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Microelectromechanical Systems and Nanotechnology: A Platform for the Next Stent Technological Era

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Abstract

Nanotechnology is the design and development of materials, structures, and devices with at least 1 dimension between the 1- and 100-nm-size scale. Manipulating matter at the atomic scale offers unique opportunities in material design particularly in biological interfaces. In this short review, we explore the disruptive technological opportunities that nanotechnology and microelectromechanical systems may offer in possible future stent designs along with safety issues that may surface with the use of nanoparticles in medical devices.

Keywords

nanotechnology, microelectromechanical systems, local drug delivery, stent design, targeted drug delivery, bottom up approach

Introduction

The Angioplasty Journey and Current Stent Technology Deficiencies

Despite the enthusiasm about the innovative way of coping with the atherosclerotic plaque, initial balloon angioplasty attempts pioneered by Andreas Grüntzig in 1977 led to the realization of the need of coping with the elastic artery recoil. Bare metal stents (BMSs) by Palmaz and Schatz surfaced as a solution to this arterial recoil, which led to the study of the high percentage of in stent restenosis due to smooth muscle cell (SMC) proliferation and neointima formation. Powerful local cellular suppression with rapamycin or paclitaxel loaded on drug-eluting stents (DESs) then became the state of the art,[1,2] which later on brought up the problem of late arterial healing. The vulnerability of DESs to in-stent thrombosis has been attributed to delayed stent struts and arterial wall reendothelization and overeaction to the stent's drug-eluting polymer surface; dual antiplatelet therapy (DAPT) has been shown to reduce thrombosis rate during the vulnerable time period (which has yet to be accurately defined); despite recommendations for at least 1 year post-stent DAPT,[3] acute thrombotic events following the stop of DAPT have occurred even a year after DES implantation.[4] It is obvious that what we experience in stent technology history is an "onion-peeling" effect where we solve a layer of problems only for new problems to arise. Whether there is an end to this effect with our advancing knowledge on nano interactions will surely be revealed to us in the years to come. In this review, we try to capture some novel micro- and nanotechnologies that combined have the potential to become the platform of the future stent technological era.

Discussion

Current Stents: Still a Passive Local Drug Delivery Platform

All current stent devices, BMS, DES, or even bioabsorbable stents, are passive in terms of sensing their environment. On the other hand, every mechanistic event (eg, arterial lumen loss due to thrombosis) in human body is manifested through changes in blood flow and/or specific biomolecules (often called biomarkers), the interactions of which we try to decipher with the help of proteomics and genomics.

Role of Microelectromechanical Systems in Stent Design

Microelectromechanical systems (MEMS) are being used in endovascular surgery as pressure gauges or intravascular

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ultrasound probes on intravascular catheters, but novel stents also, based on MEMS, have been developed and tested. Proof of concept MEMS sensors have already been produced and loaded on stents. These devices comprise a pressure or flow sensor, a power unit, an antenna for wireless data transmission through body tissues (in some designs the whole metallic stent could be an antenna called stentenna[5]) and a biocompatible hermetic package used to isolate the MEMS and protect the sensitive electronic components from corrosion and the body from hypersensitivity reactions.

Chow et al[6] have demonstrated and tested a pressure gauging MEMS with the option of loading it on a stent. It is designed with a wireless antenna for data transmission and a power module for remote powering based on electromagnetic wave propagation; an approach that is not limited to the need for proper alignment between the inductive coils, neither presents the need for proximity between the implant and the induction coil.

The sensing modules of MEMS will gradually be encapsulated within endothelial cell coverage, through fibrin deposition or neointima formation in the long term. Endothelial coverage will affect their direct access to mechanical characteristics of flow. Therefore, MEMS on stents should be designed to access blood constituents indirectly (eg, blood flow velocity detection through shear stress or electromagnetic flow detection). Encapsulation of MEMS is a serious problem resembling the in-stent restenosis of stent; these 2 phenomena are in fact foreign body tissue reaction to inorganic material. Biomolecular sensing capabilities of MEMS may also be compromised by antibodies' fouling; this side effect may be counterparted, in the case of devices detecting small molecular weight molecules, with molecular weight–selective pores through controlled diameter in the microscale.[7]

Ideally, future MEMS devices should be bioabsorbable with organic electronics such as silicon on silk[8]; in this case functionality versus absorbability should be balanced for long-term functionality till completion of the arterial reconstruction post stent implantation.

The MEMS and Stent Drug-Eluting Properties

Nonhomogenous drug delivery due to local flow (eg, turbulent flow) or plaque and stent morphology parameters (eg, hard calcified plaque and stents struts size)[9] is a hard to attack problem, which inhibits homogenous drug delivery of DES. Microneedles on stent struts designed primarily for percutaneous drug delivery[7] may be used to perforate microns in the arterial lumen especially through hard atherosclerotic plaque[10] and deliver the antiproliferative drugs on their target, for example, SMC. Three-dimensional nonplanar microfabrication technologies[11] will be necessary for this type of microfabrication on curved stent surfaces, and the fact of arterial wall injury or incomplete wall penetration of needles should be tested further prior to implementation of this technology.

