

Vascular Wall Responses to Bypass Grafting -Studies in Mice

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Avhandlingen baseras på följande delarbeten:

- I. Intimal hyperplasia in mouse vein grafts is regulated by flow
Klas Österberg, Erney Mattsson
J Vasc Res. 2005 Jan-Feb;42(1):13-20.
- II. Reduced neointima in vein grafts following a blockage of cell recruitment from the vein and the surrounding tissue.
Per Fogelstrand, Klas Österberg, and Erney Mattsson
Cardiovasc Res. 2005 Aug 1;67(2):326-32.
- III. Smooth muscle cells in mouse vein grafts are not recruited from the adjacent artery
Klas Österberg, Erney Mattsson
In manuscript
- IV. Progenitor smooth muscle cells have limited ability to regenerate arterial function and morphology
Klas Österberg, Irene Andersson, Kathryn Gradin, Göran Bergström and Erney Mattsson
In manuscript

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Abstract

Vein grafts are frequently used in bypass surgery for treatment of coronary artery disease and lower limb ischemia. Unfortunately the long-term patency is impaired by vein graft stenoses due to intimal hyperplasia (IH). It is assumed that exaggerated intimal thickening is initiated by vessel wall injuries or local flow disturbances. Accumulation and proliferation of smooth muscle cells (SMCs) are key events in the formation of IH. It has been an established opinion that these cells have their solely origin in the underlying media. This theory has been challenged by recent research, which has demonstrated recruitment of SMCs from other sources than the local vessel wall. Mice models including genetically modified strains have had a major impact on the reformed view upon vascular repair.

In this thesis, recruitment pathways of intimal SMCs and the impact of blood flow on vein graft intimal thickening were investigated.

A new mouse model, which enables studies of different blood flow through vascular grafts was established. The area of IH in vein grafts was measured in two groups, which had a 2.7 times difference in blood flow. The area was 70% larger in the low flow group compared to high flow, which shows that vein graft IH is regulated by the magnitude of blood flow.

Recruitment pathways of SMCs to IH in vein grafts were studied in genetically modified mice, expressing the enzyme LacZ. Thirty percent of the cells originated from sources apart from the grafts. External shielding of the vein grafts resulted in decreased contribution of cells from recipient mice, which point at transadventitial migration as an important recruitment pathway. SMC migration from the adjacent artery could not be detected, which indicate that the connected artery does not play any role for formation of vein graft stenoses.

The ability of externally recruited SMCs to regenerate the vessel wall was investigated by implantation of grafts in which cells had been abolished. Acellular vein grafts developed similar degree of IH as cellular vein grafts, which demonstrate that externally recruited SMCs by themselves can form intimal thickening.

Acellular arteries were also implanted. The externally recruited SMCs to the arteries had limited ability to regenerate the medial SMC population and no vasomotor function was observed. This demonstrates that recipient derived SMC progenitor cells can contribute to pathological cellular formations, but lack ability to re-establish the normal morphology and function of the arterial wall.

In conclusion, the results from this thesis show that the vein wall in response to bypass grafting develops IH, which is regulated by the magnitude of blood flow. The intimal SMCs can be derived from sources outside the vessel wall and may partly be recruited by transadventitial migration but not from the adjacent artery. The SMCs with external origin have ability to contribute to IH but not to the functional population of medial SMCs.

Key words: Intimal hyperplasia, graft stenosis, smooth muscle cells, cellular recruitment, mice