Bio-Design and Manufacturing (2022) 5:627–632
https://doi.org/10.1007/s42242-022-00193-4

PERSONAL VIEW

Future directions for research on tissue-engineered trachea

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Received: 3 September 2021 / Accepted: 13 February 2022 / Published online: 11 March 2022

As the only way for air to enter the lungs, the trachea plays an indispensable role in conducting, cleaning, and humidifying air. Tumors, trauma, and congenital disease of the trachea are serious threats to patients [1]. Local tracheal disease can be treated with a balloon or stent, but for extensive tracheal disease, tracheal reconstruction after surgical resection is the only treatment [2–4]. However, the tension of the anastomotic site also increases with expansion of the resection range, which causes a series of complications, such as poor anastomotic healing, anastomotic fistulae, and tracheal rupture, and even life-threatening complications in severe cases [5].

In clinical practice, allogeneic transplantation can most completely restore organ function. A successful connection between the blood supply and functional tissue is the key to organ transplantation. However, the trachea has a highly complex blood supply system, in which tiny blood vessels grow from the thyroid and esophagus. Doctors at first believed that the blood supply was supported by a network of tiny vessels, which would be impossible to reconnect surgically [6]. Rose et al. reported the first case of allogeneic tracheal transplantation in 1979; they implanted a transplanted trachea under the sternocleidomastoid muscle of the recipient to obtain vascularization and then performed transplantation. However, this bold attempt was ultimately unsuccessful because of the poor prognosis of the patient [7]. Subsequently, Delaere et al. reconstructed a noncircumferential, long-segment defect using a tracheal allograft that was revascularized by heterotopic wrapping in radial forearm fascia [8–10], but this operation is extremely difficult and causes additional damage to the human body. Although prevascularized tracheal transplantation is a good potential method, it has many limitations, mainly the insufficient supply of donor tracheas and immune rejection on the part of recipients [11].

Therefore, researchers have turned their attention to artificial bionic tissues, especially those that simulate the structure and function of the natural trachea. A frenzy of tracheal research is underway. In 2008, Macchiarini et al. reported the first transplantation of tracheal substitutes [12]. These researchers implanted recipient stem cells into acellular natural tracheas, cultured them in a bioreactor, and implanted them into the recipient. This prompted a strong response from the academic community. In 2012, Elliot and his colleagues reported the first child tracheal substitute transplantation, describing implantation of autologous stem cells into the decellularized donor trachea [13]. However, Wu et al. and Delaere et al. soon questioned the cell colonization and vascularization of the trachea constructed with this method, in two studies [14, 15]. Subsequently, Molins reported on the follow-up results of patients, which showed that the quality of life of patients after treatment with tracheal substitutes was poor, recurrent infections occurred, and frequent bronchoscopy treatment was required, all of which caused controversy over tissue-engineered tracheas [16].

In 2018, the *Lancet* published an editorial stating that the research of Macchiarini et al. was carried out without sufficient support from preclinical data and that the paper presented the study data in a way that was unduly positive and uncritical [12]. In other words, the clinical findings reported were not supported by the source data. This report marked the end of the research frenzy in the field of tissue-engineered tracheas [17, 18].

However, stopping development of tissue-engineered tracheas here would be like throwing away an apple because of a rotten core. Researchers began to realize that the construction of tissue-engineered tracheas could not be accomplished overnight. A new series of studies is being carried out based on the experience of earlier researchers.

There is currently a variety of strategies used in preclinical research on engineered tracheas, among which decellularization [19], three-dimensional (3D) printing [20], rolling

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Table 1 Different strategies investigated for tissue-engineered tracheas

