

Featured Article

Tissue engineering-based strategies of prevention and treatment for esophageal stenosis after endoscopic submucosal dissection

Fan Yang, Xiangyu Kong*

Department of Gastroenterology, Changhai Hospital, Naval Medical University, Shanghai 200433, China

* Corresponding author: Xiangyu Kong, Yfiona001@126.com

CITATION

Yang F, Kong X. Tissue engineering-based strategies of prevention and treatment for esophageal stenosis after endoscopic submucosal dissection. *Psycho-Oncologie*. 2025; *Psycho-Oncology Research in China*: 4565.

ARTICLE INFO

Received:

Accepted:

Available online:

COPYRIGHT



Copyright © 2025 by author(s).

Psycho-Oncologie is published by PiscoMed Publishing Pte. Ltd. This work is licensed under the Creative Commons Attribution (CC BY)

license.

<https://creativecommons.org/licenses/by/4.0/>

Abstract: Due to lower trauma and higher resection rate, endoscopic submucosal dissection (ESD) has become the preferred therapy for early esophageal cancer. Esophageal stenosis is a common complication after ESD. A variety of methods are currently used to prevent and treat this complication, including oral administration or local injection of steroid hormones, balloon dilation, and stent implantation, but none are satisfactory when lesions exceed 3/4 of the esophageal circumference. With the development of tissue engineering and regenerative medicine, various biomaterials, including synthetic materials and natural materials, have been widely used and applied in wound healing and tissue regeneration. This review summarizes advancements in tissue engineering and regenerative medicine in wound repair, and focuses on the contribution of biomaterials in the prevention and treatment of esophageal stenosis after ESD to provide reference for exploring better strategies in clinical practice.

Keywords: tissue engineering; regenerative medicine; esophageal stenosis; endoscopic submucosal dissection

1. Introduction

Esophageal cancer is a malignant tumor of the digestive tract that poses a serious threat to the life and health of Chinese residents. The five-year survival rate of patients with early esophageal cancer is much higher than that of patients with advanced esophageal cancer (95% vs. 30%) [1]. Because of the high overall resection rate [2], high radical resection rate [3], low recurrence rate, [4] and other advantages, endoscopic submucosal dissection (ESD) has become the preferred treatment for early esophageal cancer [5]. Scar contracture commonly forms on and around the wound after ESD, resulting in esophageal stenosis, which is also the most common adverse event after endoscopic treatment of early esophageal cancer. Esophageal stenosis is generally defined as the inability of a standard endoscope (9.8 mm in diameter) to pass through the narrow part of the esophageal segment [6]. Previous studies have found that resection circumferential diameter is an independent risk factor for post-ESD esophageal stenosis [7,8]. The overall incidence of stenosis after ESD for esophageal squamous cell carcinoma is 11.6% [9], while in patients with lesions exceeding 3/4 of the esophageal circumference, it can reach more than 70% [10]. Esophageal stenosis can lead to dysphagia, regurgitation, coughing, and aspiration pneumonia, which seriously affects the life quality of patients and is even life-threatening. Therefore, active prevention is essential for patients whose lesions exceed 3/4 of the esophageal circumference following ESD [1]. At present, various methods, including oral administration or local injection of corticosteroid, balloon dilation, and stent placement [11], are used to prevent and treat the post-ESD esophageal stenosis and

help reduce the degree of stricture. However, their overall efficiency remains unsatisfactory, and these approaches also have risks such as bleeding, infection, and perforation, which increase the economic and psychological burden of patients. With the development of tissue engineering and regenerative medicine, various biomaterials, including synthetic materials and natural materials, have been widely used in wound repair and tissue regeneration. This review summarizes the advancements in tissue engineering and regenerative medicine for wound repair and focuses on the contribution of biomaterials in the prevention and treatment of esophageal stenosis after ESD to provide reference for exploring better clinical strategies.

2. Pathogenesis of esophageal stenosis after ESD

2.1. Anatomy and constitution of the esophagus

The esophagus is a muscular tube that extends from the pharynx to the stomach, transporting food and water from the mouth to the stomach. It has an average diameter of 2 cm and a total length of approximately 25 cm [12,13]. Histologically, the esophagus can be divided cross-sectionally into four structural layers, namely the mucosa, submucosa, muscularis propria, and adventitia. The mucosa consists of the epithelium, lamina propria, and muscularis mucosa. The epithelium consists of non-keratinized stratified squamous epithelial cells, with cells on the surface continuously shedding and replenished through cell proliferation in the basal lamina. The lamina propria is composed of connective tissue, forming papillae that protrude into the epithelium. A small number of mucous glands exist in the lamina propria at both the upper and lower ends of the esophagus. The muscularis mucosa is made up of bundles of longitudinal smooth muscle. The esophageal muscle comprises an inner circular and outer longitudinal layer, with the upper third composed of skeletal muscle cells, the lower third containing smooth muscle cells, and the middle third having a mix of skeletal and smooth muscle. Stability of the intraesophageal environment is critical to the normality of the esophagus [14,15].

2.2. Onset and development of esophageal stenosis

Current studies generally agree that the development of esophageal stenosis consists of three stages: structural damage to the esophageal epithelial barrier, chronic inflammation, and severe fibrosis [16]. A study investigating the healing process of mucosal defects in the esophagus after EMR reported that ulcer formation and inflammatory cell invasion, subsequently followed by angiogenesis and collagen fiber hyperplasia, could be observed until complete epithelialization of the ulcer had occurred [17].

Cells synthesize cornified envelope proteins to form an intact esophageal epithelial barrier (EBB) structure. The EBB structure can effectively block the attack of foreign antigens, allergens, and H⁺ ions, thereby protecting the inner tissues [18–20]. Keratin 14 and filaggrin are key proteins for the formation of the cornified envelope in the esophageal epithelial cells of the EEB structure. Epithelial cadherin and zonula occludens serve as important proteins for esophageal epithelial cell-cell

junctions in the EEB structure, working together to maintain normal functions of the EEB [21–26]. Certain wound protection materials, such as poly(glycolic acid) sheets [27], inhibit the over-differentiation of acute-phase fibroblasts and promote uniform wound healing. This suggests that the repair of the EEB and promotion of wound re-epithelialization are essential for the treatment and prevention of esophageal stenosis after ESD.

