Biotechnology Advances 30 (2012) 1481–1492

Contents lists available at SciVerse ScienceDirect

Biotechnology Advances

journal homepage: www.elsevier.com/locate/biotechadv

Research review paper

Tissue engineering interventions for esophageal disorders — Promises and challenges

Purushothaman Kuppan, Swaminathan Sethuraman, Uma Maheswari Krishnan *

Centre for Nanotechnology & Advanced Biomaterials, SASTRA University, Thanjavur, Tamil Nadu, India

ARTICLE INFO

Available online 28 March 2012

Keywords:
Esophagus
Allografts
Acellular matrix
Nanofiber scaffold
Stem cells

ABSTRACT

The diseases of the esophagus include congenital defects like atresia, tracheoesophageal fistula as well as others such as gastro-esophageal reflux disease (GERD), Barrett's esophagus, carcinoma and strictures. All esophageal disorders require surgical intervention and reconstruction with appropriate substitutes. Primary anastomosis is used to treat most cases but treatment of long gap atresia still remains a clinical challenge. Autologous graft therapies using tissues from colon, and small and large intestine or gastric transplantations have been attempted but have constraints like leakage, infection and stenosis at the implanted site, which leads to severe morbidity and mortality. An alternative for autologous grafts are allogenic and xenogenic grafts, which have better availability but disease transmission and immunogenicity limit their applications. Use of biodegradable and biocompatible scaffolds to engineer the esophagus promises to be an effective regenerative strategy for treatment of esophageal disorders. Nanotopography of the fibrous scaffolds mimics the natural extracellular matrix (ECM) of the tissue and incorporation of chemical cues and tailoring mechanical properties provide the right microenvironment for co-culture of different cell types. Scaffolds cultured with esophageal cells (epithelial cells, fibroblast and smooth muscle cells) might show enhancement of the biofunctionality in vivo. This review attempts to address the various strategies and challenges involved in successful tissue engineering of the esophagus.

Contents

* Corresponding author at: Departments of Chemistry, Bioengineering & Pharmacy, Centre for Nanotechnology & Advanced Biomaterials (CeNTAB), School of Chemical & Biotechnology, SASTRA University, Thanjavur-613 401, Tamil Nadu, India. Tel.: +91 4362 264101x677; fax: +91 4362 264120.
E-mail address: umakrishnan@sastra.edu (U.M. Krishnan).

0734-9750/$ – see front matter
doi:10.1016/j.biotechadv.2012.03.005

1. Introduction

The esophagus is a muscular tube that connects the pharynx and the stomach. Every year 5000 to 10,000 patients are diagnosed with congenital and acquired diseases where there is a need for patch or full circumferential replacement of the esophagus (Badylak et al., 2000). Esophageal atresia with or without tracheoesophageal fistula is a major congenital problem in infants (Knottenbelt et al., 2010). The adult population is faced with a multitude of esophageal disorders that include cancer, Barrett's esophagus, GERD, and strictures (Zhu et al., 2007). Esophageal carcinoma generally affects the male population and recent statistics reveal an increase in the incidence globally (McCabe and Dlamini, 2005). Treatment of esophageal disorders requires removal of large portions of the affected area and attempt to reconstruct the same using alternate substitutes to gain active function (Tan et al., 2011). Use of gastrointestinal segments to bridge the atresial gap has been considered as a gold standard approach though post-operative complications lead to morbidity and mortality (Gaujoux et al., 2010). Alternatives to the gastrointestinal segments are allografts and xenografts comprising acellular matrices but again immunogenicity and disease transmission limit their widespread use (Badylak et al., 2000; Gaujoux et al., 2010). Hence, tissue engineering and regenerative medicine are evolving as alternative strategies to develop a mimic of the natural tissue that could be used as artificial grafts for esophagus regeneration.

Tissue engineering is the application of biological, chemical, and engineering principles toward the repair, restoration, or regeneration of living tissues using biomaterials, cells, and factors alone or in combination (Cooper et al., 2005). Several absorbable and non-absorbable grafts made of natural and synthetic materials are available for the replacement of the esophagus (Beckstead et al., 2005). However clinical problems like leakage, strictures, infections, inflammations, immune rejection, poor re-epithelization and poor muscle regeneration in the grafts are being experienced (Isch et al., 2001). Therefore there remains a challenge to develop superior biomaterials, which mimic the native extracellular milieu. This review analyzes the anatomical characteristics of the esophagus, various pathological conditions leading to its dysfunctions, current therapeutic approaches, their limitations and implications of tissue engineering strategies for reconstruction of the esophagus with a special emphasis on the ideal scaffold properties, scaffold materials, emerging trends and future directions to manage esophageal disorders.

