“Oxidative Stress In Airways and Lungs”

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Abstract
The contribution of environmental pollution to airways disease such as asthma and COPD is supported by a substantial amount of epidemiological data, such as those showing an increase in exacerbations of disease or the increase in symptoms with peaks of ambient pollutants such as ozone or particulates. A large degree of experimental data implicate oxidative stress as the mechanism by which environmental pollutants induce airway inflammation and bronchial hyperresponsiveness. In addition, there are also endogenous sources of reactive oxygen species generated from activated inflammatory cells in airways disease. There is now substantial evidence for oxidant stress in asthma and COPD and one may ask about the contribution of this process to the disease and the mechanisms. Oxidant stress can induce the activation of stress kinases and activate redox-sensitive transcription factors NF-κB and AP-1, and evidence from ozone-exposed mice indicate that this could occur through the activation of toll receptor pathways, particularly 2 and 4, indicating oxidants activating innate immune response pathways. IL-13 appears to potentiate the effect of ozone exposure. Recent studies in airway smooth muscle contractile responses demonstrate that oxidant stress is a direct cause of enhanced maximal isometric contractile response through the activation of the MAPK pathway, particularly p38. TGFbeta causes a derangement of the oxidant/antioxidant status in airway smooth muscle cells by upregulation of NOX4 and downregulation of MnSOD and catalase leading to release of ROS which contributes to cytokine release and proliferation.

Oxidative stress may contribute to corticosteroid insensitivity in airways diseases. Various mechanisms have been proposed. In both severe asthma and COPD, diseases characterised by clinical corticosteroid insensitivity, corticosteroids are less effective in inhibiting the release of proinflammatory cytokines. In macrophages, one of the mechanism of corticosteroids is to recruit HDAC2 to acetylated histone H4 associated with the GM-CSF promoter; HDAC2 knockdown by siRNA decreases sensitivity to CS. Tyrosine nitration of HDAC2 leads to a decrease in HDAC2 activity, which is also observed in COPD. Other mechanisms implicate enhanced p38 MAPK activation in both severe asthma and COPD; this could result from a reduced inducible expression of MAPK phosphatise-1 (MKP-1 or DUSP-1). This could lead to enhanced phosphorylation of GR sites or interfere with NFκB activation through histone acetylation. PI3K activation with induced phosphorylation of AKt by oxidative stress may also contribute to CS insensitivity Oxidants may alter PI3K signalling either indirectly through inactivation/activation of a receptor or altering PTEN activity or directly by deactivating protein phosphatases. The concerted activation of kinases and phosphatases underlies many of corticosteroid’s downstream effects.