Original Article

Progress of esophageal stricture prevention after endoscopic submucosal dissection by regenerative medicine and tissue engineering

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A B S T R A C T

Endoscopic submucosal dissection (ESD) has been widely accepted as an effective treatment for early esophageal cancer. However, post-ESD esophageal stricture remains a thorny issue. We herein review many strategies for preventing post-ESD esophageal stricture, as well as discuss their strengths and weaknesses. These strategies include pharmacological prophylaxis, esophageal stent and tissue engineering and regenerative medicine treatment. In this review, we summarize these studies and discuss the underlying progress and future directions of tissue engineering and regenerative medicine treatment.

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1. Introduction

Esophageal cancer is the sixth-most common causes of cancer-related mortality [1,2]. Endoscopic mucosal dissection (ESD) is an approach to endoscopic tumor resection that can completely remove large lesions for an accurate histopathological examination.

In the last decade, ESD has been widely accepted for its effectiveness [2–5]. However, residual mucosal defects after the procedure can cause an acute inflammatory reaction, deep ulcers, submucosal fibrous connective tissue hyperplasia, wall fibrosis and esophageal stricture [6].

The rate of stricture occurrence is directly correlated with the extent of ESD mucosal resection. Lesions with a diameter ≥50 mm but less than 2/3 of the esophageal circumference have a 36% chance of developing esophageal stenosis after ESD [7,8]. Stricture does not occur in most cases with mucosal defects covering less than half of the esophageal circumference, while 28% of cases with 1/2–3/4 circumferential mucosal defect develop stricture, and in cases with >3/4 circumferential mucosal defects, the rate is 94% [8]. For patients who undergo entire or almost entire circumferential mucosa resection, the incidence of stricture is 88%–100% [9]. Preventing post-ESD esophageal stricture is thus very important for ensuring a good prognosis and quality of life for patients.

2. Strategies for preventing post-ESD esophageal stricture

Although prophylactic endoscopic balloon dilation (EBD) reduces the incidence of post-ESD esophageal stricture from 92% to

59% in patients with mucosal defects covering more than 3/4 of the circumference [10], this approach is insufficient in most patients. A previous report found that more than 30 dilations are required after circumferential esophageal ESD [11]. Not only is this extremely detrimental to a patient's prognosis, it also increases the financial burden. Therefore, in recent years, a number of studies on the prevention of post-ESD esophageal stricture have been conducted. Various strategies have been tested through animal experiments and clinical studies, and these preventive measures are roughly categorized as described (Fig. 1).

2.1. Pharmacological prophylaxis

2.1.1. Steroid prophylaxis

Using steroids to prevent post-ESD stricture is a widely accepted clinical method that including oral steroid therapy, endoscopic intralesional injection of steroid therapy and steroid gel prevention. The efficacy of steroids is also widely recognized [12–19]. However, pharmacological prophylaxis is not sufficient for mucosal defects involving the entire esophagus [20]. Local steroid injection showed limited efficacy in patients with defects covering more than 75% of the circumference. And for those covering the entire esophageal circumference, it seemed to have no effect at all [21]. As reported in the article of Hirdes et al., steroid injection plus esophageal dilation failed to markedly decrease the frequency of dilation or prolong the dysphagia-free time in patients with benign anastomotic esophagogastric stricture [22].

Oral steroid therapy, especially that in high doses, may cause multiple adverse reactions, including immunosuppression, diabetes mellitus, mental disorders, osteoporosis, optical damage, peptic ulcers [6]. Disseminated nocardiosis in time of oral steroid therapy has also been reported [23]. Immunosuppression caused by steroids may also cause infections, such as candida esophagitis and pneumocystis pneumonia [24]. Meanwhile, local steroid injections (triamcinolone acetonide[TA] as the drug of choice) will increase the risk of delayed esophageal perforation [16–19] and are associated with an increased risk of candida esophagitis [25]. Modified steroid therapy [26–29], such as TA solution filling, may be the best approach at present, but for which confirmation through multicenter experiments will be needed.

