Cigarette Smoke Induced Lung Injury

Cigarette smoke (CS) is a major risk factor for chronic obstructive pulmonary disease (COPD). Free radical damage to proteins following CS exposure induces endoplasmic reticulum (ER) stress. High levels of S-glutathionylated protein disulfide isomerase (PDI) were found in the lungs of murine smokers compared with non-smokers. To decipher if S-glutathionylated PDI contributes to pro-apoptotic redox signaling, we investigated the causality between PDI S-glutathionylation, changes in its cellular localization and apoptosis. PDI spatially linked to mitochondria increased upon exposure to lethal doses of CSE, where it causes cytochrome c (Cyt c) release through the mitochondrial permeability transition pore, which in turn leads to caspase-3 mediated apoptosis. Rescue of mitochondrial function in lung cells can be achieved either by over-expressing PDIFLFL, a S-glutathionylation refractory mutant of PDI, or with pharmacological inhibition of glutathione transferase P, an enzyme that mediates S-glutathionylation, and both in turn could reduce the cytotoxicity caused by CS. We conclude that CS exposure induces PDI S-glutathionylation, and its proximity to mitochondria, where it causes Cyt c release from mitochondria, leading to intrinsic apoptosis.

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