Artificial Salivary Glands- An Innovative Treatment for Salivary Gland Dysfunction

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Abstract
Salivary glands, produce saliva, which has a protective function against the oral microbial flora and aids in mastication, taste perception and speech. Salivary gland destruction can occur through various immunological, pathological and traumatic conditions; most common are medication, Sjogren's syndrome and radiation therapy. These conditions results in salivary dysfunction, leading to dysphagia, rampant caries, mucosal infections (candidiasis), burning sensation and detoriation of, quality of life of the patient. Various local therapies and systemic secretagogues are being followed, but these do not restore the acini functions completely. Recently much research has been done in restoring the salivary gland functions by gene therapy, tissue engineering and stem cell transplantation, but each one has its own limitations e.g. gene therapy is not possible in irradiated or damaged salivary glands, as there is no remaining parenchymal tissue. Tissue engineering has provided a spectrum of newer approaches to various problems, but replacement of whole internal organ, still requires further studies and also involves few ethical concerns. Results of stem cell transplantation although have been proved in animal studies, yet it is in initial phases to provide complete salivary gland functions in humans. Therefore artificial salivary glands provide a novel approach in the treatment of salivary gland dysfunction. Here we present a review on it and discuss the various factors associated with it, which requires further research.

Key words: Bioabsorbable artificial salivary glands, gene therapy, tissue engineering, stem cell transplantation.

Introduction

The salivary glands produce 1.5 litres of saliva every day, out of which 70-75% is contributed by submandibular gland, 20-25% is contributed by parotid gland, and 5% by sublingual gland. Continuous salivary flow aids in preventing infections and caries as saliva is composed of 99.5% water and proteins, electrolytes, bactericidal and antimicrobial components accounts for 0.5%. The salivary secretions can be divided into serous and mucous, serous contains bactericidal substances e.g. thiocyanate, proteolytic enzymes, antibodies (IgA) and α-amylase. Mucous secretions prevent epithelial dehydration and facilitate chewing and swallowing and also improve taste perception and helps in speech.[1]

Salivary glands are commonly affected by various inflammatory, euplastic and obstructive diseases, which in turn affect the glandular functions. Various advances have been made in the field of treating these diseases e.g. sialography, colour-doppler sonography, computed tomography, magnetic resonance imaging, scintigraphy and sialoendoscopy, these help in proper diagnosis and designing a treatment plan which is minimally invasive, to provide better prognosis.

Causes of salivary gland dysfunction

In spite of these modern techniques, there are few conditions which have an irreversible effect on salivary gland function, namely radiation induced xerostomia and glandular or ductal injuries. Salivary glands are highly radiosensitive and complications arising due to it was first reported in 1911.[2] One of the major complications of radiotherapy is xerostomia, which is not life-threatening but causes much suffering in patient's life by causing impairment of taste, mastication, swallowing, sleep and speech pattern. Xerostomia causes reduction in oral cavity resistance towards microbial flora and initiates dry ulcerated painful mucosa.[3-7]

Approximately, 500,000 new cases of head and neck cancer occur each year worldwide.[8] In the developing countries, majority of these patients receive radiation therapy, and the salivary glands are mostly involved in the radiation field. If the therapeutic radiation exceeds -50Gy, irreversible damage occurs in the glandular epithelium, leading to salivary hypofunction.[9] Radiation results in destruction of fluid secreting acinar cells, the serous acini that are more sensitive to radiotherapy, followed by mucous acini.

The pathogenesis of salivary epithelial destruction has been meticulously studied over the years by various researchers and is classified into 4 phases.[10-14]

1) Immediate phase- occurs within first few hours of post-irradiation, in which most of the sub lethal damage is repai - red and first signs of immediate cell death becomes apparent.

2) Short phase- two weeks following radiation, in which oropharyngeal syndrome predominates and edematous changes and recovery are expressed.

3) Late phase- stabilization is achieved at cellular and tissue levels, this period takes months to occur.

4) Extended phase- a state, which depends on dose of radiation administered, linear energy transfer and pharmacological modifiers.

Similarly, facial trauma involving the salivary glands also affects their normal functions. Lewis et al., described, that 0.21% of lacerations in the facial region resulted in parotid duct or gland injuries.[15] Depending upon the mechanism of injury, contusion, hematoma or laceration can occur in the

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gland or duct, leading to immediate or late complications. Sialocele and fistula are the common immediate complications and are seen in 58% and 30% of patients with salivary gland injuries respectively.[16] Gland atrophy and strictures are late complications after glandular injuries and results in salivary gland dysfunction. Recently much research has been done in restoring the salivary gland functions by gene therapy, tissue engineering and stem cell transplantation, but each one has its own limitations for e.g., considerable progress has occurred in transferring foreign genes to different tissues in vivo. [17-23] It is done by using either viral or non-viral methods and in salivary glands it is used to repair hypo functional gland parenchyma, augment the protective functions of saliva and to secrete functional molecules directly into the bloodstream. Although animal studies have shown good results but it is seen that adenoviruses elicit a potent immune response involving innate, cellular and humoral components and still there is limited information of its application in humans.

