Biodegradabable Endovascular Stents

"Fulfilling the Mission and Then Stepping Away"

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Abstract

A stent is traditionally a metallic endovascular prosthesis designed to serve as a permanent internal scaffold to maintain or increase the lumen of a blood vessel.
Coronary stents were first introduced to prevent arterial dissections and to eliminate vessel recoil and exaggerated intimal hyperplasia associated with percutaneous transluminal coronary angioplasty (PTCA). Endovascular stents have revolutionized the treatment of coronary and peripheral vascular disease, and the application range has expanded as well to the percutaneous treatment of valvular heart disease and endovascular therapy of thoracic and abdominal aneurysms. Despite these advances contemporary endovascular stents have not eliminated restenosis, are plagued with sudden thrombosis, require prolonged antiplatelet therapy, are prone to crush deformations and may limit future treatment options in select settings. These concerns have provided the rationale for the development of bioresorbable or biodegradable stents (BDS) for the support of a body conduit or blood vessel, to keep it patent only through the healing process. These stents then degrade, principally by simple hydrolysis and are ultimately phagocytized and metabolized to carbon dioxide and water, which are of course, fully resorbed. BDS also enable longer term delivery of drugs, genes and proteins to the conduit wall. The present review describes recent advances in bioresorbable endovascular stents, focusing on strategies of rapid endothelialization.

Introduction

Rationale:

Over two decades of experience with metal endovascular stents have reveled two main limitations. One relates to their delayed endothelialization, leading to stent thrombosis, requiring prolonged dual antiplatelet therapy. The second relates to their persistence in the vessel wall. This could lead to neointimal proliferation and restenosis, stent fractures and deformations, and ultimately limit positive vessel remodeling and future revascularization options, especially coronary bypass surgery.
Our strategy to address limitations of metal endovascular stents is based upon locally available expertise at the University of Texas Southwestern Medical Center and the University of Texas at Arlington. First, is our ability to isolate endothelial progenitor cells (EPC) from peripheral blood of patients, with immunocytochemical identification and formation of a confluent monolayer of mature, functional endothelium. Second, is expertise in stent design and fabrication from biodegradable materials, specifically poly-(L-lactic acid) or PLLA. This report also details the proposed strategy of EPC capture, using a specific CD34 antibody-antigen interaction on fibronectin coated biodegradable stent material.

Contemporary metal endovascular stents:

The treatment of coronary artery disease, which remains a leading cause of mortality in the developed world, has undergone revolutionary changes in the past decade. Percutaneous coronary intervention (PCI) has become the principal method of coronary and peripheral arterial revascularization worldwide. It has been shown to reduce restenosis relative to conventional balloon angioplasty (1–3). Early designs, including the Wallstent (Schneider) and Palmaz-Schatz (Johnson & Johnson) stents were replaced

by the Micro (AVE), Multilink (ACS), and other bare metal stents (BMS) (4–7). These BMS are made out stainless steel, tantalum, and nitinol alloys, selected for their strength, elasticity, and malleability or shape memory (6–10). Coronary stents prevent arterial dissections and eliminate vessel recoil and reduce the exaggerated intimal hyperplasia leading to >50% incidence of restenosis, associated with PTCA. Though an improvement over PTCA, in-stent restenosis, which occurs in >30% of stented coronary arteries, often results in recurrent ischemic episodes that require repeat intravascular procedures and/or surgery. This restenosis is a result of in-stent neointimal hyperplasia caused by proliferation and migration of vascular smooth muscle cells (VSMCs) induced by vessel wall injury or recruited circulating smooth muscle progenitor cells (11). The pathology of restenosis stems from a complex interaction between cellular and acellular elements of the vessel wall and the blood (12). The substantial rate of stent restenosis led to the redesigning of stents in hopes of improving their antithrombotic properties and thereby reducing the rate of restenosis. Inorganic elements (e.g., gold), polymers (e.g., polylactic acid and fibrin), and immobilized drugs (e.g., heparin and abciximab) have been successfully applied to stents. However, these agents have generally caused slight decreases in thrombosis without substantially decreasing in-stent restenosis.

