Review

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Tissue engineering of vascular grafts

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Summary
Background There is a considerable clinical need for a sufficient prosthetic small-diameter substitute which can compete with autologous vessels. Currently used synthetic materials have a poor performance due to high thrombogeneicity and development of intimal hyperplasia. Tissue engineering is an interesting alternative approach for vascular graft fabrication.

Methods We briefly overviewed the development of tissue-engineered vascular substitutes including endothelialized biohybrid grafts, collagen and fibrin-based scaffolds, decellularized scaffolds, cell self-assembly approaches, and biodegradable constructs based on synthetic polymers.

Results Significant advances have been made over the past decades in the development of tissue-engineered conduits. Biomechanical weakness, one of the major limitations of biologically based grafts has been resolved and two tissue-engineered grafts are currently under further investigation for clinical application.

Conclusions Vascular tissue engineering is a promising approach to overcome the limitations of current therapies in small-diameter vascular replacement.

Keywords Vascular grafts · Small diameter · Tissue engineering · Manufacturing techniques

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Introduction

Despite significant advances in interventional revascularization procedures and pharmacological options to treat the pathology of small-diameter vessels, the demand for surgical revascularization therapies in coronary and peripheral vascular surgery is increasing continuously. Autologous vessels are the preferred materials to reconstruct vascular segments with inner diameters smaller than 5 mm. Characteristics such as low thrombogenicity, ideal biomechanical properties, and a low infection rate provide high patency rates even under low blood-flow conditions. However, many patients lack autologous vessels suitable for tissue harvest, due to comorbidities or previous interventions [1–4].

Therefore, there is a considerable clinical need for a sufficient prosthetic substitute which can compete with autologous vessels. The ideal vascular graft should be available off-the shelf, durable upon long-time implantation, have a low inflammatory potential, and should be resistant to thrombosis and infection. The graft wall itself should further be elastic and match the compliance with the native host vessel [5].

Currently available graft materials such as ePTFE and Dacron show excellent long-term results for large-caliber arterial reconstruction but have an inferior biological performance in small-diameter applications such as coronary artery bypass grafting, arteriovenous shunts, and lower limb bypass. Main reasons for small-caliber conduits' shortcomings are increased surface thromboge-

