REVIEW ARTICLE

Repairing the human esophagus with tissue engineering

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Esophageal injuries such as partial-thickness defects from mucosal resections can result in fibrosis and refractory strictures. Similarly, full-thickness patch defects like perforations can lead to leaks and fistulae. Esophagectomy done for malignant and benign conditions can cause full-thickness, long-segment, circumferential defects. These require colon or gastric conduits to maintain luminal continuity. These conduits can be associated with significant morbidities leading to poor quality of life.

The human esophagus is a nonredundant organ that has limited ability to regenerate, and, unlike other organs, the esophagus cannot be transplanted. Advances in the field of regenerative medicine have demonstrated successful restoration of the structural and functional integrity of the esophagus after the above injuries in animal models. Lessons learned from these studies are now being extrapolated to human beings, and initial results are encouraging. This review will highlight some of these advances made in repairing the esophagus by using principles of tissue engineering.

Esophageal injuries can be life threatening and can cause significant morbidity. These injuries vary from superficial, such as after endoscopic submucosal dissection (ESD), to deep and transmural-like perforations. Because the esophagus has limited ability to regenerate, these injuries can lead to refractory strictures, leaks, and fistulae. Unlike the redundant small bowel or colon in which an end-to-end anastomosis can be done after resection, the esophagus is a nonredundant organ. Attempts at transplanting cadaveric esophagus have failed.[1] Hence gastric or colon conduits are required to re-establish luminal continuity in patients who undergo esophagectomy. These conduits are associated with significant morbidity and poor quality of life.[2-13] Regenerating the esophagus would be ideal for these patients.

Partial or whole organ regeneration is now possible by using techniques of tissue engineering first described by Langer and Vacanti[14] in 1993. The majority of these techniques involved populating autologous pluripotent cells onto an allogeneic or xenogeneic extracellular matrix (ECM) and then transplanting the implant into the animal, leading to organogenesis (Fig. 1). In the recent past, these techniques have been applied increasingly to repair organ defects in human beings. Autologous pluripotent urothelial cells populated onto collagen scaffolds were used to regenerate full-thickness defects of the urinary bladder.[15] A decellularized cadaveric trachea was seeded with autologous mesenchymal stem cells to regenerate the trachea in a child born with tracheal stenosis.[16] If the damaged organ has maintained a 3-dimensional (3-D) configuration, it is now possible to regenerate the organ by transplanting pluripotent cells directly to the site of injury without using a scaffold. This review will address some of these techniques as applied to regenerating the esophagus.

PARTIAL-THICKNESS DEFECTS

After EMR and/or ESD

EMR or ESD is now the standard of care for removing dysplastic mucosa and/or superficial cancer from the esophagus.[17] Mucosal injury induces marked collagen hyperplasia by day 7, which eventually progresses to a fibrotic stricture.[18] If the mucosal resection involves >50% of the circumference, up to 70% of patients will develop a stricture.[19-21] This offsets some of the benefits of a curative EMR or ESD. Attempts to prevent post-ESD strictures by using stents, dilations, steroids, botulinum

Abbreviations: BE, Barrett's esophagus; 3-D, 3-dimentional; ECM, extracellular matrix; ESD, endoscopic submucosal dissection; FDA, U.S. Food and Drug Administration; SEMS, self-expandable metal stent (esophageal).

DISCLOSURE: *K. Dua does multicenter research and is a principal investigator for Boston Scientific, Cook Medical, and Merit Medical. Cook Medical, Inc, provided the extracellular matrix being used in the research studies. All other authors disclosed no financial relationships relevant to this publication.*

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0016-5107/$36.00
https://doi.org/10.1016/j.gie.2018.06.032