Anti-proliferative and anti-inflammatory agents have been shown to elute slowly from polymer coatings of drug eluting stents (DES) and reduce neointimal proliferation in animal models, and ultimately angiographic restenosis in human clinical trials. Two antiproliferative agents, paclitaxel (13, 14) and sirolimus (15), have been used in humans with promising results.

Another strategy currently being explored is endothelial progenitor cell mobilization and coverage on endoluminal stent surfaces. Rapid endothelial coverage could result in less activation of circulating blood cells and potentially contribute to paracrine mediators conveying antiinflammatory and antiproliferative effects downstream, limiting proliferation and migration of VSMCs induced by vessel wall injury (16). This line of events assumes that the attached cells are able to exert effects similar to the physiological actions of a normal endothelial lining.

Coronary stenting acutely freezes recoil, and the presence of a metallic stent does not seem to be associated with lesion progression or accelerated atherosclerosis of the treated site after 6 months. In the 5 year follow-up of the Belgian Netherlands Stent Study (BENESTENT I) demonstrated a sustained and persistent benefit of the stent. But it is also worth considering that permanent metal stents also limit the late favorable vascular remodeling (17). The possibility of not having a permanent metallic implant could permit the occurrence of remodeling with lumen enlargement to compensate for the development of new lesions. Long stented segments may preclude surgical revascularization, which may become necessary at a later time. Also, permanent metal stents are prone to crush deformations, especially in the peripheral arterial bed, and current DES require prolonged dual antiplatelet therapy to prevent stent thrombosis, a catastrophic clinical event. An ideal BDS, preserving the strength, elasticity, and malleability or shape memory properties of BMS and DES, in addition may act as an improved vehicle for specific local therapy with drugs or genes. These potential applications have currently been curtailed by

the difficulties associated with the development of BDS that are not only associated with a prominent inflammatory reaction, but also by the simplicity and low cost associated with manufacturing stainless steel stents. This review highlights an emerging new approach in coronary stenting using BDS. Useful copolymers and blends can be created to alter the mechanical properties and drug-release profiles of bioactive agents from polymeric structures based on these polymers.

Biodegradabable Polymer Stents (BDS)

Polymer based BDS:

PLLA, poly-(glycolic acid) (PGA), poly-(ε-caprolactone) (PCL), and poly-(d, l-lactic acid) (PDLLA) are the most frequently used aliphatic poly-α-hydroxy-acids for preparing bioresorbable stents (18–20). The semi-crystalline PLLA and PGA have high initial tensile strength, permitting a robust mechanical design (Table 1). Glass transition temperature and modulus are also represented in Table 1. Glass transition temperature is the temperature above which polymers may be annealed to improve strength and flexibility, but also below which polymers become rigid and brittle, and can crack and shatter under stress. Modulus is the measure of stiffness of a polymer. It is defined as the rate of change of stress with strain.

Table 1

Polymer	Melting point (°C)	Glass transition temperature (°C)	Modulus (Gpa)	Degradation time (months)
PGA	225–230	35–40	7.0	6–12
PLLA	173–178	60–65	2.7	>24
PDLLA	Amorphous	55–60	1.9	12–16
PCL	58–63	(−65)–(−60)	0.4	>24
PDS	N/A	(−10)–0	1.5	6–12
85/15 PDLGA	Amorphous	50–55	2.0	5–6
75/25 PDLGA	Amorphous	50–55	2.0	4–5
50/50 PDLGA	Amorphous	45–50	2.0	1–2

[a]Adapted from "Synthetic Biodegradable Polymers as Medical Devices," *MPB Archive*, March 1998.

PGA: poly(glycolic acid); PLLA: poly(L-lactic acid); PDLLA: poly(DL-lactic acid); PCL: poly(ε-caprolactone); PDS: polydioxanone; PDLGA: poly(DL-lactic-coglycolic acid).

