Future Strategies for Antiproliferative Stent Coatings

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Summary

Without a doubt, coronary stenting has revolutionized the clinical practice of interventional cardiology by reducing some of the shortcomings of balloon angioplasty, particularly abrupt vessel closure and restenosis. Clinical studies, research and development, especially the physical description of physiological processes between implant's surfaces and the physiologic environment, has led to a steady improvement of hemo- and biocompatibility. A classic example of this development strategy is the non-activating silicon carbide (a-SiC:H) coating of stents. Nevertheless, in-stent restenosis still remains an unsolved problem in the therapy of coronary artery disease. In the past several years attempts have been undertaken to overcome the incidence of in-stent restenosis. Recently, drug delivery systems with anti-proliferative agents have shown promising results in promoting and modulating the growth of vascular smooth muscle cells and endothelial cells. Further improvements can be achieved by using silicon carbide as a basis for drug delivery systems or bioactive coatings in order to modulate vascular cell growth.

Key Words

Stent coating, restenosis, drug delivery systems, angiotensin, glycosaminoglycans

Introduction

In the two decades since the first percutaneous transluminal coronary angioplasty (PTCA) was introduced in 1977 by Andreas Gruentzig, steady progress in research and development has led to advanced non-surgical treatments for obstructive coronary artery disease [1]. Especially the invention of vascular stents has undoubtedly revolutionized the clinical practice of interventional cardiology by partially reducing some of the shortcomings of balloon angioplasty, particularly abrupt vessel closure and restenosis [2]. This breakthrough in the therapy of coronary artery disease raised other questions concerning the hemocompatibility and biocompatibility of the materials used for the stent bulk. Initially, vascular stents consisting of medical stainless steel showed a high thrombogenicity leading to an undesirable post-procedural acute or subacute stent thrombosis. An understanding of the interactions between the artificial implant and the physiologic environment has led to the development of an anti-thrombogenic stent coating with silicon carbide (a-SiC:H) [3]. Though the silicon carbide coating significantly improves the hemocompatibility of vascular stents, in-stent restenosis still remains a problem in the therapy of coronary artery disease. In reducing the incidence of restenosis, novel therapy approaches such as drug-delivery systems or bioactive coatings show promise in avoiding the proliferation and hyperplasia of smooth muscle cells and endothelial cells [4]. This outlook focuses on the future possibilities of anti-proliferative coatings as an add-on coating to silicon-carbide stents.

The Problem of Restenosis

Despite the emerging enthusiasm for coronary stenting among interventional cardiologists, restenosis persists as a significant limitation. The dominant mechanism of late restenosis is assumed to be the proliferation of smooth muscle cells resulting in neointimal hyperplasia. It is suspected that this proliferation is triggered by interaction processes at the interface between the

implant's surface and the biological environment. The migratory smooth muscle cells undergo a phenotypic transformation from their normal contractile regulatory function to a proliferative state with extracellular matrix formation. In the period that follows, progressive neointimal thickening occurs, which may result in significant lumen obstruction as well as myocardial and recurrent angina symptoms. Clinical studies have shown wide variations in the angiographic and clinical incidence of in-stent restenosis, with rates varying from 10 % to as high as 58 % [5]. These rates are unacceptably high and require novel therapeutic treatments in coronary stenting.

Approaches for Anti-proliferative Coatings

Attempts to inhibit proliferation of smooth muscle cells and matrix formation have included a host of clinical trials with a wide range of agents, including corticosteroids, colchicene, angiotensin-converting enzyme-inhibitors, lipid-lowering drugs, calcium channel antagonists, angiopeptin, platelet-derived growth factor receptor antagonists, tranilast, serotonin receptor antagonists, antioxidants, nitric oxide donors, antisense oligonucleotides, and coronary irradiation via radioactive stents. Though intracoronary radiation seemed to be the most promising approach for preventing restenosis, complications like edge restenosis and late thrombosis have been reported [6,7]. Early trials in the field of anti-proliferative treatments included evaluations of corticosteroids, colchicene, angiotensin-converting enzyme-inhibitors, and calcium channel antagonists. In vitro, all of these agents showed anti-proliferative effects. Subsequent animal studies in various models showed encouraging results. Unfortunately, there is not yet any clinical evidence showing significant differences in restenosis rates between control groups and groups treated with these agents [4]. In the case of pharmaceutical approaches, the local drug concentration seems to be an important factor [8]. Delivering medication directly to the site of vascular injury via polymer-coated stents is a reasonable approach to get an adequate local drug delivery at the site of the injury [9-11]. Furthermore some biomaterials like glycosaminoglycans show in vitro an inhibition of cell adhesion and spreading. These polysaccharides can be covalently bonded to silicon-carbide coated stents. Thus, an anti-proliferative coating is formed on top of a passive biomaterial [12-14].

