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Review Article

Current status of tracheal tissue engineering

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ABSTRACT

Management of large airway defects is challenging for clinicians due to lack of effective treatment modalities and eventually interest has turned to the field of airway tissue engineering. Considerable progress has been made within the field of airway tissue engineering in recent years and herein we review these recent advances within this field as applied to regeneration and/or replacement of the trachea. Although there are many encouraging researches, we are still far from any routine clinical application of tissue engineered tracheal grafts and it is essential to perform further experimental and clinical researches in order to improve current results and to broaden the clinical application of airway tissue engineering.

Key Words: Trachea, tissue engineering, stem cell, regenerative medicine, airway, transplantation

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Introduction

The aim of regenerative medicine is to restore damaged organs by repairing and/or replacing involving cells and tissues. The two main approaches in regenerative medicine are; stem cell therapy, which means stimulating regeneration by injecting functional cells into the damaged site, and tissue engineering defined as formation of new tissues by using biocompatible materials [1]. Considerable progress has been made within the field of airway tissue engineering in recent years and the first tissue trachea transplant was performed by Macchiarini et al. in 2008 [2]. We herein review the recent advances within the field of upper airway tissue engineering as applied to regeneration and/or replacement of the trachea.

Management of large airway defects is challenging for clinicians due to lack of effective treatment modalities. Various benign or malignant disorders involving the trachea can be treated by primary reconstruction by resection and end-to-end anastomosis of the remaining trachea [3]. However, the length of resection is restricted to 6 cm in adults and 30% of the total length in children since the resection of longer segments would fail due to excessive tension at the anastomotic site [3,4]. Thus, resection and reconstruction of longer segments will only be feasible with the improvement of novel tracheal replacement modalities. Various replacement strategies, mainly focus on autologous or synthetic grafts, have been investigated in experimental and human studies. However, the results were disappointing and none of them has turned into a routine clinical procedure [2,5,6]. Due to these restrictions, interest has turned to the field of airway tissue engineering.

Engineering of a new tissue requires; (i) cells for seeding, (ii) a matrix/scaffold on which to seed the cells and (iii) a bioreactor [7-9].

Cells

Stem cells, which have the ability to self-renew and differentiation, play a critical role in tissue engineering processing of the scaffolds [9,10]. Airway scaffolds can be seeded by two main kind of cell types: Chondrocytes and epithelial cells. Although epithelial cells can easily be obtained form of nasal mucosa, their ability to recreate pseudo-stratified columnar epithelium is limited in vivo, which may lead to difficulties in mucociliary clearance and may cause post-transplant infection [11]. Chondrocytes can be obtained from a variety of sources ranging from embryonic stem cells (ESCs) to differentiated adult cells [12]. However, due to their inability to differentiate and expand appropriately when transplanted and ethical concerns make these cells inconsistent source [13,14].

Recent animal studies showed that seeding with bone marrow derived cells or progenitor cells may contribute to airway tissue regeneration and may also avoid from bacterial contamination [15-17]. Use of pluripotent cells like embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) is controversial. It has been shown in experimental models that both ESCs and iPSCs may cause rejection due to immune recognition [4]. Mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs) and amniotic fluid stem cells are all multipotent cells which can easily be obtained from recipient tissues without any ethical concerns. These kind of cells have been successfully used in many experimental studies [18-20]. The advantages of multipotent cells include their differentiation capacity, good availability, immunomodulatory effects and no need for immunosuppressive medication. Terminally differentiated cells such as smooth muscle cells, endothelial cells and chondrocytes which can easily be isolated, have also been used for tracheal replacement [2,21]. Currently, autologous bone marrow derived MSCs are the most commonly used cell type for tracheal engineering [8,22].

Scaffolds

Structural integrity of the graft depends on the scaffold. An ideal tracheal scaffold should be biocompatible, nontoxic, nontumorigenic, air and liquid tight and provide structural support. The scaffolds can be biological or synthetic.

*Biological scaffolds

The main rationale to use a biologic scaffold is providing a nonimmunogenic tissue that can be used without immunosuppressive medication. Therefore, major histocompatibility complexes (MHCs) I and II, which are responsible from immune reaction, should be removed from donor tissue (Decellularization). Various decellularization techniques can be used with chemical agents (triton X-100, sodium deoxycholate), physical or mechanical methods (agitation, perfusion) [9,23]. The remaining extracellular matrix of the decellularized organ provides the microarchitecture for adhesion, proliferation, remodeling, differentiation and angiogenesis [24,25]. Transplantation of biological scaffolds have been reported with

favorable results in many studies [2,21,25]. However, it is donor dependent, processing time of the organ is long, is expensive and carries a contamination risk.

