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Tissue-Engineered Extracellular Matrices (ECMs) as Adjuvant Scaffolds for Endovascular Aneurysmal Repair (EVAR)

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1. Introduction

Abdominal aortic aneurysms (AAA) are permanent, irreversible, localised dilatations of the aorta. Usually, they develop as a result of a progressive localised weakness within the vessel wall. They typically occur below the level of the renal arteries and have a high propensity for rupture. In fact, ruptured AAAs account for approximately 8,000 and 15,000 deaths in the United Kingdom (UK) and United States of America (USA) respectively on an annual basis (Sakalihasan et al. 2005, Thompson 2003, Vorp and Vande Geest 2005). Risk factors for their development include male gender, age >65 and a history of smoking. Other associated risk factors are connective tissue disorders that typically have a genetic predisposition, syphilitic infections and cystic medial necrosis.

Currently, there are two surgical treatments for AAA; the traditional open repair and a minimally invasive procedure known as endovascular aneurysm repair (EVAR) (Kamineni and Heuser 2004, Parodi et al. 1991, Sakalihasan et al. 2005). The endovascular technique has been widely applied in clinical practice, however important limitations persist (Egelhoff et al. 1999, Kamineni and Heuser 2004, Parodi et al. 1991). Among these limitations are device migration, endoleaks, and thrombotic occlusion. It has been suggested that tissue-engineered xenografts may play a role for preventing these complications in EVAR. In the present chapter we discuss limitations of stent-grafts deployed in the EVAR procedure. We place particular emphasis on tissue-engineered extracellular matrices (ECMs) as adjuvant scaffolds for optimisation of the EVAR procedure.

2. Aetiology of aneurysms

The arterial wall is primarily composed of 3 layers (or tunicae) that surround the luminal cavity as illustrated in Fig. 1. The inner layer (or tunica intima) consists of a monolayer of endothelial cells. A thin membrane known as the elastica interna separates the tunica intima from the tunica media and the tunica media itself consists of concentric layers of smooth muscle cells interwoven between networks of connective tissue. The tunica media is separated from the outer tunica adventitia by the elastica externa and adventitial

constituents include collagen and interspersed fibroblasts. Elastin is the predominant tissue within the aorta and it functions as the principal load bearing element of the aortic wall. During aneurysm formation degradation of elastin occurs along the walls of the aorta (Raghavan et al. 2005). It is widely believed that degradation of elastin may promote an inflammatory response within the wall leading to weakened tissue, abnormal remodelling responses and subsequent AAA development.

Fig. 1. Histological structure of arterial wall

Currently, aneurysms are classified relative to their shape and location. Fusiform aneurysms are the most common and they typically occur due to a circumferential weakness along an extended portion of the aorta with the weakened portion appearing as a symmetrical bulge. In contrast saccular aneurysms frequently form on one side of the aorta and are asymmetrical in their nature. Finally, pseudoaneurysms usually occur as a result of trauma to the aortic wall that causes all 3 layers of the vessel to separate.

3. Surgical treatment options for AAA

3.1 Open repair

Currently there are two vascular procedures available for the treatment of AAA; an open procedure and minimally invasive surgery. Open surgery involves a midline incision to gain access to the aneurysmal site. Intraoperatively, the aorta and iliac arteries are exposed and

Fig. 2. Open repair of abdominal aortic aneurysm (AAA)
(<http://www.musc.edu/radiology/interventional/index.htm>)

cross-clamped prior to incising the wall of the AAA. Intraluminal thrombi are removed and a synthetic graft is sutured *in situ* before the aneurysm is closed over the graft as illustrated in Fig. 2. Complications associated with the open method include infection, increased inpatient stay and a predisposition to acute renal failure.

3.2 Minimally invasive approaches

The minimally invasive approach involves the use of a stent graft device as illustrated in Fig 3 and this method is referred to as ‘EndoVascular Aneurysm Repair (EVAR)’. Importantly, EVAR is associated with a significant decrease in mortality and reduced duration of inpatient stay when compared to open repair; however EVAR has additional procedural risks.

