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Update on the Role of Emerging Stem Cell Technology in Head and Neck Medicine

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Stem Cells in Head & Neck Medicine

Abstract

Head and neck surgery is a broad discipline that involves the management of complex conditions such as: burns, skin cancer, head and neck cancer, congenital abnormalities and facial rejuvenation. For cancer patient's; surgery, radiotherapy and chemotherapy are often the main modes of treatment. Many patients require follow up reconstructive surgery, and the use of stem cells offers novel treatments that could aid recovery. Laryngeal, tracheal and neuronal tissues are frequently damaged by surgery in the head and neck and these tissues have little intrinsic regenerative ability. Pluripotent embryonic stem cells retain the ability to differentiate into a wide variety of cells meaning that large tissue defects can be reduced by stimulating new cell growth. Research has demonstrated potential benefits of using stem cells in facial rejuvenation procedures and the management of burns sequelae. The advancements made in the use of adult progenitor stem cells as a possible source for pluripotent stem cells (Induced pluripotent stem cells) mean that ethical considerations around the use of embryological tissue can be minimised, allowing for more research to take place. Currently the evidence base for the use of stem cells in head and neck surgery is limited, but it has now been proven that stem cells can act as a source for lost or damaged tissue in the head and neck. With continuous advancements being made in the fields of tissue engineering; it is likely that stem cells will play a major role in head and neck surgery in the future.

Keywords

Regenerative Medicine, Mesenchymal Stem Cells, Biomaterials, Scaffolds, Head and Neck Surgery

Introduction

Stem cells are undifferentiated cells that have the unique properties of differentiating into a variety of cell types and self-renewal. Embryonic stem cells (ESCs) are found on the inner wall of the blastocyst in the early embryo [1]. ESCs are the primary example of pluripotent stem cells as they are able to self-renew and differentiate into the three-germ layers: ectoderm, endoderm and mesoderm, but are incapable of forming placental tissue (Figure 1). Adult stem cells are multipotent stem/progenitor cells that are able to differentiate into specific cell lineages. Mesenchymal stem cells (MSCs) are an example of adult stem cells [2]. MSCs possess the ability to be altered to resemble pluripotent embryonic stem cells in both their morphology and growth properties by the introduction of transcription factors, by means of transfection of defined genes such as POU5F1 (POU Class 5 Homeobox 1), SOX2 (SRY (sex determining region Y) -box2), Klf4 (Kruppel-like factor-2) and cMyC (Master Regulator of cell cycle and Proliferative metabolism) [3]. These transformed adult progenitor cells are referred to as induced pluripotent stem cells (iPSCs). By using iPSCs as a source of pluripotent stem cells it is possible to minimise the ethical concerns over the use of embryonic tissue, allowing more research into the field of stem cell therapy to be undertaken. The iPSCs have been shown to express ESC markers such as: Stage Specific Embryonic Antigen-3 (SSEA-3), Stage Transformer-2 protein homolog (TRA-2-29/6E) and NANOG, whilst also expressing genes which are observed in human ESC such as: POU class 5, transcription factor 1 (POU5F1), SRY-Box Transcription factor-2 (SOX2), NANOG, Growth differentiation factor-3 (GDF3), Fibroblastic Growth Factor-4 (FGF4), Development Pluripotency Associated-2 (DPPA2), Development Pluripotency Associated-4 (DPPA4), human Telomerase reverse transcriptase (hTERT) and REX1 transcription factor (REX1), although the genes expressed show distinct expressional level at different passages during expansion [4]. One major concern with the use of both iPSCs and ESCs is the risk of teratoma formation, which should be considered when using both ESCs and iPSCs[5].