The inflammatory response is the body's typical defense against external stimuli such as bacteria, viruses, or other antigens. It requires a high degree of cooperation among all systems of the body, with the immune system playing a dominant role. Activation of the immune system usually begins with phagocytosis by macrophages [28]. Local stimulation or invasion by harmful antigens causes macrophages to migrate, phagocytose pathogens, and secrete cytokines that act on fibroblasts, thereby promoting inflammation healing and wound repair. When inflammation fails to heal in a timely manner, pro-inflammatory factors will cause the over-differentiation of fibroblasts into myofibroblasts. This leads to the accumulation of the extracellular matrix (ECM), which contributes to tissue fibrosis and ultimately results in esophageal stenosis [16]. The clinical application of steroids before and after ESD to prevent esophageal stenosis provides supportive evidence for this inflammatory mechanism.

Fibroblasts are present in most tissues and exhibits a characteristic spindle shape. They serve a crucial role in ECM secretion and granulation tissue formation. Upon the occurrence of tissue injury, fibroblasts contribute to wound healing by secreting ECM, which provides good “soil” for the body and creates new connective tissue through the deposition of fibers, elastin, and laminin. When the homeostatic environment is disrupted or the organism is under stress, fibroblasts will differentiate into myofibroblasts to promote organismal repair [29–31]. Although myofibroblasts are particularly important in physiological repair, they play different roles during different phases of physiological healing. In chronic wounds or chronic inflammation, the fibroblast-to-myofibroblast transition (FMT) can passively lead to ECM over-deposition and haphazard accumulation of cells. This ultimately causes fibrotic over-healing, which is manifested as esophageal stenosis [32–35]. Zhang et al. [36] found that local intramuscular injection of mitomycin C decreased the frequency of endoscopic dilations in patients with esophageal stenosis after ESD. This demonstrated that the hyperfibrotic mechanism resulted in esophageal stenosis.

Fibroblasts begin to proliferate 3–7 days after wound formation [37]. After one week, the inflammatory response of the wound disappears, fibrous tissue proliferation becomes evident, and epithelial cells start to proliferate and migrate from the wound margin [17]. Therefore, early post-ESD intervention to enhance mucosal repair while slowing down the fibrotic is a key strategy for preventing esophageal stenosis. The application of synthetic polymeric materials (e.g., biodegradable materials such as polyglycolic acid (PGA) and poly(lactic-co-glycolic acid) (PLGA), as well as cell sheets and ECM scaffolds constructed by tissue engineering and regenerative medicine) to postoperative esophageal stenosis after ESD reduces adverse reactions such as infection and perforation, lowers the number of subsequent balloon dilations, and avoids the pain and suffering caused to patients by repeated surgery, thereby achieving encouraging therapeutic effects.

3. Biomaterials promote wound healing and tissue repair

Biomaterials for wound healing and tissue regeneration should possess three essential characteristics, namely biocompatibility, bioactivity, and biodegradability [38].

3.1. Biocompatibility

Biocompatibility refers to the ability of a material to support cell adhesion, proliferation, and migration to its surface and subsequent passage of cells through the bulk of the material [39]. High biocompatibility ensures that contact between the implanted material and biological tissues and fluids does not impact cell function and tissues or inflammation, carcinogenesis, and cause tissue rejection [39,40]. The biocompatibility of a material can be investigated by various tests. In particular, subcutaneous implantation is a widely accepted *in vivo* method for evaluating the immunogenicity and tissue integration of novel biomaterials [41]. The United States Food and Drug Administration (FDA) has approved several natural and synthetic biomaterials, such as collagen [42], silk fibroin [43], Pluronic F127 [44], and poly- ϵ -caprolactone (PCL) [45] for use in biocompatible scaffolds either individually or in combination. Commercially available skin products include Hyalomatrix KC, EpiDex, Biobrane, Integra, polyglycolic acid/polylactic acid (PGA/PLA) (e.g., Dermagraft), poly(ethylene oxide)/poly(butylene terephthalate) (PEO/PBT) (e.g., PolyActive), and collagen (e.g., Apligraf, StrataGraft, PermaDerm, Biobrane, and Pelnac).

3.2. Bioactivity

Bioactivity refers to the ability of a biomaterial to interact with its biological environment [46]. When implanted, bioactive materials stimulate cell migration, proliferation and differentiation, and blood vessel formation, thereby influencing the rate of healing [47–49]. Under most circumstances, biomaterials that closely mimic host tissue exhibit greater bioactivity, improved cell recognition, and enhanced tissue regeneration. Therefore, many studies have reported surface modifications of biomaterials by the addition of ECM components (e.g., collagen, fibronectin, laminin, and elastin) to enhance their bioactivity. It should be noted that although the basic structure of natural ECM is composed of the same biomolecules, the proportions of the molecules differ across different tissue types or under different pathological conditions. Recent studies focus on developing biomimetic environments similar to natural tissues to modulate cellular behavior and based on specific conditions [38].

3.3. Biodegradability

Biodegradability is an important feature of biomaterials, eliminating the need for a second surgery for removal after implantation. The by-products of the degradation process must be non-toxic, easily excreted from the body, and non-interfering with other tissues [50]. It should be noted that the *in vivo* degradation kinetics of scaffolds must be regulated to avoid prevent premature loss of support or excessive persistence, which could induce necrosis or inflammation [51]. For instance, the weak mechanical strength of non-crosslinked collagen scaffolds limits their use in clinical applications. To address this issue, attempts to crosslink collagen scaffolds can be made to achieve

an optimum balance between mechanical properties and degradation rate [52]. Biodegradable scaffolds/substrates also possess an excellent potential for the provision of biological response modifiers (e.g., growth factors). Such biomaterials not only serve as a scaffold for tissue attachment to support the wound healing process, but can also act as a biofeedback-controlled drug delivery system to enhance the regenerative process [38].

