REVIEW ARTICLE

Salivary Gland Stem Cells and Tissue Regeneration: An Update on Possible Therapeutic Application

Aikaterini Mitroulia[1], Marianna Gavriiloglou[2], Poluxeni Athanasiadou[3], Athina Bakopoulou[4], Athanasios Poulopoulos[5], Prashanth Panta[6], Shankargouda Patil[7], Dimitrios Andreadis[8]

Abstract

The aim of this review is to combine literature and experimental data concerning the impact of salivary gland (SG) stem cells (SCs) and their therapeutic prospects in tissue regeneration. So far, SCs were isolated from human and rodent major and minor SGs that enabled their regeneration. Several scaffolds were also combined with "SCs" and different "proteins" to achieve guided differentiation, although none have been proven as ideal. A new aspect of SC therapy aims to establish a *vice versa* relationship between SG and other ecto- or endodermal organs such as the pancreas, liver, kidneys, and thyroid. SC therapy could be a cheap and simple, non-traumatic, and individualized therapy for medically challenging cases like xerostomia and major organ failures. Functional improvement has been achieved in these organs, but till date, the whole organ *in vivo* regeneration was not achieved. Concerns about malignant formations and possible failures are yet to be resolved. In this review article, we highlight the basic embryology of SGs, existence of SG SCs with a detailed exploration of various cellular markers, scaffolds for tissue engineering, and, in the later part, cover potential therapeutic applications with a special focus on the pancreas and liver.

Keywords: Salivary gland stem cells, Stem cell therapy, Tissue regeneration.

The Journal of Contemporary Dental Practice (2019): 10.5005/jp-journals-10024-2620

Introduction

SCs therapy has become a wide field for research since the discovery of their pluripotency. Concerning SG regeneration, SCs could be a promising treatment for xerostomia resulting from SG hypofunction. SG damage due to radiation, autoimmune diseases like Sjorgen's syndrome[1] or metabolic syndromes like diabetes,[2] and age-related degeneration are the common etiology for SG impairment. The reduction of saliva has severe effects on the patient's quality-of-life as this deteriorates taste perception, swallowing, and speech performance. It also leads to the increase in the incidence of dental caries, mucosal atrophy, and ulceration, in addition to an overall reduction of immune response against infectious agents. This may be critical in case of immunocompromized patients as dissemination of fungal, viral, or bacterial infections can be life-threatening.[1] Since there is still no efficient treatment, SG regeneration is anticipated and an SC-guided transplantation and differentiation with the assistance of scaffolds and growth factors within affecting SG could be an ideal option.[3] Apart from their own regeneration, SG, especially the minor glands found in the oral mucosa, could be an effective alternative and an easily accessible source of SG SC (Fig. 1) for the regeneration of other organs like the liver[4] and the pancreas[5] based on the morphological, embryological, and functional similarities.

The special characteristic of SCs is their ability to differentiate into any other cell type through mitosis and, for unlimited times, as long as they are provided with the right stimulus.[6] Adult SCs operate as an internal repair system and are found in various tissues.[7] Over the last decade, scientists studied the induced pluripotent SCs (iPSCs) that are adult cells that could be "reprogrammed" genetically to assume an SC-like state.[8] SC populations bearing embryonic or adult SC characteristics have been identified in human major SGs (parotid and submandibular), within their ductal system.[9,10] In humans, minor SGs the single epithelial SCs as well as SCs with both epithelial and mesenchymal characteristics have been isolated only recently.[11,12]

[1–3,5,8]Department of Oral Medicine/Pathology, School of Dentistry, Aristotle University of Thessaloniki, Greece

[4]Department of Prosthodontics and Implantology-Tissue Regeneration Unit, School of Dentistry, Aristotle University of Thessaloniki, Greece

[6]Department of Oral Medicine and Radiology, MNR Dental College and Hospital, Sangareddy, Telangana, India

[7]Department of Maxillofacial Surgery and Diagnostic Sciences, Division of Oral Pathology, College of Dentistry, Jazan University, Jazan, Kingdom of Saudi Arabia

Corresponding Author: Prashanth Panta, Department of Oral Medicine and Radiology, MNR Dental College and Hospital, Sangareddy, Telangana, India, Phone: +91 9701806830, e-mail: maithreya.prashanth@gmail.com

How to cite this article: Mitroulia A, Gavriiloglou M, *et al.* Salivary Gland Stem Cells and Tissue Regeneration: An Update on Possible Therapeutic Application. J Contemp Dent Pract 2019;20(8):978–986.

Source of support: Nil

Conflict of interest: None

Histology and Embryology of SGs

There are major and minor SGs in the head and the neck area.[13] The major SGs include the parotid (which is the largest), submandibular, and sublingual glands. SGs consist of the cells epithelial in nature, secretory called acinar, myoepithelial cells, and ductal system. The saliva is produced at the level of acini and passes through the ductal system which is composed of intercalated, striated, and excretory ducts. The intercalated ducts and the basal cells of the striated duct have been speculated as a possible position of SCs.

A conflict concerning the embryologic origin of the epithelium of SGs divides researchers. Specifically, citations refer that the parotid originates from the ectoderm, whereas the submandibular and sublingual glands derive from the endoderm. Concerning minor SGs, their origin is basically unknown, except for Von Ebner

Fig. 1: Clinically accessible minor SGs in the labial mucosa

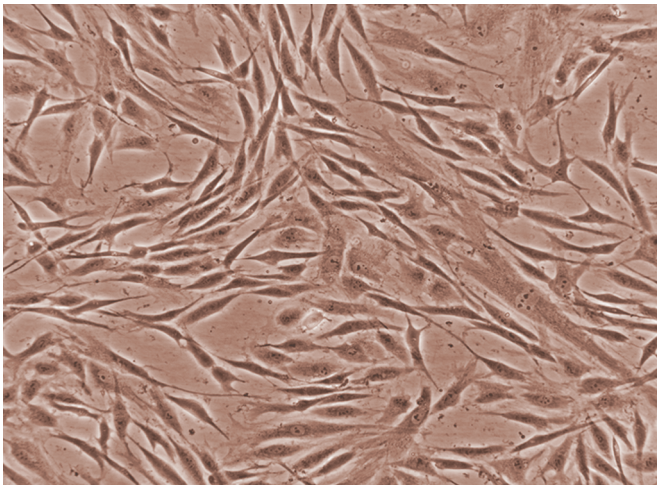

Fig. 2: SCs' culture directly derived from minor SG of the lower lip. The mesenchymal-type SC population is predominant in comparison to rounded cells of epithelial type

minor SGs which are originated from the endoderm. However, Rothova et al. used mice and Sox17-2A-iCre/R26R reporter for tracing endoderm progenitor cells during oral development.[14] In contrast to previous studies, Rothova et al. suggested that major SGs originate from the ectoderm. Palatal minor mucous glands have both endodermal and the ectodermal origin, while minor lingual SGs may be derived from the endoderm.[14] However, it is important to perform lineage tracing with endodermal Cre drivers to confirm speculations.[14] Labial SGs (LSGs) are mixed, mostly mucous, and are situated mainly in the center of the oral cavity.[12]