Fig. 3. Endovascular aneurysmal (EVAR) repair of AAA
([http:// www.musc.edu/radiology/interventional/index.htm](http://www.musc.edu/radiology/interventional/index.htm))

3.2.1 Complications associated with EVAR

Intraoperative complicatons include vascular injury during initial catheterisation and stent deployment and postoperative complications associated with EVAR include persistent blood flow outside the graft that can result in increased pressure on the aneurysmal sac and a subsequent endoleak. To date, endoleaks have been classified into 5 different subtypes and types 1-5 are illustrated in table. 1

Endoleak Type	Characteristics
1	Occurs at proximal or distal end of the stent-graft where it attaches to vessel wall
2	Precipitated by collateral flow from mesenteric or lumbar arteries
3	Tear in graft fabric and blood leaks between modular components of stent graft
4	Leak occurs through pores within the graft’s fabric
5	Occurs as a result of ‘intra-sac’ pressurisation and is commonly referred to as endotension

Table 1. Endoleaks type 1-5 and their associated clinical features (Greenhalgh and Powell 2008)

Typically, endoleaks that are classified as type 3 or type 4 resolve spontaneously; however endoleaks classified as type 1 or type 2 often require surgical intervention (Greenhalgh and Powell 2008). Treatment options for type 5 remain controversial as surgeons remain divided on advocating immediate surgical repair versus a more conservative surveillance approach (Mennander et al. 2005, Veith et al. 2002).

Migration of the stent-graft following the EVAR procedure is another complication associated with considerable postoperative morbidity. Clinically, migration can be defined as $\geq 5\text{mm}$ of distal movement of the stent-graft from its attachment site. Usually migration can be caused by inadequate attachment of the graft to the proximal neck of the aneurysm or by morphological changes within the neck of the vessel. Postoperative complications include a widening of the aneurysm that may result in decreased radial force exerted by the proximal portion of the stent *in vivo*. Radial force is an important fixation method in stent-grafts without hooks or barbs and widening of the neck inevitably predisposes these devices to migration. Less frequent complications include stenosis or occlusion of the graft or distal vessels.

On account of these complications only 5 stent-grafts with FDA approval are currently available. These are the AneuRx® and Talent® from Medtronic, the Zenith® from Cook, the Gore Excluder® and the Endologix Powerlink® (Endovascular Today, 2009). Their success is also limited by a high incidence of endoleaks and stent migration as illustrated in Table 2. Typically, the majority of stent migration failures occur after one year. A reliable method that prevents these complications from occurring is an attractive option.

Device	Type	Stent Material	Graft Fabric	Stent type	Hooks or Barbs	Documented Endoleak	Documented Migration	Reference
AneuRx	Modular external	Nitinol external	Dacron	Nitinol skeleton	No	Yes	Yes	(Zarins et al. 2001)
Talent	Modular self-expanding internal	Nitinol	Dacron	Multi nitinol stents (Bare)	No	Yes	Yes	(Criado et al. 2003)
Zenith	Modular	Stainless steel	Dacron	Z-stents	Yes	Yes	Yes	(Greenberg 2003)
Gore Excluder	Unitary external tube type and internal	Nitinol	Teflon ePTFE	Spiral shape	No	Yes	Yes	(Bush et al. 2001)
Endologix PowerLink	Unitary Body internal stent type	Cobalt-Chromium Alloy	ePTFE	Single wire Z-shaped	No	Yes	Yes	(Wang et al. 2008)

Table 2. Stent graft devices for EVAR: Their structural properties and associated complications

3.3 Possible method for improvement of EVAR

Previously, investigations for improving the stent-graft design have predominantly focussed on the mechanical aspects of the stent. In general, most of these investigations have failed and a reliable solution remains elusive. Recent investigations (Brown et al. 2006, Schoder et al., 2004, Niyyati et al. 2005, Yavuz et al. 2006) suggest that tissue-engineered extracellular matrix (ECM) scaffolds derived from xenogenic sources may have the potential to overcome limitations that are associated with traditional mechanical solutions.

4. Tissue-engineered Extracellular matrix (ECM) scaffolds

Extracellular matrices (ECMs) are biological scaffolds usually derived from xenogenic sources. They are acellular in nature and induce a host derived tissue-remodelling response after implantation while undergoing simultaneous degradation processes (Davis et al., 2010). Therefore, they may provide an attractive alternative as suitable biomaterials for improving EVAR treatment of AAA. Urinary bladder matrix (UBM) and small intestine submucosa (SIS) are two common ECM scaffolds of porcine origin that have had good clinical outcomes after surgical implantation across numerous subspecialties. These biomaterials are prepared via numerous physical, chemical and enzymatic processes.