Strategies	Advantages	Disadvantages	References
Decellularization	1. It maintains the original shape of the trachea	1. The source of the trachea is limited, involving ethical issues	[22–24]
	2. There are more cytokines in the scaffold, which is conducive to the growth and differentiation of cells	2. It is difficult to achieve standardization and mass production because of the individual differences and cumbersome process	
3D printing	1. The structure of the trachea can be customized to meet personalized needs	1. The technical threshold is high and the initial investment is large	[25–27]
	2. The device can carry a variety of biomaterials and complete the integrated assembly of biomaterials and cells	2. There are strict requirements for the printability of biomaterials	
		3. The printing conditions, such as temperature and humidity, can easily affect cell viability	
Rolling	1. The method is simple and easy to implement	1. The structure is simple and cannot be further adjusted to meet personalized needs	[21, 28]
	2. Assembling after 2D cultivation improves cultivation efficiency, which can enable standardized mass production	2. The tube wall may have a poor fusion effect and may not be completely sealed	
Electrospinning	1. The cell growth environment and mechanical properties can be adjusted through the pores of the scaffold	1. It is difficult to adjust to meet individual needs	[29–31]
	2. It is convenient to add cytokines to modify materials	2. The mechanical strength is poor compared to those for the native trachea	
Casting	1. The method is simple and easy to implement	1. The corresponding mold needs to be made in advance	[32, 33]
	2. It can carry a variety of biomaterials and cells to complete the integrated assembly	2. Additives introduced in biomaterials may affect cell viability	

[21], electrospinning, and casting are the commonly used construction methods. We show the representative strategies in Table 1.

Although these strategies enable imitation of the tracheal structure, most trachea substitutes only simulate the native trachea in morphological structure. The trachea is a complex structure; one cannot build such a complex organ with a complete structure and function without exploring and analyzing each element individually [34]. As a result, Dikina et al. proposed modular trachea construction, which has an overlapping ring structure closer to the natural trachea structure [35]. Subsequently, Xu et al. applied this structure to the trachea to further optimize the mechanical properties. To realize the simulation of tracheal structure and function, we recognize that it is necessary to carry out optimization and iterations with regard to the mechanical strength and regeneration performance of cartilage tissue, nutrient supply of connective tissue, defense function of epithelial tissue, and steady-state regulation of the immune microenvironment.

Judging from the current research progress and our own experience, the following key elements need to be solved first to realize an effective tissue-engineered trachea (Fig. 1).

Mechanical properties compatible with the natural trachea

Tracheal substitutes need longitudinal tensile and lateral compression resistance and the flexibility to resist bending caused by neck movement [36]. First of all, the choice of natural cartilage or pure biomaterials as the main support for tracheal substitutes is worth discussing. The natural cartilage is formed through cell planting and culture in vitro. Cartilage formed in this way can be called "living cartilage," and can continuously regenerate after being implanted in the body. However, pure biomaterials with sufficient mechanical strength will gradually degrade with metabolic activity, which may cause the trachea to collapse. For biomaterials that do not degrade, biocompatibility is poor, and long-term foreign body reactions will increase inflammation around the trachea substitute, creating difficult conditions for tissue repair and regeneration.

Accurate measurement of mechanical properties is a prerequisite for producing standardized tissue-engineered tracheas, but there is no standardized program for clinically applied tracheal mechanical properties testing. Currently reported test methods include residual strain monitoring,

