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Advances in Nanotechnology for the Management of Coronary Artery Disease

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Abstract

Nanotechnology holds tremendous potential to advance the current treatment of coronary artery disease. Nanotechnology may assist medical therapies by providing a safe and efficacious delivery platform for a variety of drugs aimed at modulating lipid disorders, decreasing inflammation and angiogenesis within atherosclerotic plaques, and preventing plaque thrombosis. Nanotechnology may improve coronary stent applications by promoting endothelial recovery on a stent surface utilizing bio-mimetic nanofibrous scaffolds, and also by preventing in-stent restenosis using nanoparticle-based delivery of drugs that are decoupled from stents. Additionally, nanotechnology may enhance tissue-engineered graft materials for application in coronary artery bypass grafting by facilitating cellular infiltration and remodeling of a graft matrix.

Keywords

Nanotechnology; coronary artery disease; atherosclerosis; percutaneous coronary intervention; coronary artery bypass graft

Nanotechnology and Medicine

Nanotechnology enables the engineering of materials by manipulating their atomic and molecular components' physical properties, chemistries, and assemblies. Recent advances in our understanding of disease processes at the molecular level have enabled extensive applications of nanotechnology in medicine, including fields such as diagnostics, imaging, drug delivery, and tissue engineering (Farokhzad and Langer, 2006). By precisely engineering nanomaterials to optimize their desired properties (e.g., size, surface chemistry,

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and magnetism), novel diagnostics and therapies can be developed with improved diagnostic accuracy, reduced drug toxicity, and enhanced therapeutic efficacy.

Nanotechnology Opportunities in the Treatment of Coronary Artery Disease

In this review, we focus on the application of nanotechnology in the treatment of coronary artery disease (CAD) and highlight several areas of opportunity where nanotechnology may lead to novel classes of therapeutics or enhance existing therapies. Current treatment strategies for CAD can be divided into two principal groups: (1) conservative management with medical therapies and (2) invasive management with mechanical revascularization by percutaneous coronary interventions (PCI) or coronary artery bypass graft (CABG) surgeries (Libby et al., 2011). Figure 1 provides a brief overview of each treatment strategy and the ways in which nanotechnology can be utilized.

Conservative Management of CAD and Nanoparticle-based therapies

Atherosclerosis is a chronic condition in which the arterial wall thickens and becomes inflamed as a result of atheromatous plaque formation (Libby et al., 2011). The main goals of current medical therapies are to decrease atherosclerotic plaque burden, stabilize vulnerable plaques, and prevent plaque rupture and subsequent thrombosis. Figure 2 describes potential treatment strategies along the progression of atherosclerosis, including (1) atherogenesis (lipid accumulation within the vessel wall), (2) subsequent inflammatory cascade, (3) plaque development with a necrotic core, and finally (4) plaque rupture and thrombosis.

Modulation of lipid disorders

Cholesterol is a hydrophobic molecule that requires lipoprotein carriers, which are themselves naturally occurring endogenous nanoparticles, for its transport within the circulation. Low-density lipoproteins (LDLs) carry cholesterol from the liver to peripheral tissues. When they are in excess, as in the case of hyperlipidemia, cholesterol-laden LDLs increasingly accumulate within the arterial wall and become oxidized, causing endothelial injury and inflammatory response and leading to the first step of atherosclerosis (Ross, 1999). Thus, the focus of current treatment strategies has been to decrease blood LDL levels by lipid-lowering medications such as the hydroxymethylglutaryl CoA reductase inhibitors, more commonly known as statins.

Statins have proven to dramatically reduce morbidity and mortality in patients with CAD (Shepherd et al., 1995). Multiple studies have shown that high-dose statin therapy not only lowers blood lipid levels but also exerts anti-inflammatory and anti-oxidant effects (Cannon et al., 2006). However, dose-dependent adverse effects limit the use of high-dose statin therapies. Recently, Broz et al. developed a targeted vesicle system to allow directed administration of high-dose statin while reducing toxicity in other tissues. In their study, vesicles were loaded with pravastatin and surface-functionalized with an oligonucleotide that has an affinity for inflammatory macrophages (Broz et al., 2008). The study demonstrated effective targeting of the vesicles to macrophages and improved tolerability, producing up to 15-fold reductions in cytotoxicity to muscle cells. While *in vivo* efficacy and safety studies have yet to be performed, these results may point toward a safe option for a high-dose statin therapy using nanoparticles.