Revealing the Exact Location of SCs

The presence of SCs within SGs is a controversial subject for more than a decade. SCs in the major SGs have been identified through labeling of cells with bromodeoxyuridine (BrdU). The population of label-retaining cells (LRCs), which did not express keratin 18 (an acinar/duct cell marker) or α-smooth muscle actin (myoepithelial cell marker), were considered to be the SC population. Those LRCs were specifically explored at the top of the intercalated duct but some were also observed in the excretory duct.[15]

In 2014, Andreadis et al.[12] isolated a mixed cell population from normal human labial minor salivary glands (MSGs). The population were characterized with SC properties of the mesenchymal and epithelial features[12] (Fig. 2). The superficial location of minor SGs in the lip could consist of an innovative source of adult SCs without any ethical limitation.[12] A group of scientists confirmed the presence of human MSG SCs (hMSG MSCs) in the lamina propria of oral mucosa.[16] Recently, these have been observed on the basal layer of the excretory duct and in the mesenchymal tissue between acinar and ductal epithelial structures of MSGs. They are characterized by enhanced SC capabilities with the potential to participate in tissue engineering.[16]

Use of SC Markers

SC markers are genes and their protein products that can be used to characterize various SC populations. The field of SG SC research deciphered a plethora of putative markers that have been used to identify stem/progenitor cells, but there is evidence that only a few marker positive cells have the ability to actively restore irradiated glands.[17] SC markers are also the key point to determine, which SC population could provide maximum regeneration, to achieve the best results with minimum tissue demands.

CKIT-CD117 (cell membrane protein tyrosine kinase receptor) has been detected in the excretory duct of human major SGs.[12] On the one hand, various studies have proved that c-kit+ cells are capable of proliferation and differentiation *in vitro* and *in vivo*.[18] According to Lombaert et al., transplantation of only 300 c-kit+ cells was enough to rescue SG dysfunction in a mice model.[18] This *in vivo* transplantation study points that c-kit+ cells show more SC-like characteristics than cells positive for other markers (CD133, CD49F, and CD24).[18] On the other hand, mSG glands were negative for the CKIT-CD117 marker and, in addition, CKIT-CD117+ cells in cell lineage from adult mice SGs are heterogeneous and differentiated. Long-term *in vivo* lineage tracing showed at least two CKIT-CD117 ductal cell lineages, which did not play a crucial role in cell maintenance. These results question the reliability of CKIT-CD117 as a true SG SC marker.[17]

Nanog and Oct3/4 are embryonic SC markers, detected in major SGs.[19] Interestingly, a similar pattern of Oct4 expression is also noticed in some kidney tubular cells, suggesting that they could be possible renal SCs, indicating possible similarities with SGSCs.[19]

Aldehyde dehydrogenases (ALDHs) are highly expressed in SCs and they participate in many biological activities. Various murine and human SCs like hematopoietic, neural, muscle, hepatic, and adipose SCs are found with elevated ALDH1 levels. Interestingly, human and mouse MSG SCs are characterized by a higher expression of ALDH3 rather than ALDH1. Higher levels of ALDH3 were found in SCs in comparison with those in non-SCs.[20] Another lineage tracing study has shown that ductal cells express Ascl-3, a transcriptional factor localized primarily to the ductal cell, and also express Nanog and Oct 3/4.[21]

Nestin is an intracellular SC marker expressed in cells undergoing proliferation and migration. It is strongly detected in human minor salivary gland mesenchymal stem cells (hMSGMSCs), implying its value in tissue engineering. Interestingly, in the human pancreas and SG SCs population, a similar pattern of nestin expression is seen.[17] Integrin a6b1 is a proven SG progenitor cell marker in rats. These cells' profile was expressed after duct ligation, and a6b1+ cells were able to generate both acinar-like and

duct-like structures. However, these cell lines were characterized by uncontrolled growth, so further research is required before they could be used *in vivo*.[8]

SOX2 is a transcription factor that has been considered to regulate pluripotency in various epithelial tissues. During fetal development, SOX2 plays an important role in the formation of cell types, especially in the endoderm and the nervous system. In adult sublingual glands, SOX2+ cells are the putative SCs[22] (Table 1). Interestingly, markers of SG SCs are also expressed in various SG malignancies like mucoepidermoid carcinoma.

Available Scaffolds for Tissue Engineering

Scaffolds are a really important in tissue engineering as they function as an extracellular matrix where cells adhere, proliferate, and differentiate. Therefore, scaffolds must be biocompatible and biodegradable (if necessary), so that they resemble the microenvironment of native tissue. In the presence of a scaffold, extracellular proteins and growth factors would regenerate functional organs. There has been much research on scaffolds that would be suitable for SG regeneration. Scaffolds can be subdivided into biologic (collagen, fibrin, silk, chitosan, alginate, and hyaluronic acid (HA)) and biocompatible (polyglycolic acid, poly-lactic acid, poly-lactic-*co*-glycolic acid, and polyethylene glycol) scaffolds. In addition, the biomaterial can be applied to 2D cultures and 3D cultures. In the first category, cells are cultured as a monolayer lining a tube consisting of polymers, whereas 3D cultures resemble acinar and ductal structures as cells are cultured in hydrogel matrices. For example, chitosan, a substance found in the exoskeleton of crustaceans, resembles glucosamine and has been proven to be capable of ensuing branching morphogenesis.[23] Furthermore,

Table 1: SG SC markers

Marker	*Role*	*In vitro* differentiation*	*In vivo function*	*Location*
CD24	Sialoglycoproteinic cell adhesion molecule acting expressed in progenitor cells	Human**	Yes (mouse)	Cell membrane
CD34	Marker expressed in early lympho-hematopoietic stem and progenitor cells, and embryonic fibroblasts	Human**	No	Cell membrane
CD117/CKIT	Tyrosine kinase receptor expressed in endothelial, epithelial, and endocrine cells during development	Mouse Rat** Human (<1%)	Yes (mouse)	Cell membrane
CD44	Leukocyte common antigen (LCA), hematopoietic marker	Human*	No	Cell membrane
CD271/NGFR	Low-affinity nerve growth factor receptor, SC marker	Human**	No	Cell membrane
Nanog	Embryonic SC marker	Human**	No	Intracellular
Aquaporin-1	Water channel's molecule expressed in developed SGs	Mouse**	No	Cell membrane
Oct 3/4	Embryonic SC marker	Human**	No	Intracellular
Stro-1	Early MSC marker	Human**	No	Cell membrane
Nestin	SC marker and marker of proliferating and migrating cells	Human**	No	Intracellular
CD90/Thy1	Cell adhesion molecule, expressed in hematopoietic and adult hepatic stem/progenitor cells	Human**	No	Cell membrane
CD81/TAPA	Tetraspanina molecule related to signal transduction, cell development, growth, and motility	Human**	No	Cell membrane
CD105/ endoglin	Cytokine which acts as a part of TGF-a receptor complex and participates in cell proliferation, differentiation, and migration	Human**	No	Cell membrane
CD49f/a6 integrin	Cell adhesion molecule which mediates intercellular and cell-matrix interactions and cell migration	Human** Rat***	Yes(mouse)	Cell membrane
SSEA-3	Embryonic stem cell marker	Human** Mouse **	No	Cell membrane
CD146/ MUC18	Perivascular marker associated to multipotency and MSC multilineage differentiation potential	Human**	No	Cell membrane
ALDH	Enzymes involved in aldehyde detoxification and in the metabolism of retinoic acid, biogenic amines, and neurotransmitters	Human** Mouse**	No	Cell membrane
Ascl-3	A transcriptional factor localized primarily to ductal cells	Human** Mouse**	No	Cell membrane
TRA-1-60	Embryonic SC marker related to mesenchymal, hepatic, cardiac, pancreatic, and neural cell	Human**	No	Cell membrane
CD298/Na-K-ATPase B3	Component of the cell membrane sodium pumps	Human**	No	Cell membrane

