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Improved endothelialization and reduced thrombosis by coating a synthetic vascular graft with fibronectin and stem cell homing factor SDF-1α

G. De Visscher [a,1], L. Mesure [a,1], B. Meuris [a], A. Ivanova [b], W. Flameng [a,*]

[a] Laboratory of Experimental Cardiac Surgery, Department of Cardiovascular Diseases, KULeuven, Leuven, Belgium
[b] Leuven Statistics Research Centre, KULeuven, Leuven, Belgium

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ABSTRACT

Failure of synthetic small-diameter vascular grafts is determined mainly by the lack of endothelial cells, as these cells inhibit thrombosis and intimal hyperplasia. Coating of graft material with homing factors for circulating stem cells has the potential to improve endogenous endothelialization of these grafts and to reduce graft failure. Synthetic knitted polyester grafts (6 mm diameter) were coated with FN and SDF-1α before surgical interposition in the carotid artery of sheep. Similar uncoated vascular grafts were implanted in the contralateral side as internal controls. To study the early attraction of stem cells, grafts were implanted in a first series of nine sheep and explanted after 1 or 3 days. In coated grafts, four times higher fractions of $CD34^+$ and three to four times higher fractions of $CD117^+$ cells adhering to the vessel walls were found than in control grafts ($P < 0.05$). When such coated and non-coated grafts were implanted in 12 other sheep and explanted after 3 months, all coated grafts were patent, while one control graft was occluded. EcNOS staining revealed that FN-SDF-1α coating significantly increased coverage with endothelial cells from 27 ± 4% of the graft to 48 ± 4% compared with the controls ($P = 0.001$). This was associated with a significant reduction of intimal hyperplasia (average thickness 1.03 ± 0.09 mm in controls vs. 0.69 ± 0.04 mm in coated grafts; $P = 0.009$) and significantly less adhesion of thrombotic material in the middle part of the graft ($P = 0.029$). FN-SDF-1α coating of synthetic small-caliber vascular grafts stimulated the attraction of stem cells and was associated with improved endothelialization and reduced intimal hyperplasia and thrombosis.

1. Introduction

Synthetic grafts show outstanding results after large vessel replacement. However, these grafts are much less suitable for small-caliber vessel grafting, where autologous artery or vein grafts have become the "gold standard" [1]. Patency rates are also remarkably higher for these native grafts than for prosthetic grafts [2–4]. The patency of prosthetic vascular grafts is impaired by intimal hyperplasia near the anastomotic regions, which ultimately leads to graft thrombosis [5]. The absence of viable endothelial cells (EC) on the luminal surface of prosthetic grafts induces intimal hyperplasia formation [6]. Endothelial cells also actively inhibit thrombosis and form an anticoagulant surface [7]. Several approaches have been used to seed vascular grafts with EC using harvested venous or microvascular EC, mesothelial cells or endothelial progenitor cells (EPC) and the introduction of *in vitro* maturation steps resulted in an improvement of the patency [8–12]. However, these methods are also associated with serious drawbacks, such as the supplemental procedure to harvest the cells (in the case of autologous cell use), risk of infections, long culture times and the associated high cost of the procedure.

To circumvent these problems, this study advocates a completely different approach of tissue engineering using the concept of endogenous attraction and selective seeding of progenitor cells [13]. In a previous study, a fibronectin and stromal cell derived factor 1 alpha (FN-SDF-1α) coating was used as a recellularization paradigm for heart valves and showed endothelialization after 5 months of implantation in the pulmonary position in sheep [14]. SDF-1α, a CXC chemokine, acts as a chemoattractant for hematopoietic stem cells (HSC) and can even induce the recruitment of EPC [14–16]. HSC homing mediated by SDF-1α/CXCR4 can be taken over by the α4-integrin-VCAM1/FN axis [17]. FN can present SDF-1α to cells and facilitates binding of SDF-1α to matrices [14,18].

Protein coating of vascular grafts to improve endothelialization has already been suggested by several groups [19–23]. The present authors hypothesized that impregnation of small-caliber vascular grafts with FN-SDF-1α might be useful in the *in vivo* seeding to improve endothelialization and graft function.

This study specifically looked at two types of commercially available knitted polyester grafts which are classically pre-coated

* Corresponding author. Tel.: +32 16344229.
E-mail address: willem.flameng@med.kuleuven.be (W. Flameng).
[1] Both authors contributed equally.

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