PCL is also a semicrystalline polymer with a relatively high degree of crystallinity (similar to PLLA and PGA). However, it exhibits lower strength and modulus than PLLA and PGA owing to its low glass transition temperature (below room temperature, see Table 1). PDLLA is actually amorphous and cannot exhibit crystalline structures. Its strength and modulus are lower than those of PGA and PLLA. Polydioxanone (PDS) has gained increasing interest in the medical and pharmaceutical fields owing to its excellent biocompatibility (21). Although, it is a semicrystalline polymer, it also exhibits lower strength than PLLA and PGA because it has a low glass transition temperature, similar to

PCL. Dr. Eberhart's group at University of Texas Southwestern Medical Center is one of the first research groups to investigate stents made of PDS and PLLA polymers. These polymeric stents degrade, principally by simple hydrolysis and are ultimately phagocytized and metabolized to carbon dioxide and water, which are of course, fully resorbed. The first BDS was developed by Stack & Clark of Duke University in the early 1980s, and was made up of PLLA (22, 23). It had high radial strength for one month, and in vivo studies demonstrated minimal thrombosis and inflammatory responses, with moderate neointimal growth. Tamai et al described the Igaki/Tamai stent, a PLLA monofilament based, balloon expandable zigzag coil design BDS (Figure 1). The strut thickness is 0.17 mm and the stent surface area is 24% at an arterial diameter of 3.0 mm. The stent has an expansion range of up to 4.5 mm. The stent initially autoexpands in response to the heat transmitted by a delivery balloon inflated with a 70◦C contrast-water mixture (50◦C at the balloon site). Subsequent expansion is obtained by inflation at a moderate to high pressure (6 to 14 atm). This stent continues to expand to its nominal size within the following 20 to 30 min at 37◦C. The monofilament design was a significant advancement over knitted polymeric BDS, as it significantly reduced vessel wall injury, and restenosis, as the severity of vessel injury is strongly correlated with neointimal thickness (24). In the first in man experience of the Igaki-Tamai BDS, 25 stents were deployed successfully in 15 patients. No stent thrombosis or major cardiovascular events occurred within 30 days. After 6 months, restenosis occurred in 10.5% of the patients and target lesion revascularization occurred in 6.7% (27).

Figure 1:

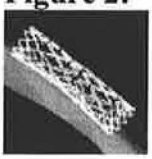
Design of Igaki-Tamai PLLA stent

Figure 1. The Igaki-Tamai stent is a premounted, balloon-expandable PLLA stent that also has the ability of self-expansion.

alloy that provides mechanical properties s steel stents. At the same time, the magnesium alloy allows controlled complete biodegradation (reabsorption) within approximately 2 months. Because of its composition of >90% magnesium, the stent is completely radiolucent and cannot be visualized by x-ray (Figure 2). This requires the use of intravascular ultrasound to evaluate the post-interventional stent expansion. However, because the stent also does not exert metallic artifacts, it has potential for noninvasive follow-up by MRI (28).

The biocompatibility of these stents depends on their solubility and their released degradation products. Their local toxicity is related to the local concentration of the elements over time. The tissue tolerance for physiologically occurring metals depends on the change of their tissue concentrations induced by corrosion. Thus metals with high tissue concentrations are the ideal candidates for bioabsorption stents.

Figure 2:



Magnesium versus stainless steel stent approximately 30 days after implantation in porcine coronaries.

Initial Clinical Trials with the Mg AMS:

The first clinical trial to test the feasibility and safety of the magnesium bioabsorbable stent was performed in 20 patients who presented with claudication due to severe peripheral vascular disease (Rutherford Class IV and V), and who were candidates for amputation. These patients had lesions in the proximal two-thirds of one or more infrapopliteal arteries, and were subjected to PCI with the magnesium stent under a compassionate base protocol. Following predilatation, the 3.0 × 15 and 3.5 × 15 mm magnesium stents were successfully deployed with good angiographic and ultrasound results. There was no evidence of blood or vessel toxicity, and the patency rates at 3 and 6 months post implantation were 89% and 78%, respectively. Limb salvage was obtained in all patients at 3 months, while at 6 months, 1 patient underwent amputation to the limb intervened upon. Duplex ultrasound and MRI demonstrated complete absorption of the stents at 3 months (29).

