Inflammation, Injury and Transcription Factors in Chronic Lung Diseases: Therapeutic Targets

Irfan Rahman, Ph.D. & Senior scientist

ELEGI Laboratory, Respiratory Medicine Unit, MRC Centre for Inflammation Research, University of Edinburgh, Edinburgh, UK.

Airway inflammation is a characteristic of many lung disorders including asthma, chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis. All these diseases involve the recruitment of immune and inflammatory cells to the lungs leading to systemic and local chronic inflammation and oxidative stress. The sources of the increased oxidative stress in these patients derive from the increased burden of inhaled oxidants, and from the increased amounts of reactive oxygen species (ROS) generated by several inflammatory, immune and various structural cells of the airways. ROS, either directly or via the formation of lipid peroxidation products such as acrolein, 4-hydroxy-2-nonenal and F2-isoprostanes may play a role in enhancing the inflammation through the activation and phosphorylation of stress kinases (JNK, MAPK, p38, phosphoinositide 3 (PI-3)-kinase/PI-3K-activated serine-threonine kinase Akt) and redox sensitive transcription factors such as NF-κB and AP-1. In addition, activation of members of the MAPK family leads to the transactivation of transcription factors such as c-Jun, activating factor-2 (ATF2), cyclic AMP response element binding proteins (CREB)-binding protein (CBP) and Elk-1. This eventually results in chromatin remodelling and expression of genes regulating a battery of distinct pro-inflammatory and antioxidant genes involved in several cellular events including apoptosis, proliferation, transformation and differentiation.

Histone acetylation is reversible and is regulated by a group of acetyltransferases (HATs) which promote acetylation, and deacetylases (HDACs) which promote deacetylation. Inflammatory gene expression is regulated by the relative activity of HATs and HDACs. In the resting cell, DNA is tightly coiled on the surface of nucleosome core (histone residues), which suppresses
gene transcription by decreasing the accessibility of the transcriptional apparatus. Acetylation of specific lysine residues present in the N-terminal tails of the core histone (specifically histone, H4) results in uncoiling of the DNA leading to increased accessibility to transcription factor binding. Histone deacetylation represses genes by limiting access to transcription factors. The presence of oxidative stress may enhance the inflammation via expression of pro-inflammatory mediators through the activation of intrinsic HAT activity of co-activator molecules (increased acetylation of lysine residues on histone proteins), leading to increased NF-kB and AP-1 activation. Oxidative stress may also inhibit the activity of HDACs (HDAC-2 levels) via a redox-dependent mechanism, activate cells for NF-kB/AP-1 binding and enhance inflammatory gene expression which may therefore lead to chronic inflammatory response in lungs. It has been shown that glucocorticoid suppression of inflammatory genes requires recruitment of HDAC-2 to the transcription activation complex by the glucocorticoid receptor. This results in deacetylation of histones and a decrease in inflammatory gene transcription. The oxidant-mediated reduction in HDAC-2 levels will not only increase inflammatory gene expression but will also cause a decrease in glucocorticoid function. This may be one of the potential reasons for the failure of glucocorticoids to function effectively in reducing inflammation in COPD.

Knowledge of the mechanisms of redox signalling, NF-kB/AP-1 regulation, the balance between histone acetylation and deacetylation and the release and expression of pro- and anti-inflammatory mediators may lead to the development of novel therapies based on the pharmacological manipulation of antioxidants in lung inflammation and injury. The effective wide spectrum antioxidant therapy that has good bioavailability and potency is urgently needed to control the localised oxidative and inflammatory processes that occur in the pathogenesis of asthma and COPD. Thiol molecules such as intracellular glutathione and thioredoxin are of central therapeutic importance in the control of redox signalling pathways. Furthermore, development of novel antioxidant compounds would be therapeutically useful in monitoring the oxidative and inflammatory biomarkers in the progression/severity of asthma and COPD.