Endothelial-Mesenchymal Transition

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key event in vascular proliferative diseases by releasing cytokines and growth factors. This activation is mediated by Shh and PDGF-BB induced activation of Smo-dependent signalling and the selective inhibitor GDC-0449 may serve as a novel and promising therapeutic strategy to prevent neointima formation.

P700 | BENCH
The novel mineralocorticoid receptor antagonist Finerenone attenuates neointima formation after vascular injury
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Background: Ischemic cardiomyopathy as a result of coronary artery disease is the leading cause for heart failure. In consequence, the novel nonsteroidal mineralocorticoid receptor antagonist, holds the promise to be safe and efficient in the treatment of patients with heart failure and/or chronic kidney disease. However, the effects on vascular function remain elusive.

Purpose: The aim of this study was to determine the functional effect of selective MRT antagonism in vascular cells in vitro and the effect on vascular remodeling following acute vascular injury in vivo.

Methods and results: Finerenone dose-dependently and significantly reduced aldosterone-induced human coronary artery smooth muscle cell (HCASMC) proliferation in a concentration-dependent manner. Furthermore, Finerenone dose-dependently and significantly prevented aldosterone-induced apoptosis in human umbilical vein endothelial cells (HUVEC) as measured with a flow cytometry based FLICA assay.

In vivo, oral application of Finerenone dose-dependently and significantly inhibited intimal and medial cell proliferation following femoral artery wire-induced injury in C57BL/6J mice as quantified by staining for Ki-67 10 days following injury (vehicle vs. 1 mg/kg/d vs. 10 mg/kg/d, each p<0.01). Concomitantly, Finerenone attenuated neointimal lesion formation following femoral artery wire-induced injury 21 days following injury (luminal stenosis, vehicle vs. Finerenone 1 mg/kg/d vs. Finerenone 10 mg/kg/d: 90.2±11.6% vs. 60.1±17.3%; p<0.1063 to vehicle, vs. 35.3±10.0%; p<0.0061 to vehicle, n=8). Furthermore, there was a trend towards an accelerated re-endothelialization of the injured vessel segments in Finerenone-treated mice three days following electric injury of the murine carotid artery.

Conclusion: Finerenone treatment significantly attenuates HCASMC proliferation as well as simultaneously preventing apoptosis of endothelial cells in vitro. This is reflected by a significantly reduced neointima formation and reduction of luminal stenosis as well as a trend towards an accelerated endothelial healing of the injured vessels. Thus, apart from its beneficial effects in heart failure therapy, Finerenone might provide favorable vascular effects through restoring vascular integrity and preventing adverse vascular remodeling.

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P702 | BENCH
Endothelial-Mesenchymal Transition: mir-101 as a new target to treat intimal hyperplasia
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Introduction: Endothelial-Mesenchymal Transition (EndMT) is a specific form of transformed dysfunctional endothelial cells activated by endothelial phenotypic and genetic factors and expresses an epithelial phenotype and lose their endothelial functions. We, and others, recently described that EndMT contributes to intimal hyperplasia and atherosclerosis.

Pro-fibrotic and inflammatory cytokines, such as IL-1β and TGFβ induce EndMT. It seems that the Angiotensin (Ang) receptor AT1 and the agonist Ang II (AngII) contribute to EndMT. It is suggested that the Ang II AT1 receptor, which is a member of the G-protein linked receptor family, activates the mitogen activated protein kinase 7 (MAPK7, also known as Erk5) to treat intimal hyperplasia.

Methods and results: We used in silico analysis to identify miRNAs that could target miR-101 expression, which was blocked by the selective MAPK7 inhibitor BIX02189 (<0.05). Furthermore, ectopic expression of mir-101 in endothelial cells reduced the expression of the effector myocardial fibrosis. Erk5 inhibits EndMT and MAPK7 activation decreases the expression of the histone methyltransferase Enhancer-of-Zeste homologue 2 (Ezh2) thereby maintaining endothelial quiescence. This decrease in Ezh2 expression may therefore be responsible for the protective effects of MAPK7 activation and may thus offer new therapeutic options for the treatment of endothelial dysfunction and intimal hyperplasia.

Conclusion(s): Under uniform laminar flow MAPK7 inhibits Ezh2 expression via activation of miR-101. In coronary artery stenosis, endothelial cells are exposed to non-uniform shear stress which decreases MAPK7 activation, miR-101 expression and concurrently increases Ezh2 expression, which may cause EndMT and intimal hyperplasia. Therefore, the restoration of miR-101 expression or the silencing of Ezh2 in the endothelium might provide novel therapeutic approaches to treat intimal hyperplasia.

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P703 | BEDSIDE
TNF-antagonists improve arterial stiffness in patients with rheumatoid arthritis: a meta-analysis
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Background: Patients with rheumatoid arthritis (RA) have a higher arterial stiffness than their age-matched healthy counterparts and an increased inflammatory burden which might be associated with their increased cardiovascular risk. While tumor necrosis factor alpha (TNF)-antagonists have been found to reduce inflammatory markers in RA, it is debatable if they have favorable effects on surrogate markers of cardiovascular outcomes.

Purpose: We conducted a meta-analysis to assess the effect of TNF-antagonists on arterial stiffness, a predictor of cardiovascular events and mortality, in RA patients.

Methods: A search of PUBMED was conducted to identify studies into the ef-