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Title: Differential actions of the endogenous docosahexaenoic acid (DHA) electrophilic derivative 17-oxo-DHA in macrophages and bronchial epithelial cells

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Body: 17-oxo-DHA is an endogenous electrophilic derivative of the omega-3 fatty acid DHA, which is generated in activated macrophages by the action of cyclooxygenase-2. In murine macrophages 17-oxo-DHA exerts dual anti-inflammatory and anti-oxidant actions. This makes 17-oxo-DHA attractive for the development of new treatments for chronic diseases characterized by persistent inflammation and oxidative stress such as chronic obstructive pulmonary disease (COPD). In the airways of COPD patients, combined activation of bronchial epithelial cells and alveolar macrophages produces a state of chronic inflammation which is further enhanced by cigarette smoke. Currently there is no therapy able to revert disease progression and the search for new drugs is highly active. In the present work, the actions of 17-oxo-DHA were evaluated in human macrophages and bronchial epithelial cells (HBE) stimulated with cigarette smoke extract (CSE) and lipopolysaccharide (LPS). We report that despite increasing intracellular glutathione and promoting Nrf2 nuclear translocation and heme oxygenase-1 expression in both cell types, 17-oxo-DHA protected macrophages from CSE-induced oxidative stress but enhanced ROS formation in CSE-stimulated HBE cells without causing cell toxicity. In macrophages, 17-oxo-DHA displayed anti-inflammatory actions by suppressing LPS-induced TNFalpha production at transcriptional level and reducing total and surface expression of Toll-like receptor 4. Overall, the present results support a differential role of 17-oxo-DHA in immune and structural cells which should be taken into account when considering this compound for drug development.