Stem Cells in Head & Neck Medicine

Head and neck surgery often involves removal of significant amounts of tissue, this is particularly true of the surgical management of head and neck cancers. These operations often require further reconstructive surgeries that use numerous tissues with poor regenerative capabilities to restore both form and function to the patient. Cartilage is an avascular tissue with no intrinsic regenerative capabilities and therefore large postoperative defects in a patient's cartilagesignificantly impede their recovery. MSCs are progenitor cells of mesodermal origin that have the ability to differentiate into chondrocytes, osteocytes and adipocytes [2]. MSCs have been isolated from an ever-expanding array of mesodermal tissues and have been shown to express a range of cell surface markers. The most common set of MSC markers have been set out by the International Society for stem cell research (ISSCR) as the minimal criteria (Table 1) [6]. However, classification is not limited to the minimal criteria set out by the ISSCR (Table 2) [7]. MSCs ability to differentiate into chondrocytes whilst retaining their own self renewing properties means they have the potential to help regeneration of cartilage defects following reconstructive surgery. Animal models have already shown that intra articular injections of MSCs are able to help regenerate articular cartilage defects [8]. However, MSCs regenerative capabilities are not limited to chondrocytes, MSC's have been shown to be capable of differentiation into a wide variety of cell types within the ex-vivo setting (Figure 2) [9]. It has also been demonstrated that MSCs can influence fibroblasts and wound healing through paracrine effects of cytokines and chemokines [10]. This ability to educate and influence the wound environment makes MSCs an attractive adjunct therapy in treating burns wounds. Mesenchymal stem cells can be isolated easily from adipose tissue, bone marrow and umbilical cord meaning they are not subject to ethical controversy surrounding the use of embryonic tissue [11]. MSCs have also been shown to have minimal alloreactivity which reduces the risk of allogeneic rejection [12]. It has also been demonstrated in mouse animal models that mice treated with MSCs derived from bone marrow saw significantly better wound healing coverage following escharotomy than those that were untreated [13]. Stromal vascular fraction (SVF), which contains adipose and mesenchymal stem cells, has also been found to improve the healing of burn

wounds by increasing proliferation, vascularisation and fibroblast activity whilst simultaneously reducing inflammation in the wound bed [14].

Unlike iPSCs, MSC's do not pose a risk of teratoma formation, which remains a major risk factor in the use of patient derived iPSCs. The capacity of stem cell use in both reconstructive surgery and tissue regeneration continues to be a multi-disciplinary area. Stem cells alone are not a fix all, golden bullet. Currently, Stem cells are utilised in a multi-component system called tissue engineering with a goal to produce a favourable outcome for the patient. Tissue engineering is best described as controlled differentiation by means of stimuli. This differentiation may be delivered by means of a scaffold system, which may or may not contain an array of chemical stimulants capable of inducing differentiation towards the tissue of interest. Furthermore, scaffolds should be capable of delivering mechanical stimulus to the naïve or differentiating cells to further guide the cells ina process known as mechanotransduction induced differentiation (Figure 3).

The use of stem cells in tissue engineering as shown in Figure 2 shows the intricate interactions between many factors such as; mechanical stimulation, scaffold/substrate stiffness, choice of stem cells, and the level of oxygen saturation. Taking all these factors into account would lead to a more suitable implant being engineered for use in patients.

Tissue Engineering

Tissue engineering was first coined in the 1988 National Science Foundation workshop. The concept of tissue engineering was championed by Caplan in the late 1980's [15, 16] with Caplan's work mainly focusing on the use of mesenchymal stem cells and the ability of MSCs to transdifferentiate between Osteogenic, chondrogenic and adipogenic phenotypes under the correct biochemical and growth factor cues [15, 17, 18]. Following this early research many other disciplines such as polymer sciences and drug release research started to collaborate in means of adding structural support and delivery

methods for stem cells to aid further in tissue engineering with a main goal of delivering a functional replacement tissue.

Biomaterials/ Bio-scaffolds

The concept of biomaterials was first proposed at the 1976 Consensus conference in the European society for biomaterials (ESB) and defined as "a nonviable material used in a medical device, intended to interact with a biological systems" [19]. Currently, the ESB has adapted the definition to: "material intended to interface with biological systems to evaluate, treat, augment or replace any tissue organ or function of the body" [19]. This adaptation highlights the progression in complexity of current biomaterials.

