European Respiratory Society
Annual Congress 2012

Abstract Number: 3426

Publication Number: 382

Abstract Group: 3.2. Airway Cell Biology and Immunopathology

Keyword 1: COPD - mechanism **Keyword 2:** Inflammation **Keyword 3:** Immunology

Title: Identification of pathogenic macrophage subpopulations in lung disease

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Body: Residential macrophages may exist in discreet subpopulations which subserve specific roles in the maintenance of tissue and immunological homeostasis. In lung, alveolar macrophages (AMΦs) comprise of >95% cells in the alveolar airspaces, where they act as the primary sentinels of pathogens. Increased alveolar macrophage numbers are observed in many animal models of COPD and also clinically in COPD patients. Currently, M2 macrophage polarisation is thought to be a contributor of lung disease, although this in vitro-derived macrophage paradigm may not completely explain the complex behaviour of AMΦs in vivo. Using flow cytometry, we have developed an approach which shows that mouse AMΦs instead form distinct subpopulations during acute inflammation and in chronic inflammatory lung disease. During acute inflammation, AMΦ subpopulations are characterised by differential Mac-1 and CD11c integrin expression rather than M1 or M2 MΦ surface markers exclusively, and display differential gene signatures ex vivo. Resolution is characterised by restoration to a single population of Mac-$1^{low/neg}$ AMΦs mirroring lung homeostasis. In contrast, SHIP-$1^{-/-}$ mice which develop chronic inflammatory lung disease spontaneously have an additional subpopulation of Mac-1^{pos} macrophages which highly expresses MMP-12. This additional AMΦ subpopulation also tracks with the induction of lung disease using SHIP-$1^{-/-}$ chimeric mice. Following this, we are now screening for markers of AMΦ subpopulations in patients with COPD. Our studies of both animal models and clinical samples may allow us to better understand the role of AMΦ subpopulations in homeostasis and disease.