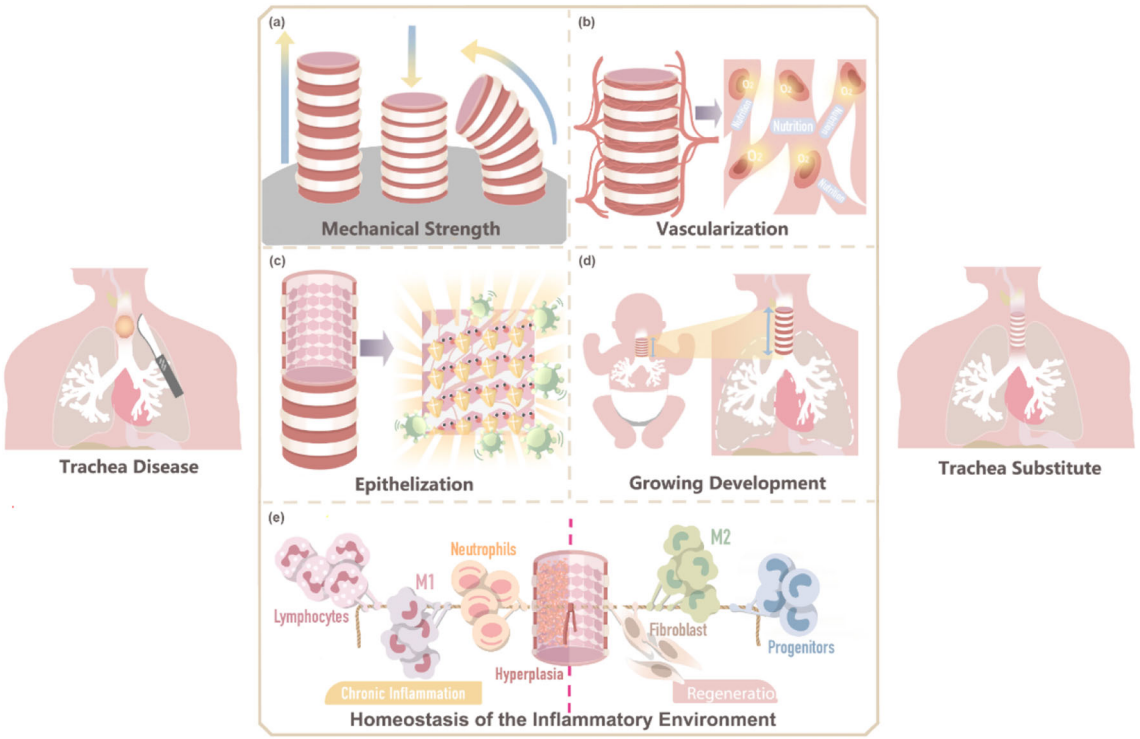

Fig. 1 The significant limitations that restrict functionalization of tissue-engineered tracheas: **a** mechanical strength; **b** vascularization; **c** epithelization; **d** growing development; and **e** homeostasis of the inflammatory environment

bending tests, measurement of pressure–volume curves, uniaxial tensile tests, and compression tests [37]. The trachea is irregular, so researchers use a single element such as cartilage or soft tissue to reflect the overall mechanical properties, making the results more reliable. Studies have shown that the tensile modulus of human tracheal cartilage is 1–16.92 MPa [38, 39], and the tensile modulus of tracheal soft tissue is 0.84–364 kPa [40, 41]. However this result can only be considered preliminary and is not enough to explain the mechanical behavior of the entire trachea. With the introduction of analytical models, finite elements, and computational simulations, this mechanical analysis method can be performed without damage through images or models, providing a new solution for tracheal mechanical performance testing [42].

Rapid vascularization of tracheal substitutes

Functional tracheal substitutes rely on abundant blood vessels to provide nutrition and oxygen. An angiogenesis rate that is too slow or insufficient vascular perfusion will expose the graft to dangerous environments, which may cause tissue necrosis, inflammatory reactions, and even airway collapse. To accelerate angiogenesis, the leading feasible solution is to prevascularize tracheal substitutes before transplantation so that they can be transplanted in situ with minimal ischemic changes.

One such method is to implant a substitute without vascular structure into recipient tissue, such as the omentum or musculocutaneous flap, so that the surrounding tissues will infiltrate the implanted trachea and establish a blood supply. Researchers have found that preimplantation of autologous endothelial cells in tracheal replacement quickly promotes angiogenesis [43, 44]. It is worth mentioning that although this method is simple and easy to implement and achieves complete vascularization of the implant, the vascularization time is relatively long, at an average of 3–4 weeks. In addition, it is often difficult for tissues and blood vessels to infiltrate materials with poor biocompatibility, and foreign body reactions prevent the materials from integrating with the body [45].

Another approach is to build the blood vessel structure on the substitute in advance. For example, hydrogels can be used to print shaped blood vessel networks [46, 47]. When implanted in the body, the preformed blood vessels are anastomosed with the blood vessels in the body. This method can quickly form directional and distributed functional blood vessels, and the graft can obtain a nutrient supply once implanted in the body. However, construction of blood vessels also involves structural and functional issues; anastomosis of preformed blood vessels with the recipient vessels has extremely high technical requirements for surgical suture. At present, this method has not been successfully applied in the area of the tissue-engineered trachea. In general, we believe that

using new techniques to achieve microvascular preforming inside tracheal substitutes and then directing vascular anastomosis to achieve immediate blood perfusion after replacing the substitutes may become a vital method [48].