Author (Year)	Application	Animal Model	Result
S.F. Badylak (1989)	Large diameter vascular graft	Canine	No thrombus formation and no intimal hyperplasia after 44 weeks. No endothelialisation of the scaffold and greater stiffness within the scaffold compared to artery
D.J. Schultz (2002)	Reparation of enterocutaneous fistula	Human	No data available
S.G. de la Fuente (2002)	Gastric reparation	Rat	Regeneration of gastric mucosa after 3 weeks
M. Chen (2001)	Small intestine	Canine	Tubular failure secondary to obstruction and leakage
M.A. Cobb (1999)	Dura mater substitute	Canine	Complete resorption after 60 days
M. Rosen (2002)	Regeneration of biliary system	Canine	Infiltration with fibroblasts after 2 weeks. Biliary epithelium replaced with native collagen after 3 months.
S.F. Badylak (2001)	Body wall repair	Canine	Preoperative tensile strength achieved after 24 months
T.G. Smith (2002)	Reparation of ureteral defect	Porcine	SIS graft replaced with urothelium and smooth muscle after 9 weeks
B.P. Kropp (1995)	Urinary bladder regeneration	Rat	Urothelium, lamina propria and smooth muscle replaced within 3 weeks

Table 3. Multisystemic applications for SIS and associated remodelling duration after *in vivo* implantation

Extensive experimental evaluation of SIS and UBM materials has been undertaken; examining sterilisation effects, cell interactions, cell growth effects, gene expression, mechanical properties, processing effects, suture retention effects and repeatability issues associated with their clinical applications (Ahn et al. 2007, Cimini et al. 2005, Freytes et al. 2005, Freytes et al. 2008, Gilbert et al. 2006, Hodde et al. 2002, Roeder et al. 1999, Sellaro et al. 2007, Teebken et al. 2000). These characterisation methods have led to a greater understanding of an ECM's biological, structural and mechanical properties. Clinical applications of ECM scaffolds are described in Table 3. Influences such as stent interaction, compliance differences, aortic endothelial cell interactions and flow effects, have not been fully characterised on ECMs using *in vitro* or *in vivo* experimental approaches.

Although UBM has been utilised to a lesser extent compared to SIS, it has been successfully applied for the treatment of dysplastic oesophageal tissue with excellent patency rates during the follow up period (Badylak et al., 2005). In addition, UBM has been applied for effectively treating strictures of the trachea with no evidence of stenosis or tracheomalacia during the follow up period (Gilbert et al. 2008). Finally, UBM has also been effectively applied for reparation of the thoracic wall in a canine model (Gilbert et al. 2007).

4.1 Constituents and preparation of ECMs

The major constituents found within mammalian ECMs are collagen, glycoproteins, glycosaminoglycans (GAGs) and growth factors as illustrated in Table 4. These constituents provide structural, functional, adhesive and stimulatory functions to their surrounding cells enabling them to survive and proliferate (Badylak et al. 2009, Baldwin 1996, Laurie et al. 1989). Naturally, the transition phase of an ECM scaffold from intact mammalian tissue to viable donor xenograft material requires several processing steps. Initially, the native tissue is manually separated from unwanted tissue structures. Tissue decellularisation is achieved through a combination of sonication, agitation, freezing and thawing processes (Badylak et al. 2009). These treatments disrupt the cell membrane and facilitate the removal of intracellular remnants. During the decellularisation process it is of paramount importance to preserve as many mechanical and biological properties of the donor ECM as possible. Disruption of collagen architecture can decrease the mechanical strength of the scaffold, removal of GAGs adversely affect its viscoelastic behaviour and the absence of growth factors will decrease the scaffold's bioinductive properties (Lovekamp et al. 2006). After the xenograft is decellularised it is then sterilised by exposure to irradiation or ethylene oxide (Rosario et al. 2008).

To date, porcine SIS and porcine UBM have been strongly favoured as potential donor scaffolds for many different surgical subspecialties. Their harvesting sites differ; however both have had a considerable degree of success when applied clinically. SIS is harvested from the small intestine and UBM originates from the urinary bladder. Their collagen components also differ to a small extent after decellularisation and sterilisation. The decellularised SIS scaffold is primarily composed of collagen type 1 (Badylak et al. 2009) with smaller amounts of collagen types 3, 4, 5, 6 also present (Badylak SF 1995). In contrast, UBM is rich in collagen types 3, 4 and 7. UBM possess an intact basement membrane which has many characteristics that favour its application to the vasculature. Importantly, a basement membrane may support the growth and differentiation of a confluent endothelial cell layer on the luminal surface of the scaffold. Different characteristics of SIS and UBM are compared in Table 5.