Tissue engineering is defined as a "combination of principles and methods of the life sciences with those of engineering to develop materials and methods to repair damaged or diseased tissues, and to create entire tissue replacements.[24] Many strategies have evolved to engineer new tissues and organs, one is local delivery of an appropriate factor at a correct dose for a defined period of time which can lead to the proliferation and differentiation of a patient's cells from adjacent sites and these cells can then participate in tissue repair or regeneration at the required site.[25] Second general strategy uses cells grown in the laboratory and placed in a matrix at the site where new tissue or organ formation is desired. Even though tissue engineering provides new approach to treat various conditions it has some manufacturing and ethical concerns. In order to maintain the reliability of the engineered product few challenges have to be met e.g., batch-to-batch repeatability in production, methods to achieve and maintain sterility, tissue procurement for cell preparations, optimal handling and storage methods and an additional and important consideration is the cost associated with each device. Ethically there is significant debate on tissue procurement for example, should the tissue source be allograft or xenograft, if it is allograft whether the donor should be paid for their tissue samples? Since fetal tissues have more growth potential should fetal tissues be used as a cell source.

Stem cell transplantation plays an important role in tissue regeneration. Stem cells are a characteristic group of cells which possess self-renewal capability and pluripotency. Research into the development of the salivary gland has revealed that cells in the duct close to the acini are believed to provide all the cell types required for the formation of acini and ducts. But still the potential of these particular stem cells to regenerate salivary gland tissue has yet to be proved since tissue regeneration is an enormously complex process involving multiple growth factors/transcription factors and their sequential expression. The molecular mechanisms underlying the regenerating process for the salivary gland are largely unknown and further research is required in this field.

In order to overcome the above mentioned difficulties, artificial salivary gland was fabricated based on the principles of tissue engineering.[26] The device consists of a blind end tube fabricated from porous, slowly biodegrad- able substratum, coated with matrix components on the inner surface of tube, in order to allow formation of polarized epithelial cell monolayer, providing unidirectional fluid secretion and is surgically implanted in the buccal mucosa with an opening in the oral cavity, similar to the natural duct system.[27,28]

These devices are made up of homopolymers and copoly mers of lactic or glycolic acid, synthesized in two shapes; a flat disk shape and a tubular shape. The advantage of these biodegradable polymers are that they offer control over structure, crystallinity, hydrophobicity, degradation rate and can be manufactured in various shapes and sizes. Their surface properties can be altered to adapt to the biological requirements for cell adhesion, growth and function.

But it is important to consider the tissue compatibility of such salivary gland devices in vivo. Although many previous studies have used biodegradable polymers to replace structures but still its application in orofacial region is not been fully proved clinically.[29]

The degradation rate of the biodegradable polymers is an important parameter in the function of these devices. Ideally the tubular scaffold should maintain structural integrity to allow formation and differentiation of cells; early degradation will result in collapse of the orifice. Adequate blood supply and neuronal stimulation also affects the formation of salivary cells. The oral mucosa is richly supplied by blood vessels, but in irradiated tissues angiogenesis is reduced adjacent to the implanted tubules as the vasculature is less by endothelial cell death and scarring of tissue.[30]

Timing of implantation of these devices is also one of the factors under debate. Post-radiation therapy often results in oral mucositis, during this period the mucosa is erythematous, ulcerated and painful, thus few researchers advice placement of these devices once complete mucosal healing has occurred (4-6 weeks post-radiation). But other school of thought is that, any delay in treatment after radiation therapy will delay the formation of salivary cells and may not provide proper formation of cells and unidirectional flow of saliva. Few cases reported that the tubule had breached the surface toward the surgical incision site on the skin and also it was difficult to secure the orifice of the device, firmly to the buccal mucosa.

Conclusion

Artificial salivary glands indeed is the treatment of choice for salivary gland hypofunction in near future, but critical study is required in the fields as mentioned earlier, in order to improve its efficacy and provide a better state of life for the patient. An important step in development of such devices would be to study the growth of primary epithelial cells on polymer substrata in vivo.

