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Annals of Otolaryngology and Rhinology

Review Article

Cell-Based Therapy for Acquired Subglottic Stenosis: A Review of Research and Future Directions

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Submitted: 25 August 2014

Accepted: 23 September 2014

Published: 29 September 2014

Abstract

Acquired subglottic stenosis (a SGS) continues to pose great challenge to patients and clinicians due to lack of effective treatment strategies. Our understanding in pathophysiology of a SGS has significantly advanced in the past decades; however, much still remains to be elucidated. The purpose of this review is to describe current state of research in acquired subglottic stenosis, and discuss future research directions. First, clinical definition and significance of a SGS are discussed. The second section focuses on review of literature that deals with the pathophysiology of a SGS. Histological studies of human samples, animal studies, and in-vitro studies are discussed. The review ends with a discussion on the potential of cell-therapy for a SGS with special attention to mesenchymal stem cell therapy.

INTRODUCTION

Subglottis stenosis (SGS) is a narrowing of the endolarynx that develops at and below the vocal folds. SGS can result in severe functional impairments, including breathing difficulty and loss of voice[1] Etiologically, SGS can be congenital or acquired.[2] As many as 92% of SGS cases are of the acquired type, the focus of this paper, with most cases being attributed to intubation injury [3].Congenital SGS arises from anomalies in developmental pathways, and will not be discussed further in this paper. The incidence of acquired SGS (a SGS) has been reported to be between 0.4% and 10% of incubated patients. [4,6]Contributing factors include duration of intubation, size of the endotracheal tube, history of tracheostomy, re-intubation, infection while intubated,and irradiation for oropharyngeal and laryngeal tumors.[5,7]In general, it is believed that pressure from the endotracheal tube causes ischemic injury, leading to ulceration or loss of laryngeal mucosa.[8]When the injury heals inadequately, excessive deposition of scar tissue leads to thickening of the subglottic mucosa tissue, which narrows the airway.[9,10] Therefore, prevention of scar tissue development and management of scar tissue are the primary needs in treatment of a SGS.

Clinical management of a SGS remains a challenge. Various pharmacological strategies have been tried to date; however, no strategy has been effective for scar reduction.[1] Consequently, surgical dilation or open surgical reconstruction of the airway has been the main treatment strategy for a SGS.[11] Surgical intervention provides adequately patent airway for many patients; however, it is not ideal as it creates an opportunity for further scarring. It has been reported that some patients require repetitive surgeries due to restenosis after surgery [12]and the severity of recurrent SGS tends to be greater for patients who have undergone multiple airway procedures.Furthermore, current surgical treatment options for the airway typically compromise voice quality and mitigate the outcome of treatment.[13]

Our understanding of a SGS pathophysiology is incomplete; however, some information has been added to the literature in the past few decades. Histological studies have characterized microstructure of the SGS tissue and revealed various presentations of a SGS [9,10] Animal studies have revealed the temporal aspect of healing process, and identified biochemical factors involved in development of stenosis.[14,17] Molecular studies have identified contributing inflammatory mediators and gene expression patterns that are distinct in a SGS tissue.[18-27]In-vitro studies have revealed intrinsic differences between fibroblasts from a SGS tissue and normal subglottic tissue.[20,22] Genomic studies have shed light on a possible mechanism that makes an individual susceptible for development of a SGS.[8,28]

New information has also come to light recently suggesting novel treatments for a SGS, such as mesenchymal stem cell (MSC)

therapy. Currently, MSC therapy is one of the most rigorously studied areas in regenerative medicine.[29,34] The effect of MSC therapy on wound healing has been studied in various tissues. It is believed that MSCs aid wound healing through at least three mechanisms: 1) migration to injured site, 2) differentiation into target cells, and 3) secretion of required factors in response to their surrounding environment.[29,32] This interactive and holistic nature of the MSCs may provide an alternative treatment modality for a SGS. Basic science research studies have shown positive effect of MSC therapy for various medical conditions, and rapidly advancing MSC therapy to preclinical studies. [31]