Currently, there are a wide range of biomaterials available for use in tissue engineering. These biomaterials can range from: ceramics such as hydroxyapatite (HA) and tri-calcium phosphate (TCP); which are used in bone regeneration [20, 21], Poly(L-lactide-co-glycolide) PLGA [22], Poly-L-lactic acid (PLLA) [23], Poly (lactide) PLA; [24] used in chondrogenesis or even co-polymers such as poly (3-hydroxybutyrate-co-3-hydroxyhexanoate) PHBHHx used in tendon repair [25]. There are at least 3 major attributes to a biomaterial which will be used as a bio-scaffold. These are: Biocompatibility, Biodegradability and Mechanical properties [19, 26, 27]. In regards biocompatibility, the implant should not induce an immune response as a complete implant or when biodegrading. Preferably there should be and inverse relationship between the rate of degradation and tissue regeneration. Ideally, prior to implantation the scaffold/implant should be able to withstand the natural forces exposed to the target tissue being replaced, which would then prevent implant failure as seen in Webb et al 2013 where all components of the implant were mechanically tested to produce the optimum scaffold for implantation [25].

Mechanical stimulation

Mesenchymal stem cells and progenitors have been shown to have distinctively different mechanical properties during their expansion in cell culture when analysed using atomic force microscopy (AFM) [28, 29]. Biomaterial based scaffolds have been used in-vivo to induce mechanical stimulation which has been shown to drive stem cell differentiation towards a target tissue. Osteogenesis has been shown to be induced by cyclic-compression loading [30], whilst shear-stress loading by means of flow-perfusion bioreactors has been shown to induce chondrogenic differentiation [31]. Implanted acellular scaffolds have also demonstrated cellular invasion into the scaffold core which comprised rat-tail collagen and cellular alignment along the force bearing fibres in tendon implants [25]. This further demonstrates the mechano-responsive capability of both mesenchymal, progenitor and tissue specific cell types. Another important possible result of mechanical loading is that during mechanical loading the extra-cellular fluid within the regenerating tissue is forced out taking waste metabolites away from the cells. When the force is relaxed fresh fluid enters the extra-cellular space replenishing cellular nutrients and oxygen (mechanical loading induced perfusion) [32].

Growth factors

Growth factors are peptide based chemical signals that are essential in embryonic and adult tissue development. The major groups of growth factors used in tissue engineering are the transforming growth factor (TGF) superfamily of growth factors, which include Bone morphogenetic proteins (BMPs), and the Fibroblastic Growth factor (FGF) family. The over expression of members of the TGF superfamily have been linked to many malignancies including breast and ovarian cancers [33]. Over expression of FGF has also been shown to be linked with malignancies [34].Therefore, during growth factor induced differentiation there must be careful consideration when selecting the concentration of growth factors used and exposure time. Most growth factor induced differentiation results in the up-regulation of transcription factors responsible for differentiation towards a cell lineage. $TGF\beta_1$ results in up-regulation of SOX9 transcription factor in chondrogenesis via the SMAD1/5/8 signal

cascade [35], whilst BMP9 up-regulates RUNX2 transcription factor for bone differentiation via SMAD1/5/8 and a heterodimeric complex SMAD4 within the cell nucleus during differentiation [36]. Conversely, BMP9 has more recently been utilised to differentiate chondroprogenitors towards a chondrocyte phenotype using 100ng/ml for 14 days. This resulted in a thin layer of cartilage when compared to traditional TGFβ_1 differentiation using pellet culture, which may indicate maturation or an osteoarthritic disease model [37]. Although growth factors initiate transcription factor expression, other co-factors such as: culture media components, mechanical stimulation, cell density and oxygen tension should be considered during the differentiation and maturation of the engineered tissue.

