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Tissue Engineering of Blood Vessels: Functional Requirements, Progress, and Future Challenges

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Abstract

Vascular disease results in the decreased utility and decreased availability of autologus vascular tissue for small diameter (< 6 mm) vessel replacements. While synthetic polymer alternatives to date have failed to meet the performance of autogenous conduits, tissue-engineered replacement vessels represent an ideal solution to this clinical problem. Ongoing progress requires combined approaches from biomaterials science, cell biology, and translational medicine to develop feasible solutions with the requisite mechanical support, a non-fouling surface for blood flow, and tissue regeneration. Over the past two decades interest in blood vessel tissue engineering has soared on a global scale, resulting in the first clinical implants of multiple technologies, steady progress with several other systems, and critical lessons-learned. This review will highlight the current inadequacies of autologus and synthetic grafts, the engineering requirements for implantation of tissue-engineered grafts, and the current status of tissue-engineered blood vessel research.

Keywords

Vascular Tissue Engineering; mechanical requirements of blood vessels; biological requirements of blood vessels; stems cells; blood vessels; cardiovascular disease

Introduction

Cardiovascular disease (CVD) affects over 71 million people in the United States of America alone and costs exceed 500 billion dollars annually. Specific to cardiovascular disease in America, the number of annual inpatient visits totaled over 7 million with over 450,000 in-patient bypass surgeries, caused in part by diet and inherited factors [1]. Despite improvements in the medical therapy of CVD, the number of vascular interventions, including bypass grafting and angioplasty with or without stenting has increased in recent years. Vascular bypass grafting and balloon angioplasty with stent placement account for a large number of procedures and are more prevalent in patients over the age of 65 years, who are less likely to have sufficient vein for use as a conduit for revascularization [2, 3]. Although autogenous veins or arteries provide the best patency rates for cardiac and

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peripheral vascular bypass grafting, many patients do not have suitable vessels, and autograft suitability may be difficult to define in advance of the bypass operation.

The replacement of large diameter vessels (>6 mm), such as the aorta, has been performed successfully with synthetic polymer prosthetics with long-term patency. However, most blood vessels within the peripheral, cerebral and cardiac vasculature display diameters of less than 6 mm. Several studies have shown that smalldiameter synthetic polymer grafts have rapid thrombus formation and intimal hyperplasia subsequent to bypass surgery, limiting their utility [3–5]. These acute and chronic phenomena were localized not only to the regions of graft anastomoses but also to the mid-graft region and these findings may also extend to larger diameter grafts [6, 7]. Synthetic vascular grafts also present a continued risk of bacterial colonization and subsequent graft infection and, in addition, are capable of promoting a low-level, chronic inflammatory response that may contribute to the development of neointimal hyperplasia. Mechanically, the compliance mismatch between a prosthetic graft (0.5–1.5%/100 mmHg) and the host artery (5–15%/100 mmHg) may also lead to neointimal hyperplasia and late graft failure. Finally, the inability of synthetic grafts to grow and adapt decreases the utility of prosthetic grafts in pediatric patients.

Motivated by these limitations, the development of a tissue-engineered blood vessel (TEBV) has progressed significantly over the past two decades. In concept, the TEBV will closely match the biomechanical aspects of healthy artery and be capable of growth, remodeling, and vasoactive responses. An endothelial cell (EC) layer will provide anti-platelet, anti-coagulant and pro-fibrinolytic properties that would decrease thrombogenesis and restenosis [8].

Functional requirements in blood vessel tissue engineering

Requirements for TEBV design may be conceptually divided into the linked areas of mechanical and biological performance. Biological-mechanical interconnectivity is often desirable, such as the contractile responses achieved with some TEBV [9], or an observed increase in compliance, from 2 to 9 %/100 mmHg, after 6 months in vivo remodeling [10]. However, maladaptive biological responses leading to premature biodegradation and mechanical failure are a common consideration for all degradable-scaffold grafts.

Mechanical requirements

International standards for Dacron and ePTFE prostheses provide a foundation for these requirements, although the complexity of tissue-engineering requires developers to look much further [11]. Mechanical considerations include burst pressure, fatigue-resistance, suture retention, kinking radius, and compliance. Designers must also consider homogeneity over the length of the prosthesis, which may be tens of centimeters [12], variations as the implant remodels, and lot-to-lot variability inherent to cell-based products. Despite broad and prolonged interest in this area, standardized mechanical targets and protocols are still evolving [13].

