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Cigarette smoke causes caspase-independent apoptosis of bronchial epithelial cells from asthmatic donors

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Epidemiologic studies have demonstrated important links between air pollution and asthma. Amongst these pollutants, environmental cigarette smoke is a risk factor both for asthma pathogenesis and exacerbation. As the barrier to the inhaled environment, the bronchial epithelium is a key structure that is exposed to cigarette smoke. Since primary bronchial epithelial cells (PBECs) from asthmatic donors are more susceptible to oxidant-induced apoptosis, we hypothesized that they would be susceptible to cigarette smoke-induced cell death. PBECs from normal and asthmatic donors were exposed to cigarette smoke extract (CSE); cell survival and apoptosis were assessed by FACS, and protective effects of antioxidants evaluated. The mechanism of cell death was evaluated using caspase inhibitors and immunofluorescent staining for apoptosis-inducing factor (AIF). Exposure of PBEC cultures to CSE resulted in a dose-dependent increase in cell death. At 20% CSE, PBECs from asthmatic donors exhibited significantly more apoptosis than cells from non-asthmatic controls. Reduced glutathione (GSH), but not ascorbic acid (AA), protected against CSE-induced apoptosis. To investigate mechanisms of CSE-induced apoptosis, caspase-3 or -9 inhibitors were tested, but these failed to prevent apoptosis; in contrast, CSE promoted nuclear translocation of AIF from the mitochondria. GSH reduced the number of nuclear-AIF positive cells whereas AA was ineffective. Our results show that PBECs from asthmatic donors are more susceptible to CSE-induced apoptosis. This response involves AIF, which has been implicated in DNA damage and ROS-mediated cell-death. Epithelial susceptibility to CSE may contribute to the impact of environmental tobacco smoke in asthma.

Keywords
Bronchial epithelium, cigarette smoke extract, apoptosis-inducing factor, asthma.