increased level of immature platelets in acute coronary syndrome (ACS) associated with adverse ischemic outcomes. The mechanisms involved in the regulation of platelet turnover per se remain discussible. The impact of mandatory pharmacological platelet suppression as a cornerstone of antithrombotic therapy of ACS on platelet turnover is poorly understood.

Purpose: of the study was to investigate associations between platelet turnover parameters, thrombopoietin (TPO), stromal cell derived factor 1 (SDF1) and myeloproliferative leukemia virus oncogene (MPL) in patients with ST segment elevation myocardial infarction (STEMI), furthermore to characterize key regulatory mechanisms of platelet turnover in STEMI as potential pharmacological target.

Methods: We report preliminary results of the on-going study. 40 male patients with STEMI were enrolled, and stratified into two groups according to clinical presentation and short-term risk scores. Mean platelet volume (MPV) and MPV to platelet count ratio were used as a surrogate marker of platelet turnover. TPO, SDF1 and MPL were chosen to characterize platelet turnover regulation, and were serially (0-1-7 days) measured with commercially available ELISA kits. Time delays, and rate characteristics were calculated from TPO, SDF1 and MPL time functions.

Results: Among already involved patients 37.5% were hemodynamically unstable, with elevated short-term risk of adverse outcomes, and suffered from early MI complications (group 1). The patients of the group 2 were comparatively but insignificantly ($p = 0.354$) younger, less likely to be a current smoker. Neither platelet count ($p = 0.814$), nor MPL (0.585), nor their ratio (0.865) were significantly different between the compared groups. Initial levels of TPO were significantly increased in group 1: 331.82 (207.04; 477.08) vs 209.06 (153.32; 298.91) pg/mL, $p = 0.044$. Within 7 days TPO levels decreased in both groups with poor and better prognosis, but the mean rate was maximal in unstable patients: 7.5 vs 0.44 pg/mL*day. We detected noticeable negative correlation between TPO, SDF1 levels and MPL (Spearman R -0.437 . . . -0.586, $p < 0.05$) more substantial in patients with better prognosis: Spearman R -0.614 vs -0.586, $p = 0.012$. Longer delays in TPO, SDF1 and MPL kinetics were revealed in patients with poor prognosis.

Conclusion: In patients with STEMI, thrombopoietin and stromal cell derived factor 1 were inversely associated with platelet turnover parameters. In hemodynamically unstable patients with elevated short-term risk of adverse outcomes, kinetics of key regulators of platelet turnover were characterized by maximal rates and delays. Our findings suggest presence of an alternative regulator of platelet turnover associated with clinically severe course of STEMI.

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Deficiency in endothelial cell tetrahydrobiopterin increases resistance vascular remodelling, blood pressure, and susceptibility to aortic abdominal aneurysm in response to angiotensin II

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The cofactor tetrahydrobiopterin (BH4) is a critical regulator of endothelial NOS (eNOS) function, eNOS-derived NO and reactive oxygen species (ROS) signalling in vascular physiology. We have previously shown that mice with selective loss of endothelial cell Gch1, encoding GTP cyclohydrolase 1 (GTPCH), an essential enzyme for BH4 biosynthesis, have mild vascular dysfunction. However, the consequence of endothelial cell BH4 deficiency in vascular disease pathogenesis is unknown. The aim of this study was to investigate the pathological consequence of Angiotensin II (Ang II) infusion in endothelial cell Gch1 deficient (Gch1fl/flTie2cre) mice.

Wild-type (Gch1fl/fl) and Gch1fl/flTie2cre mice were infused with a subpressor dose of Ang II (0.4 mg/kg/day, delivered by osmotic mini pump). Ang II caused a significant decrease in circulating BH4 levels in Gch1fl/flTie2cre mice and a significant increase in the L-NAME inhibitable production of H2O2 in the aorta. Chronic treatment with this subpressor dose of Ang II resulted in a significant increase in blood pressure in Gch1fl/flTie2cre mice but not in wild-type littermates. This finding was mirrored with acute administration of Ang II where increased sensitivity to Ang II was observed at both pressor and subpressor doses. Chronic Ang II infusion in Gch1fl/flTie2ce mice resulted in vascular dysfunction in resistance mesenteric arteries with an enhanced constrictor and decreased vasodilator response, and medial hypertrophy. Altered vascular remodelling was also observed in the aorta with an increase in the incidence of abdominal aortic aneurysm (AAA) formation in Gch1fl/flTie2ce mice.

Taken together, these studies demonstrate that endothelial cell BH4-dependent eNOS regulation/eNOS uncoupling is implicated in the pathogenesis of vascular remodelling, hypertension and the development of AAA. These findings suggest that Ang II has a profound effect on vascular pathology when combined with endothelial cell BH4 deficiency. Therefore, targeting vascular Gch1 and BH4 biosynthesis may provide a novel therapeutic target for the prevention and treatment of vascular dysfunction in patients with vascular disease.