2.1.2. Antifibrotic drugs

A variety of antifibrotic drugs are used to prevent postoperative esophageal stenosis. Mitomycin C, with its anti-fibroblast proliferation effect [30], is widely used to treat postoperative esophageal stricture in children undergoing surgery for esophageal atresia or corrosive esophageal stricture. Some researchers have also used it to prevent esophageal stricture in adults [31,32]. However, high-dose Mitomycin C treatment may cause necrosis and even perforation of the esophageal wall [33], as well as induction of DNA damage [21]. 5-Fluorouracil (5-FU) inhibits cell proliferation by inhibiting DNA synthesis and interfering with protein synthesis. However, high concentrations of 5-FU can easily cause tissue necrosis [34–36]. Local injection of botulinum toxin inhibits scar formation as well as muscle activity, helping prevent esophageal stricture and reducing stent displacement [37,38]. N-acetylcysteine is an antioxidant with anti-fibrotic effects, but it did not significantly lower the stricture rate after circumferential esophageal dissection [39]. Small interfering RNA (siRNA) blocks carbohydrate sulfotransferase 15 (ChST15), which is expressed by fibroblasts and involved in the development of fibrosis. siRNA injection can inhibit fibrosis and thereby reduce stenosis [40]. Thymosin β4 (Tβ4) inhibits fibrosis and prevent scar formation, and has been proven effective in pig model experiments [41]. However, for all of those antifibrotic drugs mentioned above, their appropriate

concentration as well as long-term safety and efficacy against esophageal stricture still need to be further evaluated in large-scale and multicenter clinical studies.

2.2. Polyglycolic acid sheet (PGAs)

PGAs protects the wound surface and reduce the contact of the wound with external stimuli, thereby inhibiting the proliferation of granulation tissue and preventing stenosis. Japanese researchers evaluated the effectiveness of PGAs in patients with non-circumferential resection [42,43]. The overall incidence of esophageal stricture in these patients was 7.7% (1/13), with a 37.5% (3/8) incidence in patients with mucosal defects ≥3/4 of the circumference of the esophageal [43].
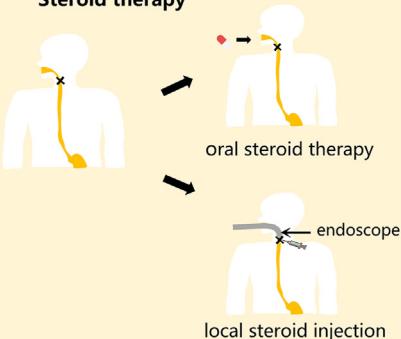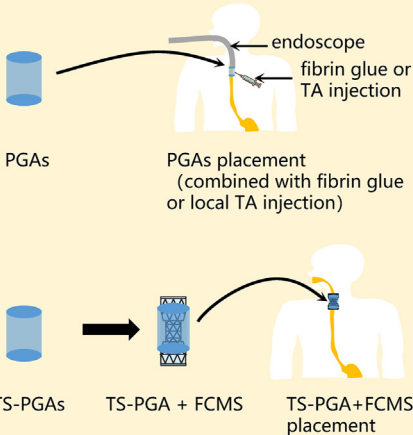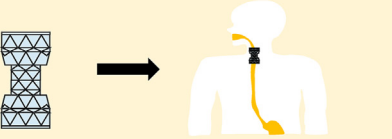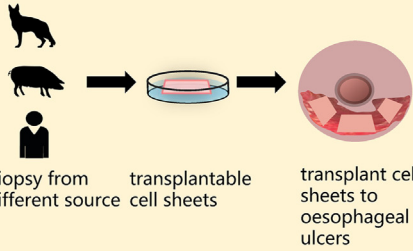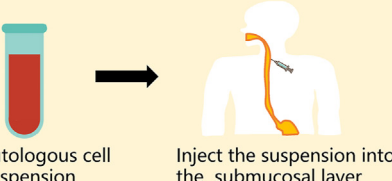
In recent years, some researchers have used PGAs combined with fibrin glue or local TA injection to prevent post-ESD esophageal stricture [43–46]. However a retrospective analysis compared the effect of PGAs + fibrin gel therapy with steroid injection and found no significant difference between the two treatment methods [42]. The study group (PGAs + fibrin glue) included 39 cases, and the control group (steroid injection) included 31 cases. The post-ESD stricture rate was 9.1% (3/33 cases) in the study group and 10.3% (3/29 cases) in the control group, showing no marked difference (p = 1.00). A clinical study was conducted in Japan among patients with superficial esophageal carcinoma covering over 1/2 the esophageal circumference who were treated with "steroid injection + PGAs", or "PGAs" or "control (without prevention)" after ESD. In the relatively low-risk group (excluding cervical esophageal cancer and entire circumferential resection), the post-ESD stenosis rates for "steroid injection + PGAs" versus "PGAs" versus "control" were 18.9% versus 41.4% versus 51.7% (p = 0.015). However, in high-risk cases, the clinical effectiveness was limited [47].

