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Tissue-engineered Vascular Grafts: Balance of the Four Major Requirements

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ABSTRACT

Tissue-engineered vascular grafts (TEVGs) have emerged as a new choice for substitution of damaged blood vessels. A passage of a new blood vessel can be regenerated through the continuous secretion of extracellular matrix of cells seeded on the TEVGs, which is not possible using conventional vascular grafts. Although great progress has been made in TEVGs technology with advances in scaffold design and cell seeding, none have been applied in clinic hitherto. This review summarized the progress of TEVGs during the recent 7 years on the basis of four major requirements of TEVGs, namely, matched mechanical properties, blood compatibility, endothelium friendliness and biodegradability, in the hope of promoting the development of TEVGs.

1. Introduction

In recent years, cardiovascular diseases have posed a great threat to human life and are ranked as one of the greatest causes of death in Western countries. Although various types of medical treatments have been developed and optimized, cardiovascular diseases still cannot be cured hitherto and one-half of survivors cannot live independently after temporary treatment [1,2]. Compared to medical treatment, vaso-transplantation is more effective in treating blood vessel failure caused by cardiovascular diseases. During the early 20th century, researchers started to fabricate artificial blood vessels with some inorganic or organic materials, such as metal, glass and silicone rubber. Currently, vascular grafts made of expanded polytetrafluoroethylene (ePTFE) and polyurethane (PU) have already been employed in clinical treatments [3,4], that, however, are not a permanent solution because of calcification, aging or even cracks emerging during long-term usage after being implanted into patients. The construction of a perfect vascular graft capable of substituting damaged blood vessels in the long term still remains to be explored.

The advent of tissue engineering has created new ways to construct vascular grafts [5]. Tissue engineering is an interdisciplinary subject of engineering and life science. The general approach of tissue engineering is to construct a bioactive organ substitute *in vitro*. Explorers first seed relative cells on the biodegradable scaffolds and provide essential growth factors or other nutrients to stimulate the proliferation of cells *in vitro*. The bioactive scaffold will then be transplanted into the wound of the patient's body. With the continuous secretion of extracellular matrix (ECM), new tissues of specific morphology and functions will be regenerated as biodegradable scaffolds are absorbed gradually [6]. Therefore, the wound part of the patient will be thoroughly replaced by a newly generated autologous tissue. Vascular graft tissue engineering, as an important part of tissue engineering, regenerates a passage of new blood vessels with a bioactive and biodegradable vascular graft constructed *in vitro* (Fig. 1) [7,8].

Natural, synthetic and composite materials are three major types of materials used to construct tissue-engineered vascular grafts (TEVGs). Natural materials are biodegradable macromolecules existing in plants or animals, including acellular matrix and proteins in ECM such as collagen, fibronectin, elastin, gelatin and polyamino acid [10,11]. Natural materials are generally biocompatible and contain abundant bioinformation for the effective recognition and adhesion of cells. Weinberg et al. first reported successful construction of biodegradable vascular grafts with collagen in 1986, and endothelial cells, smooth muscle cells (SMCs) and fibroblasts have been seeded on it [12]. However, with a fixed composition, natural material cannot be adjusted according to practical needs [6,13,14], which has largely restricted its application in vascular graft tissue engineering.

Synthetic materials, although lacking important bioinformation, are more flexible and controllable compared to natural materials, especially synthetic polymers whose mechanical strength, degradation rate, permeability, biocompatibility and other important characteristics can be precisely controlled through adjustment of polymer composition or synthetic methods. Synthetic polymers such as poly(L-lactide) acid (PLLA), poly (lactide-*co*-glycolide) (PLGA), poly(lactide-*co*-caprolactone) (PLCL), poly (ethylene glycol) (PEG), poly(4-hydroxybutyrate) (P4HB), poly-hydroxyoctanoate (PHO), poly(ε-caprolactone) (PCL), poly(dioxanone)

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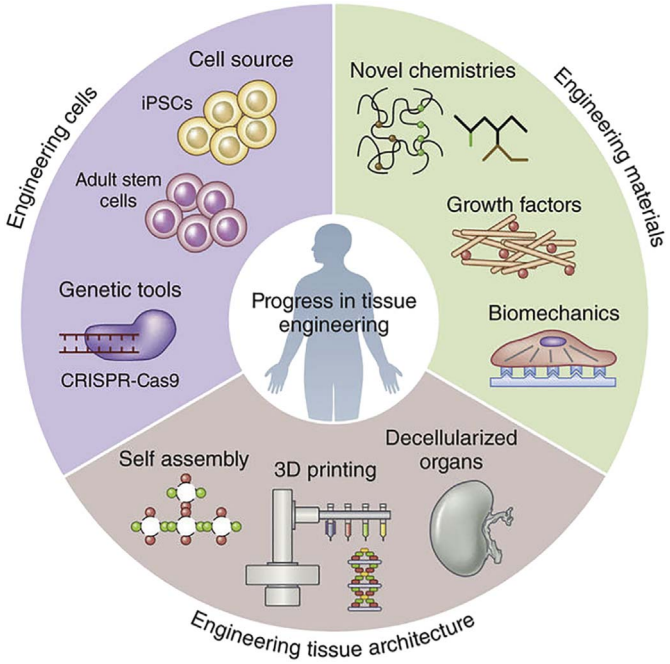

