Bioartificial Oesophagus in the Era of Tissue Engineering

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In newborns with oesophageal atresia, surgical repair and bridging of the oesophagus by primary anastomosis is successful in the majority of cases, whereas bridging of long-gap oesophageal atresia is still a surgical challenge. In these situations, delayed repair (primary hitching of the oesophagus to the prevertebral fascia waiting for spontaneous growth or the staged oesophageal lengthening [Foker technique]), myotomy, and oesophageal replacement by either gastric, jejunum, or colon transposition are possible therapeutic options. However, these techniques result in substantial morbidity and mortality rates. Immediate or late failure of oesophageal reconstruction with these techniques may lead to a critical situation in which another reconstructive attempt cannot be performed because of the lack of an appropriate oesophageal substitute. Moreover, disabling symptoms related to late complications, such as anastomotic strictures, reflux, and delayed conduit emptying, may impair the patient's development and quality of life. Therefore, finding alternative procedures for oesophageal reconstruction would be of great benefit. Attempts at oesophageal replacement by artificial nonabsorbable materials, such as Teflon, polyethylene terephthalate (Dacron), expanded polytetrafluoroethylene, or silicone, have not been successful due to their lack of biocompatibility, leading to chronic infection, anastomotic leakage, material extrusion, and strictures (1). Although it has been performed in the past, oesophageal allotransplantation is not a realistic option because of the complexity of the vascular anatomy of the oesophagus and the need for chronic immunosuppression (2). Biomaterials such as pleura, aorta, or pericardium have been used as autograft or allograft for esophageal replacement with relative success. In light of the reports by Martinod et al (3) of tracheal replacement by allogeneic aorta, we established, in a pig model, that short circumferential replacement of the cervical oesophagus by a fresh aortic allograft allowed long-term patency of the oesophageal lumen and nutritional autonomy (4). The limits of this approach were numerous: the need for a stent calibration for at least 6 months to avoid stricture formation; the potential higher morbidity and mortality rates when performing the procedure at the thoracic level, because of the less confined nature of the graft site, compared with the cervical region; and the absence of contractility and propulsive capacity of the fibrotic graft area, which limits the application of this technique to short segmental defect replacement (<4 cm).

CURRENT STATES AND PERSPECTIVES

Tissue engineering (TE) is an interdisciplinary field that applies the principles of engineering and the life sciences to the development of biological substitutes that restore, maintain, or improve tissue function. The underlying principle of TE involves the use of isolated cells combined with complex biomaterials to generate neotissues and organs in vitro and/or in vivo (Fig. 1). It is a field of growing interest, and clinical applications in airway or bladder replacements have been reported (5,6).

The ideal oesophageal substitute issued from TE would have the following characteristics: propulsive peristalsis, elasticity, capacity to resist the reflux of gastric juices, and lubricating capacities. In experimental models, replacement of the oesophagus has been performed with synthetic and natural scaffolds, mainly polyglycolic acid, type I collagen, and small intestinal, oesophageal, gastric, aortic, and dermal acellular matrix, either used alone or seeded with autologous cells. Circumferential replacement of the oesophagus by all acellular matrix, used alone without cell seeding, leads invariably to the absence of tissue remodelling and to stricture formation (7). On the contrary, patch oesophagoplasty, consisting of repairing a lateral defect of the oesophagus with a matrix, does not lead to stricture formation (8), but it does have limited clinical applications. However, this experimental model allows the analysis of biocompatibilities and tissue remodelling capacities of the different types of matrix used in TE of the oesophagus. Thus, it appears that the natural absorbable scaffolds, such as the small intestinal submucosal (SIS) acellular matrix, which is commercially available for clinical applications, gives 1 of the most satisfactory results, allowing complete regeneration of a mature muscular layer in 5 months (8).

In 2005, Badylak et al (9) showed that the conjunction of muscle cells to an acellular matrix has a protective effect on stricture formation, after circumferential replacement. The presence of these cells was associated with a reduced inflammatory and fibrotic reaction and to an enhancement of the reepithelialisation process. This concept was further confirmed by Marzaro et al (10), who showed that the addition of muscle cells to the matrix reduced the inflammatory reaction and increased the regeneration of an organized muscular layer in a patch oesophagoplasty model.