Definition of SGS

The normal lumen diameter of the subglottis is 4.5 mm to 5.5 mm in the full-term neonate. A diameter of less than 4 mm at this age is considered stenotic.[2]Clinically, morphology and severity of SGS are characterized with a classification system; the "Cotton-Myer scale" is the gold standard classification system for staging of the degree of SGS.[35] In this scale, airway occlusion of 0-50% is classified as grade I stenosis, 51-70% as grade II, 71-99% as grade III, and 100% as grade IV. Other less used classifications systems, such as the one by MaCaffrey,uses a three-tier grading system that classifies stenosis based on the lesion site.[36]Sites of lesion were the glottis, subglottis, and trachea. Stenosis that involves one site is classified as grade I, two sites is grade II and three sites is grade III. Lano*et al.* proposed a four-tier grading system based on the sites and the length of stenosis.[37] Stenosis that is confined to the subglottis or trachea that is less than 1 cm is grade I, stenosis isolated to the subglottis and greater than 1 cm is grade II, subglottic and tracheal stenosis without involvement of the glottis is grade III and with the glottic involvement is grade IV.

Clinical significance of SGS

Impact on respiratory function: SGS can occur in patients of all ages. Adults with stenosis typically remain asymptomatic up to the point where the constriction reaches less than 30% of the original diameter.[38] A computational fluid dynamics study by Brouns et al. has shown that a dramatic increase in resistance occurs when the diameter of the airway is reduced more than 70%.[39]Because the airway of a child is significantly smaller than that of an adult, children are more severely affected by SGS. The degree of impact of aSGS on infant's breathing can be appreciated when considering the relationship between diameter and area of the airway. For an infant with the airway diameter of 5mm, even 1mm of mucosal tissue thickening reduces the cross-sectional area of the airway by 36%. On the other hand, for an adult with the airway diameter of 20 mm, the same thickening will reduce the cross-sectional area of the airway by only 10%. The relationship of airway cross-sectional area and airway resistance can be calculated using Poiseuille's law.[40]According to the law, resistance is inversely proportional to the fourth power of the radius.

$$R = \frac{8l\eta}{\pi r^4}$$

Where R= resistance, l= length of the tube, η = gas viscosity, and r = radius of the tube. If radius is halved, resistance increases by a factor of 16. Therefore, what may appear to be a small change in the airway can profoundly affect its functionality for infants and children.

Impact on laryngeal function: The primary purpose of the larynx is to protect the lower airway during swallowing and generate sound source for voice. The impact of SGS alone on voice is unclear due to lack of data in the literature. Several voice outcome studies exist for children who underwent laryngotracheal reconstruction surgery for a SGS.[41-46] The main finding of these studies is that children with lesser severity of SGS, less complex medical histories, and single-stage surgical procedures are likely to have better voice quality. [41,47]However, the studies consistently found that moderate to severe dysphonia persists after the surgery. Dysphonia is primarily due to post-surgical scarring that is suboptimal for normal voicing, which then leads to a compensatory phonatory pattern such as use of supraglottic structures as a vibratory source of voice production [48]. Perceptually, voice quality is reported to be betterin children who use the true vocal folds for the vibratory source. Dysphonia among these children should not be taken lightly. Parents of these children have reported that their children's quality of life has been negatively affected by dysphonia, shown by significantly elevated Pediatric Voice Handicap Index score [49]. Moreover, serious, immediate, and negative health effects can occur if the surgically altered larynx makes it difficult for a patient to protect his or her airway during swallowing.

Current understandings of a SGS pathophysiology

Histological studies: Elucidation of pathophysiological mechanisms of a SGSbegan with histological studies. Studies that used autopsy and surgical specimens revealed several subtypes of a SGS. [9,10,50]Abnormalities in some cases were limited to soft tissue, while destruction of cartilaginous framework was observed in severe cases. The most common presentations in autopsy samples were submucosal gland hyperplasia and submucosal fibrosis.[10] Additionally, ulceration, granulation tissue, and ductal cysts were also observed 9,10] Some of the specimens had a combination of multiple subtypes. Authors attempted to infer chronological progression of the wound healing comparing samples that varied in time from injury to sample acquisition. Based on the observation, ulceration was considered as the earliest stage of healing, followed by granulation tissue formation, fibrotic tissue deposition, and scar contraction. Chronic inflammation was thought to weaken the integrity of cartilage, leading to distortion or fragmentation of the cartilage upon scar contraction, in turn worsening the stenosis.

