive compounds. Gene therapy aims to rebuild functional water channels and neutralization of inflammatory mediators. **Conclusion:** Several approaches of salivary glands regeneration that can be taken are stem cells therapy, bioengineering, and gene transfer.

**Keywords:** salivary glands regeneration; xerostomia; hyposalivation; medicine; dentistry

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### INTRODUCTION

The salivary glands have important structures and functions in the oral cavity. Various diseases, such as infectious diseases, autoimmune disorders, physical trauma to tumors and cancer, can change the function of the salivary glands and impact the patient's quality of life (QoL). Xerostomia or dry mouth, is a subjective complaint which is often accompanied by a decrease in the amount of salivary secretion or hyposalivation. Hyposalivation can be measured objectively through a sialometry.<sup>1,2</sup> Xerostomia is one of the symptoms that arise due to salivary gland hypofunction, it can be caused by aging, side effects of using drugs, autoimmune disorders or effects of gland and neck radiation. Salivary glands regeneration is important for developing treatments on manage xerostomia and hyposalivation because of the irreversible damage of salivary glands.<sup>1,3-6</sup> A literature search using Science Direct and PubMed yielded results between 1973 and 2022, and the results were evaluated to identify the most promising

approaches and for future research. The keywords of the search strategy were "salivary gland regeneration" and "xerostomia" or "hyposalivation". Furthermore, the objective of this review is to describe the current approach of salivary glands regeneration for management of xerostomia and hyposalivation.

### REVIEW

#### Salivary Glands

The salivary glands consist of 3 main pairs of salivary glands, namely the parotid, submandibular and sublingual glands. And minor salivary glands numbering about 600 to 1000 are located in the labial mucosa and buccal mucosa, palate, lingual, floor of the mouth and retromolar of the oral mucosa.<sup>1,2,7,8</sup> The salivary glands are composed of parenchyma and stroma constituents. The parenchyma consists of secretory endings, called acini cells, which secrete primary saliva. Acini cell connected to intercalated

duct, striated duct, and secretory duct that a system of ducts that modify salivary product. Acini cells are composed of serous or mucous cells, or mucus cells but lined by serous cells.<sup>9-12</sup>

Histologically, the salivary glands are classified according to their structure, composition and secretion. All ductal systems have ductal lengths and diameters that vary depending on the type of gland. There are three kinds of ductal segments, namely intercalated ducts, striated ducts and excretory ducts, which belong to the major salivary glands. All three have long and branching ducts, but the difference is that the sublingual and minor glands do not have striated ducts while the other glands have all duct segments.<sup>2,12-14</sup>

Myoepithelial cells are one of the systems that support the process of salivary secretion, contractile cells that have a star-shaped structure that surrounds the acini and intercalated ducts in the salivary glands. Myoepithelial cells are innervated by the autonomic nervous system and have a role in communicating with salivary flow by compressing the acini and ducts during contraction, and also providing structural resistance to the parenchyma during secretion.<sup>7,8,15-17</sup>

Almost all the protein in the salivary glands, comes purely from the acini cells of the salivary glands and not from the bloodstream. In contrast to whole saliva, there are about 2.500 proteins in whole saliva mixed with desquamated epithelial cells, gingival crevicular fluid and intraoral microorganisms and only 10% is estimated to be derived from the salivary glands. Whole saliva in the oral cavity has a composition of more than 99% water and less than 1% protein and salt. Every day, the normal production of saliva every day is about 0.6 L and produced by the major salivary glands is about 90% and the minor glands are less than 10% of secretions.<sup>1,18,19</sup>

### Xerostomia

Xerostomia or dry mouth is caused by salivary gland dysfunction, which can be in the form of disturbances in the quantity or quality of saliva produced and can result in hyposalivation, as well as changes in saliva composition. It is estimated that 5% to 46% of the general population suffer from xerostomia, with precipitating factors including age, gender, stress, degenerative diseases and medications contributing to decreased salivary secretion. Aging is a physiological cause of xerostomia. In addition, drugs can also cause considerable xerostomia, Sjögren's syndrome and head-and-neck radiation therapy also cause the majority of xerostomia cases.<sup>1,5,9,20</sup>