4. Application of biomaterials in the prevention and treatment of esophageal stenosis after ESD

Bioactive materials can influence the wound microenvironment and promote wound healing at the molecular level by relying on their chemical, physical, and biological properties, or by acting as carriers of bioactive substances. To fulfill the three basic characteristics of biomaterials, material design can be performed in accordance with their bioactive components. Researchers have attempted to apply various biomaterials currently used for skin repair to the prevention and treatment of esophageal stenosis after ESD, thus providing a novel modality for clinical treatment.

4.1. Cell-mediated modifications

Cells are a key component of tissue-engineered wound grafts and can be obtained from autologous, allogeneic, or xenogeneic sources. Prominent advantages of autologous cells include the lack of immune rejection and a low level of tumorigenicity due to limited epigenetic manipulation [38]. Common cell sources include autologous keratinocytes [53], autologous adipose-derived stromal cells [54], mesenchymal stem cells [55], and esophageal epithelial cells [56]. Keratinocytes have an unlimited proliferative capacity and do not undergo senescence [57]. Some researchers have evaluated the transplantation of single-cell suspensions of cultured keratinocytes into natural fibrin sealant matrices. In acute burn wounds and chronic wounds, human autologous keratinocytes in the fibrin sealant matrix can effectively adhere to and spread over the wound, resulting in its re-epithelialization. Encouraging results and complete dermal-epidermal reconstitution have been achieved in full-thickness burns [58]. Fibroblasts are the primary cellular component of the dermis. They serve a key role in the wound healing process by secreting proteins, cytokines, and growth factors that support ECM formation and keratinocyte functions [59,60]. Adipocytes, which participate in the regeneration of skin and skin appendages during wound healing, have received increasing attention in recent years. Previous research has shown that the conversion of myofibroblasts to adipocytes has a positive effect on scarless wound healing, which is characterized by reduced wound contraction and decreased hair follicle formation [61]. Mesenchymal stem cells are characterized by their certain degree of plasticity in the mesenchymal lineage. They promote tissue regeneration through the production of growth factors (GFs), cytokines and chemokines [62]. Endoscopic injection of cell suspensions into the superficial layers of the wound is a commonly used therapeutic strategy, with the use of the aforementioned types of cells reported in the literature. However, this cell therapy method is still in the animal experimentation stage and has not yet progressed to clinical applications in humans. The long in vitro culture period also limits its application in the prevention of

esophageal stenosis.

4.2. Cell barrier construction

Cell-based therapy relies on the retention and survival of transplanted cells at the wound site. However, direct injection of cell suspensions has certain drawbacks, such as low cell viability and rapid diffusion. This has led to the extensive exploration of autologous cell sheets. The retention of cell membrane proteins and ECM in cell sheets allows for stable adhesion to mucosal defects. Takagi et al. [63] first proposed the use of oral mucosal epithelial cell sheets, and the researchers subsequently advanced their research to the clinical trial stage [64]. Small pieces of mucosal tissue were collected from the oral cavity of patients and incubated *in vitro* for 16 days. The resultant epithelial cell sheets were endoscopically implanted into mucosal defects. Endoscopic examinations performed once weekly after the surgery revealed that complete re-epithelialization of the trauma occurred at a median time of 3.5 weeks, with none of the nine patients developing symptoms of esophageal stenosis. Jonas et al. [65] also investigated the safety and efficacy of oral mucosal epithelial cell sheets in humans. Five patients underwent extensive ESD that entailed $\geq 75\%$ of the circumference, and the results demonstrated that autologous cell sheet transplantation is safe and feasible in a Western population, exerting a protective effect on post-ESD wounds and reducing the risk and extent of stricture formation. Kanai et al. [66] performed an animal experiment on the efficacy of autologous epidermal cell sheets, in which eight pigs underwent circumferential ESD. The degrees of stenosis of the experimental and control groups at 2 weeks postoperatively were 56% and 88%, respectively ($P < 0.01$), indicating that the autologous epidermal cell sheets provided certain preventive effects against esophageal stenosis after ESD. Kobayashi et al. [67] conducted a proof-of-concept study in which six pigs were divided into three groups for intervention at 2 weeks after ESD. The two pigs of the transplantation group underwent six epidermal cell sheet transplants, with five of the six transplants being successful. Results showed that the stricture rates of these pigs (55% and 60%) were lower than those of the control (92.2% and 87.7%) and EBD (71.7% and 78.2%) groups. This demonstrated that epithelial cell transplantation alleviated re-strictures after ESD with good safety and stability.

4.3. Tissue engineering carriers

The rapid development of tissue engineering in recent years has brought biodegradable hydrogel materials with controllable physicochemical properties and biocompatibility [68] into focus. These materials can function independently as a barrier or serve as tissue engineering carriers for tissue transplantation. Hydrogels can adapt to wound areas of any shape and size, undergo rapid gelation, produce a relatively uniform distribution of graft cells, and maintain a high water content close to that of natural tissue [69,70]. However, an inherent limitation of hydrogel networks is their small pore size, which only allows diffusion of the culture medium, metabolites, and nutrients while hindering the migration of transplanted cells outside the scaffold. This suggests that hydrogels may be better suited as a barrier than as a carrier. Therefore, hydrogels may possibly serve as ideal carrier systems in skin wound

healing where direct cell-cell communication between grafted and host cells is not intended and grafted cells mainly exert their functional role through paracrine signaling [71].