Constituents	Features
Collagen	<ul style="list-style-type: none">• Most abundant protein within ECMs• More than 20 different types have been identified• Provides distinct mechanical and physical properties to the ECM
Laminin	<ul style="list-style-type: none">• Large adhesion glycoprotein• Involved in cell and tissue differentiation• Promotes tissue development and angiogenesis
Fibronectin	<ul style="list-style-type: none">• Extracellular glycoprotein• Promotes host biocompatibility• Induces cell adhesion by binding to membrane-spanning receptor proteins known as integrins
Glycosaminoglycans	<ul style="list-style-type: none">• Mucopolysaccharides• Bind covalently to a protein core to form a proteoglycan molecule• Act as a reservoir when cells stop growth factor production• Enables ECMs to store growth factors that may be used during tissue regeneration
Growth Factors	<ul style="list-style-type: none">• Present in small quantities within ECMs• Naturally occurring substances capable of stimulating cellular growth, proliferation and differentiation

Table 4. Constituents of ECM scaffolds and their associated biological features

Extracellular Matrix	Characteristics
Small Intestinal Submucosa (SIS)	<ul style="list-style-type: none">• Derived from porcine jejunum• Primarily composed of the submucosal layer and the stratum compactum of the tunica mucosa• Mainly consists of type 1 collagen
Urinary Bladder Matrix (UBM)	<ul style="list-style-type: none">• Derived from the porcine urinary bladder• Possesses an intact basement membrane consisting of collagen types 4 and 7

Table 5. Differentiating the characteristics of SIS from UBM

4.2 Immunogenic response after implantation

Theoretically, an implanted ECM should not elicit an immediate or delayed immune response due to its acellular and avascular nature (Allman et al. 2001, Ho et al. 2004, Sandusky et al. 1992). However, we know that elimination of all nuclear materials and cell membrane products is almost impossible despite extensive measures taken during the decellularisation process. Therefore, it is expected that the recipient should mount an immune response against the graft’s cell remnants and arguably, against the intact

xenogenic proteins. This hypothesis has been extensively studied by assessing the host's cell-mediated T-helper 1 (rejection) and T-helper 2 (accommodation) immune responses to implanted xenografts (Strom et al. 1996, Zhai et al. 1999).

Results from preliminary studies on mice are favourable, as the implanted SIS scaffold elicits an immune lymphocytic response that is predominately Th2-like (Allman et al. 2001). The Th-2 pathway stimulates the production of interleukins IL-4, IL-5, IL-6 and IL-10. These interleukins promote graft acceptance and prevent the activation of neighbouring inflammatory macrophages (Bach et al. 1997, Chen and Field 1995). Activation of the Th2 pathway also promotes effective tissue remodelling, structural repair and functional recovery of the injured tissue after graft acceptance (Piterina AV 2009). Undoubtedly, activation of this humoral response is encouraging as activation of the alternate lymphocytic pathway (i.e. Th1) produces an acute inflammatory reaction. Cytokines such as IL-2, interferon (IFN) gamma and tumour necrosis factor (TNF) beta activate neighbouring macrophages and stimulate the differentiation of CD 8+ cells to a cytotoxic phenotype. This host derived inflammatory response ultimately leads to xenogenic graft rejection (Abbas et al. 1996, Matsumiya et al. 1994).

The terminal alpha 1,3 galactose epitope (Gal-epitope) is present in cell membranes of all mammals except humans and concerns over the epitope's inflammatory potential exist (Galili 1993, Koren et al. 1994). In humans this epitope (i.e. antigenic determinant) is recognised by IgM, IgG and IgA antibodies that mediate hyperacute or delayed graft rejection through complement fixation and antibody dependent cell mediated cytotoxicity (Good et al. 1992, Koren et al. 1994, Schussler et al. 2001). The potential for complement activation has been investigated with results suggesting that it does not occur when the graft is implanted (McPherson et al. 2000). Researchers have attributed the absence of host immune responses to the distribution of the epitope within the xenograft and to the minute quantities that are present (McPherson et al. 2000). In whole organ transplantation levels of the Gal-epitope are expectantly higher and these high levels have been linked to chronic graft rejection (Schussler et al. 2001). Currently, methods of eliminating the epitope prior to scaffold implantation are under investigation and it has been suggested that treatment of the xenogenic scaffold with alpha galactosidase during the decellularisation process is a potential solution. Should clinical concerns persist it might also be possible to harvest the graft material from transgenic Gal-knockout pigs that are bred specifically for tissue engineering purposes.