*It has been reported that murine[18] and human[41] stem/progenitor cells can be cultured into salispheres (primary spheres) via an enrichment culture *in vitro*

**Salispheres culture method

***Monolayer culture method

chitosan was chemically coupled to nano-fiber scaffolds and it was demonstrated that they could lead to increased proliferation compared to nano-fibers themselves and, at the same time, without cytotoxicity.[24] Matrigel is another potential scaffold which is derived from Engelbreth–Holm–Swarm (EHS) mouse sarcoma cells, which contain not only basement membrane proteins such as collagen IV, laminin, fibronectin, entactin, and perlecan but also multiple angiogenic and growth factors that regulate cell growth and differentiation.[25] This product has achieved successful results but only *in vitro* and is speculated as unsuitable for clinical translation as its components are not xeno-free and the basement membrane proteins derived from mouse sarcoma do not meet the requirements of the current good manufacturing practice (GMP) regulations by the FDA.[26]

Noteworthy, a whole de-cellularized organ has been considered as an ideal bio-scaffold. The de-cellularized scaffold contains only its extracellular matrix proteins and native structures, but without any cellular components. It could adhere to the cells and lead to the expression of some differentiation markers, highlighting it as another potential scaffold for SG regeneration.[27]

Polymers can also be used as substrates for SG regeneration, but scaffolds without extracellular matrix coating cannot provide cell adherence or growth. Shin et al. conducted a study in which human parotid epithelial cells were cultured on matrigel, on poly ethylene glycol (PEG) hydrogel and also on micropatterned poly-caprolactone (PCL) nano-fibrous microwells, which were assembled by photo-patterning of PEG hydrogel in the presence of an electrospun PCL nano-fibrous scaffold. Results showed that a higher level of salivary epithelial markers, tight junction proteins, E-cadherin, and F-actin were expressed in PCL nano-fibrous microwells.[28] In another study, PEG hydrogels were suggested as more suitable scaffolds for SG regeneration, while with the introduction of the appropriate growth factors and extracellular matrix (ECM) proteins, they control cell behavior and additionally their stiffness is controlled by the amount of PEG macromeres.[29] "Ideal matrix stiffness" is an important characteristic, and high stiffness is undesirable in tissue regeneration.[30] The basic problem with polymers is the possibility of inflammation due to their degradation products. Moreover, a silk fibroin scaffold with primary SG epithelial cells from rat major SGs has been established. The cells expressed acinar characteristics and produced amylase *in vitro*. Thus, silk fibroin is also a promising scaffold for SG regeneration as it is a natural product, biocompatible, and biodegradable with a wide range of elasticities.[31] Another biocompatible and biodegradable scaffold is a 3D scaffold based on HA, which is abundant in the human body. A 3D HA-based hydrogel scaffold leads to the expression of CD44 and CD168 (RHAMM) markers from human SCs in rodent hosts.[32]

Last but not least, a separate reference should be made to nano-fiber scaffolds, which need to be studied further for their establishment in tissue engineering. Nano-fiber and microfiber scaffolds can be created from electrospinning polymers such as poly-L-lactic-*co*-glycolic acid (PLGA) so that they can mimic the architecture of the basement membrane that surrounds the acinar and epithelial cells. Their ability to stimulate embryonic branching morphogenesis is confirmed and are also considered as the scaffolds that promote the most *in vivo* like cell morphology, in contrary with microfiber scaffolds.[33] Nano-fiber scaffolds can also be coupled with other substrates like chitosan as mentioned previously. Electrospun nano-fibers are preferred because their micromechanical characteristics (such as diameter, shape, strength, or composition of fibers) can be easily regulated and they can also carry signaling molecules (genes and drugs), which are necessary for differentiation guidance.[34]

3D bio-printing has also been a technological breakthrough in medicine, which enables the exact display of human organs into 3D structures. Designs are fabricated using the computer-aided design (CAD) software and images are obtained via computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound (US), and 3D printers use this data to produce 3D volumetric structures through a layer-by-layer deposition of materials.[35] Inkjet printers, laser-based printers, and micro-extrusion printers are the most commonly used 3D printers, and synthetic polymers, ceramics, and polymeric hydrogels are the most common printable materials.[35] Considering their biocompatibility and tenability, polymeric hydrogels are suggested as the best materials for tissue printing.[36] Therefore, 3D-printed scaffolds could be designed for each patient and could be excellent for tissue regeneration due to their ability to mimic anatomical features in great detail. Concerning dentistry, attempts have been made to use this technique for the regeneration of periodontal complex, bone, and cartilage in the craniofacial area and for whole teeth regeneration,[37] but examples of trials for SG regeneration through 3D printing are still lacking in the literature. It is also remarkable that cells and growth factors are not combined in the polymer mixture as they are susceptible to the high temperatures during the bio-printing process.[35,38] Conclusively, 3D printing is a challenge in tissue regeneration and we are still far from the creation of functional organs in the laboratory. However, 3D printing has a great scope in the future and will become feasible for clinical transplantation purposes. Despite all these findings, the ideal scaffold for *in vivo* SG regeneration has not yet been established, and further studies are needed.

Experiments, Accomplishments, and Therapy Potentials

Transplantation in Murine

The use of SCs as a treatment option for hyposalivation has been an ambitious plan for over a decade. The first attempt was made in 2004, but SCs failed to differentiate into saliva producing acinar cells or myoepithelial cells in rat SGs, 4 weeks after transplantation.[39] This study established the feasibility of a successful and biocompatible transplantation with the simultaneous cell adhesion.[39] On the contrary, the detection of Sca-1/c-kit+ cells' population from mice SGs and their differentiation into hepatic cells when cultured in matrigel and into a pancreatic lineage with the presence of glycagon-like-peptide 1 (GLP-1) was a breakthrough of the same year.[40] Lombaert et al.[18] later cultured *in vitro* c-kit+ SCs that originated from murine submandibular glands and injected into severely damaged irradiated murine SGs. These cells managed to express amylase and mucin, while rescuing the glands hypofunction at some point.[18] Based on this ability of c-kit cells to repair damaged SGs, investigators have tried to translate this in humans. Another study proved that c-kit-positive cells could also be isolated from human exocrine ducts, organize in salispheres, and express amylase and mucin, promising an equivalent restoring ability.[41] Transplantations of SCs from various tissues are currently being conducted and evaluated for efficacy and safety.

