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ADVANCES OF REGENERATIVE MEDICINE IN DEFECT SURGERY LOWER RESPIRATORY TRACT

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Abstract
Abstract: this article studies the achievements of regenerative medicine in surgery of lower airway defects. Today, early innovative diagnosis and prevention of tracheal defects is one of the most urgent problems in medicine.

Keywords: evolution, instrumental diagnostics, defects, plasticization methods.

Introduction

The key role in the formation of the reconstructive direction of surgery of extensive lower respiratory tract injuries is attributed to cell and tissue engineering. Advanced developments of regenerative medicine create a sure springboard for a completely new direction in surgery, when it is possible to replace the affected area and the whole organ with artificially grown material (Omori K. et al., 2008; Ott L.M. et al., 2011; Jungebluth P. et al., 2012; Elliot M. J. et al, 2012; Luo X. et. al, 2013; Kojima K. et al, 2014; Brouwer K.M. et al, 2013; Gonfiotti A. et al, 2014; Weiss D.J. et al, 2014; Sevastyanov V.I., 2014, 2015; Law J.X. et al., 2016; Alexandrov et al., 2017; Dennis J.E. et al., 2017; Gao B. et al., 2019; Hamilton N.J.I., et al., 2019; Dhasmana A. et al., 2020).

This thesis study explores the potential of regenerative medicine in restoring the integrity of the airways, particularly the trachea. However, such an advanced field of medicine may become in demand not only in tracheal reconstruction but also be developed in other areas of surgery (Fulco I. et al., 2014; Mumme M. et al., 2016; Wiggenhauser P.S. et al, 2017; Cabiati M. et al. 2018). An

increasing number of works based on the implantation of an artificially engineered cellular component are found in the literature.

Cell-engineered constructs are a biomedical product and are a matrix populated with a cell suspension.

CECs are obtained in two ways. In the first case they are grown in a bioreactor in vitro, in the second case - directly in a living organism in vivo. Cells, as an integral element of bioengineered structures, can be used at different stages of differentiation. The possibility of using undifferentiated cells in clinical practice has become a subject of attention of scientists all over the world, as it marked a new era in medicine. The term "stem cell" was proposed in 1909, but the question of the admissibility of its use still causes controversy (Maximov A., 1909). So the use of embryonic and fetal stem cells is limited by the legislation. Ethical expertise on the introduction of postnatal stem cells into practice does not cause serious disputes. But hematopoietic stem cells, multipotent mesenchymal stromal cells and tissue-specific progenitor cells have less potency (Hakobyan A.S. et al., 2010). The idea of using stem cells is gaining popularity, as it is a promising direction not only in clinical practice, but also in pharmaceutics. Numerous publications consider the advantages and disadvantages of stem cell application (Eremeeva M.V., 2010; Semchenko V.V., 2012; Gumerov T.A., 2014.; Wang L. et al., 2017; Lynch T.J. et al., 2018; Zhong Y. et al., 2019; Nakamura R. et al., 2020).

Another component of the cell-engineered construct is the scaffold. It is a kind of substrate on which the cell culture is applied. At first glance, the framing role of the scaffold in the system may seem to be only auxiliary, but this conclusion is erroneous. Cell proliferation and the degree of cell attachment on the matrix surface depend on the properties of the scaffold. Initially, artificial materials were considered for the role of the substrate, but they were not capable of absolute biodegradation, and some of them emitted toxic degradation products during resorption. The natural component of the scaffold was much more compliant with safety requirements. CECs based on collagen, elastin, fibronectin, and chitosan have been described. The most frequent in the literature are works with the use of gelatin, alginates, spidroin, silk fibroin, hyaluronic acid (Weidenbecher M. et al., 2007; Zang M. et al., 2011; Moisenovich M.M. et al., 2012; Novikova I.S., Storublevtsev S.A., 2012; Tani A. et al., 2013; Nakaegawa Y. et al., 2016; Suzuki R. et al., 2016; Cañibano-Hernández A. et al., 2017). The obtained engineered tissue and organ equivalents should be biocompatible with the recipient, as otherwise there is a threat of rejection of the construct. In addition, CECs should not provoke inflammatory and carcinogenic process. The implanted structure must retain its original physical parameters. The requirements to CICs are increasing due to the growing popularity of the technique.

SIC "Kurchatov Institute" published the materials of the study of subcutaneous implantation of laboratory mouse scaffold. The histological study showed revascularization of the scaffold, as well as intensive proliferation of recipient cells on its surface. The chitosan-based substrate was biocompatible with the "host" organism (Kopylov A.N. et al., 2014).