Observations in histological studies with surgical specimen from partial cricotracheal resection, in which a section of the airway is removed to open the airway, were somewhat different from the cadaveric study.[50] All of the specimens presented with a thick layer of cell-poor, firm fibrous scar tissue, squamous metaplasia of the epithelium, loss of glands with dilation of the remaining glands, formation of cysts, and loss of tunica elastic. Perichondrium of the cricoid cartilages was partially or entirely lost. Ectopic bone formation was present in some specimens. The absence of ulceration and granulation tissue in these specimens is likely due to chronicity of the wound.

Molecular studies: Advances in molecular technology and increasing interest in growth factor therapy led researchers to examine biochemical pathways that were involved in development of a SGS. The studies focused on several growth factors shown to be involved in wound healing in other tissues. Vasoendothelial growth factor (VEGF) and transforming growth factor-β (TGF-β) were the most frequently studied growth factors.[12,23,27,51,52]A study by Rahbar *et al*. examined specimens from five pediatric patients with a SGS, and found that VEGF-A mRNA was strongly expressed in the suprabasal epithelial levels.[23] VEGF-A receptors, VEGFR-1 and VEGFR-2, are also strongly expressed in endothelial cells in the granulation tissue. Expression of these mRNAs was not observed in the well-established scar tissue, indicating that VEGF plays an important role in actively healing a SGS tissue.

TGF-β1 is an isoform in the TGF-β family, which is known to play a critical role in multiple stages of the wound healing process,[53,54]abnormal levels of TGF-β have been suggested as pathogenesis of abnormal wound healing.[55]High levels of TGF-β1 triggers differentiation of fibroblasts to myofibroblasts, which induces contraction of scar, resulting in excessive scarring. Findings from immunohistochemical studies of a SGS tissue have been inconsistent. One study observed strong expression of TGF-β1 in the aSGS tissue.[26] On the other hand, such expression of TGF-β1 was not confirmed in another study. [27] Presence of myofibroblasts in the tissue is indicated by expression of α-smooth muscle actin. One immunohistochemical study observed increased levels of α-smooth muscle actin in a SGS tissue, suggesting fibroblast-myofibroblast differentiation plays a role in development of a SGS.[56]

Why only a small subgroup of intubated patients develops a SGS has been an enduring question for clinicians. Recent case-control genomic studies hypothesized that the patients who develops a SGS are inherently more susceptible to abnormal wound healing and attempted to identify genetic markers that indicate the susceptibility to acquired laryngotracheal stenosis. [8,28] Findings have been reported on single nucleotide polymorphisms (SNPs) in CD14, matrix metalloproteinase-1 (MMP-1) and TGF-β1. A study that examined four TGF-β1 SNPs (-800 G/A rs1800469, -509 C/T rs1800469, codon 10, codon 25) reported that the ratio of individuals with -509 C/T rs1800469 was significantly higher in the control group, suggesting that this polymorphism may provide protective function against development of stenosis. On the other hand, the study found an elevated ratio of individuals with -509 C/C rs1800469 in the case group, suggesting that this genotype may indicate increased susceptibility for the stenosis.[28] Another study reportedan increased risk for development of stenosis withrs1799750 G/G and -/G genotypes of MMP-1, and possible protective function of the rs2569290 G/A genotype of CD14.[8]

Animal studies: Controlled, time-course experiments provide insight into temporal aspects of wound healing process; however, performing such experiments with human subjects is not possible for obvious ethical and health concerns. Alternatively, animal models have been used to study healing process of subglottic tissue and contributory factors for development of a SGS.

