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RESEARCH ARTICLE

SALVARY GLAND STEM CELLS: A REVIEW

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ABSTRACT

Stem cell (SC) therapy has a promising future for tissue regenerative medicine. SCs have drawn attention in recent years because of their accessibility, plasticity, and high proliferative ability. SC and Progenitor cells have the ability to rescue and repair injured tissue and partially restore organ function. SCs or progenitor cells are class of undifferentiated cells that are able to differentiate into specialized cell types. They are capable of renewal, differentiation into all lineage of an organ and useful in regenerating tissues. Salivary gland stem cells (SGSC) are characterized by their potential for self-renewal and differentiation. They can replenish damaged cells. SGSC have been identified in many tissues within mouse and human. This substantial progress in understanding salivary gland (SG) functioning and recent identification of SC and progenitor cell population in SG provides basis for studies towards development of a SC based therapy for xerostomia.

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INTRODUCTION

The human SGs are divided in two distinct groups, the major SG which includes Parotid, Submandibular and Sublingual glands. The other group includes minor SGs of upper aero digestive tract. The Major function of SG is to secrete saliva which plays a significant role in lubrication, digestion, immunity and overall maintenance of homeostasis within human body (Christopher Holsinger, 2007). Patients with irreversible loss of SG function are seen in various conditions like head and neck radiation, Sjogren's syndrome, uncontrolleddiabetes, sarcoidosis, renal diseases, surgical removal of glands (Coppes *et al*., 2011). Such patients suffer from considerable loss of morbidity and reduction in their quality of life because of salivary glands dysfunction. This lead to severe xerostomia, dysphagia, dental caries, oropharyngeal infections, ulcerations, impaired taste sensation, difficulty in wearing denture, nocturnal discomfort, diminished mucosal wound healing (Sumita, 2014). Unfortunately there is no adequate treatment for patients with such irreversible glandular damage (Sumita, 2014). Currently pharmacological approaches aims to increase the secretory capacity of surviving acinar cells but this approach is not feasible if few or no acinar cells remain in the gland. Therefore alternate treatment strategies to restore acinar cells in damaged SG are required (Sumita, 2014). The focus of recent researches in medical field has been increasing on regenerative therapy using stem cells. Based on major advances made in the field of stem cell research, stem cell base therapy holds a promising future (Vagishkumar, 2015). Herein we present a review on current state of knowledge of SGSCs and their implications in treatment of various SG diseases.

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SALIVARY GLAND ANATOMY AND PHYSIOLOGY

SG consists of parenchyma(the secretory unit and associated ducts) and stroma (the surrounded connective tissue that penetrated and divides gland into lobules).The SG are exocrine glands that secretes saliva through ducts from flask like, blind ended secretory structure called salivary acini. The secretory unit consists of acinar cells which are mucus and serous type. Serous acini are roughly spherical and release a watery protein secretionvia exocytosis. The serous acinar cells are pyramidal with basally located nucleus surrounded by dense cytoplasm and secretory granules at apex. Mucous acini store viscous, slimy glycoprotein (mucin) within secretory granules that become hydrated when released to form mucin. Mucinous acinar cells are columnar with flattened, basally situated nuclei and water soluble granules that make intracellular cytoplasm appear clear. Mixed or seromucousacini contain components of both type, but one type of secretory unit may dominate. Mixed secretory unit are commonly observed as serous demilunes or half-moons capping mucous acini.

