Current research and development of tissue engineered venous valve**☆

Yuan Jian-ming, Dang Rui-shan, Shen Man-ru, Zhang Chuan-sen

Abstract

OBJECTIVE: To review the current research of tissue engineered venous valve at home and abroad, to analyze the developing trend of tissue engineered venous valve in the clinical application.

METHODS: A computer retrieve was performed among PubMed, ProQuest Health & Medical Complete database, Springer English Academic Journal Full-text database, Elsevier Full-text database between January 2000 and August 2009, with the key words of “tissue engineering venous valve”, and the language was limited to English. At the same time, Chongqing VIP database, Qinghua Academic Journals Database, Chinese Biomedical Literature database were also screened on computer by using the key words “tissue engineered venous valve”, and the language was limited to Chinese. In addition, the relevant monographs were manually checked.

RESULTS: The comprehensive analysis shows that an ideal method to construct tissue engineered venous valve is to combine progenitor cells with multipotent adult progenitor cells for the batched incubation in allogenic acellular vein scaffolds, *in vivo* environment can be maximally simulated through constant pressure perfusions on the three-dimensional culture system, thus seed cells can well grow into functional tissue engineered venous valve on the scaffold materials. This study provides experimental basis for clinical application of venous valve tissue engineering.

CONCLUSION: At present, tissue engineered venous valve research has made considerable progress and encouraging results, brings first lights for deep venous insufficiency for patients, and exhibits wide application in the field of deep venous insufficiency treatment.

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BACKGROUND

For the treatment of deep venous insufficiency caused by primary valve dysfunction, valve damage after thrombosis and recanalization, as well as congenital valve insufficiency, venous valve transplantation is often considered as the last choice. However, autologous venous valve transplantation is unsatisfactory due to limited source, few damage, valve strength is not strong enough and valve vein diameter is difficult to meet the required standards[1]. While the allograft valve and prosthetic valve must be life-long anticoagulated, which is prone to thrombosis, embolism, and anticoagulation-related bleeding complications, thus affecting the patient survival and quality of life. In recent years, cardiovascular tissue engineering technology makes it possible to construct tissue engineered venous valve. Studies have shown that, no matter how many pairs of deep vein valves, only a pair of functional valve can significantly improve the blood reflux[2]. So constructing tissue engineered venous valve containing at least a pair of venous valve may replace a venous valve with insufficient functions, and becomes a focus of cardiac and vascular surgery basic and clinical research. Ideal tissue engineered venous valve should have a 3-layer structure similar with that of the natural valve, strong mechanical properties, can bear the transmural pressure and shear stress of blood flow on the valves; the surface should be completely endothelialized, better anti-thrombotic formation and anti-platelet adhesion; no immunogenicity; have the growth and repair functions.

So far, only Kalka *et al*[3-4] have reported the successful construction of tissue engineered venous valve and applied it in animal experiments in 2003 and 2009, many researchers are still on the process and research methods still need further exploration. Therefore, a practical and efficient exploration on tissue engineered venous valve construction methods is particularly important.

OBJECTIVE

Through a review of the literatures on tissue engineered venous valve published in recent years in major magazines in China and abroad, this study was aimed to summarize a practical and effective methods, and analyze the clinical application prospect of tissue engineered venous valve. By comparison on the seed cells, scaffolds and bioreactor, a suitable, ideal, practical construction method is summarized.

DATA AND METHODS

Retrieval strategy

The first author performed the data retrieval for this study.

By use of “tissue engineering, venous valve, construction” as the English keywords, the related articles were searched on PubMed, ProQuest Health & Medical Complete database, Springer English Journal Full-text database, Elsevier Full-text database between January 2000 and August 2009.

By use of “tissue engineering, venous valve, construction” as the Chinese keywords, Chongqing VIP database, Qinghua Academic Journals Database, Chinese Biomedical Literature database were also screened between January 2000 and August 2009. Theory and Practice of Tissue Engineering, Stem

Cells, Introduction to Biological Materials, and related bilingual conference proceedings were manually searched.
All the search time were defined until August 2009.
Literature search has no language restrictions.
Inclusion criteria: ① The source of seed cells for tissue engineering. ② Types and preparation of tissue engineered scaffolds. ③ Bioreactors applied in tissue engineering. ④ tissue engineered venous valve. ⑤ The articles recently published or published in the authorized journal were preferred.
Exclusion criteria: ① Repeated study. ② Meta analysis.

Quality assessment
Each literature met the inclusion criteria is evaluated based on the following aspects: ① Basic research mainly involves the source of seed cells, scaffold preparation and tissue engineered venous valve constructed in the bioreactor. ② *In vivo* research is mainly related to tissue engineered venous valve research in animals.

RESULTS

Literature retrieval and quality assessment
A total of 76 relevant documents were retrieved, 35 of them met the inclusion criteria, while 41 articles were excluded due to the duplication or Meta analysis. Among 35 included articles, 4 are domestic and the rest are foreign research reports. There were 11 articles related to seed cells of tissue engineered venous valve construction[1-11], 13 related to biological materials of tissue engineered venous valve construction[12-24], and 12 related to bioreactor of tissue engineered venous valve construction[25-35].