Cell-based Therapy

Adipose-derived cells (ADSCs) were isolated and transplanted into mice and accomplished to differentiate into endothelial cells, which improved blood flow, an important factor for saliva flow. ADSCs were considered as cells with strong potential of restoring many parts of SGs without infiltrating the surrounding tissue.[42]

In a different model, during the same time, bone marrow cells were examined as a possible source of therapeutic SCs and were engrafted into mice and rats. The mouse model reacted better than the rat model as bone marrow SCs accomplished functional regeneration of the SGs. It should also be noted that acinar-like cells used in the same study showed better-restoring capability than bone marrow cells.[43] Lately, trans-differentiation was observed in acinar cells. These cells have been found to improve saliva secretion, reduce apoptosis, and help microvessel regeneration in mice.[54]

As progress in rat and mice models is accomplished, studies begin to create human SCs cultures and assess their potential. A novel *in vivo* model of a tissue-engineered SG from human SG progenitor cells was investigated with the culturing of human SG cells in HA hydrogels. Injections of human SCs into rodents led to saliva production and regeneration of irradiated murine SGs, for the first time due to a self-regenerating kit+ cells population.[44] At the same time, SG tissues were characterized by an activation of the Wnt pathway, which is crucial for the self-renewal *in vitro*.[44]

Nevertheless, first-in-man mesenchymal SCs use for radiation-induced xerostomia (MESRIX) was conducted in 2017, including a double-blinding clinical trial with autologous adipose-derived MSC therapy or placebo therapy (no results yet). Evidence still needs to be evaluated and further investigated as this study is established as the first clinical trial in humans intending to estimate feasibility, efficacy, and safety of such project.[45] These studies point out at the possible application of this method especially for xerostomia induced by radiation exposure in head and neck cancer patients.

Autologous SCs Transplant in SGs

Cell-based therapy[26] can also be used, when glands are partially or globally injured, they can be restored by transplanting cells at the end of the treatment. These SCs are isolated and preserved in cultures before treatment.[18] However, due to aging, patients contain less number of SCs. To overcome this, recent studies focus on the use of growth factors[51] or the ALDH3 activator[20] so as to increase the number of kit+ cells *ex vivo*. Cryopreservation can be a therapy solution as Neumann et al. developed a SC banking model where SG CD49f+ CD29+ cells were preserved up to 3 years without any distortion.[52]

Regeneration Methods/Gene Therapy

Therapy potentials of xerostomia aim for SG regeneration and their functional restoration. However, so far, no such therapy was found. Current, innovative therapies include gene therapy which is a method that uses transferred genes into cells so as to treat a disease or correct a cellular dysfunction. Promising results have been reported in a clinical trial, where 5 of 11 enrolled subjects had an increased saliva flow rate over the first 42 days. Their irradiated parotid glands was delivered AdhAQP1, which is the first-generation serotype 5 adenoviral (Ad5) administering the hAQP1 gene.[46] Remarkably, all five subjects reported higher levels of parotic saliva flow rates even 5 years later.[47] Another study used a hybrid serotype S adenovirus vector as a transferring means for human KGF gene.[48] Saliva flow was increased and acinar cell proliferation occurred. In addition, concurrent transient activation of Wnt/β-catenin pathway in male mice preserved SG function by inhibition of apoptosis and preservation of functional SCs.[49]

Another alternative gene therapy is gene activation. ALDA-89 is a selective ALDH3 activator, which enriched kit+/CD90+ SC population. Higher levels of ALDH3 were examined in those cells in comparison with those in non-SCs. This led to increased proliferation and preservation of SG SCs.[20] The improvement of saliva secretion could be achieved by retrograde injection of siRNA-coated nano-particles, which ensures direct accessibility to gland parenchyma. This method targeted a pro-apoptotic Pkcδ gene, which was silenced and apoptosis was prevented.[50]

Bioengineering of SG Germ

The glandular function could be restored with the implantation of a glandular structure bioengineered *in vitro*. Recently, a bioengineered SG germ was transplanted into adult mice, resulting in the regeneration of SG function.[53] Morphogenesis was successful through epithelial and mesenchymal interactions. The existing ducts and the transplanted SGs were reconnected. Specifically, the transplanted submandibular gland was capable for saliva secretion, protection of the oral cavity from bacteria, and restoration of normal swallowing.

Tissue Engineering with Scaffolds

A biocompatible scaffold that simulates gland's microenvironment and pluripotent cells that preserve salivary markers consists of tissue engineering. Embryonic SCs[55] and induced pluripotent SCs[56] can be a treatment option, as they are stable and without oncogenic potential. The cells are seeded in a scaffold so as to recreate an artificial gland.[57,58] A hydrogel culture system was capable of maintaining 3D salivary spheroid structures and for acini-like structures *in vitro*, whereas it retained viability, when transplanted into rats. In addition, poly lactic-glycolic acid is a promising scaffold, as it supports branching of fetal SMGs.[59] Moreover, a study used SGs cells derived from a 3D coculture of mouse ES cells and human SG-derived fibroblasts. *In vitro,* the cells are supposed to have the neogenetic ability, though it is still unclear whether they maintain stability *in vivo*.[55] Another research approach is to use the HSY cell line, which are neoplastic epithelial cells that are derived from transplanted human parotid gland adenocarcinoma to athymic mice tumors, for bioengineering therapy. These cells are morphologically similar to intercalated duct cells, which are a reservoir of progenitor SCs.[60]

Pancreas: A Gland of Great Significance, Quite Similar to SGs

The pancreas is a gland that produces both hormones and enzymes, playing a crucial role not only in nutritional balance but also in reserving energy for cellular activities. It includes three types of cells: acinar, ductal, and endocrine cells.

There have been numerous efforts to define the areas which home the SCs and to highlight their possible contribution in therapy. In contrast to other organs, the pancreatic SCs are rare in postnatal tissues. Specifically, the replacement of β-cells depends mainly on the expansion of pre-existing rather than differentiation of SCs.[61] Nevertheless, when the pancreas is injured through a duct ligation experiment, a neogenesis of β-cells was detected from Neurog3-expressing islet progenitors.[62] It is thought that pancreatic ducts[63] and pancreatic duct glands (PDGs)[64] contain committed precursors,

which have confined proliferative capabilities. Recently, adult SC populations have been found in the biliary tree both for the pancreas and the liver. These discrete areas of SCs are called niches. Niches consist of peribiliary glands (PBGs), which contain biliary tree SCs (hBTSCs). These cells are precursors to pancreatic SCs (hPSCs).[65]

Regarding possible regenerative potential using SCs derived from the oral cavity, Govindasamy et al. used human dental pulp SCs (DPSCs) to differentiate them into β-cells.[66] They were *in vitro* functioned and secrete insulin and C-peptide in a glucose-dependent manner.[66] SGs and pancreas developmentally originate from the foregut. This might explain the phenotypic similarities and analogous properties of these two functionally different cell populations. Apart from their similar origin, exocrine glands including the pancreas, the liver, and SGs develop via branching morphogenesis. During morphogenesis, each epithelium interacts with gland's mesenchyme directing gland's branching morphogenesis. Even though they express different SC markers (embryonic and adult), they could differentiate into ectoderm-, mesoderm-, and endoderm-derived cells.[67] As exocrine glands, both SGs and the pancreas have glandular SCs (GSCs), which can differentiate into multiple cell types and have plasticity.[67] Hepatocyte and pancreatic islet-like cells were observed when salivary gland progenitor-1 (SGP-1) cells were cultured on type-I collagen dishes. SGP-1 was obtained after the ligation of the submandibular gland.[68] The same research team succeeded in differentiating human SG progenitor cells in spherical cultures into NKX6.1 and neurogenin-3 expressing cells which are expressed at the early islet stage.[69] Insulin and albumin were expressed after differentiation of swine SGP cells in spherical culture, suggesting that they could be used in endodermal regeneration. SGSCs formed pancreatic clusters when they were cultured with activin A, exendin-4, and retinoic acid. They express Pdx1, pan polypeptide, and neurogenin-3 which are pancreatic cell markers.[70] Differentiation of mouse SG-derived progenitors (mSGPs) into a pancreatic endocrine lineage was successful, when cultured with glucagon-like peptide-1 (GLP-1)[40] (Fig. 3 and Table 2).