Testing of burst pressure and mechanical resistance to catastrophic rupture/ tearing of the vascular prosthesis is required to ensure the graft can withstand physiologic variations in pressure. For example, the average pressure in the arterial circulation close to the heart is 100 mmHg, but in the femoral or popliteal artery, while standing, is about 250 mmHg, owing to the contribution of hydrostatic pressure. Conversely, pressures in the cerebral vasculature are generally lower; 60–100 mmHg [14]. However, a significantly challenging vessel to replace is the common carotid. This is due not only to high flowrates (approximating 200mL/min) but turbulent and recirculating flows at the internal/external carotid bifurcation and carotid sinus [14–17]. Thus there is still much debate as to the best

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approach to treat carotid atherosclerotic disease; stenting, endarterectomy, with or without a patch material or bypass grafting [18–21]. High burst pressures are clearly desirable. However, whether TEBV must match native vein, artery, or simply be at a level above maximum physiologic pressure remains debated. In pigs, investigators have suggested that TEBV with burst pressures as low as 600–700 mm Hg can be implanted in the arterial circulation without observed dilatation [22]. Typical burst pressure testing involves the steady inflation of a blood vessel/ tissue engineered construct to a pressure at which the construct starts to rupture. Porous constructs are tested by inflating either a flexible elastomer, with a stiffness negligible to that of the material being tested, in the tubular construct, or sealing the pores of the construct with a material of negligible mechanical strength. Burst pressures are measured with systems that apply increasing internal pressure loads, and record outer diameter and internal pressure. Specimens are typically maintained in physiologic buffer (37°C PBS) during testing. Of particular note is the inflation rate to bursting of tissue engineered constructs: typical inflation rates that compensate for potential creep and stress relaxation of materials in a physiologic setting have been established to be around 0.2 mL/s [23]. However, faster inflation rates have been shown to drastically increase the expected burst pressure, as the material rapidly inflates with little to no deformation. Further, it is important for grafts to remain fatigue resistant, ensuring their structural components and mechanical properties do not alter with repeated cycling in a pulsatile flow setting [24, 25]. Notably, extrapolation of burst pressure from the ultimate tensile stress of flat strips or ring specimens may over-estimate direct burst pressure measurements [13]. Interestingly, for specific TEBV systems non-invasive prediction of burst pressure from stiffness measurements at low pressures has been demonstrated [26]. Typical burst pressures of native vasculature and synthetic alternatives are shown in Table 1.

Compliance and fatigue may be evaluated with similar test fixtures. Compliance is calculated from the percent change in internal radius over a physiologic range of pressure (80–120 mmHg) and is often expressed in units of %/100 mmHg. The pressurized inner radius must often be calculated from images of the pressurized outer diameter, the inner diameter at rest, and the assumption of incompressibility of the graft wall. Typical compliances are dependent on the locale of the vessel, arterial or venous or synthetic, detailed in Table 1 [2, 27–30]. Similar to burst pressure, the mechanical response of constructs is dependant on the rate at which scaffold inflation is performed due to time-dependant phenomena such as stress relaxation [23, 31, 32]. Further, it is critical to evaluate the compliance of tissue constructs in physiologically relevant conditions that simulate the native environment: flowrates, flow medium, pulsatile flow, pressure gradients and temperature. The reader is directed to the following references for further vessel specific mechanical properties [2, 27–30]. Fatigue testing may consist of sustained static, cyclic, or stepwise pressures profiles, followed by an assessment of the burst pressure or compliance to monitor any change from initial strength. Although the importance of short-term fatigue tests is clear, when significant biodegradation and remodeling is anticipated the predictive value of long-term in vitro fatigue tests may be limited.

Suture retention strength is measured by placing a suture 2 mm from the end of a vessel specimen and measuring the force required to dislodge the suture in a physiologically relevant condition and rate: 1 mm/s, 37°C [11]. Typical suture retention strengths of native vasculature range widely depending on vessel type (Table 1) [30, 31, 33–36].

Biological requirements

Biological failure occurs due to different modes depending on whether it occurs acutely, over the first weeks/months, or longer-term over months to years. The acute response is usually characterized by blood material interactions that lead to non-specific protein

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adsorption and subsequent blood clotting or thrombosis on the graft luminal surface. The chronic response to vascular graft implantation is determined in part by the remodeling of the implant, as pannus tissue grows in from the anastamotic regions or transmurally, and long term material interactions with the host, such as biodegradation and scar tissue formation [51–53].