The results of this study have led to a clinical trial with the magnesium stent in coronary arteries. The PROGRESS study is designed as a safety study in 65 patients in 7 European centers. The intravascular ultrasound follow-up scheduled at 4 months will determine whether these stents are indeed disappearing and will indicate what the restenosis rate will be. The initial implantation of these stents in the coronary arteries was successful, with good apposition of the stent imaged by IVUS.

Currently, magnesium stents are not visible by X-ray and are not loaded with drugs for the prevention of restenosis. The need for such a drug will be determined by the results of the clinical trials since the recoil is minimized with the use of a metallic stent and the trigger for continuous inflammation is gone shortly after stent deployment. This stent will result in less restenosis than is seen with bare metal stents. If drugs are essential to control restenosis, they can be loaded with another bioabsorbable polymer or without an additional vehicle using the magnesium as the platform for those drugs.

Endothelial Progenitor Cell (EPC)

Isolation and Mobilization after a focal Endovascular Injury:

Endothelial dysfunction plays a major role in atherosclerosis, and can result in plaque disruption and acute coronary events (30). Replenishment of a damaged endothelium is likely to have a beneficial influence.

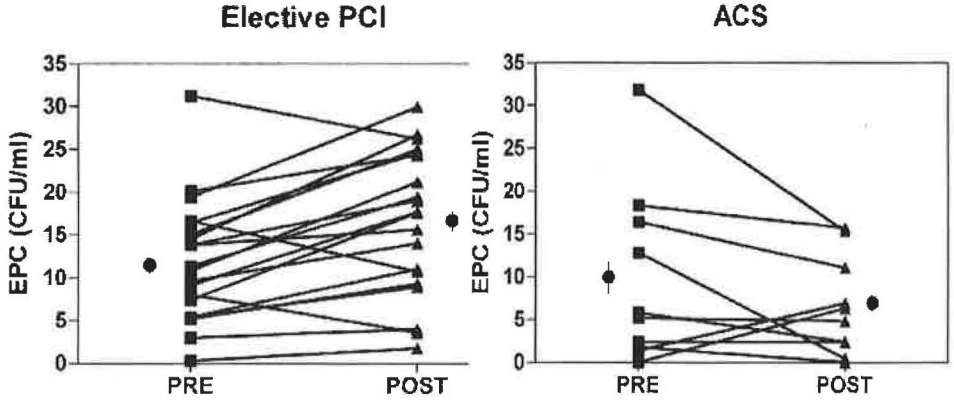
Asahara et al elegantly demonstrated that EPC mobilized from the bone marrow can be detected in peripheral blood mononuclear cells and are capable of forming functional endothelium (31). Circulating levels of endothelial progenitor cell (EPC) are known to be associated with cardiovascular risks and disease states, and carry prognostic significance

(32, 33). Therapeutic strategies to home in EPC to sites of endothelial injury and denudation in the coronary vasculature have already been demonstrated (34). However, EPC mobilization triggered by a focal coronary endothelial injury induced by percutaneous coronary intervention (PCI) has not been demonstrated. In our recent study we investigated whether PCI triggers EPC mobilization detected by increased levels of EPC colony forming units (EPC-CFU) in the peripheral circulation (35).

EPC form typical colony-forming units morphologically, and transform into cobblestone monolayers after 2-3 weeks. Surface markers found to be characteristic for EPC are (vWF+, CD31+, CD34+, and CD45-). EPC also take up acetylated LDL, and make limited tube structures in 3-dimensional culture. In addition, when cocultured with differentiated endothelial cells (HUVEC), labeled EPC are readily incorporated into tube structures in Matrigel. Thus, EPC-CFUs are capable of giving rise to phenotypical endothelial-like cells.

