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Elastomers in vascular tissue engineering

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Abstract

Elastomers are popular in vascular engineering applications, as they offer the ability to design implants that match the compliance of native tissue. By mimicking the natural tissue environment, elastic materials are able to integrate within the body to promote repair and avoid the adverse physiological responses seen in rigid alternatives that often disrupt tissue function. The design of elastomers has continued to evolve, moving from a focus on long term implants to temporary resorbable implants that support tissue regeneration. This has been achieved through designing chemistries and processing methodologies that control material behavior and bioactivity, while maintaining biocompatibility *in vivo*. Here we review the latest developments in synthetic and natural elastomers and their application in cardiovascular treatments.

Graphical Abstract

Introduction

Successful tissue engineering strategies have an inherent requirement to appropriately mimic the natural mechanical properties and signaling cues of host tissues. This is particularly relevant for the vasculature, which presents a dynamic environment that is highly sensitive to compliance mismatch [1]. This requirement for mechanical compliance can be achieved through the use of elastic materials, tailored to match the native tissue to facilitate integration. Two main classes of elastomers exist for cardiovascular engineering: synthetic polymer materials and natural proteins that are often derived from the tissues they are

seeking to repair. In selecting an appropriate elastomer for a given application, a number of properties must be considered. The ability to tailor the material mechanically, control degradation to determine implant lifespan, design signaling cues to promote bio-integration and ensure biocompatibility with the local environment are all critical in dictating the ultimate success of a given implant.

Synthetic elastomers

Polyurethanes

Polyurethanes (PUs) are a broad group of copolymer materials composed of aliphatic or aromatic units linked with polar urethane groups. PUs are synthesized through the poly-addition of long chain polyols, di- or triisocyanates combined with a short chain extender to increase mechanical strength [2]. When higher mechanical strength is required, precursors with multiple functional groups are used to produce a 3D cross-linked final structure. Given the range of chemistries that can be employed, formulations of PUs can exhibit a wide range of mechanical and biological properties [3].

In vitro assessments of PU cytocompatibility have demonstrated that a range of cell types such as epithelial, endothelial and fibroblasts attach and proliferate well on PU surfaces [4]. When exposed to blood, PUs present a hemocompatible surface, resisting thrombosis to make them a candidate for vascular applications [5].

The design of PUs has undergone a substantial philosophical change over recent time. Early formulations designed to serve as long term vascular implants suffered from adverse responses, with unforeseen biodegradation due to hydrolysis, micro cracking and enzymatic degradation [6]. Along with weakening the material structure, the degraded products of these chemistries were cytotoxic, resulting in their clinical failure [4]. Long term PU formulations have since seen various improvements, including reduced byproduct cytotoxicity by transitioning away from the use of aromatic diisocyanates. These formulations have also been employed as vascular drug delivery vehicles that show promise *in vitro* [7]. Clinically, long-term PUs remain a popular choice in the construction of catheters (Vialon), where their smooth surface simplifies insertion and provides a low resistance to flow that resists thrombosis [8].

Modern approaches to PU design have also focused on producing biodegradable PUs designed to operate as temporary healing agents to promote tissue repair [9]. By utilizing high elasticity PUs, thin patterned film cardiac patches have been produced that support cardiomyocyte attachment and growth in linearly aligned organizations. When implanted, these cell-laden films restore contractile tissue of cardiac muscle post infarction, and may be later resorbed, leaving behind only the healthy tissue [10]. PUs have also been applied to the construction of various small diameter vascular conduits, where they display 40% patency in a rat model after 8 weeks. These are further enhanced with the addition of 2-methacryloyloxyethyl phosphorylcholine (MPC), which improves patency to 92% [11], highlighting the benefit of combinatorial drug delivery approaches to further promoting PU biocompatibility.

PCL—Poly(ϵ -caprolactone) (PCL) is a bioresorbable polymer that is used in vascular medicine on account of its ease of production, mechanical properties and generally favorable biocompatibility [4]. PCL is synthesized by processing ϵ -caprolactone or 2-methylene-2,3-dioxepane precursors through catalyst or free radical-driven ring-opening polymerization techniques. The resulting PCL is a hydrophobic, semi-crystalline polymer, which is highly miscible and simple to manipulate [12].

While initially overlooked due to its slow degradation rate (2–3 years), new appreciations for the benefits of PCL have emerged on account of its rheological and viscoelastic properties. This, coupled with its relatively low cost of production and FDA approval have seen it increasingly used in combination with other polymers destined for vascular use [13].

When designing PCL grafts, the method of manufacture is vitally important in establishing correct mechanical behavior for the implantation site [14]. For example, cast PCL undergoes plastic deformation when exposed to long-term cyclic strain, making it unsuitable for vascular graft construction. This issue is averted by producing electrospun PCL grafts that have improved elasticity and better mimic ECM fiber morphology compared to their cast counterparts [15].

