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Advantages of bilayered vascular grafts for surgical applicability and tissue regeneration

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ABSTRACT

Nanofibrous scaffolds are part of an intense research effort to design the next generation of vascular grafts. With electrospinning, the production of micro- and nano-fiber-based prostheses is simple and cost effective. An important parameter for tissue regeneration in such scaffolds is pore size. Too small pores will impede cell infiltration, but too large pores can lead to problems such as blood leakage. In this study, bilayered grafts were made by electrospinning a high-porosity graft with a low-porosity layer on either the luminal or the adventitial side. Grafts were characterized in vitro for fiber size, pore size, total porosity, water and blood leakage, mechanical strength, burst pressure and suture retention strength, and were evaluated in vivo in the rat abdominal aorta replacement model for 3 and 12 weeks. In vitro blood leakage through these bilayered grafts was significantly reduced compared with a high-porosity graft. All grafts had an excellent in vivo outcome, with perfect patency and no thrombosis. Cell invasion and neovascularization were significantly reduced in the grafts with a low-porosity layer on the adventitial side, and there was no significant difference between the grafts in endothelialization rate or intimal hyperplasia. By tailoring the microarchitecture of biodegradable vascular prostheses, it is therefore possible to optimize the scaffold for tissue regeneration while preventing blood leakage, and thus facilitating applicability in the clinic.

1. Introduction

Since clinically available synthetic vascular prostheses do not offer satisfactory outcomes for small diameter vessel replacements (<6 mm), new alternatives need to be developed [1]. Tissue engineering is a fast growing field where biomaterials, cells, bioactive molecules and engineering concepts are combined to restore, replace or improve a biological tissue. Where biostable materials have failed, tissue engineering could bring new solutions to the shortage in small diameter vascular grafts. There are two main types of tissue-engineered vascular grafts: shelf-ready grafts, where in situ tissue regeneration leads to a cellularized vascular replacement; and cell-seeded vascular grafts, which are cellularized in vitro before implantation. Obtaining appropriate in situ regeneration with a shelf-ready prosthesis is challenging [2], but pre-seeded prostheses have long manufacturing times and require costly laboratory settings, which could be unaffordable for many clinical centers. Developing shelf-ready vascular prostheses therefore remains the real challenge in the field [3].

Scaffold characteristics have a strong influence on in situ tissue regeneration. When cells interact with a scaffold, they sense both the material (ionic and electrostatic interactions) and the microarchitecture (local geometry—film, fibers, spheres, sponge; porosity and local compliance). One important aspect is porosity: too small pores will impede cell infiltration and no regeneration will take place, but with too large pores, cells will not be able to bridge the pores and generation of a tissue in the voids will be slow [4]. Since different types of cells have different sizes and morphologies, the optimal scaffold pore size for each is different and can vary from 5 to 500 μm [5].

While microscopically the pores should be large for better cell infiltration, macroscopically this can lead to the problem of blood leakage through the graft wall. During cardiovascular surgery, patients receive a systemic heparin treatment to avoid blood clot formation, but this also prevents clotting in the graft wall to stop any leakage. In the clinic, to prevent bleeding from highly porous grafts such as knitted Dacron, either a sealant is applied (e.g., collagen, fibrin or gelatin) or pre-clotting is performed by the surgeon [6]. Preclotting is a simple process where the graft is left for several minutes in the patient's non-heparinized blood [7]. A clot forms in the

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