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The role of nitric oxide and VEGFR-2 signaling in post ischemic revascularization and muscle recovery in aged hypercholesterolemic mice

Authors:
G Wirth¹, P Korpisalo¹, H Hakkarainen¹, S Laidinen¹, S Yla-Herttuala¹, ¹University of Eastern Finland, A.I.Virtanen Institute for Molecular Sciences, Dpt of Biotechnology and Molecular Medicine - Kuopio - Finland,

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Introduction: Vascular endothelial growth factor (VEGF) via angiogenic signaling through its receptor 2 (VEGFR-2) is generally considered to have a major role in ischemic tissue recovery. Still, despite numerous clinical and preclinical studies, angiogenic therapies do not have an established role in the treatment of ischemic cardiovascular diseases. While misleading preclinical modelling has been suggested a possible cause for the discrepancies between theory and translation (Dragneva G et al 2013 Dis Model Mech) we wanted to explore how crucial VEGFR-2 signaling is in subacute ischemic recovery in aged, genetically hypercholesterolemic mice.

Methods: Hypercholesterolemic LDLR-/-ApoB100/100 mice (age 6-21 months) underwent unilateral hindlimb ischemia operation. The mice then received either L-NAME (nitric oxide synthase inhibitor; 50mg/kg) or NaCl control i.p. starting four days after ischemia induction, or adeno viral (Ad) soluble VEGFR-2 or AdLacZ control (10e11vp) i.m. gene transfer three days post-operatively. Contrast enhanced ultrasound imaging, photoacoustic imaging and histological studies were carried out to evaluate perfusion recovery, oxygen saturation and tissue responses, respectively. All animal experiments were licensed according to the Finnish legislation.

Results: When administrated after the initial opening of collateral vessels, the treatment with either systemic L-NAME or intramuscular AdsVEGFR-2 reduced capillary size and delayed perfusion recovery in the LDLR-/-ApoB100/100 mice. Interestingly, the vasoconstrictive treatments did not result in worsened muscle morphology as compared to the controls. In fact, the oldest L-NAME treated animals (13-15 months of age) seemed to even benefit from the vasoconstrictive treatment with more normal muscle (28% vs 5% in the controls) and less necrosis (9% vs 27% in the controls) in the histological analysis 11 days post operation.

Conclusions: VEGFR-2 signaling or endothelial nitric oxide production does not seem indispensable for post ischemic muscle recovery after the initial opening of the collateral vessels in aged hypercholesterolemic mice. Moreover, some level of vasoconstriction may even be helpful to support muscle regeneration after ischemia.