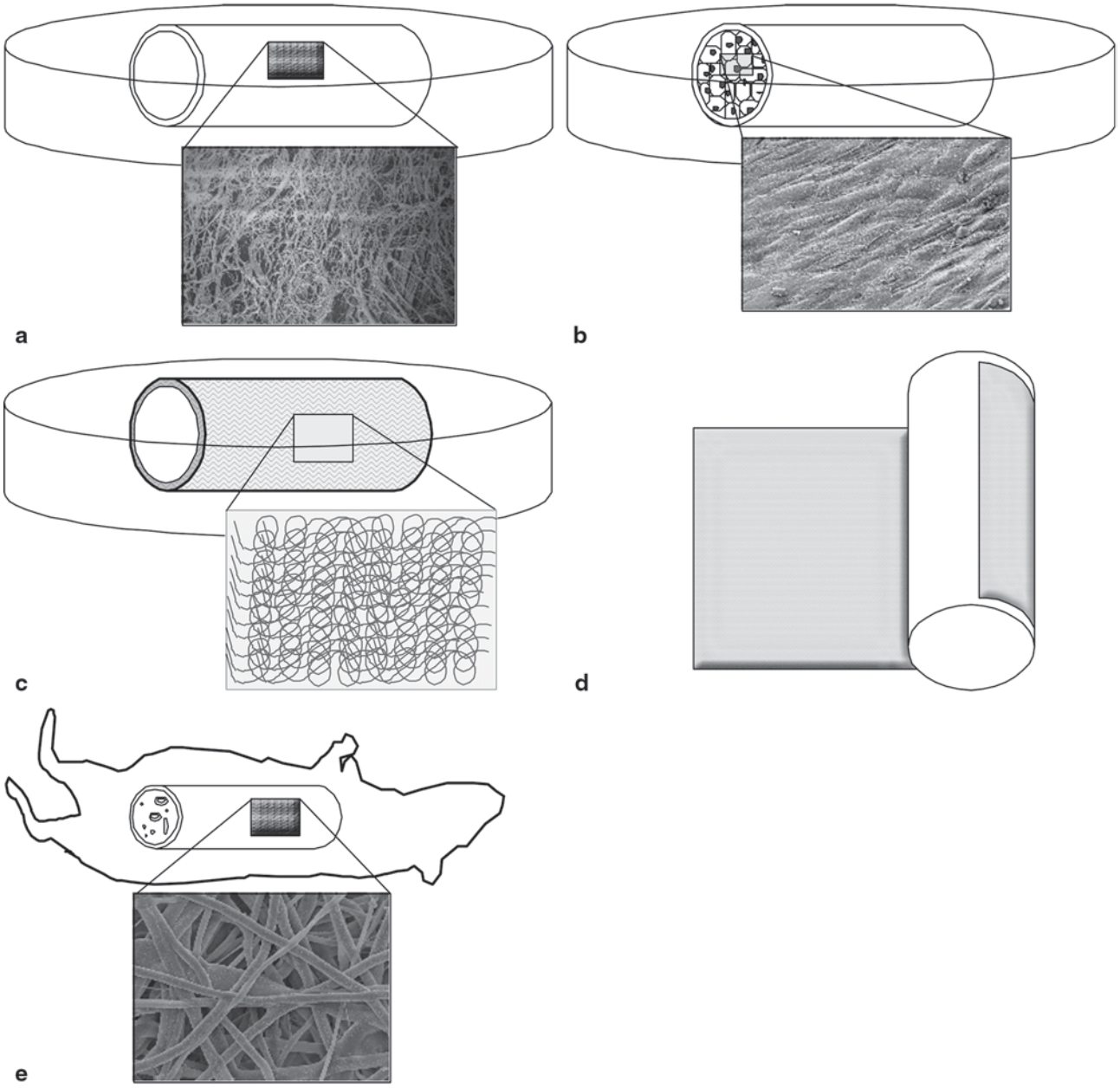

Fig. 1 Schematic representation of different techniques in vascular tissue engineering: decellularized scaffolds (**a**), endothelialized biohybrid graft (**b**), collagen and fibrin-based scaffold (**c**), cell self-assembly approaches (**d**), and biomimetic graft cellularized in vivo (**e**)

nicity caused by the absence of a functional endothelium and the development of intimal hyperplasia caused by compliance mismatch and chronic inflammation. Especially in low flow situations, synthetic grafts demonstrate low patency rates [6–9]. Furthermore, synthetic substitutes are often prone to microbiological contamination which requires implant removal. Although much effort is underway to improve the performance of synthetic substitutes by the use of different materials and surface modifications techniques, these substitutes do not match the performance of native tissues so far [10–13].

Tissue engineering and regenerative medicine

Tissue engineering is an encouraging approach to overcome the limitations of artificial nonviable materials by creating biologically active vascular prostheses which are in part (biohybrid graft) or completely composed (totally engineered blood vessels (TEBV)) of viable tissue [14–17]. Natural or synthetic scaffolds are populated with vascular-specific host cells in vitro by various preseeding techniques, or vitalization of the graft is completely directed to spontaneous cell reconstitution in situ after implantation (Fig. 1).

Vascular scaffolds without remodeling potential

Endothelialized biohybrid grafts

The first tissue engineering approach in vascular graft development was the creation of endothelial cell-seeded biohybrid grafts to enhance the patency of small-caliber vascular grafts. Endothelial cells release various substances which are crucial for the inhibition of thrombosis and neointimal hyperplasia. Seeding of viable, autologous endothelial cells onto the prosthetic graft lumen has been applied experimentally for the first time by Herring et al. [18]. In a single-stage procedure, autologous cell transplantation has been performed immediately before the implantation of the prosthetic conduit using a subcutaneous vein segment for cell harvest. The first clinical results were disappointing but could be improved by using other cell sources than microvascular endothelium [19, 20]. Later, a double-stage approach which involves lining of endothelial cells and a postseeding period in vitro between cell harvest and graft implantation, was successfully applied by Zilla and his group [21, 22]. Cell retention rates on the graft surface have been further increased by flow pretreatment or shear stress in vitro preconditioning [23, 24]. Long-term clinical patency data of the biohybrid prostheses are encouraging and comparable with native vein grafts for femoropopliteal bypass applications [25]. Newer approaches aimed to improve the seeding efficacy by the use of progenitor cells, genetically modified cells [26] or by the optimization of the adhesive properties of the graft surface [27].

