Implantation of atelocollagen sheet for vocal fold scar

Yo Kishimoto[1,2], **Nathan V. Welham**[1], and **Shigeru Hirano**[2]

[1] Division of Otolaryngology-Head and Neck Surgery, Department of Surgery, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA

[2] Department of Otolaryngology-Head and Neck Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Abstract

Purpose of review—This article reviews recent advances in scaffold-based interventions for the treatment of vocal fold scarring, with a particular emphasis on atelocollagen sheet implantation in the vocal fold lamina propria.

Recent findings—Scaffold-based therapies have demonstrated therapeutic promise in both pre-clinical and early clinical studies. Recent research has begun to shed light on the interactions between scaffold material properties, encapsulated and infiltrating cells, stimulatory molecules such as growth factors, and external regulatory variables such as stress, strain and vibration. The atelocollagen sheet, a cross-linked collagen material with abundant micropores, has an established clinical track record as a scaffold for dermal and epidermal repair and exhibited potential therapeutic benefit in a recent study of patients with vocal fold scarring and sulcus vocalis.

Summary—Scaffolding is one of the useful tools in tissue engineering and atelocollagen sheet implantation has shown to be effective in vocal fold regeneration. However, many of the scaffold materials under investigation still await clinical translation, and those that have been investigated in human patients (such as the atelocollagen sheet) require additional research in appropriately powered placebo controlled studies.

Keywords

biologic scaffold; phonosurgery; regenerative medicine; tissue engineering

Introduction

Although the treatment of many voice disorders has improved alongside advances in voice therapy and phonosurgery, there remains no optimal therapeutic strategy for vocal fold scarring. Vocal fold scarring generally occurs following mucosal injury and inflammation, and is often induced by physical trauma, surgical resection, irradiation and infection [1,2,3]. It irrevocably changes the biomechanical properties of the native mucosa and impairs vibratory function for phonation, resulting in a severe, intractable dysphonia [4,5]. Given the importance of voice to human communication and social interaction, scar-induced dysphonia can cause significant personal and professional handicap in many individuals. [6,7] Consequently, there remains a pressing need for new and effective therapies for this condition.

Correspondence to: Yo Kishimoto, MD, Division of Otolaryngology-Head and Neck Surgery, Department of Surgery, University of Wisconsin School of Medicine and Public Health, 5136 Wisconsin Institutes for Medical Research, 1111 Highland Avenue, Madison, WI 53705-2275, USA, Tel: +1-608-265-2268 y_kishimoto@ent.kuhp.kyoto-u.ac.jp.

Recent developments in the fields of regenerative medicine and tissue engineering have yielded promising new approaches to the restoration/replacement of disordered tissues. Early work in experimental models of vocal fold scarring suggests that these regenerative strategies hold therapeutic benefit and can lead to functional tissue improvement. The purpose of this review article is to summarize recent developments in this area with a focus on scaffold-based interventions, particularly the implantation of atelocollagen in the vocal fold lamina propria.

Vocal fold wound healing and scar formation

Any successful therapeutic approach to vocal fold scarring is dependant on a comprehensive understanding of its pathophysiology. Research conducted over the past 10 years has provided a detailed profile of the lamina propria extracellular matrix (ECM) changes that are characteristic of chronic scar, such as dense and/or disorganized collagen deposition, increased fibronectin abundance, and decreased elastin, decorin and hyaluronic acid (HA) abundance [3,8]. These protein and glycan changes have been observed in both human and animal vocal fold mucosae [8,9,10,11,12]. Initial changes in the vocal fold mucosa following injury are predominantly directed by migratory inflammatory cells [13]; subsequent remodeling is directed by resident vocal fold fibroblasts (VFFs) and transdifferentiated myofibroblasts [14]. Evidence from a number of biological systems, including the vocal fold, suggests that manipulating fibroblast-myofibroblast behavior is critical to improving scarring outcome [15,16]. Mucosal repair culminating in mature scar formation takes approximately six months in humans [17], dogs [9] and rabbits [10]; two months in rats [11]; and four-to-six weeks in mice [12].

