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Review

Bioresorbable vascular scaffolds: Biodegradation, drug delivery and vascular remodeling☆

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ABSTRACT

The metallic stents with durable polymers have been effective in reducing the need for revascularization, but the permanent presence of the metal and polymer have been associated with persistent inflammation, hypersensitivity reactions and incidence of thrombosis. Recent innovations of bioresorbable polymers are in development which could serve as temporary scaffolds that degrade into molecules and eventually resorb overtime, and leave the artery free of any permanent prosthetic constraints. The transient scaffolding has the advantages of restoring blood vessel to natural state, improve vasomotor tone and increase lumen enlargement because of expansive remodeling following completion of polymer resorption. The success of bioresorbable vascular scaffolds will depend on the degradation timeline, such that the elastic recoil of the blood vessel and negative remodeling which could potentially lead to restenosis are prevented. Bioresorbable scaffolds with bulky backbone and thick struts could lead to prolonged biodegradation, alter blood flow dynamics and increase thrombogenicity. The development of bioresorbable scaffolds is challenging because of the complexity of finding an ideal balance of polymer biodegradation and controlled drug release over time, such that the fractional drug released achieves optimal inhibitory concentration until the blood vessel remodels to a stable set point. This review discusses the various types of biodegradable materials, factors affecting biodegradation, drug release kinetics, vascular biocompatibility, adaptive vascular remodeling, and challenges in the development of bioresorbable scaffolds to treat vascular restenosis.

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Abbreviations: ALK, alkaline phosphatase; BMP-2, bone morphogenetic protein-2; MGP, matrix γ-carboxyglutamic acid protein; NO, nitric oxide; OPN, osteopontin; PLLA, poly-L-lactide; PLGA, poly-D,L-lactide-*co*-glycolide; O_2^-, superoxide anion.

☆ Disclaimer: This article reflects the views of the author and should not be construed to represent FDA's views or policies.

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1. Introduction

Although metallic stents are effective in preventing recoil and constrictive remodeling, they have limitations because of the permanent presence of the prosthesis and polymer that hinder the natural healing process of the blood vessel, resulting in persistent local inflammation, fibrin deposition, delayed neointimal formation, uncovered struts and thrombogenicity [1]. The non-erodable polymer stays permanently after the antiproliferative drug is completely eluted, which may induce hypersensitivity reactions, inflammatory cell infiltrates, and delay re-endothelialization [1]. It is likely that durable polymer coating on the permanent metallic stent implants pose the risk of continuous interaction with the intimal layer leading to physical irritation and endothelial dysfunction. The presence of a foreign body within the artery wall can be a source of chronic vessel wall inflammation, induce oxidative stress, interfere with endothelial recovery, and delay vessel wall healing [1,2]. Furthermore, increased rigidity of the permanent stent may alter the pulsatile profile of blood flow and affect shear stress, leading to vasomotor tone dysfunction and late-catch up restenosis. Thus, there is a continued search for an alternative approach to treat a transient vascular healing problem, and restore normal blood vessel function [2].

The concept of bioresorbable scaffolds has emerged as an alternative to overcome the long-term complications of permanent metal prosthesis to treat arterial restenosis [2–4]. The temporary scaffold would allow the blood vessel to remodel to its natural anatomic configuration and overcome complications such as chronic inflammation, hypersensitivity reactions and prothrombotic state. Bioresorbable scaffold materials provide temporary physical support to prevent blood vessel collapse and maintain luminal patency, and subsequently disappear after vascular remodeling [4]. The absence of a rigid permanent prosthesis allows restoration of vasomotion, maintain shear stress, reduce the risk of late complications and favor positive vascular remodeling (Table 1). If successful, the bioresorbable scaffolds could have the potential advantages of combining the short-term lumen support and serve as a drug delivery system to inhibit neointimal formation [4,5].

2. Biodegradable materials

Biodegradable polymers are comprised of monomers linked to one another through functional groups and contain unstable links in the backbone that allow hydrolytic degradation through de-esterification. Biodegradable polymers offer an attractive combination of degradation into inert monomers and elimination from the body via metabolic pathways. Biodegradable polymeric materials include polyesters, polyanhydrides, polyurethanes, polyorthoesters, polyester amide, polyamino acid and tyrosine-derived polycarbonates [6].

Table 1
Comparison of permanent metallic stents and temporary bioresorbable scaffolds.

	Metallic stents	Bioresorbable scaffolds
• Acute recoil/constrictive remodeling	Prevented	Prevented
• Expansive remodeling	No effect	Beneficial
• Vessel geometry	Altered	Preserved
• Vasomotion restoration	No effect	Beneficial
• Persistent irritation	Present	Absent
• Late lumen gain	No effect	Beneficial
• Endothelial recovery	Near complete	Complete

2.1. Polymer chemical composition

The most commonly used biodegradable polymers in medical devices are aliphatic polyesters, that include poly-L-lactide (PLLA), poly-D-lactide (PDLA), poly-D,L-lactide (PDLLA), poly-L-glycolide (PGA), poly-ε-caprolactone (PCL), poly-trimethylene carbonate, and their copolymers such as poly-D,L-lactide-*co*-glycolide (PLGA) and poly-lactide-*co*-caprolactone. One of the simplest aliphatic polyesters is polylactide, which has high crystallinity, high melting point and low solubility, and is commonly used in sutures and orthopedic devices [4]. Aliphatic polyesters of the PLLA family can be modified to exhibit various types of mechanical properties and degradation profiles by utilizing different combinations of stereo-copolymers [6,7]. Lactic acid is a chiral molecule and exists as two stereo-isomeric forms of D- and L-lactic acid, and the polymerization of these two monomers in different proportions could form a variety of compounds with different properties of biodegradation profiles. PLLA homopolymer is semi-crystalline due to high regularity of its polymer chain, whereas PDLLA polymer is amorphous because of irregularities and racemic mixture of monomers that disrupts crystallinity. As a result, PDLLA degrades at a faster rate than PLLA due to lower crystallinity [3]. For drug delivery systems, PDLLA appears to be suitable because it enables more homogeneous dispersion of drug loaded into the polymer matrix [8].

PGA is a highly crystalline polymer because it lacks methyl side groups of the PLLA, but its bonds are prone to hydrolysis [8,9]. The co-polymer PLGA could display a wide range of degradation profiles by varying the ratio between its monomer constituents. Degradation rates could also be influenced by hydrophobic/hydrophilic balance and crystallinity [8]. Lactic acid is more hydrophobic than glycolic acid and hence lactide-rich PLGA copolymers are less hydrophilic, absorb less water, and subsequently degrade more slowly [8,9]. Copolymer of 50:50 PGA and PLLA degrades more rapidly than either homopolymer alone, because copolymerization with PLLA interrupts the crystallinity of PGA and allows penetra-