Dendritic cells are crucial for cardiovascular remodeling and modulate neutrophil gelatinase-associated lipocalin expression upon mineralocorticoid receptor activation

Araos, Patricio

Prado, Carolina

Lozano, Mauricio

Figueroa, Stefanny

Espinoza, Alexandra

Berger, Thorsten

Mak, Tak W.

Jaisser, Frédéric

Pacheco, Rodrigo

Michea, Luis

Amador, Cristián A.

Background:Adaptive immunity is crucial in cardiovascular and renal inflammation/fibrosis upon hyperactivation of mineralocorticoid receptor. We have previously demonstrated that dendritic cells can respond to mineralocorticoid receptor activation, and the neutrophil gelatinase-associated lipocalin (NGAL) in dendritic cells is highly increased during aldosterone (Aldo)/mineralocorticoid receptor-dependent cardiovascular damage. However, the interrelationship among dendritic cells, target organs inflammation/fibrosis induced by mineralocorticoid receptor, and NGAL-dependence remains unknown.Objective:We studied the role of dendritic cells in mineralocorticoid receptor-dependent tissue remodeling and whether NGAL can modulate the inflammatory response of dendritic cells after mineralocorticoid receptor activation.Methods:Cardiovascular and renal remodeling induced by Aldo and high-salt diet [nephrectomy-Aldo-salt (NAS) model] were analyzed in CD11c.DOG mice, a model which allows dendritic cells ablation by using diphtheria toxin. In addition, in-vitro studies in NGAL-knock out dendritic cells were performed to determine the

immunomodulatory role of NGAL upon Aldo treatment.Results:The ablation of dendritic cells prevented the development of cardiac hypertrophy, perivascular fibrosis, and the overexpression of NGAL, brain natriuretic peptide, and two profibrotic factors induced by NAS: collagen 1A1 and connective tissue growth factor. We determined that dendritic cells were not required to prevent renal hypertrophy/fibrosis induced by NAS. Between different immune cells analyzed, we observed that NGAL abundance was higher in antigen-presenting cells, while in-vitro studies showed that mineralocorticoid receptor stimulation in dendritic cells favored NGAL and IL-23 expression (p19 and p40 subunits), which are involved in the development of fibrosis and the Th17-driven response, respectively.Conclusion:NGAL produced by dendritic cells may play a pivotal role in the activation of adaptive immunity that leads to cardiovascular fibrosis during mineralocorticoids excess.