Mineralocorticoid Receptor (MR) activation induces the expression of Neutrophil Gelatinase-Associated Lipocalin (NGAL) in dendritic cells in vitro and during the aldosterone-dependent hypertension

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Introduction: Inadequate activation of the Mineralocorticoid Receptor (MR) promotes hypertension, inflammation and fibrosis. Neutrophil Gelatinase-Associated Lipocalin (NGAL), a pro-inflammatory/fibrotic glycoprotein, is a target of MR-genomic upregulation in cardiovascular cells, and is increased in immune cells during inflammation. Recently, we have demonstrated that NGAL is crucial for hypertensive effects of aldosterone-salt (NAS) challenge in mice. The specific cell types that modulate the NGAL production during Aldosterone (Aldo)-dependent hypertension are unknown.

The aim was to characterize the NGAL expression in mouse immune cells, and to study the effect of MR activation on the NGAL and pro-inflammatory cytokines expression in dendritic cells (DCs).

Methods: Male C57Bl6 mice were treated in groups Sham and NAS (200μg/kg/d, 28 days). Peripheral blood mononuclear cells (PBMC) were isolated, and CD4+ CD8+ T cells, B cells, DCs and Macrophages (Mφ) were sorted from spleen. DCs and Mφ were cultured from WT and NGAL-KO mice and treated with Aldo (100nM) or vehicle for 24hrs. NGAL and cytokines mRNAs abundance was measured by qRT-PCR.

Results: NAS mice presented high systolic blood pressure (123 mmHg vs. Sham 101±6 mmHg, p<0.05), cardiac and renal hypertension. Additionally, NAS treatment induced a selective increase in the recruitment of activated-CD8+ cells, B cells and granulocytes in lymph nodes. NGAL abundance was higher in PBMC, DCs and Mφ, which were further increased in NAS mice (c<3-fold vs. Sham, p<0.05 mRNA). In vitro MR activation by Aldo in DCs, but not in Mφ, induced an upregulation of NGAL and of cytokines involved in the adaptive immune response: TGF-β1 and IL-23p19 (n=4, p<0.05). Interestingly, the NGAL absence in DCs prevented this overexpression.

Conclusion: The MR activation and their subsequent NGAL induction in DCs could play a pivotal role in the inflammation observed during the Aldo-dependent hypertension.