On the stimulatory effect of microglial cells on angiogenesis

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ABSTRACT

Angiogenesis, the process by which new vessels sprout from pre-existing vessels, is fundamental to development, tissue growth and repair. The main aim of this thesis was to investigate the role of microglia on angiogenesis. We adapted the rat *ex vivo/in vitro* aortic ring model to the mouse in a 3-D culture system. In paper I, we show that ablation of microglia in the retina leads to a poorly developed vascular network. The aortic ring model, supplied with microglia, demonstrated that microglia have a direct positive effect on angiogenic sprouting. The angiogenic effect was mediated by soluble factor/factors, and cell-cell contacts were not required. We also show that the microglia-derived angiogenic factor(s) is distinct from vascular endothelial growth factor-A. Moreover, the sprouting aortic ring induces oriented migration of microglia towards the aortic ring. In paper II, we analysed the microglia transcriptome. We found that microglia express known activators and inhibitors of angiogenesis that might have a role in retinal blood vessel development. The aortic ring system was also used as a complement to *in vivo* analyses to address the function of sphingosine-1-phosphate receptor 1 ($S1P_1$) on angiogenesis (paper III). The results indicate that $S1P_1$ is required within endothelial cells to counteract VEGF-A-signalling and prevent endothelial hyper-sprouting. In paper IV, expression of green fluorescent protein in endothelial/hematopoietic cells using *Tie2-Cre* was used to mark transplanted bone marrow-derived cells. The study aimed to address if grafted bone marrow derived cells can differentiate into pancreatic β-cells in mice. The major part of the thesis concerns the establishment and use of the mouse aortic ring as a model for angiogenesis. Importantly, application of the system enabled us to identify a direct positive effect of microglia on angiogenesis and to test putative modifiers. This could be further pursued by microarray analyses. The presented work might therefore provide a platform for the identification of molecules that regulate angiogenesis.

Key words: microglia, angiogenesis, aortic ring.
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I. **Simin F. Rymo**, Holger Gerhardt, Fredrik Wolfhagen Sand, Richard Lang, Anne Uv, Christer Betsholtz.
A Two-Way Communication between Microglial cells and Angiogenic Sprouts Regulates Angiogenesis in Aortic Ring Cultures.
PLoS One. 2011 Jan 10;6(1):e15846.

II. **Simin F. Rymo**, Zulfeghar A. Syed, Anne Uv and Christer Betsholtz.
A transcriptional profiling approach to identify microglia-derived factors that stimulate angiogenesis in aortic ring cultures.
Manuscript

III. Konstantin Gaengel, Kazuhiro Hagikura, Colin Niaudet, Lars Muhl, Staffan Nyström, **Simin F. Rymo,** Bàrbara Laviña Siemsen, Jennifer Hofmann, Lwaki Ebarasi, Long Long Chen, Karin Strittmatter, Guillem Genove, Pernilla Roswall, Peter Lönneberg, Per Uhlen, Anne Uv, Arindam Majumdar, Richard L. Proia and Christer Betsholtz.
$S1P_1$ is a critical regulator of angiogenesis.
Manuscript

IV. Anders H. Rosengren, Jalal Taneera, **Simin Rymo**, and Erik Renström.
Bone marrow transplantation stimulates pancreatic β-cell replication after tissue damage.
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