Iizuka et al. [72] and Sakaguchi et al. [73] evaluated the application of PGA sheets with fibrin glue in the prevention of esophageal stenosis after ESD. The two studies respectively included patients with mucosal defects of more than half and three-quarters of the esophageal circumference, and the ultimate incidence rates of esophageal stenosis were 7.7% and 37.5%, respectively. These results demonstrated the safety and effectiveness of this method. On this basis, other researchers have explored combination therapies using PGA sheets with scaffolds, steroids, and other medications. Chai et al. [74] performed PGA sheet-coated stent placement in 34 patients with mucosal defects exceeding 75% of the esophageal circumference. The final incidence rate of esophageal stenosis was 20.5% (7/34), which was lower than that of patients who underwent stent placement alone (46.9%, 15/32, $P = 0.024$). Sakaguchi et al. [75] analyzed the efficacy of PGA shielding in combination with steroid injection and found that compared with PGA shielding alone or steroid injection alone, the combination therapy was the only significantly effective method in the prevention of stenosis ($P = 0.012$). Nishimura et al. [27] investigated the application of basic fibroblast growth factor-soaked PGA sheets to the wound bed followed by fibrin glue spraying for fixation. Results indicated that suppressing myofibroblast activation during the acute phase effectively prevented esophageal constriction in pigs. From the studies described above, it is evident that PGA sheets are not merely capable of acting as a protective barrier but also as a drug carrier to prevent esophageal stenosis after ESD. In addition, PGA sheets are highly advantageous in terms of safety, with no adverse events reported thus far. Tang et al. [76] conducted an animal experiment in which carboxymethyl cellulose (CMC) sheets were applied in a porcine model of esophageal stenosis. Results showed that the experimental group ($n = 7$) had a significantly lower rate of esophageal mucosal stenosis, less fibrosis in the submucosal layer, milder damage to the muscularis propria, and a higher degree of re-epithelialization. Therefore, the use of CMC sheets on mucosal defects is a promising method for the prevention of esophageal stenosis after ESD surgery. After modification by tissue engineering, CMC sheets may also serve as drug delivery systems [77] that can achieve more desirable prevention and treatment effects when used in combination with other drugs that effectively improve esophageal stenosis, such as steroids and botulinum toxin type A.

Zhang et al. [78] carried out a prospective study in which 15 patients with extensive superficial esophageal lesions were consecutively treated with ESD and esophageal mucosal autografting. During follow-up, it was found that seven patients (46.7%) developed esophageal stenosis, with the strictures of all patients successfully attenuated after endoscopic balloon dilation (EBD) or endoscopic radial incision. Building on previous findings, Liu et al. [79] constructed autologous esophageal mucosal patches on PGA felt, which was subsequently structured onto a metal mesh stent. Temporary implantations of the stents were performed in 25 patients, and the stents were removed 6–8 weeks postoperatively. Within an average follow-up period of 10.2 months, 14 patients (56%) did not develop stenosis, and no complications occurred except for stent migration in two patients. These results indicated that the

proposed method is a safe and effective approach. Apart from autologous esophageal mucosal transplantation, the transplantation of other tissues has been less studied. At present, autologous gastric mucosal transplantation, autologous buccal mucosal transplantation, and autologous dermo-epidermal transplantation have been reported. Hochberger et al. [80] first attempted to cover mucosal defects after ESD using autologous gastric mucosa, which was collected through the anterior wall of the gastric antrum and fixed with clips and an uncovered mesh stent. Results revealed stenosis-free healing of the operated esophageal segment and the non-occurrence of clinical complications during 32 months of follow-up. Liu et al. [81] reported a case of successful prevention of post-ESD esophageal stenosis by using autologous buccal mucosa with PGA and a self-help inflatable balloon. During the surgery, autologous buccal mucosal tissue cut into small pieces was fixed on a PGA felt that was sutured to the surface of a self-help inflatable balloon. The balloon was subsequently attached to the ESD wound surface. After the surgery, the balloon was inflated six to eight times a day until removal at 8 weeks postoperatively. Within a follow-up period of 9 months, there were no occurrences of postoperative esophageal stenosis or adverse events such as perforation, bleeding, or wound infection. Zou et al. developed autologous skin grafts and conducted a case-matched controlled study [82]. Results showed that patients who underwent stent placement combined with autologous skin grafting had a lower incidence rate of postoperative stenosis than the stent-only group (36.8% vs. 78.9%, $P = 0.020$). This validated the efficacy of autologous skin grafts in preventing esophageal stenosis after circumferential ESD and provided a feasible solution for the implantation of similar materials.

Despite the promising results described above, the degradation time of currently available biodegradable materials is still considerably shorter than the healing time of esophageal wounds. Therefore, such materials are incapable of serving a role throughout the entire process of esophageal healing, and their protective effects towards wounds remain limited. This is a challenge that needs to be addressed, and the construction of more stable structures is necessary to strike a balance between mechanical strength and degradation rate.

4.4. Extracellular matrix (ECM)

On the basis of preserving cytokines that play a role in wound healing and removing potential immunogenic substances from cells, the decellularization method can be adopted to retain the ECM for the preparation of scaffolds or ECM patches. Nieponice et al. [83] first explored the efficacy of ECM for the prevention of esophageal stenosis after ESD. ECM scaffolds were prepared by decellularization of porcine bladders, implanted in five dogs of the experimental group by balloon positioning during the postoperative period, and fixed with biodegradable adhesive. Dogs of the control group did not receive any intervention. Results indicated that the incidence rates of esophageal stenosis in the experimental and control groups after 2 months were 0% (0/5) and 60% (3/5), respectively. Schomisch et al. [84] compared the effects of self-expanding silicone stents that were respectively covered with ECM from three tissue sources (bladder, dermis, and small intestine submucosa) with stents without ECM coverage in the prevention of esophageal stenosis after EMR. A

different conclusion was obtained, with results indicating that the ECM-covered stents did not alter remodeling sufficiently to prevent esophageal stenosis formation after EMR, when compared with the control group. Recently, Zhou et al. [85] conducted a single-center prospective clinical study in which seven patients at high risk for developing esophageal stenosis underwent transplantation using porcine-derived decellularized dermal matrix patches fixed with metal stents. Results showed that the incidence of postoperative stenosis was 42.9% (3/7), with the median number of postoperative endoscopic balloon dilatations (EBDs) being 2. Notably, all patients who underwent circumferential ESD developed stenosis during the follow-up period, whereas only one of the five patients with non-circumferential ESD developed esophageal stenosis. This suggests that ECM materials may be effective in preventing esophageal stenosis after ESD, but have limited effects on esophageal stenosis caused by large mucosal defects.