A riamcinolone-soaked PGA plus fully covered metal stent (TS-PGA + FCMS) was used to prevent stricture after extensive dissection of the esophageal mucosa in a recent study [48]. Nine patients with superficial esophageal squamous cell neoplasms (SESCNs) (mucosal defect sizes: 3/4 in 1, 4/5 in 2, 1/1 in 6) were treated with TS-PGA + FCMS immediately after ESD, and stents were taken out 4–6 weeks after surgery. The incidence rate of stricture was 33.3% (3/9) (all in patients with circumferential resection [3/6]).

2.3. Esophageal stent

Esophageal metal stents were originally used for the minimally invasive treatment of esophageal fistula and unresectable malignant esophageal stenosis, with complications such as pain, granulation tissue hyperplasia and stent shifting [49–51]. In recent years, with the continuous improvement and development of stent materials and performance, stent implantation has become an acceptable treatment option for refractory esophageal stricture.

Esophageal stents include self-expandable metal stents (SeMS) [52–54], biodegradable stents [54,55], drug eluting stents, anti-displacement stents, etc. However, using SeMS stents has a higher incidence rate of complications such as granulation tissue hyperplasia, thoracodynia [56] and stent shifting [57]. Biodegradable stents made by polydioxanone implanted in pigs will induce inflammation, massive granulation hyperplasia and food stagnation in the stent, which suggests that biodegradable stents have chance to cause severe hyperplastic tissue reactions and even worsen stricture [21]. And there have been few reports on the utility of drug-eluting stents and anti-displacement stents, so there has not yet been any confirmation of their clinical efficacy.

Therapy	Advantages	Disadvantages
Steroid therapy		
oral steroid therapy / local steroid injection (endoscope)	-widely accepted clinical application -recognized effectiveness	-not sufficient for mucosal defects involving the entire esophagus -potential risk for multiple adverse reactions
Polyglycolic acid sheet(PGAs) therapy		
PGAs / PGAs placement (combined with fibrin glue or local TA injection) (endoscope, fibrin glue or TA injection) TS-PGAs / TS-PGA + FCMS / TS-PGA+FCMS placement		-no significant difference when compared with steroid injection -limited clinical effectiveness for mucosal defects of entire circumference -lack of clinical evaluation in large-scale, multicenter prospective studies -complexity and high cost
Esophageal stent Therapy	-various types of stents to meet different requirements -acceptable treatment for refractory esophageal stricture	-various complications include pain, granulation tissue hyperplasia, stent shifting, etc -Difficulties in stent fixation and granulation tissue hyperplasia prevention -lack of confirmed effectiveness through clinical experimental data
esophageal stent / esophageal stent placement		
Cell sheet transplantation	-structurally and functionally rebuilding normal tissues -viable new method for resolving circumferential esophageal stricture -confirmed effectiveness in preclinical and clinical experiments	-requirement of clinical evidence in large-scale, multicenter prospective studies for some types of cell sheets
biopsy from different source / transplantable cell sheets / transplant cell sheets to oesophageal ulcers		
Injection of autologous cell suspension	-feasible and simple	-potential risk of increasing tumor progression rate
autologous cell suspension / Inject the suspension into the submucosal layer		

There are ways to prevent stent displacement, for example, using endoscopic suture-anchoring devices or attaching the stent to the patient's nose or ear with silk and dental floss. Some have chosen new double-sided brackets (stents with an inner polyurethane layer or an outer uncovered nickel-titanium alloy mesh) to solve this problem [21]. However, the effectiveness of these stents has yet to be confirmed through clinical experimental data, and the issues of proliferation of granulation tissue and optimal timing of stent removal still need to be addressed.

2.4. Tissue engineering and regenerative medicine

Tissue engineering technology structurally and functionally rebuilds normal tissues and promotes early re-epithelialization to prevent post-ESD stricture. This approach includes cell sheet transplantation, extracellular matrix biomaterial transplantation, autologous transplantation and endoscopic autologous cell suspension injection, among others (Fig. 2).

2.4.1. Cell sheets transplantation

In cell sheet transplantation, isolated cells are cultured *in vitro* and, with the help of supporting materials, are transplanted to the mucosal defects. At present, autologous oral mucosal epithelial cell (OMEC) sheets, autologous skin epidermal cell sheets and adipose tissue-derived stromal cell (ADSC) sheets are the main types of tissue engineering cell sheets used to prevent post-ESD esophageal stricture.