The MEMS technology may also provide solutions to the problem of potential rupture of drug-releasing platform, which may lead to drug dose dumping. Drug distribution to a large number of individual microreservoirs that release the drug through gradual electrochemical degradation of gold that covers the opening of the nanoliter reservoirs may provide a controlled and stable release according to the local environment needs. This platform has already been tested in vivo by Shawgo et al.[12] Microfabricated drug reservoirs are already in existence,[7] but none of them is refillable. Technologies that will be able to display this "refueling" characteristic will be most welcome for long-term release of drug in the site of interest.

The MEMS for Other Uses in Vascular Surgery

The MEMS actuators have already been proposed to remotely control the radial strength and hence the diameter of a stent in hard calcified plaques. Moreover, stand-alone MEMS such as CardioMEMS are finding their way to market for wireless abdominal aortic aneurysm intrasac pressure measurement in order to detect endoleaks, stent migrations, and aneurismal sac expansions accurately, timely, and noninvasively. Similar technologies may soon be embedded in smaller caliber stents used for peripheral and coronary interventions and provide the edge of the early and local detection of postimplantation sequelae prior to acute events that may be fatal.

The MEMS have proved their value as sensors, platforms for local drug delivery (LDD), and mechanical actuators, but the more we delve into the bottom of the size scale the more we realize that targeted LDD is currently the most fruitful path to counteract restenosis. This is a size scale where biochemical events rule. At this scale, nanotechnology has a crucial role that we are just beginning to harness.

Nanotechnology and Targeted LDD

Local immunosuppressant therapy, powerful and nontargeted, has proven to be clinically potent; it was adopted through DES platforms and is still in use with continuous refinement of the drug delivery vectors.

Current drug delivery properties of DES are monotonous where a more dynamic in situ drug-elution method is needed, one that will promote artery healing with the right drug and/or dosage for every phase of postimplantation physiological sequelae. At first, the target is to reduce hyperplasia of SMCs and immediate thrombosis due to artery denudation; in the long term, there is a need for complete arterial endothelial cell coverage. We are gradually moving from a lumen diameter restoration model to a holistic arterial reconstruction model with the latest supposed to be presented by bioabsorbable stents[13] but not yet fully verified by clinical trials.[13]

Nanotechnology-mediated LDD has been mainly focused in cancer treatment,[14] but most of the methods can be applied in every field where LDD is needed. We seek to control specific local arterial physicochemical properties or create vectors in the nanoscale called nanoparticles in order to achieve LDD with the added option of targeted and controlled release kinetics, an option lacking from current DES technology.

Targeting the denuded artery post stent implantation through systemic delivery is a difficult task due to high shear stress on arterial wall, which renders difficult the accumulation

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of nanoparticles on the wall. A phenomenon similar to enhanced retention and permeability (ERP) of tumor vascular endothelium in post stent implantation arterial wall, which can be used for augmented local nanoparticle concentration, has been reported by Uwatoku et al[15] and van Beusekom et al.[16] Nevertheless, despite the possibility for enhanced vascular permeability of the damaged arterial lumen, some kind of surface functionalization of drug vectors will be needed for enhanced LDD and more complex nanoparticle to arterial wall interactions.

Site and even cell specificity of drug delivery needs to be implemented. Endothelial targeting moieties have been analyzed by Weissleder et al[17]; and vascular cell adhesion molecule 1, a biomarker present at atherosclerotic sites has been shown to be a potential target for stented arteries. Other epitopes like $a_v\beta_3$-integrins, tissue factor, and fibrin clots[18,19] are candidates for site-specific targeting. Functionalization of polymer nanoparticles embedded on bioabsorbable stents may provide the next platform for drug delivery on bioabsorbable stents.

Prolonged decreased cell adhesion when and where needed may be facilitated with Si nanowires, which already have displayed sustained anti-biofouling properties,[20] a property that is extremely important in drug release reservoirs where cell and/or antibody adhesion can silence the drug elution.

Concepts and proof of them in animals have been conducted with metallic stents and magnetic nanoparticles. One team has preloaded endothelial cells with biodegradable superparamagnetic nanoparticles, which rendered the cells magnetically susceptible. This was used to guide these cells on metallic stent wires through magnetic induction of the stent with a uniform external magnetic field.[21] One added benefit of this nanoparticle-mediated technology is the freedom of choice for the drug/drugs loaded on the nanoparticles. Magnetic nanoparticles may be delivered intravenously and guided with uniform magnetic fields to the stented part of the artery due to the magnetizing effect of the external field to the susceptible metallic stent. A limitation of this technology is the current trend of shifting toward nonparamagnetic materials for stents (eg, bioabsorbable scaffold technology); limitation that may be overridden with the use of magnetic nanoparticles embedded in a nonparamagnetic polymer scaffold to render it magnetically susceptible or with the use of antibody–antigen matching for nanoparticles' and stent's surface.