An alternative approach to decrease vascular lipid burden is to modulate the levels and effects of high-density lipoproteins (HDLs) in the blood (Lan Hsia et al., 2000). HDL transports cholesterol from peripheral tissues to the liver by a process called reverse cholesterol transport (RCT). HDL also appears to exert other atheroprotective effects such as

reducing inflammation and preventing endothelial dysfunction. Improving circulating HDL levels has become an attractive goal in treating atherosclerosis. Nanotechnology can be utilized to synthesize biomimetic HDL. One such example is a liposomal formulation with dimyristoyl phosphatidylcholine (DPMC), a key HDL surface molecule that mediates the extraction of cholesterol from peripheral tissues. Cho et al. recently reported that cholesterol-fed rabbits, when infused with DMPC liposomes, had significantly decreased aortic cholesterol content and plaque volume (Cho et al., 2010). These results show that modulating LDL and HDL levels with nanoparticles offers therapeutic opportunities for atherosclerotic plaque suppression and regression.

Anti-inflammatories

The initial inflammatory response in atherosclerosis includes up-regulation of cytokine and adhesion molecules that promote monocyte recruitment. The recruited “inflammatory” monocytes then migrate to the vessel wall and differentiate into macrophages, the key cellular elements of atherosclerosis (Libby et al., 2011). Macrophages take up oxidized LDLs, transform into lipid-filled foam cells, and further express inflammatory cytokines, thus continuing the cycle of inflammation. Various approaches have been taken to mitigate this inflammatory process.

Leuschner et al. reported significantly decreased plaque burdens after nanoparticle-assisted systemic delivery of a short interfering RNA (siRNA) silencing CCR2, a key chemokine receptor that stimulates inflammatory monocyte recruitment (Leuschner et al., 2011). Synthetic siRNA can effectively attenuate its target protein production but cannot readily cross the cell membrane due to its large size and negative charge (Blow, 2007). Thus, the development of formulations for effective delivery of siRNA to target cells has been a major challenge on the path to its widespread clinical application. As shown by the work of Leuschner et al., nanoparticles may provide a suitable delivery vehicle for siRNA, effectively suppressing inflammation in atherosclerosis.

Nanoparticles may also assist the delivery of glucocorticoid, a potent anti-inflammatory agent that was previously shown to reduce macrophage accumulation in atherosclerotic lesions in a cholesterol-fed rabbit model (Poon et al., 2001). Glucocorticoids have unfavorable pharmacokinetic profiles, including rapid clearance and a large volume of distribution, resulting in the need for frequent administration of high doses and causing significant adverse effects such as diabetes, hypertension, and osteoporosis. Liposomal formulation may overcome these limitations by prolonging circulatory half-lives, thereby improving drug accumulation in vascular endothelium. Lobatto et al. recently reported significant reductions of inflammation in atherosclerotic plaques after liposomal glucocorticoid therapy (Lobatto et al., 2010). Although more safety studies are needed, nanoparticle-based glucocorticoid therapy may become an attractive option to treat atherosclerosis.

Another innovative technique developed by McCarthy et al. uses light activatable nanoagents to directly ablate macrophages and thus reduce plaque inflammation (McCarthy et al., 2010). In the study, dextran-coated iron-oxide nanoparticles were loaded with phototoxic agents. In an ApoE knockout mouse model, the nanoparticles were selectively taken up by macrophages within atherosclerotic plaques and induced massive death of macrophages when irradiated, without causing significant skin toxicity. These results highlight the potential use of light-activated nanocarrier systems as a safe alternative to reduce inflammation by effectively ablating macrophages.

