# DEVELOPMENTAL ORIGIN AND MOLECULAR REGULATION OF VASCULAR SMOOTH MUSCLE CELLS

Akademisk avhandling

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av

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Avhandlingen baseras på följande delarbeten:

I. Wasteson P, Johansson BR, Jukkola T, Breuer S, Akyürek LM, Partanen J, Lindahl P: **Developmental origin of smooth muscle cells in the descending aorta in mice.** *Development (2008) May;135(10):1823-32*

II. Petit MM, Lindskog H, Larsson E, Wasteson P, Athley E, Breuer S, Angstenberger M, Hertfelder D, Mattsson E, Nordheim A, Nelander S, Lindahl P: **Smooth muscle expression of lipoma preferred partner is mediated by an alternative intronic promoter that is regulated by serum response factor/myocardin.** *Circ Res. (2008) Jul 3;103(1):61-9*

III. Nyström HC, Johansson ME, Wasteson P, Lindblom P, Betsholtz C, Gan L, Lindahl P, Bergström G: **Neointimal hyperplasia of the mouse carotid artery – role of Ang II and PDGF-B.** *Manuscript*

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**Abstract:**

Several pathologies of the vascular system have been suggested to be dependent on the smooth muscle cells (SMCs) that build up the vessel wall.

Aortic SMCs have been proposed to derive from lateral plate mesoderm. It has further been suggested that induction of SMC differentiation is confined to the ventral side of the aorta and that cells later migrate to the dorsal side. In this thesis, the developmental origin of aortic SMCs was investigated using recombination-based lineage tracing in mice. It was shown that aortic SMCs are derived from the somites and not from lateral plate mesoderm. Moreover, vascular SMCs are not recruited by a ventral-to-dorsal migration. Lateral plate mesoderm-derived SMCs on the ventral side of the aorta were shown to express SMC markers early in development. It was however demonstrated that these cells are replaced by SMCs of somitic origin at E10.5.

Lipoma preferred partner (LPP) has recently been identified as a SMC marker involved in cell migration. In this thesis, the transcriptional regulation of the LPP gene was studied. In particular it was investigated whether LPP transcription is dependent on serum response factor (SRF)/myocardin. With bioinformatic tools, an alternative transcriptional promoter was predicted within the LPP gene. This promoter was further analyzed using quantitative RT-PCR, chromatin immunoprecipitation, electrophoretic mobility-shift assays, luciferase reporter experiments and SRF-deficient cells/tissues. It was demonstrated that the alternative promoter binds SRF in vitro. It was also shown that it has transcriptional capacity, which is dependent on SRF/myocardin. The alternative promoter directs LPP expression in SMCs in vivo.

Finally, a carotid artery ligation model was used in this thesis to investigate the proposed roles of angiotensin II (Ang II) and platelet-derived growth factor B (PDGF-B) in neointimal hyperplasia. Experiments were performed in wild type mice and PDGF-B retention motif knockout mice. It was shown that PDGF-B mRNA was increased by carotid artery ligation while expression of PDGF receptor β was unaffected. The ligation induced a neointima formation that was further accelerated by Ang II administration. Neointima formation was unaffected by knockout of the PDGF-B retention motif or inhibition of the PDGF receptor β.

**Key words:** smooth muscle cell, aorta, cell origin, lateral plate mesoderm, paraxial mesoderm, lipoma preferred partner, serum response factor, neointimal hyperplasia, angiotensin II, platelet-derived growth factor B.

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