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Experimental reconstruction of an abdominal wall defect with electrospun polycaprolactone-ureidopyrimidinone mesh conserves compliance yet may have insufficient strength

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ABSTRACT

Purpose: Electrospun meshes mimic the extracellular matrix, which may improve their integration. We aimed to compare polycaprolactone (PCL) modified with ureidopyrimidinone (UPy) electrospun meshes with ultra-lightweight polypropylene (PP; Restorelle) reference textile meshes for in vivo compliance. We chose UPy-PCL because we have shown it does not compromise biomechanical properties of native tissue, and because it potentially can be bioactivated.

Methods: We performed *ex vivo* biomechanical cyclic loading in wet conditions and in vivo overlay of full-thickness abdominal wall defects in rats and rabbits. Animals were sacrificed at 7, 42 and 54 days (rats; n = 6/group) and 30 and 90 days (rabbits; n = 3/group). Outcomes were herniation, mesh degradation and mesh dimensions, explant compliance and histology. High failure rates prompted us to provide additional material strength by increasing fiber diameter and mesh thickness, which was further tested in rabbits as a biomechanically more challenging model.

Results: Compliance was tested in animals without herniation. In both species, UPy-PCL-explants were as compliant as native tissue. In rats, PP-explants were stiffer. Contraction was similar in UPy-PCL and PP-explants. However, UPy-PCL-meshes macroscopically degraded from 30 days onwards, coinciding with herniation in up to half of animals. Increased fiber and mesh thickness did not improve outcome. Degradation of UPy-PCL is associated with an abundance of foreign body giant cells until UPy-PCL disappears.

Conclusion: Abdominal wall reconstruction with electrospun UPy-PCL meshes failed in 50%. Degradation coincided with a transient vigorous foreign body reaction. Non-failing UPy-PCL-explants were as compliant as native tissue. Despite that, the high failure rate forces us to explore electrospun meshes based on other polymers.

Abbreviations: FBGC, foreign body giant cells; GPC, gel permeation chromatography; H&E, hematoxylin & eosin; PCL, polycaprolactone; TF, thicker fiber; TM, thicker mesh; UPy, ureidopyrimidinone; UPy-PCL, ureidopyrimidinone-polycaprolactone; Mn, the number average molecular weight; Mw, the weight average molecular weight

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1. Introduction

Abdominal wall hernia is common with a lifetime prevalence of over 30% (Primatesta and Goldacre, 1996). It is usually operated electively, and today a tension-free mesh repair technique is recommended by the European Hernia Society (Simons et al., 2009). Mesh reconstructions have a lower recurrence rate than sutured repair without an increase in postoperative pain (Grant et al., 2002). However, the use of meshes may lead to complications including infection, exposure, migration, adhesions, occasionally persistent pain and a potential effect on fertility in men (Brown and Finch, 2010; Peeters et al., 2014). Mesh complications are believed to be caused by persistence of the material, chronic inflammation, contraction and a high stiffness (Brown and Finch, 2010; Cobb et al., 2005). Textile meshes, typically made of polymer polypropylene (PP), are the most commonly used implants in general surgery and gynecology, and this is therefore also used in this study. Depending on the weight and textile fabric, PP may cause an adverse host response (Brown and Finch, 2010; Cobb et al., 2005). To reduce the risk for that, clinicians have moved towards lightweight macroporous polypropylene constructs with better properties (Brown and Finch, 2010). Despite that, there might still be complications (Mukthinath et al., 2016).

Development of novel meshes has been advocated to decrease graft-related complications (Bringman et al., 2010). A mesh used to repair a structural defect should be strong enough under tension and flexible at rest. As an implant, it needs to be biocompatible and induce an appropriate host response. Durable materials cause a chronic inflammatory reaction, which obviously could be avoided by using degradable polymers. The pace of degradation should be chosen such that the mesh remains supportive, until newly formed tissue can resist the forces. An alternative to knitted textile meshes is the use of an electrospun matrix. Those matrices have been widely used in tissue engineering for restoration of vessels, cartilage, bone, peripheral nerve, spinal cord and skin (Braghirolli et al., 2014). Through different electrospinning parameters, polymers, surface modifications and functionalization (incorporation of biomolecules) one can determine biomechanical properties and the ultimate host response. Electrospinning permits the production of extracellular-matrix-like three-dimensional structures with nano-scale fibers (Boudriot et al., 2006). The nano-fibrous architecture can improve cell-material interactions (Woo et al., 2003). Electrospun matrices have been shown to support cell adhesion (fibroblasts), production of connective tissue (Vashaghian et al., 2017) and a nano-fibrous surface can temper the inflammatory response at the interleukin level (Andersson et al., 2003). One example of a slowly degradable (6–7months) three-dimensional synthetic web on the market is Gore Bio A (William Gore, Flagstaff, Arizona, USA). Gore Bio A is composed of poly(ethylene terephthalate)/chitosan and manufacturing utilizing a melt-spinning technique. This material was tested in animal model as a subcutaneous implant (Yeo et al., 2014), as a reinforcement of a sutured defect (Peeters et al., 2013; Lopez-Cano et al., 2013), yet to our knowledge no yet to bridge a defect. Clinical uncontrolled studies in inguinal, hiatal and ventral hernia repair have been done (Symeonidis et al., 2013; Agrusa et al., 2014; Rosen et al., 2017), and one controlled trial on ventral hernia repair is on-going (López-cano et al., 2014).