The graft's response to potential host derived pathogenic micro-organisms has also raised concerns among vascular surgeons as graft infection is associated with considerably morbidity. The xenograft's response to Gram-positive and Gram-negative bacteria has been evaluated and compared to conventional synthetic graft materials (i.e. polytetrafluoroethylene) in animal studies (Badylak et al. 2003). Interestingly, xenogenic ECM materials were resistant to persistent bacterial infection after deliberate contamination at the graft implantation site. This has been attributed to the presence of multiple low-molecular weight peptides that survive the decellularisation and sterilisation processes (Brennan et al. 2006, Sarikaya et al. 2002). These peptides demonstrate bacteriostatic activity against micro-organisms and inhibit bacterial proliferation for up to 12 hours after initial exposure. Their antimicrobial activity protects the remodelling site from circulating pathogens (Brennan et al. 2006). However, their origin and structural homology to natural antimicrobial peptides (AMP) and defensins are important aspects that have not been

clarified to date. Their spectrum of activity and pathways of incorporation are also poorly understood. These factors need to be thoroughly investigated so the extent of their antibacterial role can be clearly established.

4.3 Remodelling and degradation

Biological growth factors found within SIS and UBM are key contributors to cell growth and tissue regeneration (Babensee et al. 2000, Tabata 2004, Tabata 2005). Proteoglycans facilitate their survival during matrix decellularisation and sterilisation by functioning as storage vessels (Hodde et al. 2005). As the matrix is implanted growth factors are released stimulating angiogenesis, host cell infiltration and mitogenesis (Table 6). Matrix degradation coincides with this and the degradation process is influenced by host derived enzymatic and cellular processes (Badylak 2007). During the degradation process growth factors dissociate from their binding proteins and are activated to promote tissue neovascularisation. Matrix degradation and growth factor activation continues until the ECM scaffold is completely replaced by host cells (Clyne and Edelman 2009).

Growth Factor	Function
Vascular Endothelial Growth Factor (VEGF)	Regulates angiogenesis by controlling blood vessel formation and growth
Platelet Derived Growth Factor (PDGF)	Deposition of granulation tissue and stimulation of angiogenesis
Bone Morphogenetic Protein (BMP)	Stimulates formation of bone and cartilage
Keratinocyte Growth Factor (KGF)	Epithelialisation of wounds during healing
Fibroblast Growth Factor (FGF)	Induces growth of fibroblasts and endothelial cells during wound healing
Transforming Growth Factor (TGF-beta)	Reorganization of matrix molecules to improve dermal architecture and reduce scarring

Table 6. Bioinductive growth factors found within the ECMs and their functions

Common growth factors that influence tissue remodelling responses include ‘Vascular Endothelial Cell Growth Factor’ (VEGF) and ‘basic Fibroblast Growth Factor (bFGF)’ as illustrated in Table 6. VEGF has been shown to stimulate angiogenesis, vascular permeability and endothelial cell proliferation and migration while bFGF encourages wound healing (Ferrara et al. 1992). Other retained growth factors within the ECM include keratinocyte growth factor (KGF) which mediates epithelial cell proliferation and differentiation (Alpdogan et al. 2006) and platelet-derived growth factor-beta-polypeptide (PDGF-BB) which promotes chemotaxis, proliferation, angiogenesis and tissue remodelling. It appears that the strong remodelling effect exerted by biological growth factors is accentuated by cryptic peptides that are also released from the implanted scaffold during the degradation process. These peptides are involved in recruiting circulating bone-marrow derived cells that can partake in long-term tissue remodelling processes (S. F. Badylak et al. 2001, Zantop et al. 2006). An ability to be completely degraded while stimulating a native remodelling response over a relatively short period of time is perhaps ECM’s most attractive feature (Badylak et al.

2000, Davis et al. 2011, Gilbert et al. 2007). These impermanent properties were investigated by determining the rates of *in vivo* graft degradation and excretion in canine models during the nineties (Badylak et al. 1998, Kropp et al. 1995, Kropp et al. 1996a, Kropp et al. 1996b, Vaught et al. 1996). Studies show that xenogenic ECMs are rapidly degraded and absorbed when implanted in the genitourinary tract with up to 90% of the scaffold being replaced by host tissue within 28 days (Badylak et al. 1998, Record et al. 2001). Generally, excretion rates of all ECMs vary between 28 and 90 days depending on the type of tissue that is being remodelled (Allman et al. 2001, Badylak et al. 1998, Record et al. 2001). Naturally, the process may be prolonged when multiple layers of xenogenic scaffold are implanted (e.g. 90-120 days). Shortly after the degradation process the ECM briefly enters the blood stream and is excreted via the kidneys through glomerular filtration. This has been shown by measuring quantitative studies of ^{14}C -labelled SIS after augmentation cystoplasty in canine models (Record et al. 2001). More than 50% of the scaffold was removed from the implantation site at 28 days and almost 100% of the scaffold was replaced by 100 days. During the follow up period 95% of degradation products were found in the host's urine (Badylak et al. 2000, Record et al. 2001).

