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 mesen-
teric 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 lympho-
cytes 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
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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 sup-
porting 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 spe-
cifically 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 inflamma-
tory cytokines. In the MR KO mice, we will analyze the effect of MR defi-
ciency 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 oxida-
tive 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 altera-
tions were prevented by the Sp pre-treatment.

Conclusion: The protective effect of Sp against renal I/R that was previ-
ously 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 antagonism could alleviate cyclosporin-induced nephrotoxicity in renal transplant recipients?
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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 modu-
lying the expression of vasoactive factors. Our team has shown that MR is
expressed in endothelial and vascular smooth muscle cells (VSMC). There-
fore, 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 histolog-
ical 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 Gel-
tinase Associated Lipocalin), a kidney damage marker. CsA induced NGAL
expression in proximal tubules (immunohistochemistry); this effect is pre-
vented 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 trans-
plant recipients treated with Cyclosporine is currently ongoing.

0303
Deleterious effects of Tenascin-C on cardiac remodeling induced by pressure overload involve microenvironment inflammation
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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 embryogen-
ysis, wound healing and cancer. Several studies suggest a potential role of
inflammation induced by the expression of Danger Associated Molecular Pat-
terns (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 sacrificed
6 weeks after a transverse aortic constriction (TAC). Echocardiographic mea-
surements 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 fibro-
blasts were transduced by lentivector expressing GFP or TN-C. TN-C pro-
duction 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 remo-
deling. It also induces expression of pro-inflammatory genes in cardiac fibro-
blasts as well as pro-inflammatory macrophages polarization. Further studies
are required to better understand the exact role of this protein in heart failure.