Oxygen Tension

Oxygen tension has been shown to significantly influence differentiation [38]. Most cell culture is conducted at 21% O_2 environment, but alveolar epithelial cells are exposed to O_2 levels between 13 - 14%, adipose tissue is exposed to O_2 levels between 3 - 8%, bone is exposed to O_2 levels between 2 – 5% and cartilage is exposed to O_2 levels between 1.4 - 2% [39]. Dale et al showed that embryonic stem cells could be differentiated towards a tendon lineage at an oxygen tension of 2% but not 21% using BMP12 and 13 [40]. Gomez-Leduc et al showed oxygen tension <5% reduced the presence of mature chondrocyte markers when compared to 21% O_2 differentiation using TGFβ_1 [41]. Modulation and control of oxygen tension should not be overlooked when tissue engineering a construct for use in research or patient implantation.

Head and Neck Surgery

Head and neck surgery remains a broad discipline involving a wide range of surgical techniques. Surgery of the head and neck involves the management of congenital abnormalities, trauma, burns and malignancy. Head and neck malignancies continue to be very challenging to treat. Surgical

removal often remains the gold standard treatment, followed by adjunct chemotherapy, radiotherapy and further reconstructive surgery. These surgeries often result in both large defects in structures such as trachea and vocal tissue and iatrogenic damage to neuronal tissue. Stem cells unique regenerative capabilities means they could potentially play a major role in treating these patients and restoring lost function when utilised in conjunction with tissue engineering.

Cranial Nerves

Commented [HS1]: This section has been altered in response to the reviewers comment on neuronal tissue. We focused specifically on cranial nerves as a section on cervical nerves was also considered although the body of research to support this section was felt to be lacking. As a result the title has been changed as per the reviewers comments to reflect the focus on cranial nerves

Nerves in the head and neck are often susceptible to damage during surgery. Damage to these nerves can result in areas of facial paralysis, sensory deficit and difficulties in phonation and swallowing, all of which can severely affect a patient's quality of life.

Recurrent Laryngeal Nerve

Commented [HS2]: Sub-Headings have been included for the facial nerve and RLN sections and they have been split into two separate subsections

The recurrent laryngeal nerve is a branch of the vagus nerve that takes an indirect course through the neck supplying the intrinsic muscles of the larynx and sensation to the inferior portion of the larynx. Damage to the recurrent laryngeal nerve may result in vocal cord paralysis or hoarseness of the voice. A 20-year longitudinal study found that surgical procedures were the most common cause of injury to this nerve with thyroidectomy causing the majority (80%) of iatrogenic bilateral vocal fold immobility[42]. A recent study demonstrated the potential benefit of stem cells on returning function after transection of the recurrent laryngeal nerve. A group of 33 mice had their recurrent laryngeal nerve transected before being treated with a stem cell scaffold. Following the treatment 80% of the mice treated with the hybrid-transplantation of skeletal muscle-derived stem cells and bioabsorbable scaffold showed spontaneous movement of their vocal folds during breathing [43]. It has been demonstrated that laminin protein that is found in the extracellular matrix can play an important role in inducing embryonic and neuronal stem cells to differentiate and aid in the regeneration of nervous tissue[44]. A study by Li Yu et al. found that by using a PLGA biomaterial scaffold embedded with laminin

chitosan they were able to promote recurrent laryngeal nerve growth in a rat model [45]. By utilising the interplay between the biomaterials and the stem cells researchers are able to create microenvironments that allow stem cells to guide and sustain neuronal tissue growth. More recently Li Yu has also shown that the use of adipose-derived mesenchymal stem cells or differentiated Schwann-like adipose-derived mesenchymal stem cells result in improved healing and regeneration of the laryngeal nerve when compared to the use of extracellular matrix alone. When the mesenchymal stem cells were injected at the injury site a higher density of myelinated nerve fibre, thicker myelin sheath, improved vocal fold movement and better recovery of nerve conduction capacity were observed [46]. These results highlight the possible adjunct therapeutic advantage that stem cells could introduce when considering autologous tissue grafting.

Commented [HS3]: This section has been expanded to include a greater volume of recent research that helps to demonstrate the potential advancements being made in the use of stem cells with biomaterial scaffolds.