4.4 Mechanical properties

ECMs' remodelling capacity is dependent on the preservation of bioinductive growth factors during the sterilisation process. Similarly, its mechanical effectiveness is largely dependent on preserving intact collagenous arrangements and adhesive glycoproteins during this process. This is highlighted by the scaffold's mechanical response to different sterilisation techniques. Studies have shown that the graft's uniaxial and biaxial mechanical properties are significantly reduced after exposure to gamma irradiation, electron beam irradiation and ethylene oxide (Freytes et al. 2008). The reduction in mechanical strength is dose-dependent and this emphasises the preparation difficulties encountered between graft sterilisation and constituent preservation techniques (Gouk et al. 2008).

Short-term mechanical limitations are also present during the initial remodelling response (Davis et al. 2011). Typically, both SIS and UBM show a decrease in mechanical strength after implantation that is caused by a temporal imbalance between the rate of scaffold degradation and the rate of infiltrating host cell deposition (Gilbert et al. 2007). While the rapid degradation rate of implanted genitourinary ECMs is often lauded, one must consider the temporal mismatch that occurs between xenograft degradation and host-derived matrix deposition. One study demonstrated a 30-fold decrease in bladder compliance (in comparison to the pre-operative status) after canine urinary bladder was replaced with SIS (Kropp et al. 1996b).

Short-term strength limitations have been addressed by increasing the number of layers within the implanted scaffold as a single layer of implanted SIS has proved insufficient for most load bearing organs. The graft's mechanical strength increases by 150% simply by increasing the number of layers of SIS layers from 2 to 4 (Freytes et al. 2004). Importantly, the imbalance between matrix degradation and deposition is temporary in nature and is only relevant until the host's remodelling capability equates to or surpasses the ECM's degradation rate. A rapid remodelling response can occur once infiltrating host cells self-organise and begin producing their own ECM. This results in a time dependent return to expected mechanical strength and site-appropriate mechanical behaviour after xenogenic implantation (S. Badylak et al. 2001, Badylak et al. 2005, Liang et al. 2006).

5. ECMs as potential vascular grafts

A number of studies have investigated SIS's potential as a tissue-engineered vascular substitute. Initially, Badylak *et al.* replaced a segment of canine aorta in 1989 with a tubularised SIS scaffold (Badylak *et al.* 1989). Results from this preliminary study demonstrated patency of the aorta during the follow up period. Importantly, adverse effects such as infection, thrombosis, intimal hyperplasia and hypertension were avoided. Histological assessment after follow up revealed organised, dense non-thombogenic collagenous connective tissue. However, there was no evidence of endothelial cell growth on the luminal surface of the SIS graft after 44 weeks. The authors concluded by suggesting that SIS merits further investigation as a large diameter graft for aortic replacement purposes. Consequentially, SIS was subsequently investigated as a potential small diameter graft in a canine model (Lantz *et al.*, 1990) where the biological scaffold replaced the carotid and femoral artery (Lantz *et al.* 1990). Like Badylak *et al.*, results from this study indicated no evidence of endothelial growth on the scaffold's luminal surface. Luminal and abluminal surfaces of the scaffold were comprised of dense organised collagenous tissue, with no evidence of infection, propagating thrombus or intimal hyperplasia.

A more comprehensive study by Sandusky *et al.* also evaluated SIS as a small calibre vascular graft for carotid arteries in canine models in 1992 (Sandusky *et al.* 1992). A sample size of 24 canine models was included in this study over a period of 180 days where gold standard saphenous vein grafts were directly compared with SIS scaffolds. Results from this study revealed endothelialisation of the SIS scaffold with transmural growth of capillaries and infiltrating smooth muscle cells from the host. In addition, no significant differences were noted between saphenous vein grafts and SIS scaffolds when intimal thickening was compared in this study. In 1995 Hiles *et al.* assessed the mechanical properties of SIS as a potential aortic graft in a canine model (Hiles *et al.* 1995). Their study demonstrated that host tissue completely replaced the SIS scaffold and that the remodelled scaffold had appropriate physical and mechanical properties to adequately function in a vascular system. However, compliance values from the remodelled SIS construct were three-fold lower than compliance values of a normal thoracic aorta (Hiles *et al.* 1995).