Silicon Carbide as an Ideal Basis for Anti-proliferative Coatings

316L stainless steel, although it has superior mechanical properties, exhibits a relatively poor biocompatibility. It was already shown that reduced activation of cells and proteins can only be achieved by a surface coating with physical properties adapted to the physiologic environment. Silicon carbide in an amorphous, hydrogen-rich, phosphorous-doped modification (a-SiC:H) is such a material with optimized biocompatibility [3]. Silicon-carbide coated stainless steel thus guarantees an optimal performance regarding long-term stable passive behavior. The silicon-carbide coating is therefore an ideal substrate for anti-proliferative coatings of different kinds. On the one hand, the a-SiC:H layer covers the stainless steel completely, even though a biodegradable drug delivery coating disappears after several weeks or months. On the other hand, the a-SiC:H coating offers dangling bonds and carbon atoms, which opens the possibility of forming a covalent attachment of bioactive macromolecules to the stent's surface.

Drug Delivery Systems

The list of materials used to coat metal stents in an attempt to reduce their inherent thrombogenicity and decrease the incidence of in-stent restenosis is long and ever increasing. In drug delivery systems, drug-polymer composites are referred to as monolithic matrices. When non-degradable matrices are used, drugs are delivered through sustained release by means of particle dissolution and diffusion through the cavitating network of the matrix. This approach allows extended drug release using formulations with reported release durations ranging from hours to decades. Biodegradable polymer systems have also been used to formulate drug-delivery matrices. Biodegradable polymer matrices provide sustained delivery of pharmacological agents both by drug dissolution and by matrix degradation in vivo, leading to the release of entrapped agents. The coating of a pharmaceutical stent with a biodegradable polymer offers the attractive possibility that the drug-polymer system could disappear after a desired period of drug release [10,15]. For a sufficient polymer-drug coating of a silicon carbide stent and a long-term release of the desired agent, Poly(D,L-Lactide) (PLA) and Poly(D,L-Lactide-co-Glycolide)

(PLGA) are biocompatible materials useful for a variety of applications, including the design and properties of the controlled-release systems for pharmaceutical agents. In recent years, PLA and PLGA have been extensively investigated for use as implantable biodegradable carriers for controlled release of drugs. Their long clinical usage in surgical sutures underscores their biocompatibility in physiological environments, where they are hydrolyzed into metabolic products that are eliminated from the body. The degradation rates and the release profiles depend on molecular weight, copolymer composition, and the crystallinity of the polymer and polymer end groups, all of which control water access to the ester linkage of the polymers and therefore affect the degradation velocity [16]. Silicon carbide coated stents can be coated with a layer of PLA or PLGA containing the drug by dip coating or spray coating techniques. Several drugs can be considered as candidates for stent coatings preventing in-stent restenosis. A promising approach is the local delivery of a pharmaceutical agent that specifically inhibits cell proliferation of vascular smooth muscle cells (VSMC). As angiotensin II is known as a potent growth-promoting factor of VSMC, choosing a special drug to regulate the renin-angiotensin-system in a specific manner should modulate the growth of VSMC and endothelial cells. The local delivery of such an agent should lead to an anti-proliferative effect, thus avoiding undesirable in-stent restenosis [17]. Influencing this system in a specific manner should minimize the side effects reported in clinical studies on known anti-proliferative drugs.

Bioactive Coatings

Regarding the reduction of the incidence of in-stent restenosis, the application of several glycosaminoglycans such as chitosan, hyaluronic acid, as well as their composites and derivatives, several reports show promising results in modulating the growth of VSMC and EC [12,13]. Glycosaminoglycans and derived composite materials are of interest for this type of application, since carbohydrate moieties interact with many cell adhesion molecules and matrix glycoproteins [18]. These substances are also applied in the field of tissue engineering to control the cellular interactions at the tissue-biomaterial interface by adjusting specific material parameters. Consequently, it is expected that by varying the surface composition of glycosaminoglycans at the phase boundary between the stent and the vascular cells, the tissue growth of VSMC and EC can be modulated. Using an existing technology for dip coating, glycosaminoglycans can be covalently bonded to the silicon carbide surface via a spacer molecule [19,20]. Crosslinking the network of coated glycosaminoglycans should result in a stable bioactive layer with long-term anti-proliferative effects.

Conclusion

Despite the phenomenal pace of stent design technology and the improvements in biocompatibility that have been achieved with the silicon carbide coating, the incidence of in-stent restenosis remains unacceptably high. To address this problem, intense research is being conducted in order to find new stent coatings. Coatings with specific polymer-drug composites or with specific glycosaminoglycans show promising results in modulating the proliferation of vascular smooth muscle cells and endothelial cells.

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