Of note is the small population of patients that have infection during implantation (eg.*Staphylococcus epidermidis*) which typically populates the anastamotic regions of a graft and is estimated to be as high as 1–6% [54].

The generation of a luminal layer that prevents non-specific protein adsorption and a subsequent immune response is a significant problem that has challenged the field till present, especially with the current synthetic standard of care which uses hydrophobic materials that present surfaces that are entropically more favorable for blood protein adsorption than hydrophilic surfaces. However, to circumvent the potential for thrombus formation, novel biomaterials strive to combine hydrophilicity and resistance to protein adsorption through surface modifications or the use of a luminal layer of endothelial cells. A quiescent EC layer has been shown to be vital to promoting an (i) anti-platelet, (ii) anti-coagulant and (iii)pro-fibrinolytic surface [55–60]. Conversely, occlusion due to activation of the present or neo-endothelial cells is of major concern [5, 60–63].

Biochemical and chemical modifications, including homing of cells using CD34 antibody conjugated to graft surfaces, stromal derived factor-1 (SDF-1) an inducer of endothelial progenitor cell migration from the bone marrow, and plasma treatment of surfaces facilitate neo-endothelialization of vascular grafts. Although the source of the repopulating EC is still debated (bone marrow endothelial progenitor cells/circulating progenitor cells/ECs from the nascent vasculature), endothelial cells play a pivotal role in the biocompatibility of blood-contacting materials. Moreover, the former strategies of creating a homing-like environment for cell adhesion and localization is preferred for an “off-the-shelf” product that does not require pre-seeding with ECs that often have limited proliferative potential due to the age of the patient and the time required for EC isolation, culture, seeding and preconditioning to ensure seeded cells do not slough off in a hemodynamic environment [64, 65]. Recent canine and baboon studies have suggested that immediate recapitulation of the EC layer in vitro or soon after in vivo implantation may not be required for short term (6month) graft performance [44], but is still thought to be essential for long term graft survival [66–68].

Smooth muscle cells (SMC) represent another important cellular component of the vascular wall. In normal pulsatile blood flow, the SMC layer contributes to the vascular tone and medial compliance of the vessel. However, in a variety of specific disease states, they are indicated in the progression of atherosclerosis through myointimal hyperplasia [69]. Although much work has focused on the use of luminal EC seeded grafts, SMC seeded grafts have shown the potential for improved host integration, increased medial contractility, and medial cellularization [70]. Additionally, several groups have shown the importance of SMC to aid in the development of the vascular media which is essential for biomechanical function of the vessel. Specifically, they have shown SMC secretion and rearrangement of the matrix into helical or circumferential orientations, more closely mimicking native structure [9, 71, 72]. Similar to the need to maintain a quiescent state for endothelial cells, the phenotypic expression of smooth muscle cells is critical to recapitulation of medial function. When SMCs are expanded in culture prior to seeding, they frequently adopt a non-contractile, proliferative, synthetic phenotype due to the loss of actin filaments [73, 74]. Development of a contractile SMC phenotype depends on a milieu of factors including local stress/strains, growth factors, and paracrine/ autocrine signaling [75, 76]. Correct phenotype is essential in preventing medial thickening and intimal hyperplasia from proliferative

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SMCs. The reader is referred to a review by Chan-Park et al for more details [77]. A variety of other cell types, both native and non-native to vasculature have been used for repopulation of tissue engineering vascular grafts. Of note, work with stem cells, including endothelial progenitor cells and mesenchymal stem cells, umbilical cord cells and peritoneal cells is discussed in detail herein.