Electrospun PCL grafts replacing the abdominal aorta in rats (1.5 – 2 mm ID) outperform similar ePTFE grafts, remaining patent to at least 18 months [16]. However, at 12 months cellular infiltration regresses, leading to the formation of calcified lesions due to insufficient metabolic exchange and signaling factors [17]. Carotid artery replacements in a pig model have also shown benefits over ePTFE in a short-term study [18]. These studies demonstrate the potential for PCL-based grafts if concerns for long term cell viability can be addressed by providing additional cues to support cell survival.

PGS—Poly(glycerol sebacate) (PGS) has widespread application in tissue engineering on account of its thermoset elastomeric properties, biocompatibility and favorable degradation characteristics [19]. PGS is most commonly formulated from glycerol and sebacic acid, which helps underpin its biocompatibility, with both constituents naturally occurring in the body. Both these precursors also have long histories of use *in vivo* and FDA approval for food use and medical applications respectively [20]. Synthesis typically employs a two-step process of poly-condensation followed by crosslinking. A number of variations to this methodology have been reported, such as varying precursor concentrations and employing photo-crosslinking to allow *in vivo* polymerization [21].

The elastomeric properties of PGS originate from the three dimensional network of covalently cross-linked random coils within its structure and hydrogen bonding of the backbone hydroxyl groups [4]. Common techniques to vary the mechanical nature of PGS are to modify the temperature, precursor concentration and curing time during synthesis. By altering these parameters, properties such as the Young's and tangent moduli can be altered [22]. Furthermore, PGS can be processed into a range of forms such as thin films or electrospun constructs that exhibit a wide range of mechanical and cell interactive behaviors.

Degradation of PGS occurs predominantly through surface degradation due to cleavage of ester linkages. This is advantageous in that PGS undergoes a gradual loss of mechanical strength, maintaining predictable mechanics in comparison to materials undergoing bulk degradation [19].

Growth of numerous vascular cell types has been validated on PGS including cardiomyocytes [23], aortic endothelial cells [24], smooth muscle cells [25] and fibroblasts [19]. Casting PGS for cell interactions requires some optimization, as subtle change can have profound impacts on cellular responses. Soft PGS inhibits cardiomyocyte proliferation, while pre-conditioning restores a favorable growth profile [23]. Studies of platelet attachment to assess blood compatibility have demonstrated the PGS outperforms other commonly used polymers such as ePTFE and PLGA in these tests [26]. PGS scaffolds also promote cells to express and deposit elastin and collagen to further enhance the material, increasing the tensile strain 5 fold after 3 weeks [27]. PGS-PCL copolymers designed to mimic the mechanical nature of heart valves have also been shown to promote organized endothelial cell growth [28].

PGS sheets implanted within the left ventricle completely resorb following implantation at a rate of 0.2 mm/month without any discernable immunological response [29]. Other studies support this finding, attributing the low immune response to the surface erosion degradation characteristics that operate to resist lymphocytic infiltration resulting in minimal fibrous capsule formation [30].

Natural Proteins

Collagen

Collagen is found ubiquitously throughout the body, typically organized in triple helix fibers that impart strength and flexibility to their tissue environment. Over 22 varieties of collagen have been described, with the most predominant being I–V [31]. Although it features a very high Young's modulus (up to ~1 GPa), collagens display high resilience and reversible deformation that confirm its elastic nature [32].

Collagen is usually obtained by harvesting animal tissues, which are purified and treated with stabilizing agents such as glutaraldehyde (GA) to control degradability. Being naturally derived, special care must be taken through this process to control for batch variation, purity and the risk of transmitting infectious agents [33]. Additionally, the use of cross-linkers such as GA to stabilize materials requires optimization to avoid causing tissue calcification when implanted [34].

Collagen-based cardiac patches derived from bovine pericardium (CardioCel) [35] have allowed for the delivery of mesenchymal stem cells (MSC) in human patients for cardiac repair [36]. The Omniflow Vascular Prosthesis (OVP), created by preimplanting a silicone rod within sheep before removing and stabilizing the deposited collagen has been used as a graft for femoral artery repair and peripheral bypass with around 20,000 implants since 1990 [37]. These outperform ePTFE materials by resisting neointimal hyperplasia, however only limited endothelialization is observed in clinical explants [38].

New research has focused on transitioning towards non-animal sourced collagen to address ethical and safety concerns with techniques. Results have been promising, with synthetic collagen matching or outperforming commercial options such as Zyderm in early *in vivo* immunological evaluations [39].

Silk

Silk fibers are produced naturally by some arthropods and display varying mechanical properties dependent on their species of origin. Of these, the silk worm *Bombyx mori* is most commonly used for tissue engineering applications [40]. Silk fibers originating from *B. mori* are made up of a fibroin component encased within an adhesive sericin coat. Studies reporting immunological activation in response to silk sutures containing sericin proteins [41] have driven a large body of work devoted to creating biomaterials derived from the purified fibroin component. However, sericins have since been found not cause a foreign body response, which rather is initiated by the combined fibroin-sericin structure [42].

The primary structure of silk fibroin consists of repeating hydrophobic bulk domains that form beta sheets during isolation. The final properties of silk fibroin materials are therefore heavily dependent on the method of processing used, which alters the extent of beta sheet formation, and has implications on degradability of the final product [43].