Much work has been done in nanoparticle drug delivery systems in stented arteries in animals with no active targeting but only systemic administration that takes advantage of denuded artery ERP phenomenon; systemic and nontargeted use of lipid and polymeric nanoparticles and results of their use have been reviewed by Brito et al.[22] Results seem to indicate that the nontargeted use of nanoparticles leads to systemic toxicity in animal models due to the potent nature of the drugs loaded on the nanovectors and the nontargeted nature of the delivery to the site of interest. This highlights that without targeting functionalization of their surface toward the stented artery wall, nanoparticles are not the holy grail of drug delivery.

Other Stent-Related Nanotechnology Approaches

Vessel thrombosis and restenosis at the onset of arterial endothelial denudation have been well documented,[23] and the early coverage of the artery with endothelial cells may prove to be an effective strategy in the artery reconstruction era of today. Since complete endothelization of the denuded arterial wall is a factor related to restoration of the normal function of the artery[23] anti-CD 34 antibody–coated stents have been proposed and tested clinically[24] in order to recruit progenitor endothelial cells stemming from bone marrow and circulating in the blood. Nevertheless, the anti-CD 34 antibody is not endothelial specific, leading as well to the recruitment of other deleterious progenitor cells such as that of SMCs.[25] Despite the failure of this progenitor cell recruitment example, there is a display of the paradigm shift in the current stent technology trying to harness the local biophysical parameters in order to assist artery healing.

A common problem with all stents is that their surface is not "cell friendly," that is their surface topology leads cells to react to it as a foreign body. Current stents may be likened to artificial coral reefs on sunk ships where late and incomplete coverage will take place but the natural "seeding" is missing; artificial coral reefs can never reach the richness of fauna and flora of natural ones. There is evidence of increased endothelial cell proliferation on nanostructured surfaces of metal stents with activation of platelets affected not only by the material but also by the surface topology of the same material.[26] Loya et al[27] propose the formation of nanopillars on stent metal through radiofrequency sputtering that proved to be superior in vitro in contrast to metals with no nanotopology. Shen et al[28] report enhanced in vitro bovine endothelial cell proliferation in nitinol micropatterned surfaces with micropores and microgrooves combined with a plasma deposited silicon oxide nanocoating. Increased endothelization of nanorough surfaces seems to be material independent as there are reports of same improved cytoadhesion on polymeric surfaces that have been treated to present nanotopology[29]; a fact which is very important in the coming era of bioabsorbable stent's generation. Nanostructured materials promote initial blood protein absorption that enhances the following cellular adhesion; this fact seems to make the difference between nanotopology and conventional surfaces in terms of biocompatibility of bioengineered materials.[30]

Safety of Nanoparticles

The profound advantages of nanoparticle systems have already led to their adoption in commercial products, without enough data about their human and ecological safety. Early nanotoxicological experiments failed to present reliable dose-dependent data about nanoparticles due to complex size and chemical composition interactions of diffusion and agglomeration. Nanoparticles are an extension of the classic concept of the molecule[31]; for these supramolecular structures new methods of study of their biodistribution should be

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invented. Smaller particles (below 100 nm) tend to diffuse and agglomerate with greater velocity (not taking into account the possibility of active targeting of tissues) rendering classical toxicology methods inefficient. There is no definite answer considering the safety of nanoparticle systems as this is system and tissue dependent and defies the classic molecular mechanisms of biodistribution of drugs. For example, small metal nanoparticles may have long-term detrimental effects due to their continuous nonmass-dependent catalytic activity inside cells that produce reactive oxygen species in the long term. For a recent complete review on the subject of nanoparticle toxicology, reader is referred to the article by Wendelin J. Stark.[31]

Conclusion

Current solutions to atherosclerosis-related arterial stenosis are in fact mechanical solutions to a complex phenomenon that is manifested mechanically but is rooted in complex biological interactions. The DES platform is a first step toward the manipulation of the biology of the phenomenon, although we use powerful inhibitors in a nontargeted fashion. Despite the progress in material science of stents, no trojan horse solution to arterial restenosis exists yet. Microtechnology in terms of sensing devices may de-passivate current stents and enable full monitoring of the arterial reconstruction process. Nanotechnology may enable targeted drug delivery and enhanced biocompatibility of current stents through the manipulation of nanotopological surface features. It is our opinion that the combination of these 2 disruptive technologies will enable a platform for the next generation of stents. Stent platforms with early warning systems and targeted drug elution may not be far fetched even with today's technology, nevertheless clinical studies will have to prove enhanced safety and results prior to the wide adoption of this new technologies.

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