rence of remodeling in mice lacking AT2R or IL-17. In both AT2R-/- and IL-17-/- mice diameter expansion did not occur whereas T cells and myeloid cells accumulation around the HF artery was not affected. IL-17 infusion (5ng/h, Alzet osmotic minipump) to nude mice and to AT2R-/- mice restored HF remodeling to control level. In order to confirm the role of AT2R in flow-mediated remodeling in another vascular territory, neovascularization was examined using an ischemic skin flap model in AT2R-/- mice. As in mesenteric arteries, the absence of AT2R prevented diameter expansion in the arteries feeding the skin flap.

Conclusion: we demonstrate for the first time the involvement of lymphocytes T cells polarization into TH17 by angiotensin II type 2 receptor in flow-mediated outward remodeling of resistance arteries.

0307

Role of vascular mineralocorticoid receptor in renal injury induced by ischemia/reperfusion

Jonatan Barrera-Chimal (1), Sonia Prince (1), Soumaya El Moghrabi (1), Norma Bobadilla (2), Fouad Fadel (1), Frederic Jaisser (1)
(1) Inserm U872 Team 1, Centre de Recherche des Cordeliers, Paris, France – (2) Molecular Physiology Unit, Instituto de Investigaciones Biomedicas, UNAM and INNSZ, Mexico City, Mexique

Introduction: Acute kidney injury (AKI) is defined as an abrupt decrease (48h) in kidney function. One of the main causes of AKI is ischemia/reperfusion (I/R). AKI is related with high mortality, chronic kidney disease development and cardiac alterations like heart failure and arrhythmias. Mineralocorticoid receptor (MR) antagonism with spironolactone (Sp) prevents tubular injury and renal dysfunction induced by I/R in the rat. Although there is information supporting a role for aldosterone and MR in kidney injury, it remains unexplored the specific role of the MR expressed in the vasculature in mediating the deleterious effects of aldosterone during renal I/R.

Objective: To study the effect of inducing I/R in mice lacking the MR specifically in the endothelial cells or in the vascular smooth muscle cells.

Methods: To test if Sp is also able to prevent renal injury induced by I/R in the mice with the C57BL/6 background (same as MR KO mice) we included three groups of mice: 1) Sham, 2) I/R 20 min and 3) I/R 20 min + Sp pre-treatment. We analyzed the presence of renal dysfunction and inflammatory cytokines. In the MR KO mice, we will analyze the effect of MR deficiency after renal I/R in an acute phase (24h) and in chronic kidney disease development (after 4 weeks). In the acute studies the mechanisms that will be explored include: polarization of macrophages, endothelial injury and oxidative stress. In the chronic studies we will test if the wild type or MR knockout mice develop CKD as a consequence of renal I/R.

Results: Mice underwent renal I/R developed injury characterized by increased serum creatinine and urea levels, urinary Hsp72 and elevation in the mRNA of TNF-alpha and MCP-1 pro-inflammatory cytokines. These alterations were prevented by the Sp pre-treatment.

Conclusion: The protective effect of Sp against renal I/R that was previously reported in the rat is also observed in the C57BL/6 mice and supports the study of the MR KO mice in the renal I/R setting.

0339

Does mineralocorticoid receptor antoganism could alleviate cyclosporin-induced nephrotoxicity in renal transplant recipients?

Cristian Amador (1), Jean-Philippe Bertocchio (1), Aldjia Hocine (1), Jenny Lancon (1), Soumaya El Moghrabi (1), Guillaume Galmiche (1), Jean-Paul Duong Van Huyen (2), Sylvie Lavaud (2), Olivier Toupance (2), Philippe Rieu (2), Frederic Jaisser (1)
(1) Centre de Recherches des Cordeliers, Paris, France – (2) Hôpital Maison Blanche, Néphrologie-Hémodialyse-Transplantation, Reims, France

Introduction: Cyclosporine-induced Nephrotoxicity (CIN) is a major adverse event but its pathophysiology remains unclear. Mineralocorticoid Receptor (MR) pharmacological antagonism prevents CIN in rats by modulating the expression of vasoactive factors. Our team has shown that MR is expressed in endothelial and vascular smooth muscle cells (VSMC). Therefore, genetic MR manipulations in endothelium or VSMC modify vascular function. Our working hypothesis is that vascular MR activation plays a key role in CIN.