Facial Nerve

The facial nerve is one of the most common cranial nerve injuries following trauma to the head and neck, with facial paralysis occurring in 50% of cases of transverse fractures of the temporal bone [47]. Traumatic facial nerve injuries may result from transection, bony impingement on the nerve or intraneural hematoma [47]. These injuries can be partial such as crush injuries or they can involve complete transection of the nerve which poses an additional challenge as cut ends of the nerve often retract leaving a gap. Currently the options for surgical repair of these segmental nerve defects is limited. Nerve autografts are considered to be the gold standard treatment despite the fact that nerve autografts leave a donor site deficit and are therefore in limited supply [48]. Interestingly it has been demonstrated in a rabbit model of facial nerve injury that nerve conduits implanted with neural stem cells are not inferior to nerve autografts in terms of regeneration and repair. 10mm gaps in rabbit facial nerves were treated with chitosan conduit, collagen protein sponge, nerve growth factor (NGF), and neuronal stem cells (NSC). When compared with gaps treated by autograft or chitosan conduit and collagen sponge it was found that the nerves treated with NSC implanted conduits were thicker than the nerves treated with the autografts or conduit alone and electroneurophysiological detection

showed no significant difference between groups [49]. This study demonstrates that there when comparing nerve autografts with NSC derived stem cells in a bio-scaffold there is no significant difference in nerve regeneration and that using conduits embedded with the appropriate stem cells may be equal to nerve autografts.

Although the studies above show promising results they are all animal models which limits their translation to human trials. However more recently small scale studies involving human subjects have begun to appear in the literature. A study of 8 patients who had all suffered traumatic transection of their facial nerve found significant clinical improvement in angulation of the mouth and closure of the eye as well as improvements in electroneuronography following injection of MSCs at the site of the nerve transection. Although these results are very promising the scale of the study is very small and patients were only followed up for 6-month time period, so it is unclear whether these benefits were maintained [50] .

Commented [HS4]: The section covering the facial nerve has been made into its own individual subheading and it has been greatly expanded with current research into animal models to demonstrate the potential benefit that could be achieved. The section towards the end describing early small scale work in human trials has been kept but moved to the end of the passage

Tracheal Tissue

Primary cancer of the trachea is quite rare, but it is associated with high mortality [51, 52] . The first paediatric, stem cell-based tissue engineered tracheal transplant undertaken in 2012 showed promising results [53]. However, more recently the use of stem cells in tracheal transplantation has been subject to a great deal of controversy as Paolo Macchiarini, a pioneer of the use of stem cell seeded tracheal transplants, has been accused of research misconduct and unethical experimental operations after a number of his patients died after receiving his transplants. This incident demonstrates the risks that experimental stem cell procedures could have for patients and highlights the need for closer regulation and monitoring in future trials. Current research into 3D printed nanofiber artificial trachea has demonstrated that by combining the artificial fibres with iPSC-derived MSCs and chondrocytes it is possible to create a functional epithelized, cartilaginous airway [54]. The success of this stem cell

infused artificial scaffold shows the importance of identifying populations of stem cells that have the capability to differentiate into cartilaginous tissue. Recent studies have highlighted a population of stem/progenitor cells that reside within the tracheal C-ring [28]. The cell population expressed common MSC markers and were shown to be capable of tri-lineage differentiation. However, the isolated stem/progenitor cells were shown to undergo calcification when differentiated towards a chondrocyte lineage using the growth factors: Transforming Growth Factor Beta-1 ($TGF\beta_1$) at a concentration of 10ng/mL or Bone Morphogenic Protein-9/Growth Differentiation Factor-5 (BMP9/GDF5) at concentration of 100ng/ml. This may suggest that further optimisation of differentiation components is required [28]. Despite this researchers have gone on to show that isolated autologous bone marrow derived stem cells are able to differentiate into chondrocytes when exposed to $TGF\beta_1$ in an in vivo transplantation of a genipin linked tracheal scaffold [55]. Currently the concerns surrounding stem cell usage with tracheal tissue limit its application in clinical practice but it is possible that future studies may elucidate the potential of these cells for reconstructive surgery of the trachea.