Anti-angiogenics

The formation of neovessels within atherosclerotic plaques is another key feature of more advanced disease states. It has been suggested that extensive plaque angiogenesis may promote plaque growth, intra-plaque hemorrhage, and plaque instability, increasing the risk of plaque rupture (Moreno et al., 2004). Hypothesizing that therapies to inhibit angiogenesis may stabilize or regress atherosclerotic plaques, Winter et al. developed $\alpha_v\beta_3$ integrin-targeted nanoparticles to deliver Fumagillin, a potent anti-angiogenic drug, specifically to the site of atherosclerosis where angiogenesis is active (Winter et al., 2006). The clinical use of Fumagillin has been limited due to its significant adverse neurocognitive effects, especially when used in high doses. Targeted nanoparticle-assisted drug delivery may improve its therapeutic window by achieving adequate drug concentration at the site of disease with a reduced systemic dose. Accordingly, Winter et al. demonstrated significantly reduced angiogenesis and subsequent plaque burden after a single injection of targeted Fumagillin-loaded nanoparticles given at one third of a typical dose. In a subsequent study, the same group demonstrated a sustained anti-angiogenic effect of the nanoparticle-assisted Fumagillin treatment when coupled with statin therapies in a cholesterol-fed rabbit model (Winter et al., 2008).

Anti-thrombotics

As atherosclerotic plaques grow, a necrotic lipid core surrounded by a fibrous cap forms within the plaques. Degradation of the cap and subsequent rupture may induce intracoronary thrombosis, which then leads to obstruction of coronary blood flow and subsequent myocardial ischemia or infarction (Libby et al., 2010). Exploiting the fact that thrombin is a rate-limiting factor in the clotting cascade and platelet activation, Myerson et al. developed nanoparticles that are surface-functionalized with a highly effective irreversible thrombin inhibitor, D-phenylalanyl-L-prolyl-L-arginyl-chloromethyl ketone (PPACK) (Myerson et al., 2011). PPACK, despite its highly selective, potent thrombin-inhibiting property, has largely been limited in clinical use due to its rapid clearance. By covalently attaching PPACK to the surface of long-circulating perfluorocarbon-core nanoparticles, significant improvements in anti-thrombotic activity in a mouse arterial thrombosis model were observed. Similarly, Peters et al. developed targeted micellar nanoparticles encapsulating hirudin, a potent natural thrombin inhibitor (Peters et al., 2009). In the study, the nanoparticles were surface-functionalized with fibrin-binding peptides, thereby targeting the sites of fibrin-rich clots. Although the team succeeded in demonstrating *in vivo* targetability of hirudin-encapsulated micelles, their anti-thrombotic efficacy remains untested.

PCI and Nanomedicine Strategies to Assist Stent Technologies

Percutaneous coronary interventions (PCI) have revolutionized the treatment of obstructive CAD (Serruys et al., 2006). While placement of bare metal stents (BMS) provides mechanical support to achieve vascular patency, it also causes significant injury to the arterial wall, accelerating neointimal hyperplasia and subsequent in-stent restenosis. Drug eluting stents (DES) were thus introduced to prevent restenosis by releasing anti-proliferative drugs to the site of intervention and subsequently have become the treatment of choice for CAD. Despite their extensive clinical use, they are not without risks. DES have been associated with delayed endothelialization and increased thrombogenicity, requiring extended treatments with anti-platelet therapies (Stone et al., 2007). Additionally, in-stent restenosis is still observed in 3-20% of patients after DES (Dangas et al., 2010). Consequently, alternatives to DES such as bioabsorbable or biodegradable stents or antibody-coated stents to recruit endothelial progenitor cells have been the subjects of active research (Pendyala et al., 2012).

