

ABSTRACT

THE ROLE OF HYPOXIA INDUCIBLE FACTORS IN LUNG DEVELOPMENT AND COBALT-INDUCED LUNG INJURY

By

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The increasing use of disposable electronics and growing industrialization of nation's economies have drastically raised the risk of exposure to toxic metals. One of these metals, cobalt, is used widely in several industries involved in the production of coloring agent for ceramics, hard metal alloys, sintered carbides, drilling and grinding tools. Cobalt (or hard metal) asthma caused by the inhalation of cobalt containing dust is characterized by airway constriction, alveolitis, fibrosis and associated giant cell interstitial pneumonitis. The characterization of cobalt-induced toxicities demands comprehensive understanding of the effects of toxicants on cell signaling and the downstream changes in gene expression. It is well established that cobalt is a hypoxia mimic due to its ability to induce hypoxia-like gene expression responses. To enhance our understanding of cobalt-induced toxicity and determine the role of its ability to mimic hypoxia signaling in the process, we generated a doxycycline inducible lung-specific Hypoxia inducible factor 1a (HIF1a) deficient system in mice. In utero, lung specific deletion of HIF1a resulted in altered surfactant metabolism and defects in alveolar epithelial differentiation that led to premature death due to respiratory distress. In contrast, the in utero deletion of HIF2oc (another prominent form of HIFa) from the lungs did not affect the viability

of neonates. Interestingly, the removal of both HIF1a and HIF2a from the lungs during development led to the birth of phenotypically normal pups, suggesting that the loss of HIF2a can rescue the lethal phenotype associated with the loss of HIF1a from the lungs. Microarray analysis of the lungs from HIF1 α Δ/Δ, HIF2 α Δ/Δ and HIF1/2 α Δ/Δ identified sets of genes, involved in various cellular pathways such as surfactant metabolism and vesicular trafficking that were specifically affected in the HIF1 α Δ/Δ neonates and these results suggest possible mechanistic information for the role of HIFs in lung development.

In order to elucidate the role of epithelial derived-HIF1 α signaling in cobalt-induced lung injury, we deleted the transcription factor postnatally. These mice were exposed to cobalt chloride via oropharyngeal aspiration. Compared to control mice, mice that were HIF1 α deficient in their lungs exhibited airway infiltration of eosinophils associated with airway epithelial changes, including mucus cell metaplasia and increased levels of the chitinase-like proteins YM1 and YM2. These results suggested that airway epithelial-derived HIF1 α plays a critical role in modulating the inflammatory response of the lung. Moreover, its disruption leads to a tissue that is biased towards a Th2-like response and exhibits an asthma-like phenotype following cobalt challenge. Taken together, the striking differences observed following cobalt exposure in the two mice suggests that they will be a powerful tool to understand the relationship between allergy-induced asthma, hypoxia, and inflammation.