2. Anatomy and function

The esophagus is a complex, hollow, thick muscular canal that connects the pharynx and the stomach. It transverses three anatomical planes (neck, thorax, and abdomen) and has a length of 20–25 cm in an adult (Tan et al., 2011). Functional esophagus is divided into upper esophageal sphincter (UES), esophageal body and lower esophageal sphincter (LES) (Fisichella and Patti, 2002). Fig. 1 shows the schematic representation of functional esophagus with its muscle layers (Fig. 1A). The esophagus consists of three types of cells that include squamous epithelial cells, fibroblasts, and smooth muscle cells, which form the four layers of the esophagus such as mucosa, submucosa, muscularis externa, and adventitia (Fig. 1B) (Zhu and Ong, 2009). Epithelial cells are present in the lumen, fibroblasts are present within the submucosa while the circular and longitudinal smooth muscle cells are localized towards the periphery (Saxena et al., 2009a).

The mucosa is a basal membrane that consists of non-keratinized squamous epithelial cells and can produce the mucus, which protects the esophagus from mechanical stress caused by the food bolus (Beckstead et al., 2005). The proliferative capacity of the cells was limited in basal zone and the migration of cells from basal zone to lumen results in proliferation and expression of different markers. Epithelial cell proliferation and differentiation are regulated by various factors, such as extracellular calcium, retinoic acid, and vitamin D_3 (Squier and Kremer, 2010). Lamina propia and a smooth muscle layer cover the epithelium.

The main components of submucosa are collagen types I and III, arranged in a criss-cross pattern, which forms a loose connective tissue that consists of blood vessels and mucus glands (Natali et al., 2009). Muscularis externa contains inner circular and outer longitudinal smooth muscle cells (Fig. 1B). Upper part of the muscle layer has skeletal muscle cells, distal part has smooth muscle cells and middle part has both types of cells (Fig. 1B) (Radenkovic et al., 2010). Outermost layer of the esophagus is the adventitia, which covers the muscle layer and the adventitia is composed of loose soft connective tissue, rich in blood and lymph vessels, adipose tissue and simple squamous cell epithelium (Fig. 1B) (Natali et al., 2009).

The esophagus propels bolus and liquids to the stomach through peristaltic movement caused by the alternate contraction and relaxation of smooth muscle cells. Peristaltic contraction is initiated by either extrinsic or intrinsic neural pathways (Wingate, 1993). Longitudinal muscles ahead of the bolus contract to expand the esophagus while the circular muscles behind the bolus of food contract to push it toward the stomach. Food normally passes through the esophagus

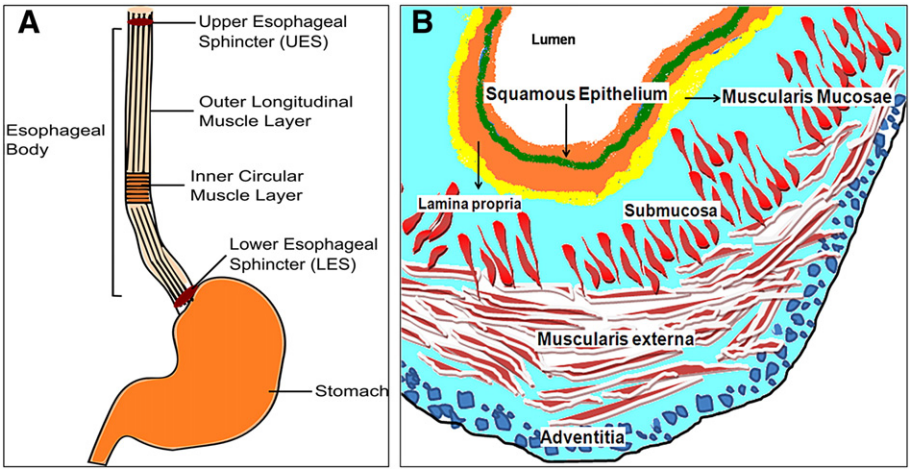

Fig. 1. Schematic representation of [A] functional esophagus with its muscle layers; [B] different layers of the esophagus.