Mediation of the immune response due to surgical trauma and foreign body reaction is critical to graft performance. Several groups have attempted to create functional tissue replacements that serve to passively prevent acute and chronic rejection. This has been done through the incorporation of bioactive materials, tailoring of degradation of biodegradable polymers to leach minimally cytotoxic degradation products, and incorporation of biomimetic moieties, such as collagen, elastin, and glycosaminoglycans [2, 3, 78–84]. However, there has been a recent trend to actively modulate the inflammatory response of tissue replacements by incorporation of moieties that strive to curtail adverse inflammatory responses such as neutrophil invasion, macrophage polarization and modulation of the adaptive immune response, notwithstanding the use of immunocompromised animal models [85–87]. Further, recent studies have demonstrated the importance of ensuring that the local environment of the graft is maintained to be non-inflammatory. Specific to macrophage polarization, Ariganello and colleagues have shown the utility of decellularized matrices to direct macrophage polarization to a non-inflammatory phenotype that would promote healing and resolution, instead of inflammation [88, 89]. The incorporation of bone marrow mesenchymal stem cells (BM-MSCs) within tissue engineered and biodegradable scaffolds has been widely reported. Specific to vascular grafts, bone marrow derived stem cells have been shown to differentiate into endothelial progenitor like-cells [90–93], as well as other vascular wall cellular constituents, smooth muscle cells [94, 95]. In addition to repopulating ECM-based scaffolds, MSC have also been shown to attenuate the inflammatory and immune responses associated with surgical trauma and implants. MSC have the ability to direct macrophage polarization toward an M2 phenotype (healing/ resolution) over an M1 phenotype (inflammatory), down-regulate MHC and co-stimulatory molecule expression, decrease inflammatory cytokine expression (TNF-α, IL-12, IFN-γ), increase anti-inflammatory cytokine expression (IL-10), promote T-regulatory cell proliferation and interfere with lymphocyte replication [96–101].

In vitro tests for TEBV include standard biocompatibility assays and, depending upon the design concept, may extend to consideration of cell supportive properties, hemocompatibility, and vasoactivity. Cytocompatibility is usually established with seeding of human EC, SMC and fibroblasts. To simulate features of the innate immune response, groups have used bio-similar environments with the addition of secretion products from inflammatory cells, such as macrophages and neutrophils, to simulate degradation in vivo and in vitro [5, 29, 53, 102–104]. In vitro hemocompatibility is typically determined with the use of whole blood clotting times, platelet adhesion and morphology, and activation states of inflammatory cells on vascular biomaterials in a variety of systems: static clotting time / platelet adhesion and morphology assays, flow loops and AV shunt models, preceding in vivo implants [5, 30, 105–108].

In vivo studies typically commence in rodents. Despite small vessels (< 1 mm), murine systems provide the potential to test constructs with human cells in nude [109] or severe combined immunodeficiency (SCID) mice [110]. Mouse models have been developed to incorporate intravital molecular imaging to track labeled cells and protease activity [109]. Rat models allow the assessment of human-cell constructs in (immune compromised) athymic animals [33], using slightly larger 1–2 mm inner diameter test vessels. A recent review highlights pitfalls to anticipate as investigators proceed to large animal models [12].

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Evolving concepts and current status of TEBV technology

Collagen and other biopolymers

Traditional "cell-plus-scaffold" tissue engineering was first applied to blood vessel constructs by Weinberg and Bell in 1986 [111]. Employing a collagen gel cultured with SMC and EC, they observed a near-confluent and biologically active EC luminal surface. However, maximum burst pressures in the range of 400 mmHg necessitated the additional support of a Dacron mesh. Several other studies have used collagen or other biologically derived blood vessel constituents to recapitulate the features of a blood vessel in scaffolds, with limited success, given the weak nature of collagen gels [7, 112, 113]. Strategies incorporating cells, matrix components and intracellular biomolecules have been shown to improve the mechanical strength of collagen-based constructs by compaction and re-organization of collagen fibril architecture [114–118]. In particular, Seliktar et al. have demonstrated the ability of seeded cells and mechanical conditioning to rearrange collagen fibrils circumferentially, leading to increased strength [119]. Our research group has observed high burst pressures using a biomaterial composite consisting of crosslinked, oriented collagen microfibers reinforcing a matrix comprised of a recombinant elastin analogue [82].

Fibrin is of interest as an alternative biopolymer scaffold due to advantages including its natural role in wound healing, widespread clinical acceptance as a tissue sealant and the potential for generating an autologous biomaterial from the patients' own blood [120]. Cummings et al. found that while fibrin vascular constructs were weaker and more extensible than collagen, fibrin-collagen composites displayed higher strength and gel compaction than collagen alone [121]. Fibrin gels have also been shown to stimulate SMC to synthesize elastin, an important component of the artery wall, which is neglected in many collagen-based TEBV [122]. Short segments (1.5 – 2.0 cm) of TEBV from fibrin cultured with either bone-marrow derived progenitor cells or SMC and seeded with EC demonstrated vasoactivity and have been implanted as interpositional grafts in the lamb external jugular vein [123, 124]. Recently, a bioreactor design capable of simultaneously processing six TEBV from fibrin with human dermal fibroblasts resulted in burst pressures of 1400 – 1600 mmHg after 5 to 7 weeks of culture [26]. The resulting compliance was 2–5 %/ mmHg and low suture retention strengths were compensated by the addition of polymeric cuffs from poly(lactic acid). Fibrin-based approaches have also been augmented through the addition of growth factors via sustained delivery systems in order to enhance and sustain cellular in-growth [125].

