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Title: Regulatory T cells in pulmonary arterial hypertension

Dr. Alice 17697 Huertas alicehuertas@gmail.com MD [1,2,3], Dr. Ly 17698 Tu ly.tu@inserm.fr [1,2,3], Dr. Natalia 17699 Gambaryan natachagam@gmail.com [1,2,3], Dr. Barbara 17700 Girerd barbara.girerd19@gmail.com [1,2,3], Dr. David 17701 Montani davidmontani@gmail.com MD [1,2,3], Dr. Christophe 17702 Guignabert christophe.guignabert@inserm.fr [1,2,3] and Prof. Dr Marc 17703 Humbert marc.humbert@bct.aphp.fr MD [1,2,3]. [1] INSERM U999, LabEx LERMIT, Centre Chirurgical Marie Lannelongue, Le Plessis-Robinson, France ; [2] Service De Pneumologie, Centre National De Référence De L'Hypertension Pulmonaire Sévère, Hôpital Bicêtre, AP-HP, DHU Torino, Le Kremlin-Bicêtre, France and [3] Faculté De Médecine, Université Paris-Sud, Le Kremlin-Bicêtre, France .

Body: Increasing evidences support the hypothesis that immune mechanisms may play a key role in pulmonary arterial hypertension (PAH) onset or progression, but the underlying mechanisms are still unclear. We have recently shown that regulatory T cells (Treg) are dysfunctional in idiopathic PAH (iPAH) in a leptin-dependant manner (Huertas, A. et al. ERJ 2012; 40:895-904). Despite these findings, it is still unknown whether the immunopathogenesis is similar among all PAH forms, and whether these immune mechanisms can be controlled to block PAH onset and/or progression. Here, we first analyzed circulating Treg functional status in different groups of PAH patients: iPAH (n=25), heritable (hPAH, n=20), pulmonary veno-occlusive disease (PVOD, n=10), scleroderma-associated (SSc-PAH, n=11) and we compared them to controls (n=20) by flow cytometry. We found that STAT3 phosphorylation is decreased in Treg in all PAH groups as compared to controls, underlying the key role of Treg dysfunction in PAH pathogenesis. We also demonstrated that Treg are inhibited in a leptin-dependent manner in all PAH groups, except for hPAH. To elucidate the leptin-dependent immune mechanisms in PAH onset, we used rats deficient in leptin receptor (ZDF-/-) in a chronic hypoxia-induced model of pulmonary hypertension (Hx-PH). Strikingly, Hx-PH ZDF-/- rats maintain functional Treg and they develop less severe Hx-PH as compared to wildtype controls. Taken together, our results clearly indicate a crucial role for Treg in PAH immunopathogenesis, highlighting that Treg dysfunction may represent an important “second hit” in PAH onset and/or progression. These results shed light on new promising therapeutical targets in PAH treatment. Support: FRM Josso Award 2010.