2.4.1.1. Autologous OMEC sheets. Autologous OMEC sheets were first transplanted at post-ESD esophageal mucosal defects in three dogs in 2006. Compared with the significant stricture that developed in the control group, the animals in the experimental group showed no esophageal stricture even after four weeks [58]. Takagi et al. successfully transplanted OMEC sheets from seven volunteers to three dogs with esophageal defects after ESD, indicating that human OMEC sheets can adhere and proliferate in the dog esophagus [59]. Endoscopic OMEC sheets were transplanted to prevent post-ESD stricture in nine patients with superficial esophageal squamous carcinoma in 2012, eight of them did not develop esophageal stricture [60]. Jonas et al. transplanted human OMEC sheets into 5 patients (3 received circular resection, and 2 with 9−10 cm in length) [61]. One week later, squamous cells were visible in the transplanted area, while the non-transplanted surface was mostly covered with fibrin. The median time to complete re-epithelialization was three weeks under endoscopy. Three patients developed stricture, which required dilation 2, 4, or 5 times, suggesting that this transplantation reduced both the risk for and extent of stricture. Another recent study also confirmed the effects of OMEC sheets. Yamaguchi et al. airlifted 10 patients' oral mucosa collected at Nagasaki University Hospital to Tokyo Women's Medical University for cell culture and cell sheet production, subsequently airlifting the tissues back to the hospital for endoscopic post-ESD esophageal mucosa transplantation. They adopted a new method reported by Hirose et al. using poly(N-isopropylacrylamide) (PIPAAm) for cell capture [62]. These cell sheets retained good biological effects despite being transported more than 1200 km over 7 h. No post-ESD stricture, dysphagia or other complications occurred in six patients after the surgeries, proving the safety and effectiveness of OMEC sheets over long distances and long transport times [63]. This concentrated culture and distribution method, breaking geographical and technical

limitations, may make it possible for almost all hospitals to perform cell sheets transplantation in the future.

In recent years, the regenerative potential of the exosomes produced by OMEC sheets has become a topic of focus. As shown in a study [64], exosomes from OMEC sheets have a regenerative effect on skin wound healing, and "cell sheet production waste" can be transformed into therapeutic drugs that may promote a new concept of cell sheets + exosome therapy for early esophageal cancer patients. However, how best to use exosomes to treat esophageal wounds and how to achieve adhesion of exosomes to wounds must still be studied. This issue may be key to whether or not OMEC sheets and exosomes can be combined for clinical treatment in the future.

2.4.1.2. Autologous skin epidermal cell sheets. Kanai et al. implanted cell sheets from autologous skin of four pigs into defects after circumferential esophageal ESD, with another four animals used as controls. Two weeks after surgery, the pigs in the experimental group showed mild esophageal stricture and few inflammatory cells at the defects and histologically appeared to have early regenerative epithelium with mild fibrosis in the muscle layer. In contrast, the control group showed less regenerative epithelium with a thicker submucosal layer and fibrous tissue invasion in the muscle layer [65]. However, at present, there are only a few pre-clinical studies on autologous skin epidermal cell sheets, and the sample size is too small, with no evidence from clinical trials. This has made it difficult to draw any hard conclusions from those studies.

2.4.1.3. ADSC sheets. ADSCs are easy to isolate and have paracrine activity, participating in local immune regulation, cell recruitment and neovascularization, which can regulate the interaction of keratinocytes and fibroblasts and inhibit the development of excessive fibrosis [66]. At present, ADSC sheets have been used clinically for wound healing. In terms of the prevention of esophageal stricture, ADSC double-cell sheets were used for transplantation after hemi-circumferential ESD in a pig model in a previous study [67]. One of the 6 pigs (16%) in the ADSC group developed severe esophageal stricture, compared with 100% (5/5) in the control group. Furthermore, the ADSC group had a lower frequency of eating difficulties (17% vs. 80%), confirming that the transplantation of allogeneic ADSC sheets can reduce the degree of stricture and delay the development of fibrosis. ADSCs have anti-inflammatory properties, local immunomodulatory effects, neovascularization induction and the ability to differentiate into mesenchymal and non-mesenchymal lineages, which may explain the principle of esophageal stricture prevetion [68].

2.4.1.4. Cell sheet engineering. Cell sheet engineering utilizes temperature-sensitive polymers, such as PIPAAm and mcc, to form stent-free, transplantable cell sheets without the use of protein hydrolases to avoid the loss of cell surface proteins and extracellular matrix (ECM) caused by mechanical or enzymatic treatment [69]. This approach has been shown to have high potential in the treatment of various diseases, such as bone, periodontal, skin and blood vessel diseases, but its therapeutic potential in gastrointestinal tissue has not been studied. Preclinical studies in animals and clinical studies all proved the strong regeneration ability of cell sheets prepared by cell sheet engineering, so this approach is expected provide new esophageal mucosa transplantation material in the future.