Biodegradable and bioresorbable synthetic polymers

In addition to biopolymers, biodegradable synthetic polymer scaffolds, such as polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone (PCL), polyurethanes (PU), and related copolymers or composites have been extensively studied [9, 72, 126–131]. Typically these scaffolds are pre-seeded with cells using a variety of techniques, including static seeding, dynamic seeding, vacuum aided seeding, or electrostatic seeding and conditioned in a bioreactor to ensure the cells can withstand physiologic blood flow [132–134]. In a well-studied example of the biodegradable polymer approach, Niklason and colleagues have fabricated TEBV using PGA seeded with SMC and cultured at 1–2% cyclic mechanical strain in a bioreactor for 7 to 8 weeks, followed by EC seeding [9]. In collaboration with Humacyte, Inc, this group has developed TEBV scaffolds generated from PGA seeded with allogeneic SMCs, conditioned in a bioreactor, and subsequently decellularized. Acellular specimens were studied in a baboon AV shunt model, and scaffolds with a luminal EC coating were investigated in a canine peripheral and coronary bypass. A potential disadvantage of this strategy is the relatively low levels of endothelialization (14±8%) [44].

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Further, in a challenging model of porcine carotid grafting, they showed that decellularized, engineered grafts resisted both thrombosis and intimal hyperplasia. Head-to-head comparisons with autologous vein grafts showed that decellularized, engineered grafts had less neointima formation and superior patency rates after 30 days. The etiology of this advantage may be related to decreased activation of the mTOR pathway in engineered grafts as compared to vein, though this result remains to be confirmed in other studies *(personal communication)*.

With respect to the proliferative capacity of the cells used in tissue engineered constructs, aging is associated with decreasing telomere length and directly related to decreased doubling capacity. To overcome this limitation, Poh et al. have demonstrated an increase in the population doublings of adult VSMCs through retroviral infection with the telomerase reverse transcriptase subunit (hTERT) [64]. Despite improvement, mechanical strength remained too low, potentially due to reduced collagen synthesis [135, 136]. To circumvent the challenges of SMCs, human mesenchymal stem cells (MSC) were used in an 8 week protocol involving proliferation and differentiation phases [80]. Collagen matrix synthesis and substantial conversion to an SMC phenotype were demonstrated, but burst pressures remained at approximately 400 mmHg. These biodegradable systems have confirmed that: (i) non-degraded polymer fragments can amplify stresses and dramatically compromise strength; (ii) collagen organization, as well as quantity, is required for strength; (iii) low compliance may be due to the absence of organized extracellular elastin sheets, as well as sub-physiologic SMC contractility [137, 138].

The vascular tissue engineering system developed by Shin'oka and colleagues uses similar biodegradable polymers. Employing porous ε-caprolactone and L-lactide copolymer reinforced with a PGA fabric, seeded with cultured autologous venous cells, they reported the first clinically effective TEBV implants [139]. By substituting autologous bone-marrow mononuclear cells (BMC), the cell culture step was avoided in subsequent implants [131]. Given the cost, delay, contamination potential, as well as dependence on xenogenic serums in culture medium, avoidance of prolonged in vitro culture represented a significant advantage. Notably, in these reports the TEBV implants repaired congenital defects in the pulmonary circulation of a pediatric population, while most TEBV applications must address more demanding mechanics of the arterial circulation, as well as the limitations of autologous cells obtained from elderly donors. Early efforts to adapt the technology to arterial implants have been reported [140]. Despite initial suggestions that BMCs differentiate and proliferate as the TEBV is incorporated [131, 141], recent analysis in SCID/beige mice found no evidence that the implanted cells persist longer than about one week [86]. BMCs appear to accelerate in vivo remodeling by paracrine recruitment of host monocytes. The authors also suggest that, in turn, accelerated monocyte infiltration triggered enhanced repopulation by host SMC and EC. Regardless of technique employed, the persistence of seeded cells and the ability to withstand hemodynamic forces (shear in the lumen or compressive in the vascular wall), remaining a desired phenotype, or differentiation along specific lineages (for stem cells), and maintainence of viable cytokine/chemokine expression, is critical to graft success [85, 134, 142].

