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Vascular remodelling in the absence and presence of cGKI

Robert Lukowski*[1], Dominik Bernhard[1], Pascal Weinmeister[1], Susanne Feil[2], Michael Gotthardt[3], Joachim Herz[4], Stefan Massberg[5], Franz Hofmann[1] and Robert Feil[2]

Address: [1]Institut für Pharmakologie und Toxikologie, TU München, Germany, [2]Interfakultäres Institut für Biochemie, Universität Tübingen, Germany, [3]Max-Delbrück-Centrum für Molekulare Medizin, Berlin-Buch, Germany, [4]Department of Molecular Genetics, UT Southwestern, Dallas, USA and [5]Deutsches Herzzentrum, TU München, Germany

Email: Robert Lukowski* - Lukowski@ipt.med.tu-muenchen.de

* Corresponding author

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The signaling molecule nitric oxide (NO) is of crucial importance for smooth muscle cell (SMC) function and exerts numerous, sometimes opposing effects on vascular proliferative diseases, such as atherosclerosis and restenosis. Under physiological conditions many effects of NO are mediated via the cyclic guanosine-3',5'-monophosphate (cGMP)/cGMP-dependent protein kinase type I (cGKI) pathway. In the cardiovascular system protective effects of NO signaling have been generally attributed to cGMP/cGKI. In contrast, novel genetic evidence from the analysis of atherosclerosis-prone mice indicated that endogenous cGKI accelerated plaque growth and, thus, was pro-atherogenic. However, in restenosis after intra-arterial interventions, such as balloon angioplasty or stent placement the mediator(s) of NO signals, in particular the role of endogenous SMC cGKI is unclear. Towards a better understanding of cGKI and its function in restenosis the Cre-loxP site-specific recombination system was used to generate conditional cardiac and SMC cGKI knockout mice. To test whether the lack of cGKI in SMCs affects the injury-induced vascular remodelling conditional mutants and control mice were analysed by morphometry and immunohistochemistry at different time points after injury, in a normolipidemic situation as well as on an apolipoprotein E-deficient genetic background. In addition, by continuous administration of sildenafil the cGMP/cGKI pathway was chronically activated in wild type mice subjected to the injury.

Taken together, the analysis of different mouse models of vascular proliferative diseases suggests a context-specific relevance of the cGMP/cGKI pathway for atherosclerosis and restenosis.