Fig. 1. Strategies of post-ESD Esophageal Stricture Prevention. There are various strategies of post-ESD esophageal stricture prevention, each owning specific advantages and disadvantages. Abbreviation: PGAs, polyglycolic acid sheet; TS-PGA, triamcinolone-soaked polyglycolic acid sheet; TA, triamcinolone acetonide; FCMS, fully covered metal stent.
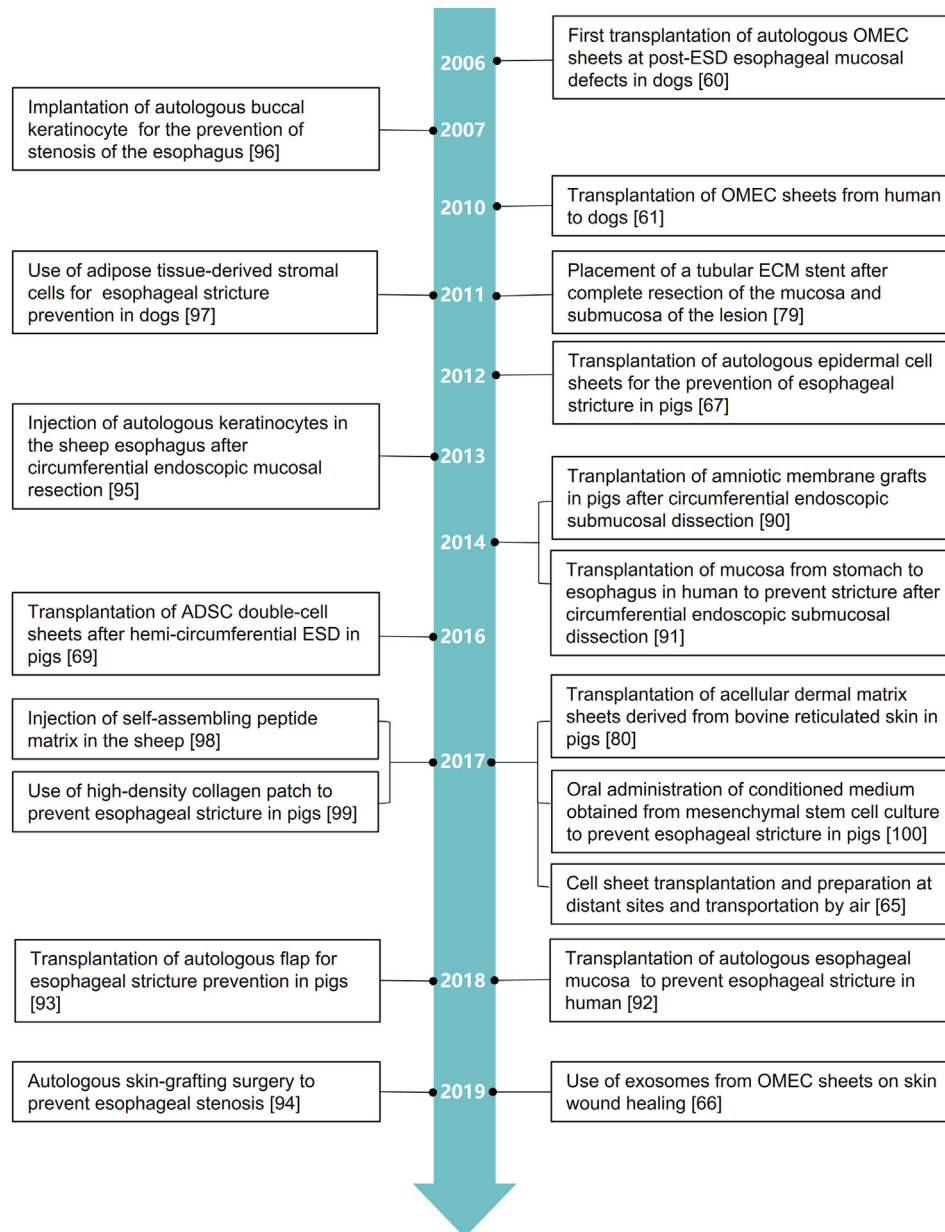
Fig. 2. Timeline of the Treatment Strategies for Prevention of post-ESD Esophageal Stricture on Regenerative Medicine and Tissue Engineering.

Principal studies on the pre-clinical and clinical applications of cell sheets are shown in Table 1.

