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Oxidative stress and regulation of glutathione in lung inflammation.

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Abstract

Inflammatory lung diseases are characterized by chronic inflammation and oxidant/antioxidant imbalance, a major cause of cell damage. The development of an oxidant/antioxidant imbalance in lung inflammation may activate redox-sensitive transcription factors such as nuclear factor-KB, and activator protein-1 (AP-1), which regulate the genes for pro-inflammatory mediators and protective antioxidant genes. Glutathione (GSH), a ubiquitous tripeptide thiol, is a vital intra- and extracellular protective antioxidant against oxidative/nitrosative stresses, which plays a key role in the control of pro-inflammatory processes in the lungs. Recent findings have suggested that GSH is important in immune modulation, remodelling of the extracellular matrix, apoptosis and mitochondrial respiration. The rate-limiting enzyme in GSH synthesis is gamma-glutamylcysteine synthetase (gamma-GCS). The human gamma-GCS heavy and light subunits are regulated by AP-1 and antioxidant response elements and are modulated by oxidants, phenolic antioxidants, growth factors, and inflammatory and anti-inflammatory agents in lung cells. Alterations in alveolar and lung GSH metabolism are widely recognized as a central feature of many inflammatory lung diseases such as idiopathic pulmonary fibrosis, acute respiratory distress syndrome, cystic fibrosis and asthma. The imbalance and/or genetic variation in antioxidant gamma-GCS and pro-inflammatory versus antioxidant genes in response to oxidative stress and inflammation in some individuals may render them more susceptible to lung inflammation. Knowledge of the mechanisms of GSH regulation and balance between the release and expression of pro- and anti-inflammatory mediators could lead to the development of novel therapies based on the pharmacological manipulation of the production as well as gene transfer of this important antioxidant in lung inflammation and injury. This review describes the redox control and involvement of nuclear factor-kappaB and activator protein-1 in the regulation of cellular glutathione and gamma-glutamylcysteine synthetase under conditions of oxidative stress and inflammation, the role of glutathione in oxidant-mediated susceptibility/tolerance, gamma-glutamylcysteine synthetase genetic susceptibility and the potential therapeutic role of glutathione and its precursors in protecting against lung oxidant stress, inflammation and injury.

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- Cystine/metabolism
- Disease Susceptibility
- Glutamate-Cysteine Ligase/metabolism
- Glutathione/biosynthesis
- Glutathione/metabolism*
- Humans
- Inflammation/metabolism
- Lung/metabolism
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- Smoking/metabolism
- Transcription Factor AP-1/physiology
- Transcription Factors/physiology
- gamma-Glutamyltransferase/metabolism

Substances:

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- Glutathione
- gamma-Glutamyltransferase
- Glutamate-Cysteine Ligase

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