In this recent study from our laboratory, CD34/CD31 positive EPC colony forming units (EPC-CFU) were quantified by a blinded observer in peripheral blood samples from 8 control patients with angiographically normal coronary arteries and in 30 patients with coronary artery lesions, before and 12 h after PCI. All patients (n=38) had one or more CV risk factors. Ten patients presented with acute coronary syndrome (PCI_{ACS}), and the rest (n=20) underwent elective PCI (PCI_{Elect}). At presentation, there were no significant differences in EPC-CFU counts between the PCI_{Elect}, PCI_{ACS}, and control groups ($P>0.05$). We then determined whether PCI triggered EPC mobilization into the peripheral circulation. The majority (17/20, 85%) of patients receiving an elective PCI displayed increases in EPC-CFU, with the mean EPC-CFU (colonies/ml blood) increasing from 11.8 ± 1.5 before to 16.5 ± 1.8 after stent placement, P=0.0009). In contrast, only 2 of 10 patients (20%) with ACS showed evidence of EPC mobilization, with mean EPC-CFU levels nonsignificantly decreasing (9.5 ± 3.2 before vs. 6.5 ± 1.8, after PCI, P=0.20) (Figure 3). These changes in circulating EPC levels before and after PCI were not accompanied by a significant change in WBC counts (x 10^7/ml blood) in the PCI_{Elect} (1.9 ± 0.08 before vs.1.8 ± 0.1 after PCI, p=0.22) or PCI_{ACS} (2.0 ± 0.1 before vs. 1.7 ± 0.1 after PCI, p=0.30) groups.

Figure 3:



EPC-CFU in PCI_{Elect} group and PCI_{ACS} group are shown before (EPC pre) and after (EPC post) PCI. EPC-CFU levels increased in the PCI_{Elect} (P=0.0009) but not in the PCI_{ACS} (P=0.20) group.

In this study, we investigated the effect of a discrete endovascular insult on human EPC recruitment into the peripheral circulation. By focusing on a defined clinical procedure, we were able to compare EPC levels before, and early after the manipulation, at reproducible time points, avoiding possible non-specific perturbations. In addition, the vascular prosthesis presented a relatively limited, standardized intervention, and the procedure did not introduce other major vascular perturbations such as surgical wounds or cardiopulmonary bypass, aside from the catheterization itself.

We found that the majority of patients receiving PCI on an elective basis showed a significant early increase in circulating EPCs. While the average EPC-CFU count increased by only 40%, the second sample was drawn only 12 h after intervention, an early time point chosen to include patients stable enough for early discharge from the hospital. By contrast, in animal studies, circulating EPC levels peak approximately 7 days following a defined vascular injury (36). In addition, all patients in this group possessed multiple cardiac risk factors and by definition had coronary artery disease. Thus, EPC recruitment after PCI may not have been as robust as in normal individuals, although PCI in this latter group cannot be studied.

In contrast to patients receiving elective PCI, the group of patients suffering from ACS failed to recruit EPC into their peripheral blood within 12 h after PCI. In addition, the initial pre-PCI EPC-CFU counts, obtained within 24 h of an acute clinical syndrome, were not different from either the elective PCI or control groups, which itself suggests a failure to respond to a presumed fresh thrombotic focus. Besides being presented with a foreign surface (PCI), this group differed from the elective PCI group insofar as myocardial ischemia was present. However, ischemic myocardium itself is not likely to account for the lack of EPC recruitment in this group. In fact, circulating EPC levels appear to increase rather than decrease in response to myocardial infarction or exercise-induced myocardial ischemia, though at later time points (37, 38). Instead, our findings are more easily reconciled with the hypothesis that acute coronary events are associated with failure of EPC recruitment.

