Review

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Macromolecular Approaches to Prevent Thrombosis and Intimal Hyperplasia Following Percutaneous Coronary Intervention

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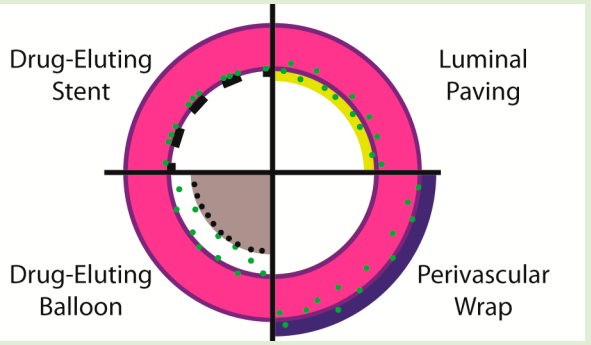
ABSTRACT: Cardiovascular disease remains one of the largest contributors to death worldwide. Improvements in cardiovascular technology leading to the current generation of drug-eluting stents, bioresorbable stents, and drug-eluting balloons, coupled with advances in antirestenotic therapeutics developed by pharmaceutical community, have had a profound impact on quality of life and longevity. However, these procedures and devices contribute to both short- and long-term complications. Thus, room for improvement and development of new, alternative strategies exists. Two major approaches have been investigated to improve outcomes following percutaneous coronary intervention including perivascular delivery and luminal paving. For both approaches, polymers play a major role as controlled research vehicles, carriers for cells, and antithrombotic coatings. With improvements in catheter delivery devices and increases in our understanding of the biology of healthy and diseased vessels, the time is ripe for development of novel macromolecular coatings that can protect the vessel lumen following balloon angioplasty and promote healthy vascular healing.



INTRODUCTION

Despite improvements in technology and healthcare fields, coronary artery disease (CAD) remains the number one killer of Americans, with approximately 34.3% of deaths attributed to CAD each year.[1] CAD is caused by atherosclerosis, the accumulation of plaque on artery walls, which blocks blood flow to the heart muscle and surrounding tissue. In an effort to improve patient quality of life and prevent further complications like heart attack, the removal of the occlusions from the vessel wall is critical. Percutaneous coronary intervention (PCI), perhaps one of the most innovative medical inventions of the century, has become an effective method for the treatment of CAD. PCI, first developed in 1977 by Andreas Grȍntzig and also referred to as percutaneous transluminal coronary angioplasty, is an invasive cardiovascular procedure performed to mechanically widen narrowed vessels in the heart.[2] Over the past 10 years, the number of PCI procedures performed in the United States has increased by 33%, with over 1.3 million interventions implemented in 2006.[1,3,4] Further, an estimated 83.6 million American adults (>1 in 3) have one or more types of cardiovascular disease. Of these, 42.2 million are estimated to be ≥60 years of age.[5]

Although coronary revascularization was transformed by balloon angioplasty, vessel recoil or vasospasm, resulting in the immediate loss of luminal diameter due to vascular constriction stemming from vessel damage inflicted during balloon inflation, caused concern.[4,6−9] The introduction of intracoronary stenting, metal tubes, or scaffolds implanted in the vessel during balloon angioplasty reduced elastic recoil of the vessels by 37.5%;[10] however, stenting also created new challenges associated with the implantation of a blood-contacting biomaterial including thrombosis, the formation of blood clots, and neointimal hyperplasia.[11] While thrombosis issues are largely overcome by using systemic anticoagulants, neointimal hyperplasia often prompts the need for a second procedure.[12,13]

This review seeks to provide context for current treatments for PCI, detailing both a historical overview of modern treatments, and an overview of the pathology of restenosis. In order to approach macromolecular therapeutic design for PCI, an understanding of the pathology of restenosis and arteries is needed. Thus, this article starts with the pathology and then discusses modern approaches to local delivery from balloon catheters and stents. This is followed by an overview of the therapeutics currently delivered from balloons and stents, complimented with a summary detailing their mechanism of action and limitations. Next, alternative approaches using macromolecules are discussed and lessons learned from these studies are highlighted. The review concludes with a short discussion of limitations and suggests future directions for use of macromolecules toward the development of novel therapeutic devices to improve outcomes following PCI.