5. Summary and future prospects

In conclusion, many studies have investigated the prevention of esophageal stenosis after ESD, but most of them remain at the stage of animal experimentation and lack clinical trial data for validation. Evidence suggests research seem to suggest that combination therapy is more effective than monotherapy. In patients undergoing extensive ESD for lesions affecting more than 3/4 of the esophageal circumference, combination therapy may still offer some preventive effects. This also indicates that treatment strategies for the prevention of typical esophageal stenosis cannot be directly applied to refractory esophageal stenosis. Novel preventive methods based on tissue engineering and regenerative medicine are highly promising, but their technical difficulties and high cost remain challenges that need to be addressed before they can be applied in clinical practice.

Conflict of interest: The authors declare no conflict of interest.

Abbreviations

CMC	Carboxymethyl cellulose
EBD	Endoscopic balloon dilatation
ESD	Endoscopic submucosal dissection
EBB	Esophageal epithelial barrier
ECM	Extracellular matrix
EMR	Endoscopic mucosal resection
PGA	Polyglycolic acid

References

1. He J, Chen WQ, Li ZS, et al. China guideline for the screening, early detection and early treatment of esophageal cancer (2022, Beijing). *Zhonghua Zhong Liu Za Zhi*. 2022; 44(6): 491-522.
2. Lorenzo D, Barret M, Leblanc S, et al. Outcomes of endoscopic submucosal dissection for early oesophageal squamous cell neoplasia at a Western centre. *United European Gastroenterology Journal*. 2019; 7(8): 1084-1092. doi: 10.1177/2050640619852260
3. Tomizawa Y, Friedland S, Hwang JH. Endoscopic submucosal dissection (ESD) for Barrett's esophagus (BE)-related early

- neoplasia after standard endoscopic management is feasible and safe. *Endoscopy International Open*. 2020; 08(04): E498-E505. doi: 10.1055/a-0905-2465
4. Han C, Sun Y. Efficacy and safety of endoscopic submucosal dissection versus endoscopic mucosal resection for superficial esophageal carcinoma: a systematic review and meta-analysis. *Diseases of the Esophagus*. 2020; 34(4). doi: 10.1093/dote/doaa081
5. Park CH, Yang DH, Kim JW, et al. Clinical practice guideline for endoscopic resection of early gastrointestinal cancer. *Intestinal Research*. 2021; 19(2): 127-157. doi: 10.5217/ir.2020.00020
6. Minamide T, Kawata N, Maeda Y, et al. Clinical outcomes of endoscopic submucosal dissection for superficial circumferential esophageal squamous cell carcinoma. *Gastrointestinal Endoscopy*. 2023; 97(2): 232-240.e4. doi: 10.1016/j.gie.2022.09.027
7. Yu X, Liu Y, Xue L, et al. Risk factors for complications after endoscopic treatment in Chinese patients with early esophageal cancer and precancerous lesions. *Surgical Endoscopy*. 2020; 35(5): 2144-2153. doi: 10.1007/s00464-020-07619-z
8. Chen M, Dang Y, Ding C, et al. Lesion size and circumferential range identified as independent risk factors for esophageal stricture after endoscopic submucosal dissection. *Surgical Endoscopy*. 2020; 34(9): 4065-4071. doi: 10.1007/s00464-020-07368-z
9. Kim JS, Kim BW, Shin IS. Efficacy and Safety of Endoscopic Submucosal Dissection for Superficial Squamous Esophageal Neoplasia: A Meta-Analysis. *Digestive Diseases and Sciences*. 2014; 59(8): 1862-1869. doi: 10.1007/s10620-014-3098-2
10. Isomoto H, Yamaguchi N, Minami H, et al. Management of complications associated with endoscopic submucosal dissection/ endoscopic mucosal resection for esophageal cancer. *Digestive Endoscopy*. 2013; 25(S1): 29-38. doi: 10.1111/j.1443-1661.2012.01388.x
11. Zhang Y, Zhang B, Wang Y, et al. Advances in the prevention and treatment of esophageal stricture after endoscopic submucosal dissection of early esophageal cancer. *Journal of Translational Internal Medicine*. 2020; 8(3): 135-145. doi: 10.2478/jtim-2020-0022
12. DeNardi FG, Riddell RH. The Normal Esophagus. *The American Journal of Surgical Pathology*. 1991; 15(3): 296-309. doi: 10.1097/00000478-199103000-00010
13. Edwards DA. The oesophagus. *Gut*. 1971; 12(11): 948-956. doi: 10.1136/gut.12.11.948
14. Zhang Y, Bailey D, Yang P, et al. The development and stem cells of the esophagus. *Development*. 2021; 148(6). doi: 10.1242/dev.193839
15. Rosekrans SL, Baan B, Muncan V, et al. Esophageal development and epithelial homeostasis. *American Journal of Physiology-Gastrointestinal and Liver Physiology*. 2015; 309(4): G216-G228. doi: 10.1152/ajpgi.00088.2015
16. Yang F, Hu Y, Shi Z, et al. The occurrence and development mechanisms of esophageal stricture: state of the art review. *Journal of Translational Medicine*. 2024; 22(1). doi: 10.1186/s12967-024-04932-2
17. Honda M, Nakamura T, Hori Y, et al. Process of healing of mucosal defects in the esophagus after endoscopic mucosal resection: histological evaluation in a dog model. *Endoscopy*. 2010; 42(12): 1092-1095. doi: 10.1055/s-0030-1255741
18. Candi E, Schmidt R, Melino G. The cornified envelope: a model of cell death in the skin. *Nature Reviews Molecular Cell Biology*. 2005; 6(4): 328-340. doi: 10.1038/nrm1619
19. Akiyama M, Matsuo I, Shimizu H. Formation of cornified cell envelope in human hair follicle development. *British Journal of Dermatology*. 2002; 146(6): 968-976. doi: 10.1046/j.1365-2133.2002.04869.x
20. Bouwstra JA, Helder RWJ, El Ghalbzouri A. Human skin equivalents: Impaired barrier function in relation to the lipid and protein properties of the stratum corneum. *Advanced Drug Delivery Reviews*. 2021; 175: 113802. doi: 10.1016/j.addr.2021.05.012
21. Wang Z, Zhou H, Zheng H, et al. Autophagy-based unconventional secretion of HMGB1 by keratinocytes plays a pivotal role in psoriatic skin inflammation. *Autophagy*. 2020; 17(2): 529-552. doi: 10.1080/15548627.2020.1725381
22. Kim BE, Kim J, Goleva E, et al. Particulate matter causes skin barrier dysfunction. *JCI Insight*. 2021; 6(5). doi: 10.1172/jci.insight.145185
23. de Koning HD, van den Bogaard EH, Bergboer JGM, et al. Expression profile of cornified envelope structural proteins and keratinocyte differentiation-regulating proteins during skin barrier repair. *British Journal of Dermatology*. 2012; 166(6): 1245-1254. doi: 10.1111/j.1365-2133.2012.10885.x
24. van Roy F, Berx G. The cell-cell adhesion molecule E-cadherin. *Cellular and Molecular Life Sciences*. 2008; 65(23): 3756-

