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Research review

Tissue-engineered lymphatic graft for the treatment of lymphedema

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ARTICLE INFO

Article history:
Received 12 May 2014
Received in revised form
11 July 2014
Accepted 23 July 2014
Available online 30 July 2014

Keywords:
Lymphedema
Tissue engineering
Lymphatic graft
Nanotechnology
Lymphatic regeneration

ABSTRACT

Background: Lymphedema is a chronic debilitating condition and curative treatment is yet to be found. Tissue engineering approach, which combines cellular components, scaffold, and molecular signals hold great potential in the treatment of secondary lymphedema with the advent of lymphatic graft to reconstruct damaged collecting lymphatic vessel. This review highlights the ideal characteristics of lymphatic graft, the limitation and challenges faced, and the approaches in developing tissue-engineered lymphatic graft.
Methods: Literature on tissue engineering of lymphatic system and lymphatic tissue biology was reviewed.
Results: The prime challenge in the design and manufacturing of this graft is producing endothelialized conduit with intraluminal valves. Suitable scaffold material is needed to ensure stability and functionality of the construct. Endothelialization of the construct can be enhanced via biofunctionalization and nanotopography, which mimics extracellular matrix. Nanocomposite polymers with improved performance over existing biomaterials are likely to benefit the development of lymphatic graft.
Conclusions: With the in-depth understanding of tissue engineering, nanotechnology, and improved knowledge on the biology of lymphatic regeneration, the aspiration to develop successful lymphatic graft is well achievable.

1. Introduction

Lymphedema is a debilitating condition resulting from dysfunction of lymphatic system characterized by progressive soft tissue swelling, which commonly involves the limbs and genitalia. Lymphedema is categorized into primary and secondary lymphedema. Primary lymphedema is rare and caused by genetic defects. Secondary lymphedema is common and caused by acquired damage secondary to surgical resection (lymph node clearance), tumor

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http://dx.doi.org/10.1016/j.jss.2014.07.059

infiltration, parasitic infection, and radiation-induced fibrosis.

In the United Kingdom alone, there are estimated 240,000 people living with lymphedema [1]. Despite the wide practice of breast conserving surgery and minimal lymphatic intervention, the world wide incidence of secondary lymphedema remains high with an estimate of 295,320 patients developing upper-limb lymphedema yearly after breast cancer surgery [2]. This huge number highlights the critical clinical need to treat surgery-induced secondary lymphedema.

The current armamentarium of therapeutic intervention involves nonsurgical and surgical treatment. Nonsurgical treatment includes bandaging and physiotherapy, which does not prevent progression of disease and results in poor quality of life. The surgical treatment of lymphedema has evolved tremendously over the years. In 1990, Baumeister [3] reported the use of lymphatic (lymphaticolymphatic) bypass graft to bridge damaged lymphatic vessels using autologous lymphatic graft harvested from ventromedial part of the thigh. Although reporting a volume reduction of 80% compared with preoperative conditions, this technique did not gain popularity because of the high risk of donor site morbidity. Following the same principle, Campisi [4] used vein graft (lymphatic-venous-lymphatic shunt) and reported volume reduction of 75% in almost half of his patients. Several other form of surgical treatment such as liposuction (suction-assisted lipectomy), subcutaneous excision, and ablative surgery with skin grafting were practiced but with poor outcomes. In the recent years, surgical treatment of lymphedema has evolved into supermicrosurgical approach. The techniques undertaken are lymphatic bypass surgery (lymphaticovenular anastomosis) and vascularized lymph node transfer. Most authors reported a modest improvement in limb volumes (decrease of 30%–50%), although some patients experienced more significant improvement [5]. However, none of these techniques are curative and they are exclusively for patients in early stages of lymphedema.

With these challenges in mind, tissue-engineered lymphatic graft is an ideal alternative that should be explored for the treatment of secondary lymphedema as it is likely to offer greater versatility and therapeutic power. The engineered lymphatic graft can be used to bridge defects involving collecting lymphatic vessels because of surgical resection or as a bypass for congenital cause of blockade to lymphatic circulation. Furthermore, it could also benefit patients with venous impairment in the same lymphedema limb that are not suitable candidate for lymphovenous shunt. To match the properties of native lymphatic vessel, an ideal lymphatic graft should be durable, able to maintain patency, easy to sterilize, nontoxic, nonallergenic, and noncarcinogenic. In terms of handling, it should be kink resistant, easy to suture, and have adequate fatigue strength. The goal of tissue-engineered lymphatic graft is to reproduce the structure, function, and cellular organization of a native collecting lymphatic vessel.

This article aims to discuss the tissue engineering approaches in developing lymphatic graft and the unique limitations and challenges involved. This review also features the advancement in the knowledge of lymphatic biology, with emphasis on lymphatic regeneration and the molecular signals involved.

2. Tissue engineering of lymphatic graft

The lymphatic system can be partitioned into five sections: lymphatic capillary, collecting lymphatic, lymph nodes, lymphatic trunk, and lymphatic duct (Fig. 1). The collecting lymphatic vessels contain intraluminal (secondary) valves and endothelial cells that are spindle shaped with continuous basement membrane, pericytes, and associated smooth muscle cell cover enabling intrinsic contractility of the vessels [6]. Collecting lymphatic vessels are made up of functional subunits known as lymphangion, which propels lymph in a peristalsis manner. Lymph flow is driven by local forces and affected by neighboring musculoskeletal movement and vasomotion. The collecting lymphatics have similar wall as of blood vessels and its smooth muscle tissue contains specialized pacemaker cells that regulate spontaneous electrical activity (Table 1) [7].

Lymphatic system regulates extracellular fluid homeostasis by preserving tissue fluid balance, involved in immune response and absorption of dietary fat. The amount of lymph formation and flow rate is dependent on the characteristics of extracellular matrix (ECM), type of tissue, and the degree of swelling [8].

The lymphatic network is lined by specialized endothelial cells known as lymphatic endothelial cells (LECs). The LECs embryologically originate from out pouching of blood endothelial cells from cardinal vein, and they both share close structural similarities. About 300 genes are expressed differentially between blood endothelial cells and LECs, which includes LEC-specific genes (lymphatic vessel hyaluronan receptor 1, vascular endothelial growth factor receptor 3, prox1, podoplanin, and β-chemokine receptor D6), integrins, cadherins, proinflammatory cytokines, and chemokines [9].

Three key aspects that tissue engineering could benefit lymphatic system are development of artificial lymphatic graft (Fig. 2), regeneration of lymphatic network via lymphangiogenesis, and engineering artificial lymph node.

Developing tissue-engineered lymphatic graft involves proper material selection and fabrication of scaffold to create an environment conducive for LEC growth and for lymphatic regeneration. Although artificial lymphatic graft has yet to be successful, it holds great potential as there is possibility of translating technology and knowledge from tissue-engineered vascular graft. Regenerating lymphatic network is a long-standing challenge for tissue engineers as it required self-organization of endothelial cells into a network of conduits *in vivo*. A possible solution is with the use of stem cell technology and growth factors to form an extensive network of lymphatic capillary, which drains into existing or neighboring collecting lymphatic. Artificial lymph node that is immunologically functional was successfully engineered by Watanabe *et al*. [10]. Although this artificial organ does not enhance lymphatic circulatory function, nevertheless this is a step forward in achieving alternative treatment for lymphedema in future.

The challenges involved in developing lymphatic graft differ from vascular graft. The major differences are the mechanical property and hydrostatic pressure. Lymphatic system is a low pressure and pulseless system compared with