PATHOBIOLOGY OF RESTENOSIS

In order for researchers to prevent the damages associated with PCI and restenosis, it is important to first understand its pathobiology. Restenosis is characterized by a progression of inflammation,[14,15] granulation,[15] smooth muscle cell (SMC)

Received: May 28, 2014
Revised: June 18, 2014
Published: June 25, 2014

   dx.doi.org/10.1021/bm5007757 | Biomacromolecules 2014, 15, 2825−2832

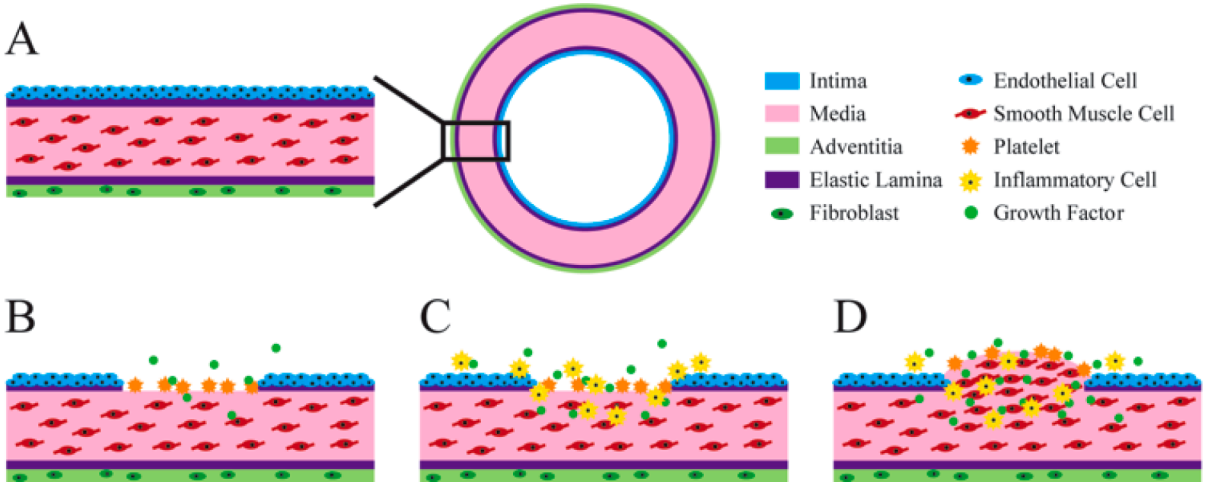


Figure 1. Schematic representation of (A) a healthy vessel and (B–D) the progression of restenosis in an injured vessel following PCI (not to scale). (A) Blood vessels have three distinct layers, intima, media, and adventitia, which are separated by elastic lamina. In a normal vessel, the intima is comprised of a monolayer of ECs, while the media contains circumferentially aligned SMCs in a matrix of collagen. (B) After PCI, ECs are denuded from the wall exposing the underlying collagen matrix to which platelets can bind, activate and secrete growth factors. (C) Growth factors secreted from activated platelets recruit inflammatory cells to the site of injury and (D) stimulate SMC proliferation, migration, and ECM synthesis, ultimately resulting in intimal hyperplasia.

proliferation,[16−18] and extracellular matrix (ECM) deposition[18,19] (Figure 1). The occurrence of restenosis following PCI is attributed to trauma during the procedure, triggering an array of mechanical and biological activities implicated in the healing process. This progression can be exacerbated by the presence of a stent, which acts as a nucleation site for clotting and inflammation. In uninjured vessels, the innermost layer of vessel wall, the intima, is comprised of a monolayer of endothelial cells (EC), which forms a tight barrier between the lumen of the blood vessel and the rest of the vessel wall (Figure 1A). This nonthrombogenic barrier aids in the prevention of clots, protects against inflammation, and is responsible for signaling the underlying medial layer.[20−22]

Trauma during PCI strips the ECs from the vessel wall, resulting in the elimination of important endothelium-derived antithrombotic factors such as nitric oxide (NO) and plasminogen activator inhibitor, among others.[23,24] Furthermore, the disruption of the EC layer also exposes the underlying medial layer, comprised of circumferentially aligned SMCs organized throughout a matrix composed mainly of collagen I and III (Figure 1B).[25] The exposure of the collagen matrix provides inherent targets for platelet adhesion, activation, and aggregation,[26,27] stimulating thrombus formation and the secretion of diverse pro-coagulant and mitogenic substances.[28,29] Inflammatory cells, such as neutrophils, lymphocytes, and monocytes, are recruited to the site of injury by surface expression of adhesion molecules, such as P-selectin, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1, by both the injured endothelial cells and activated platelets (Figure 1C).[28,30] Furthermore, the expression of P-selectin has been shown to accelerate the rate at which fibrin formation and deposition occurs, which is important as fibrin stabilizes thrombi (blood clots).[31]