Vascular scaffolds with remodeling potential

However, the function of composed nondegradable biohybrid grafts is often impaired by limited long-term survival and poor proliferation of endothelial cells on synthetic surfaces and an impeded biological remodeling process. This has led to new concepts focusing on entirely biologically based implants that exhibit all the functional characteristics of normal blood vessels. The graft should consist of a functional, nonthrombogeneic endothelium, an extracellular matrix with desirable viscoelastic properties and sufficient mechanical strength, and populated by metabolically active and contractile smooth muscle cells. This implies the use of a biodegradable scaffold which serves as a promoting matrix for host cell ingrowth and has the potential of adaptive, long-term remodeling according to the needs of the host vessel, like unrestricted growth capacity in juvenile organisms. A considerable challenge in the application of biodegradable grafts is the maintenance of adequate strength during the remodeling period. A prerequisite for safe patient application is a balanced process of material degradation and adequate host cell reconstitution with subsequent synthesis of extracellular matrix graft.

Collagen and fibrin-based scaffolds

Weinberg and Bell [28] were the first who designed a tissue-engineered graft using cell-seeded collagen tubes. The biological scaffolds enabled cell-mediated remodeling but had to be reinforced with synthetic sleeves to achieve adequate mechanical properties. To improve the mechanical strength, a crucial factor in developing collagen-based constructs, cell-mediated graft restructuring techniques have been developed [29]. Constructs showed significant improvements in biomechanical properties, but till date their application is still limited to low-pressure vasculature [30]. Cell impregnated fibrin-based scaffolds have also been used to engineer exclusive tissue-derived grafts, which have the advantage of easy harvesting of graft constituents from the patient [31]. Weak tensile strength of grafts [32] could be increased by improvement of engineering techniques [33].

Decellularized scaffolds

Naturally derived materials such as decellularized scaffolds possess properties that are desired in biomedical applications. These substitutes reveal the three-dimensional architecture of the extracellular matrix (ECM) and are composed of ECM-proteins thereby featuring cell-signaling components, which favor adhesion, migration, proliferation, and differentiation of host cells. Furthermore, they have nearly ideal biomechanical properties. Tissues from different locations (small intestine, blood vessels) and species (allogeneic, xenogeneic donors) and various decellularization approaches have been investigated [34]. Preclinical and clinical studies revealed sufficient host cell reconstitution and great remodeling potential [35–40]. We could show in our own studies that allogeneic as well as xenogeneic vascular implants performed well in long-term applications [41]. Xenogeneic conduits revealed low immunological response and led to topical remodeling indicated by morphological transformation from a muscular artery toward an elastic vessel which had vasoreactive competence [42]. However, although decellularized matrix grafts show great potential in small-diameter applications, potential risks of residual immunogeneicity and microbiological contamination have limited widespread clinical use so far.

Cell self-assembly approaches

Cell-based tissue-engineered constructs without the support of a scaffolding system were created by L'Hereux. The scaffolds were fabricated by the use of mesenchymal cells which were grown in overconfluence thereby producing self-assembled tissue sheets. These cell sheets are further processed in vitro using a mandrel to form a tubular structure. During a prolonged incubation period, the cells arranged circumferentially and produced large amounts of extracellular matrix [43]. These conduits

could withstand high pressures and are currently under investigation for hemodialysis access grafts in human patients [44].

Biodegradable synthetic polymer-based constructs

In vitro preseeded scaffolds

Synthetic biodegradable scaffolds have been used predominantly for in vitro tissue engineering approaches because spontaneous cell attachment in vivo was insufficient and the grafts were susceptible to aneurysmatic dilatation or rupture. Biodegradable constructs are often based on polylactic acid (PLA), polyglycolic acid (PGA), or poly-epsilon-caprolactone (PCL) materials which are approved as suture materials and whose degradation rates can be modulated by copolymerization techniques. In 1999, Niklason et al. [45] showed for the first time that in vitro engineered grafts using PGA and animal-derived cells, have sufficient mechanical strength and reveal structural similarities to native vessels. However, when human cells were applied tissue-engineered grafts, they demonstrated mechanical weakness. Thus, for a long time, clinical application was restricted to low-pressure applications. Albeit Shinoka [46] successfully demonstrated long-term performance of preseeded grafts in the application of congenital malformation surgery. Recently Niklason and her team were able to create an allogeneic human tissue-engineered blood vessel using PGA meshes which had adequate strength for arterial circulation [47]. These conduits showed a superior in vivo performance when evaluated as arteriovenous shunts in a baboon model [48].