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The possible participation of telocytes as tissue modulators in normal and pathological human aorta

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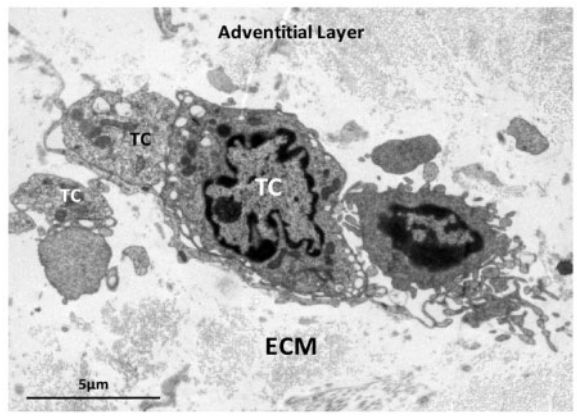
Introduction: Telocyte (TC) is an interstitial cell type with a small cellular body and extremely long tentacle-like extensions. TCs are cells that perform important roles in several organs, such as gut, liver, kidneys and heart, including muscular, connective and epithelial tissues. Apparently, TCs form a three-dimensional (3D) interstitial network by homocellular and heterocellular communication and are involved in the maintenance of tissue homeostasis, remodelling, regeneration, repair and angiogenesis. However, this cellular type has not yet been described in the normal or pathological human aorta. Ascending aorta aneurysms (AscAA) and dissections (AD) are two pathological conditions where tissue destruction is observed. This destruction involves all 3 vascular layers and is histopathologically characterized by fibrillar extracellular matrix (ECM) breakdown that, depending on the cellular and tissue response, can culminate in dilation or acute rupture. Thus, these two diseases are shown to be excellent biological models for the study of telocyte funtions.

Purpose: This study aimed to verify the presence and organization of TCs in the normal aortic wall and of patients presenting AscAA and AD.

Methods: Serial sections of aortas from 10 cases of AscAA, 10 AD and 10 controls were submitted to immunostain/immunofluorescence technique for CD34+, vimentin, PDGFRβ or analyzed by transmission electron microscopy (TEM).

Results: In all cases, double-labeled immunofluorescence and ultrastructural analysis evidenced the presence of TCs in adventitia and transition with the media layer. The TCs were arranged linearly between two layers forming a sort of delimitation network and bordering the outer elastic lamella. In the pathological condition (AscAA/AD) the TCs were more present and presented a different disposition when compared to the normal aorta. These TCs presented more prolongations, clearly surrounded by vesicles, presenting a typically secretory phenotype, interacting with vascular smooth muscle cells and apparently participating in the neovasculogenesis process.

Conclusions: These findings present for the first time the presence of TCs in normal and pathological human aorta and strengthen our hypothesis of the attempt by TCs to restore the damages occurred both in AscAA/AD. Our findings also reinforce the possible involvement of TCs in the maintenance of tissue homeostasis, remodelling, regeneration, repair and angiogenesis.



Abstract P351 Figure. Telocyte in Human Aorta

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A role for p130Cas in venous sprouting and lymphangiogenesis in the zebrafish

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Introduction: Bcar1/p130Cas is an important adaptor protein downstream of receptor tyrosine kinases, G-protein-coupled receptors, and integrin signalling. It is required for the migration of endothelial cells and vascular smooth muscle cells in response to VEGF or PDGF stimulation in vitro. It is also upregulated in many cancers and associated with increased metastasis and poor prognosis. While global knockout causes embryonic lethality in the mouse due to severe cardiovascular defects, no further reports discuss its role in the vascular system in vivo.

Purpose: We generated a zebrafish knockout model and used a combination of vascular reporters to interrogate p130Cas function during embryonic, regenerative (caudal fin regeneration model), and pathophysiological angiogenesis (tumour angiogenesis). Based on the in vitro data from the literature, we expected to observe migratory defects of endothelial cells.

Methods: We used confocal and light sheet microscopy, as well as optical projection tomography to image live embryos, as well as a genetic, inducible liver cancer model in adult transparent zebrafish. A variety of transgenic vascular reporters, including the tg(fli1a:nEGFP)y7 line, allowed tracking of single endothelial cells. The optical projection tomography model was used to globally image, longitudinally, live adult zebrafish.

Results: Bcar1-/- zebrafish are viable and fertile, showing no gross morphological defects, neither in embryonic development nor adulthood. Furthermore, they are able to regenerate the caudal fin upon amputation.

However, we observed a failure of venous sprouting and subsequent deformation of the caudal vein plexus of p130Cas-deficient embryos which also impacted the development of the parachordal lymphangioblasts and caused a delay in the formation of the thoracic duct. The caudal vein plexus resolved but exhibited distorted and dilated veins.

Conclusions: We present here a novel model for interrogating p130Cas function in vivo. While the zebrafish bcar1-/- mutant is not lethal, this allows investigation of more subtle effects in physiological and pathophysiological angiogenesis. We find a specific requirement for venous sprouting in the caudal vein plexus; this also impacts the initial development of the lymphatic system in the trunk. We are currently investigating other vascular beds dominated by venous sprouting, as well as tumour angiogenesis, and the signalling mechanism underlying this defect.