Leukocytes, stimulated by a chemical gradient produced by SMCs in the injured area, migrate into the tissue and release growth factors, including platelet derived growth factor (PDGF),[32] transforming growth factor,[33−35] basic fibroblast growth factor,[36] and epidermal growth factor.[37−39] The release of growth factors from these activated leukocytes, as well as from platelets and SMCs, stimulate SMC proliferation and migration to the neointimal layer of the vessel wall (Figure 1D).[16−18] The released cytokines and growth factors also cause the synthesis of ECM components by SMCs.[40,41] The combined migration of SMCs into the intima coupled with ECM synthesis results in neointimal hyperplasia and reduced blood flow.

LOCALIZED THERAPEUTIC DELIVERY FROM STENT AND BALLOON PLATFORMS

To overcome the intimal hyperplasia resulting from PCI coupled with the use of bare metal stents, drug-eluting stents (DES) were employed to locally deliver antirestenotic therapeutics. Since FDA approval of the first DES, it is estimated that approximately 4.5 million DESs have been implanted, accounting for more than 75% of all stents deployed.[42−44] To include therapeutic agents on stents, drugs are either applied directly to the stent[45−47] or impregnated within polymer matrices.[48−50] These polymeric matrices have been designed to provide long-term release in vivo. Although DESs have reduced restenosis rates by as much as 37.5% compared to bare metal stents, the occurrence of late-stent thrombosis due to delayed arterial healing, incomplete re-endothelialization, and local inflammation, has raised concerns about their use.[10,51] The underlying reason for the development of late-stent thrombosis from DESs remains unknown; however, it is most likely due to the coupling of several factors, including delayed endothelialization,[52] adverse effects of the polymer coatings,[53] neointimal growth over a longer period,[54] and early discontinuation of systemic antiplatelet therapy.[55,56]

Bioresorbable stents (BRS) were developed for use in place of DESs, eliminating the potential consequences associated with permanent metal implants, as BRSs provide mechanical support to the vessel wall for a defined period of time following PCI prior to their subsequent resorption.[57] BRSs, fabricated from either a polymer or metallic alloy, are of interest as they provide the radial strength and low recoil characteristics necessitated by traditional metal stents, while allowing gradual and predictable release of impregnated therapeutics during the

dx.doi.org/10.1021/bm5007757 | Biomacromolecules 2014, 15, 2825−2832

resorption of the scaffold.[58,59] While BRSs protect against vessel occlusion stemming from elastic recoil and can release therapeutics similar to DESs, the potential for strut fracture, leading to constrictive remodeling, and concerns regarding fragments of the degradable stents breaking free and subsequently occluding small vessels exist.[60] In addition to the unique consequences associated with BRS, additional complications may arise; similar to bare metal and drug-eluting stents, an initial mismatch in compliance between the scaffold and the surrounding tissue exists, as well as the potential for delayed endothelialization and the challenges associated with the development of thrombosis remain unclear.[61]

An alternative to DESs and BRSs is drug-eluting balloons (DEBs), which have recently shown promising results with eliminating the complications caused by stents.[62] However, unlike both DESs and BRSs, the time frame for local therapeutic delivery from DEBs is much shorter. The ability of the balloon to transfer clinically relevant amounts of drug has encouraged the pursuit of DEBs as effective treatment options for the delivery of antirestenotic medication during PCI.[62] Furthermore, as the prolonged exposure of the stent to blood is eliminated, the required time for antiplatelet therapy is shortened in DEB-only PCI procedures.[63] Two of the main strategies for local delivery from balloons have occurred via elution of drug solution from porous balloon catheters[64−66] and drug-coated balloons.[62,67,68] Porous balloons are able to directly transfer drugs to the adjacent vessel wall using inflation pressure, which forces the solution from the balloon lumen to the tissue of the vessel wall; however, a delicate balance between sufficient pressure to deliver agents into the wall of the vessel, yet prevent mechanical wall damage must be achieved.[64,65,69,70] The use of drug-coated balloons presents another strategy for local delivery. Therapeutics, coated onto the surface of the balloon typically with carriers, are transferred to the vessel wall at the time of inflation.[63,68,71] In this case, premature drug release prior to balloon inflation and during transfer to the vessel wall, caused by rapid dissolution of hydrophilic carriers, remains a major complication of these drug-coated balloons.[72] While both DEB strategies are intriguing and may prove efficacious over use of stents, the porous balloon has the additional benefit that it can deliver hydrogel precursors, or even molecular coatings to the damaged surface of the vessel to form soft, antithrombotic coatings on the vessel lumen.