Methods: Female mice with low-salt diet were used: 1) Pharmacological approach: Control (Vehicle), Cyclosporine-A (CsA, 100mg/kg/d) and CsA + Can (CsA + Canrenoate 30mg/kg/d, MR antagonist); 2) Genetic approach: MR KO in VSMC (MRKO-VSMC) or in Endothelial Cells (MRKO-EC) treated or not with CsA.

Results: Body weight loss is greater in Cyclosporine-treated groups ($p<0.05$). Renal function is impaired ($p<0.05$) and CsA induces renal histological damages that are prevented by MR antagonism or by MR KO in VSMC but not in endothelial cells. Canrenoate and MR KO in VSMC also prevent Cyclosporine-induced renal expression (mRNA) of NGAL (Neutrophil Gelatinase Associated Lipocalin), a kidney damage marker. CsA induced NGAL expression in proximal tubules (immunohistochemistry); this effect is prevented by MR antagonism and MR KO in VSMC but not in endothelial cells.

Conclusions: We show that MR antagonism has beneficial effect on Cyclosporine-induced renal damages that, at least partially, involve VSMC MR. The underlying cellular mechanisms are currently under investigation. A clinical trial testing the safety of MR antagonism (Eplerenone) in renal transplant recipients treated with Cyclosporine is currently ongoing.

0303

Deleterious effects of Tenascin-C on cardiac remodeling induced by pressure overload involve microenvironment inflammation

Dounia Abbadi (1), Fanny Laroumanie (1), Anne-Catherine Prats (2), Angelo Parini (1), Nathalie Pizzinat (1)
(1) I2MC, Toulouse, France – (2) Tradgene UPS EA4554, Toulouse, France

Backgrounds: Tenascin-C (TN-C) is an extracellular matrix glycoprotein slightly presented in adult tissue but transiently expressed upon tissue injury. It is a well-known regulator of multiple cellular functions during embryogenesis, wound healing and cancer. Several studies suggest a potential role of inflammation induced by the expression of Danger Associated Molecular Patterns (DAMPs) in the development of heart failure. These molecules are able to synthesize pro-inflammatory cytokines through Toll Like Receptors (TLRs). TN-C is considered as a DAMP through its property to induce the expression of pro-inflammatory cytokines *via* TLR4. Moreover, its expression is increased in various cardiac diseases. Here, we investigate the role of TN-C on cardiac remodeling induced by pressure overload as well as its impact on cardiac fibroblasts and bone marrow derived macrophages.

Methods and results: C57BL/6 mice WT and KO for TN-C were sacrified 6 weeks after a transverse aortic constriction (TAC). Echocardiographic measurements showed that KO mice did not exhibit an increased size of the left ventricular cavity and had a better fractional shortening compared to WT mice after TAC. The deletion of TN-C prevented pro-inflammatory environment and attenuated fibrosis. To better understand the role of TN-C, cardiac fibroblasts were transduced by a lentivector expressing GFP or TN-C. TN-C production by fibroblasts stimulated their expression of pro-inflammatory cytokines and chemokines like TNFα or CCL2. Moreover TN-C increased phagocytic activity of bone marrow derived macrophages and nitrite release in the supernatant suggesting a pro-inflammatory macrophages polarization by TN-C.

Conclusions: TN-C seems to have a deleterious effect on cardiac remodeling. It also induces expression of pro-inflammatory genes in cardiac fibroblasts as well as pro-inflammatory macrophages polarization. Further studies are required to better understand the exact role of this protein in heart failure.

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