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Review article

Elastic materials for tissue engineering applications: Natural, synthetic, and hybrid polymers

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ABSTRACT

Elastin and collagen are the two main components of elastic tissues and provide the tissue with elasticity and mechanical strength, respectively. Whereas collagen is adequately produced *in vitro*, production of elastin in tissue-engineered constructs is often inadequate when engineering elastic tissues. Therefore, elasticity has to be artificially introduced into tissue-engineered scaffolds. The elasticity of scaffold materials can be attributed to either natural sources, when native elastin or recombinant techniques are used to provide natural polymers, or synthetic sources, when polymers are synthesized. While synthetic elastomers often lack the biocompatibility needed for tissue engineering applications, the production of natural materials in adequate amounts or with proper mechanical strength remains a challenge. However, combining natural and synthetic materials to create hybrid components could overcome these issues. This review explains the synthesis, mechanical properties, and structure of native elastin as well as the theories on how this extracellular matrix component provides elasticity *in vivo*. Furthermore, current methods, ranging from proteins and synthetic polymers to hybrid structures that are being investigated for providing elasticity to tissue engineering constructs, are comprehensively discussed.

Statement of Significance

Tissue engineered scaffolds are being developed as treatment options for malfunctioning tissues throughout the body. It is essential that the scaffold is a close mimic of the native tissue with regards to both mechanical and biological functionalities. Therefore, the production of elastic scaffolds is of key importance to fabricate tissue engineered scaffolds of the elastic tissues such as heart valves and blood vessels. Combining naturally derived and synthetic materials to reach this goal proves to be an interesting area where a highly tunable material that unites mechanical and biological functionalities can be obtained.

Abbreviations: ECM, Extracellular matrix; GAGs, Glycosaminoglycans; ELN-gene, Elastin gene; RER, Rough endoplasmic reticulum; EBP, Elastin-binding protein; GAS, Galacto-sugars; LCST, Lower critical solution temperature; T_g, Glass transition temperature; ELAC, Electrochemically aligned collagen; ELP, Elastin-like polypeptide; PLA, Poly (lactic acid); PEG, Poly(ethylene glycol); PGS, Poly(glycerol-co-sebacate); POC, Poly(1,8-octanediol-co-citrate); PLLA, poly(L-lactic acid); PU, Polyurethane; PCL, Poly(ε-caprolactone); PHA, Poly(hydroxyalkanoate); P4HB, Poly(4-hydroxybutyrate); GelMA, Methacrylated gelatinl; PHB, Poly(3-hydroxybutyrate); PHBHHx, Poly(3-hydroxybutyrate-co-3-hydroxyhexanoate); PLGA, Poly(lactic-co-glycolic acid); PGCL, Poly(glycolide-co-ε-caprolactone); PTMC, poly(1,3-trimethylene carbonate); PA, Polyacrylamides; PAA, Poly(acrylic acid); PGA, poly(glycerol adipate); PSBS, Poly(styrene-butadienestyrene); PSEBS, Poly(styrene-ethylene-butadiene-styrene); LDLA, L,D-lactic acid; PLCL, Poly (l-lactide-co-ε-caprolactone); PGLCL, poly(glycolide-co-L-lactide-co-ε-caprolactone); AP, Aniline pentapeptide; HDI, Hexamethylene diisocyanate; PDMS, Polydimethylsiloxane; PIBMD, Poly(isobutyl-morpholinedione); SELP, Silk elastin-like polypeptides; AKELP, Mimic of the hydrophilic-, alanine-, and lysine-rich part of tropoelastin; PNIPAAm, Poly(N-isopropylacrylamide); PLA-HEMA, Polylactide-2-hydroxyethyl methacrylate; OEGMA, Oligo(ethylene glycol); PNPHO, A complex water-soluble polymer containing PNIPAAm, PLA/HEMA, and OEGMA; PEGDA, Poly(ethylene glycol) diacrylate.

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1. Introduction

Tissue engineering is a fast growing field that aims at generating functional constructs that mimic the structure and properties of the extracellular matrix (ECM) of the native tissues. Although many studies have been carried out in the field of tissue engineering, the number of constructs that are brought to the clinics is still limited [1,2]. The limited clinical translation of engineered tissues is mainly because many applications such as heart valve and blood vessel replacements require the construct to be mechanically functional upon implantation [3]. Thus, understanding the functional mechanical properties of native tissues and how to mimic these properties in an engineered construct is essential [4–7].