CURRENT THERAPUETIC TREATMENTS AND LIMITATIONS

An understanding of the mode of action, as well as the strengths and weaknesses, of antirestenotic compounds, in addition to the limitations of stents as described above, supports innovation around new approaches to improve upon PCI. Advances within the pharmaceutical and scientific communities have enabled medical researchers to develop a wide range of antirestenotic therapeutics. As restenosis is generally limited to the area of intervention, the investigation of local delivery of antirestenotic compounds from both balloons and stents has become an integral topic in modern research. The overall goal of the developed therapies is to target the key processes involved in the healing response leading to restenosis, including platelet activation, inflammation, SMC proliferation and migration, and ECM synthesis.[50,73]

Antirestenotic therapeutics are classified in four categories: antiproliferative, anticoagulant, anti-inflammatory, and pro-healing. The most popular antirestenotic therapeutics are the antiproliferative compound, paclitaxel, and anti-inflammatory agent, sirolimus. Table 1 lists the DESs, BRSs, and DEBs currently utilizing these therapeutic compounds in their formulations. Paclitaxel, which is employed as the active ingredient in the formulations of several DESs approved for use in the United States and Europe, as well as several BRSs and DEBs approved for use in Europe, effectively targets and inhibits SMC proliferation.[49,74] Similarly, the anti-inflammatory compound sirolimus, and several of its analogs, are currently utilized as therapeutics in numerous FDA approved DESs, in addition to several BRSs currently approved in Europe, as these compounds have effectively limited the immunogenic response caused by PCI and have been shown to decrease SMC proliferation and migration in vivo.[48,75−82] However, both paclitaxel and sirolimus, like many antiproliferative and anti-inflammatory compounds, are not cell specific and, therefore, their effects are not limited purely to SMCs; rather, these therapeutics exhibit a negative response on EC proliferation and migration, ultimately hindering complete healing of the vessel wall.[80,82,83]

Similar to antiproliferative and anti-inflammatory therapeutics, both anticoagulant and pro-healing therapeutics have shown success with minimizing some of the key processes leading to restenosis; however, compounds in these two classes are not utilized clinically on angioplasty balloons or stents due to consequences associate with each category.[1,9,76,83,84] Anticoagulant compounds, with the exception of heparin, demonstrate poor mechanisms for re-endothelialization of the injured vessel wall and as such, provide partially endothelialized, fibrin-rich sites creating a stimulus for surface-induced thrombosis.[85−87] Alternatively, pro-healing biologics, which are characterized by their ability to support re-endothelialization of the arterial wall, have been reported to minimize the extent of SMC proliferation, platelet adhesion, and collagen synthesis.[19,88−90] Still, this class of antirestenotic therapeutics does not attenuate every aspect of restenosis; adverse inflammatory responses,[91,92] as well as decreased vasoconstrictive properties of injured vessels,[93] have resulted after treatment with pro-healing drugs. Therefore, as each of the four classes of antirestenotic therapeutics demonstrates detriments for the prevention of restenosis regardless of systemic delivery or local delivery via stents or coated balloons, there is a need to develop new approaches to combat thrombosis and neointimal hyperplasia.