Between epithelial cells and basal lamini of acinus, flat myoepithelial cells (basket cells) form a lattice work and possess cytoplasmic filaments on their basal side to aid in contraction, thus forced secretion of the acinus. They are also observed around the intercalated ducts. The acini first secrete through small canaliculi into the intercalated ducts, which in turn empty into striated ducts within glandular lobules. The intercalated duct comprised of irregular myoepithelial cell layer lines with squamous or low cuboidal epithelium. Striated ducts have distinguishing basal striations due to membrane invagination and mitochondria. The next segment of the duct system is marked by appearance of inter lobular excretory ducts within the connective tissue of glandular septa (Christopher Holsinger, 2007). Saliva produced by SG is crucial in process of digestion, lubrication and protection in body. Saliva is actively produced in high volumes relative to mass of salivary glands and is almost completely controlled extrinsically by both parasympathetic and sympathetic division of autonomic nervous system. Saliva comprises of 99.5% water and 0.5% electrolytes (sodium, potassium, calcium, magnesium, chloride, bicarbonates, phosphates, iodine), mucus (glycoproteins andmucopolysacchrides), enzyme (α amylase, lingual lipase, kallikrein) antimicrobial agents (IgA, lysozymes, lactoperoxidase, lactoferrin) (Humphery, 2001).

SALIVARY GLAND EMBRYOGENESIS-A KEY TO REGENERATION

The SGs are of different embryonic origins. The parotid gland is ectodermal in origin whereas the submandibular and sublingual glands are endodermal in origin, making them unique and potentially not interchangeable from SC point of view. However all SGs develop through a similar pattern of morphogenesis that is driven by the elements of extra cellular matrix, fetal hormones and cells which can differentiate. Differentiation of these parenchymal cells is initiated early in the sequence of SG development by an interaction between oral epithelium and its adjacent mesenchyme and neurons .The process of cellular differentiation within epithelial rudiment causes channeling of salivary epithelial cells into a biochemically diverse group of exocrine cellular phenotypes. Fibroblast growth factors, cytokines, antiapoptic proteins and extra cellular proteins are involved in SG development. Thus epithelial and mesenchyme interaction also seems to be important in regeneration of SGs (Khalil, 2016; Denny *et al*., 1977).

STEM CELLS

SCs are defined as "unspecialized human or animal cells that can produce mature specialized cell body and at same time replicate themselves." SCs divides in to daughter cells which can either enter a path of differentiation in to specialized cell or remain stem cells, thereby ensuring that a pool of SCs constantly replenished in adult organ. The mode of cell division characteristic of SCs is asymmetric and is necessary physiological mechanism for maintenance of the cellular composition of tissues and organs in body. Most tissue repair in mammals is dedifferentiation-independent events resulting from activation of preexisting stem cells or progenitor cells. SCs or progenitor stem cells are denominator for all types of regeneration. Based on their potency to differentiate, SCs are divided in to categories like Totipotent SC (can differentiate in to embryonic and extra embryonic cell types), Pluripotent SCs (descendent of totipotent cells differentiate in to nearly all cells derived from any of the 3 germ layers), Multipotent SCs (differentiate in to cells closely related to family of cells), Oligopotent SCs(differentiate into few cells), Unipotent SCs(differentiate into only one cell type) (Motwani *et al*., 2016; Mao, 2008).

SALIVARY GLAND STEM CELLS

Currently Embryonic SC, induced pluripotent SCs, Mesenchyme SCs and Adult SCs are being studied for their potential application in cell based therapies. Human embryonic SCs in treatment of xerostomia is not being reported yet and may also be hazardous due to their inherent teratogenicity. They have demonstrated various tendencies to acquire karyotype abnormalities during in vitro culture studies. Mesenchymal SCs (with mesodermal and neuroectodermal origin) are able to differentiate into cells of mesodermal origin like adipocytes, chondrocytes, osteocytes and also can give rise to representative lineage of three embryonic layersand are prospective source of adult stem cells. Induced pluripotent SCs are reprogrammed adult human cells to form embryonic stem like cells. Oral fibroblasts are able to form induced pluripotent cells in lab however drawback is that the transcription factors used are well known oncogenes. Adult SCs (somatic or tissue derived) are organ restricted and hence do not form teratomas. They only form cell lineages of organ from which they are derived. Adult SCs play an important role in formation, maintenance and repair of tissues in which they reside by their self-renewal and differentiation (Coppes, 2011). They are closely related to remnants from embryonic development.

