

**ACTIVATION OF EPITHELIAL SIGNAL TRANSDUCTION PATHWAYS
CYTOKINE PRODUCTION AND AIRWAY INFLAMMATION
FOLLOWING DIESEL EXHAUST EXPOSURE**

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Title

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Abstract

Adverse health effects of ambient air pollution are well recognised and include increased morbidity and mortality in respiratory and cardiovascular diseases. Diesel engines are major contributors to ambient particulate matter pollution and diesel particles have been shown to have strong toxicological and oxidative properties.

Mechanistic aspects of diesel engine exhaust exposure have been investigated in bronchial mucosal biopsies sampled during bronchoscopy of human subjects exposed in a validated experimental exposure set-up. Two exposure series were performed. Two separate groups of 15 healthy subjects each were exposed to filtered air and diesel exhaust during 1 hour in random order. The first exposure series was performed with the engine at idling with a PM₁₀ concentration of 300 µg/m³ and the second was carried out during urban cycle (European Transient Cycle) running conditions with 270 µg particles/m³. Bronchoscopies with sampling of bronchial mucosal biopsies were performed 6 hours after exposure. Diesel exhaust enhanced the expression of the cytokines IL-8 and GRO-α in the bronchial epithelium suggesting that the epithelium plays a major role in mediating the neutrophil-dominated airway mucosal inflammation. The bronchial expression of Th₁ and Th₂ cytokines was evaluated, addressing the hypothesis that diesel exhaust would induce a Th₂ airway response. Diesel exhaust enhanced the expression of Th₂ related cytokine IL-13 whereas the expression of Th₁ cytokines was unaffected. The investigation of epithelial signal transduction pathways, by means of newly developed and validated cytoplasmic and nuclear stainings for key transcription factors and kinases, demonstrated that exposure to diesel exhaust increased the nuclear translocation of redox sensitive signal transduction components including phosphorylated (p)-p38-MAPK, p-JNK, p-c-jun (AP-1) and p65 (NFκB). These findings indicate novel mechanistic aspects to be involved in the airway response to particulate air pollution. The expression of epidermal growth factor receptor (EGFR) as well as phosphorylated C-terminal Tyr 1173 increased significantly following DE exposure. The findings are consistent with the upregulation of p38 and JNK MAPkinases as well as increased NFκB expression. The MEK-ERK pathway was not affected and Src related phosphorylation was absent.

Diesel exposure at urban European transient cycle running conditions resulted in upregulation of the vascular adhesion molecule expression in the bronchial mucosa as signs of an early inflammatory response, while infiltration of inflammatory cells had not yet occurred. Differences in organic composition and particle concentration in the exhaust compared to idling situation may have influenced the outcome.

This thesis has added a mechanistic basis for the diesel exhaust induced airway inflammation in-vivo in humans. It is concluded that activation of epithelial signal transduction pathways, cytokine production and increased endothelial adhesion molecule expression play important roles in the airway inflammatory response to diesel exhaust.

Key words: Particulate matter, diesel exhaust, airway inflammation, transcription factor, mitogen-activated protein kinase (MAPK), epidermal growth factor receptor (EGFR)

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