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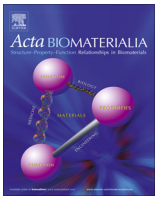

Review article

Challenges in vascular tissue engineering for diabetic patients

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ABSTRACT

Hyperglycemia and dyslipidemia coexist in diabetes and result in inflammation, degeneration, and impaired tissue remodeling, processes which are not conducive to the desired integration of tissue engineered products into the surrounding tissues. There are several challenges for vascular tissue engineering such as non-thrombogenicity, adequate burst pressure and compliance, suturability, appropriate remodeling responses, and vasoactivity, but, under diabetic conditions, an additional challenge needs to be considered: the aggressive oxidative environment generated by the high glucose and lipid concentrations that lead to the formation of advanced glycation end products (AGEs) in the vascular wall. Extracellular matrix-based scaffolds have adequate physical properties and are biocompatible, however, these scaffolds are altered in diabetes by the formation AGEs and impaired collagen degradation, consequently increasing vascular wall stiffness. In addition, vascular cells detect and respond to altered stimuli from the matrix by pathological remodeling of the vascular wall. Due to the immunomodulatory effects of mesenchymal stem cells (MSCs), they are frequently used in tissue engineering in order to protect the scaffolds from inflammation. MSCs together with antioxidant treatments of the scaffolds are expected to protect the vascular grafts from diabetes-induced alterations. In conclusion, as one of the most daunting environments that could damage the ECM and its interaction with cells is progressively built in diabetes, we recommend that cells and scaffolds used in vascular tissue engineering for diabetic patients are tested in diabetic animal models, in order to obtain valuable results regarding their resistance to diabetic adversities.

Statement of Significance

Almost 25 million Americans have diabetes, characterized by high levels of blood sugar that binds to tissues and disturbs the function of cardiovascular structures. Therefore, patients with diabetes have a high risk of cardiovascular diseases. Surgery is required to replace diseased arteries with implants, but these fail after 5–10 years because they are made of non-living materials, not resistant to diabetes. New tissue engineering materials are developed, based on the patients' own stem cells, isolated from fat, and added to extracellular matrix-based scaffolds. Our main concern is that diabetes could damage the tissue-like implants. Thus we review studies related to the effect of diabetes on tissue components and recommend antioxidant treatments to increase the resistance of implants to diabetes.

Contents

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1. Introduction

Diabetes, one of the major risk factors for cardiovascular diseases, is increasing to epidemic proportion worldwide [1], currently affecting 8% of the world's population and more than 29 million people in the United States alone [2].

Hyperglycemia, resulting from deficiency in insulin secretion (Type 1 Diabetes) or insulin resistance (Type 2 Diabetes), coexists with dyslipidemia, oxidative stress, and inflammation, significantly increasing the risk of cardiovascular diseases [3,4]. One of the major complications of diabetes is associated with accelerated atherosclerosis and vascular wall stiffening, the hallmark of diabetes [5]. Despite extensive research and progress in the treatment of cardiovascular diseases, there are still numerous amputations and vascular related deaths associated with diabetes. AHA states that about 500,000 coronary artery bypass graft procedures are performed every year in the US. Additionally, about 12 million patients in the US have a form of peripheral arterial disease and the American Diabetes Association estimates that 20–50% of them are diabetic [6,7].

Over the last several years, diabetic patients have not shared the same decline in arterial disease-related mortality as non-diabetic patients [8]. Patients with diabetes still have a high incidence of restenosis after receiving drug-eluting stents [9], and coronary artery bypass grafting occlusions are more common among diabetics versus non-diabetics at 1-year angiography [10]. The autologous arteries and veins are the "gold standard" for coronary artery bypass grafting, but 1/3 of patients (about 140,000 each year) do not have vessels suitable for grafting. Vascular synthetic grafts with medium and large diameters function well, but small-diameter grafts fail rapidly (50% patency rate by two years) and cryopreserved cadaveric veins have only 30% patency rates after 12 months [11–13]. Therefore, there is a major need for vascular grafts with long-term stability and patency for diabetic patients.