ALTERNATIVE STRATEGY FOR RESTENOTIC TREATMENT

Two major approaches have been investigated to improve outcomes following PCI. The first approach is to place therapies on the adventitial side of the vessel, such that the therapeutic will diffuse from outside of the vessel wall into the medial and intimal layers. These perivascular remedies aim to suppress intimal hyperplasia without potential side effects stemming from direct contact with blood and further disruption of the endothelium. Perivascular methods include delivery of cells and polymeric formulations.[94,95] The second approach is to deliver therapeutics to the lumen of the blood vessel. Approaches to the latter concept include delivery of nanoparticles and paving of the vessel lumen.[96,97]

Investigations aiming to improve PCI outcomes through delivery of therapeutic treatments peripheral to the blood vessel show promising results, but are limited by surgical access to

Table 1. Summary of Coronary DESs, BRSs, and DEBs Impregnated with Paclitaxel or Sirolimus, and Derivatives, Currently Approved or in Clinical Trials in the U.S. and Europe[a]

therapeutic	device (manufacturer)	type	coating	strut
Paclitaxel				
	Infinnium (SMT)[b]	DES	PLLA, PLGA, PLC, PVP	SS
	Ion (Boston Scientific)[b,c]	DES	SIBS	PtCr
	Taxus Express (Boston Scientific)[b,c]	DES	SIBS	SS
	Taxus Liberte (Boston Scientific)[b,c]	DES	SIBS	SS
	Danubio (Minvasys)[b]	DEB	butryl-tri-hexyl citrate	
	Dior II (Eurocor)[b]	DEB	shellac	
	Elutax SV (Aachen Resonance)[b]	DEB	unknown	
	In.Pact Falcon (Medtronic)[b]	DEB	urea	
	Lutonix DCB (BARD)[b]	DEB	polysorbate/ sorbitol	
	Pantera Lux (Biotronik)[b]	DEB	butryl-tri-hexyl citrate	
	Primus (Cardionovum)[b]	DEB	shellac	
	SeQuent Please (B. Braun Melsungun)[b]	DEB	iopromide	
Sirolimus				
	Cypher (Cordis)[b,c]	DES	PEVA, PBM	SS
	Supralimus (Sahajanand Med Tech)[b]	DES	PLLA, PLGA, PLC, PVP	SS
Everolimus				
	MiStent (Micell Technologies)[b]	DES	PLGA	CoCr
	Promus Element (Boston Scientific)[b,c]	DES	PVDF-HFP	PtCr
	SYNERGY (Boston Scientific)[b]	DES	PLGA	PtCr
	Xience V (Abbott)[b,c]	DES	PVDF-HFP	CoCr
	Absorb BVS (Abbott)[b]	BRS	PLLA	PDLLA
Zotarolimus				
	Endeavor (Medtronic)[b,c]	DES	PC	CoCr
	Resolute (Medtronic)[b,c]	DES	BioLinx	CoCr
Novolimus				
	DESyne (Elixir)[b]	DES	PLA	CoCr
	DESolve (Elixir)[b]	BRS	PLLA	PLLA
	DESolve 100 (Elixir)[b]	BRS	PLLA	PLLA
Biolimus				
	Axxess (Biosensors Europe)[b]	DES	PLA	Nitinol
	BioMatrix (Biosensors Europe)[b]	DES	PLA	SS
	Nobori (Terumo)[b]	DES	PLA	SS

[a]Abbreviations: CE, Conformité Européenne; CoCr, cobalt chromium; PC, tyrosine-derived polycarbonate polymer; PBM, poly(*n*-butyl methacrylate); PDLLA, poly(D,L-lactide); PEVA, poly(ethylene covinyl acetate); PLA, polylactic acid; PLC, 75/25 poly-L-lactide; PLGA, poly(lactide-*co*-glycolide); PLLA, poly-L-lactic acid; PtCr, platinum chromium; PVDF-HFP, poly(vinylidene fluoride-hexafluoropropylene); PVP, polyvinylpyrrolidone; phosphorylcholine; SIBS, poly(styrene-*b*-isobutylene-*b*-styrene); SS, stainless steel. [b]CE approved. [c]FDA approved.

implant the perivascular therapies, in addition to the PCI procedure needed to clear the occluded vessel. Briefly, Nugent, Rogers, and Edelman seeded ECs on Gelfoam mats, composed of compressed gelatin, prior to surgically inserting the mats peripheral to the vessel. Once surgically transplanted, factors secreted by the ECs were found to influence SMC response to vessel injury, ultimately resulting in decreased intimal hyperplasia following balloon angioplasty.[98] In further work, Nugent et al. demonstrated that perlecan, a proteoglycan secreted by the seeded ECs was responsible, at least in part, for the suppression of intimal hyperplasia.[99] The findings are encouraging because they highlight the importance of communication between smooth muscle cells and endothelial cells in vessel health, thus, provide further insights into potential therapeutic strategies.