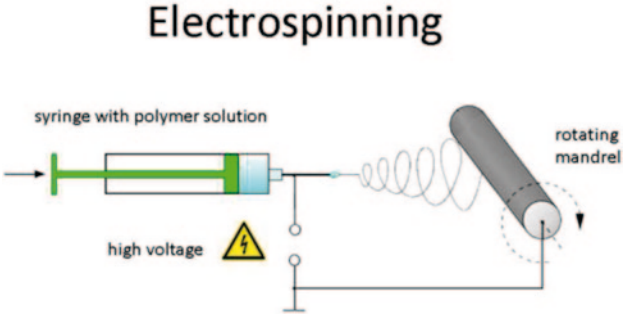

Fig. 2 Schematic diagram of the electrospinning device. In an electromagnetic field created by a high voltage supply, polymers in volatile solvents are caused to elongate and splay into fibers. The fibers adhere to the grounded surface of a cylindric mandrel

Biomimetic grafts recellularized in vivo

It has been shown that nanofibrous meshes promote cell adhesion, proliferation, and differentiation because their architecture is very similar to the natural extracellular matrix ([49], Fig. 2). Applied in vivo without a preseeding procedure (in situ tissue engineering), these scaffolds induce cell population and subsequent remodeling after implantation [50–52].

Electrospinning is a frequently used technique to fabricate nano- or microfibrous scaffolds for tissue-engineering applications [53–56]. The principle of this fabrication technique is very simple. In an electromagnetic field created by a high voltage supply, polymers in volatile solvents are caused to elongate and splay into fibers. The fibers adhere to the grounded surface of a cylindric mandrel (Fig. 3). By varying the fabrication parameters, grafts with different fiber diameter, pore size, and porosity can be manufactured [57]. Natural (collagen, elastin) and synthetic polymers (polylactid acid, polyglycol acid, and polydioxanon, polyurethane) have been used as candidate materials for the creation of electrospun matrices. To improve the desired biomechanical properties of the grafts, single polymers are often blended to create hybrid materials [58].

Orientated to mimic the desirable biomechanical properties of decellularized conduits we developed electrospun conduits which reveal adequate porosity for increased cell migration and match the compliance of the host vessel without biomechanical impairment

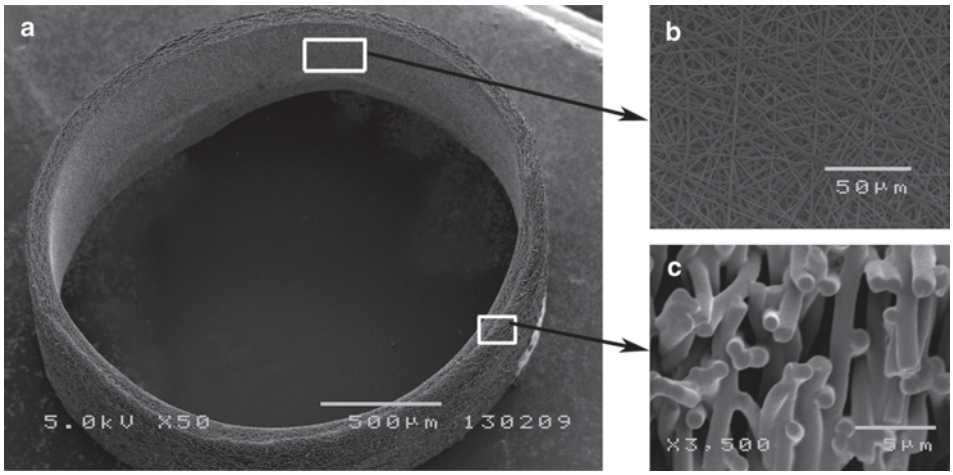

Fig. 3 Scanning electron microscope (SEM) micrograph of an electrospun small-diameter graft with 1.5 mm inner diameter. Gross appearance (**a**), random orientation of nano- and micro fibers on the luminal surface (**b**), and cross section of the electrospun fibrous graft wall (**c**)

