Nanosurface modification of titanium and titanium coated stainless steel coronary stents for preferential cell functions

ABSTRACT

Surface modification of metallic implants is proposed as a viable means to alleviate the problems related to in-stent restenosis. Amongst the various surface modification strategies, surface nanotexturing is highlighted as a promising approach to improve the cellular behavior and tissue integration of biomedical implants. This thesis work focuses on developing a polymer-less and drug-free nanostructured coating on coronary stents to promote the natural growth of an intact, functional endothelium which could serve as a smooth barrier, preventing platelet aggregation and proliferation of smooth muscle cells and thereby addressing the issue of in-stent restenosis. To demonstrate this, as a first step, an array of unique, integrated TiO$_2$ nanostructures of distinct morphologies viz., Nanoleaves, Nanopores, and Nanorods were developed on metallic titanium (Ti) surfaces using a simple, aqueous chemistry based hydrothermal route. Influence of various surface nanotopographies on the proliferation and functionality of vascular endothelial and smooth muscles cells were investigated in-vitro. Nanostructuring resulted in significantly enhanced cellular viability and proliferation of endothelial cells, with raised levels of nitric oxide and substantially decreased smooth muscle cell proliferation. To propose this strategy of surface modification for translation on to clinically used metallic stents, it is imperative that the surface be also hemocompatible - an essential attribute for any blood contacting device. Direct blood interaction studies of TiO$_2$ nanostructures of varied morphologies on contact with human blood was carried out in-vitro, and also after endothelialisation of the substrate, to study the influence of endothelial layer on blood components. Hemocompatibility was also evaluated under dynamic flow conditions in an in-vitro circulation model using nanostructured stent prototypes. Nanomodified surfaces showed negligible hemolysis, insignificant thrombus formation with no alterations in the normal clotting times, and minimal inflammatory
reaction under constant shear and static conditions. Endothelialized nanomodified Ti surfaces showed substantially reduced adhesion, activation as well as aggregation of platelets compared to that of control surface. The endothelium formed on the nanosurfaces was found to be anti-thrombotic, with increased expression of genes contributing to anti-thrombogenicity and subsequent down regulation of thrombogenic genes. Consequently, having established the in-vitro efficacy of nanostructures in promoting endothelialization, the titania nanomorphology that exhibited the best cell response was selected for surface modifying one of the most widely used stent material, viz., Stainless steel (SS). This was then translated on to the currently available bare metal SS coronary stents via a TiO\textsubscript{2} nanotexturing approach through precursor mediated hydrothermal processing, after sputter coating the SS substrate/stent with metallic titanium. Nanomodified TiO\textsubscript{2} coatings on SS demonstrated better corrosion resistance, elasticity, and adhesion strength compared to that on metallic Ti. Nanomodified SS also showed better vascular cell response with preferential rapid endothelialization and enhanced nitric oxide production, while reducing smooth muscle cell proliferation in comparison to bare SS. Moreover, nanostructured TiO\textsubscript{2} coatings on SS coronary stents demonstrated better mechanical stability and durability which are favourable for its use in stenting applications. These beneficial effects suggest the potential use of such stable, easily scalable nanostructures on coronary stent surface as a viable option to regulate the fundamental factors responsible for in-stent restenosis. This polymer-less, drug-free strategy of stent surface modification could possibly be a promising alternative to the currently used expensive drug eluting approaches.