3788. doi: 10.1007/s00018-008-8281-1
25. Biswas KH. Molecular Mobility-Mediated Regulation of E-Cadherin Adhesion. *Trends in Biochemical Sciences*. 2020; 45(2): 163-173. doi: 10.1016/j.tibs.2019.10.012
26. Beutel O, Maraschini R, Pombo-García K, et al. Phase Separation of Zonula Occludens Proteins Drives Formation of Tight Junctions. *Cell*. 2019; 179(4): 923-936.e11. doi: 10.1016/j.cell.2019.10.011
27. Nishimura Y, Ono M, Okubo N, et al. Application of polyglycolic acid sheets and basic fibroblast growth factor to prevent esophageal stricture after endoscopic submucosal dissection in pigs. *Journal of Gastroenterology*. 2023; 58(11): 1094-1104. doi: 10.1007/s00535-023-02032-4
28. Siegel I. Phagocytosis: Macrophage-Lymphocyte Interactions. *JAMA: The Journal of the American Medical Association*. 1981; 246(10): 1127. doi: 10.1001/jama.1981.03320100063037
29. Lu P, Takai K, Weaver VM, et al. Extracellular Matrix Degradation and Remodeling in Development and Disease. *Cold Spring Harbor Perspectives in Biology*. 2011; 3(12): a005058-a005058. doi: 10.1101/cshperspect.a005058
30. Phan QM, Sinha S, Biernaskie J, et al. Single-cell transcriptomic analysis of small and large wounds reveals the distinct spatial organization of regenerative fibroblasts. *Experimental Dermatology*. 2020; 30(1): 92-101. doi: 10.1111/exd.14244
31. Phan QM, Fine GM, Salz L, et al. Lef1 expression in fibroblasts maintains developmental potential in adult skin to regenerate wounds. *eLife*. 2020; 9. doi: 10.7554/elife.60066
32. Kumar V, Ali MJ, Ramachandran C. Effect of mitomycin-C on contraction and migration of human nasal mucosa fibroblasts: implications in dacryocystorhinostomy. *British Journal of Ophthalmology*. 2015; 99(9): 1295-1300. doi: 10.1136/bjophthalmol-2014-306516
33. Seo BR, Chen X, Ling L, et al. Collagen microarchitecture mechanically controls myofibroblast differentiation. *Proceedings of the National Academy of Sciences*. 2020; 117(21): 11387-11398. doi: 10.1073/pnas.1919394117
34. Shu DY, Lovicu FJ. Myofibroblast transdifferentiation: The dark force in ocular wound healing and fibrosis. *Progress in Retinal and Eye Research*. 2017; 60: 44-65. doi: 10.1016/j.preteyeres.2017.08.001
35. El-Asmar KM, Hassan MA, Abdelkader HM, et al. Topical mitomycin C application is effective in management of localized caustic esophageal stricture: A double-blinded, randomized, placebo-controlled trial. *Journal of Pediatric Surgery*. 2013; 48(7): 1621-1627. doi: 10.1016/j.jpedsurg.2013.04.014
36. Zhang Y, Wang X, LIU L, et al. Intramuscular injection of mitomycin C combined with endoscopic dilation for benign esophageal strictures. *Journal of Digestive Diseases*. 2015; 16(7): 370-376. doi: 10.1111/1751-2980.12255
37. Werner S, Grose R. Regulation of Wound Healing by Growth Factors and Cytokines. *Physiological Reviews*. 2003; 83(3): 835-870. doi: 10.1152/physrev.2003.83.3.835
38. Hosseini M, Shafiee A. Engineering Bioactive Scaffolds for Skin Regeneration. *Small*. 2021; 17(41). doi: 10.1002/sml.202101384
39. Hutmacher DW. Scaffolds in tissue engineering bone and cartilage. *Biomaterials*. 2000; 21(24): 2529-2543.
40. Li X, You R, Luo Z, et al. Silk fibroin scaffolds with a micro-/nano-fibrous architecture for dermal regeneration. *Journal of Materials Chemistry B*. 2016; 4(17): 2903-2912. doi: 10.1039/c6tb00213g
41. Chouhan D, Chakraborty B, Nandi SK, et al. Role of non-mulberry silk fibroin in deposition and regulation of extracellular matrix towards accelerated wound healing. *Acta Biomaterialia*. 2017; 48: 157-174. doi: 10.1016/j.actbio.2016.10.019
42. Ju YM, Yu B, West L, et al. A novel porous collagen scaffold around an implantable biosensor for improving biocompatibility. II. Long-term in vitro/in vivo sensitivity characteristics of sensors with NDGA- or GA-crosslinked collagen scaffolds. *Journal of Biomedical Materials Research Part A*. 2009; 92A(2): 650-658. doi: 10.1002/jbm.a.32400
43. Kundu B, Rajkhowa R, Kundu SC, et al. Silk fibroin biomaterials for tissue regenerations. *Advanced Drug Delivery Reviews*. 2013; 65(4): 457-470. doi: 10.1016/j.addr.2012.09.043
44. Suntornnond R, Tan EYS, An J, et al. A highly printable and biocompatible hydrogel composite for direct printing of soft and perfusable vasculature-like structures. *Scientific Reports*. 2017; 7(1). doi: 10.1038/s41598-017-17198-0
45. Houshyar S, Kumar GS, Rifai A, et al. Nanodiamond/poly-ε-caprolactone nanofibrous scaffold for wound management. *Materials Science and Engineering: C*. 2019; 100: 378-387. doi: 10.1016/j.msec.2019.02.110
46. Stratton S, Shelke NB, Hoshino K, et al. Bioactive polymeric scaffolds for tissue engineering. *Bioactive Materials*. 2016; 1(2): 93-108. doi: 10.1016/j.bioactmat.2016.11.001
47. Han Y, Li Y, Zeng Q, et al. Injectable bioactive akermanite/alginate composite hydrogels for in situ skin tissue engineering. *Journal of Materials Chemistry B*. 2017; 5(18): 3315-3326. doi: 10.1039/c7tb00571g