Comprehensive analysis of literature evidence
The source of seed cells
The choice of seed cells is critical for constructing tissue engineering, so a suitable seed cell is the most important issue for tissue engineered venous valve construction[1-2]. Ideal seed cells should have easy access to obtain and culture, does not cause immune rejection, amplify productively, adhere strongly to the scaffolds, similar function with autologous cells of the valve[3]. Cell elements of natural venous valve consist of endothelial cells, smooth muscle cells, fibroblasts and myofibroblasts, *etc*[4]. At present, seed cells for tissue engineered venous valve are mainly endothelial cells, endothelial progenitor cells[5-6], myofibroblasts, adult multipotent progenitor cells and so on. The construction of artery and venous valve depends on the re-endothelialization of vessel wall and venous valve wall, endothelium can anti-thrombosis, prevent platelet adhesion, prevent leukocyte adhesion and prevent smooth muscle cell proliferation, endothelial dysfunction or endothelial cells cover loss will lead to vascular and venous valve calcification, then induce thrombosis and dysfunction. In order to maintain a long-term function of tissue engineered venous valve, endothelial cells should be planted in the stent inner surface and then re-endothelialized. Teebken *et al* [7-8] have completed re-endothelialization of tissue engineered venous valve through implanting receptor sheep venous wall endothelial cells in allogeneic acellular sheep valved venous stent surface. The constructed tissue engineered venous valve grafted to the sheep great saphenous veins or external jugular vein, the venous valve graft were shown to conduce good functions six months later. Tang *et al*[9-10] have achieved success on the construction of cardiac and vascular valves using bone marrow mesenchymal stem cells. However, endothelial cells and fibroblasts are adult cells, with a short life, slow growth and easy to fall off, in order to the transplanted cells can grow longer in the stent, many researchers recommend the use of immature cells such as endothelial progenitor cells and adult multipotent progenitor cells. Endothelial progenitor cells are endothelial cell precursor cells, belonging to multipotent stem cells, exist in the bone marrow, umbilical cord blood and peripheral blood, they can differentiate into endothelial cells; multipotent adult progenitor cells[11], under the suitable conditions, can develop into an intact individual, derived from adult mature organs such as bone marrow, liver, skin and others. These two kinds of seed cells can well solve cell aging and easy falling, so endothelial progenitor cells and multipotent adult progenitor cells may be ideal for tissue engineering cells.

Scaffold type and preparation
Tissue engineering scaffolds used are equal to the basic framework for constructing tissues and organs, provides three-dimensional and metabolic environment for the cell proliferation, their overall structure and compositions determine the shape and size of newly formed tissues and organs, so it plays an important role in the tissue engineering.
Developed in recent years, cardiovascular tissue engineering research has developed a biodegradable porous scaffold consisting of collagen fiber and elastic fiber, but it is limited to construct arterial tissue engineering, there is no report related to venous valve scaffold. From the current literature, we can summed up that tissue engineered venous valve scaffold material includes acellular natural and synthetically synthetized scaffold[12-16].
Acellular natural scaffold is to remove the cells, soluble proteins and other components from allogeneic veins through Triton-X100 plus ammonia water method, simple trypsin and other methods, to keep the collagen, elastin and other important scaffolds, which can not only eliminate immunogenicity, but also have three-dimensional structure and mechanical properties, good biocompatibility with cells, favoring cell adhesion and embedding growth, increasing cell coverage, good hemodynamics, can adapt to high pressure and high flow in the vascular lumen, it is an ideal valve tissue scaffold[17-18].
Teebken *et al*[8] prepared sheep allograft acellular venous valve scaffold for tissue engineered venous valve construction, and obtained short-term initial success; Li *et al*[12] achieved satisfactory outcomes by applying bovine external jugular vein to prepare allogenic acellular scaffold, which shows acellular venous scaffold has a broad application prospect in the field of tissue engineered venous valve.
In 2002 and 2004, Pavcnik *et al*[19] respectively applied endovascular stent-supported acellular small intestinal submucosa as a venous valve graft, which was transferred percutaneously to sheep jugular vein, one month later receptor sheep endothelial cells, fibroblasts and other cellular components were shown to adhere and migrate to the graft surface and inner, the graft has a similar function with autologous valve. Pavcnik *et al*[20-21] sutured acellular valved veins on the nickel titanium endovascular stent containing

memory code, used a guided sheath placed in the iliac vein, instead of lower limb deep venous valve, to execute function and also achieved good effect. Although the synthetic polymer vascular stent is effective on the tissue engineering, polymolecular polymer materials have some inevitable drawbacks as following: ① the instability of non-degradable materials. ② spreading infectious diseases among materials. ③ homologous genes rejection between different materials. Therefore, biodegradable polymer scaffold is a development direction for tissue engineered scaffolds[22-24].

