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Tissue engineering: an option for esophageal replacement?

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Esophageal replacement is required in several pediatric surgical conditions, like long-gap esophageal atresia. Although several techniques have been described to bridge the gap, all of them could be followed by postoperative complications. Esophageal tissue engineering could represent a valid alternative thanks to the recent advances in biomaterial science and cellular biology. Numerous attempts to shape a *new esophagus* in vitro have been described in the last decade. Herein, we review the main studies on the experimental use of nonabsorbable and absorbable materials as well as the development of cellularized patches. Furthermore, we describe the future perspectives of esophageal tissue engineering characterized by the use of stem cells seeded on new biopolymers. This opens to the construction of a functional allograft that could allow an anatomical replacement that grows with the children and does not severely impair their anatomy.

There are several conditions, both congenital and acquired, where esophageal replacement is needed. In Pediatric Surgery, the primary indication for esophageal replacement is long-gap esophageal atresia, secondary to a failure to achieve end-to-end esophageal anastomosis. Several techniques have been described to overcome the long-gap: esophageal-lengthening techniques (flap, spiral myotomy, gastric division), transmediastinal thread, and esophageal substitution (colonic interposition, gastric tube esophagoplasty, jejunal interposition, gastric interposition).[1] Although it is debatable which of these techniques represents the best option, there is a consensus in the literature that all of them could be followed by postoperative complications (dysmotility and dysphagia, stricture formation, and gastroesophageal reflux disease) and impaired quality of life.[2-4]

Therefore, the development of new treatment strategies for esophageal replacement is an area requiring further investigations. In the last few years, tissue engineering has emerged as a possible solution to replace the physiologic functions of tissues lost due to disease or injury.[5] It requires the use of a cell source as well as the use of matrices to support and guide tissue regeneration.[6] This field of science has deeply benefited from progresses in material science (ie, nanoparticles) and the discovery of stem cells. The latter in particular has dramatically changed the possibility of in vitro tissue neogenesis. Esophageal tissue engineering can be taken into consideration to generate a functional organ that could be implanted either at birth or after failure of primary anastomosis. It is likely that in the future this option will have a role in the clinical setting thanks to recent and significant advances in biomaterial science, bioreactor technology, and molecular biology, including cell characterization, isolation and expansion, as well as the development of novel surgical techniques.

Herein, we review the history of esophageal tissue engineering, starting from reports on the use of prosthetic materials up to cellularized patches with particular attention to the most recent new developments in the field (Table 1).

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Table 1 Overview of studies of the last decade on esophageal tissue engineering

Author	Year	Scaffold	Cell type	Type of experimentation
Takimoto	1998	Silicone tube	—	in vivo (dog)
Shinhar	1998	Vicryl® mesh	—	in vivo (dog)
Badylak	2000	Extracellular matrix (from small gut or bladder submucosa)	—	in vivo (dog)
Lopes	2006	Porcine small gut submucosa	—	in vivo (rat)
Lynen Jansen	2004	Vicryl® and PVDF meshes	—	in vivo (rabbit)
Isch	2001	Decellularized human collagen	—	in vivo (dog)
Bhrany	2006	Rat decellularized esophagus	Rat esophageal epithelial cells	in vitro and in vivo (rat)
Ozeki	2006	Rat decellularized esophagus	Esophageal epithelial cells	in vitro
Urita	2007	Gastric acellular matrix	—	in vivo (rat)
Watanabe	2005	Gore-Tex vascular graft	—	in vivo (goat)
Grikscheit	2003	Organoid unit (mesenchymal core)	Rat esophageal epithelial cells	in vivo (rat)
Hayashi	2004	Pig type I collagen sheet	Human esophageal epithelial cells, human dermal fibroblasts, human smooth muscle cells	in vivo (rat)
Beckstead	2005	Alloderm, PLLA, PLGA75, PLGA50, PCL/PLLA	Rat esophageal epithelial cells	in vitro
Marzaro	2006	Pig decellularized esophagus	Autologous smooth muscle cells	in vitro and in vivo (pig)

Abbreviations: PVDF, polyvinylidene fluoride; PLLA, poly(L-lactic acid); PLGA75, poly(lactic-co-glycolic) acid (75:25); PLGA50, poly(lactic-co-glycolic) acid (50:50); PCL/PLLA, polycaprolactone/poly(L-lactic acid) (50:50).