Liver: An Approach for Hepatic Differentiation

Liver's essential metabolic, endocrine, and exocrine functions are of vital importance for the preservation of life. It regulates blood composition by modulating and releasing glucagon as per needs; processes hemoglobin for iron storage; and produces cholesterol, albumin, clotting factors, and a wide variety of other important proteins. It consists of two groups of cells; parenchymal hepatocytes and biliary epithelial cells, and non-parenchymal cells such as Kupffer cells, stromal cells and stellate cells of mesodermal origin. It is worth mentioning that in case of injury and mass loss, liver possesses the admirable capacity of regeneration which is accomplished through replication of mature adult hepatocytes and other hepatic cell types.[71]

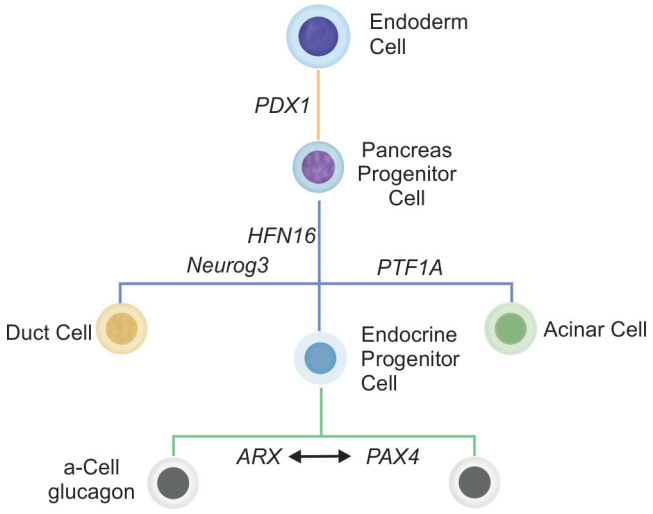

Fig. 3: Different pancreatic cells derived from endodermal cell lineage

Table 2: Pancreatic SCs markers

Endoderm Induction markers*	CD184, CD117, EPCAM, CD49e, CD51, CD141, and CD238
Pancreatic progenitor marker	Sox9
Mature islet cell surface markers	FXYD2, tetraspanin7 (TSPAN7), Tmem27, δ-, α- and β-cell surface antibodies, and pan-islet antibodies
Endocrine surface markers	DDR1, DNER, Pdx1, MafA, Ngn3, NeuroD, NKX6.1, and Ptf1a
Surface markers of hormone-positive cells	SEZ6L2, DISP2, LRP11, and CD24
Acinar epithelial cell markers	NKX6.1 and Ptf1a
Ductal epithelial cell markers	CD133 and CD149f

*None of these is exclusively specific for endoderm lineage[77]

Stem/progenitor cells present in the liver have been thoroughly investigated through several researches and *in vivo* experiments. The fact that hepatocytes are capable of achieving a significant clonal expansion suggests that they themselves could possibly consist of hepatic SCs. However, studies have shown that in case of a severe liver injury, a potential SC population located within the intrahepatic biliary tree is activated and gives rise to a bio-potential cell population called the "oval cells" that can differentiate into hepatocytes. Oval cell populations are positive for hepatocyte and bile ductal cell markers such as albumin, fetoprotein alpha-fetoprotein (AFP), cytokeratin 19, and other bile duct antigens and also contain hematopoietic cell surface antigen-positive cells. Liver regeneration does not include the proliferation of these types of SCs. On the contrary, oval cells are noticed during progenitor-dependent liver regeneration, which has been shown under different experimental conditions.[72] One representative protocol[73] combined the administration of 2-acetylaminofluorene (2-AAF) with partial hepatectomy and results showed that under these circumstances, 2-AAF suppressed hepatocytes proliferation and oval cells appeared in the peri-portal area before regeneration. It has also been suggested that when all other means of regeneration fail, a third population of hematopoietic SCs derived from bone marrow can differentiate into hepatocytes or oval cells and rescue the liver.[74]

Identification and isolation of hepatic SCs are assisted by several stem/progenitor markers including epithelial cell adhesion molecule (EpCAM), CD133 (prominin), CD44 (hyaluronan receptors), ALDH hedgehog proteins, NCAM and CXCR4. Hepatic SCs can also be culture selected with a hormonally defined medium, called Kubota's medium, that supports hepatic progenitors but not mature cells.[75] Biomatrix scaffolds that contain extracellular matrix components, matrix-bound cytokines, and growth factors could provide the necessary chemical signals for a stable scaffolding that can be used for inducing hepatic SCs into liver fetes or just for the

Table 3: Correlation between Pancreatic and Liver SC markers with SG SC markers

Markers	*SGs*	*Pancreas*	*Liver*	*Role*
CD24	Sialoglycoprotein adhesion molecule expressed in progenitor cells	Surface markers of hormone-positive cells[77]	–	Pluripotency marker during SC differentiation
CD34	CD34+ cells human parotid, sublingual and submandibular glands[78]	–	CD34+ cells from human fetal liver express biliary epithelial markers CK7, CK8, and CK18[79]	Cell surface glycoprotein General marker for progenitor cells
CD44	Human SCs[80]	Pancreatic mesenchymal SCs (pMSC) that generate at least two germ layer cells, including endoderm-derived cells, but still no convincing evidence of pancreatic lineage cells[81]	–	Hematopoietic marker
CD90 (Thy1)	Human SCs[80]	Pancreatic mesenchymal SCs (pMSC)[81]	Human hepatic progenitor cells (HPCs)[82]	Cell adhesive molecule
Sox-2	Regulates acinar cell development in SG[83]	*	–	Transcriptional regulator in pluripotent SCs
CD133	Ductal SC expression in humans[84]	Potential reservoir of side population of adult stem/progenitor cells that express CD133[85]	–	Transmembrane glycoprotein and SC marker

*Undetermined role

maintenance of mature hepatic cells for many weeks (>8 weeks) without loss of their viability.[76]

Several researches have been conducted to prove whether or not, tissue SCs from the liver could undergo trans-differentiation to cells of other tissues and *vice versa*. For example, submandibular SGs originate from the endoderm and the ectoderm which indicates the possible presence of endodermal progenitor cells. This case was investigated by Okimura et al. in their experiment when they cultured cells obtained from the ligated SG and identified colonies of epithelium-like cells. Then they singled out and purified the cells by limited dilution, and one of the cells designated SGP-1 was used for further experiments. The hematopoietic SC marker CD34 and hepatic oval cell markers such as albumin, AFP, and cytokeratin-19 were all negative, but when SGP-1 cells were transplanted into the liver via the portal vein, these cells were integrated into the hepatic trabecule and produced the albumin. When SGP-1 cells were cultured with collagen type 1, they were differentiated into hepatic and pancreatic lineages. In conclusion, the multipotent progenitor cells isolated from the rat SG have characteristics of tissue SCs and can differentiate into cells of endodermal lineages.[68] Recently, a study on minor SG cells proved their ability to express liver-associated markers (ALB, CYP3A4, AAT, and CK18) *in vitro*, which also improved severe acute liver damage in severe-combined immunodeficiency (SCID) mice when injected *in vivo*.[4] It would be a great step to combine minor SG cells with those organs cells for the purpose of tissue regeneration (Table 3).