Fig. 1. Three vital elements in tissue engineering: engineering cells, engineering materials and engineering tissue architecture.
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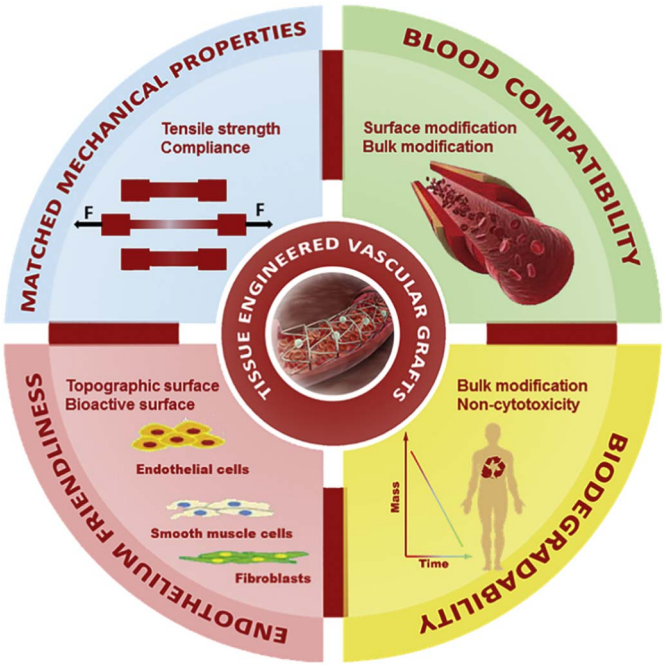
(PDO) and poly(ester urethane) urea (PEUU) have been extensively employed in the research of vascular graft tissue engineering [15,16].

Today, various types of novel biodegradable polymers have been developed to construct vascular grafts. As a qualified TEVG, it has to possess at least four major characteristics: matched mechanical properties, blood compatibility, endothelium friendliness and biodegradability (Scheme 1). Based on these four major characteristics, this review summarized the latest developments of TEVGs fabricated using synthetic polymers, in the hope of reviewing the past and looking into the future.



Scheme 1. Four major requirements for TEVGs: matched mechanical properties, blood compatibility, endothelium friendliness and biodegradability.

2. Techniques for Fabricating TEVGs

Three-dimensional (3D) printing [17,18], solvent casting [19], phase separation spinning [20] and electrospinning [21] are four major techniques to fabricate TEVGs, among which, electrospinning is the most extensively explored and applied. It can be applied to fabricate TEVGs with a single polymer component or a mixed polymer component [22], a seamless surface [23] or a micro patterned surface [24], and TEVGs with a different degree of fiber alignment [25] (Fig. 2) as well, capable of mimicking the niches of endothelial cells. In addition, the porosity of TEVGs can be easily adjusted by controlling the parameters of electrospinning, including the component and ratio of synthetic polymers, voltage, the flowing rate of the polymer solution and the distance between the nozzle and collector [26]. The porosity of TEVGs is also related to its mechanical strength. In general, good porosity always represents weak mechanical strength [27]. Ju et al. fabricated a bilayer scaffold with different pore sizes for the outer layer and the inner layer. When the fiber diameter increased from 0.27 μm to 4.45 μm, the Young's modulus decreased from 2.03 MPa to 0.26 MPa [28]. Therefore, electrospinning can be easily applied to adjust the mechanical strength of the TEVGs through the control of fiber diameter and porosity. In addition to porosity, electrospinning can also fabricate TEVGs with specific topography such as microgrooves, which will induce the oriented growth of endothelial cells [29].

However, the permeability of the scaffold prepared using electrospinning cannot be well-controlled. The permeability directly decides the molecular exchange between the enclosed graft and the exterior blood environment. Perfect permeability should allow the free transportation of essential nutrients and metabolic waste of cells while preventing immunogenic molecules from entering the grafts [30]. To produce TEVGs with good permeability, the phase separation spinning technique is the best choice. The phase separation spinning technique was initially employed to fabricate hollow fibers used in blood purification devices, where the mass transport properties are very important [15,20,31,32]. The device for fabricating TEVGs using the phase separation spinning technique has an inner tube and outer tube. The polymer solution was injected from the outer tube while the bore solution was injected from the inner tube. The polymer will precipitate immediately when poured into the coagulation bath and a type of membrane will be closely packed inside while a porous outside will be formed (Fig. 3) [33]. Pore-forming agents can sometimes be added into the polymer solution to increase the interconnectivity among all the pores. With an increase in pore-forming agent concentration, pore size will be enlarged while having no effect on the number of pores [34]. The permeability and porosity of the graft can be well-controlled by varying the components of bore solution, coagulation solution, flow rate of bore solution and polymer solution and the distance between the nozzle and the coagulation solution [35]. Fig. 4 contrasts the morphology of grafts prepared using electrospinning and those by phase separation spinning. The electrospun nanofiber is obviously denser than the latter. Various types of biodegradable synthetic polymers have been fabricated into vascular grafts using phase separation spinning. Yang et al. prepared an elastomeric-polyester-urethane-based hollow fiber membrane favoring cell adhesion and growth whose molecular transport rate was approximately 0.5–3.5 $\times 10^{-6}$ cm/s [32].

In addition to electrospinning and phase separation spinning, which are the most commonly used in vascular graft tissue engineering, 3D printing is another newly developed technique in recent years. Compared to traditional electrospinning and phase separation spinning, the reproducibility of 3D printing is better while the processing progress is easier with precise control of all the parameters [37]. Actually, each fabricating technique has its own pros and cons. It is relatively difficult to meet all the requirements of TEVGs by adjusting the parameters of a single technique. Combining two or three of them may be a better choice. Soletti et al. combined electrospinning with phase separation spinning (Fig. 5). The porous inner layer of TEVG with good