Bioresorbable vascular grafts are incorporated into the recipient through host mediated degradation systems that include as enzymoloysis, oxidation and hydrolysis, while allowing for concomitant repopulation of the scaffold with native cells. Wolfe et al have shown that bioresorbable electrospun polydioxane (PDO) or PCL scaffolds elicited varying tissue factor expression when exposed to monocytes; demonstrating no greater risk of thrombotic occlusion than ePTFE [143]. Other groups have used a variety of bioresorbable polymeric constructs showing mechanical and biological utility [2, 144–146]. Campbell et al have developed an interesting technique wherein the host's peritoneal cavity is used as a

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bioreactor to construct hierarchical tissue. They implanted silastic tubing in the peritoneal cavity of rats and rabbits for 2 weeks, which resulted in scaffolds that had developed layers of ECM, and were populated with myofibroblasts and mesothelium. 10–20 mm long grafts were subsequently implanted in the host animal, with greater than 4month patency. Their technique has been extended to the development of a variety of soft tissues including vas deferens, bladder and uterus [147, 148]. Vito's group have developed a method for the in vivo or ex vivo stretching of arterial segments in suitable media conditions for generation of blood vessels. They have studied several aspects of the biomechanical regimes that effect remodeling and growth of vessels [149–152]. These studies were further carried into collagen based gels which have been seeded with cells and show morphological changes in ultrastructure and cellular behavior as a function of mechanical conditioning [119].

Cell-sheet tissue engineering

TEBV fabricated from cell sheet-based tissue engineering consist entirely of autologous cells and secreted matrix proteins. Initially, sheet-based TEBV consisted of SMC or fibroblasts cultured with ascorbic acid for approximately 30 days to form cohesive sheets [8]. The SMC sheet was wrapped about a tubular support to create the vessel media, matured for one week, wrapped with a fibroblast-sheet "adventitia," matured for 7 weeks, and then seeded with EC. This process was replaced with a scheme consisting of a decellularized internal membrane fabricated from a fibroblast sheet, a living adventitial layer, and a seeded endothelial layer, requiring a total of 28 weeks of culture [33]. This design demonstrated favorable mechanics for implantation in the arterial circulation, and these TEBV have been successfully implanted as arteriovenous fistulas in high-risk patients [153]. This groundbreaking progress with a sheet-based tissue engineering system has been encouraging, although long culture times remain an important factor in keeping costs high and limiting application to non-urgent indications. Similar work has been done by other groups that have developed rolling techniques with localized regions of specific cells types or synthetic/biosynthetic materials such as PLLA, collagen and elastin [82, 85, 154].

Decellularized tissue scaffolds

This technique maintains the native extracellular matrix proteins that provide both structural integrity and instructive cues for cellular ingrowth. By incubating bone marrow derived cells in decellularized canine carotid arteries, Cho et al. demonstrated cellular incorporation into the scaffold and subsequent differentiation of these cells into endothelial and vascular smooth muscle cells and subsequently into 3 distinct vessel layers [94]. Zhou et al have shown that heparin and VEGF modified decellularized canine carotids grafts have higher 6 month patency rates than unmodified grafts [155]. In a similar study, Zhou et al showed that heparin immobilized on decellularized grafts implanted in rats supplemented with 14days of granulocyte-colony stimulating factor, had higher patency and lower neointima formation compared to controls; due to homing of circulating EPCs to the graft surface, demonstrating the potential for cytokine treatment post surgical intervention [156]. Further, potential changes in the long term mechanical response associated with decellularization protocols, specifically the shape of the pressure-diameter curves, and how they relate to compliance is of concern [157]. Other decellularized tubular conduits have been investigated for vascular tissue engineering. Specifically, aorta [158, 159], umbilical arteries [4], saphenous vein [46], ureter [160, 161], and small intestinal submucosa (SIS) [162, 163] to name a few. Cryolife, Inc, have constructed a vascular graft from decellularized bovine tissue that shows high patency in a canine model, with host cell repopulation of the prosthesis [164]. From the same company, Synergraft®, decellularized bovine ureter, has shown the potential to be used in humans as a blood vessel replacement. However, early results show the potential for aneurysm formation [165], poor long term patency as hemodialysis access shunts, (14% at

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1year) [166], similar to ePTFE access grafts [167]; and infection and inflammation due to potential residual xenoantigen [168].

