ON CELLULAR SOURCES FOR INTIMAL HYPERPLASIA
AFTER VASCULAR INTERVENTIONS

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Göteborgs Universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Academicum, Sahlgrenska Akademien, Göteborg
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av

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Avhandlingen baseras på följande delarbeten:


IV Reduced neointima in rabbit following a more severe balloon-injury. Per Fogelstrand, Stefan Mellander, Erney Mattsson. Submitted.
Vascular interventions for the treatment of symptomatic atherosclerosis fail in up to 40% of the cases during the first year. One important reason is the development of a narrowing process known as intimal hyperplasia (IH). The cells forming IH resemble smooth muscle cells (SMCs) from the media of the arterial wall. Therefore the media has generally been regarded as the cellular origin for IH. However, there are reports indicating that other cellular sources might be involved.

The aim of this thesis was to investigate which cellular sources participate in the development of intimal hyperplasia after bypass surgery and balloon injury. Furthermore, we wanted to investigate, if the inhibition of one cellular source could reduce intimal hyperplasia. Studies were made in pig and rabbit. Specific aims were: 1/ To evaluate the blood, the adjacent artery, the media, the adventitia, and the surrounding tissue as cellular sources to intimal hyperplasia 2/ To evaluate the contribution of blood-borne mononuclear cells to IH 3/ To evaluate, if depletion of the cells in the media reduces intimal hyperplasia after vascular interventions.

We found that the adjacent artery at the anastomoses and the surrounding tissue contributed cells in a bypass model in pig. Blood-borne mononuclear cells were labeled ex vivo and retransfused after bypass implantation and balloon injury in pig. These cells were later found in the IH. Some of these cells co-expressed markers for smooth muscle cells suggesting a transdifferentiation from a blood-borne mononuclear to a tissue forming cell. In a balloon injury model in rabbit we found that the media with its SMCs was the main cellular source and that adventitial cells did not contribute to the IH.

After depletion of the medial SMCs by a more severe balloon trauma in rabbit and by photodynamic therapy in the bypass model in pig we found less IH compared with controls, suggesting the media and its cells to be an important source after both interventions.

In conclusion, the results presented in this thesis show that cells from the media, the surrounding tissue, the adjacent artery, and blood-borne mononuclear cells can contribute to IH. By depletion of the cells in the media, intimal hyperplasia following both bypass surgery and balloon injury is reduced.

**Key words:** Intimal hyperplasia, vascular intervention, smooth muscle cell, blood-born mononuclear cell, prosthetic graft, balloon injury, pig, rabbit