Autologous epithelial cells seeded, as cell sheets, on oesophageal ulcerations promote oesophageal healing and reduce submucosal inflammation (11). Moreover, the presence of epithelial cells enhances muscle regeneration after patch oesophagoplasty (12). Finally, epithelial cells protect from stricture formation after circumferential replacement of the oesophagus by a substitute made of polyglycolic acid and muscle cells (13).

Growth factors, such as keratinocyte growth factor (14), basic fibroblast growth factor (15), and epidermal growth factor (16), could be added to the culture media to promote epithelial cell migration, proliferation, adhesion, and stratification. On the contrary, 1 of the advantages of using natural scaffold, such as the SIS, is that it already contains different growth factors (fibroblast growth

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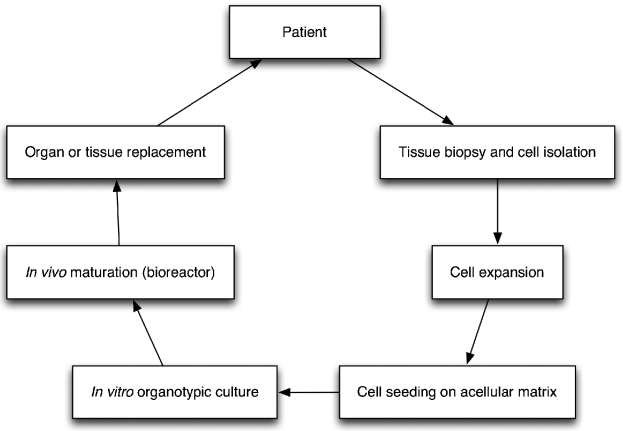

FIGURE 1. Tissue engineering global concept.

factor 2, transforming growth factor-β, and vascular endothelial growth factor) and their inhibitors, in their native-state tridimensional ultrastructure, sufficient to initiate growth and differentiation of implanted cells (17).

Based on these observations, the hybrid approach, consisting of assembling individual tissue components (acellular matrix, muscle, and epithelial cells) in vitro and later mixing them to form composite tissue, is 1 of the most promising approaches in TE of the oesophagus, and has been proven to be successful in short oesophageal replacement (13). Another successful approach has consisted in transplanting oesophagus organoid units (mesenchymal cores surrounded by epithelial cells), seeded on biodegradable polymer tubes (18). However, clinical applications of this model are limited by the embryonic nature of the cell component.

Inability to provide oxygen and nutrients to neotissues both in vitro and immediately after implantation is still a major limitation. Advances in scaffolds composition and design, bioreactor technology, the creation of precapillary and vessels networks in biological scaffold, and the use of proangiogenic factors may help to overcome this difficulty. Meanwhile, temporary implantation of the substitute in a natural bioreactor, such as the great omentum (6,13) or the muscle (14) before replacement, has been proved to be beneficial. Thus, Hayashi et al (14) showed that the maturation of a construct made of collagen sheet added to muscle and epithelial cells and fibroblasts in the latissimus dorsi muscle of an athymic rat allowed the formation of a structured oesophageal wall, whereas no such differentiation was observed in a control group cultured in vitro for 2 weeks.

CONCLUSIONS

Because of the relative simplicity of the anatomy and physiology of the oesophagus, the success of its regeneration could be a milestone in the attempt to generate other parts of the gastrointestinal tract. However, oesophageal replacement is conceivable only if the neoformed organ has physiological similarities to the native oesophageal tissue, namely the possibility for propagating contractions coupled with relaxation processes, to enable the progression of the food bolus into the stomach. Oesophageal contractility and relaxation phenomena are strongly related to the presence of healthy muscle tissue and protective mucosal layer, associated with an organized functional nervous tissue. Therefore, the hybrid approach, using a nonimmunogenic absorbable acellular matrix such as the SIS and epithelial and muscle cells for the in vitro construction of an organotypic cultured tissue, followed by the in situ maturation of the substitute, seems promising for the creation of a bioartificial oesophagus.

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