Nanotechnology could offer a new avenue for the improvement of current stent technology. The nanotechnology applications can be divided into two groups based on their therapeutic strategies: an anti-restenosis strategy to prevent smooth muscle cell proliferation and a pro-healing strategy to restore functional endothelium (Figure 3). In the anti-restenosis strategy group, nanoparticles are engineered to deliver anti-proliferative drugs to the site of interventions for effective suppression of neointima formation after PCI. Decoupled from stents, nanoparticles may allow spatiotemporal control of drug delivery to maximize anti-proliferative effects while minimizing systemic toxicity. In the pro-healing strategy group, nanotechnology can be utilized to actively recruit endothelial cells to the site of intervention for restoration of endothelium, which in turn may prevent thrombus formation and neointimal hyperplasia.

Nanotechnology with an Anti-Restenosis Strategy following PCI

Systemic Nanoparticle Delivery—Nanoparticles have been used to deliver a variety of drugs (both small molecules and gene products) to prevent arterial stenosis. One such example is a liposomal nanoparticle loaded with bisphosphonate, a potent inhibitor of monocytes and macrophages. The clinical use of bisphosphonate has been limited due to its poor cell membrane permeability requiring high systemic doses (Danenberg et al., 2002). When encapsulated in liposomes, however, bisphosphonates can be readily taken up by monocytes or macrophages, effectively inactivating the cells and inhibiting their proliferation. Danenberg et al. hypothesized that transient inactivation of macrophages by liposomal bisphosphonates at the time of vascular injury could decrease subsequent restenosis that is typically mediated by excessive inflammation (Danenberg et al., 2002). In the study, Danenberg et al. reported that treatment with liposomal alendronate, a potent bisphosphonate, at the time of stent implantation in a lipid-fed rabbit model resulted in significant reductions in neointimal formation and arterial stenosis (Danenberg et al., 2003). Liposomal alendronate formulations are currently being tested in a phase II, dose-finding, randomized, multi-center, prospective, double blinded study.

Another example is the albumin-based-nanoparticle delivery of paclitaxel, a mitotic inhibitor with potent anti-proliferative effects. Paclitaxel has been used extensively for the prevention of restenosis in the form of drug-eluting stents. Albumin has a number of advantages for delivery of paclitaxel, including its ability to reversibly bind paclitaxel and also its natural affinity to vessel walls by binding to glycoprotein VI-receptors on endothelial cells, facilitating transportation of drugs across the endothelial cells (Stinchcombe, 2007). Kolodgie et al. demonstrated a dose-dependent reduction in stent restenosis after infusion of albumin-based, paclitaxel-loaded nanoparticles (Nab-Paclitaxel) (Kolodgie et al., 2002). Subsequently, the systemic delivery of Nab-paclitaxel was tested in patients undergoing BMS placement for safety and optimal dosing and found to be well tolerated without significant toxicity (Margolis et al., 2007).

Targeted Drug Delivery for Preventing In-stent Restenosis—Targeted, systemic nanoparticle delivery of drugs specific to the sites of vascular injury has been an attractive goal given the potential to concentrate drugs at the site of disease while minimizing systemic toxicity. Several markers including $\alpha_v\beta_3$ integrin, VCAM-1, tissue-factor, and subendothelial extracellular matrix proteins such as collagen IV or chondroitin sulfate proteoglycans (CSPGs) have been identified as potential targets for injured endothelium (Brito and Amiji, 2007). Joner et al. developed a novel prednisolone-encapsulated liposomal formulation targeted to CSPGs and demonstrated preferential localization of drugs to the sites of stent-induced injury and subsequent reduction in restenosis in atherosclerotic rabbits (Joner et al., 2008). Likewise, Chan et al. developed a collagen-IV targeting, paclitaxel-encapsulated polymeric nanoparticles called *nanoburrs*, and reported significant improvement in arterial

stenosis after targeted nanoparticle treatment in a rat carotid injury model (Chan et al., 2011). In another study, Lanza et al. reported similar anti-restenotic effects with paclitaxel-loaded nanoparticles targeted to tissue factor, a transmembrane glycoprotein that is over-expressed after vascular injury (Lanza et al., 2002).