Our attention was deservedly attracted by the work of Liu Y. et al. In the experiment, a 5 cm long collagen-conjugated prosthesis was implanted into the trachea of ten dogs. The histological picture demonstrated partial colonization of the inner surface of the implant by pseudomembranous ciliated epithelium (Liu Y. et al., 2016).

To successfully colonize the substrate with epithelial cells for efficient tracheal reconstruction, the constituents of the scaffold were evaluated based on various parameters

including mechanical strength, volume degradation, cell attachment and spreading, metabolic activity, focal adhesion formation, and differentiation into ciliated and bocaloid cells (Varma R. et al., 2018).

In the search for a safe CEC, a two-stage methodology for its development has been proposed. The idea in the first stage is based on the creation of a scaffold based on natural extracellular matrix. The cadaveric allograft underwent a decellularization procedure. By means of various factors the allograft was freed from the donor cell culture losing immunogenic properties. By the amount of residual DNA in the donor organ it was possible to estimate the efficiency of cell removal from the tissue. The result of decellularization depended on the origin of the tissue and the specific physical, chemical and enzymatic methods used (Gilbert T.W. et al., 2006; Guimaraes A.B. et al., 2019).

The need for a detailed detergent approach is dictated by the high risks of loss of allograft functionality. The structural integrity and concentration of extracellular matrix components in the tracheal allograft relative to the native organ depended on decellularization cycles (Haykal S. et al., 2012). Serious complications can develop with the progression of the number of decellularization cycles (Baiguera S. et al., 2014). We present the results of studies suggesting that a significant decrease in glycosaminoglycan levels may contribute to the loss of mechanical integrity of the biotrachea. Overcoming the structural changes that cause an imbalance in cartilage matrix equilibrium is necessary to optimize the clinical effect (Partington L. et al., 2013).

In search of a gentle method of decellularization of the trachea and bronchi, gamma radiation was tested. The technique had a perverse effect, as it promoted irreversible structural changes of the framework (Johnson C.M. et. al., 2017).

The cell-free scaffold was obtained by a delicate laser-assisted exposure method. The mechanical strength of the scaffold met the requirements of CIC (Xu Y. et al., 2017).

Vacuum decellularization was very effective. It did not cause structural disruption of the framework while being cost-effective as it was carried out in nine days (Butler C.R. et al., 2017). Comparable enzymatic decellularization required three to eight weeks. Bioreactors have been developed as acceptable conditions for complete deprivation of the native organ cellular component. With their help it became possible to reduce the loss of mechanical and biochemical properties by the allograft. Successful studies of various decellularized matrices in animals and patients with tracheal lesions are presented in the literature (Zhang F. et al., 2013).

At the second stage of CIC creation, the cell-free structure obtained by decellularization was populated with recipient cells. Thus, biomatrices could be personalized and this is their undeniable advantage.

Hung S.H. and associates evaluated the feasibility of transplantation of decellularized tracheal skeleton for reconstruction of segmental tracheal defects in rabbits. At the end of the observation period, it was found that regeneration of respiratory epithelium as early as two weeks after surgery was satisfactory, but the tubular structures were compromised, which eventually led to the death of the animals on days 7-24 of the experiment. This outcome was probably predetermined by the unsuccessful choice of decellularization method (Hung S.H. et al., 2016).

Considering that the dense cartilaginous framework of the trachea may impede cell migration and provoke inadequate cartilage regeneration, a laser micropore method was proposed to make the tracheal sample porous to facilitate cell colonization (Xu Y.et al., 2019).

There is work on introducing CICs based on a copolymer of lactic and glycolic acids, polytrimethylene carbonate, into the tracheal and bronchial defect zone. Chondrocytes were seeded on the porous scaffold. The degree of mechanical strength of the matrix exceeded previously tested variants, so it was less susceptible to chondromalacia (Yan B. et al., 2017).

Currently, there is a sufficient number of papers on the topic of cell and tissue engineering that present an impressive evidence base on the feasibility of different hydrogel variants (Vadalà G. et al., 2017; Weinstein-Oppenheimer C.R. et al., 2017; Tan Q.W. et al., 2017).

Risbud M. et al. cite the lack of epithelial lining on the surface of tracheal prostheses as one of the causes of tracheal prosthesis failure. Human respiratory epithelial cells cultured with hydrogel showed normal morphology and growth. The hydrogel provided growth of a mixed population of differentiated epithelial cells and could be used to coat tracheal prostheses (Risbud M. et al., 2001).

