Tubulin-folding cofactor E deficiency is associated with vascular dysfunction and endoplasmatic reticulum stress of vascular smooth muscle cells

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Funding Acknowledgement: Type of funding sources: Foundation. Main funding source(s): This work was supported by grants of the German Federal Ministry for Education and Research (BMBF01EO1003 and BMBF01EO1503), the DFG Major Research Instrumentation Programme (DFG INST 371/47-1 FUGG) as well as the Boehringer Ingelheim Foundation. PW received funds from the German Research Foundation in support of his work (DFG WE4361-4-1 and WE 4361/7-1). KS, TM and PW are PIs of the DZHK.

Introduction: Endothelial function assessed via flow mediated dilatation (FMD) has shown to predict risk in individuals with established cardiovascular diseases, whereas its predictive value is uncertain in the setting primary prevention.

Purpose: The aim of the current work was to discover and evaluate novel mediators of vascular dysfunction in the general population and in conditional knock-out transgenic animal models.

Methods: In order to identify novel targets that were negatively correlated with FMD and investigate their contribution in vascular function, a Genome Wide Association Study (GWAS) of 5,000 participants was performed and subsequently immune cell-, endothelial- and vascular smooth muscle cell (VSMCs)-targeted conditional knockout mouse models were generated and characterized.

Results: GWAS analysis revealed that single nucleotide polymorphisms (SNPs) in the tubulin folding cofactor E (TBCE) gene were negatively correlated with FMD and TBCE expression in the peripheral blood mononuclear cells (PBMCs). Myelomonocytic cell-targeted TBCE deficiency did not lead to any vascular dysfunction in vivo in the LysM+Cre+/–TBCEfl/fl mice. Endothelial-targeted TBCE deficiency led to an NLR family pyrin domain containing 3 (NLRP3)-dependent activation of the inflammasome in the endothelial cells of Tie2-ERT2Cre+/–TBCEfl/fl mice. Importantly, VSMC-targeted TBCE deficiency was associated with endothelial dysfunction, increased aortic wall thickness and endoplasmatic reticulum (ER) stress-mediated VSMC hyperproliferation in vivo (SMMHC-ERT2Cre+/–TBCEfl/fl), paralleled by calnexin upregulation. Administration of the blood pressure hormone angiotensin II exacerbated the vascular dysfunction and phenotype. Administration of the ER stress modulator tauroursodeoxycholic acid to the SMMHC-ERT2Cre+/–TBCEfl/fl mice reversed vascular dysfunction, paralleled by induction of Raptor/Beclin-1-dependent autophagy both in vitro and in vivo.

Conclusion: TBCE and tubulin homeostasis in the vascular musculature seem to be novel markers of vascular function and represent a new druggable target for the treatment of ER-stress-mediated vascular dysfunction.