Translational challenges

At present, TEBV use in humans has required at least a bone marrow aspiration and brief cell seeding for pediatric pulmonary artery replacement and up to 28 weeks of maturation of rolled fibroblast sheets to withstand arterial pressures for use as arteriovenous conduits in patients requiring dialysis. Advanced cell or biomaterial technologies may drive the next generation of solutions. In particular, the recent recognition that BMC are likely to survive only transiently and cellular repopulation is driven by monocyte infiltration may suggest new cell and biomaterial strategies for TEBV researchers [86]. In addition, early results translating biodegradable polymer scaffold systems to the arterial circulation in mice suggest that protocols requiring as little as 1 week maturation in culture may be attainable [140].

Research timeline, regulatory, and economic issues

McAllister et al. have argued that the unique challenges inherent to translating cell-based therapies, including tissue-engineering, will benefit from the application of several distinct strategies [169]. In particular, the authors note that researchers should include an early focus on proof-of-principle with human cells and anticipate an extended (20 year) R&D timeline. A focus on modeling the cost-effectiveness of the technology is emphasized, but not until later in this timeline, as clinical trials are planned. Regulatory approval pathways for tissue-engineered products are still evolving, and the cost of quality assurance is expected to be a challenge given the small lot sizes of tissue-engineered products [170].

Summary and future directions

Small diameter arteries in the human body are prone to atherosclerosis depending on vessel location, size, hydrodynamic considerations, concomitant disease and a milieu of environmental and genetic factors. Peripheral artery disease is commonly treated with 3 main techniques when the patient does not respond to medication and exercise: (i) angioplasty and stenting, (ii) endarterectomy, and (iii) bypasss/interposition grafting.

The design of a tissue engineered vascular graft to supplant the diseased arteries' function requires consideration of mechanical, biological and clinical factors that influence behavior in vitro and in vivo. To date, tissue engineered products have yet to replace the current "gold standard" of an autologous artery or vein. Much progress has been made in determining the key factors that contribute to the eventual success of a vessel graft. Mechanical considerations include (i) a sufficient burst pressure to prevent catastrophic failure of the vessel and long-term fatigue resistance, (ii) a suitable compliance that approximates that of the vessel to prevent mechanical mismatch, and (iii) a strong enough suture retention strength to permit implantation and tolerate hydrodynamic and mechanical forces at the anastomosis. Biological and clinical considerations include (i) generation of a non-fouling luminal surface to prevent from thrombosis, (ii) mediation of the immune response due to surgical trauma and potential graft rejection and regeneration, and (iii) evaluation in an in vivo environment.

Several groups have demonstrated the efficacies of various strategies that range from modifications of existing ePTFE/Dacron™ grafts to acellular/cellularized constructs to de novo engineering of tissue substitutes that mimic native vessels. TEBV derived from cell-sheet tissue engineering and degradable synthetic polymer scaffolding have demonstrated early clinical success and continued progress with several additional systems suggests that these technologies will continue to evolve. Clinical success will be determined by utilizing a

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"bottom-up" approach wherein recapitulation of the fundamental features of the vascular wall, incorporation of key elements that obviate thrombosis and acute graft failure, and potentially a cellular component that will direct the unavoidable inflammatory response towards healing, will be critical to the design of regenerative therapies for vascular tissue engineering.

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Table 1

Mechanical properties of common blood vessels and current synthetic replacements. Ranges represent average values from cited studies.

	Compliance (%/100 mmHg)	Suture Retention Strength (grams-Force)	Burst Pressure (mmHg)
	Coronary: 8.0–17.0 [37, 38],		
	Carotid: 5.0–14.7 [39, 40],		
	Femoral: 6.0–14.1 [41, 42],		
	Popliteal: 4.7–8.5 [41],		2200–4225 [43, 44]
Artery	Internal thoracic artery:6.5–12.0 [13, 43]	88–200 [13, 33]	
	Saphenous: 0.7–2.6 [33, 39, 43],		1600–2500 [33, 43, 44, 46]
Vein	Umbilical: 1.5–3.7 [39, 45]	180–250 [33, 44, 46]	
	PTFE: 0.2–0.9 [39, 47],		
Synthetic grafts	Dacron: 0.76–1.9 [39, 47]	250–1200 [48, 49]	2580–8270 [50]