Hydrogels are one of the most attractive biomaterials for regenerative engineering because they can be converted into tissue mimetic 3D scaffolds to support cell growth. This is due to their similarity to native extracellular matrix. Advanced nano- and microtechnologies have greatly improved the ability to control the properties and functionality of hydrogel materials. The physical, chemical and functional modulation of hydrogels for the design and construction of biomimetic tissues are highlighted (Guan X. et. al., 2017).

In 2011, the Lancet published data on successful tracheo-bronchial transplantation performed by Jungebluth P. et al. A 36-year-old man who underwent surgical treatment and radiation therapy for oncological lesions of the lower respiratory tract was found to have a recurrence of the disease with the localization of the tumor process in the distal trachea and main bronchi. Removal of the neoplasm contributed to the extensive defect of the lower respiratory tract. This area was replaced with a bioartificial nanocomposite populated with autologous bone marrow mononuclear cells.

No life-threatening complications were registered in the postoperative period. At the control five months after surgery, no data for progression were observed (Jungebluth P. et. al., 2011).

In patent RU 2453291 published in 2012, M.I. Davydov et al. proposed a bioengineered construct containing allogeneic chondrocytes to replace tracheal injury (Davydov et al., 2012).

In 2013, the patent RU 125464 was published. Batukhtina E.V. et al. proposed CIC, which is a bilayer plate of cellular elements without the help of foreign framework or matrix. The strength between the elements of the construction was provided by intercellular contacts. To fix the plate, it is proposed to suture it (Batukhtina E.V. et al., 2013). This technique is certainly promising, but the use of suture material for fixation of the cell-engineered construct in the defect zone is not reliable enough.

Bolton W.D. published successful results of the replacement of an extended tracheal defect with allogenic cell-free dermal matrix in clinical practice. A 38-year-old female patient several months after undergoing surgical intervention in the volume of hemithyroidectomy in 2001 complained of swallowing disorders. An esophageal-tracheal fistula was revealed. In the course of diagnostic search oncologic process was suspected. In order to verify the disease, resection of the esophagus and trachea in the affected area was performed for histologic examination. The length of the removed segment of the esophagus was 7 cm, the length of the trachea in the area of its posterior and right wall was 8 cm and 5 cm, respectively. The volume of the resected tissues was adequate for pathologic examination. Hodgkin's lymphoma was diagnosed. The size of the formed defects did not allow to perform esophageal reconstruction and determined the radical treatment tactics. In the case of an extended tracheal defect AlloDerm with the size of 6x10 cm was successfully

used. The publication noted that four years after the operation the patient is alive and adapted to normal life (Bolton W.D. et al., 2017).

Analyzing the achievements and failures of regenerative medicine, it is impossible to bypass the scientific scandal that broke out in the world community in 2014 and is associated with the name of a professor at Karolinska University. In 2008, a group of scientists led by Macchiarini P. performed an engineered trachea transplant. The donor trachea was stripped of its cellular component, and the resulting framework was populated with the recipient's own stem cells. The trachea was created in vitro. In 2009, an exceptional operation was performed - the trachea was grown in vivo. In the future, in terms of improving the methodology, the use of nanocomposite materials was envisioned. Transplantation of the synthesized organ was also performed in Russia. In 2014, the myth about the uniqueness and universality of the technique was debunked. The real picture showed an extremely high lethality, including in a Russian patient. In our opinion, the proposed method of reconstruction did not have a sufficient preclinical experimental base, which was one of the reasons for the failure. The scale of the conflict was enormous, about the activities of the

Macchiarini P. documentaries were released: "Experimenten" (2015g.), "Heliedabouteverything" (2018g.) (Macchiarini P. et al., 2008; Kolpakov G., 2012; Corbascio M., et al., 2014; Abbot A., 2016; Vogel G. et al., 2016; Teixeira da Silva J.A., 2017). In 2014, the scientific journal "Annals of Biomedical Engineering" presented the results of an experimental study of a group of scientists led by Shin Y.S. A tracheal wall defect with the dimensions of 5x10 mm was formed in six rabbits. The defect zone was replaced with CIC. A 5x12 mm skeleton was formed from crushed and decellularized porcine articular cartilage, which was populated with mesenchymal stem cells. Implant viability was assessed at 6 and 10 weeks after surgery. No signs of respiratory distress were observed in any individual. CT-picture, endoscopic examination, histology results confirmed the effectiveness of the method (Shin Y.S. et al., 2015).

