Regulation of gene expression in the vascular wall

Akademisk avhandling

som för avläggandet av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg, fredagen den 17 april 2009 kl 9.00

av Erik Larsson

Fakultetsopponent: Professor Joseph M. Miano, University of Rochester, USA

Avhandlingen baseras på följande delarbeten:

I. Predictive screening for regulators of conserved functional gene modules (gene batteries) in mammals
Nelander S, Larsson E, Kristiansson E, Mansson R, Nerman O, Sigvardsson M, Mostad P, Lindahl P
BMC Genomics, 2005. 6(1):68

II. SRF regulates transcription of the smooth muscle marker LPP via an alternative promoter
Petit M*, Lindskog H*, Larsson E*, Wasteson P, Nelander S, Athley E and Lindahl P
Circ Res, 2008. 103(1):61-9
*These authors contributed equally

III. Identification of a core set of 58 gene transcripts with broad and specific expression in the microvasculature
Wallgard E, Larsson E, He L, Hellström M, Armulik A, Nisancioglu MH, Genove G, Lindahl P and Betsholtz C
Arterioscler Thromb Vasc Biol, 2008. 28(8):1469-76

IV. The DRAM locus at 12q23 is associated with hypertension
Larsson E, Wahlstrand B, Hedblad B, Hedner T, Kjeldsen S, Melander O and Lindahl P
Submitted

V. Screening for microvascular miRNAs: miR-145 is enriched in microvessels, is expressed in pericytes and is a regulator of Fli1
Larsson E, Fredlund-Fuchs P, Bondjers C, Barkefors I, Genove G, Heldin J, Harvey SJ, Kreuger J and Lindahl P
Manuscript

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Regulation of gene expression in the vascular wall

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Blood vessel growth and function are closely related to a number of pathological conditions, including tumor angiogenesis, wound healing and atherosclerosis. Smooth muscle cells (SMC) and endothelial cells (EC), the two major constituents of the vascular wall, are both characterized by the expression of unique phenotypic marker genes, many of which have vital roles in blood vessel development and disease. We therefore sought to obtain a more complete picture of vascular-specific gene expression, gene regulation and genetic variation.

We performed an unbiased computational screen to identify cases of transcriptional coregulation in mammalian cell differentiation. This generated a number of novel hypotheses, one of them being that the SMC marker gene lipoma-preferred partner (LPP) could be activated by serum response factor (SRF), a known master regulator of SMC differentiation. Using chromatin immunoprecipitation, gel shift assays, reporter assays and transgenic mouse models, we showed that LPP belongs to the category of SMC-specific genes that are regulated by SRF, an important insight because LPP has a role in the control of SMC migration.

By combining in-house and public genome-wide expression data, we identified 32 novel EC-specific mRNAs. A number of these, such as the G-protein coupled receptors Gpr116 and Ramp2, represent putative drug targets. By integrating our results with data from published genome-wide association studies, we investigated if genetic variation in EC-specific genes contributes to human disease. Independent replication of selected SNPs in 10,505 individuals revealed that a variant in one of the novel EC markers, DRAM, is associated with the development of essential hypertension.

Finally, the role of microRNAs (miRNA), an abundant class of small regulatory RNAs, was evaluated in the microvasculature. Through screening of public expression data, we identified a novel microvascular-enriched miRNA, miR-145, and showed that overexpression of this molecule leads to reduced cell migration.

In conclusion, we identified novel vascular marker genes and provided insights into the regulation of such genes. In addition, we showed that genetic variation in a novel EC marker gene contributes to the development of hypertension in the human population.

Keywords: smooth muscle, endothelium, angiogenesis, SRF, myocardin, LPP, gene regulation, genetics, microRNA

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