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Title: LSC 2013 abstract - Overexpression of IRF5 ameliorates house dust mite-mediated airway hyper-responsiveness via macrophage polarisation towards a classically activated phenotype

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Body: Introduction: Recently, we identified the transcription factor IRF5 as a master regulator of pro-inflammatory macrophage polarization (Krausgruber et al, Nature Immunology, 2011). Here, we investigate the role of IRF5 in the pathogenesis of allergic airways disease. Objectives: 1) To investigate the expression of IRF5 in the murine lung. 2) Explore the potential of IRF5 over-expression for treatment of airway inflammation. 3) Define the mechanism by which over-expression of IRF5 effects allergic airway responses. Methods: First, we characterised the kinetics of IRF5 expression in the lung after HDM challenge. Next, in order to ascertain the role of IRF5 in allergic airway responses, we treated mice intra-nasally with an adenoviral vector containing IRF5 or a control virus; mice were then exposed to house dust mite (HDM) extract. Results: IRF5 was significantly elevated in HDM treated mice, 24h after HDM instillation. IRF5 overexpression resulted in ablated airway hyper-reactivity, reduced eosinophilia and diminished Th2 cytokines in the lung, compared to control mice after three weeks of allergen challenge. These observed changes in the pathogenesis of allergic disease were associated with a switch from an alternatively activated macrophage signature in the lung, to that of a classically activated macrophage phenotype. Conclusions: These data, for the first time, identify IRF5 as a key component in allergic airway disease and as a putative target for the development of therapies for the treatment of asthma.