In vitro cell attachment and growth on silk fibroin scaffolds is typically low, largely on account of its structure and hydrophobicity. Cultures of endothelial, fibroblast, peripheral blood mononuclear and mesenchymal stem cells on silk scaffolds display slow growth rates, however are able to infiltrate porous scaffolds once established [44].

A range of efforts have been made to improve cellular interactions with silk scaffolds. To reduce the surface hydrophobicity, oxygen plasma treatment has shown to be successful in improving cellular attachment and growth [45]. Another effective strategy has been to combine silk fibroin with extracellular matrix proteins such as collagen [46], fibronectin and elastin [47]. Through this strategy, the cell interactive and mechanical properties are improved, with silk fibroin – elastin films showing dramatically (1.3 MPa vs ~6 GPa) greater elasticity, resembling that of native vascular tissue [48].

Degradation of silk is influenced by the properties of the material, such as beta-sheet content, location of the implant and the method of fabrication. The primary mechanism for silk degradation *in vivo* is through the actions of proteases (collagenase, protease K, alpha-chymotrypsin), which generally target regions between beta sheets [49]. Silk fibroin structures that allow the infiltration of immune cells such as macrophages will undergo remodeling and degradation [50]. This immunological action is due to activation of the complement cascade by silk fibroin materials, which generally persists through to 14 days post implantation and by 12 weeks no inflammatory cells are present [51,52].

When electrospun into small diameter vessels (1–3 mm diameter), silk fibroin grafts display good biocompatibility, remaining patent after 1 month and 85% patent after 12 months, outperforming PTFE control grafts in a rat abdominal aortic model [53]. Further improvements continue to be investigated to enhance endothelialization, which require 12

weeks to achieve 90% coverage. Silk-PCL-elastin hybrids are mechanically attractive, but are yet to be tested for cell compatibility [54]. Proof-of-concept grafts incorporating heparin into the silk structure to improve hemocompatibility have also shown promise, improving blood contact, while supporting cell growth [55].

Elastin

Elastin is a natural component of the vascular ECM, where it performs vital roles in providing mechanical resilience to tissues, and mediating a range of cellular processes. Within arteries, elastin comprises up to 50% of the dry weight where it persists throughout life due to its high stability, with a half-life of ~70 years [56].

The dominant component of elastic fibers is tropoelastin, a 60 kDa protein that features a well-described alternating hydrophobic-hydrophilic domain structure[57]. Signaling interactions mediated by tropoelastin occur primarily through adhesion-based mechanisms operating through integrins, glycosaminoglycans and the elastin binding protein [58]. Cell attachment and proliferation on tropoelastin materials has been demonstrated on many cell types, including fibroblasts, endothelial cells, progenitor cells [59] and cardiomyocytes [60]. Tropoelastin materials also exhibit excellent blood compatibility, resisting both platelet adhesion and thrombus formation that make them desirable for cardiovascular engineering [58].

The introduction of recombinant technology has enabled large scale production of tropoelastin and catalyzed its use in the construction of biomedical devices. Tropoelastin is amenable to many production techniques, where its high stability allows it to maintain its structure and cell-interactive properties in harsh conditions such as those seen during electrospinning.

Cardiovascular patches fabricated from tropoelastin mimic cardiac tissue are able to support cardiomyocyte alignment and function, which begin beating on the elastic substrate [61]. Compliance validations *in vivo* also demonstrate that electrospun tropoelastin – PCL arterial grafts maintain their mechanical properties post implantation, with compliance, elastic modulus and burst pressure remaining unchanged in a rabbit carotid interposition model [62]. Tropoelastin coatings in a sheep carotid model display 79% less neointimal hyperplasia than ePTFE grafts and enhanced endothelialization, addressing the major issues facing current generation grafts [63].

Future Directions

In selecting a graft material for a given location, a main criterion is achieving compliance with the native site. More elastic candidate materials such as PGS, collagen and elastin offer the opportunity for closely matching arterial compliance. For instance, these materials all offer a Young's moduli between 0.5–1 MPa, placing them at an appropriate range of arterial blood vessels, such as the common carotid artery (750kPa) [65]. Less elastic materials such as PU, PCL and silk have utility when used together with more elastic materials. Here, they can enhance the mechanical strength of the overall material, increasing properties such as

burst pressure, while maintaining appropriately matched elasticity to produce in a more resilient final graft [67].

Elastomers represent clear advantages when engineering constructs destined for vascular biological tissues. There continues to be exciting advancements with optimized chemistries and new methods of fabrication allowing for well-tailored biocompatible materials that outperform current vascular treatment standards in pre-clinical tests. Ongoing investigations that employ a combinatorial approach to produce hybrid materials that extract greatest benefits from each will continue to be explored and are likely to shape the next generation of patient treatment.

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Highlights

- Elastic materials can mechanically match the dynamic tissues found in the vasculature
- Elastomers can be processed using different techniques such as casting or electrospinning to tailor their properties
- Synthetic options offer lower costs of production, but natural elastomers often contain important cell signaling cues
- Current trends aim at producing temporary constructs with controlled degradation
- Combinatorial approaches utilizing multiple elastomers or secondary components such as drugs show the greatest promise