Progress has been made in tissue engineering that holds great promise to treat vascular diseases [14,15]. A typical approach in tissue engineering is based on a biodegradable and biocompatible scaffold (based on natural or synthetic polymers, including promising elastomeric polymers [16,17]) with mechanical properties similar to the target tissue, seeded with autologous stem cells, chemically and mechanically stimulated in a vascular bioreactor, followed by implantation, that leads to remodeling and maturation into fully functional vascular grafts [18,19] (Fig. 1).

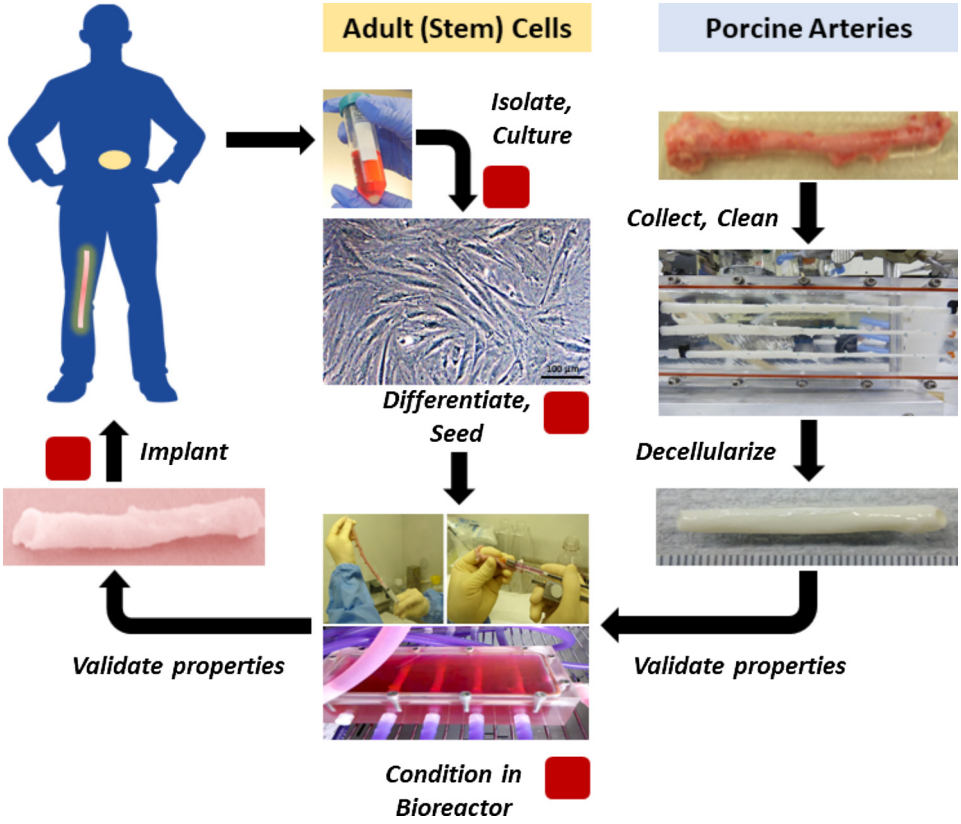

Fig. 1. Extracellular matrix (ECM) based vascular graft tissue engineering paradigm and potential effects of diabetes. A typical scenario is depicted whereby ECM-based scaffolds would be derived from decellularized blood vessels or other tubular conduits generated in vitro from ECM components, 3D printed scaffolds or cell sheets. Adult stem cells or terminally differentiated cells would be isolated from the patient (adipose tissue or other sources), cultured, propagated and seeded within and/or onto scaffolds. The constructs will be conditioned chemically and mechanically for maturation in specific bioreactors as needed before implantation as vascular grafts into diabetic patients. Validation of scaffold properties (mechanical, biological) before and after seeding and maturation is mandatory. Some ECM based scaffolds might not require cell seeding or bioreactor conditioning and may possibly be implanted directly. Red boxes designate areas of research where diabetic conditions might exert an influence on this tissue engineering approach. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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