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Title: MIF/CD74 contributes to the endothelial pro-inflammatory phenotype in pulmonary arterial hypertension

Dr. Ly 16633 Tu ly.tu@inserm.fr [1,2], Mrs. Morane 16638 Le Hiress moranelh@gmail.com [1,2], Dr. Nicolas 16639 Ricard nic.ricard@gmail.com [1,2], Mrs. Carole 16640 Phan phan.carole@gmail.com [1,2], Dr. Andrei 16641 Seferian andreiseferian@yahoo.com MD [1,2,3], Dr. Barbara 16644 Girerd barbara.girerd@bct.aphp.fr [1,2,3], Prof. Elie 16648 Fadel e.fadel@ccml.fr MD [1,2], Dr. Frances 16651 de Man fs.deman@vumc.nl [4], Dr. Gael 16652 Jalce gael.jalce@gensyntex.com [5], Dr. David 16653 Montani david.montani@bct.aphp.fr MD [1,2,3], Prof. Gerald 16654 Simonneau gerald.simonneau@bct.aphp.fr MD [1,2,3], Prof. Marc 16656 Humbert marc.humbert@bct.aphp.fr MD [1,2,3], Dr. Alice 16657 Huertas alicehuertas@gmail.com MD [1,2,3] and Dr. Christophe 16658 Guignabert christophe.guignabert@inserm.fr [1,2]. [1] UMR 999, INSERM, Le Plessis-Robinson, France, 92350 ; [2] School of Medicine, Univ Paris-Sud, Le Kremlin-Bicêtre, France ; [3] Reference Center, Pneumology Dept., AP-HP, Bicêtre Hospital, Le Kremlin-Bicêtre, France ; [4] Dept. of Pulmonology, VU University Medical Center, Amsterdam, Netherlands and [5] Faculty of Pharmacy, Univ Paris-Sud, Chatenay-Malabry, France .

Body: Rationale: Inflammation and endothelial dysfunction are considered two primary instigators of pulmonary arterial hypertension (PAH). CD74 is a receptor for the cytokine macrophage migration-inhibitory factor (MIF). This ligand/receptor complex initiates survival pathways and cell proliferation, triggers the synthesis/secretion of major pro-inflammatory factors and cell adhesion molecules. Objectives: We hypothesized that MIF and endothelial-CD74 are over-expressed and over-activated in PAH and contributes to pulmonary endothelial cells (P-ECs) pro-inflammatory phenotype. Results: Circulating MIF levels is increased in serum of idiopathic PAH (iPAH) patients as compared to controls and T-cells lymphocytes represent a cause of this overabundance. In addition, CD74 is highly expressed in the endothelium of muscularized distal pulmonary arteries as well as in cultured P-ECs from iPAH and contributes to an exaggerated recruitment of PBMC to P-EC in iPAH. Over-activation of CD74 by MIF induces production of interleukin (IL)-6 and monocyte chemoattractant protein (MCP)-1 and causes an increase in intercellular adhesion molecule (ICAM)-1 protein level. These effects are partially abolishes in presence of the selective MIF antagonist ISO-1. Finally, we found that daily treatment of rats with ISO-1 for 2 weeks started 2 weeks after a subcutaneous monocrotaline injection partially reverses development of pulmonary hypertension and this is associated with decreased of IL-6, MCP-1 and inflammatory cell infiltration. Conclusions: We report here that CD74 and MIF are markedly increased and activated from iPAH patients and contribute to the abnormal pro-inflammatory phenotype of P-EC in PAH.