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Title: Pulmonary senescence in chronic obstructive pulmonary disease is primarily mediated by persistent DNA double strand breaks

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Body: Chronic obstructive pulmonary disease(COPD) is an age associated disease caused mainly by cigarette smoking. Deregulated repair, tissue regeneration and lung regression are the hallmarks of COPD. Cellular senescence is a signal transduction program leading to irreversible cell cycle arrest. The growth arrest can be triggered by many different mechanisms including recognition by cellular sensors of DNA double-strand breaks leading to the activation of cell cycle checkpoint responses and recruitment of DNA repair foci. The execution of regenerative programs in lung and remote organs is closely linked to viability or senescence of resident cells as well as progenitor cells derived from the circulation. We propose COPD to be a disease of premature lung senescence and aim to decipher markers of DNA damage, repair and senescence in animal models of smoke induced emphysema as well as in smokers with and without COPD. Results: Cellular senescence could be successfully assessed by staining for β-galactosidase and evaluation of senescence associated heterochromatin foci (SAHF), reflecting condensed chromatin, in the nuclei. DNA double strand breaks and cell cycle arrest could be demonstrated by up regulated 53-BP1, γH2AX and p21. Paraffin lung sections from Smoked Mice and Human COPD samples were investigated for markers of senescence, DNA damage and repair. Markers of DNA double strand breaks and senescence seem to be prominently up regulated in the diseased samples. Our results stronly indicate that the senescence in case of COPD is primarily driven by the persistent DNA double-strand breaks due to prolonged cigarette smoking.