2.4.2. Extracellular Matrix(ECM)

ECM is a fiber network composed of proteins, proteoglycans and glycosaminoglycans, arranged in a specific three-dimensional structure. ECM not only serves as a scaffold for maintaining the structural integrity of multicellular organisms but also plays a key role in the survival and differentiation of cells and tissues. It regulates many biological processes, including stem cell differentiation [70], angiogenesis [71,72], innervation and wound healing [73—75], and is also indispensable for embryonic development and the maintenance of homeostasis in cells and organs. Therefore, ECM can be used as an ideal biological material to promote the repair of damaged tissues. In recent years, tremendous development has been made in manufacturing ECM biomaterials, including the development of decellularization technology and ECM-based bio-hybrid materials engineering.

2.4.2.1. Decellularization technology.
Tissue decellularization has been applied for a long time. Early studies included the use of crushing and freeze—thaw cycles to decellularize muscle tissue, or described the use of allogeneic decellularized dermal matrix or autologous keratinogenic cells for skin reconstruction [76]. In 1989, the small intestinal submucosa (SIS) was first used as a vascular stent.

In recent years, due to the development of ECM stents manufacturing methods, the materials of acellular tissue have been widely used in clinical tissue repair and reconstruction. ECM stents have been used extensively in hernia repair, skin defect repair, breast reconstruction, heart valve and pericardial repair. With the wide use of these materials, many preclinical and clinical studies

Table 1
Principal studies about pre-clinical and clinical application of cell sheets.

Study	Intervention	Types	Numbers	ESD/EMR	Outcome	Ref No.
Ohki et al., 2006	Dogs' OMEC Sheets	Dogs	3(3 in control)	180° in range, 5 cm in length	Transplanted group: complete wound healing and no observable stenosis; Control group: noticeable fibrin mesh and host inflammation.	[58]
Takagi et al., 2010	Human OMEC Sheets	Dogs	3	half of the circumference, 2 cm in diameter	Transplanted hOMEC sheets attached to the ulcer surface; The epithelium observed at the ulcer site expressed cytokeratin in all epithelial cell layers; CD29 and Ki67 sparsely localized in the basal layer.	[59]
Ohki et al., 2012	Human OMEC Sheets	Human	9	half to fully circumferential	8 patients experienced no dysphagia or stricture; 4 patients experienced high fever ($\geq$38.0 °C) for a few days; 1 patients had stricture and need endoscopic balloon dilation for 21 times.	[60]
Jonas et al., 2016	Human OMEC Sheets	Human	5	3 of circumferential resection, 2 of 9—10 cm in length	No changes in the cell sheet morphology could be detected that would reflect overall necrosis; After 1 week squamous cells could be visualized in the transplanted areas, whereas non-transplanted surfaces of the post-ESD defects were mostly covered by fibrin; 3 patients developed strictures requiring 2 to 5 dilatation sessions.	[61]
Yamaguchi et al., 2017	Human OMEC Sheets	Human	10	more than 5/6 of the total circumference	1 patients had transient high-grade fever and chest pain; 6 patients remained free of adverse events up to 67 weeks later and even at the last follow-up; 4 patients suffered dysphagia that required a maximum of 7 sessions of EBD with a median of 1.5 sessions (mean 2.75); No reoccurrence of disease in any of the patients after treatment with the cell sheets.	[63]
Kanai et al., 2012	Autologous epidermal cell sheets	Pigs	4(4 in control)	the total circumference	The control group showed severe esophageal constriction after 2 weeks; The transplanted group showed early reepithelialization and mild fibrosis in the muscularis.	[65]
Perrod et al., 2016	Adipose tissue-derived stromal cell (ADSC) double cell sheet	Pigs	6(6 in control)	hemi-circumfe-rential ESD	Animals from ADSC group showed less frequent alimentary trouble (17% vs 80%; P = 0.08) and higher gain weight on day 28; pCLE demonstrated a compatible cell signal in 4 animals of the ADSC group at day 3; In ADSC group, 1 out of 6 animals developed a severe esophageal stricture to 100% (5/5) in the control group; A decreased degree of stricture was showed in the ADSC group on day 14 (44% vs 81%) and day 28 (46% vs 90%); Histological analysis showed a decreased fibrosis development in the ADSC group, in terms of surface (9.7 vs 26.1 mm^2) and maximal depth (1.6 vs 3.2 mm).	[67]

have begun to use acellular matrix for muscle and heart repair, and in recent years, for esophageal tissue repair. In patients with esophageal superficial adenocarcinoma, the normal epithelium of the esophagus can be restored by placement of a tubular ECM stent after complete resection of the mucosa and submucosa of the lesion [77]. Similar results were also observed in Han et al.'s study, where they used acellular dermal matrix sheets derived from bovine reticulated skin and implanted them into the resection areas of seven Bama mini-pigs after esophagus ESD, fixing them with metal clips. No animals in the acellular dermal matrix sheets group showed obvious esophageal stricture, while 42.8% (3/7) of those in the control group had stricture. The degree of stricture in the control group was more severe than that in the acellular dermal matrix sheets group (39.8% vs. 17.2%; P = 0.01) [78].

