Abstract: 340

Altered vascular remodeling in the mouse hind limb ischemia model in Factor VII activating protease (FSAP) deficiency

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Background: The factor VII activating protease (FSAP) is a multifunctional circulating plasma serine protease. Human genetic studies and investigations in FSAP-/- mice suggest a role for FSAP in stroke, thrombosis and atherosclerosis. This study was designed to investigate the role of FSAP vascular remodeling processes related to arteriogenesis and angiogenesis in the mouse hind limb ischemia model.

Methods: Femoral artery ligation was performed on FSAP-/- mice and C57Bl/6 mice. FSAP vs control (ctrl) proteases were injected intra muscularly into the upper hind limb after occlusion of the femoral artery and Laser Doppler Perfusion Imaging was performed up to 3 weeks. Furthermore, immune histochemistry and morphometrical analysis were done to quantify angiogenesis and arteriogenesis.

Results: A significant delay in blood restoration was still determined after one week (FSAP i.m.0.60±0.08 vs. ctrl 0.87±0.14, n=11). After 3 weeks, the FSAP i.m group had reached the plateau of the ctrl group demonstrating the same perfusion index (FSAP 0.90±0.03 vs. ctrl 0.91±0.06, n=5). While the capillary density (cells/mm²) within the gastrocnemius muscle, reflecting angiogenesis, remained nearly unchanged in the ctrl group, we observed a compelling twofold increase of capillary density for the FSAP treated animals within the first wk after ligation (1720±250 vs. 925±150 capillaries/mm², n=11, p<0.001). Perfusion was not different between the genotypes but there were 2.5-fold more collateral arteries in the adductor muscle of FSAP-/- mice (p<0.5) which was associated with a higher infiltration of monocytes (p<0.5). Capillary density in the gastrocnemius muscle was not altered.

Conclusion: In the absence of endogenous FSAP arteriogenesis is enhanced and this is associated with a greater infiltration of monocytes but angiogenesis is unchanged. Exogenous FSAP had the opposite effect of arteriogenesis. Thus, apart from regulating coagulation processes in the blood FSAP is a regulator of vascular wall remodelling.