Traditional interventions and their limitations

Various behavioral, pharmacological and surgical interventions have been offered in an attempt to improve or regenerate scarred vocal fold mucosa. Voice therapy offers patients a means to maximize the efficiency of an imperfect vibratory glottal source, in addition to addressing behavioral issues such as compensatory hyperfunction [18]. Steroid injections are often used to reduce inflammation in the acute phase of wound healing [19]. These treatment approaches offer some benefit, but do not directly address the underlying ECM dysfunction in the chronically scarred vocal fold [1].

Traditional surgical approaches to improving vocal fold scar include injection laryngoplasty, medialization thyroplasty, scar excision and/or lysis [1,2,20]. Injection laryngoplasty and medialization thyroplasty provide vocal fold augmentation that generally improves vocal fold closure and entrainment for phonation; however, neither approach is able to regenerate the optimal vibratory properties of the native mucosa. Further, the majority of injectates with desirable viscoelastic properties are readily absorbed over time. Scar excision involves resecting fibrotic tissue with the expectation that subsequent wound healing is regenerative; scar lysis attempts to improve vibratory function by shortening longitudinal scar bands into smaller segments. Both of these approaches are generally reserved for severe cases and outcomes are highly dependant upon individual patient healing capacity.

Emerging scaffold-based interventions

Tissue engineering is focused on the regeneration of biological structures and systems using a combination of scaffolds, cells and growth factors under appropriate conditions [21]. This therapeutic paradigm has been adopted by a number of vocal fold researchers in an attempt to prevent, attenuate and reverse vocal fold scarring. Although cell and growth factor-based therapies have shown some restorative effects in experimental studies, combining these approaches with an appropriately matched scaffold environment may bring these therapies

even closer to achieving complete regeneration. In general, a restorative scaffold should be biocompatible and biodegradable, match the volume dimensions of the target structure, and provide a permissive environment for cell infiltration, proliferation and regenerative behavior.

HA is the most well-studied synthetic scaffold material employed in human and animal vocal fold scarring research. As the unmodified HA molecule is rapidly degraded in vivo, most recent studies have utilized cross-linking or other forms of chemical modification to extend HA residence time. Hallen et al. [22] injected cross-linked HA into the uninjured rabbit vocal fold. They identified residual HA material up to 12 months post-injection with progressive fibroblast infiltration, connective tissue ingrowth and no evidence of foreign body reaction. In series of studies, Thibeault et al. [23,24,25] injected different formulations of a chemically modified HA gelatin hydrogel into rabbit vocal folds at the time of injury. Hydrogel injected vocal folds exhibited improved viscoelastic properties compared to saline injected controls at both early and late time points, supporting the regenerative potential of this scaffold material when introduced to the acute wound environment. In a study focused on intervention during the remodeling phase of wound healing, Jahan-Parwar et al. [26] reported therapeutic benefit following injection of cross-linked HA into canine vocal folds one month following laser-induced injury, compared to a single saline injected control. Finck et al. [27,28] reported ongoing gradual improvement in vocal function following lamina propria implantation of esterified HA after microflap-based benign lesion excision in human patients. A control group subjected to the same microflap procedure without HA implantation failed to demonstrate equivalent benefit.

Collagen has been a popular injection laryngoplasty material since the mid-1980s [29], and has also recently been investigated as a scaffold for vocal fold tissue engineering. Kanemaru et al. [30*] injected cultured autologous mesenchymal stem cells (MSCs) encapsulated in 1% hydrochloric acid atelocollagen into injured canine vocal folds and reported therapeutic benefit. Although the relative contribution of the MSCs and atelocollagen scaffold was not investigated in this experiment, the cells appeared to proliferate within the scaffold in vivo, leading the authors to conclude that atelocollagen is a suitable scaffold material for MSC-based vocal fold tissue engineering.

An alternative approach to using engineered synthetic scaffolds such as the HA and collagen derivatives described above involves autologous, allogeneic and xenogeneic tissue materials, either in native or decellularized states. Tsunoda et al. [31] performed autologous temporalis fascia transplantation in a series of sulcus vocalis patients and noted gradual improvement in maximum phonation time, vibratory closure pattern and mucosal wave excursion over time. Immunohistochemical examination of herniated fascia removed from a single patient seven days post-transplantation revealed actively proliferating (Ki-67 positive) cells in the scaffold. Additional unpublished data suggests that both autologous fascia transplantation and allogeneic (cadaveric) decellularized dermis (AlloDerm; LifeCell Corporation, Branchburg, NJ) implantation are helpful for the treatment of sulcus vocalis in certain patients [20].

