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Title: Blood outgrowth endothelial cells are senescent and dysfunctional in COPD due to increased DNA damage; implications for endothelial dysfunction

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Body: Introduction: Cardiovascular disease (CVD) is a major cause of death in COPD. The molecular pathways that lead to endothelial dysfunction and CVD in COPD remain unclear. DNA damage has been recognized as an important contributor in aging disorders. Blood outgrowth endothelial cells (BOEC) -alternatively named Late endothelial progenitor cells- could serve as a research tool to investigate endothelial defects in COPD patients. Aim and objectives: To examine whether BOEC exhibit increased DNA damage linked to dysfunctional characteristics, illustrating the underlying molecular process of endothelial dysfunction in COPD. Methods: BOEC were isolated from peripheral blood samples received from 16 healthy non-smokers (age +/- SEM, 57 +/- 2.7yr; 5 males), 10 healthy smokers (57 +/- 2.6yr; 5 males) and 16 COPD patients (67 +/- 1.6yr; 11 males). DNA damage was assessed by measuring two markers of double-strand break formation, 53BP1 and γ-H2AX, by immunostaining. Endothelial senescence was measured by senescence-associated β-galactosidase (SA-β-Gal) activity, and sirtuin(SIRT)1 protein levels by Western blotting. Results: BOEC from smokers and COPD patients showed markers of increased DNA damage and displayed significantly reduced SIRT1 protein levels and increased senescence compared to healthy non-smokers. Conclusions: The results from our study demonstrate that BOEC from smokers and COPD patients display increased DNA damage linked to epigenetic molecular dysfunction and increased senescence. These defects may contribute to endothelial dysfunction and cardiovascular events in smokers and patients with COPD.