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Title: Chemokinome characterization in human lung macrophages following stimulation with Th2-type cytokines IL-4 or IL-13

Dr. Stanislas 18858 Grassin Delyle s.grassindelyle@gmail.com [1], Dr. Amparo 18859 Buenestado amparo.buenestado@gmail.com [1], Ms. Charlotte 18860 Abrial abrial.charlotte@gmail.com [1], Mrs. Marion 18861 Brollo m.brollo@hopital-foch.org [1], Dr. Emmanuel 18862 Naline upresea220@orange.fr [1] and Prof. Dr Philippe 18863 Devillier p.devillier@hopital-foch.org MD [1]. [1] UPRES EA220, Laboratoire de Pharmacologie Respiratoire, Hôpital Foch, UVSQ, Suresnes, France, 92150 .

Body: Background: Macrophages may acquire polarized phenotypes, the two extremes being the proinflammatory (M1) and immunoregulatory (M2) phenotypes characterized by surface markers and chemokinome profiles. Reprogramming of AM toward a partially M2-polarized phenotype has been suggested to contribute to COPD pathogenesis. We thus sought to characterize the phenotype of human lung macrophages (LM) following stimulation with the Th2-type cytokines IL-4 and IL-13. Methods: LM were isolated from human resected lungs challenged for 24 or 48hrs with IL-4 or IL-13 (1-150 ng/mL). Cytokines transcript expression was assessed with RT-qPCR, whereas proteins of M1 (TNF-α, CCL3, CCL4 and CXCL8) and M2 cytokines (CCL13, CCL17 and CCL22) were quantified in supernatants. Results: Unstimulated LM exhibited a rather undifferenciated phenotype, with weak M1/M2 cytokines expression. On the other hand, transcriptome analysis of 80 cytokines gene revealed that only four M2-type transcripts levels were increased (4- to 8-fold) following stimulation with IL-13 (CCL13, CCL17, CCL22 and CCL26). M2-type cytokine production at the protein level was also concentration-dependently increased (3- to 20-fold), whereas M1 cytokines were unaffected. CCL13 and CCL22 increase was maximal at 48hrs, while the maximum was reached at 24hrs for CCL17. The results obtained with IL-4 were similar, except that IL-4 potency was greater than IL-13 since the low 10 ng/mL concentration provided submaximal cytokines increases. Conclusions: Our data demonstrate that IL-4 and IL-13 favours LM polarization toward the immunoregulatory M2 phenotype characterized by the expression of CCL13, CCL17, CCL22 and CCL26.