48. Li Y, Han Y, Wang X, et al. Multifunctional Hydrogels Prepared by Dual Ion Cross-Linking for Chronic Wound Healing. *ACS Applied Materials & Interfaces*. 2017; 9(19): 16054-16062. doi: 10.1021/acsami.7b04801
49. Zhou Y, Gao L, Peng J, et al. Bioglass Activated Albumin Hydrogels for Wound Healing. *Advanced Healthcare Materials*. 2018; 7(16). doi: 10.1002/adhm.201800144
50. Mikos AG, McIntire LV, Anderson JM, Babensee JE. Host response to tissue engineered devices. *Adv Drug Deliv Rev*. 1998; 33(1-2): 111-139.
51. Tabata Y. Biomaterial technology for tissue engineering applications. *Journal of The Royal Society Interface*. 2009; 6(suppl_3). doi: 10.1098/rsif.2008.0448.focus
52. Nam K, Kimura T, Funamoto S, et al. Preparation of a collagen/polymer hybrid gel designed for tissue membranes. Part I: Controlling the polymer–collagen cross-linking process using an ethanol/water co-solvent. *Acta Biomaterialia*. 2010; 6(2): 403-408. doi: 10.1016/j.actbio.2009.06.021
53. Zuercher BF, George M, Escher A, et al. Stricture prevention after extended circumferential endoscopic mucosal resection by injecting autologous keratinocytes in the sheep esophagus. *Surgical Endoscopy*. 2012; 27(3): 1022-1028. doi: 10.1007/s00464-012-2509-8
54. Honda M, Hori Y, Nakada A, et al. Use of adipose tissue-derived stromal cells for prevention of esophageal stricture after circumferential EMR in a canine model. *Gastrointestinal Endoscopy*. 2011; 73(4): 777-784. doi: 10.1016/j.gie.2010.11.008
55. Mizushima T, Ohnishi S, Hosono H, et al. Oral administration of conditioned medium obtained from mesenchymal stem cell culture prevents subsequent stricture formation after esophageal submucosal dissection in pigs. *Gastrointestinal Endoscopy*. 2017; 86(3): 542-552.e1. doi: 10.1016/j.gie.2017.01.024
56. Su S, Pang T, Wang Y, et al. Prevention of Esophageal Stricture after Endoscopic Submucosal Dissection with an Autologous Esophageal Epithelial Cell Suspension: An Animal Study. *Discovery Medicine*. 2023; 35(179): 1026. doi: 10.24976/discov.med.202335179.98
57. Abbas O, Mahalingam M. Epidermal stem cells: practical perspectives and potential uses. *British Journal of Dermatology*. 2009; 161(2): 228-236. doi: 10.1111/j.1365-2133.2009.09250.x
58. Kopp J, Jeschke MG, Bach AD, et al. Applied tissue engineering in the closure of severe burns and chronic wounds using cultured human autologous keratinocytes in a natural fibrin matrix. *Cell Tissue Bank*. 2004; 5(2): 89-96.
59. El-Ghalbzouri A, Gibbs S, Lamme E, et al. Effect of fibroblasts on epidermal regeneration. *British Journal of Dermatology*. 2002; 147(2): 230-243. doi: 10.1046/j.1365-2133.2002.04871.x
60. Wang JHC, Thampatty BP, Lin JS, et al. Mechanoregulation of gene expression in fibroblasts. *Gene*. 2007; 391(1-2): 1-15. doi: 10.1016/j.gene.2007.01.014
61. Plikus MV, Gay DL, Treffeisen E, et al. Epithelial stem cells and implications for wound repair. *Seminars in Cell & Developmental Biology*. 2012; 23(9): 946-953. doi: 10.1016/j.semcdb.2012.10.001
62. Phinney DG. Functional heterogeneity of mesenchymal stem cells: Implications for cell therapy. *Journal of Cellular Biochemistry*. 2012; 113(9): 2806-2812. doi: 10.1002/jcb.24166
63. Takagi R, Yamato M, Murakami D, et al. Fabrication and Validation of Autologous Human Oral Mucosal Epithelial Cell Sheets to Prevent Stenosis after Esophageal Endoscopic Submucosal Dissection. *Pathobiology*. 2011; 78(6): 311-319. doi: 10.1159/000322575
64. Ohki T, Yamato M, Ota M, et al. Prevention of Esophageal Stricture After Endoscopic Submucosal Dissection Using Tissue-Engineered Cell Sheets. *Gastroenterology*. 2012; 143(3): 582-588.e2. doi: 10.1053/j.gastro.2012.04.050
65. Jonas E, Sjöqvist S, Elbe P, et al. Transplantation of tissue-engineered cell sheets for stricture prevention after endoscopic submucosal dissection of the oesophagus. *United European Gastroenterology Journal*. 2016; 4(6): 741-753. doi: 10.1177/2050640616631205
66. Kanai N, Yamato M, Ohki T, et al. Fabricated autologous epidermal cell sheets for the prevention of esophageal stricture after circumferential ESD in a porcine model. *Gastrointestinal Endoscopy*. 2012; 76(4): 873-881. doi: 10.1016/j.gie.2012.06.017
67. Kobayashi S, Kanai N, Tanaka N, et al. Transplantation of epidermal cell sheets by endoscopic balloon dilatation to avoid esophageal re-strictures: initial experience in a porcine model. *Endoscopy International Open*. 2016; 04(11): E1116-E1123. doi: 10.1055/s-0042-116145
68. Liu X, Inda ME, Lai Y, et al. Engineered Living Hydrogels. *Advanced Materials*. 2022; 34(26). doi: 10.1002/adma.202201326