Depth of injury is an important factor in a SGS development. Damage to perichondrium of the cricoid cartilage has been shown to result in deformation of the cartilage while injury limited to the soft tissue lining heals without such deformation.[57,58]The depth of injury dictates the degree of resultant stenosis.[14] A rabbit model has been used to examine how extent (i.e. circumferential vs. quadrant) and depth (full- vs. partial-thickness) affect healing of the subglottic tissue. Electrocautery was used to create the full-thickness wound, reaching to perichondrium of the cricoid cartilage. These animals died from airway obstruction after the surgery regardless of the extent of the injury. On the other hand, there was no mortality with animals who received a partial-thickness wound via HCl or $AgNO_3$ chemical cautery.

The roles of growth factors and cytokines have also been studied in animal models. Elevated expression of TGF-β1 that was seen in human a SGS tissue was also confirmed with a rat a SGS model, which demonstrated that TGF-β1 expression peaked during the first 24-48 hours and decreased to baseline by 24 days after full-thickness injury.[51]Increased expression of fibronectin and type I procollagen were observed 1, 7, and 21 days after the injury. The study also explored the effectiveness of anti TGF-β1 antibody treatment that was given locally to the wound site using an osmotic pump. The experimental group showed decreased expression of fibronectin and type I procollagen compared to the control group which received a saline infusion. The effect of anti TGF-β1 was confirmed also with a canine a SGS model; thelesser degree of stenosis and greater survival time compared to control animals was demonstrated.[52]

The role of inflammatory mediators has also been examined in a few studies. Interleukin-1β (IL-1β) is known to amplify the activity of macrophages [59] and stimulates production of other cytokines such as IL-6, IL-8, and PGE2 during the inflammatory phase.[20]Prostaglandin E2(PGE2) is involved in regulation of inflammatory response and activity of mesenchymal cells such as fibroblasts. In a time-course experiment using a rabbit model, Branski *et al.* demonstrated elevation of IL-1β in secretions 4-18 hours after subglottic injury.[18] Elevation of PGE2 was seen 7-19 hours after the injury. Another study from the same group showed a higher PGE2 level in secretions collected from injury with greater extent.[20] Together, these findings suggest that IL-1β and PGE2 are involved in wound healing process in the subglottis.

It is widely recognized that aging affects the wound healing process. The most intriguing case is seen with fetal wounds, which heal without scarring up to the second trimester.[60] Whether this scarless wound healing also occurs in fetal subglottic tissue has been examined. Dohar *et al.* performed thyrotomy followed by cricoidotomy and circumferential cauterization of the subglottic mucosa on adult and fetal rabbits, and demonstrated that airway mucosa of fetal rabbits healed without scar.[14] The difference in fetal and adult tissue healing was demonstrated also by a gene expression study. Li-Korosky *et al.* focused on one of the ECM proteins, fibronectin, which is encoded by Fn1.[19] The study examined the difference in mRNA expression levels of splicing variants of Fn1, extra domain A (EDA), extra domain B (EDB), and a variable region (V) between skin and airway mucosal tissue from fetal, weanling, and adult rabbits. The findings indicated that there are age- and tissue-specific differences in the expression

levels of these Fn1 variants. The tissue specific difference was shown in adults as the greater induction of Fn1 variants in airway wounds than in skin wounds.

Although the rabbit is the most frequently used model in a SGS studies, some researchers have explored utility of the mouse model .[61,62]Because of the availability of various genetically engineered mutants that allow researchers to study function of specific gene, the mouse model has an advantage over other animal models. Despite this advantage, the mouse model has been infrequently used for a SGS studies due to high mortality rate after airway surgery. In order to circumvent the mortality issue, an *ex-situ,* heterotopic transplantation model has been recently developed.

