

## Role Of HMGB1 Signaling In Silica-Induced Lung Inflammation And Fibrosis

L. B. Joseph<sup>1</sup>, J. A. Cervelli<sup>1</sup>, N. M. Bremer<sup>1</sup>, Y. Kim<sup>1</sup>, D. A. Elzind<sup>1</sup>, V. Castranova<sup>2</sup>, A. J. Gow<sup>1</sup>, J. D. Laskin<sup>3</sup>, D. L. Laskin<sup>1</sup>

<sup>1</sup>Rutgers University, Piscataway, United States of America, <sup>2</sup>NIOSH, Morgantown, United States of America, <sup>3</sup>University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, Piscataway, NJ, United States of America

**Corresponding author's email: lbjoseph@rci.rutgers.edu**

Chronic exposure to quartz (crystalline silica) leads to the development of small airway disease and fibrosis, a process thought to be mediated, at least in part, by silica-induced oxidative stress at cell surfaces in the lung. Oxidative stress activates the  $\beta$ -catenin signaling pathway which is important in mediating cellular proliferation, a key step in fibrogenesis. When activated,  $\beta$ -catenin translocates into the nucleus where it binds to high mobility group box-1 (HMGB1), a chromosomal protein regulating expression of genes controlling cellular proliferation. HMGB1 is also passively released from necrotic cells; subsequent binding to the receptor for advanced glycation end products (RAGE) on macrophages stimulates inflammatory mediator production. In the present studies, we analyzed the potential role of HMGB1 in silica-induced inflammation and fibrosis. C57BL/6J mice were treated with silica (1 mg/kg Min-U-Sil 5) by intratracheally instillation. After 7 days, we found increased expression of cyclooxygenase-2 and inducible nitric oxide synthase in the lung, enzymes mediating the production of proinflammatory/cytotoxic prostaglandins and reactive nitrogen species. This was associated with increased expression of HMGB1 in macrophages and the appearance of soluble RAGE in bronchoalveolar lavage. We also found that Wnt1 and nuclear  $\beta$ -catenin protein expression were upregulated in the lung of silica-treated animals, while glycogen synthase kinase- $\beta$ 3 (GSK- $\beta$ 3), which functions to negatively regulate  $\beta$ -catenin signaling, was down regulated. This was correlated with increased proliferating cell nuclear antigen staining, the development of fibrotic lesions, and functional alterations in the lung. These data suggest that HMGB1 and downstream signaling pathways may be important in both silica-induced inflammation and fibrosis. Supported by NIH CA132624, ES004738, ES005022, AR055073, GM034310 and HL074115

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