Topic 24 – Hypertension: Mecanisms – A

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0166
Changes in resistance arteries expression of extracellular nucleotides signaling partners during arterial hypertension.

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Cardiovascular diseases are the leading cause of mortality in industrialized countries and their prevalence increases with aging populations. Small arteries constitute the main site of peripheral vascular resistance and play a key role in the regulation of blood pressure. Vascular tone is exacerbated in hypertensive (HBP) and accompanied by a hypertrophy of the arterial wall. Although signaling by extracellular nucleotides is important in vascular homeostasis its contribution to vascular pathologies affecting small arteries remain poorly understood. We evaluated here the expression pattern of nucleotides signaling pathway in resistance arteries vs aorta in mice. Genes of interest including P2 receptors, ectonucleotidases (CD39, CD73) and heme channels (connexins, connexins, connexins, connexins) were investigated by quantitative RT-PCR. Their expression in resistance arteries was assessed in Angiotensin II-treated mice, spontaneously hypertensive rats (SHR) and, since HBP is related to age, in 24-month old mice. Our results showed that several genes are more expressed in aorta (P2ry2 and connexin 43) while others are expressed specifically (P2ry1, connexin 37) or preferentially (P2ry6) in small arteries. The latest might be involved in pathologies affecting the small arteries. With HBP, we observed a decreased connexin 37 and 40 expression level in Angiotensin II-treated mice and in SHR respectively and both decreased with aging. Interestingly, CD39 (tone regulator) decreased in the two models of HBP and with aging. Such decrease in nucleotidase activity may enhance P2 receptors activation and increase vascular contractility/tone. This is especially true considering P2Y6 (tone promoter) that increased with aging. Further studies may allow us to evaluate the contribution of these mediators in the development of small arteries defect in aging associated or not with HBP. Signaling by extracellular nucleotides may constitute new therapeutic targets in the treatment of HBP.

0202
Deficiency in nitric oxide decreases the microcirculation reactivity in response to acetylcholine but is not always associated with a higher blood pressure in mice

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Endothelial dysfunction is associated with cardiovascular diseases and can be evaluated in clinical setting for risk stratification in patients. Flow mediated dilation (FMD) or local acetylcholine (ACh) administration are used to assess endothelial dysfunction in arteries but also in microcirculation (MC) using Laser Doppler Flowmetry (LDF). In our study, we aim to investigate the role of nitric oxide (NO) in the endothelial response of microcirculation in vivo. Laser Doppler perfusion was measured at baseline and in response to ACh administration by tonometry or during hyperemic response due to local heating at 44°C. At day 3, we observed a slight increase in SBP only in BALBc mice treated with L-NAME (+13 mmHg), not maintained at day 7. Conversely, at day 7, we observed an increase in SBP (+30 mmHg) only in L-NAME-treated C57BL6 mice. MC flow response to ACh was decreased by 65% and 58% in BALBc and C57BL6 mice at day 3 and 7, respectively, and by 68% in C57BL6 mice only after 7 days of L-NAME treatment compared to untreated mice. No difference was observed in response to local heating, neither between strains nor after L-NAME treatment. In conclusion, skin microcirculation reactivity can be routinely assessed in vivo in mice. Our results show that a part of the transitory ACh-induced microcirculation flow increase is NO-mediated. Moreover, this decrease in NO bioavailability in microcirculation is not always associated with increase in systemic BP. Further studies are now required in order to determine if the microcirculation response to ACh could be a marker of coronary endothelial function in animal models as it is in human.

0362
Interleukin 17 production induced by angiotensin II type 2 receptor activation in T cells drives flow-mediated outward remodeling of mouse resistance arteries

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Objective: Flow (shear stress)-mediated outward remodeling of resistance arteries is involved in collateral growth during postischemic revascularization. Besides the NO pathway the involvement of inflammatory factors and reactive oxygen species has been suggested in this remodeling although the mechanism and the sequence remains unknown. As T cells drive the inflammatory response, we investigated their role in flow-mediated remodeling. Mouse mesenteric resistance arteries (250μm internal diameter) were submitted in vivo to a chronic increase (144±18 to 239±25 μl/min) in blood flow. Arteries were collected for in vitro analysis after 1 to 7 days.

Results: After 1 week, remodeling occurred in high flow (HF) arteries (diameter increased from 242±21μm to 324±20μm, n=xx per group, P<0.01) in control mice. No remodeling occurred in nude mice and in mice treated with anti-CD3 antibodies. In control arteries lymphocyte T cells accumulated around HF arteries at day 1 (shown using both immunohistology and flow cytometry) and they expressed angiotensin II type 2 receptor (AT2R). In isolated T cells AT2R stimulation induced preferentially IL-17 production (20±6pg/ml to 50±5pg/ml, n=xx per group, P<0.01). We then tested the occur-

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