European Respiratory Society
Annual Congress 2013

Abstract Number: 3815

Publication Number: 3514

Abstract Group: 3.2. Airway Cell Biology and Immunopathology

Keyword 1: Epigenetics **Keyword 2:** Airway smooth muscle **Keyword 3:** Monocyte / Macrophage

Title: Bromodomain and extra-terminal (BET) proteins regulate antioxidant gene expression

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Body: Background: Oxidative stress, a key pathogenic factor in COPD, arises due to reactive oxygen species (ROS) accumulation and defective antioxidant defences in the lungs. The latter is partly due to acetylation of the antioxidant gene activator nuclear factor E2-related factor 2 (Nrf2). Bromodomain and extra-terminal (BET) proteins regulate gene transcription by binding to acetylated proteins and recruiting transcriptional regulators to gene promoters. Their role in antioxidant gene regulation is unknown. Aims & Objectives: Determine the role of BET proteins in antioxidant gene expression in human primary airway smooth muscle cells (ASMCs) and THP1 monocytic cells. Methods: BET proteins were inhibited using the selective inhibitor (+) - JQ1 [JQ1]. mRNA and protein expression was determined by real-time PCR and western blotting, respectively. Results: In ASMCs, JQ1 (50-1000nM) increased the mRNA of Nrf2-mediated antioxidants haem oxygenase (HO)-1 (~5-fold; $p<0.05$), NADPH: quinone oxidoreductase 1 (NQO1) (~6-fold; $p<0.05$) and GCL catalytic subunit (GCLC) (~4-fold; $p<0.05$), in a concentration-dependent manner. The up-regulation of HO-1 (~3-fold; $p<0.05$), NQO1 (~2.5-fold; $p<0.05$) and GCLC (~2-fold; $p<0.05$) mRNA by JQ1 (300nM) occurred 8-24hrs post-treatment. Concomitantly, JQ1 (300nM) increased Nrf2 mRNA (~1.8-fold; $p<0.01$) and protein (~3-fold; $p<0.05$), and reduced the expression of the Nrf2 inhibitor Kelch-like ECH-associated protein 1 (Keap1). JQ1 had the same effect in THP1 cells. Conclusions: BET proteins may augment antioxidant defences and prevent oxidative stress in addition to their known anti-inflammatory and anti-proliferative actions. They have potential as novel therapeutic targets in COPD.