Commented [HS5]: More papers have been included in the tracheal section to both highlight the stem cell work being done surrounding artificial tracheal structures and their similarities to human tissue when embedded with stem cells and also how stem cells have been induced to differentiate into chondrocytes under specific cell enviroments

Vocal Tissue

Commented [HS6]: This section has also been expanded to include more studies and a more in depth look at examples of recent and current research that demonstrate the potential of stem cell therapy better.

Surgical management of laryngeal cancer involves a partial or total laryngectomy. Partial laryngectomy will have an impact on voice quality and speech intelligibility regardless of surgical technique due to damage to the vocal folds [56]. Human vocal fold epithelium has very little proliferative capacity and as a result it has been difficult to produce models that allow for more research into novel therapies. The use of stem cells could allow for regeneration of these damaged tissues as it has been demonstrated that a 3D model of vocal fold mucosa can be reliably created by using ESC-derived epithelial cells and human primary vocal fold fibroblasts [57]. It has even been shown that human iPSCs can be modulated by FGF to produce a vocal fold mucosa that is able to mimic inflammatory response to smoke exposure seen in human vocal fold tissue [58]. Reconstructive phonosurgery will also often lead to scarring of the vocal folds further worsening dysphonia in some patients. A recent systematic review of the use of

MSCs as a treatment for vocal fold scarring in pre-clinical studies found promising results, although it is difficult to assess whether these positive findings will be seen in human clinical trials [59]. It is unclear exactly how MSCs interact with the vocal fold mucosa at a tissue level to minimise scarring but it has been demonstrated in a rat model that MSCs can supress $TGF\beta_1$ signalling in vocal fold fibroblasts aiding their anti-fibrotic effect. Interestingly it was also noted that bidirectional paracrine signalling meant that the native vocal fold fibroblasts were also able to regulate the ECM in the MSCs [60]. Similar positive effects on organisation of the ECM collagen matrix have been observed on animal models involving vocal fold resection. The lamina propria of rabbits vocal folds was resected and human MSCs were injected at the site of resection. Histological analysis demonstrated a reduced inflammatory response with Increased levels of CD163+ anti-inflammatory macrophages and greater organisation in the collagen matrix [61]. Although much of the work investigating stem cells effects on vocal tissue healing has been completed in animal models early work in human clinical trials is also promising, showing improvements in phonation following treatment, although more large-scale research is needed to fully assess these claims [62].

Soft Tissue Regeneration

Commented [HS7]: This subsection has been changed to "Soft Tissue Regeneration" as suggested by the reviewer. It has now been split into 3 sub sections.

As well as aiding in the regeneration and healing of neuronal and cartilaginous tissue, stem cells can play an important role in soft tissue regeneration in the head and neck.

Head and Neck Burns

Commented [HS8]: This subsection has been reworked with more added to put a greater focus onto burns that affect the head and neck specifically.

The use of stem cells in burn patients is multifaceted as they can help to regenerate epidermal tissue, educate the wound environment and model the healing process to reduce fibrosis and scar formation. Currently autologous skin grafts are widely used but problems can arise when there is not a sufficient or appropriate donor site area [63]. Burn injury sequalae such as hypertrophic scarring, contracture and

pigmentation changes in the skin often require rehabilitation and physiotherapy [64]. This can produce unique challenges in the head and neck as scar contractures in the neck can have a negative impact on breathing, phonation and mastication and will often require reconstructive surgery. Adipose derived stem cells have been shown to improve chronic neck scar contracture and wound healing following radiation burns [65, 66]. Post burn scars in the face and neck can create a significant psychological burden for patients recovery. Nanofat injections containing stromal vascular fraction rich in adipose-derived stem cells have been shown to produce significantly improved scar appearance when injected at the site of none hypertrophic postburn scars in patients [67]. This research highlights that stem cells may play an important role in helping to improve postburn scarring in the face.

Facial Scarring

Commented [HS9]: This section now looks specifically at how soft tissue regeneration can be applied to scars in the face and what benefits stem cell therapy can provide.

