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 hemocompatibility 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
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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 physiological 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 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.

References


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