Secreted Matrix Metalloproteinase-9 of Proliferating Smooth Muscle Cells as a Trigger for Drug Release from Stent Surface Polymers in Coronary Arteries

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Cardiovascular diseases are the leading causes of death in industrialized countries. Atherosclerotic coronary arteries are commonly treated with percutaneous transluminal coronary intervention followed by stent deployment. This treatment has significantly improved the clinical outcome. However, triggered vascular smooth muscle cell (SMC) proliferation leads to in-stent restenosis in bare metal stents. In addition, stent thrombosis is a severe side effect of drug eluting stents due to inhibition of endothelialization. The aim of this study was to develop and test a stent surface polymer, where cytotoxic drugs are covalently conjugated to the surface and released by proteases selectively secreted by proliferating smooth muscle cells. Resting and proliferating human coronary artery smooth muscle cells (HCASMC) and endothelial cells (HCAEC) were screened to identify an enzyme exclusively released by proliferating HCASMC. Expression analyses and enzyme activity assays verified selective and exclusive activity of the matrix metalloproteinase-9 (MMP-9) in proliferating HCASMC. The principle of drug release exclusively triggered by proliferating HCASMC was tested using the biodegradable stent surface polymer poly-l-lactic acid (PLLA) and the MMP-9 cleavable peptide linkers named SRL and AVR. The specific peptide cleavage by MMP-9 was verified by attachment of the model compound fluorescein. Fluorescein release was observed in the presence of MMP-9 secreting HCASMC but not of proliferating HCAEC. Our findings suggest that cytotoxic drug conjugated polymers can be designed to selectively release the attached compound triggered by MMP-9 secreting smooth muscle cells. This novel concept may be beneficial for stent endothelialization thereby reducing the risk of restenosis and thrombosis.

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