Nonabsorbable materials

The history of reconstructive surgery of the esophagus dates back to the beginning of the last century, as in 1907 Bircher first reported the use of a tube of skin to substitute the esophagus.[7] The use of prosthetic materials as a patch for esophageal defects was then reported by Neuhof and Ziegler, who first applied granulation tubes for experimental replacement of the esophagus in 1922.[8] From then onwards, extensive research has been performed in several animal models, with the aim of devising the construct which best resembled a native esophagus. Researchers developed several animal models to replicate the lack of native esophagus and used a wide range of biological and/or synthetic prosthetic materials to bridge the gap. In 1983, Fukushima and coworkers fabricated a silicon rubber tube surrounded by a Dacron mesh, which was implanted in 16 dogs as esophageal replacement.[9] Surprisingly, 44% of these dogs survived more than 1 year, and 25% of them more than 6 years. The submucosa near the anastomoses was similar to that of the native esophagus, but the central portion of the implanted tube presented fibrous tissue, while neither muscle cells nor glands were present. This pioneering report demonstrated for the first time that nonabsorbable materials do not allow proper tissue ingrowth. To overcome this issue and to reduce postimplantation complications such as prosthesis infection or migration, researchers developed either extractable constructs or absorbable materials. In 1998, Takimoto and coworkers designed an artificial esophagus made of a silicone tube covered with antigenic collagen to be extracted at 4 weeks from implantation.[10] This prosthetic material had the advantage of being gradually replaced by regenerated host tissue, so that when silicone stents were removed, highly regenerated esophageal tissue was left in situ. At histology, the neo-esophagus showed stratified flattened epithelium, longitudinal and circular muscle layer, and glands.

Absorbable materials

Other groups have focused on absorbable constructs. In 1998, Shinhar and coworkers reported the use of collagen-coated vicryl mesh, which served as substrate for the growth of esophageal wall elements in a dog model of esophageal reconstruction.[11] The newly created esophageal wall incorporated the mesh, which then disappeared, leaving no trace of its presence. In 2000, Badylak and coworkers reported the use of porcine-derived, extracellular matrix patches derived from either the small intestinal submucosa or the urinary bladder submucosa.[12] These patches, applied to repair partial circumference esophageal defects in a dog model, were rapidly absorbed within 2 months. Similar results were confirmed in a rat model by Lopes and coworkers, who described the presence of nerve growth, possibly suggesting neo-innervation.[13] However, Lynen Jansen and coworkers demonstrated in a rabbit model of esophageal replacement that anastomotic leakage rate was higher using absorbable mesh than with nonabsorbable ones, like PVDF (polyvinylidene fluoride).[14]

Acellular matrices

To reduce complications related to the immunogenicity against foreign bodies, in the last decade, many research groups focused on the development of acellular matrix tis-

sue scaffolds. In 2001, Isch and coworkers first reported the use of decellularized human collagen (AlloDerm) in dogs.[15] All dogs survived, and none experienced episodes of dysphagia, leak, or stricture, as ruled out at esophagogram and autopsy. Moreover, histologic partial re-epithelialization of the patch with neovascularization was observed. This study started the novel concept that decellularized human collagen could provide a valuable framework for esophageal healing. Following this pivotal paper, two other contemporary research groups reported the development of compatible decellularized esophagus in a rat model, both describing decellularization protocols and immunocytochemistry studies on seeded epithelial cells.[16,17] In 2007, Urita and coworkers reported further experience with gastric acellular matrix, which also provided satisfactory mucosal regeneration of the esophagus without stenosis or dilation.[18] However, these authors first reported that, although acellular matrices proved to be good scaffold for epithelial proliferation, esophageal muscle regeneration was not enhanced. To improve the unsatisfactory results obtained with acellular matrices, growth factors have also been used. Acellular collagen sponge scaffold and an acellular collagen gel scaffold in combination with basic fibroblast growth factor (bFGF) using a canine model were compared. Histological analysis confirmed a significantly large amount of blood vessels in the bFGF-containing collagen gel group as compared with the collagen gel group without bFGF.[19]

Finally, to overcome the issue of absent peristaltic contractility in artificial esophagi, in 2005 Watanabe and coworkers developed nickel–titanium shaped memory alloy coils, which were placed in an annular manner on a Gore-Tex vascular graft.[20] Interestingly, low-voltage electrical current passing through the coils generated peristaltic movements in the artificial esophagus implanted in a goat model.