Richter *et al.* conducted an airway mucosal wound characterization study with C57BL/6 mice.[62] Injured laryngotracheal complexes (LTC) were transplanted into the dorsal subcutaneous "pocket" of recipient mice. The transplanted LTCs survived four weeks, which was the end point of the experiment. Compared to uninjured control, the injured group presented with increased epithelial and lamina propria thickness, and random distribution and high concentrations of connective tissue within the lamina propria. These findings were similar to observations made with other animals. Ghosh *et al.* also used the *ex situ* murine model to examine immunological aspects of subglottic mucosa wound healing.[61] C57BL/6 mice underwent mechanical and chemical injury to their airway, and their LTCs were transplanted into the dorsal cutaneous pocket of C57BL/6 mice or severe combined immunodeficiency (SCID) mice. Absence of granulation tissue formation was observed with LTCs transplanted in SCID mice three weeks after injury, indicated that circulating B and/or T cells are responsible for granulation tissue formation during wound healing. Caution is needed for generalization of these results to humans due to inter-specie differences;[63] however, these studies demonstrated potential of the murine model in a SGS studies.

In-vitro studies: Fibroblasts have been the main focus of in-vitro studies in a SGS as these cells are considered the primary contributor to scar generation. It is well recognized that fibroblasts are highly heterogeneous based on their origins, and their subtypes differ in their morphological, functional, and genetic characteristics.[64,65]Studies with fibroblasts from other types of tissue have shown that fibroblasts from healthy and pathological tissues behave differently, suggesting aberrant healing may be due to the altered function of pathological fibroblasts.[66]This concept, whether such intrinsic differences may account for pathophysiological process of a SGS, has been tested in several studies.

As mentioned previously in this paper, differentiation of fibroblasts to myofibroblasts is involved in scar tissue generation, a process regulated by TGF- β1. Sensitivity of fibroblasts to TGF-β1 was examined with the cells from human a SGS lesions, fetal skin, and newborn foreskin. It was shown that fibroblasts from a SGS lesions responded most sensitively to TGF-β1, and yielded highest-fold induction of mRNA levels for ECM proteins.[24] The effect of TGF-β1 has been examined also with fibroblasts derived from rat tracheas. Treatment with TGF-β1 increased expression of α-smooth muscle actin, which implied the differentiation into myofibroblasts. The treatment also altered mRNA expression of fibronectin, MMP-2, MMP-9, TIMP-1 and TIMP-2, and increased contraction of collagen gels,[56] suggesting that TGF-β1 regulates the process of fibrotic tissue remodeling in the tracheal mucosa tissue.

The effect of other inflammatory mediators on fibroblasts has also been studied. Sandulache *et al.* investigated the effect of IL-1β on fibroblasts from normal human adult and fetal tracheas, and SGS lesions.[20] When stimulated by IL-1 β, fibroblasts derived from SGS lesions produced more PGE2 than fibroblasts from healthy tissues. In a rabbit model, Singh *et al.* demonstrated that contraction of fibroblasts derived from a SGS lesions differ from that of fibroblasts derived from normal tracheal mucosa. Treatment of these cells with PGE2 revealed that a SGS fibroblasts did not respond to PGE2 as sensitively as fibroblasts from normal tracheal mucosa.[22] Together, these findings indicate that fibroblasts from SGS lesions are intrinsically different from others.

Although these studies have shown characteristics that are unique to fibroblasts from a SGS tissue, their findings are limited by the use of a monoculture system. The monoculture system lacks biological components present in the native tissue. Behavior of fibroblasts is affected by the environment in which they are cultured.[67] For example, the secretory profile of fibroblasts changes when they are cultured with epithelial cells. Such co-culturing has not been used in a SGS studies, but it may provide better insight into the pathophysiological processes.

Future directions: "Cell Therapy" for a SGS

Along with the search of effective molecular targets for restoration of damaged tissue, tremendous interest in the use of tissue regeneration for the treatment of a SGS has grown in the past few decades. Regenerative medicine was born out of transplant medicine, which was challenged by the shortage of donor organs and rejection of the transplanted organs by recipients.[68]The overarching goal of regenerative medicine is to create living, functional tissues to repair or replace damaged or lost tissue.[69]Cell therapy is a subarea of regenerative medicine that involves transplantation of cells.[70]The basic premise of cell therapy is that the transplanted cells are able to promote regeneration or restoration of damaged tissue by overriding pathological biochemical pathways that led to a disease. Selection of cell type for transplantation is determined by the function that is required of the cells. Desired features of donor cells are: 1) ability to survive and systematically release a therapeutic gene product; 2) ability to target specific local repair; and 3) ability to systematically repair or replace a diseased organ.[70]