The appearance of tissue hydrogels obtained from the submucosal layer of the SIS has expanded the options for decellular material beyond lamellar and mesh materials [79]. ECM hydrogels consist of one or more purified ECM proteins and have broad potential applications. We can optimize the low viscosity and gel kinetics of the pregel solution by processing the viscous soluble pregel ECM material to achieve minimally invasive injection [76]. This method has been implemented in tissues and organs, such as fat, cartilage, dermis, intestine, liver, lung, muscle and bladder, but has not yet been applied to esophageal tissue.

The decellularization technique removes cells and antigen components in tissues and preserves the ECM while limiting damage to the ECM. Decellularization methods include freeze—thaw cycles, agitation, ultrasound or mechanical pressure combined with detergents, ionic solutions and/or enzyme treatments. However, these methods inevitably lead to some degree of ECM destruction [80—82].

In recent years, there have also been some advances in decellularization technology. The non-enzymatic decellularization protocol described by Mallis can decellularize cells with just a single decellularization cycle, keeping the ECM well-preserved and retaining collagen, elastin and sGAGs while completely removing the cells [83].

Although decellularization techniques have achieved success in clinical applications, some problems remain. For example, heterogeneity of the donor tissue may lead to heterogeneity of the decellularization process and further to heterogeneity of the decellularized tissue. In addition, difficulty in ECM patch fixation and issues of stent displacement remain huge challenges to be addressed. Self-expandable stents with sutures have been shown to be unable to prevent post-ESD esophageal stricture [84]. However, an achalasia balloon stent plus degradable polyurethane adhesive injection was able to prevent the stent from slipping, although it the connection between the graft and esophagus was affected [85], and this approach might cause acellular dermal matrix membrane deformation [86]. The method of using metal clips to fix ECM patch seems to have achieved some good results [78], but this needs to be verified in clinical trials. At present, endoscopic suturing of biological stents seems to be the expected direction of progress, but the feasibility and technical difficulty remain to be discussed.

2.4.2.2. ECM-based biohybrid material. ECM is a natural template for biomaterials. Although many ECM analogues have been developed, such as polymer hydrogels, natural biopolymer alginate, chitosan, cellulose, filament, they lack the complex biochemical properties and three-dimensional ultrastructure of ECM. In the last 10 years, substantial progress has been achieved towards ECM-based biomaterials, including the fractionation and characterization of ECM components and the development of decellularization techniques for the preservation of native mammalian ECM structure and composition [87].

Biomaterials for functional tissue repair can be broadly divided into two main categories: synthetic materials and natural materials. Synthetic materials are usually composed of artificial polymers, metals or other synthetic substrates. They have low heterogeneity and good mechanical strength and degradability but are likely to cause inflammation in the host. Natural materials are usually processed from the entire ECM or purified single ECM components (collagen, laminin and fibronectin), which is highly heterogeneous but is friendly to the host's immune response. Therefore, combining the characteristics of the two, reECM biomaterial engineering can use technologies such as nano-fiber lithography, electrospinning and three-dimensional printing to combine ECM components with synthetic polymer components to achieve complementary advantages [87]. By combining blocks of natural tissue ECM with synthetic polymer components, the best of both materials can be included in one scaffold. This combination will be termed an ECM-based biohybrid material.