The release of small molecules and biologics from the periphery of the vessel wall has also proven interesting. One strategy included the delivery of polymers that produce or release NO, a compound released by ECs to induce vasorelaxation and minimize SMC migration, both of which suppress intimal hyperplasia.[100] Alternatively, researchers have investigated perivascular delivery of the antiproliferative and anti-inflammatory compounds used in drug eluting stents.[101,102] Gene delivery is also a target therapy, as demonstrated by the use of cationic polyethylenimine complexes to deliver genes from periadventitial reservoirs.[103] Finally, biodegradable polymers can be used to delivery therapeutics, such as Sunitinib, an inhibitor of both PDGF and vascular endothelial growth factor, both of which are implicated in hyperplasia.[104] The periadvential delivery approach is sufficiently flexible to allow delivery of a variety of therapeutics including cells, small molecules, biologics, and combinations thereof.

Delivery of therapeutics from outside the blood vessel has proven to be effective in animal models; however, this method of treatment comes with advantages and disadvantages. One main advantage of perivascular delivery is the ability to implant therapeutics without further compromising or damaging the lumen of the diseased vessel. There are also fewer size limitations to the implant, as perivascular wraps are not anticipated to directly affect blood flow by taking up key luminal real estate or to serve as a nidus for thrombosis. Finally, perivascular materials may employ multiple strategies for therapeutic delivery including controlled release of NO to suppress vasoconstriction and SMC migration, as well as the release of antiproliferatives, and potentially even the transplantation of endothelial cells. These materials are not without complications however; a main disadvantage is that they do require a more invasive, open surgery for implantation. While limiting with respect to PCI, these approaches may be particularly useful in alternative procedures where synthetic grafts or vein grafts are deployed, and in surgical arteriovenous fistula creation, where open surgery facilitates implantation of the perivascular devices.

Conversely, therapeutic delivery to the lumen of the blood vessel can be performed coincident with PCI, thus negating the requirement for additional surgical procedures. This concept is not new and was reviewed as early as 1994 by Slepian.[105] Hill-West et al. demonstrated in 1994 that photopolymerization of polyethylene glycol (PEG) hydrogel barriers within the lumen of the blood vessel both prevented platelet adhesion and also significantly suppressed intimal hyperplasia in both a rat arterial crush injury and a rabbit balloon angioplasty model.[106] While limited by the need to isolate the blood vessel and stop blood flow, the work showed that thin (~13 μm) hydrogel layers were sufficient to suppress hyperplasia. West and Hubbell later

demonstrated that degradable photopolymerized PEG hydrogel barriers, which degraded over a 24 h period, were equally as effective at suppressing intimal hyperplasia as nondegradable PEG hydrogel barriers, as determined 2 weeks following balloon angioplasty. This result is hypothesized to be due to the suppression of initial thrombus formation that ultimately leads to inflammation and vessel wall thickening.[107] While limited by the need to stop blood flow and manipulate the vessel to ensure polymerization occurs only on the luminal surface, these studies were pivotal in showing that suppression of early interactions between the newly denuded vessel surfaces and blood-borne factors is critical to healthy vessel healing.

In an alternative strategy with a focus to develop vascular paving materials that better match the vessel wall mechanical properties, Ashton et al. developed blends of polycaprolactone and polyurethane.[108] The incorporation of polyurethane improves compliance of the polymer, while the polycaprolactone is slowly degradable and thus could be used as a controlled release depot. While this particular construct was investigated for abdominal aortic aneurism indications, where it may be necessary to have a permanent component, the ability to deliver therapeutics intraluminally may be of importance in some PCI applications. In addition, if the surface can be made nonthrombogenic, this kind of approach may reduce the need for aggressive antiplatelet therapies, used to prevent thrombosis on blood-contacting materials that come with many complications. Similarly, Livnat, Beyer, and Seliktar developed an interpenetrating network of PEG and alginate in the form of a thin film.[109] The film was deployed coincident with a stent to form a barrier between the stent and the vessel wall. This approach allowed delivery of the antithrombotic paving material during a standard procedure without the need to stop blood flow for a prolonged period of time. However, it does not overcome the placement of a stent, and its associate complications.

