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Title: Evidence for a critical contribution of pericytes in pulmonary arterial hypertension pathogenesis

Dr. Nicolas 457 Ricard nicolas.ricard@inserm.fr [1,2], Dr. Ly 458 Tu ly.tu@inserm.fr [1,2], Dr. Alice 459 Huertas alice.huertas@inserm.fr MD [1,2], Ms. Carole 460 Phan carole.phan@inserm.fr [1,2], Ms. Morane 461 Le Hiress morane.le-hiress@inserm.fr [1,2], Prof. Elie 462 Fadel e.fadel@ccml.fr MD [1,2], Prof. Marc 463 Humbert marc.humbert@bct.aphp.fr MD [1,2,3] and Dr. Christophe 464 Guignabert christophe.guignabert@inserm.fr [1,2]. [1] Cardiovascular Research Department, INSERM UMR 999, LabEx Lermit, Le Plessis-Robinson, France ; [2] Faculté de Médecine, Université Paris-Sud, Le Kremlin-Bicêtre, France and [3] Centre de Référence de l'Hypertension Pulmonaire Sévère, DHU Thorax innovation, CHU Bicêtre, AP-HP, Le Kremlin-Bicêtre, France .

Body: Rationale: Pericytes and their crosstalk with endothelial cells (ECs) are critical for the development of a functional microvasculature and vascular remodeling. It is also known that pulmonary endothelial dysfunction is intertwined with the initiation and progression of pulmonary arterial hypertension (PAH). Objectives: We hypothesized that pulmonary endothelial dysfunction, characterized by abnormal fibroblast growth factor (FGF)2 and interleukin (IL)-6 signaling, leads to abnormal microvascular pericyte coverage causing pulmonary arterial medial thickening. Results: In human lung tissues, the number of pericytes is substantially increased (up to 2-fold) in distal PAH pulmonary arteries as compared to controls. Interestingly, in our murine retinal angiogenesis model, both FGF2 and IL-6 administration increased pericyte coverage. Furthermore, human pulmonary pericytes exhibit, in vitro, an accentuated proliferative and migratory response to conditioned media from human pulmonary idiopathic PAH (iPAH) ECs as compared to conditioned media from control ECs. Importantly, by using an anti-FGF2 neutralizing antibody, we attenuated these proliferative and migratory responses, whereas by using an anti-IL-6 neutralizing antibody, we decreased the migratory response without affecting the proliferative response. Finally, we found that both FGF2 and IL-6 affect the differentiation of pulmonary pericytes into contractile smooth muscle-like cells. Conclusions: This is the first report of abnormal pericyte coverage in distal pulmonary arteries in human PAH. We are also showing that this phenomenon is directly linked with pulmonary endothelial dysfunction.