Current treatments for xerostomia can be divided into four main categories: (1) preventive therapy; (2) symptomatic treatment (palliative); (3) local or topical salivary stimulation; and (4) systemic salivary stimulation. Successful therapy of xerostomia and hyposalivation often involves a combination of agents based to the patient's needs. Transcutaneous electrical nerve stimulation and acupuncture as alternative approaches are also being studied, but must be supported by increased water consumption or

fluid requirements and we are exclude in this review. This review provides the current approaches of salivary glands regeneration, as such stem cells therapy, bioengineering, and gene transfer and provide illustration of brief mechanism each salivary glands regeneration.<sup>1,21,22</sup>

Permanent damage causing irreversible damage the salivary glands can result in impaired production and function of the salivary glands. Permanent damage to the salivary acini secreting cells of the salivary glands or loss of innervating signals causes xerostomia, and hyposalivation. Currently, there is no remedy and xerostomia has a severe impact on the health and well-being of patients. Oral function can also be impaired, speaking, eating, swallowing, chewing food and tasting food, has a major impact on the patient's health, QoL, and health care costs. And the importance of salivary gland regenerative therapy is expected to improve the patient's QoL.

### Stem Cells Therapy

The use of stem cell therapy, is a promising and promising regenerative therapeutic approach, not only for the salivary glands but also for other organs as a whole. Stem cell therapy based approaches have been used worldwide and are currently being implemented and have an 11.9% success rate of clinical intervention for xerostomia. Stem cells derived from mesenchymal tissue are the most frequently used source of stem cells, also because of their most abundant availability and ability to harvest them in non-invasive treatments. Mesenchymal stem cells are stem cells taken from bone marrow, adipose tissue, or umbilical cord blood, or it can be from tissue in teeth. There have been no reports on the long-term safety of interventional mesenchymal stem cell transplantation, but it has the potential to metastasize to other tissues or organs. In addition, its use has the potential to cause excessive tissue fibrosis, and its various properties and effectiveness based on the source of the stem cells.<sup>3,4,11,23-25</sup>

Stem cells therapy aims to repair damaged at the cellular level, they stimulating acini cells, multiplying and differentiating to replace dead or damaged acini cells. The approach principle for stem cell transplantation interventions is to encourage endogenous stem cell or progenitor cells (eg, SOX2+, KRT14+ and 15+) or late-differentiating cells (eg, MIST1+) to recruit tissue. In addition, the support of the nervous system, blood vessels and nutrition, maintain signalling pathway, as well as promoting ductal cells is very necessary in the regeneration of the salivary glands.<sup>3,4,11,23-25</sup>

### Bioengineering acini cells

Another regenerative strategy is through the use of biotechnology to regenerate salivary glands. Acini cells isolated from salivary glands cultured on many modified cell lines were able to implant into murine submandibular glands, particularly around the ducts, after ductal ligation injury. The success effectiveness of cells transplanted by salivary engraftment into recipients is still far from optimal, therefore, a number of studies have been carried out to

optimize signalling methods and the cellular environment to enhance engraftment.<sup>12,19</sup>

Transplantation of bioactive compounds directly into salivary glands is a potential therapeutic option, including administration and injection into the main duct, which has previously been done for the delivery of many active ingredients, including growth factors, primary cells, cytokines, or antioxidants via adenoviral vectors.<sup>12,19,26</sup>

### Gene therapy

Gene therapy that has been carried out has a principle approach to rebuilding functional water channel and neutralizing inflammatory mediators. Some diseases with salivary gland dysfunction usually have a reduction in the number of functional water channel, therefore this therapy has the potential and aims to rebuild the water channel to increase fluid permeability and increase salivary secretion. For example, human AQP1 gene transplantation interventions via adenovirus are being developed.<sup>12,27-31</sup>

Neutralization of inflammatory mediators is also an approach that can be done through gene therapy. This is a potential treatment option for patients with inflammatory salivary gland diseases, such as Sjögren's syndrome. Neutralization of B cell activating factor and proliferation-inducing ligands led to a significant reduction in CD138+ inflammatory cells. Decreases in the amount of IgG and IgM in the saliva produced by the salivary glands have also been reported. This therapy also has its own challenges despite reported increasing efficacy, including the risk of recipients increasing immune responses, and the development of inflammation, off-target effects, and insertion mutagenesis, which require further research.<sup>12,27-29</sup>

### CONCLUSION

The success of xerostomia therapy is still a topic of research and in the clinical world, so it is still being developed. Several approaches of salivary glands regeneration that can be taken are stem cells therapy, bioengineering, and gene transfer.

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