Cellularized patches

The first report of a cell-seeded esophageal patch dates back to 1994, when Sato and coworkers reported the creation of a three-dimensional structure composed of cultured human esophageal epithelial cells, polyglycolic acid mesh, and collagen.[21] Human esophageal epithelial cells were isolated from normal mucosa resected from specimens of esophageal cancer patients and cultured on the surface of the collagen gels in which polyglycolic acid mesh were embedded. The engineered tubes were subsequently wrapped in the latissimus dorsi muscle flaps of athymic rats, which were killed at different time points up to 28 days after grafting. Histology of specimens obtained at 8 days after grafting showed that rat fibroblasts infiltrated from the muscle and angiogenesis appeared in the collagen layer, whereas by 20 days after grafting, epithelium grew up to 15 cell layers, similar to human esophagus. In 2003, Grikscheit and coworkers described the use of esophagus organoid units to replace a portion of abdominal esophagus.[22] These units, described previously by the same group in other areas of the gut,[23] are based on multicellular units, containing a mesenchymal core surrounded by a polarized intestinal epithelium, capable of generating all the cells of the intestine. The units were isolated from neonatal and adult rats, labeled with Green Fluorescent Protein by means of viral infection, and subsequently implanted onto nonwoven polyglycolic tubes. Constructs were first transplanted in the peritoneum of recipient rats, where they grew as single lumen, mobile cysts of the omentum, with no histological aberrations. After 4 weeks, a group of rats underwent further surgery, consisting of interposition of the abdominal esophageal construct between the native esophagus and the native stomach. In this first report, authors proved the feasibility of growing a patent conduit in vitro and transplanting it on an in vivo model of esophageal gap. Although organoid units represent an interesting approach, their number in the intestine is generally low. For this reason, further attempts have been tried using cells from various sources. In 2004, Hayashi and coworkers reported the development of a neo-esophagus engineered using cultured human esophageal epithelial cells, smooth muscle cells, fibroblasts, and collagen.[24] First, the smooth muscle cells obtained from aortic media and dermal fibroblasts skin derive were embedded onto collagen sheets obtained from human tendons. Secondly, esophageal epithelial cells derived from normal mucosa of surgical specimens of patients affected by esophageal cancer were seeded on the final constructs. Engineered constructs were transplanted on the latissimus dorsi muscle of athymic rats, covered with lyophilized porcine dermis and finally extirpated after 7 to 14 days. At histology, constructs were similar to the laminar structure that characterizes the human esophageal epithelial, submucosal, and proper muscle layers. Vascular supply was granted by the latissimus dorsi, as in Grikscheit's model, by the omentum.[22] In 2005, Beckstead and coworkers looked at the interaction of esophageal epithelial cells with natural and synthetic scaffolds.[25] Parameters like calcium concentration, scaffold composition and pore size, epithelial behavior on synthetic and natural scaffolds were analyzed. Authors concluded that both decellularized human skin (AlloDerm) and degradable polyesters (PLLA, PLGA75, PCL/PLLA) supported esophageal epithelial cell adhesion and proliferation. However, natural scaffolds proved to lead to architecturally correct morphology with no need of induced modifications. Finally, in 2006, Marzaro and coworkers produced esophageal substitutes composed of homologous esophageal acellular matrix and autologous smooth muscle cells, both isolated from the esophagus of newborn pigs.[26] Authors implanted both of these constructs (acellular matrices + smooth muscle cells) and acellular matrices alone in vivo after creating a porcine esophageal wall defect. Constructs containing autologous smooth muscle cells proved to have less severe inflammation and showed an early organization in small fascicules.

Future perspectives

Thanks to the above described recent advances in esophageal tissue engineering, the ultimate paradigm for esophageal replacement could be a functional allograft, which allows more anatomical replacements and grows with the child and does not severely impaired his/her anatomy. Future progress on the field will go in parallel with the identification and use of: 1) new sources of cells, and 2) new biopolymers.