Conclusion

SC research expands the knowledge concerning therapeutic opportunities for SG hypofunction, and even other glandular organ failures. An autologous treatment using patient's own SCs may provide an easy, low-cost, and a less complicated solution. Also, such approaches will exhibit ideal tissue tolerance and no local inflammation following transplantation. SCs without regard to their tissue of origin universally express great potential to regenerate, opening a new door to individualized therapy. Especially, the prospect of using SCs derived from minor SGs could be even less traumatic, and an efficient source of SC therapy in the near future.

However, SC therapeutic application is currently limited by several issues including immunological host vs graft reactions which needs to be considered. Their capability to differentiate into various cell lines makes it difficult to reach a functional tissue differentiation. Long-term possibility of carcinogenesis, somatic mutations, epigenetic defects induced during reprogramming, and their lack of stability *in vivo* are significant limitations of SCs, especially embryonic and pluripotent SCs, which prevents from using them in therapies.[55,56] Further clinical studies are needed, to overcome these barriers and to attain the promises of SC-based regenerative medicine. Besides, surmounting these limitations will give us the opportunity to understand in detail not only disease's pathogenesis but also the complexity of embryogenesis. SCs hold a tremendous potential, so reducing the limitations can lead to unlimited possibilities. It would be even exciting and optimistic for tissues such as SGs, the liver, the pancreas, and even thyroid and the kidney to exchange SCs and provide each other regeneration.

References

1. Tanasiewicz M, Tomasz Hildebrandt T, et al. Xerostomia of Various Etiologies:A Review of the Literature. Adv Clin Exp Med 2016;25: 199–206. DOI: 10.17219/acem/29375.
2. Ivanovski K, Naumovski V, et al. Xerostomia and salivary levels of glucose and urea in patients with diabetes Prilozi. Prilozi 2012;33: 219–229.
3. Holmberg KV, Hoffman MP. Anatomy, biogenesis and regeneration of salivary glands. Hoffman Monogr Oral Sci 2014;24:1–13.
4. Zhang C, Li Y, et al. Therapeutic potential of human minor salivary gland epithelial progenitor cells in liver regeneration. Sci Rep 2017;7:12707. DOI: 10.1038/s41598-017-11880-z.
5. Okumura K, Nakamura K, et al. Salivary Gland Progenitor Cells Induced by Duct Ligation Differentiate Into Hepatic and Pancreatic lineages. Hepatology 2003;38:104–113. DOI: 10.1053/jhep.2003.50259.
6. Weissman IL. Stem Cells: Units of Development, Units of Regeneration, and Units in Evolution. Cell 2000;100:157–168. DOI: 10.1016/S0092-8674(00)81692-X.