Alternatively, “stents” themselves instead of injured vessels can serve as a target for nanoparticle-assisted drug delivery. Chorny et al. developed a biocompatible, paclitaxel-loaded magnetic nanoparticle that is attracted to the stent struts and adjacent arterial tissues in the presence of a magnetic field, facilitating the localization of nanoparticles and effective inhibiting of in-stent restenosis (Chorny et al., 2010).

Nanotechnology with a Pro-Healing Strategy following PCI

Endothelial cells play critical roles to maintain proper functioning of the coronary arteries (Kipshidze et al., 2004). They produce vasoactive compounds for dynamic regulation of coronary blood flow, modulate hemostasis and thrombolysis, and control the migration and proliferation of smooth muscle cells. Because PCI result in near-complete denudation of endothelium, extensive efforts have been made to promote endothelial growth on a stent surface.

Nanotechnology offers potential solutions to facilitate endothelialization. Kushwaha et al. developed a self-assembled nanofibrous matrix mimicking an endothelial extracellular matrix (Kushwaha et al., 2010). In this study, a nanofibrous matrix was designed to attract endothelial cells while serving as a surrogate reservoir of nitrogen oxide (NO), a key cytokine to limit smooth muscle cell proliferation and platelet adhesion and enhance re-endothelialization. The matrix was comprised of peptide amphiphiles biomimetic scaffolds, an endothelial cell-adhesive peptide ligand, a NO-donating polylysine group as a reservoir of NO, and the metalloprotease-2 mediated cleavage site for slow degradation of the nanofibrous matrix to aid in the sustained release of NO. Kushwaha et al. reported that this NO-releasing nanofibrous matrix resulted in significantly improved endothelialization while effectively suppressing smooth muscle cell proliferation and platelet cells adhesion *in vitro*. Similarly, Ceylan et al. developed a bioactive stent coating by conjugating peptide amphiphile nanofibers with (1) an REDV epitope that selectively promotes endothelial cell adhesion and spreading over smooth muscle cells and platelets and (2) a Dopa molecule that forms a strong hydrogen bond with hydrophilic surfaces of stainless steel, thereby securely immobilizing the nanofiber on the stent surface (Ceylan et al., 2011). Ceylan reported an improved endothelial cell adhesion, spreading, and proliferation on a nanofiber-coated stent compared to a bare stent. While more studies are needed to assess their *in vivo* applicability, these ECM-mimicking nanofibrous matrix may provide an efficient platform for bioactive stent development, promoting endothelial cell recovery on a stent surface.

Polyak et al. used an alternative strategy to improve endothelial healing using magnetically responsive cell therapy (Polyak et al., 2008). First, endothelial cells were loaded with magnetic nanoparticles (MNP) and then injected to rats with stainless steel stents placed in their carotid arteries. When a magnetic field was applied, these MNP-loaded cells were preferentially driven to the stented area and remained attached. While this use of magnetically responsive cells to facilitate stent re-endothelialization may provide a useful alternative for vascular healing after stent placement, further studies are warranted to assess long-term viability and functionality of the endothelial cells after delivery to the stent surface.

CABG and Nanotechnology for Creation of Biosynthetic Grafts

A coronary artery bypass graft (CABG) surgery requires a patient's disease-free vascular graft to bypass severely diseased, obstructed coronary vessels and restore coronary blood flow (Rathore et al., 2012). To date, patients' own blood vessels have served as primary vascular conduits for the surgery, but they are often not available as they may also be diseased or have already been used for prior surgeries. To address this need for vascular graft materials, there have been extensive efforts to create tissue engineered vascular grafts (TEVGs). Nanotechnology may assist to enhance current TEVG applications. Stankus et al. created a vessel-mimicking, small-diameter conduit by concurrent (1) electrospinning of a biodegradable polymer to form ECM-mimicking nanoscaffold and (2) electrospraying of smooth muscle cells to facilitate cell attachment to the scaffold (Stankus et al., 2007). The study reported that the conduits were highly cellular and flexible, with mechanical properties resembling native arteries. Alternatively, Hashi et al. used mesenchymal stem cells seeded to electrospun biodegradable nanofibrous scaffolds and demonstrated the synthesis of cellular grafts with well-organized endothelial and smooth muscle cell layers comparable to native vessels, with long-term patency (Hashi et al., 2007). These studies suggest that electrospun nanofibrous scaffolds may promote efficient cellular infiltration and matrix remodeling, making them ideal tissue-engineered vascular grafts.

