Oxidative Stress-Induced Mitochondria Alteration In Human Airway Smooth Muscle Cells And Mesenchymal Stem Cells

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Rationale

Exposure to cigarette smoke (CS) is the primary cause of chronic obstructive pulmonary disease (COPD). Reactive oxygen species (ROS) produced by CS, as well as by infiltrating inflammatory cells, in conjunction with compromised antioxidant defenses in the lungs of COPD patients, results in oxidative stress. Oxidative stress leads to defective function of lung cells, such as airway smooth muscle cells (ASMCs), driving airway inflammation and remodelling. Mitochondrial dysfunction caused by oxidative stress leads to changes in cell survival and inflammatory responses. Mitochondrial transfer between mesenchymal stem cell (MSC) and airway cells has been shown to reverse mitochondrial dysfunction in lung disease models. We investigated the effect of oxidative stress on mitochondrial function and viability of ASMC and MSCs.

Methods

ASMCs dissected from bronchi or tracheas of healthy transplant donor lungs were treated with H_2O_2 (50 μM, 100 μM and 200 μM) or cigarette smoke extract (CSE) (10%, 25%, 50% and 75%) for 2 hrs, 4 hrs and 24 hrs. A cessation group was also included, in which the H_2O_2 or CSE was removed at 4 hrs and replaced with serum-free medium for the next 20 hrs. Changes in mitochondrial membrane potential (ΔΨm) and ROS levels were evaluated by JC-1 and MitoSOX staining respectively. Cell viability was measured by MTT assay. Human induced-pluripotent stem cell-derived mesenchymal stem cells (iPSC-MSC) were similarly treated for 4 hrs and 24 hrs and the same parameters were measured.

Results

CSE increased mitochondrial ROS levels (max ~10-fold; $p<0.05$) and reduced ΔΨm (max ~60%; $p<0.05$) in ASMCs in a concentration- and time-dependent manner. The treatment with H_2O_2 increased mitochondrial ROS (max ~1.7-fold; $p<0.05$) and reduced ΔΨm (max ~30%; $p<0.05$) in a concentration- and time-dependent manner in ASMCs. Both CSE (max ~40%; $p<0.05$) and H_2O_2 (max ~40%; $p<0.05$) reduced ASMC viability in a concentration- and time-dependent manner. After removal of H_2O_2 4hrs post- exposure, mitochondrial dysfunction persisted; in contrast, removal of CSE led to partial recovery. Treatment of iPSC-MSCs with CSE and H_2O_2 also led to increased mitochondrial ROS levels, decreased ΔΨm and loss of cell viability.

Conclusions

H_2O_2 and CSE can induce mitochondrial ROS accumulation and ΔΨm and cell viability loss in ASMCs and iPSC-MSCs. Although stem cell mitochondrial transfer may be an appealing strategy for reversing mitochondrial dysfunction in disease, caution is required as stem cells may also show mitochondrial damage under oxidative stress.

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