The use of stem cells is the main paradigm of recent cell therapy research.[71] Stem cells differ from terminally differentiated cells in their ability to self-renew and differentiate into multiple lineages. Stem cells are broadly categorized into two types: embryonic stem cells and adult stem cells; or based on their potency: totipotent, pluripotent, and multipotent cells. Totipotent cells can give rise to all cell types of an organism and placenta. In mammals, zygotes are the only totipotent cells. After few cycles of cell division, the cells begin to specialize and become pluripotent cells. Embryonic stem cells are pluripotent

cells that are derived from inner cell mass of the blastocysts. Embryonic stem cells can give rise to all cell types in all germ layers (i.e. endoderm, mesoderm and ectoderm); however, they lack in the ability to give rise to an entire organism. As the development continues, these pluripotent stem cells continue to divide and give rise to the progenitor cells that are specific to a particular tissue. As the cells become more specialized, their potency becomes reduced to multipotency. Adult stem cells are these multipotent progenitors, and they undergo several rounds of cell division to become terminally differentiated mature cells. Adult stem cells are present in various differentiated tissues in an undifferentiated state.[70] There are several lineages of adult stem cells including hematopoietic, epithelial, neural, skin, and mesenchymal stem cells. The main functions of adult stem cells are to maintain and repair the tissue. It is this characteristic of the cells and their potency that stimulated research on adult stem cells for treatment and prevention of aberrant wound healing.

Mesenchymal stem cells (MSCs) has been of particular interest to wound healing researchers and enthusiastically studied for their potential use for anti-scarring therapy. Several characteristics of MSCs make them attractive for such application. MSCs are multipotent progenitor cells that have capacity to differentiate into various types of cells as needed. [32] MSCs also secrete various bioactive molecules that regulate biochemical activities in a wound when stimulated by their environment.[29,31] MSCs are also immune-privileged, which addresses the immune rejection issue associated with allogenic cell transplants.[31,72]In addition to being biologically flexible, MSCs are also thought to be therapeutically practical as they are relatively easy to obtain. The cells can be isolated from multiple types of tissue, such as bone marrow,[29] adipose tissue,[34] synovial tissue,[73] amniotic fluid,[74] umbilical cord,[75] and fetal tissue for autologous transplantation, and are also available from allogeneic and commercial sources.

MSCs were first described by Friedenstein in 1968 as fibroblast-like non-hematopoietic cells in the bone marrow that adhere to plastic and formed fibroblastic colonies *in vitro*. [32] These cells were first named fibroblastic colony-forming units (CFU-Fs) and it was later found that they can differentiate into multiple mesenchymal cell types both *in vitro* and *in vivo*. [32] As the understanding of the cells advanced, these cells were described under different names, such as osteogenic stem cells and marrow stromal stem cells. The term "MSCs" was coined by Caplan in 1991,[76] and it is a commonly used term in the current literature.[77] However, a new term "multipotent mesenchymal stromal cells" has been recently suggested by the International Society for Cellular Therapy (ISCT).[78] Besides the terminology, debate on the defining criteria for the cells continues partly due to a lack of specific marker for MSCs. Currently, it is recommended that MSCs should be defined as a combination of their physical, functional and phenotypic properties.[77] The following criteria must be met: the cells should be 1) adherent to plastic, 2) able to differentiate into osteoblasts, adipocytes and chondroblasts *in vitro*, and 3) are positive for CD73, CD90, CD105, and negative for CD11b or CD14, CD19, or CD79α, CD34, CD45, and HLA-DR. [32,77,78] In addition to these markers, positive expression of CD44, CD71, ganglioside GD2, and CD271, and absence of CD80, CD86, and CD40 are considered as general characteristics of human MSCs.[77]