References

1. Holmes S. Xerostomia: etiology and management in cancer patients. Support Care Cancer 1998;6:348-55.
2. Bergonie J, Silverman S, Stephens LC. Reaction processes after irradiation. Arch Elect Med 1977;19:241-45.
3. Gravenmade EJ, Panders AK. Clinical applications of saliva

substitutes. Front Oral Physiol 1981;3:154-61.
4. Fox PC, Van der ven PF, Valdez IH. Xerostomia: Evaluation of a symptom with increasing significance. J Am Dent Assoc 1985;110:519-25.
5. Vissink A, Gravenmade EJ. A clinical comparison between commercially available mucin- and CMC- containing saliva substitutes. Int J Oral Surg 1983;12:232-38.
6. Nakamoto RY. Use of saliva substitute in post radiation xerostomia. J Pros Dent 1979;42:539-42.
7. Shaw MJ, Kumar NDK, Aframian DJ. Oral management of patients following oncology treatment: literature review. Br J Oral and Maxillofacial Surg 2000; 8:519-24.
8. Vokes EE, Weichselbaum RR, Lippman SM and Hong WK. Head and Neck cancer. N Engl J Med 1993;328:184-92.
9. Taylor SE, Miller EG. Preemptive pharmacological intervention in radiation-induced salivary dysfunction. Proc Soc Exp Biol Med 1999; 21:14-25.
10. Vissink A, Konings AWT, Ligeon EE, Gravenmade EJ. Irradiation-induced changes in secretion and composition of rat saliva. J Biol Buccale 1990;18:3-8.
11. Vissink A, Gravenmade EJ, Ligeon EE, Konings AWT. A functional and chemical study of radiation effects on rat parotid and submandibular, sublingual glands. Radiat Res 1990;124:259-65.
12. Vissink A, Downs JD. Contrasting dose rate effects of irradiation on rat salivary gland function. Int J Radiat Biol 1991; 61: 275-82.
13. Phillips RM. X-ray- induced changes in function and structure of rat parotid gland. J Oral Surg 1970;28:432-37.
14. Rice JC, Izutsu KT, Truelove EL. Rat parotid gland pathophysiology following 137Cs irradiation. Radiat Res 1982;90:330-38.
15. Lewis G, Knottenbelt JD. Parotid duct injury: is immediate surgical repair necessary? Injury 1991;22:407-09.
16. Parekh D, Glezerson G . Post-traumatic parotid fistulae and sialoceles. A prospective study of conservative management in 51 cases. Ann Surg 1989;209:105-11.
17. Scheller EL, Krebsbach PH. Gene therapy: Design and prospects for craniofacial regeneration. J Dent Res 2009;88: 585-96.
18. Voutetakis A, Bossis I, Kok MR, Zheng C. Salivary glands as a potential gene transfer for gene therapeutics of some monogenetic endocrine disorders. J Endocrinol 2005;185: 363-72.
19. Barka T, Hendrika M. Retrovirus- mediated gene transfer into rat salivary gland cells in vitro and in vivo. J Histo Cyto 1997; 45:1533-45.
20. Baum BJ. Prospects for re-engineering salivary glands. Ann NY Acad Sci 2000;14:84-88.
21. Kagami H, Wang S. Restoring the functions of salivary glands. Int J Radiat Oncol Biol Phys 2008;14:15-24.
22. Kaigler D, Mooney D. Tissue engineering's impact on dentistry. J Dent Educ 2001;65:456-62.
23. Isabelle M, Lombaert A, Stephens LC. Rescue of salivary gland function after stem cell transplantation in irradiated glands. Proc Soc Exp Biol Med 2008;3:01-13.
24. Baum BJ, Mooney DJ. The impact of tissue engineering on dentistry. J Am Dent Assoc 2000;131:309-18.
25. Malhotra N, Kundabala M, Acharya S. Current strategies and applications of tissue engineering in dentistry--a review Part 2. Dent Update. 2009;36(10):639-42, 644-66.
26. Tyagi P, Dhindsa MK. Tissue engineering and its implications in dentistry. Indian J Dent Res 2009;20:222-26.
27. Baum BJ, Wang S, Cukierman, Songers L. Re-engineering the functions of a terminally differentiated epithelial cell in vivo. Ann NY Acad Sci 1999;875:294-01.
28. Wang S, Cukierman E, Landon V. Extracellular matrix protien- induced changes in human salivary epithelial cell organization and proliferation on a model biological substratum. Biomaterials 1999;20:1043-56.
29. Aframian DJ, Redman RS, Yamano S, Nikolovski J, Cukierman E, Yamada KM, et al . Tissue compatibility of two biodegradable tubular scaffolds implanted adjacent to skin or buccal mucosa in mice. Tissue Engin 2002;8:649-62.
30. Kashima HK, Kirkham JR, Andrews JR. Postradiation sialadenitis. A study of the clinical features, histopathologic changes and serum enzyme variations following irradiation of human salivary glands. Am J Roentgenol Radium Ther Nucl Med 1965;77:94-98.

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