Returning to approaches that preclude the need to use permanent implants, an intriguing method for coating the luminal surface of a blood vessel is using layer-by-layer technology. This method improves upon early hydrogel techniques as it does not require initiator and photopolymerization, nor does it require insertion of a cylindrical mold to prevent polymerization throughout the lumen of the blood vessel. However, it does require temporary elimination of blood from the surface to be treated, and blood flow must be interrupted for several minutes for each layer that is deposited. First reported by Thierry et al. layer-by-layer deposition of polyelectrolytes was used to suppress platelet deposition on damaged arteries and release therapeutics locally.[110] Using chitosan to first create a cationic adhesive layer on the anionic vessel wall, alternating layers of chitosan and hyaluronic acid were built up to form 5 bilayers. The bilayers were found to be strongly adhesive and able to prevent platelet binding. In addition, they were able to incorporate polyarginine, which while reducing the incorporation of hyaluronic acid, also decreased platelet adhesion by 30%, presumably due to increased NO generation, over films lacking polyarginine. Regardless of the mechanism, this study demonstrated that the approach not only suppresses platelet binding, but can also be adapted for incorporation of drugs to further improve outcomes. Future studies will need to address the inability to form these layers in the presence of blood and the length of time needed to form each layer to adapt it to current angioplasty techniques. Further information about this approach can be found in reviews by Groth and Lendlein[111] and by Kerdjoudj et al.[112]

Taking yet another tactic, Kastrup et al. developed an adhesive hydrogel that could be painted directly onto atherosclerotic plaques to both deliver therapeutics and to reinforce the plaque fibrous cap.[113] An alginate catechol was synthesized that could both be cross-linked by oxidation, via addition of periodate, and also take advantage of the bioadhesive properties of the phenolic catechol moiety to cross-link the alginate to the surface of the plaque. The gel was found to withstand physiological shear stress and deliver therapeutics. As the approach delivers therapeutics directly to the plaque, with the aim to shrink the plaque and increase blood flow, it precludes the need for balloon angioplasty. Limitations of the approach include the need for about 15 min for cross-linking; this time will need to be decreased significantly if it is to become clinically relevant. However, it is an exciting tactic as it may eliminate the need for PCI, and its associated complications, in cases that are diagnosed sufficiently early, where the immediate need to increase the lumen size, and thus blood flow, are not needed.

Other approaches look to deliver polymer through porous balloons, directly to the site of PCI, such that these polymers rapidly bind to the vessel wall and form thin films. Building on earlier work that used PEG-diisocyanate to reduce thrombus formation on Dacron vascular grafts, Deglau et al. delivered *N*-hydroxysuccinimide-PEG (NHS-PEG) to the arterial surface using the Boston Scientific Remedy balloon.[114] NHS forms covalent cross-links with primary amines, thus, allowing the polymer to graft to both endothelial cells and denuded vascular surfaces. In a rabbit femoral angioplasty model, 67% of the grafted polymer remained covalently bound 72 h postdelivery compared to the amount of polymer grafted at time zero. The loss of polymer coating is attributed to protein turnover at the injury site.[115] While no data is presented on long-term suppression of intimal hyperplasia, there will likely be a positive impact based on early suppression of platelet binding. Interestingly, the grafted polymer also contained biotin. As avidin binds strongly to biotin (K_a = 10^{15} L/mol), the biotin was used to subsequently deliver avidin-conjugated microparticles, via intravenous injection, to the luminal vascular coating. While the vast majority of the microparticles were washed away after 72 h, nanoparticles with a higher surface area may prove more stable. Importantly, this study shows that the luminal coatings can be adapted to not only inhibit early platelet binding and activation, as well as the subsequent biological events that lead to intimal hyperplasia, but also they can be used to target therapeutics to the site of injury.[115]

Aiming to mimic the antithrombotic properties of the native glycocalyx, a 2011 study by Paderi et al. demonstrated that the glycosaminoglycan dermatan sulfate could be conjugated to collagen-binding peptides and subsequently delivered through a porous angioplasty balloon at the site of angioplasty to rapidly coat the luminal surface of denuded blood vessels.[116] Dermatan sulfate, a glycosaminoglycan (GAG) native to arteries, mimicked the anionic nature of the GAG-rich glycocalyx on the endothelial cell surface, while the collagen binding peptides supported rapid and prolonged binding of the GAG only to collagen exposed following balloon injury. The material, DS-SILY, was delivered over 15−30 s using a porous delivery balloon, which served to slow blood flow and deliver the compound to the intervention site; flow was restored immediately following delivery. Results suggested reduced