*Synthetic Scaffolds

Due to some of the above mentioned disadvantages of biological scaffolds novel alternatives were desired. Synthetic scaffolds are not donor dependent, can be customized according to patients' requirements, are relatively inexpensive and the processing time is shorter than biological ones. Ideally, these scaffolds should provide a microarchitecture for host cells to function in. Many kinds of biodegradable materials such as, Marlex mesh (Chevron Philips Chemical Company LP, USA), polyethylene/polypropilen oxide (Pluronic F-127, Invitrogen, Paisley, UK), polypropylene mesh, have been investigated for this purpose [3]. Despite progressive development and application of these synthetic materials in animal studies, few clinical studies have been reported [16,26]. Therefore, further studies are warranted to develop ideal materials and bring them to clinic.

Bioreactors

In order to provide ideal conditions for tissue or organ regeneration, native environment should be mimicked by using a bioreactor. There are two kinds of bioreactor system available. In vitro systems include physiologic, metabolic and biomechanical parameters required for the target tissue [4,9]. Various kinds of bioreactors have been developed including spinner-flask, rotating-wall, compression, strain, hydrostatic, flow-perfusion, and combinatorial bioreactors for clinical transplantation of the scaffolds [2,26-28]. In vivo bioreactor concept was based on the use of the own body as a natural bioreactor. This method provides an ideal environment, reduces contamination risks and is cost-effective [29]. Despite these promising clinical researches Further work is required to develop bioreactors within airway tissue engineering and the optimal conditions required for scaffold seeding before implantation.

First tissue engineered tracheal patch was created by Walles et al. by using a decellularized porcine jejunum seeded with autologous muscle cells and ciliated respiratory epithelium [21]. Due to insufficient mechanical strength this approach was thought to be unsuitable for tracheal transplantation. In 2008, Macchiarini et al. performed a tissue engineered transplant to the left main bronchus by using a decellularized trachea allograft seeded with bone marrow derived MSCs and nasal epithelia cells. This transplant remained open over its entire length, completely recellularized with respiratory epithelium, and had normal ciliary function during 5-year follow up. Although a recurrent stenosis had observed in the native trachea close to the site of anastomosis, their results were found to be safe and promising [2,30]. In 2011, Jungebluth et al. replaced the trachea with a customized bioartificial nanocomposite graft seeded with autologous bone-marrow mononuclear cells via a bioreactor. They gave erythropoietin and granulocyte colony-stimulating factor in order to increase the regenerative capacity and bioactivity of the scaffold. They did not observe any major complications, the anastomoses were patent and the scaffold was lined with a vascularised neomucosa, and was partly covered by nearly healthy epithelium [26].

In summary, transplantation of trachea is a challenging procedure and no ideal solution has been discovered so far. Due to the adverse effects of lifelong immunosuppression allogenic transplantation could not maintain its clinical feasibility and tissue engineered tracheal grafts has become the current promising therapeutic alternative. Despite many encouraging researches, the mechanism of tracheal tissue regeneration and host response to seeded cells is not fully understood and thus, we are still far from any routine clinical application of tissue engineered tracheal grafts. Further experimental and clinical researches have to be performed to improve current results and broaden the clinical application of airway tissue engineering.