Baranovsky D.S. et al. cultured in vitro human atrial fibrillation epithelium. The cellular substance to be studied was obtained from tracheal biopsy of patients 18-55 years old. Functional properties of the cultured epithelium are similar to healthy tracheal mucosa (Baranovsky D.S. et al., 2015).

A 2016 publication proposes a tissue-engineered trachea patented in China (Patent CN 105853022A) (Fu Wei, 2016). The advantage of the present invention is dictated by the fact that the trachea skeleton had excellent support ability, could be formed in two weeks. But this model only focused on the construction of cartilage framework. The work did not consider the regeneration of the mucosa-submucosa framework.

In the work of Gilevich I.V. for the treatment of tracheal stenosis, a tissue-engineered construct representing a synthetic scaffold populated with bone marrow mononuclear cells was proposed. Under in vitro conditions, attachment and proliferation of undifferentiated cells on the surface of the matrix was performed, and differentiation was continued after implantation of the scaffold in monkeys. Thus, the presented study successfully utilized a living organism as a bioreactor. Application of granulocyte colony-stimulating growth factor and erythropoietin for stimulation of regeneration had a positive effect (Gilevich I.V., 2017).

"Journal of Plastic, Reconstructive&Aesthetic Surgery" in 2018 presented the materials of the work of Hirsch T. and colleagues. The results of the study spoke about the feasibility of using implants that are alginate scaffolds colonized with stem cells of fat origin. This method is proposed for autologous soft tissue reconstruction (Hirsch T. et al., 2018).

In October 2018, the results of tracheal reconstruction in sheep with composite biomaterial were published. A polymer containing various forms of carbon fibers impregnated with polysulfone was used to create cylindrical tracheal implants with a length of 3 cm and a diameter of 2.5 cm. The inner surface of five implants was additionally coated with polyurethane to promote the migration of respiratory epithelium. At the end of the observation period, the outer surfaces of the implants were covered with tissue that resembled to varying degrees the histologic structure of the normal tracheal wall. The inner surfaces of the prostheses were covered only with vascularized connective tissue. Internal polyurethane coating did not improve the outcomes of tracheal reconstruction and promoted excessive granulation, which contributed to moderate to severe stenosis at tracheal anastomoses (Ścierski W. et al., 2018).

Developed in industrial interests at the end of the twentieth century, 3D printers gained a stable position in medicine.

The rapid development of this direction allowed today's science to have in its arsenal printed medical instruments, prostheses, implants and, of course, living tissues and organs - the product of bioprinting (Lazarenko V.A. et al., 2018). Three-dimensional printing has established itself in maxillofacial surgery, traumatology and orthopedics, reconstructive and plastic surgery. Bioprinting has become a predominant direction in reconstructive surgery of organs and tissues of the respiratory system for the last decade (Tseluiko S.S. et al., 2016). There are many developments on implantation of synthetic tissue and organ equivalents created on 3D printers used in severe tracheobronchomalacia (David A. et al., 2013; Jung S.Y. et al., 2016). Reconstruction of 2 cm long tracheal defects using a 3D printed polycaprolactone implant in rabbits with a short-term perspective has been described in the literature. Significant granulation tissue formation decreased survival rate, so there was a need to improve the method aimed at limiting excessive granulation growth (Chan D.S. et al., 2019).

The journal Biomaterials published optimistic results of an in vivo experiment based on the replacement of a rabbit tracheal defect with a hydrogel produced using a 3D printer. The hydrogel was a natural silk fibroin polymer made using glycidyl methacrylate (Hong, H. et al., 2020). A fabricated artificial trachea with mechanical properties similar to native trachea has been published. The possibility to stimulate the regeneration of tracheal mucosa and cartilage through the optimal combination of a bilayer tubular framework and cells derived from induced human pluripotent stem cells is described. The artificial trachea framework was fabricated from the inside from polycaprolactone nanofibers and from the outside from 3D printed polycaprolactone microfibers. In addition, human bronchial epithelial cells, mesenchymal stem cells, and chondrocytes were used to maximize the regeneration of tracheal mucosa and cartilage in vivo (Kim I.G. et al., 2020). Bioengineered tracheal prostheses are biocompatible, non-toxic, porous and have a 3D biomimetic ultrastructure with good mechanical strength to ensure efficient tissue regeneration (Dhasmana A. et al., 2020).

Today, trachea and bronchi printed on 3D printers are no longer perceived as some exotic trend in medicine.

The increased interest in reconstructive and restorative surgery of the trachea, based on developments in the field of cell and tissue engineering, has a serious scientific and practical argumentation.

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