European Respiratory Society
Annual Congress 2013

Abstract Number: 787

Publication Number: P481

Abstract Group: 4.3. Pulmonary Circulation and Pulmonary Vascular Disease

Keyword 1: Pulmonary hypertension **Keyword 2:** Inflammation **Keyword 3:** Immunology

Title: Granulysin in pulmonary veno-occlusive disease

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Body: Background: Pulmonary Veno-Occlusive Disease (PVOD) shares many similarities with precapillary Pulmonary Arterial Hypertension (PAH), from risk factors to clinical or hemodynamic presentation. The need to establish a correct diagnosis of PVOD is justified by the worse prognosis of these patients and by their risk of developing severe pulmonary edema with specific PAH therapy. Aims and objectives: To show that the cytolytic subpopulation of inflammatory cells is differently regulated in PAH and PVOD patients and to identify a biological tool to distinguish these two entities. Methods: The functional status of the cytolytic compartment was studied through epigenetic analysis of the Granulysin (GNLY), a powerful effector for these subpopulations in explanted lungs and in PBMC. Flow cytometry allowed analysis of circulating cytolytic cells and GNLY contents. A GNLY-specific ELISA allowed measurement of GNLY serum concentrations. Results: A decrease in GNLY demethylation in the DNA extracted from PBMC and lungs was found in PVOD but not in PAH. This was associated with a decrease in populations and subpopulations of cytotoxic T-(CTL), and Natural Killer T-(NKT) cells, and an increase of Natural Killer-(NK) populations. Despite the reduced GNLY-containing cells in PVOD, GNLY serum levels were higher, suggesting these cells were wasting their content. Furthermore, the increase of GNLY concentration in the serum of PVOD was higher than in PAH patients. Conclusions: PVOD is characterized by alterations of circulating cytotoxic cell-subpopulations and by epigenetic dysregulation within the GNLY gene. Our findings may be helpful to

develop needed biological tools in order to screen for suspected PVOD in patients with pulmonary hypertension.