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Cigarette smoke-induced mitochondrial dysfunction and oxidative stress in

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SCOPE OF THE STUDIES

In the first three chapters we investigate a new pathophysiological paradigm, where mitochondrial dysfunction is crucial for disease development and progression. Mitochondria are crucial for cellular energy production, ROS management and regulation of cell death. In **chapter 1** we investigated whether cigarette smoke extract (CSE) disturbs the mitochondrial respiratory chain function leading to decreased production of intracellular energy (ATP). Furthermore, we investigated whether energy depletion by cigarette smoke (CS) is crucial in the routing of apoptotic-triggered cells towards necrosis.

CS can be separated into a gaseous and particulate phase. Reactive oxygen species (ROS) that are present in gaseous-phase of CS are thought to be the most important factor of the oxidative damage and stress present in chronic obstructive pulmonary disease (COPD). However these components are hardly able to enter the cell due to the presence of unpaired electrons and will therefore primarily react with the anti-oxidants present in the epithelial lining fluid. On the other hand, the particulate phase contains lipophilic components that can easily enter the cell and the systemic circulation. In **chapter 2** we investigated whether these lipophilic components have a direct interaction with mitochondria, leading to increased production of mitochondrial ROS. We also investigated whether increased production of mitochondrial ROS induces ROS-mediated cellular damage.

The airway epithelium provides an efficient barrier for the underlying tissue against toxic compounds present in CS. To maintain this barrier, two crucial protection systems are of importance:

- 1) cell replacement and regeneration of the epithelium
- 2) management of intracellular ROS-metabolism

Mitochondria are the key players in both systems. Normal cell removal and cell replacement in tissue remodeling is regulated by apoptosis (39). Mitochondria regulate apoptosis by the release of pro apoptotic mediators and supply of ATP. Although, mitochondria are the largest source of intracellular ROS, all major anti-oxidants are present within the mitochondria. In **chapter 3** we investigated whether heme oxygenase-1 was also an important antioxidant present in mitochondria. In the same chapter we studied the protective role of heme oxygenase-1 on mitochondrial function and CS-induced cell death.

A second important mechanism of the airway epithelium to ensure an appropriate defense against the highly reactive compounds present in CS is to keep a balance between ROS and antioxidants. Reduced glutathione plays a key role in the cellular redox balance. In **chapter 4** we investigated whether components of the gas phase of CS react irreversibly with the free thiol group of glutathione. A non-reducible glutathione derivates will reduce the pool of reduced glutathione. This may lead to a lack of protection against oxidative stress.

Epithelial injury and recovery are important in the pathogenesis of COPD. In **chapter 5**, oxidative stress and the damage that may result from it have been studied in quiescent and proliferating airway epithelial cells. It was hypothesized that resistance and recovery would be dependent on the concentration of the oxidative agent but also on the duration of exposure and on the quiescent and proliferating state of airway epithelial cells. This was studied in vitro by measuring morphology, viability and cell death pathways.

Oxidative stress has been implicated in many diseases. For example, accelerated atherosclerosis and fibrosis develop in prolonged smokers but also in transplanted patients which are treated with the immunosuppressive cyclosporine A. This contributes to the development of chronic transplant dysfunction. It has been suggested that mitochondrial ROS production play an important underlying role. Cyclosporine A is a well known inhibitor of the mitochondrial permeability transition pore. In **chapter 6** we investigated whether closure of the mitochondrial permeability transition pore by cyclosporine A results in a concomitant increase in mitochondrial membrane potential and production of ROS.

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