Organic Dust Induces Inflammatory Gene Expression in Lung Epithelial Cells Via ROS-Dependent STAT-3 Activation

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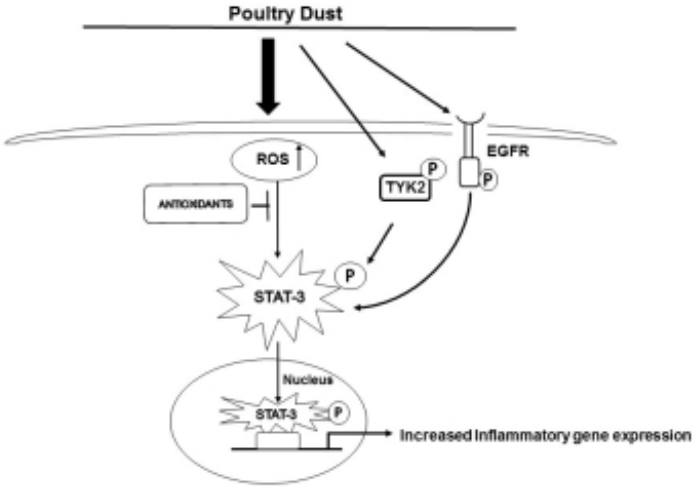
RATIONALE: Exposure to dust in agricultural and animal environments, known as organic dust, is associated with the development of respiratory symptoms and respiratory diseases. Inflammation is a key feature of lung pathologies associated with organic dust exposure, and exposure to organic dust induces the levels of several immune and inflammatory mediators. However, information on transcription factors and cellular and molecular mechanisms controlling the production of immune and inflammatory mediators by organic dust is limited. METHODS: Dust from a poultry farm served as a model organic dust, and the effects of aqueous extracts of poultry dust on the involvement of signal transducer and activator of transcription 3 (STAT-3) in the control of interleukin (IL)-6, IL-8, IL-1β, TNF-α, ICAM-1, PTGS2/COX-2 expression were studied in Beas2B and normal human bronchial epithelial cells in vitro and in mouse lungs in vivo. STAT-3 activation was inhibited using stattic chemical inhibitor or by siRNA knockdown, and effects on target gene expression was determined by western blotting, ELISA, and real-time qRT-PCR. The effects of antioxidants such as n-acetylcysteine (NAC), dimethylthiourea (DMTU) and 1-(2-Cyano-3, 12, 28-trioxooleana-1, 9(11)-dien-28yl)-1H-imidazole (CDDOIm) on Tyr705 phosphorylation was examined by western blotting to understand the involvement of oxidative stress in STAT-3 activation by dust extracts. Tyrosine kinases mediating STAT-3 activation such as TYK2 and EGFR were identified by chemical inhibition or siRNA knockdown. The effects of stattic on IL-8 promoter activity were determined by transient transfection analysis and luciferase assay. RESULTS: We found that dust extracts activated STAT-3 in Beas2B and normal human bronchial epithelial cells and in mouse lungs. Chemical inhibition and siRNA knockdown of STAT-3 suppressed induction of immune and inflammatory mediator levels. Activation of STAT-3 was suppressed by antioxidants indicating that oxidative stress is important for the activation. Chemical inhibition and siRNA knockdown experiments demonstrated that STAT-3 activation is dependent on the activation of Tyk2 and EGFR tyrosine kinases. CONCLUSION: Our studies show that poultry dust extracts control the induction of immune and inflammatory mediator levels via a cellular pathway involving oxidative stress mediated STAT-3 activation by Tyk2 and EGFR tyrosine kinases. (Research supported by CDC/NIOSH Grant U54 OH007541)



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