Stromal Cell-Derived Factor-1α Releasing Metallic Stent for Accelerated Re-endothelialization Mediated by Mobilization and Recruitment of Endothelial Progenitor Cells

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Statement of Purpose: The damage of endothelial layer is a critical factor for in-stent restenosis and thrombosis. The restoration of a damaged endothelium might be a fascinating strategy to reduce late stent thrombosis and restenosis. It has been reported that endothelial progenitor cells (EPCs) can differentiate to endothelial cells and then enhance re-endothelialization. We hypothesized that stromal cell-derived factor-1α (SDF-1α) act as a key chemokine for the mobilization and recruitment of EPCs. Recently, many reports demonstrated that the concentration-gradient of SDF-1α facilitates to recruit bone marrow-derived EPCs to injured lesions. In this study, SDF-1α was coated on a cobalt-chromium alloy (Co-Cr) plate and the release profile of SDF-1α was controlled and the homing effect of EPCs was investigated.

Methods: Dopamine-conjugated heparin was synthesized to coat heparin on Co-Cr surface without any treatment. Then, the modified heparin was coated on Co-Cr specimens. Heparin-coated Co-Cr surfaces were examined by contact angle, ATR-FTIR, and Toluidine blue assay, characterizing the successful coating of heparin. Change of heparin amount coated on Co-Cr surface in accordance with coating temperature was confirmed. Finally, SDF-1α was incubated with the coated heparin. Amounts of bound SDF-1α and released SDF-1α were measured by ELISA and the EPC recruitment by released SDF-1α was evaluated by a chemotaxis assay using fibrin gel.

Results: Dopamine-conjugated heparin was synthesized successfully. Dopamine-conjugated heparin showed IR signals that presented in both dopamine and heparin. Heparin amount coated on Co-Cr surface increased in accordance with coating temperature. In ATR-FTIR result, heparin-coated surface displayed peaks at 1550 and 1650 cm^{-1} in wavenumber, which indicates amide bonding. Heparin-coated surface not affected cell viability. Heparin-coated surface increased nitrogen and sulfur compositions and SDF-1α-loaded one presented an increase in nitrogen but not sulfur than heparin-coated one. The quantity of SDF-1α bound to heparin increased in the added concentration-dependent manner. SDF-1α was released for over one month. Chemotaxis assay revealed that soluble SDF-1α released from a form bound to heparin has chemo-attractive effect on EPCs. These results suggest that heparin-coated Co-Cr surface releasing SDF-1 is able to induce the recruitment of EPC, which the site may be an injured area and the endothelium of the injured lesion may be restored.

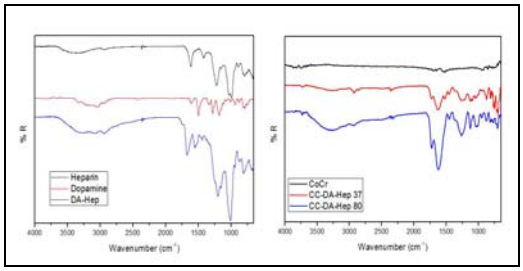

Figure 1. ATR-FTIR spectra of the dopamine conjugated heparin and coated Co-Cr surfaces.

Table 1. XPS elemental compositions and water contact angles of the control and each modified Co-Cr surface.

Samples	Elemental compositions (%)				Contact angle
	C%	O%	N%	S%	
Co-Cr (CC)	27.33	72.67	0	0	71.2 ± 1.8
CC-DA-Hep	70.75	21.04	7.67	0.54	22.5 ± 0.3
CC-DA-Hep -SDF-1α	66.29	20.97	12.74	0	41.2 ± 1.4

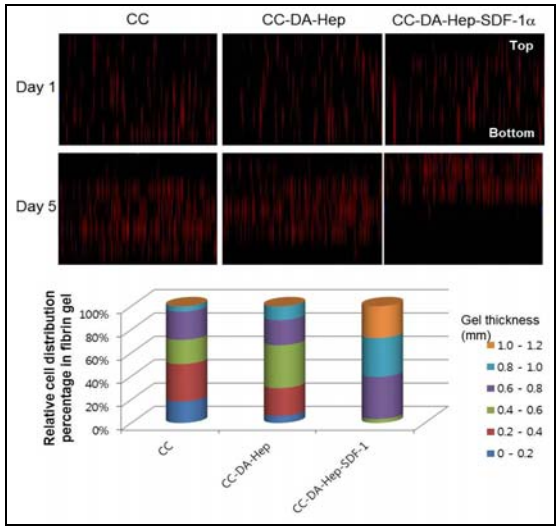

Figure 2. Chemotaxis assay of SDF-1 loaded heparin-coated Co-Cr surface in fibrin gel.

Conclusions: Heparin-coated metal surface was utilized to load SDF-1 and to achieve the controlled release. SDF-1 released from heparin-coated surface revealed chemo-attractive effect.

References:

1. Ting Ting Lau, *et al., Expert Opin. Biol. Ther.*, 2011;11(2):189-197.
2. Jung YS, *et al., Biomaterials*, 2012;33:295-303.