Recent research focused on xenogeneic decellularized scaffold implantation in the lamina propria has employed bovine vocal fold mucosa [32,33] and porcine liver stroma [34]. Xu et al. implanted decellularized bovine vocal fold mucosa in the cartilaginous rat vocal fold following injury and observed elevated collagen and glycosaminoglycan (GAG) abundance compared to non-implanted injured controls [32]. Complete scaffold turnover occurred by three months post-implantation. Follow-up work using the same experimental model demonstrated the potential of this scaffold as a delivery system for the anti-fibrotic molecule hepatocyte growth factor (HGF) [33]. Gilbert et al. [34] utilized porcine liver-derived ECM

for vocal fold reconstruction following injury in a canine model, selected in part because the native liver is rich in HGF. No significant differences in elastin and GAG abundance were observed between scaffold-treated and non-treated control samples; however, the scaffold-treated group exhibited an elevated ratio of type III to type I collagen, in addition to elevated overall collagen deposition. The authors concluded that although complete regeneration was not achieved, their scaffold-based strategy promoted collagen subtype accumulation approximating that of the normal vocal fold and is therefore worthy of additional investigation.

Effects of scaffolds on cells

The majority of candidate scaffolds proposed for vocal fold tissue engineering were initially selected based on favorable physical and biological features, such as biocompatibility, biodegradability and viscoelasticity; however, recent work has given additional attention to the effect of the scaffold material on resident cell phenotype. Regardless of whether cells are encapsulated in a scaffold prior to implantation, or infiltrate from surrounding tissues following implantation, interaction between the scaffold and various cell types is a critical parameter in the optimization of therapeutic outcome. A number of studies have demonstrated the ability of both synthetic and decellularized scaffolds to support VFF proliferation and synthesis of appropriate ECM constituents in three-dimensional culture [35,36,37,38,39]. Recent reports have also suggested that engineered scaffold parameters such as mesh size, gelatin concentration and HA molecular weight directly influence ECM synthesis by resident VFFs [25,40,41]. Further, external biomechanical stimuli including stress, strain and vibration appear to be important co-modulators of cell behavior within the scaffold environment [42,43].

Recent work by Badylak et al. [44] highlights the potential impact of scaffold composition on infiltrating cell phenotype following in vivo implantation. Rat abdominal wall tissue was excised and replaced with either decellularized porcine small intestinal submucosa (SIS), carbodiimide cross-linked SIS, or an autologous tissue graft. Infiltrating macrophage phenotype and eventual repair outcome varied as a function of scaffold type, suggesting that the scaffold manufacturing process can have a significant influence upon initial host cell response and subsequent remodeling events. This study highlights the necessity of considering both therapeutically delivered and infiltrating cells when attempting to optimize tissue engineered constructs, and is an important area for ongoing investigation.

Atelocollagen sheet implantation

Researchers at Kyoto University recently reported on the therapeutic potential of a commercial atelocollagen sheet (Terudermis, Olympus Terumo Biomaterials Corporation, Tokyo, Japan) as a candidate scaffold for vocal fold tissue regeneration [45**]. This material, which differs from the 1% hydrochloric acid atelocollagen formulation utilized for MSC delivery by Kanemaru et al. [30*], is biocompatible and biodegradable in humans and has previously been used to promote healing of postsurgical dermal and epidermal defects [46]. The sheet is composed of dehydrothermally cross-linked fibrillar atelocollagen and heat-denatured atelocollagen derived from bovine skin, and is 3 mm thick with abundant 50–500 μm diameter micropores. Its physical composition confers collagenase resistance, a prolonged residence time in vivo, and sufficient porosity for cellular infiltration. Initial scaffold development and early animal experiments confirmed maintenance of scaffold structure and successful cell infiltration four weeks following implantation [47].

