Journal of Visceral Surgery (2016) 153, 21—29

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

REVIEW

# Esophageal tissue engineering: Current status and perspectives

T. Poghosyan[a,b], J. Catry[b,c], M. Luong-Nguyen[b,c], P. Bruneval[d], T. Domet[b,e], L. Arakelian[b], R. Sfeir[f], L. Michaud[f], V. Vanneaux[b,e], F. Gottrand[f], J. Larghero[b,e], P. Cattan[b,*,c]

[a] *Service de chirurgie digestive, oncologique et métabolique, hôpital Ambroise-Paré, AP—HP, 92100 Boulogne-Billancourt, France*
[b] *CIC de biothérapies, Inserm UMR 1160, institut universitaire d'hématologie, hôpital Saint-Louis, 1, avenue Claude-Vellefaux, 75010 Paris, France*
[c] *Service de chirurgie générale, digestive et endocrinienne, hôpital Saint-Louis, AP—HP, 75010 Paris, France*
[d] *Service d'anatomopathologie, hôpital européen Georges-Pompidou, AP—HP, 75015 Paris, France*
[e] *Unité de thérapie cellulaire, hôpital Saint-Louis, AP—HP, 75010 Paris, France*
[f] *Centre de référence des affections congénitales et malformatives de l'œsophage, CHRU de Lille, 59000 Lille, France*

Available online 17 December 2015

**KEYWORDS**
Tissue engineering;
Esophagus;
Bioengineering;
Absorbable scaffold

**Summary** Tissue engineering, which consists of the combination and *in vivo* implantation of elements required for tissue remodeling toward a specific organ phenotype, could be an alternative for classical techniques of esophageal replacement. The current hybrid approach entails creation of an esophageal substitute composed of an acellular matrix and autologous epithelial and muscle cells provides the most successful results. Current research is based on the use of mesenchymal stem cells, whose potential for differentiation and proangioogenic, immune-modulator and anti-inflammatory properties are important assets. In the near future, esophageal substitutes could be constructed from acellular ''intelligent matrices'' that contain the molecules necessary for tissue regeneration; this should allow circumvention of the implantation step and still obtain standardized *in vivo* biological responses. At present, tissue engineering applications to esophageal replacement are limited to enlargement plasties with absorbable, non-cellular matrices. Nevertheless, the application of existing clinical techniques for replacement of other organs by tissue engineering in combination with a multiplication of translational research protocols for esophageal replacement in large animals should soon pave the way for health agencies to authorize clinical trials.


* Corresponding author.
*E-mail address:* pierre.cattan@aphp.fr (P. Cattan).

http://dx.doi.org/10.1016/j.jviscsurg.2015.11.009

## Introduction

Reconstruction after esophagectomy for benign disorders (caustic burns, peptic strictures...) or cancer usually relies on gastric or colonic translocations or, more rarely, free or pediculized jejunal grafts. The treatment of long-segment esophageal atresia can also require such transplants, either initially or after failure of lengthening procedures and/or the esophageal anastomosis. In these settings, the treatment of a relatively short diseased segment of esophagus requires replacing the entire esophagus. The same is true for esophageal strictures that are refractory to endoscopic dilatations. These esophageal reconstructions are associated with high morbidity and mortality, and the functional outcome is often far from perfect, marred by reflux, delayed emptying of the esophageal transplant or dumping syndrome [1]. Moreover, strictures or distensions occur in the long term [2], requiring intermittent anastomotic dilatations or re-operations. Reconstruction failure results in therapeutic deadlock, requiring lifelong feeding jejunostomy. It therefore seems reasonable to look for esophageal substitutes that would allow replacement of only the diseased segment of the esophagus while avoiding the sacrifice of other intra-abdominal organs.

## Previously-evaluated alternatives to traditional esophageal reconstruction techniques

In the quest for traditional esophageal replacement, several approaches have been tested.

### Synthetic prosthetic interpositions

Utilization of synthetic materials (Teflon, Dacron...) has limited clinical application and has not been followed by reproducible success, essentially because of the high rate of foreign body rejection, anastomotic fistula and stricture. When these materials are not rejected, absence of biocompatibility routinely leads to chronic infection with intense fibrosis, preventing subsequent esophageal tissue remodeling techniques [3].

### Allogenic esophageal grafts

The limitations of esophageal allografts are essentially vascular. Esophageal vascularization derives from multiple sources (inferior thyroid arteries, bronchial arteries, intercostal arteries), rendering graft revascularization impossible. To overcome this difficulty, composite thyro-tracheo-esophageal grafting, revascularized by anastomosis of the inferior thyroid arteries to the carotids has been performed [4]. Both the magnitude of such a procedure and the necessity of immunosuppression limit its clinical application.

### Tissue autografts or allografts

Pleural, pericardial, dermal, musculofascial, intercostal muscular and aortic autografts and allografts have been used for esophageal reconstruction. In the 1950s, encouraging results were obtained in animals and in humans using aortic grafts [5]. Occasionally, this technique allowed normal feeding, and Malpighian epithelial regeneration was observed on explanted grafts. However, in the great majority of cases, severe stricture of the graft quickly developed [6]. More recently, we analyzed the capacity of esophageal regeneration in a mini-pig model using aortic allograft protected by an esophageal endolumenal stent [7,8], in analogy to the tracheal replacement model published by Martinod et al. [9]. Our animal model showed that a patent lumen permitting nutritional autonomy could be obtained but required periodic calibration with bougies during 6 months. The graft was the site of intense fibrosis at 12 months, and did not exhibit any tissue remodeling toward an esophageal phenotype. This limited the feasibility and the possibility of functional success for extended replacement of the esophagus.

## Tissue engineering or regenerative medicine

Within the rapidly developing domain of regenerative medicine [10], tissue engineering was defined by Langer and Vacanti [11] as an interdisciplinary field that applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function [12]. In practice, a substitute organ composed of elements judged to be necessary for tissue remodeling toward the desired organ phenotype is implanted in an individual. Most often, autologous cells, such as epithelial cells, muscle cells, or mesenchymal stem cells are harvested through tissue biopsies. Thereafter, *in vitro* cellular expansion is followed by seeding of an acellular matrix with these cells, then maturation of the substitute organ element in a tissue incubator, either *in vivo* within the latissimus dorsi muscle or the greater omentum, or *in vitro*. Organ replacement is then performed, the substitute being considered as an autograft. This approach has been used with success in humans to replace the bladder [13], the urethra [14], heart valves [15] and to reconstruct the vagina [16] (Fig. 1).

## Tissue engineering of the esophagus

Esophageal substitutes originating from tissue engineering should ideally have the following characteristics: peristaltic activity, elasticity, lubricative capacity, and resistance to gastro-esophageal reflux. Research in this domain has included analysis of matrix properties, the identification and harvesting of cells that can be seeded into these matrices, the conditions for cell seeding, and the capacity of the substitutes to promote the development of the esophageal phenotype *in vivo*.

## Matrices

The role of the matrix is to provide a scaffold for the cells and to deliver the biochemical signals necessary to enhance cell integration, differentiation, survival and growth, and angiogenesis, in order to guide tissue regeneration. Ideally, the matrix should be biocompatible, non-immunogenic, easily available, and fabricated with a large array of forms and sizes, and it must be authorized for human use to enhance the application of experimentally proven concepts. The matrix should be biodegradable, destined to be replaced