Another study by Roeder *et al.* also investigated the compliance, burst pressure and remodelling effects of SIS as a small diameter vascular graft (Roeder *et al.* 2001). Findings from their study demonstrated a degree of tissue remodelling with improved compliance at the site of the implanted SIS scaffold. The authors concluded by suggesting that mechanical properties of the remodelled SIS scaffolds were similar to the vessel of the animal model that was replaced. Ovine models have also been utilised to assess SIS's potential as a small diameter vascular graft (Pavcnik *et al.* 2009). One study, evaluated the implanted SIS scaffolds with angiography during their follow up period. Angiographic assessment of implanted SIS scaffold revealed a multitude of complications that included stenosis of the anastamotic site, aortic dissections, recurrent aneurysmal formation and diffuse dilatations of the implanted scaffold.

Although SIS has been extensively investigated as a potential vascular replacement scaffold it is interesting to note that UBM has never been previously investigated for this purpose. Encouragingly, more recent studies have suggested that UBM merits further investigation as a potential vascular substitute (Badylak 2005, Brown *et al.* 2006). After the preparation process UBM can be manipulated into many different physiological configurations. Its

malleable nature in conjunction with its biocompatibility may provide researchers with an alternative ECM scaffold for vascular replacement purposes.

6. Justification of ECMs in EVAR

In EVAR failure of the implanted stent most frequently occurs one year after surgical implantation as discussed in section 3.2.1. However, ECMs take approximately 3 months to induce a constructive tissue remodelling effect (Badylak 2005, Gilbert et al. 2008). Therefore, a tissue-engineered ECM is likely to reabsorb within this 12 month timeframe and provide a secure seal that could potentially prevent the complication of stent migration.

6.1 Disadvantages of biodegradable polymers

The potential for biodegradable polymers as potential vascular replacements in EVAR stent-grafts has previously been investigated. Poly D, L-lactic-glycolic acid co-polymer (PLGA) and Poly ϵ -caprolactone (PCL) are 2 polymers that have been assessed *in vivo* and *in vitro* as potential vascular substitutes. In one study the degradation rates of both polymers were assessed and compared *in vivo* and *in vitro*. Results demonstrated that degradation rates of both scaffolds occurred at a more rapid rate *in vivo* compared to *in vitro*. Hydrolysis of PLGA and PCL polymers were influenced by the concentration of carboxylic acid end-groups. Therefore, it appears that degradation products of both polymers may serve as catalysts for reactions in static conditions, which are likely to accelerate degradation. This study suggests that by-products of the initial degradation influence the effect of cell infiltration (Sung et al. 2005). Therefore, these initial studies imply that biodegradable polymers are unsuitable in the setting of EVAR as they are associated with undesirable by-products that adversely affect their degradation rate (Sung et al. 2005).

6.2 Configurations of ECM stent grafts for EVAR

SIS has been investigated in a stented environment on the abdominal aorta of ovine models where remodelling of the SIS scaffold onto the aortic wall was assessed by Yamada *et al.* (Yamada et al. 2001). In this study the SIS stent graft was manufactured by sandwiching the stent between two sheets of SIS as illustrated in Fig. 4. Results demonstrated no evidence of stenosis and no evidence of endoleak formation around the implanted stent grafts. Histological assessment showed incorporation of the graft into the wall of the aorta with a dense neo-intima replacing the SIS scaffold. Endothelialisation occurred in areas where the graft was in direct contact with the aortic wall and central portions of the graft were partially endothelialised after the 12 week follow up period. A similar study by Noishiki et al., 2001 reported comparable results to Yamada *et al.* with a partial endothelium forming on the implanted SIS hybrid stent graft (Noishiki et al. 2001).

After these promising results the performance of SIS covered endografts (stent devices) implanted into ovine femoral arteries was investigated by Nakata *et al.* in 2003. The study compared the performance of the SIS covered endografts to non-covered nitinol stents and PTFE covered endografts. In their conclusion the authors suggest that SIS and bare metal nitinol stents display similar attachment features to the aortic wall and performed superior to a poly-tetra-fluoro-ethylene (PTFE) covered stent also included in the study (Nakata et al. 2003). It should also be noted that both SIS endografts and bare nitinol stent exhibited eccentric intimal hyperplasia with eventual occlusion of the stented vessel during the follow

up period. A study by Schoder *et al.* also investigated SIS in the setting of EVAR repair (Schoder et al. 2004). In this study the SIS scaffold was suspended against the wall of the aorta as illustrated in Fig. 5. Results from this study suggest that this deployment method is promising for the prevention of type 2 endoleaks. In addition, results also demonstrated evidence of a host derived tissue remodelling response during the follow up period. A detailed analysis of the remodelling response revealed an established endothelium along the distal and proximal regions of the scaffold with poor endothelialisation of its central portion.