Complete epithelialization of tracheal substitutes

The epithelialization of the inner wall of the tracheal substitute is the critical factor in cleaning up the airway and fighting off infection [49]. The absence of pseudostratified ciliated columnar epithelium leads to sputum retention and airway infection, resulting in airway obstruction and even collapse. In addition, studies have shown that there is an interaction between respiratory epithelial cells and vascular endothelial cells, which jointly regulate tracheal repair and reconstruction [1, 50–52]. The question of how to realize the extraction of natural epithelial cells, expansion in vitro, and integration with other parts to form a tracheal substitute containing epithelial lining cells is an urgent problem [51]. We believe that functionalized tissue modules of epithelial cells formed in vitro are feasible. Therefore, realizing the efficient preparation and transfer of these functionalized modules and exploring the optimal integration strategy will become the focus of future work in this area [52].

Homeostasis of the inflammatory environment in tracheal substitutes

It is foreseeable that when tracheal substitutes are implanted in the body, infiltrates from the surrounding tissues will induce inflammatory hyperplasia while recruiting the surrounding tissues to grow into it [20]. Finding a way to effectively control the degree of inflammatory response in the surrounding tissues and maintain the homeostasis of the local immune microenvironment will be the key to the successful application of tracheal substitutes. There are different stages of tissue repair, and the body can maintain the homeostasis of the inflammatory microenvironment through the recruitment of inflammatory cells and the secretion of related factors [53]. Therefore, most strategies focus on manipulation of biomaterial-intrinsic properties, addition of bioactive factors that mediate recruitment, the M1-to-M2 transition of macrophages, or inclusion of immunomodulatory cell types [45, 54]. These strategies can lead to effective immune regulation. It is more important for research in this field to explore the complex mechanisms at the tissue, cell, and molecular levels in the immune microenvironment.

Synchronization with receptor development

Reoperation due to growth-related graft mismatch and long-term graft dysfunction is the leading cause of postoperative morbidity and mortality in pediatric patients [55, 56]. The growth and development of the tracheal substitute are also critical for children. The human trachea increases in length by 8 cm during adolescence [57]. If the tracheal substitute cannot grow as the body develops, this may cause growth restriction of the recipient or tearing of the graft anastomosis [58]. Therefore, non-degradable materials must first be excluded as tracheal substitute materials for children. Degradable materials, meanwhile, do not have a supporting effect after being consumed and metabolized and are also not suitable for tracheal substitutes, as explained above. Therefore, it is crucial to develop tracheal substitutes that can adapt to the needs of growth [13, 59]. Construction of tissue with regenerative capacity is the key to the simultaneous development of tracheal substitutes and receptors.

In general, it is clear that the construction of artificial trachea substitutes is still in its infancy. A mature tracheal substitute for clinical use must have all these elements. Due to the limitations of the substitutes mentioned and the current conventional methods for the construction of tubular tracheas, some scholars have proposed innovative construction methods. For example, Martinod et al. reported a study on the use of stented aortic matrices for tracheal repair in 2018 [60]. For the 20 recipients, tracheal stents were removed at an average of 18.2 months after surgery, with a median follow-up of 3.9 years and a survival rate of 76.9%. Epithelial and cartilage regeneration were found in the tissue samples after transplantation, which was attributed to the influence of the peritracheal microenvironment; this could provide a new direction for the development of tracheal substitutes. However, this method lacks preclinical research, and there is insufficient evidence to explain its performance, which makes it difficult to replicate and promote. Meanwhile, collection of aortic samples is hampered by inadequate donor sources and ethical issues.

At present, there is still a long way to go to realize the practical application of tracheal substitutes. The tissue-engineered trachea is a vast research topic which will require a wide range of studies. It is necessary to divide the tissue-engineered trachea into various tissue modules, such as enhancement of the mechanical properties of cartilage, finding a suitable material, and achieving epithelial function defense, and then clearly break them down into smaller areas one by one.

Acknowledgements Supported by the projects from the National Natural Science Foundation of China (Grant Nos. 81770091, 81970091, 82000099), Shanghai Pulmonary Hospital Innovation Team (Grant Nos. FKCX1906).

Author contributions HT was involved in conceptualization and writing—original draft. WS was involved in conceptualization. HT and YC helped in visualization. YS was involved in writing—review & editing of the manuscript. CC was involved in funding acquisition, supervision, and writing—review & editing of the manuscript.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human or animal subjects performed by any of the authors.

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