dx.doi.org/10.1021/bm5007757 | *Biomacromolecules* 2014, 15, 2825−2832

platelet binding to coated surfaces in vitro, as well as inhibited vasospasm or elastic recoil, following PCI. In addition, this work showed that DS-SILY did not bind to the healthy endothelium and is thus unlikely to affect function of these intact cells. In follow-on studies in the Ossabaw pig model, Scott et al. further demonstrated that delivery of DS-SILY inhibited both early platelet binding to the blood vessel at the angioplasty site, as well as intimal hyperplasia 28 days postangioplasty, in the presence or absence of bare metal stents.[117] These studies demonstrate that as we begin to understand the biological triggers to disease states, tissue healing, and regeneration, we can combine that knowledge with our understanding of polymer chemistry as a means of developing new polymers that are able interact intimately with tissues to improve healing and regeneration.

CONCLUSIONS AND FUTURE PERSPECTIVES

Since the revolutionary development of balloon angioplasty, we have gained a significant understanding of the biological triggers that lead to vasoconstriction, thrombosis, restenosis, and ultimately reduced blood flow following balloon angioplasty. While stents were developed to resist elastic recoil, vascular paving studies have shown that recoil can be eliminated, or at least significantly reduced simply by eliminating platelet contact from the lumen surface for about 24 h following PCI. This calls into question the need for deployment of metal stents in cases where PCI does not result in dissection of the vessel and allows development of biomimetic polymers that can be used to temporarily repave the vascular surface to protect the vessel from platelet binding and the subsequent recruitment of neutrophils and monocytes. Table 2 shows the ideal characteristics of paving materials. The ability to synthesize multifunctional polymers also provides the opportunity to incorporate drug delivery into these polymer coatings. As shown by Deglau et al.[115] researchers can think beyond delivery of therapeutics at the time of PCI, but can also engineer particle capture systems into the paving material to recharge the therapeutic for longer-term delivery. By capitalizing on our ever-increasing understanding of the biology of the vascular system, biomacromolecules can be developed that work with the biology to induce healthy healing without the long-term consequences of implantation of foreign materials.

Table 2. Characteristics of an Ideal Lumen Paving Material

aspects	properties
biocompatibility	Nonthrombogenic, endothelial cells compatible, anti-inflammatory, inhibit intimal hyperplasia
mechanical	Resistant to physiological shear stress, flexible, must expand and contract with vessel wall, vessel wall adhesive
safety	Fragments must not detach and occlude smaller vessels, must not occlude blood flow due to material thickness or thrombosis
compatible with PCI	Must not require additional surgery, deliverable though low profile catheter including from balloon surface, through porous balloon, or hollow catheter, Deliverable in the presence of blood, Does not stop blood flow for greater than 2 min, complete delivery only to target site.

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Notes

The authors declare the following competing financial interest(s): Alyssa Panitch owns greater than 5% of Symic Biomedical, a company planning to enter into an agreement to license this technology from Purdue Research Foundation. This does not alter the authors' adherence to all the *Biomacromolecules* policies on sharing data and materials.

ACKNOWLEDGMENTS

Funding for this research was through NIH R01HL106792. R.A.S. is supported by a NSF Graduate Research Fellowship (DGE-1333468).

ABBREVIATIONS

CAD, coronary artery disease; PCI, percutaneous coronary intervention; SMC, smooth muscle cell; ECM, extracellular matrix; EC, endothelial cell; NO, nitric oxide; PDGF, platelet-derived growth factor; DES, drug-eluting stent; FDA, Food and Drug Administration; BRS, bioresorbable stent; DEB, drug-eluting balloon; PEG, polyethylene glycol; NHS, *N*-hydroxysuccinimide; GAG, glycosaminoglycan; CE, Conformité Européenne; CoCr, cobalt chromium; PC, tyrosine-derived polycarbonate polymer; PBM, poly(*n*-butyl methacrylate); PDLLA, poly(D,L-lactide); PEVA, poly(ethylene covinyl acetate); PLA, polylactic acid; PLC, 75/25 poly-L-lactide; PLGA, poly(lactide-*co*-glycolide); PLLA, poly-L-lactic acid; PtCr, platinum chromium; PVDF-HFP, poly(vinylidene fluoride-hexafluoropropylene); PVP, polyvinylpyrrolidone; phosphorylcholine; SIBS, poly(styrene-*b*-isobutylene-*b*-styrene); SS, stainless steel

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