

The Role of Thioredoxin in Human Mesothelial Cell Death induced by Crocidolite Asbestos

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Asbestos has been shown to cause various lung diseases like asbestosis, lung cancer and malignant mesothelioma. Previous research from our laboratory has shown that exposure to crocidolite asbestos fibers lead to the generation of a large amount of reactive oxygen species (ROS) and depletion of glutathione (GSH) levels transiently over a 24h period. Thioredoxin is a ubiquitous antioxidant protein that maintains the redox state of the cellular milieu, but the effects of asbestos exposure on the transcription and redox state of thioredoxin have not been investigated. We show that Trx1 mRNA levels are increased in human mesothelial cells (LP9) by asbestos. When oxidized, thioredoxin 1 (Trx 1) is unable to interact with apoptosis signal- regulated kinase 1 (ASK 1) leading to the activation of the programmed cell death pathway. Asbestos exposure at high concentrations *in vitro* leads to ~50% cytotoxicity. Because of the amount of ROS generated by asbestos within the cells there is a need to ascertain whether the cell death observed directly correlates to the extent of oxidation of thioredoxin. Our recent studies have shown that asbestos exposure of LP9 cells leads to extensive oxidation of thioredoxin at concentrations of asbestos fibers that cause 50% cell death. We used redox Western blots to determine the proportion of oxidized versus reduced thioredoxin present in cells exposed to asbestos. Sodium arsenite was used as a positive control for thioredoxin oxidation. To further confirm that the redox state of thioredoxin is indeed directly related to the cell death observed, thioredoxin reductase inhibitors (auranofin and 1-chloro-2, 4-dinitrobenzene (DNCB)) and small interfering RNA (siRNA) approach will be employed. We expect to see a direct correlation between asbestos - induced thioredoxin oxidation and cell death which will reveal a novel mechanism by which asbestos harnesses the cell's own programmed cell death pathways.