New sources of cells

Alongside the cell populations so far used for cellularized patches, stem cells could be considered the future approach for esophageal regeneration. Stem cell populations like mesenchymal stem cells (MSC), embryonic stem (ES) cells, induced pluripotent stem (IPS) cells, and amniotic fluid stem (AFS) cells could potentially be used (Figure 1). Protocols to reliably select, culture, and expand these cell populations have been well established. Moreover, some of these cells have already been used in the clinical practice. Among those, MSCs are certainly the ones more extensively investigated for both tissue engineering and cell therapy. They are multipotent stem cells which can differentiate into osteoblasts, chondrocytes, myocytes, adipocytes, beta-pancreatic islet cells, and neuronal cells. MSCs have been used widely in tissue engineering, and their application in the regeneration of bone and cartilage tissues has rapidly progressed toward clinical practice. Regarding the intestine, very little has been achieved so far. In 2004, Epperly and coworkers demonstrated that esophageal progenitor cells, isolated from adult mouse bone marrow, home and proliferate in the irradiated esophagus of recipient mice.[27] Particularly, these cells proved to differentiate into esophageal squamous epithelium. Recently, Sarosi and coworkers have confirmed that bone marrow progenitor cells contribute to esophageal regeneration.[28] However, in a peculiar environment like that of an irradiated rat esophagus, these cells appeared to contribute to the rise Barrett's metaplasia. At the other end of the spectrum, ES cells, pluripotent stem cells derived from the blastocyst, are able to differentiate into all derivatives of the three primary germ layers: ectoderm, endoderm, and mesoderm. Because of their plasticity and potentially unlimited capacity for self-renewal, ES cell therapies have been proposed for regenerative medicine and tissue replacement after injury or disease. However, to date, no medical treatments in humans have been approved from ES cell research, and no application of ES cells on esophagus tissue engineering is found in the literature. This is mainly due to the fact that their use is associated with tumorogenic and immunogenic and ethical concerns. However, it has recently been reported that embryonic-like cells, defined as iPS, can be artificially derived from adult cells.[29-31] In particular, they can be generated by inducing a forced expression of certain genes on an adult somatic cell:

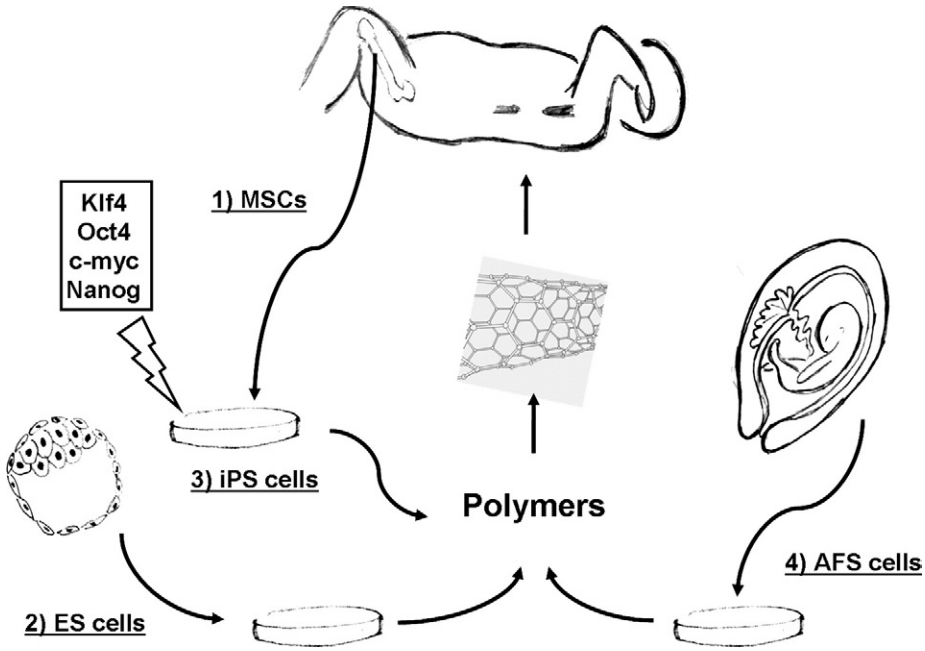

Figure 1 Sources of stem cells. Mesenchymal stem cells (MSCs) can be derived from the bone marrow of a patient with esophageal atresia and expanded in vitro. The same cells can be either directly seeded onto a polymer or transfected as to express stemness genes (Klf4, Oct4, c-myc, Nanog), hence becoming induced pluripotent stem (iPS) cells. iPS will then be expanded in vitro and seeded onto a polymer. Alternatively, embryonic stem (ES) cells can be derived from a donor blastocyst, expanded in vitro, and finally seeded onto a polymer. Ultimately, amniotic fluid stem (AFS) cells can be collected from the amniotic fluid of a donor or of the same patient with prenatal diagnosis of esophageal atresia. AFS cells will be expanded in vitro and seeded onto a polymer. The polymer seeded with either cell type will finally be transplanted to replace the native esophagus.

