Abstract: P366

A novel growth factor promotes endothelial recovery following vascular injury and prevents neointima formation

Authors:
F J Kloss¹, J Dutzmann¹, M Korf-Klingebiel¹, M Reboll¹, S Pretzer¹, M Haertle¹, R Musmann¹, J Bauersachs¹, K C Wollert¹, D G Sedding¹, ¹Hannover Medical School, Cardiology and Angiology - Hannover - Germany,

Topic(s):
Atherosclerosis, Cerebrovascular Diseases, Aneurysm, Restenosis

Citation:
Cardiovascular Research (2018 ) 114 (Supplement 1 ), S93

Background: A recently identified growth factor (Fx) was shown to augment cardiac repair after myocardial infarction. The effects of Fx on endothelial regeneration following vascular injury as occurring during PCI have remained elusive. Therefore, we characterized the effects of Fx on endothelial regenerative capacity in vitro, and re-endothelialization and neointima formation in vivo.

Methods and Results: Assessing the effects of Fx on human coronary artery endothelial cells (EC) in vitro, we observed a dose dependent increase of EC proliferation as determined by Bromodeoxyuridin incorporation (maximal 1.5 ± 0.1-fold vs. control with 10 ng/mL Fx, p<0.0001, n=5). This effect was comparable to the effect of vascular endothelial growth factor A (1.4 ± 0.1-fold vs. control with 50 ng/mL VEGFA, p<0.0001, n=5). Moreover, Fx dose-dependently enhanced total EC number (maximal 1.7 ± 0.2-fold vs. control with 100 ng/mL Fx, p=0.004, n=5). Live cell imaging of a modified scratch wound assay revealed an accelerated wound healing response of EC (43 ± 6 % in vehicle vs. 80 ± 3 % endothelial coverage in EC treated with 100 ng/mL Fx, p=0.0005, n=5), with a significant increase in the directional migration of EC in response to Fx. In vivo, re-endothelialization was determined 3 days after electric injury of mouse carotid arteries. Fx (10 µg/day) or vehicle (PBS only) were continuously delivered subcutaneously (s.c.) via osmotic minipumps starting immediately after surgery, preceded by a single i.v. bolus of 10 µg Fx. As determined by Evan’s Blue staining, Fx resulted in a significant acceleration of endothelial recovery (39.3 ± 6.5% vs. 17.8 ± 3.2% in vehicle group, p=0.009, n=4-7). The effect of s.c. Fx treatment on neointima formation was assessed after wire-induced injury of the mouse femoral artery. Neointimal lesion formation was significantly reduced in Fx-treated mice (Neointima/media ratio: 1.00 ± 0.06 in vehicle vs. 0.56 ± 0.04 in Fx-treated mice, p<0.0001, n= 6-10).

Conclusion: A recently identified growth factor significantly improves EC proliferation and migration in vitro and accelerates re-endothelialization following injury of the murine carotid artery in vivo. In addition, treatment with Fx prevents SMC proliferation and neointima lesion formation. This new factor may hold promise as a novel therapeutic tool to enhance functional EC recovery and prevent neointima formation.
Abstract: A novel growth factor promotes endothelial recovery following vascular injury and prevents neointima formation.


Background: A recently identified growth factor (Fx) was shown to augment cardiac repair after myocardial infarction. The effects of Fx on endothelial regeneration following vascular injury as occurring during PCI have remained elusive. Therefore, we characterized the effects of Fx on endothelial regenerative capacity in vitro, and re-endothelialization and neointima formation in vivo.

Methods and Results: Assessing the effects of Fx on human coronary artery endothelial cells (EC) in vitro, we observed a dose dependent increase of EC proliferation as determined by Bromodeoxyuridin incorporation (maximal 1.5 ± 0.1-fold vs. control with 10 ng/mL Fx, p<0.0001, n=5). This effect was comparable to the effect of vascular endothelial growth factor A (1.4 ± 0.1-fold vs. control with 50 ng/mL VEGFA, p<0.0001, n=5). Moreover, Fx dose-dependently enhanced total EC number (maximal 1.7 ± 0.2-fold vs. control with 100 ng/mL Fx, p=0.004, n=5). Live cell imaging of a modified scratch wound assay revealed an accelerated wound healing response of EC (43 ± 6 % in vehicle vs. 80 ± 3 % endothelial coverage in EC treated with 100 ng/mL Fx, p=0.0005, n=5), with a significant increase in the directional migration of EC in response to Fx. In vivo, re-endothelialization was determined 3 days after electric injury of mouse carotid arteries. Fx (10 µg/day) or vehicle (PBS only) were continuously delivered subcutaneously (s.c.) via osmotic minipumps starting immediately after surgery, preceded by a single i.v. bolus of 10 µg Fx. As determined by Evan's Blue staining, Fx resulted in a significant acceleration of endothelial recovery (39.3 ± 6.5% vs. 17.8 ± 3.2% in vehicle group, p=0.009, n=4-7). The effect of s.c. Fx treatment on neointima formation was assessed after wire-induced injury of the mouse femoral artery. Neointimal lesion formation was significantly reduced in Fx-treated mice (Neointima/media ratio: 1.00 ± 0.06 in vehicle vs. 0.56 ± 0.04 in Fx-treated mice, p<0.0001, n=6-10).

Conclusion: A recently identified growth factor significantly improves EC proliferation and migration in vitro and accelerates re-endothelialization following injury of the murine carotid artery in vivo. In addition, treatment with Fx prevents SMC proliferation and neointima lesion formation. This new factor may hold promise as a novel therapeutic tool to enhance functional EC recovery and prevent neointima formation.