2.4.3. Autologous transplantation

Despite many studies on the subject being conducted, findings concerning autologous transplantation of post-ESD esophageal stricture remain limited. Amniotic membranes were implanted into 10 pigs (AM group) with esophageal circumferential defects. Compared with the control group, the AM group and esophageal stent-alone group pigs had a significantly reduced incidence of symptomatic stricture on day 14 [88]. However, all animals still developed esophageal stricture on day 35, suggesting that the amniotic membrane, while delaying the onset of esophageal stricture, is of limited use. Hochberger et al. transplanted patients' autologous gastric mucosa to the esophageal mucosa defect areas after circumferential esophageal ESD and fixed the tissue with metal stents. The defects were almost completely healed after six months, suggesting the effectiveness of gastric mucosal transplantation for stricture prevention [89]. Similar results were also observed in Liao et al.'s study, as they selected nine patients with early esophageal cancer who underwent circumferential esophageal dissection for autologous esophageal mucosa transplantation. During the follow-up period, 8 patients had no difficulty in swallowing, and the survival rate of esophageal mucosa patch was 96.5% [90]. Tang et al. performed circumferential esophageal submucosal dissection on 6 pig models (N = 6). In the autologous flap group (N = 3), autologous flaps were made, placed at the site of resection and fixed with metal clips. The control group (N = 3) only underwent endoscopic submucosal dissection. Three weeks after the operation, the animals in the autologous flap group had slight stricture, while obvious stricture was observed in the control group [91]. However, this experiment was only a short-term experiment in a small sample of pigs, so the effects of autologous skin flap transplantation cannot be confirmed yet. In clinical patients, Chai et al. first performed autologous skin graft surgery (ASGS) to prevent esophageal stricture after complete circular endoscopic submucosal tunnel dissection (ccESTD). They removed skin grafts from the outside of the patients' right thigh, attached them to esophageal stents and placed them in the defect. Thus far, the outcomes of nine patients (one in 2018 and eight in 2019) have been reported. No perforation, bleeding, wound infection or stent displacement was observed in the seven-month follow-up. Although the sample size was small, the findings suggest that ASGS is a safe and effective strategy for preventing post-ESD esophageal stricture [92].

In summary, few studies have been conducted on autologous transplantation of esophageal stricture after ESD, and the effect still needs to be confirmed in a large sample of clinical cases.

2.4.4. Endoscopic injection of autologous cell suspension

Endoscopic injection of autologous cell suspension is a technique that involves extracting cells from the oral cavity, skin or adipose tissue to prepare a suspension for endoscopic injection. At present, the autologous cell suspensions used to prevent esophageal stricture post-ESD include OMEC suspension, skin keratinocyte suspension and ADSC suspension. Endoscopic injection of autologous cell suspension has some positive effect on the prevention of stenosis, as confirmed in studies of pigs, sheep and dogs [93—95]. Compared with cell sheet transplantation, the direct injection of a suspension is feasible and simple. Furthermore, it overcomes the defects covering strict preparation technique and difficulty in fixation of cell sheets. However, some scholars are skeptical about whether or not this approach will increase the risk of tumor progression, which is also a problem that needs to be studied and solved in the future.

2.4.5. Other treatments related to tissue engineering technology

This includes self-assembling peptide matrix, high-density collagen patch, mesenchymal stem cell conditioned medium. Barret et al. used SAP matrix for wound dressing after ESD and confirmed its effectiveness in preventing esophageal stricture in pig models. The incidence of 14-day esophageal stricture was 40% in the SAP group (N = 5) compared to 100% in the control group (N = 5) (P = 0.2) [96]. Aoki et al. performed circumferential esophageal mucosa dissection on six pigs and treated the wounds in the treatment group with high-density collagen patches. Compared to the control group, the treatment group had a significantly higher patency rate on both the traumatic oral and anal sides at day 14 and a significantly higher rate of mucosal reepithelialization [97]. Similar results were also observed in Mizushima et al.'s study, who found that mesenchymal stem cell CM can prevent the formation of stricture after submucosal dissection of esophagus in pigs [98]. However, all of the above experiments involved a small sample size and were short-term animal experiments.

3. Conclusion

In conclusion, we reviewed various strategies of post-ESD esophageal stricture prevention. Each of these strategies inevitably has its own limitations. For steroid therapy, although it has been used in many clinical treatments, it has shown a limited effect on preventing esophageal stricture in cases with large mucosal defects (especially defects covering more than three-quarters of the circumference of the esophagus), and the accompanying adverse reactions are also a major problem to be solved for clinical application. The safety and effectiveness of Mitomycin C, 5-fluorouracil 5-FU, botulinum toxin, L-cysteine, siRNA, thymosin 4 and other anti-scar drugs still lack reliable clinical data. While PGA plus fibrin glue therapy has a similar efficacy to that of steroid therapy, it is not widely used in clinical settings because of its complexity and cost. As for esophageal stents, issues with granulation tissue hyperplasia, stent displacement and esophageal ulcers need to be solved by researchers in the field of stent materials and characteristics, stent fixation and other fields. However, tissue engineering technology, which has become a hot topic in recent years, prevents esophageal stenosis after ESD by structurally and functionally rebuilding normal tissues and promoting early re-epithelialization. It may thus become a viable new method for resolving post-ESD esophageal stricture, especially for circumferential esophageal stricture. However, more clinical evidence is needed to fully confirm its safety and effectiveness.

Various methods can promote the development of tissue engineering technology and applications, such as expanding the clinical sample size; comparing the safety and effectiveness of steroid therapy research, diagnosis and treatment of related complications; and improving the available materials and technology to reduce the cost and facility requirements.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgements

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