Viewed in light of recent advances in the pathogenesis of the vulnerable plaque, our data suggest that humans respond to vascular injury with a rapid early mobilization of EPC into the peripheral circulation. Further, patients with deficient re-endothelialization of sites of coronary endothelial injury may have an increased risk of plaque rupture and ensuing ACS. The lack of EPC response in ACS patients to PCI may also partly explain the higher risk for stent thrombosis in this patient subset compared with recipients of elective PCI (39, 40). Endothelial coverage of implanted stent surfaces, which may be impeded by vascular stem cell exhaustion or, in theory, cytostatic drug elution, may represent a logical target for novel therapeutic strategies.

EPCs for Rapid Endothelialization of BDS:

In a normal artery, an endothelial cell (EC) lining inside the vessel serves a barrier function, whereas vascular devices do not have this lining on their surfaces. It takes a

long time for the host ECs to migrate and grow on the surfaces of vascular devices after the interventions. For instance, endothelial cell regrowth was not fully complete until 32 weeks after stent placement in dogs (41). In addition, complete restoration of an EC lining was obtained 12 months after stent placement in human and porcine coronary arteries (42, 43). Seeding endothelial cells or capturing of endothelial progenitor cells from the blood onto the stent surfaces could promote rapid establishment of a functional endothelium lining or endothelialization, a "natural barrier" that reduces the implant's adverse reactions toward the prostheses.

Recent discoveries of EPC have shown that it might be an ideal autologous cell sources for use to enhance the endothelialization on vascular prostheses. These lead to the development of identifying new EPC sources and novel strategies and techniques to characterize, isolate, and differentiate of EPC for endothelial regeneration to treat cardiovascular diseases (44). Seeding endothelial cells to enhance the endothelialization process has been reviewed elsewhere (45). The current review will focus on EPC capturing on vascular prostheses, to induce endothelialization of the prosthetic surfaces and reduce the incidence of adverse reactions triggered by the prostheses.

EPC- capture on vascular prostheses:

A functional intact endothelium layer could inhibit the thrombosis and neointimal hyperplasia that follow vascular injury or prosthetic implantation (46). Autologous EPCs could be used to endothelialize vascular prostheses. Indeed, transplantation of circulating EPCs into the lumen of denuded carotid arteries of rabbits improved endothelial function and enhanced endothelialization (47).

Another approach to restore the endothelial lining on vascular prostheses is to isolate EPCs from blood, expand *ex vivo*, and seed them on the surface of vascular prostheses prior to implantation. Studies have shown the EPC retention after stent expansion, and a complete endothelial coverage on both the stent struts and the denuded vessel surface (48, 49). The recovery of the endothelium layer by seeding EPCs ensured nonthrombogenic properties of these prostheses (50). Limitations of the seeding approach are the extensive culture time need to grow a large enough number of cells and the loss of seeded cells during the implantation process.

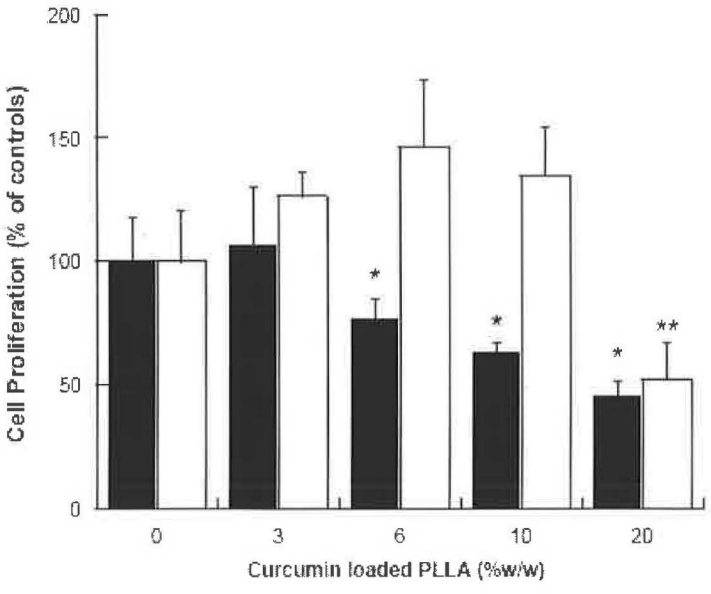
To overcome the limitations mentioned above, a technique called "autoseeding" or capturing of EPC has been proposed. In this method, substances with high affinity for EPCs, for example, anti-CD34 antibodies are coated on the surfaces of vascular prostheses to attract circulating EPCs *in vivo*. Complete endothelialization of the anti-CD34 antibody pre-coated polytetrafluoroethylene (ePTFE) vascular graft was seen only 3 days after implantation (51). HEALING-FIM (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth-First In Man), the first human clinical investigation using the capturing technology (murine monoclonal anti-human CD34 antibodies covalently bound to a stainless steel stent via the polysaccharide intermediate coating) also verified the rapid endothelialization and no thrombosis after six months of the stent deployment (52). This capturing approach is getting increasing attentions because it is convenient and can