7. Wagers AJ, Weissman IL. Plasticity of Adult Stem Cells. Cell 2004;116:639–648. DOI: 10.1016/S0092-8674(04)00208-9.
8. Pringle S, Van Os R, et al. Concise review: Adult salivary gland stem cells and a potential therapy for xerostomia. Stem Cells 2013;31: 613–619. DOI: 10.1002/stem.1327.
9. Okumura K, Shinohara M, et al. Capability of Tissue Stem Cells to Organize into Salivary Rudiments. Stem Cells Int 2012;2012:502136. DOI: 10.1155/2012/502136.
10. Aure MH, Arany S, et al. Salivary Glands, Stem Cells, Self-duplication, or Both? J Dent Res 2015;94:1502–1507. DOI: 10.1177/0022034515599770.
11. Zhang H, Boddupally K, et al. Defining the Localization and Molecular Characteristic of Minor Salivary Gland Label-Retaining Cells. Stem Cells 2014;32:2267–2277. DOI: 10.1002/stem.1715.
12. Andreadis D, Bakopoulou A, et al. Minor salivary glands of the lips: a novel, easily accessible source of potential stem/progenitor cells. Clin Oral Invest 2014;18:847–856. DOI: 10.1007/s00784-013-1056-6.
13. ISBN: 9780323485180 eBook.
14. Rothova M, Thompson H, et al. Lineage tracing of the endoderm during oral development. Dev Dyn 2012;241:1183–1191. DOI: 10.1002/dvdy.23804.
15. Kimoto M, Yura Y, et al. Label retaining cells in rat submandibular gland. J Histochem Cytochem 2008;56:15–24. DOI: 10.1369/jhc.7A7269.2007.
16. Lu L, Li Y, et al. Characterization of a Self-renewing and Multi-potent Cell Population Isolated from Human Minor Salivary Glands. Sci Rep 2015;5:10106. DOI: 10.1038/srep10106.
17. Kwak M, Ninche N, et al. c-Kit+ Cells in Adult Salivary Glands do not Function as Tissue Stem Cells. Sci Rep 2018;8:14193. DOI: 10.1038/s41598-018-32557-1.
18. Lombaert IM, Brunsting JF, et al. Rescue of Salivary gland function after stem cell transplantation in irradiated glands. PLoS One 2008;3:e2063. DOI: 10.1371/journal.pone.0002063.
19. Lin SL. Concise review: deciphering the mechanism behind induced pluripotent stem cell generation. Stem Cells 2011;29:1645–1649. DOI: 10.1002/stem.744.
20. Banh A, Xiao N, et al. A Novel Aldehyde Dehydrogenase-3 Activator Leads to Adult Salivary Stem Cell Enrichment *In Vivo*. Clin Cancer Res 2011;17:7265–7272. DOI: 10.1158/1078-0432.CCR-11-0179.
21. Bullard T, Koek L, et al. Ascl3 expression marks a progenitor population of both acinar and ductal cells in mouse salivary glands. Dev Biol 2008;320:72–78. DOI: 10.1016/j.ydbio.2008.04.018.
22. Patel VN, Hoffman MP. Salivary gland development: a template for regeneration. Semin Cell Dev Biol 2014;25-26:52–60. DOI: 10.1016/j.semcdb.2013.12.001.
23. Yang TL, Young TH. The enhancement of submandibular gland branch formation on chitosan membrane. Biomaterials 2008;29(16): 2501–2508. DOI: 10.1016/j.biomaterials.2008.02.014.
24. Cantara SI, Soscia DA, et al. Selective functionalization of nanofiber scaffolds to regulate SG epithelial cell proliferation and polarity. Biomaterials 2012;33:8372–8382. DOI: 10.1016/j.biomaterials.2012.08.021.
25. Kleinman HK, Martin GR. Matrigel: basement membrane matrix with biological activity. Semin Cancer Biol 2005;15:378–386. DOI: 10.1016/j.semcancer.2005.05.004.
26. Lombaert I, Movahednia MM, et al. Concise Review: Salivary Gland Regeneration: Therapeutic Approaches from Stem Cells to Tissue Organoids. Stem Cells 2017;35:97–105. DOI: 10.1002/stem.2455.
27. Gao Z, Wu T, et al. Generation of Bioartificial salivary gland using whole organ decellularized Bioscaffold. Cells Tissues Organs 2014;200:171–180. DOI: 10.1159/000371873.
28. Shin HS, Kook YM, et al. Functional spheroid organization of human salivary gland cells cultured on hydrogel-micropatterned nanofibrous microwells. Acta Biomater 2016;45:121–132. DOI: 10.1016/j.actbio.2016.08.058.
29. Shubin AD, Felong TJ, et al. Development of poly (ethylene glycol) hydrogels for salivary gland tissue engineering applications. Tissue Eng Part A 2015;21:1733–1751. DOI: 10.1089/ten.tea.2014.0674.
30. Peters SB, Naim N, et al. Biocompatible Tissue Scaffold Compliance Promotes Salivary Gland Morphogenesis and Differentiation. Tissue Eng Part A 2014;20:1632–1642. DOI: 10.1089/ten.tea.2013.0515.
31. Zhang BX, Zhang ZL, et al. Silk fibroin scaffolds promote formation of the ex vivo niche for salivary gland epithelial cell growth, matrix formation, and retention of differentiated function. Tissue Eng Part A 2015;21:1611–1620. DOI: 10.1089/ten.tea.2014.0411.
32. Pradhan-Bhatt S, Harrington DA, et al. A Novel *In Vivo* Model for Evaluating Functional Restoration of a Tissue-Engineered Salivary Gland. Laryngoscope 2014;124:456–461. DOI: 10.1002/lary.24297.
33. Sequeira SJ, Soscia DA, et al. The regulation of focal adhesion complex formation and salivary gland epithelial cell organization by nanofibrous PLGA scaffolds. Biomaterials 2012;33:3175–3186. DOI: 10.1016/j.biomaterials.2012.01.010.
34. Ma B, Xie J, et al. Rational design of nanofiber scaffolds for orthopedic tissue repair and regeneration. Nanomedicine (Lond) 2013;8: 1459–1481. DOI: 10.2217/nnm.13.132.
35. Obregon F, Vaquette C, et al. Three-dimensional bioprinting for regenerative dentistry and craniofacial tissue engineering. J Dent Res 2015;94:143S–152S. DOI: 10.1177/0022034515588885.
36. Annabi N, Tamayol A, et al. 25th anniversary article: rational design and applications of hydrogels in regenerative medicine. Adv Mater 2014;26:85–124. DOI: 10.1002/adma.201303233.
37. Amrollahi P, Shah B, et al. Recent advancements in regenerative dentistry: A review. Mater Sci Eng C Mater Biol Appl 2016;69: 1383–1390. DOI: 10.1016/j.msec.2016.08.045.
38. Hutmacher DW, Sittinger M, et al. Scaffold-based tissue engineering: rationale for computer-aided design and solid free-form fabrication systems. Trends Biotechnol 2004;22:354–362. DOI: 10.1016/j.tibtech.2004.05.005.
39. Sugito T, Kagami H, et al. Transplantation of cultured salivary gland cells into an atrophic salivary gland. Cell Transplant 2004;13:691–699. DOI: 10.3727/000000004783983567.
40. Hisatomi Y, Okumura K, et al. Flow cytometric isolation of endodermal progenitors from mouse salivary gland differentiate into hepatic and pancreatic linerage. Hepatology 2004;39:667–675. DOI: 10.1002/hep.20063.
41. Feng J, van der Zwaag M, et al. Isolation and characterization of human salivary gland cells for stem cell transplantation to reduce radiation-induced hyposalivation. Radiother Oncol 2009;92:466–471. DOI: 10.1016/j.radonc.2009.06.023.
42. Kojima T, Kanemaru S, et al. Regeneration of radiation damaged salivary glands with adipose-derived stromal cells. Laryngoscope 2011;121:1864–1869. DOI: 10.1002/lary.22080.
43. Lin CY, Chang FH, et al. Cell therapy for salivary gland regeneration. J Dent Res 2011;90:341–346. DOI: 10.1177/0022034510386374.
44. Pringle S, Maimets M, et al. Human Salivary Gland Stem Cells Functionally Restore Radiation Damaged Salivary Glands. Stem Cells 2016;34:640–652. DOI: 10.1002/stem.2278.
45. Grønhøj C, Jensen DH, et al. First-in-man mesenchymal stem cells for radiation-induced xerostomia (MESRIX): study protocol for a randomized controlled trial. Trials 2017;18:108. DOI: 10.1186/s13063-017-1856-0.
46. Baum BJ, Alevizos I, et al. Early responses to adenoviral-mediated transfer of the aquaporin-1 cDNA for radiation-induced salivary hypofunction. Proc Natl Acad Sci U S A 2012;109:19403–19407. DOI: 10.1073/pnas.1210662109.
47. Alevizos I, Zheng C, et al. Late responses to adenoviral-mediated transfer of the aquaporin-1 gene for radiation-induced salivary hypofunction. Gene Ther 2017;24:176–186. DOI: 10.1038/gt.2016.87.
48. Zheng C, Cotrim AP, et al. Prevention of radiation induced salivary hypofunction following hKGF gene delivery to murine submandibular glands. Clin Cancer Res 2011;17:2842–2851. DOI: 10.1158/1078-0432.CCR-10-2982.
49. Hai B, Yang Z, et al. Concurrent transient activation of Wnt/beta-catenin pathway prevents radiation damage to salivary glands. Int J Radiat Oncol Biol Phys 2012;83:e109–e116. DOI: 10.1016/j.ijrobp.2011.11.062.