Declaration of conflicting interests

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References

1. Atala A. Regenerative medicine strategies. J Pediatr Surg 2012; 47: 17-28.
2. Macchiarini P, Jungebluth P, Go T, Asnaghi MA, Rees LE, Cogan TA, et al. Clinical transplantation of a tissue-engineered airway. Lancet 2008; 372: 2023-30.
3. Grillo HC. Tracheal replacement: a critical review. Ann Thorac Surg 2002; 73: 1995-2004.
4. Jungebluth P, Macchiarini P. Airway transplantation. Thoracic surgery clinics. 2014; 24: 97-106.
5. Birchall M, Macchiarini P. Airway transplantation: a debate worth having? Transplantation 2008; 85: 1075-80.
6. Sato T, Tao H, Araki M, Ueda H, Omori K, Nakamura T. Replacement of the left main bronchus with a tissue-engineered prosthesis in a canine model. Ann Thorac Surg 2008; 86: 422-8.
7. Fishman JM, Lowdell M, Birchall MA. Stem cell-based organ replacements-airway and lung tissue engineering. Semin Ped Surg 2014; 23: 119-26.
8. Fishman JM, Wiles K, Lowdell MW, De Coppi P, Elliott MJ, Atala A, et al. Airway tissue engineering: an update. Expert opinion on biological therapy. 2014; 14: 1477-91.
9. Lim ML, Jungebluth P, Ajalloueian F, Friedrich LH, Gilevich I, Grinnemo KH, et al. Whole organ and tissue reconstruction in thoracic regenerative surgery. Mayo Clin Proc 2013; 88: 1151-66.
10. Fishman JM, De Coppi P, Elliott MJ, Atala A, Birchall MA, Macchiarini P. Airway tissue engineering. Expert Opin Biol Ther 2011; 11: 1623-35.
11. Berg M, Ejnell H, Kovacs A, Nayakawde N, Patil PB, Joshi M, et al. Replacement of a tracheal stenosis with a tissue-engineered human trachea using autologous stem cells: a case report. Tissue Eng Part A 2014; 20: 389-97.
12. ungebluth P, Moll G, Baiguera S, Macchiarini P. Tissue-engineered airway: a regenerative solution. Clin Pharmacol Ther 2012; 91: 81-93.
13. Cedervall J, Ahrlund-Richter L, Svensson B, Forsgren K, Maurer FH, Vidovska D, et al. Injection of embryonic stem cells into scarred rabbit vocal folds enhances healing and improves viscoelasticity: short-term results. Laryngoscope 2007 ;117: 2075-81.
14. Svensson B, Nagubothu RS, Cedervall J, Le Blanc K, Ahrlund-Richter L, Tolf A, et al. Injection of human mesenchymal stem cells improves healing of scarred vocal folds: analysis using a xenograft model. Laryngoscope 2010; 120: 1370-5.
15. Go T, Jungebluth P, Baiguero S, Asnaghi A, Martorell J, Ostertag H, et al. Both epithelial cells and mesenchymal stem cell-derived chondrocytes contribute to the survival of tissue-engineered airway transplants in pigs. J Thorac Cardiovasc Surg 2010; 139: 437-43.
16. Jungebluth P, Haag JC, Lim ML, Lemon G, Sjoqvist S, Gustafsson Y, et al. Verification of cell viability in bioengineered tissues and organs before clinical transplantation. Biomaterials 2013; 34: 4057-67.
17. Seguin A, Baccari S, Holder-Espinasse M, Bruneval P, Carpentier A, Taylor DA, et al. Tracheal regeneration: evidence of bone marrow mesenchymal stem cell involvement. Thorac Cardiovasc Surg 2013; 145: 1297-304 e2.
18. Miettinen JA, Salonen RJ, Ylitalo K, Niemela M, Kervinen K, Saily M, et al. The effect of bone marrow microenvironment on the functional properties of the therapeutic bone marrow-derived cells in patients with acute myocardial infarction. J Transl Med 2012; 10: 66.
19. Mirabella T, Cilli M, Carlone S, Cancedda R, Gentili C. Amniotic liquid derived stem cells as reservoir of secreted angiogenic factors capable of stimulating neo-arteriogenesis in an ischemic model. Biomaterials 2011; 32: 3689-99.
20. Turner CG, Klein JD, Steigman SA, Armant M, Nicksa GA, Zurakowski D, et al. Preclinical regulatory validation of an engineered diaphragmatic tendon made with amniotic mesenchymal stem cells. J Pediatr Surg 2011; 46: 57-61.

21. Walles T, Giere B, Hofmann M, Schanz J, Hofmann F, Mertsching H, et al. Experimental generation of a tissue-engineered functional and vascularized trachea. The Thorac Cardiovasc Surg 2004; 128: 900-6.
22. Giordano A, Galderisi U, Marino IR. From the laboratory bench to the patient's bedside: an update on clinical trials with mesenchymal stem cells. J Cell Physiol 2007; 211: 27-35.
23. Wallis JM, Borg ZD, Daly AB, Deng B, Ballif BA, Allen GB, et al. Comparative assessment of detergent-based protocols for mouse lung de-cellularization and re-cellularization. Tissue Eng Part C Methods 2012; 18: 420-32.
24. Conconi MT, De Coppi P, Di Liddo R, Vigolo S, Zanon GF, Parnigotto PP, et al. Tracheal matrices, obtained by a detergent-enzymatic method, support in vitro the adhesion of chondrocytes and tracheal epithelial cells. Transpl Int 2005; 18: 727-34.
25. Macchiarini P, Walles T, Biancosino C, Mertsching H. First human transplantation of a bioengineered airway tissue. J Thorac Cardiovasc Surg 2004; 128: 638-41.
26. Jungebluth P, Alici E, Baiguera S, Le Blanc K, Blomberg P, Bozoky B, et al. Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study. Lancet 2011; 378: 1997-2004.
27. Asnaghi MA, Jungebluth P, Raimondi MT, Dickinson SC, Rees LE, Go T, et al. A double-chamber rotating bioreactor for the development of tissue-engineered hollow organs: from concept to clinical trial. Biomaterials 2009; 30: 5260-9.
28. Plunkett N, O'Brien FJ. Bioreactors in tissue engineering. Technol Health Care 2011; 19: 55-69.
29. Jungebluth P, Bader A, Baiguera S, Moller S, Jaus M, Lim ML, et al. The concept of in vivo airway tissue engineering. Biomaterials 2012; 33: 4319-26.
30. Gonfiotti A, Jaus MO, Barale D, Baiguera S, Comin C, Lavorini F, et al. The first tissue-engineered airway transplantation: 5-year follow-up results. Lancet 2014; 383: 238-44.