reduce the loss of the pre-coated cells during the process of implantation (e.g. stent expansion). An extracellular matrix (ECM) protein or its derivatives such as fibronectin, gelatin, or polysaccharide is usually applied on the prosthetic surfaces as the intermediate coating to bind the antibody to the metallic stent (48, 49, 52). This coating tends to enhance EPC adhesion and proliferation on the surfaces of the vascular prostheses. Of ECM proteins such as fibronectin, laminin, collagen, and vitronectin, fibronectin is best for use to enhance endothelial cells on the prosthetic surfaces made of polymeric poly(L-lactic acid) (PLLA).

In addition to antibodies, ligands that have a high affinity for EPCs are also used for attracting of EPCs onto the prosthetic surfaces. For example, one study using cyclic Arg-Gly-Asp (cRGD) precoated stents to capture EPCs found an early complete EC coverage 4 weeks after implantation, and a significantly reduced restenosis compared to the control groups 12 weeks post-implantation (53). VEGF-coated coronary stents have also been used to accelerate endothelialization and reduce thrombosis on the stents (54). In addition, fibronectin together with VEGF have been found to promote the migration and differentiation of EPCs into ECs. These findings provide us a lot choices to make the protein or ligand coated vascular protheses to capture EPC.

Even though drug eluting stents (DES) are commonly used to prevent coronary artery in-stent restenosis, the effects of these drugs on EC biology have not been well understood. Our work on DES of curcumin-eluting PLLA materials showed the inhibitory effects on the proliferation of smooth muscle cells, but not the proliferation of ECs when grown on a low dose of curcumin loaded PLLA (55) (Figure 4). The discriminating effects toward these cells may clinically be useful. For example, capturing EPCs onto DES can also be developed to have both capacities to enhance endothelialization while delivering therapeutic agents that reduce adverse clinical reactions.

Figure 4.