69. Wang C, Varshney RR, Wang DA. Therapeutic cell delivery and fate control in hydrogels and hydrogel hybrids. *Advanced Drug Delivery Reviews*. 2010; 62(7-8): 699-710. doi: 10.1016/j.addr.2010.02.001
70. Griffin DR, Archang MM, Kuan CH, et al. Activating an adaptive immune response from a hydrogel scaffold imparts regenerative wound healing. *Nature Materials*. 2020; 20(4): 560-569. doi: 10.1038/s41563-020-00844-w
71. Peura M, Kaartinen I, Suomela S, et al. Improved skin wound epithelialization by topical delivery of soluble factors from fibroblast aggregates. *Burns*. 2012; 38(4): 541-550. doi: 10.1016/j.burns.2011.10.016
72. Iizuka T, Kikuchi D, Yamada A, et al. Polyglycolic acid sheet application to prevent esophageal stricture after endoscopic submucosal dissection for esophageal squamous cell carcinoma. *Endoscopy*. 2014; 47(04): 341-344. doi: 10.1055/s-0034-1390770
73. Sakaguchi Y, Tsuji Y, Ono S, et al. Polyglycolic acid sheets with fibrin glue can prevent esophageal stricture after endoscopic submucosal dissection. *Endoscopy*. 2014; 47(04): 336-340. doi: 10.1055/s-0034-1390787
74. Chai NL, Feng J, Li LS, et al. Effect of polyglycolic acid sheet plus esophageal stent placement in preventing esophageal stricture after endoscopic submucosal dissection in patients with early-stage esophageal cancer: A randomized, controlled trial. *World Journal of Gastroenterology*. 2018; 24(9): 1046-1055. doi: 10.3748/wjg.v24.i9.1046
75. Sakaguchi Y, Tsuji Y, Sato J, et al. Repeated steroid injection and polyglycolic acid shielding for prevention of refractory esophageal stricture. *Surgical Endoscopy*. 2023; 37(8): 6267-6277. doi: 10.1007/s00464-023-10111-z
76. Tang J, Ye S, Ji X, et al. Deployment of carboxymethyl cellulose sheets to prevent esophageal stricture after full circumferential endoscopic submucosal dissection: A porcine model. *Digestive Endoscopy*. 2018; 30(5): 608-615. doi: 10.1111/den.13070
77. Silva OA, Pellá MG, Sabino RM, et al. Carboxymethylcellulose hydrogels crosslinked with keratin nanoparticles for efficient prednisolone delivery. *International Journal of Biological Macromolecules*. 2023; 241: 124497. doi: 10.1016/j.ijbiomac.2023.124497
78. Zhang Y, Mao XL, Zhu W, et al. Esophageal Mucosal Autograft for Preventing Stricture After Widespread Endoscopic Submucosal Dissection of Superficial Esophageal Lesions. *Turkish Journal of Gastroenterology*. 2022; 33(4): 312-319. doi: 10.5152/tjg.2021.201032
79. Liu Y, Li Z, Dou L, et al. Autologous esophageal mucosa with polyglycolic acid transplantation and temporary stent implantation can prevent stenosis after circumferential endoscopic submucosal dissection. *Annals of Translational Medicine*. 2021; 9(7): 546-546. doi: 10.21037/atm-20-6987
80. Hochberger J, Koehler P, Wedi E, et al. Transplantation of Mucosa From Stomach to Esophagus to Prevent Stricture After Circumferential Endoscopic Submucosal Dissection of Early Squamous Cell. *Gastroenterology*. 2014; 146(4): 906-909. doi: 10.1053/j.gastro.2014.01.063
81. Liu Y, Dou L, Song T, et al. Successful prevention of post-endoscopic submucosal dissection esophageal stenosis by using autologous buccal mucosa with polyglycolic acid and self-help inflatable balloon. *Gastrointest Endosc*. 2023.
82. Zou J, Chai N, Linghu E, et al. Autologous skin-grafting surgery to prevent esophageal stenosis after complete circular endoscopic submucosal tunnel dissection: a case-matched controlled study. *Surgical Endoscopy*. 2020; 35(11): 5962-5970. doi: 10.1007/s00464-020-08081-7
83. Nieponice A, McGrath K, Qureshi I, et al. An extracellular matrix scaffold for esophageal stricture prevention after circumferential EMR. *Gastrointestinal Endoscopy*. 2009; 69(2): 289-296. doi: 10.1016/j.gie.2008.04.022
84. Schomisch S, Yu L, Wu Y, et al. Commercially available biological mesh does not prevent stricture after esophageal mucosectomy. *Endoscopy*. 2013; 46(02): 144-148. doi: 10.1055/s-0033-1344997
85. Zhou X bin, Li S wei, He S qin, et al. Transplantation of acellularized dermis matrix (ADM) plus fully covered metal stent to prevent stricture after circumferential endoscopic submucosal dissection of early esophageal cancer (with video). *Regenerative Therapy*. 2021; 18: 441-446. doi: 10.1016/j.reth.2021.10.002