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Title: Low levels of heme oxygenase-1 in induced sputum of lung cancer patients as a marker of defective cytoprotection

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Body: Background: Lung cancer is a leading cause of morbidity and mortality worldwide, resulting in substantial economic and social burdens that are constantly increasing. There is a strong correlation between inflammation and oxidative stress and malignant transformation. Heme oxygenase-1 (HO-1) is a cytoprotective enzyme that plays a central role in the defense against oxidative stress. HO-1 has anti-inflammatory, anti-proliferative and anti-apoptotic properties and is involved in the regulation of immunological balance in a wide range of lung diseases, including lung cancer. Aims: To investigate the role of HO-1 as an anti-oxidant and anti-inflammatory enzyme in the pathogenesis of lung cancer, by comparing its activity in induced sputum (IS) of patients with lung cancer, patients with COPD and healthy nonsmokers controls. Methods: IS was conducted according to a standard protocol. HO-1 levels were measured in IS supernatant by a biliverdin reductase-dependant reaction using bilirubin as end product. Results: 90 subjects (31 with lung cancer, 29 with COPD and 30 healthy nonsmokers) underwent IS and HO-1 level measurements. Mean HO-1 levels were significantly ($p<0.0001$) lower in lung cancer patients compares to COPD patients and healthy controls, (0.645, 1.192 and 1.628 respectively). There was a negative correlation between the lung cancer stage and HO-1 activity. Conclusions: HO-1 activity is reduced in patients with lung cancer and correlates with disease severity, suggesting its protective effect as an antioxidant enzyme. These findings may propose a role of agents stimulating HO-1 as a novel therapeutic approach in lung cancer.