Th17 INFLAMMATION AND PULMONARY HYPERTENSION

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Background: Pulmonary arterial hypertension (PAH) is a severe disease resulting in right heart failure, in which inflammation and autoimmunity mechanisms may play a role.

Aim: To decipher the PAH fingerprint on the immune response orchestrated by dendritic and T cells (DC and LT).

Methods: We performed an immunophenotyping of monocyte-derived DC (MoDC) and circulating lymphocytes from PAH and control patients by flow cytometry, and analyzed the cytokine profile of both populations after stimulation and/or coculture. We tested the immunomudulatory effects of dexamethasone (Dex) on these parameters, and confirmed by an epigenetic approach, the PAH immune polarization in blood DNA.

Results: Under similar differentiation/activation conditions, PAH MoDCs display similar profile of costimulatory molecules as compare to controls. However, PAH MoDCs expressed higher level of the LT activating molecules CD86 and CD40 after Dex pretreatment than controls. This was associated with an increased expression in p40 (IL12 and IL23 subunit) and a reduced migration toward CCL21. Both with and without Dex, PAH MoDC induced a higher activation/proliferation of CD4+ LT, associated to a reduced expression of IL4 (Th2 response) and higher expression of IL17 (Th17 response). In PAH venous blood, we found a specific depletion of CD4+ LT, possibly recruited in pulmonary vascular lesions. Purified PAH CD4+ LT expressed higher level of IL-17 after activation than controls. At last, there was a significant increase in the % of demethylated DNA at the IL17 promoter, in the PAH blood DNA as compared to controls.

Conclusions: We highlighted a Th17 immune polarization in PAH patient; a polarization involved in several chronic inflammatory and autoimmune conditions.