Much effort has been invested for identification of MSCs in a particular organ and tissue. Experimental approaches for MSC identification vary between researchers; however, three main types of approaches exist. The first is labeling the cells *in vivo* using the specific MSC markers. The second is tracking the cells to see their distribution by extracting the cells from an animal, labeling them in culture and transplanting them back to another animal.[79] The third approach is systematic isolation of MSCs from different organs and tissues and conduct functional characterization analysis in culture.[77] Recent investigations demonstrated that MSCs are present in nearly all post-natal organs and tissues [80], and in their microvasculature.[81]

Promising results demonstrated in *in vitro* studies quickly advanced MSCs to preclinical and clinical trial studies. A number of preclinical *in vivo* studies have shown the positive effect on wound healing including increased neovascularization, re-epithelialization, and cellularity, decreased local inflammatory response, rapid wound closure, and greater wound tensile strength.[31] Although the exact mechanism is still unknown, it is believed that MSCs enhance wound healing through multiple mechanisms. Upon injury, MSCs migrate to the wound site through the circulatory system and from the nearby blood vessels. This is referred as "homing" of the cells. MSCs then secrete "trophic factors," which are molecules that regulate biochemical activities of other cells at the wound site, and/or differentiate into various types of cells that are required for reconstruction of tissue. Trophic factors of MSCs enhance wound healing by attenuating inflammation, promoting angiogenesis, and inhibiting fibrosis. MSCs also have immunomodulatory effect, such as attenuating the acute immune response to injury by inhibiting recruitment, proliferation, and biological activity of mast cells, T cells, B cells, and natural killer cells.[31] When stimulated by the surrounding biochemical environment of the wound, MSCs secret enumerous trophic factors. One of the factors is PGE2, which modulates the response of resident leukocytes and macrophages from pro-inflammatory to anti-inflammatory.[82] The expression of anti-inflammatory cytokines signals resident fibroblasts to upregulate MMP and downregulate production of collagen and other ECM molecules, resulting in formation of granulation tissue that is less dense and more fibrotic.[31] MSCs are also known to express pro-angiogenic factors such as VEGF and bFGF [32] that promote formation of new blood vessels. MSCs prevent scarring by secreting anti-fibrotic cytokines and growth factors such as HGF and bFGF that promote ECM turnover and inhibit fibroblast-myofibroblast differentiation.

The application of MSCs for promoting wound healing in head and neck tissue has been proposed,[30]and a body of literature that indicates therapeutic potential of MSCs for airway diseases is emerging. One of the landmark studies is transplantation of a tissue-engineered trachea by Macchiarini *et al.*[83]Th e recipient was a 30 year-old female with left main bronchus malacia. The authors used a decellularized cadaveric trachea as a framework, which was seeded with recipient's epithelial cells and chondrogenic MSCs. The seeded construct was incubated in a custom-made bioreactor for 96 hours and implanted in

the patient. The authors confirmed successful engraftment of the construct and growth of tracheal mucosa, and reported significant functional improvement of the patient. Although the precise role of MSCs in this successful outcome is not inducible, the study suggests potential application of MSCs in previously unmanageable cases of airway stenosis.

The use of MSCs for treatment of vocal fold scars is a highly active area of research. Several preclinical investigations have been conducted both *in vitro* and *in vivo*. Hanson *et al.* compared fibroblasts from the vocal fold with MSCs derived from adipose tissue and bone marrow (BM). All cell types were tested for their cell surface markers, immune phenotypic characteristics, and differentiation potential. Based on the finding that the vocal fold fibroblasts shared characteristics of MSCs, the authors proposed that the vocal fold fibroblasts are MSCs resident in the vocal fold.[84]Two rabbit-model studies tested the effect of BMderived human MSCs to the vocal fold. The MSCs were injected immediately upon creation of injury. An anti-scarring effect was demonstrated as improved viscoelasticity and less signs of scarring in MSC-treated groups compared to control groups [85,86] MSCs were embedded in tissue-engineered constructs in other studies. Kanemaru *et al.* used a canine model and showed that direct injection of BM-derived MSC suspended in 1% HCl at elocollagen prevented atrophic changes observed in the control group.[87] Johnson *et al.* used a rat model to assess the effect of BM-derived MSC alone and BM-MSC suspended in a synthetic extracellular matrix on the one-month old vocal fold scar.[88] BM-MSC suspended in a sECM resulted in outcomes more favorable in ECM production, hyaluronan metabolism, myofibroblast differentiation, and production of TGF-β1. Although direct comparison of results from these animal studies is difficult, all studies suggest an anti-scarring effect for MSCs. Further investigations are desired to determine appropriate timing of administration, most effective delivery method, dosage and safety. Timing may be a critical factor as MSC treatment has been shown effective only when given before the scar becomes well-established.[32]