Summary and Future Directions

Nanotechnology promises tremendous opportunities for treating CAD. Nanoparticles may provide a safe and efficacious delivery platform for various drugs whose clinical utilities are otherwise limited due to their systemic toxicity or unfavorable pharmacokinetic properties. Biomimetic nanofibrous scaffolds may assist coronary stent applications by facilitating rapid restoration of endothelium at the site of intervention. Additionally, various nanotechnology approaches, such as nanospinning and nanopatterning, may enhance tissue-engineered graft materials for CABG by facilitating cellular infiltration and remodeling of a graft matrix.

Many challenges remain for a successful implementation of nanotechnology in the management of CAD. First, *in vivo* safety and biocompatibility of nanomaterials must be carefully examined for potential toxicity or host immune response. Second, various biophysicochemical properties, such as serum stability or drug release profiles, need to be optimized and orchestrated for improved efficacy. Finally, the clinical applicability of nanotechnology needs to be tested and justified as in randomized trials, which is particularly challenging given the paucity of prior clinical data and experience. Thus, active collaborations among scientists, engineers, and clinicians are critical for successful application of nanotechnology to advance current treatment of CAD.

In conclusion, the advances in nanotechnology, combined with our increasing understanding of molecular pathogenesis of coronary artery disease, have significantly improved existing therapies and led to the creation of potential therapeutic applications for the management of coronary artery disease, with greater benefits to come as researchers continue to push the envelope.

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Conservative Management medical therapies

↓ **LDL**
↑ **HDL**
↓ **Inflammation**
↓ **Angiogenesis**
↓ **Thrombosis**

Synthetic HDL

Drug Delivery

Medical
therapy

Heat-induced
Ablation

Management
of CAD

Invasive Management revascularization

PCI

Drug Delivery

↓ **Restenosis**

Endothelial Cell
Recruitment

↑ **Endothelialization**

CABG

Tissue Engineered
Vascular Graft

↑ **Graft success**

Figure 1. Current management of coronary artery disease and the overview of nanotechnology opportunities

For conservative management, nanotechnology can be utilized to create synthetic HDLs, deliver drugs that are otherwise difficult to be used clinically due to poor pharmacokinetic profiles or systemic toxicity, and reduce plaque inflammation by heat-induced ablation of macrophages using light-activated targeted nanoparticles. For invasive management with coronary revascularization with either PCI or CABG, nanotechnology can assist to deliver anti-proliferative drugs to prevent stent restenosis, facilitate re-endothelialization over stent struts with nanofibrous scaffolds, and create biosynthetic tissue-engineered grafts with improved cell attachment and viability.

Figure 2. Progression of atherosclerosis and therapeutic strategies

The main goal for the treatment of CAD is to control atherosclerosis, a multi-step process of chronic vascular inflammation and subsequent plaque formation. Current treatment strategies have been developed to modulate blood lipid levels, decrease inflammation or angiogenesis within atherosclerotic plaques, and prevent clot formation.

Figure 3. Anti-restenosis versus pro-healing strategies after PCI

In the anti-restenosis strategy, in-stent neointima formation can be prevented by nanoparticle-assisted delivery of anti-proliferative, anti-inflammatory drugs, or by heat-induced ablation of inflammatory cells with light-activatable nanoparticles. In the pro-healing strategy, re-endothelialization can be facilitated by using nanofibrous scaffolds that mimic extracellular matrix in vessels, or by using magnetic nanoparticles for enhanced delivery of cells to stent struts under magnetic field.