Several approaches have been undertaken towards isolating and characterizing SGSCs. Ligation of the major excretory ducts of salivary gland created dysfunctional and apoptoticacinar cell environment resulting in proliferation of intercalated and excretory duct cells. Label retaining cell studies using nucleotide analogues such as bromodeoxyuridine and ^{3}H-thymidine proliferating cell have demonstrated these proliferating cells and have also demonstrated that acinar cells themselves also poses a limited degree of proliferation. This study suggested that cells capable of proliferation and differentiation representing potent SGSCs population reside within ducts of SG.

Another study isolating SGSCs from parotid gland via lateral paratoidectomy in vitro followed by flow cytometry showed these cells are strongly positive for classic mesenchyme stem cell (MSC) markers like CD13, CD29, CD44 and CD90 and is negative for HSC markers CD 34, CD 45.These cells further displayed MSC like characteristics by demonstrating adipogenic, osteogenic and chondrogenic differentiation when grown in to respective induction Medias. In vitro floating sphere culture study, revealed cellular expression of Sca-1, c-kit and musahsi-1 by submandibular gland derived SGSCs. A 10 day period immunohistochemistry staining was performed to analyze the organization and development of salispheres. On first day H&E, PAS, CK7, CK14 staining showed that cultured salispheres contained ductal and acinar cells. Acinar cells mostly disappeared on 3rd day and reappeared on 5th day in culture. On 10th day salisphere composition was dominated by acinar cells. RT-PCR also showed that amylase expression increased by 25 folds after 20 days. These results thus suggested that these salispheres forming cells originated from salivary ducts and have differentiated into amylase producing acinar cells. Thus such studies have helped to localize SGSCs within the salivary ducts.

In vitro experiments on rats using human SGSCs from parotid and submandibular gland resulted in recovery of radiation damaged SG of rats. X-ray irradiator was used to generate radiation induced hypo salivation in rats. Human SGSCs were then transplanted into glands. After 60 days salivary flow of the irradiated group treated with human SGSCs was twice that of PBS group but was still less in comparison to undamaged group. Also the average body weight of treated rats was slightly increased in comparison to PBS group. In another experiment irradiated mice treated with 3 day cultured salisphere resulted in formation of ductal structures at injection site. 90 days after irradiation there was an increase in acinar cell surface area and saliva production in salisphere treated mice as compared to untreated mice. After purifying salispheres to a c-kit positive population, cells were capable of differentiating into acinar cells in vitro. Transplantation of this small number of cells (300-1000) per gland improved saliva production in 69% in vivo irradiated mice.

Some of the studies have use monolayer technique using proliferative colonies of presumed SG progenitor cells from rat SGs. This culture was added with epidermal growth factor and hepatocyte growth factor. After 7 days culture demonstrated expression of cytokeratin 18 and 19,c-Met,amylase,aquaporin-5,vimentin,alpha smooth muscle act in which are ductal, acinar and myoepithelial differentiation marker proteins. This was suggesting that putative SG progenitor cells are responsive to growth factor mediated stimulation (Denny, 2014; Pringle *et al*., 2013; Lombaert *et al*., 2008; Egusa *et al*., 2012; Yoo *et al*., 2014; Hegde *et al*., 2014).

FUTURE PERSPECTIVES OF APPLICATION OF SGSCs

One of the major recent advances in field of medicine is treatment using living cells. SC therapy is a better option to prevent and repair damage of tissues induced by degenerative processes due to auto-immune responses, radiation-side effects or other cytotoxic events. SGSCs can be effectively applied in various SG conditions like-

SALIVARY GLAND NEOPLASMS

Majority of SG neoplasms are benign and most commonly affected is the parotid gland.80% of them is pleomorphic adenomas. They are slow growing and encapsulated. Mucoepidermoid carcinoma is most common malignant neoplasm followed by adenoid cystic carcinoma, squamous cell carcinoma and carcinoma arising from pleomorphic adenoma. Benign tumors requires careful surgical excision, recurrent tumors require more extensive treatment, including wider surgical margins and postsurgical radiotherapy. Malignant salivary tumors are excised including regional lymph nodes at risk for tumor spread accompanied with radiotherapy and chemotherapy resulting in post-surgical permanent xerostomia.

