European Respiratory Society
Annual Congress 2013

Abstract Number: 2632
Publication Number: 4861

Abstract Group: 5.1. Airway Pharmacology and Treatment
Keyword 1: Cell biology **Keyword 2:** Comorbidities **Keyword 3:** COPD - mechanism

Title: Endothelial progenitor cells are dysfunctional in smokers and COPD patients due to increased DNA damage and senescence

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Body: Introduction: Cardiovascular disease (CVD) is a major cause of death in smokers and COPD patients. DNA damage has been recognized as an important contributor in COPD and CVD. Aim: To investigate the role of DNA damage pathways in endothelial dysfunction in smokers and COPD patients. Methods and results: Blood outgrowth endothelial cells (BOEC) were isolated and expanded in vitro from circulating endothelial progenitors, from healthy non-smokers, healthy smokers and COPD patients. In vitro, BOEC from smokers and COPD patients showed increased DNA double-strand breaks (measured by γ-H2AX, 53BP1) and senescence (senescence associated-β-galactosidase activity, p16 and p21 levels) compared to non-smokers. Senescence negatively correlated with sirtuin-1 (SIRT1) expression and activity, a protein deacetylase that inhibits DNA damage and cellular senescence. Inhibition of DNA damage response by silencing of ataxia telangiectasia-mutated (ATM) kinase resulted in up-regulation of SIRT1 expression and decreased senescence. Interestingly, treatment of BOEC from COPD patients with the SIRT1 activator resveratrol or a selective ATM inhibitor rescued the senescent phenotype. Using an in vivo mouse model of angiogenesis, we demonstrated that senescent BOEC from COPD patients are dysfunctional, displaying impaired angiogenic ability and apoptosis compared to non-smokers. Conclusions: BOEC from smokers and COPD patients have reduced angiogenic ability in vivo and display increased DNA damage and senescence, associated with reduced SIRT1 expression. These defects may contribute to endothelial dysfunction and CVD and could potentially constitute therapeutic targets for intervention.