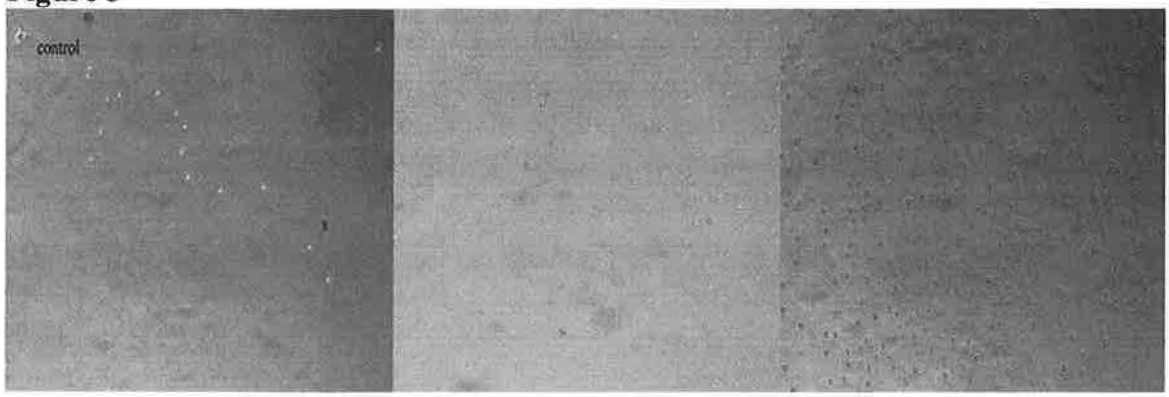


Inhibition of smooth muscle cells (SMC) and EC growth upon exposure of different doses of curcumin loaded in PLLA materials. Curcumin was loaded into PLLA materials at different doses as previously described (55). Human aortic SMCs and EC were grown on curcumin-loaded PLLA surfaces for 3 days. Cell proliferation was quantified using Pico Green DNA assays of the

*cell lysis samples and normalized with the DNA of the control samples. Control samples were cells (SMCs or ECs) grown on PLLA without curcumin loading. Results of cell proliferation were presented as mean ± SEM (% of controls). *Statistically significant difference compared to the control for SMCs (solid black bars) with $p<0.05$ ($n=6$) and **statistically significant difference compared to the control for ECs (open white bars) with $p<0.05$ ($n=6$). Control was the cell growth on PLLA without curcumin loading.*

Also, we have demonstrated that conjugation of CD 34+ antibodies onto fibroncectin-incorporated PLLA captured more $CD34^+$ EPCs than PLLA controls after 30 minutes of incubation in vitro (Figure 5). EPCs grown to confluence on our PLLA stents have the ability to stay on the surface even with the stresses of balloon expansion.

Figure 5



A B C

EPC adhesion on (A) PLLA, (B) PLLA coated with fibronectin (C) PLLA coated with fibroncectin and anti-CD34+ antibody. EPCs (CD34+ EPCs) were incubated on bare PLLA, PLLA coated with fibroncectin, and PLLA coated with fibroncectin and anti-CD34+ antibody for 30 minutes, at seeding density of 1.5×10^4 cells/cm^2.

The potential of microporous bioresorbable polymer stents formed from poly(L-lactic acid) (PLLA)/poly(ε-caprolactone) (PCL) blends to function both to provide mechanical support and as reservoirs for local delivery of therapeutic molecules and particles to the vessel wall has been reported by Rajasubramanian G et al, at our institution (56). Tubular PLLA/PCL stents were fabricated by the flotation-precipitation method, and helical stents were produced by a casting/winding technique. Because of the potential of direct gene transfer into the vessel wall to ameliorate thrombosis and neointimal proliferation, the authors investigated the capacity of these polymer stents to function in the delivery of recombinant adenovirus vectors to the vessel wall. In vitro, virus stock was observed to readily absorb into, and elute from these devices in an infectious form, with suitable kinetics. Successful gene transfer and expression was demonstrated following implantation of polymer stents impregnated with a recombinant adenovirus carrying a nuclear-localizing βGal reporter gene into rabbit carotid arteries. These studies suggest that surface-modified polymer stents may ultimately be useful adjunctive devices for both mechanical support and gene transfer during percutaneous transluminal revascularization.

Future Directions:

Though biodegradable polymer stents and biocorrodible metallic stents seem to be ultimate candidates for the ideal stent, further research is required before they can substitute the conventional bare metal or drug-eluting stent. If so, they may eliminate the need for prolonged antiplatelet therapy and will be compatible with future noninvasive imaging of the coronary tree.

By controlling the ideal absorption time and rate, they can be useful for other applications such as angiogenesis and gene transfer. Once they deposit the drug locally, the vehicle as a whole will disappear in the surrounding tissue. In the meantime, it would be interesting to follow whether the bioabsorbable stent concept will be adopted and thus eliminate the current practice in which many patients chronically carry metal prostheses in their coronary arteries.

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