Bioreactor applications

Currently, the major problem in the methods of constructing tissue engineered valve is to determine whether cells can effectively adhere and grow into the scaffold, according to previous studies, most of the cells could grow on the internal and external surfaces of the scaffold. Bioreactors can effectively solve this problem, it can well simulate *in vivo* environment, make the seed cells growing in the scaffold as their growth *in vivo*, maximize the cell functions and form good tissues and organs. But there are different types of bioreactors, with varied parameters, the results of different laboratories is difficult to compare with each other. Teebken *et al*[7-8] have placed sheep acellular venous valve scaffold to the rotating bioreactor, forming 2 spaces in venous valve stent and between the stent and the reactor, then periodically injecting a variety of cell suspension to the space, thus successfully constructing tissue engineered venous valve. Abilez *et al*[25] recently reported a new three-dimensional culture system to culture mouse embryonic stem cells, which are shown to grow into the polymer scaffold; Buttafoco *et al*[26] achieved the best culture results, using dynamic culture reactor, to change the pulse frequency at different times and accordingly alter shear force of the medium, the smooth muscle cells also grew into the polymer scaffold; Gulbins *et al*[27] placed the saphenous vein endothelial cells into specially prepared DEVELOPED tube, connecting rotating incubation device, suspended cells were incubated and accelerated to adhere to the surface by rotation, cells can grow into a scaffold. In addition, the bioreactors used for tissue engineering also includes pulse reactor designed to meet the particularity of cardiovascular tissues[28-29]; reactor providing tension for the tendon tissues[30]; anti-membrane bioreactor[31], mechanical agitation bioreactor[32], perfusion bioreactor[33], air-lift bioreactor[34], hollow fiber bioreactor[35]. As different cells need different environments and parameters, there is no a bioreactor yet to fully simulate physiological environment, type of bioreactor and related parameter may determine the success of tissue engineered venous valve construction.

CONCLUSION

In summary, we can summarize an ideal method of tissue engineered valve construction, that is combine endothelial progenitor cells with multipotent adult progenitor cells for the batched growth in the acellular allogenic vein stent, give constantly pressure in the three-dimensional perfusion culture system, maximally simulate *in vivo* environment, thus seed cells can well grow on the scaffold material and serve as a functional tissue engineered venous valve.

In vivo studies on tissue engineered venous valve, as a major national research project in the field of venous valve insufficiency transplant surgery, has made considerable progress and encouraging results, so we can see the hope of clinical application. However, this emerging technology is still in the exploration and in animal models, there are many technical issues and clinical practices needed to be overcomed, in particular, how to further improve the capacities of seed cell adhesion, proliferation and differentiation, how to maintain long-term effect of tissue engineered venous valve after transplantation. However, with the development of tissue engineering technology and tissue engineering study of venous valve, these problems will be certainly overcomed, tissue engineered venous valve is potential to be widely applied, within the next 5-10 years in clinical, benefiting more and more deep venous dysfunction patients.

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Conflicts of interest: No related issues.
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What's already known: The source of tissue engineering seed cells, tissue engineered scaffold preparation, tissue engineered bioreactor applications, tissue engineered venous valve *in vitro* construction.
What's this study added: Introducing the source of ideal seed cells, scaffold material selection and bioreactor applications in fields of tissue engineered venous valve construction in a deepen and detailed manner, comprehensively and informatively reporting the development of tissue engineered venous valve in recent years, presenting and analyzing the clinical application prospect of tissue engineered venous valve in the field of deep vein valve function insufficiency surgical treatment.
Clinical application significance: Successful construction of tissue engineered venous valve will be a breakthrough in venous valve transplantation surgery, tissue engineered venous valve is possible to be applied in clinical practice within the next 5-10 years, and would benefit more patients with deep venous dysfunction.

组织工程化静脉瓣的研究现状与发展趋势**☆

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摘要

目的：综述国内外组织工程静脉瓣的研究现状，分析组织工程化静脉瓣在临床应用的发展趋势。

方法：应用计算机检索 2000-01/ 2009-08 PubMed 、 ProQuest Health& Medical Complete 数据库、Springer 英文期刊全文数据库、Elsevier 全文数据库相关文章，检索词为“tissue engineering venous valve”，并限定文章语言种类为 English。同时计算机检索 2000-01/2009-08 重庆维普科技期刊数据库、清华同方学术期刊数据库、中国生物医学文献数据库相关文章，检索词为“组织工程静脉瓣”，并限定文章语言种类为中文。此外还手工查阅相关专著数部。

结果：综合分析，可归纳总结出一种比较理想的组织工程化静脉瓣构建方法是将内皮祖细胞和多能成体祖细胞联合应用，分批种植在同种异体来源的脱细胞静脉支架上，在三维立体培养系统上不断加压灌注，最大程度模拟体内环境，使种子细胞能很好的在支架材料上生长成有功能的组织工程化静脉瓣。为组织工程化静脉瓣的临床应用提供实验基础。

结论：目前组织工程化静脉瓣的研究取得了相当大的进展和令人鼓舞的成绩，为深静脉功能不全患者带来了曙光，在深静脉功能不全治疗领域有广泛的应用前景。

关键词：组织工程静脉瓣；种子细胞；支架材料；生物反应器

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