Prohealing Multifunctional Endothelium Nanomatrix Coated Stents

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Statement of Purpose

Stents are the most common cardiovascular implants used in the treatment of cardiovascular diseases. However, there are concerns about in-stent restenosis with bare metal stents (BMS) and late stent thrombosis and late inflammatory responses with drug-eluting stents (DES). Despite the promise of recently developed strategies to overcome the challenges of current stents, there remain many emerging concerns and limited success. Development of innovative strategies to restore endothelium healing while limiting the risk of late stent thrombosis, inflammatory responses, and restenosis is critical for the success of stents. The goal of this study is to demonstrate the prohealing effects of the novel multifunctional endothelium nanomatrix coated stent, which will minimize the risks of late stent thrombosis, restenosis, inflammatory responses, and incomplete endothelialization. Our overall hypothesis is that the prohealing multifunctional endothelium nanomatrix can enhance stent efficacy by promoting endothelial healing on the surface of the stent.

Research Design and Methods

Peptide amphiphiles (PAs) with either a cell adhesive ligand (YIGSR) or polylysine nitric oxide donors (KKKKK) were synthesized and mixed in a 9:1 molar ratio to form PA-YK. Nitric oxide-releasing PA-YK-NO was developed by reacting PA-YK with nitric oxide. PA-YK-NO self-assembled into nanofibers through water evaporation without use of organic solvents and was verified by TEM. Nitric oxide release profiles were studied with Chemiluminescence and Griess assays. Proliferation of human umbilical vein endothelial cells and human aortic smooth muscle cells was also evaluated. Platelet adhesion to collagen I, stainless steel, PA-YK, and PA-YK-NO was investigated using fluorescently-labeled blood. Adhesion and differentiation of endothelial progenitor cells was also studied. Preliminary animal studies in a rabbit iliac artery model were conducted.

Results

TEM confirmed that PA-YK successfully assembled in nanofibers of uniform diameter of 7-8 nm. The nitric oxide release profile from PA-YK-NO displayed an initial burst release in the first 48 hours of measurement followed by slow, sustained release over 60 days. Human umbilical vein endothelial cell proliferation was significantly increased on PA-YK-NO compared to PA-YK; conversely, human aortic smooth muscle cell proliferation was significantly decreased. Both PA-YK and PA-YK-NO significantly reduced platelet adhesion compared to both collagen I and stainless steel.

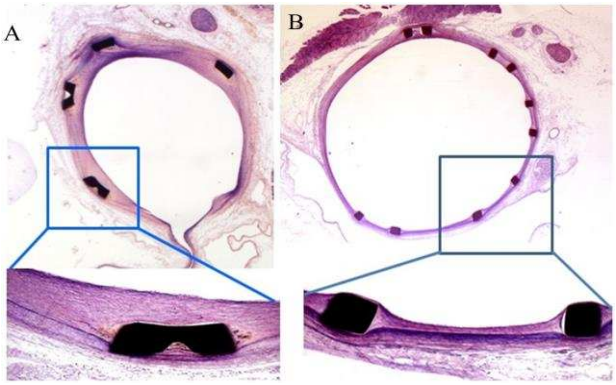

Figure 1: Histological sections of stents implanted in rabbit iliac artery after 4 weeks. (A) Control BMS. (B) PA-YK-NO coated stent.

Endothelial progenitor cell adhesion was significantly higher on PA-YK and PA-YK-NO compared to the control; endothelial marker expression was also significantly increased on PA-YK-NO. Preliminary rabbit studies showed that stent coatings are stable, had minimal inflammation and thrombosis, and exhibited high endothelial cell coverage with reduced neointimal formation (figure 1), demonstrating the efficacy of the prohealing multifunctional endothelium nanomatrix in vivo.

Conclusion

We have successfully developed a prohealing multifunctional endothelium nanomatrix that can enhance endothelialization and inhibit smooth muscle cell proliferation and platelet adhesion. Preliminary rabbit iliac artery studies demonstrated excellent stent structural integrity in circulating blood, high endothelial cell coverage, reduced restenosis, and no thrombosis. Therefore, this nanomatrix has vast potential to enhance stent efficacy by promoting endothelial healing and reducing neointimal formation, inflammation, and thrombosis. Future studies will include evaluation of stent efficacy in rabbit iliac arteries for up to six months as recommended by the FDA for DES pre-clinical trials in order to assess mature restenosis and late stent thrombosis.

References:

1. Kushwaha et al, Biomaterials 2010 ; 31 :1502-1508
2. Andukuri et al, Tissue Engineering, Part C 2012

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