Fig. 4. Sandwiched stent composed of SIS (Yamada et al., 2001)

Fig. 5. SIS stent graft deployed inside an AAA (Schoder et al., 2004)

In 2005 Niyiyati *et al.* assessed the potential for SIS as an intrahepatic protocaval shunt. Only one device remained functional in 6 animals after a 14 day experimental time period (Niyiyati et al. 2005). Intuitively, the authors discouraged SIS in this setting. The configured SIS stent device and the implanted SIS stent are illustrated in Fig. 6 A and B. Histological assessment of the luminal surface after follow up demonstrated a smooth neointima on the surface of the functional stent.

Fig. 6. (A) Stent SIS configuration, (B) Gross section through excised graft implantation (Niyyati et al. 2005)

A more recent study investigated the effects of different stent grafts on the portal vein of canine models (Ishii et al., 2005). In this study, four different stents were assessed, bare metal stent, PTFE covered stent, Dacron covered stent and an SIS covered stent. The study concluded that SIS covered stents confer no advantages in comparison to other conventional stent grafts. In fact PTFE consistently outperformed the other 3 stents and was recommended as the most suitable stent for implantation into the portal vein. In 2006 the endothelialisation of an implanted SIS stent graft was compared with Dacron and PTFE in an ovine model. In this study the stent grafts were inserted into the thoracoabdominal aorta and endothelialisation of the stent graft was assessed during the follow up period (Yavuz et al. 2006). Results showed that Dacron exhibited the greatest and most progressive amount of endothelialisation. In comparison, SIS demonstrated progressive tissue remodelling and a moderate amount of neointimal formation.

7. Concept solution

A potential mechanism for improving the performance of the EVAR stent-graft is the insertion of a tissue-engineered stabilisation collar at the proximal and distal ends of the device as illustrated in Fig. 7.

A tissue-engineered 'stent-collar' may prevent common complications such as endoleaks and graft migration. Intuitively, a number of important critical issues need to be addressed prior to implementation of this possible solution. Compliance of the scaffold in tubular structures and the reduction in the scaffold's strength caused by interactions with the 'stent-graft' should be investigated. Compliance issues may arise due to fluid flow and elastic characteristics of the arterial wall exerted on the tissue-engineered scaffold. Furthermore, radial forces exerted by the stent-graft induce stress loadings on the surface of the tissue-engineered scaffold. Structural properties of the scaffold also need to be accurately characterised. The scaffold's potential to induce cellular attachment and host derived tissue-remodelling responses need to be explored. Contact between the tissue-engineered material and arterial wall may result in cell infiltration from the host's endothelium (Fig. 8). To date

the majority of these questions remain unanswered and require further research to adequately develop ECM scaffolds into AAA endovascular treatment.

Fig. 7. Possible solution for optimisation and stabilisation of the stent graft during EVAR. (Adapted from <http://www.medtronic.com/your-health/abdominal-aortic-aneurysm/getting-a-device/surgery>)

Fig. 8. ECM collar interacting with aortic wall to anchor the stent-graft and prevent migration of the device

8. Conclusions

In this chapter we have examined key issues associated with medium-term failure of endovascular stents used in the EVAR procedure. Common complications associated with EVAR include endoleaks and migration of the deployed stent. Although tissue-engineered xenografts offer an attractive alternative for improving the EVAR procedure, it is notable that implantation of ECM scaffolds into stented environments have shown conflicting results to date. Encouragingly, the advent of alternative types of biological ECMs, such as UBM, has opened up new avenues for researchers with an interest in optimizing the EVAR procedure. Development of a tissue-engineered scaffold that optimizes the performance of the stent-graft remains a valuable possibility and exciting option for the future.

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Tissue Engineering may offer new treatment alternatives for organ replacement or repair deteriorated organs. Among the clinical applications of Tissue Engineering are the production of artificial skin for burn patients, tissue engineered trachea, cartilage for knee-replacement procedures, urinary bladder replacement, urethra substitutes and cellular therapies for the treatment of urinary incontinence. The Tissue Engineering approach has major advantages over traditional organ transplantation and circumvents the problem of organ shortage. Tissues reconstructed from readily available biopsy material induce only minimal or no immunogenicity when reimplanted in the patient. This book is aimed at anyone interested in the application of Tissue Engineering in different organ systems. It offers insights into a wide variety of strategies applying the principles of Tissue Engineering to tissue and organ regeneration.

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