Altered Nrf2/Keap1-Bach1 equilibrium in pulmonary emphysema

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Résumé en anglais	BACKGROUND: Oxidative stress, resulting from the increased oxidative burden and decreased level of antioxidant proteins, plays a role in the pathophysiology of smoking-related pulmonary emphysema. Expression of several antioxidant proteins, such as heme oxygenase-1 (HO-1), glutathione peroxidase 2 (GPX2) and NAD(P)H:quinone oxidoreductase 1 (NQO1), results from an equilibrium created by positive or negative regulation by the transcription factors Nrf2, Keap1 and Bach1, respectively. However, whether the expression of these transcription factors is altered in emphysema and could account for decreased expression of antioxidant proteins is not known. A study was undertaken to investigate the expression and subcellular localisation of Nrf2, Keap1 and Bach1 as potential regulators of HO-1, GPX2 and NQO1 in alveolar macrophages, a key cell in oxidative stress, in lung surgical specimens from non-smokers without emphysema and smokers with and without emphysema. METHODS AND RESULTS: Western blot, immunohistochemical and laser scanning confocal analysis revealed that the Nrf2 protein level decreased significantly in whole lung tissue and alveolar macrophages (cytosol and nucleus) in patients with emphysema compared with those without emphysema. Conversely, Bach1 and Keap1 levels were increased in patients with emphysema. These modifications were associated with a parallel decrease in the expression of HO-1, GPX2 and NQO1 at the cellular level, which was inversely correlated with airway obstruction and distension indexes, and increased macrophage expression of the lipid peroxidation product 4-hydroxy-2-nonenal. Silencing RNA experiments in vitro in THP-1 cells were performed to confirm the cause-effect relation between the loss of Nrf2 and the decrease in HO-1, NQO1 and GPX2 expression. Nrf2/Keap1-Bach1 equilibrium was altered in alveolar macrophages in pulmonary emphysema, which points to a decreased stress response phenotype. CONCLUSIONS: This finding opens a new view of the pathophysiology of emphysema and could provide the basis for new therapeutic approaches based on preservation and/or restoration of such equilibrium.
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