Specific to a SGS, fetal fibroblasts havebeen considered as a potential cell source.The scarless healing observed in fetuses has been attributed to the intrinsic abilities of fetal fibroblasts.[89] Sandulache *et al.* compared the effect of fibroblasts derived from fetal skin, adult skin and airway mucosa on subglottic wounds in a rabbit model. The wound was treated by topically delivered fibroblasts in hyaluronic acid gel suspension with mucosal wound dressing.[90] Engraftment of the fibroblasts was confirmed and the transplanted cells survived as long as 21 days. The degree of inflammation was similar between all cell types; however, fetal fibroblasts survived longer than fibroblasts from the adult dermis and subglottic mucosa. Concentration of TGF-β 1 expression was observed around transplanted fibroblasts, suggesting that the active tissue remodeling process was initiated by these cells.

While gaining tremendous popularity and showing promising therapeutic potential, the uncertainty in defining MSC's molecular identity raised some skepticism in whether the observed therapeutic effects can be truly attributed to "MSCs."[91-94] MSCs are thought to be "stem cells" because their ability for self-renewal and differentiation potential. However, it has become evident that MSCs and fibroblasts share many characteristics including morphology, cell-surface markers, differentiation potential, immunologic properties and gene expression that they are indistinguishable using current methods.[92,95] Furthermore, studies have shown that both MSCs and fibroblasts have immune modulatory and anti-inflammatory effects.[91] Perhaps to reflect this ambiguity, some researchers prefer a term "mesenchymal *stromal* cells" over "mesenchymal *stem* cells." It appears that further investigation will continue to determine whether the "MSCs" and "fibroblasts"are distinct entities, and to which the therapeutic effects should be attributed.

CONCLUSION

Airway mucosa scarring is the major contributing factor for a SGS. Management of a SGS continues to be difficult as there is no effective treatment for resolving the scar tissue. Currently, airway obstruction due to a SGS is managed with reconstruction surgery, which poses a risk of recurrence that may require repeated surgeries. Moreover, while patent airways are re-established, there can be multiple functional sequel related to surgery. There is a great need for development of minimally invasive treatment strategies for a SGS.

Past a SGS studies have revealed some important aspects of subglottic mucosal wound healing. Pharmacological therapy has yielded conflicting results at the clinical level. Growth factor therapy has been explored, and animal studies have shown some favorable results. Pharmacological and growth factor therapies are able to target only certain biochemical pathways. In contrast, MSCs are able to regulate behaviors of other cells flexibly by secreting various factors according to their biochemical environment. This flexibility makes MSCs highly attractive for treatment of a SGS as the wound healing process is complex and individualized. Promising outcomes in preclinical and clinical studies in other tissues support the use of MSC-based cell therapy. Alternatively, fibroblasts may also be as capable as MSCs for treatment of a SGS. Whether cell-therapy would be a solution to a SGS management is an intriguing question that remains to be explored.

ACKNOWLEDGEMENT

The authors would like to thank Lisa Kelchner, Ph.D., CCC-SLP, BCS-S for providing in valuable comments and edits that contributed to improving this paper.

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Cite this article

Ishikawa K, Elluru RG (2014) Cell-Based Therapy for Acquired Subglottic Stenosis: A Review of Research and Future Directions. Ann Otolaryngol Rhinol 1(1): 1003.