50. Arany S, Benoit DS, et al. Nanoparticle-mediated gene silencing confers radioprotection to salivary glands *in vivo*. Mol Ther 2013;21:1182–1194. DOI: 10.1038/mt.2013.42.
51. Patel VN, Lombaert IM, et al. Hs3st3-modified heparan sulfate controls KIT1 progenitor expansion by regulating 3-O-sulfotransferases. Dev Cell 2014;29:662–673. DOI: 10.1016/j.devcel.2014.04.024.
52. Neumann Y, David R, et al. Long-term cryopreservation model of rat salivary gland stem cells for future therapy in irradiated head and neck cancer patients. Tissue Eng Part C Methods 2012;18:710–718. DOI: 10.1089/ten.tec.2012.0013.
53. Ogawa M, Oshima M, et al. Functional salivary gland regeneration by transplantation of a bioengineered organ germ. Nat Commun 2013;4:2498. DOI: 10.1038/ncomms3498.
54. Lim JY, Yi T, et al. Intraglandular transplantation of bone marrow-derived clonal mesenchymal stem cells for amelioration of post-irradiation salivary gland damage. Oral Oncol 2013;49:136–143. DOI: 10.1016/j.oraloncology.2012.08.010.
55. Kawakami M, Ishikawa H, et al. Functional transplantation of salivary gland cells differentiated from mouse early ES cells *in vitro*. Hum Cell 2013;26:80–90. DOI: 10.1007/s13577-013-0061-z.
56. Ono H, Obana A, et al. Regenerating salivary glands in the microenvironment of induced pluripotent stem cells. Biomed Res Int 2015;2015:293570. DOI: 10.1155/2015/293570.
57. Pradhan-Bhatt S, Harrington DA, et al. Implantable three-dimensional salivary spheroid assemblies demonstrate fluid and protein secretory responses to neurotransmitters. Tissue Eng Part A 2013;19:1610–1620. DOI: 10.1089/ten.tea.2012.0301.
58. Pradhan S, Liu C, et al. Lumen formation in three dimensional cultures of salivary acinar cells. Otolaryngol Head Neck Surg 2010;142:191–195. DOI: 10.1016/j.otohns.2009.10.039.
59. Sequeira SJ, Soscia DA, et al. The regulation of focal adhesion complex formation and salivary gland epithelial cell organization by nanofibrous PLGA scaffolds. Biomaterials 2012;33:3175–3186. DOI: 10.1016/j.biomaterials.2012.01.010.
60. Nelson J, Manzella K, et al. Current cell models for bioengineering a salivary gland: a mini-review of emerging technologies. Oral Dis 2013;19:236–244. DOI: 10.1111/j.1601-0825.2012.01958.x.
61. Dor Y, Brown J, et al. Adult pancreatic beta-cells are formed by self-duplication rather than stem-cell differentiation. Nature 2004;429: 41–46. DOI: 10.1038/nature02520.
62. Murtaugh LC, Kopinke D. Pancreatic stem cells StemBook. The Stem Cell Research Community, Stem Book, ed.: Schier AF. Last revised September 6, 2008. Published July 11, 2008.
63. Bonner-Weir S, Toschi E, et al. The pancreatic ductal epithelium serves as a potential pool of progenitor cells. Pediatr Diabetes 2004; 5(Suppl 2):16–22. DOI: 10.1111/j.1399-543X.2004.00075.x.
64. Strobel O, Rosow DE, et al. Pancreatic duct glands are distinct ductal compartments that react to chronic injury and mediate Shh-induced metaplasia. Gastroenterology 2010;138:1166–1177. DOI: 10.1053/j.gastro.2009.12.005.
65. Wang Y, Lanzoni G, et al. Biliary tree stem cells, precursors to pancreatic committed progenitors: evidence for possible life-long pancreatic organogenesis. Stem Cells 2013;31:1966–1979. DOI: 10.1002/stem.1460.
66. Govindasamy V, Ronald VS, et al. Differentiation of dental pulp stem cells into islet-like aggregates. J Dent Res 2011;90:646–652. DOI: 10.1177/0022034510396879.
67. Gorjupa E, Dannerb S, et al. Glandular tissue from human pancreas and salivary gland yields similar stem cell populations. Eur J Cell Biol 2009;88:409–421. DOI: 10.1016/j.ejcb.2009.02.187.
68. Okumura K, Nakamura K, et al. Salivary Gland Progenitor Cells Induced by Duct Ligation Differentiate Into Hepatic and Pancreatic Lineages. Hepatology 2003;38:104–113. DOI: 10.1053/jhep.2003.50259.
69. Sato A, Okumura K, et al. Isolation, tissue localization, and cellular characterization of progenitors derived from adult human salivary glands. Cloning Stem Cells 2007;9:191–205. DOI: 10.1089/clo.2006.0054.
70. Baek H, Noh YH, et al. Autonomous isolation, long-term culture and differentiation potential of adult salivary gland-derived stem/progenitor cells. J Tissue Eng Regen Med 2014;8:717–727. DOI: 10.1002/term.1572.
71. Michalopoulos GK. Liver regeneration. J Cellular Philosophy 2007;213:286–300. DOI: 10.1002/jcp.21172.
72. Fausto N, Campbell JS. The role of hepatocytes and oval cells in liver regeneration and repopulation. Mech Dev 2003;120:117–130. DOI: 10.1016/S0925-4773(02)00338-6.
73. Xiang S, Dong HH, et al. Oval cell response is attenuated by depletion of liverresidenr macrophages in the-2AAF/Partial hepatectomy rat. PLoS One 2012;7:e35180. DOI: 10.1371/journal.pone.0035180.
74. Lagasse E, Connors H, et al. Purified hematopoietic stem cells can differentiate into hepatocytes *in vivo*. Nat Med 2000;6:1229–1234. DOI: 10.1038/81326.
75. Lanzoni G, Oikawa T, et al. Concise review: Clinical programs of stem cell therapies for liver and pancreas. Stem Cells 2013;31:2047–2060. DOI: 10.1002/stem.1457.
76. Wang Y, Cui CB, et al. Lineage restriction of human hepatic stem cells to mature fates is made efficient by tissue-specific biomatrix scaffolds. Hepatology 2011;53:293–305. DOI: 10.1002/hep.24012.
77. Holtzinger A, Streeter PR, et al. New markers for tracking endoderm induction and hepatocyte differentiation from human pluripotent stem cells. Development 2015;142:4253–4265. DOI: 10.1242/dev.121020.
78. Togarrati PP, Sasaki RT, et al. Identification and characterization of a rich population of CD34+ mesenchymal stem/stromal cells in human parotid, sublingual and submandibular glands. Sci Rep 2017;7:3484. DOI: 10.1038/s41598-017-03681-1.
79. Sidney LE, Branch MJ, et al. Concise review: evidence for CD34 as a common marker for diverse progenitors. Stem Cells 2014;32: 1380–1389. DOI: 10.1002/stem.1661.
80. Maria OM, Maria AM, et al. Cell surface markers CD44 and CD166 localized specific populations of salivary acinar cells. Oral Dis 2012;18:162–168. DOI: 10.1111/j.1601-0825.2011.01858.x.
81. Jiang FX, Morahan G. Pancreatic stem cells remain unresolved. Stem Cells Dev 2014;23:2803–2812. DOI: 10.1089/scd.2014.0214.
82. Weiss TS, Lichtenauer M, et al. Hepatic progenitor cells from adult human livers for cell transplantation. Gut 2008;57:1129–1138. DOI: 10.1136/gut.2007.143321.
83. Emmerson E, May AJ, et al. SOX2 regulates acinar cell development in the salivary gland. Elife 2017 Jun 17;6, 10.7554/eLife.26620.
84. Nanduri LS, Lombaert IM, et al. Salisphere derived c-Kit+ cell transplantation restores tissue homeostasis in irradiated salivary gland. Radiother Oncol 2013;108:458–463. DOI: 10.1016/j.radonc.2013.05.020.
85. Augstein P, Loudovaris T, et al. Characterization of the Human Pancreas Side Population as a Potential Reservoir of Adult Stem Cells. Pancreas 2018;47:25–34.