SALIVARY GLAND DISEASES

Can be classified as infections such as acute sialadenitis, chronic sialadenitis, viral sialadenitis and non-infectious diseases like sialectasis (excretory duct obstruction), sialolithiasis (stone or calculi), sialodenosis. Treatment for infections is systemic antibiotic therapy. Sialoliths are sometimes treated surgically.

RADIATION INDUCED SALIVARY GLAND DYSFUNCTION

Most of the head and neck tumors are commonly treated with radiotherapy. The SGs often are (partially) located within the radiation portal during radiotherapy for head and neck resulting radiation-injury to SG tissue which may result in life-long salivary gland impairment severely reducing the post treatment quality of life of the patients. Thus head and neck radiotherapy has serious and detrimental side-effects on the oral cavity and patient experiences persistent complaint of a dry mouth.

SJOGRENS's SYNDROME

it is a debilitating systemic autoimmune disorder associated with inflammation of epithelial tissues particularly exocrine glands, lacrimal glands commonly affecting women in the 4^{th} and 5^{th} decade of life. Typical oral findings are salivary hypofunction, ductal inflammation, and acinar destruction. Other manifestations are keratoconjuctivitis, synovitis, neuropathy, vasculitis, and disorders of the skin, thyroid gland, urogenital system, respiratory, and gastrointestinal tracts. In the late-stage Sjogren's patient, where all fluid producing acinar cells have been replaced by connective tissue, salivary stimulants will not be helpful. Hence restoring or replacing SG using SC is important.

SYSTEMIC DISEASES ASSOCIATED WITH SALIVARY DYSFUNCTIONS

Other autoimmune conditions associated with Sjogren's syndrome having salivary dysfunctionincludes rheumatoid arthritis, scleroderma, lupus, HIV+ infected individuals and those with acquired immunodeficiency syndrome (AIDS) frequently experience salivary dysfunction from lymphocytic destruction of the glands and assequel of medications. Associations have also been made between uncontrolled diabetes, peripheral neuropathies, and salivary dysfunction. Patients suffering from Alzheimer's disease, Parkinson's disease, strokes, and cystic fibros is also show decreased salivary secretion (Ship, 2000; Scully, 2005).

NEED FOR STEMCELL BASED THERAPY

Problems associated with xerostomia seen in above SG dysfunctions further debilitate patient's condition. Most of these patients are old and respond even more dramatically to hyposalivation. Xerostomia patients show dry and cracked lips, angular chelitis, and furrowed, desiccated, sticky tongue. Dry oral mucosal tissues become susceptible to trauma; oral mucositis leads to pain and increased likelihood of developing microbial infections. One of the most common infections in patients with salivary dysfunction is oral candidiasis and second frequent infection is new and recurrent dental caries. Edentulous and partially edentulous adults using removable prosthetic devices have diminished denture retention, which will impact adversely chewing, swallowing, speech, and nutritional intake. Speech and eating difficulties can impair social interactions and may cause some patients to avoid social engagements. Various medications, sialagogues, salivary stimulants and preventive treatment modalities have been implied to relieve above symptoms of salivary dysfunctions but is not sufficient and are temporary. Hence a permanent and effective treatment is required.

Based on above detailed knowledge of salivary gland anatomy, physiology, embryogenesis, disorders, stem cells and various advances in stem cell based therapies SGSCs hold a great potential in treatment modalities.

CHALLENGES

A major difficulty with SC therapy is to identify the SC. The cultures contain many different cells and are a challenge to identify specific cell types. When stem cells are identified and then isolated from tissues, appropriate solutions must be created to trigger these cells into the desired cell types. Finally, even though the cells may be identified, isolated and grown, there are supplementary issues like immune response and efficiency. A person's immune system can identify the transplanted cells as foreign bodies and that it can generate an immune reaction that results in refusal of the new cells. Despite rapid progress in studies of cell-based therapies, this novel technology has yet to gain acceptance in ordinary practice. Since cell-based therapy is still expensive, determination of adequate treatment targets should be an important research goal to facilitate its widespread use.

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