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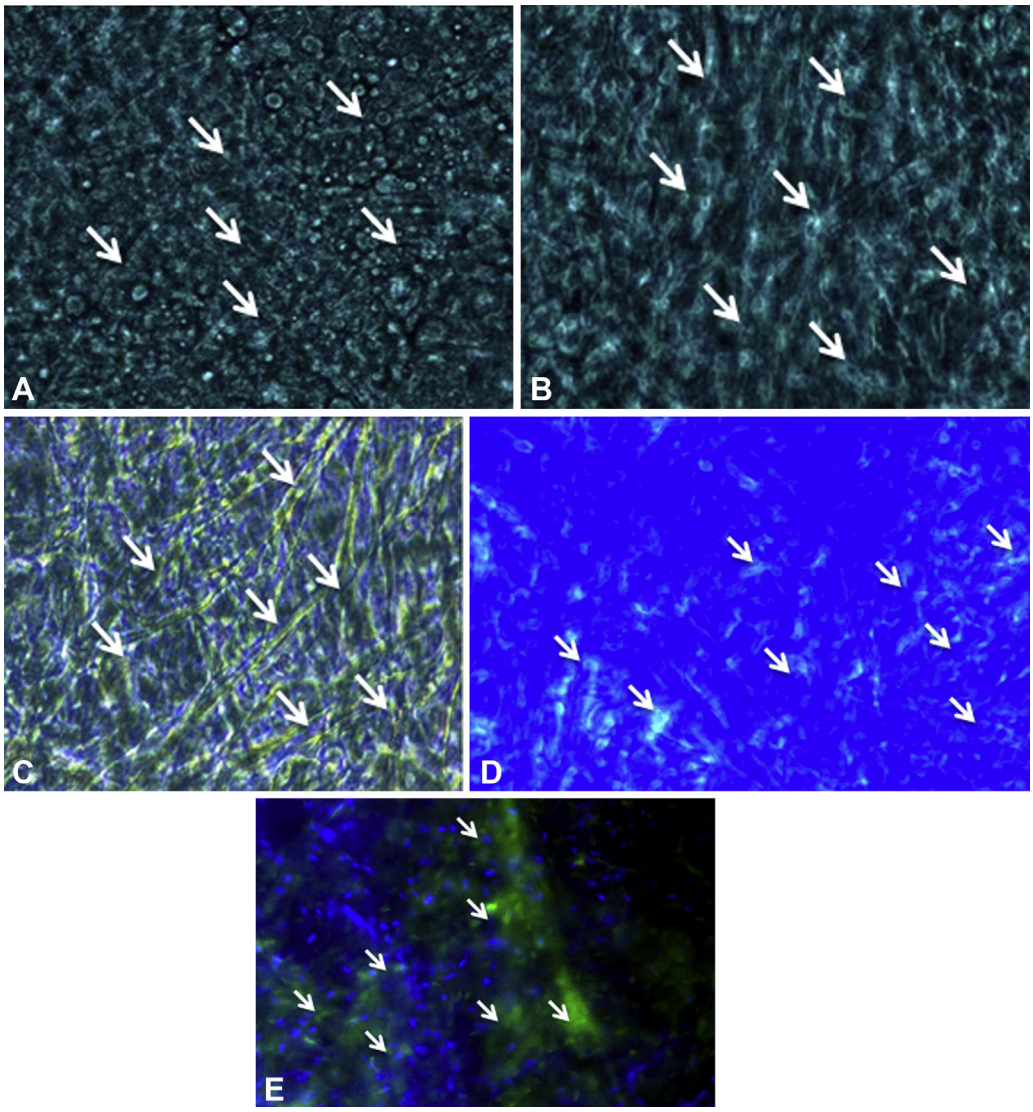

Figure 1. Porcine-derived extracellular matrix (SIS; Cook Medical, NC) was populated with human mesenchymal stem cells. **A,** As shown by arrows (spindle-shaped cells), mesenchymal stem cells growing at 4 hours (unstained, orig. mag. ×20). **B,** Mesenchymal stem cells growing at 8 hours (unstained, orig. mag. ×20). **C,** Mesenchymal stem cells growing at 4 days (unstained, orig. mag. ×20). **D,** Extracellular matrix with viable mesenchymal stem cells (*arrows*) as tested by the trepan blue exclusion method (orig. mag. ×20). **E,** This image confirms the cells as CD73+ mesenchymal stem cells *(green)* by immunofluorescent staining (immunofluorescent staining with fluorescent tagged anti-human CD73 antibodies, orig. mag. ×20).

toxin, or biodegradable polyglycolic-acid sheets have given mixed results.[21-32] Stimulating natural mucosal regeneration or tissue engineering of the mucosa after ESD is being investigated. Because the 3-D configuration of the esophagus is still maintained in partial-thickness defects, the majority of these studies have involved approaches that do not require scaffolds.

Animal studies: partial-thickness defects

Adipose tissue–derived stromal cells have pluripotent potentials. Honda et al[33] injected these cells at ESD sites in 5 dogs. Compared with 76% luminal constriction in the control group, luminal narrowing in the study group was 45% ($P < .008$). The number of micro vessels in the submucosal layer was 16.2/unit area in the study group as compared with 7.4 in the control group ($P = .007$). Fibrosis of the muscularis propria was observed only in the control group. Sakurai et al[34] found similar results by injecting autologous keratinocytes obtained from oral mucosal at the ESD site in a porcine model. In another recent study, a conditioned medium was created by culturing human fetal amnion-derived mesenchymal stem cells and applying them to the ESD bed by endoscopy or by making the pig swallow the medium.[35] Stricture formation rates were significantly lower in the study group compared with controls. Histology of the esophagus showed decreased infiltration of neutrophils and macrophages in the study group as compared with controls. Instead of using synthetic biodegradable material like polyglycolic acid,[30-32] Ohki et al[36] cultured oral