Oct-3/4 and certain members of the Sox gene family (Sox1, Sox2, Sox3, and Sox15) are considered crucial transcriptional regulators involved in the induction process, whereas some members of the Klf family (Klf1, Klf2, Klf4, and Klf5), the Myc family (C-myc, L-myc, and N-myc), Nanog, and LIN28 have been identified to increase the induction efficiency. iPS cells, first produced in 2006 from mouse cells and in 2007 from human cells, could represent an important advancement in stem cell research, as they can have therapeutic uses, without the controversial use of embryos. Moreover, they can be derived in an autologous setting overcoming risks of rejections associated with ES cells. However, their ability to form teratomas when injected in immunocompromised animals still raises concerns about their possible clinical applications in the short term. Nonteratogenic, pluripotent stem cells have recently been described by our group. AFS cells are pluripotent stem cells present in the amniotic fluid that can be both safely expanded in culture and delivered in vivo.[32] Discarded cultures of AFS cells collected for prenatal diagnostic tests are obtained through a transabdominal approach during gestation (14 weeks to term), selected using c-kit, and expanded in vitro. For esophagus tissue engineering, it can be hypothesized to harvest the AFS cells from the fetus with prenatal suspect of esophageal atresia, expand the cells during gestation, and implant them at birth after engineering in a three-dimensional construct. However, the prenatal diagnosis of esophageal atresia is still rare and in large series do not represent more than 10%.[33,34] On the other hand, patients with pure esophageal atresia (no fistula) commonly associated with long-gap esophageal atresia, can be suspected prenatally.

New biopolymers

Traditionally, the synthetic and natural biomaterials serve as scaffolds for specific cell type or specific tissue applications. In this perspective, ideal scaffolds should provide structural support, chemical stability, or degradability and physical properties matching the surrounding tissues. On the other hand, the scaffold should promote cell viability, proliferation, and differentiation.[35]

Major advances in polymer science have occurred in the last few years. The three-dimensional aspect of the polymer can now be completely arranged to the surgical needs. Injectable polymers can be used for filling tissue defects and guiding the regeneration process.[35] These matrices can be polymerized in vivo using different mechanism (ie, temperature, light) and could eventually be preabsorbed with various growth factors and cytokines to promote neoangiogenesis and innervation of the construct. They provide a scaffold on which cells grow and organize themselves. As the cells begin to secrete their own extracellular matrix, the polymer degrades and is eventually eliminated from the body, resulting in completely natural tissue replacement.[36] Tissue-engineered cell sheets created using autologous oral mucosal epithelial cells could be endoscopically transplanted in an ulcered esophagus in a canine model. Thanks to temperature-responsive matrices, oral mucosal epithelial cells were cultured under normal conditions at 37°C and harvested by a simple reduction in temperature to 20°C. The transplanted cell sheets were able to adhere to and survive on the underlying muscle layers in the ulcer sites, providing an intact, stratified epithelium.[37]

However, as reported in the previous paragraph, the use of undifferentiated cells raise the issue of adequate new biomaterial which is fundamental for the success of the clinical application. Immature cells possess two important properties that need to be accurately controlled: their high self-renewal activity and their multilineage differentiation potential. This new class of biomaterials should recreate in vivo, within the scaffold, an artificial stem cell niche that drives the stem cell self-assembly into a functional tissue. In particular, they must be able to regulate the implanted cell–cell cross talking and the cell–host tissue interactions. Therefore, in addition to conventional properties such as surface topography, bulk and surface physicochemical property, other biomaterial/scaffold intrinsic properties are becoming extremely relevant for defining the artificial stem cell niche. For example, the scaffold porosity or the biomaterial diffusion coefficient defines the flux of endogenous or exogenous factor toward the implanted stem cell or the host tissue, defining the stem cell microenvironment within the scaffold.

These aspects need to be controlled in space and in time. The characteristics of the environment should follow the temporal evolution of the cell requirement for the different stages of stem cell differentiation. These processes will end in a space-controlled stem cell differentiation reproducing the hierarchy and the structural topology of natural tissues. This latter aspect is related to the biomaterial/scaffold ability to induce multiple cell type generation. In this context, a new class of biomaterial needs to be designed, starting from the definition of the artificial stem cell niche.

In conclusion, esophageal replacement remains associated with complications and poor quality of life. Tissue engineering could, in the near future, become a valid therapeutic tool thanks to the continued advances in material science and cell biology.

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