Native tissues consist of two major components: cells and the ECM. The ECM consists of nonfibrous macromolecules such as glycosaminoglycans (GAGs) and fibrous components such as elastin. Although nonfibrous components are present in a relatively low content in elastic tissues, they play an important role in the proper mechanical functionality of these tissues [8]. In heart valves, for example, the GAG-rich layer is able to absorb the shocks during opening and closing of the valve [4]. Fibrous components, mostly collagen and elastin, are the major elements that provide mechanical functionality to elastic tissues. Collagen fibers provide strength and structural support to the tissue. Elastin, however, provides elasticity and is therefore mostly present in elastic tissues such as lungs, heart valves, and blood vessels [2,9]. To engineer a tissue *in vitro*, scaffolds are designed to provide initial mechanical stability to the construct and to allow the cells to produce the proper amount of the ECM with time. While the amount of collagen produced by the cultured cells is abundant, the amount of elastin is limited [10–12]. Therefore, it is essential to artificially introduce elasticity into the scaffold materials [13,14].

Elasticity can be tailored to the scaffold by using native elastin derivatives [2] or synthetic elastomers [9]. While the use of native elastin proves to be difficult owing to its large batch-to-batch variations [15], synthetic materials, which have a high tunability, may cause problems regarding the biological functionalities, especially by hindering cell adhesion [16]. Combining different natural and synthetic materials with different functionalities, to form hybrid-like structures, can address the limitations of both native elastin and synthetic elastomers and thus offer a promising future approach for the engineering of elastic tissues.

In this review, various elastic materials used for tissue engineering applications are discussed. First, elastin synthesis, *in vivo* procedure for fiber assembly, and occurrence of elastin in different tissues are explained. Next, the current available elastic materials from biological, recombinant, and synthetic sources for tissue engineering purposes are discussed. Finally, hybrid materials, as promising candidates for tissue engineering applications, are highlighted.

2. Native elastin

2.1. Elastin biosynthesis

Cells produce elastin as the precursor tropoelastin before it is transported outside the cells [17]. After alignment through coacervation, the protein is crosslinked to form the mature elastin [18]. The majority of the elastin synthesis takes place in the late fetal and early neonatal stage [11]. For humans, elastin production starts between weeks 17 and 19 of pregnancy and continues into early childhood before slowing down [14,19]. In line with this, Johnson *et al.* indicated that aortic cultures from 1 to 3 day old chickens showed a decreasing trend of elastin synthesis with time [20]. They linked this decreasing trend to the half-life time of elastin mRNA, which decreased from 25 h in 1 day old chickens to only 7 h in 8 week old chickens [20]. Because elastin has a half-life time of approximately 70 years, during which it can go through billions of extension and relaxation cycles without losing its function [2], production and remodeling of elastin is not essential during adulthood except in the case of damage to the elastin fibers due to an injury. The elastin fibers produced in the case of injury are disorganized and therefore do not have mechanical functionalities same as those of the elastin produced during early life [11]. Several exogenous factors influence the production of elastin after injury, such as tumor necrosis factor-a, interleukin 1b, insulin-like growth-factor-1, and transforming growth factor [21].

The formation of mature elastic fibers, also known as elastogenesis, starts with the translation of the elastin gene (ELN gene) inside the cell nucleus and its transcription into tropoelastin in the rough endoplasmic reticulum (RER) (Fig. 1A, I) [22]. The gene coding for tropoelastin is a single coding gene that can have alternative splicing, thereby resulting in different isoforms of tropoelastin [17]. In humans, the resulting tropoelastins possess a weight of approximately 70 kDa [23] and consist of alternating parts: a hydrophilic part containing predominantly alanine and lysine, known as the crosslinking domain and a hydrophobic part containing the repeating sequence of Val-Pro-Gly-Val-Gly (Fig. 1B) [24].

Inside the cells, tropoelastin is bound to a chaperone, an elastin-binding protein (EBP), that prevents intracellular coacervation. Coacervation is a conformational reorganization of molecules in a

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