Hypertrophic scars are notoriously difficult to manage but recent work has suggested that MSCs may play a role in helping to prevent their formation. It has been shown in a mice model that when MSCs are combined with fibroblasts and introduced to the wound environment they can alter the fibroblast activity via paracrine effects preventing the formation of hypertrophic scar tissue [68]. The discovery of MSCs in adipose tissue has meant that autologous fat grafting is now being utilised more frequently in the treatment of facial scarring. A recent review demonstrated that clinical improvement in scars has been demonstrated in almost every area of the face, especially if scarring is derived from burns, trauma, degenerative diseases, and radiotherapy although the authors did raise concerns over the fact that there is considerable variability in outcome between different patients receiving the same treatment [69]. Despite this, autologous fat grafting has been shown to be as effective at treating acne scarring as established techniques such as fractional carbon dioxide laser (FxCR). It was shown that just one treatment using autologous adipose tissue-derived adult stem cells provided significant global improvement when compared to 3 treatments involving FxCR over a 3-month period [70].

Epidermal Stem Cells

Epidermal stem cells are found in both the epidermis and the hair follicle of the skin. Cultured epithelial autografts containing these epidermal stem cells have become an established treatment in burn injuries [63]. Advancements in tissue engineering have meant that the epidermal stem cells have been combined with fibrin matrices in attempts to improve durability and to try and minimise rejection of the graft. As well as concerns over durability, cost and rejection of transplanted tissue, there are also concerns over mutation accumulation over several cell passages of cell division [71]. However, recently it has been shown that a limited number or transgenic epidermal stem cells were able to regenerate the entire epidermis, once again demonstrating the potential that these cells have in treating major burn injuries [72]. It is worth noting that the stem cells role in aiding the regeneration of the epidermis is not limited to the treatment of burn injuries. It is possible that stem cells epidermal regenerative capabilities could be applied to surgical defects in the head and neck to aid in regeneration of dermal tissue. Recent studies in animal models have demonstrated that tonsillar MSCs incorporated into wound beds significantly promoted the repair of surgical defects in mice with a considerable impact on the augmentation of epidermal and dermal regeneration [73]. It has already been demonstrated in patients who have undergone surgery to their head and neck that higher levels of pro-inflammatory cytokines such as interleukin-1β, interleukin-8, and Matrix metalloproteinase -9 are associated with both greater incidence of postoperative complications and length of stay in hospital [74]. The paracrine factors released by MSCs are intricately linked with the modulation of the inflammatory environment and they play an important role in regulating levels of these pro inflammatory cytokines [73]. By utilising stem cells in head and neck surgery it is possible that inflammatory response could be reduced, helping to improve postoperative outcomes and complications following surgery in the head and neck.

Commented [HS10]: Here the epidermal regenerative capabilities of stem cells have been linked directly to surgery in the head and neck as per the suggestion by the reviewers.

Discussion

Following the discovery of induced pluripotent stem cells and tissue specific reservoirs of adult stem cells i.e. Tracheal C-ring, there has been a wealth of research that has investigated stem cells as a novel therapy to treat all kinds of disease. Much of this work has looked at stem cells regenerative abilities with countless animal models demonstrating positive results. As a result, stem cells remain a promising therapeutic option for tissue regeneration and wound healing in the field of head and neck surgery. However, despite this wealth of information demonstrating the potential benefits of stem cells in all areas of head and neck surgery, there is a distinct lack of evidence in human trials. Very recently there has been an increase in the number of small-scale case reports showing that stem cell therapy can be a viable therapy in humans. Advancements in bioactive implants, 3D bioprinting and tissue engineering mean that implants containing stem cells are surviving longer and undergoing lower levels of immune rejection and human trials are becoming more feasible. But even with the increase in the number of studies investigating the benefit of stem cell use in humans, large scale randomised control trials and cohort studies with long term follow will be needed to assess the true potential of stem cells before they can truly be considered as a viable therapy of the future.

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