Atelocollagen sheet implantation in the vocal fold lamina propria is a straightforward procedure consisting of four steps (Figure 1): Elevation of a microflap, microdissection and excision of underlying scar tissue, implantation of the collagen sheet, and wound closure. In

contrast with injection-based interventions, this procedure involves the physical removal of scar tissue prior to placement of the therapeutic scaffold. The hypothesis of this treatment approach is that presence of the atelocollagen sheet facilitates regenerative ECM synthesis and remodeling within the lamina propria. Kishimoto et al. [45**] reported the outcome of atelocollagen sheet implantation in six patients with post-cordectomy scar and sulcus vocalis. The majority of patients exhibited gradual improvement in aerodynamic, acoustic and videostroboscopic parameters six months following implantation, although inter-patient variation was observed. Although this study reported on a small number of patients and did not include a control group, these findings suggest that atelocollagen sheet implantation holds therapeutic potential in certain patients with vocal fold scarring and is worthy of additional research.

In anticipation of future cell-scaffold applications, Ohno et al. [48*] examined the ability of the atelocollagen sheet to support bone marrow derived stromal cells (BMSCs) in three-dimensional culture. Seeded BMSCs adhered to the sheet, proliferated, and synthesized ECM proteins. Although ECM production capacity represents just one aspect of cell phenotype, it appears that the atelocollagen sheet is biocompatible with this cell type and may be suitable as a scaffold to support the delivery of a number of therapeutic cell populations.

Future directions in scaffold-based therapy

Scaffold-based therapies for the treatment of vocal fold scarring remain in their infancy, however this area of tissue engineering is gaining momentum with increasing representation in the wider literature. In addition to ongoing technological advances in materials science, detailed investigation of the influence of scaffolding materials on cells, the turnover and replacement of scaffolds by cells, and the role of growth factors and other molecules in these processes are still needed. Many of the scaffold materials under investigation still await clinical translation, and those that have been investigated in human patients (such as the atelocollagen sheet) require additional research in appropriately powered placebo controlled studies. Further, the majority of published experimental work in animal models has focused on the attenuation and prevention of scar formation by introducing scaffold materials at the time of injury. Future research should give additional attention to the applicability of scaffold-based therapies to the chronically scarred vocal fold.

Conclusions

Scaffold-based therapies for vocal fold scarring are under investigation by an increasing number of research groups and show therapeutic promise in both pre-clinical and early clinical studies. Recent research has begun to shed light on the interactions between scaffold material properties, encapsulated and infiltrating cells, stimulatory molecules such as growth factors, and external regulatory variables such as stress, strain and vibration. The atelocollagen sheet has an established clinical track record as a scaffold for dermal and epidermal repair and exhibited potential therapeutic benefit in a recent study of patients with vocal fold scarring and sulcus vocalis. Significant additional research with this candidate scaffold is required prior to its endorsement for widespread clinical use.

Acknowledgments

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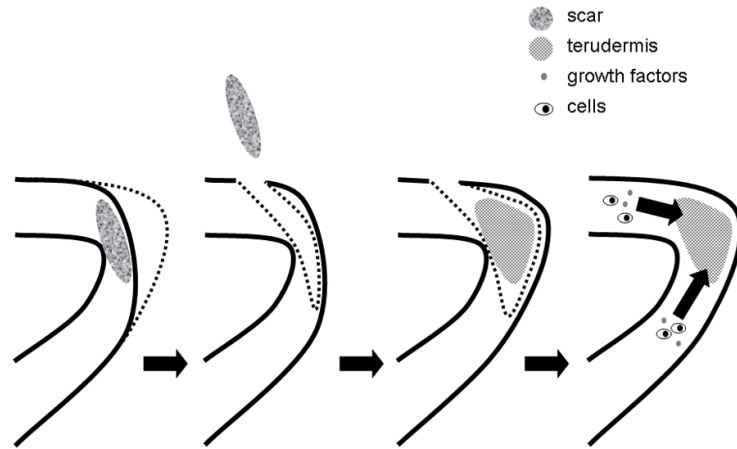
Figure 1.
Schematic illustrating atelocollagen sheet implantation. An incision is made lateral to the scarred site and underlying scar tissue is dissected with a microdissector. Following the removal of scar tissue, the atelocollagen sheet is implanted in a subepithelial pocket. The microflap is put back into its original position and the pocket is closed with a suture or fibrin glue to prevent dislocation of the material. The sheet holds an extended residence time and is infiltrated by cells and possibly growth factors from surrounding tissues. Adapted from [45]