We decided to electrospun a UPy-PCL scaffold, i.e. polycaprolactone (PCL) polymer modified by dimerizing quadruple hydrogen bonding 2-ureido-4[1 H]-pyrimidinone (UPy) moieties. PCL is one of the many polymers that can be used as a backbone for electrospinning. It has been used in research for bone and vessels regeneration guidance (Lam et al., 2008; Mrówczynski et al., 2013). *Ex vivo* it has sufficient biomechanical strength (Chakroff et al., 2015) and induces a minimal foreign body response (Palmer et al., 2014). When UPy is bound to PCL it impacts in vitro degradation: UPy-PCL degrades mainly via an oxidative pathway compared to PCL alone, which is sensitive to enzymatic and hydrolytic degradation (Brugmans et al., 2015). UPy-modification of polymers is a novel approach, which allows to bind e.g. bioactive peptides to the electrospun matrix. It allows a modular approach to gain control over cellular behavior and activity (Kieltyka et al., 2012; Dankers et al., 2007; De Feijter et al., 2015). By functionalization of a matrix it may be possible to create e.g. a bilayered scaffold with adhesive and anti-adhesive surface on each side (Mollet et al., 2014). UPy-hydrogels have also been shown to be a slow-release drug-carrier to the myocardium in a porcine model of myocardial infarction (Bastings et al., 2014). We earlier showed that UPy-PCL explants have biomechanical properties comparable to that of native tissue (Hympanova et al., 2017). Herein we aimed to test their in vivo performance in appropriate models for abdominal wall hernia surgery. Initial screening was on the rat model and further longer term testing was on rabbits (Ozog et al., 2011a). When shown reasonably effective, our next step would be to bind bioactive peptides that may improve tissue ingrowth (cell adhesion, proliferation, extracellular matrix production) or reduce infections.

2. Material and methods

2.1. Meshes

Ureidopyrimidinone-polycaprolactone (UPy-PCL) polymer was obtained from SupraPolix BV (Eindhoven, the Netherlands) and electrospun by Coloplast A/S (Humlebaek, Denmark). Details about polymers, spinning and sterilization are described in Supplement 1. Meshes were characterized for fiber size distribution and directionality by scanning electron microscopy (Supplementary Fig. 1). Based on initial clinical results the fiber diameter or mesh thickness was increased and tested in rabbits (Table 1). Standard textile ultra-lightweight polypropylene meshes (Restorelle®; Coloplast A/S) were used as controls. Rectangular mesh samples were weighed and measured to establish density and underwent *ex vivo* cyclic uniaxial loading for 10 cycles in wet conditions for determination of comfort zone stiffness values (Supplement 2, Table 1).

Table 1
Characteristics of the materials used in this study.

	Macroporous polypropylene (Restorelle®)	Electrospun polycaprolactone modified with ureidopyrimidinone (UPy-PCL)		
		Standard	Thicker mesh	Thicker fiber
Mesh thickness (μm)	300	250–400	500–800	250–400
Fiber size (μm)	80.0	1.8–3.2	1.8–3.2	3.6–6.4
Density (g/m^2)	19.0	38.5–47.2	59.6 – 72.3	46.6 – 63.6
Comfort zone stiffness (N/mm)	1.58 ± 0.19 *	0.66 ± 0.02 *, #	1.70 ± 0.10 #	0.90 ± 0.07
Number of implants in rats (7, 42, and 56 † days)	12	18	0	0
Number of implants in rabbits (30 and 90 days)	12	12	6	6

* and # represent a significant difference between groups ($p < 0.05$), † the rats were euthanized earlier than the scheduled 90 days, due to failure of the implant. The comfort zone stiffness UPy-PCL data were not normally distributed.