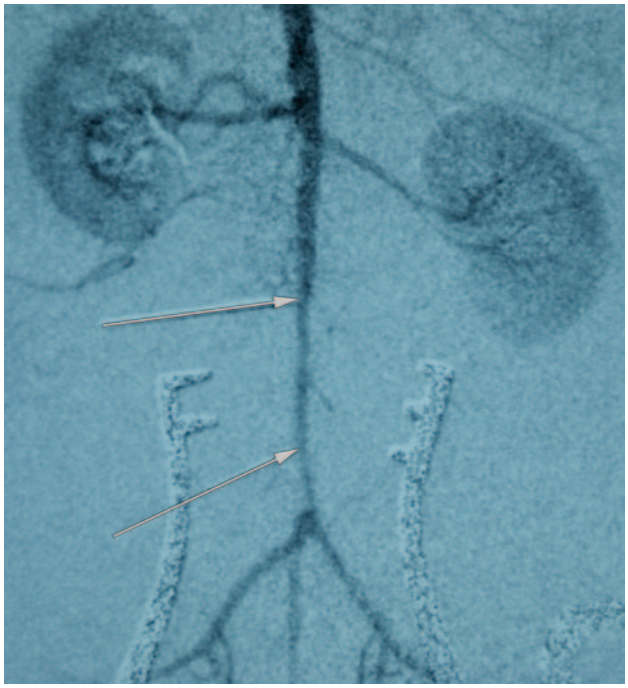

Fig. 4 Angiography of an electrospun small-diameter graft after 12 months of implantation. The proximal and distal anastomoses are marked by *arrows*

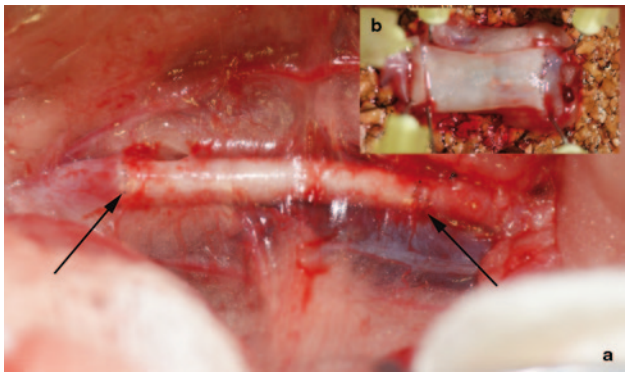

Fig. 5 Representative biodegradable, electrospun graft in situ after 12 months of implantation. Prosthesis shows no signs of aneurysmatic dilatation (**a**). The luminal surface is free of clots (**b**)

[59, 60]. New synthesized biodegradable thermoplastic elastomers revealed excellent biocompatibility data in vitro and showed good surgical handling characteristics [61]. We found in long-term applications of degradable polyurethane grafts in small animal models, high patency rates and graft remodeling without aneurysmatic failure (Fig. 4 and 5). Scaffolds revealed a very low inflammatory potential and showed good tissue integration ([62], Fig. 6).

Our future strategies will focus on further graft improvement concerning biomechanical features and on the creation of polymers with tailored degradation properties for every individual patient to lower the risk of insufficient remodeling.

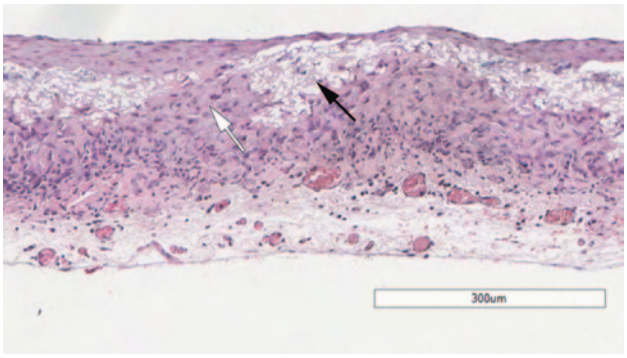

Fig. 6 Representative histology (hematoxylin and eosin (H&E) staining) of a biodegradable prosthesis 12 months after implantation in a rat model. The remodeled graft area is marked by a *white arrow* and the residual graft area by a *black arrow*

Conclusion and challenges to solve in the future

Significant advances have been made over the past decades in the development of tissue-engineered conduits. Due to a paradigm shift in vascular tissue engineering, biological approaches are favored at present. Biomechanical weakness, one of the major limitations of biologically based grafts has been resolved and two tissue-engineered grafts are currently under further investigation for clinical application. However, regulatory pathways have to be defined for biologically derived products such as autologous or allogeneic tissue grafts to comply with safety issues and guarantee consistent product quality. Furthermore, patient waiting times limit the application of autologous approaches to elective surgical procedures. Intense efforts are currently underway to create biocompatible polymers with adequate biomechanical properties, low inflammatory potential, and the potential of cell attraction to provide for a sufficient ready-to-use graft. Therefore, research on appropriate synthetic scaffolds for in situ tissue engineering will still have its qualification in future.

Conflict of interest

Helga Bergmeister, Magdalena Strobl, Christian Grasl, Robert Liska, and Heinrich Schima declare that they have no conflict of interest.

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