Cadmium induces MUC8 expression in human airway epithelial cells

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INTRODUCTION

Background: Inhalation of cadmium can lead to development of inflammatory airway diseases such as acute pulmonary edema and chronic obstructive pulmonary disease. In inflammatory airway diseases, expression of mucins is increased, which leads to increased morbidity and mortality of the affected patients. However, no study on the effect of cadmium on expression of mucin genes in airway epithelial cells has been reported. Therefore, this study was conducted in order to investigate the effect and the brief signaling pathway of cadmium on expression of mucin genes in human airway epithelial cells.

Methods: In mucin-producing human NCI-H292 airway epithelial cells and primary cultures of normal nasal epithelial cells, the effect and signaling pathway of cadmium on expression of mucin genes were investigated using reverse transcription-polymerase chain reaction (RT-PCR), real-time PCR, enzyme immunoassay, and immunoblot analysis with several specific inhibitors and small interfering RNA (siRNA).

Results: Cadmium increased MUC8 expression in Toll-like receptor (TLR) 4 mRNA expression. Cadmium significantly activated phosphorylation of extracellular signal related kinase 1/2 (ERK1/2) mitogen-activated protein kinase (MAPK) and p38 MAPK. ERK1/2 MAPK inhibitor, p38 MAPK inhibitor, TLR4 siRNA, ERK1/2 MAPK siRNA, and p38 MAPK siRNA significantly blocked cadmium-induced MUC8 mRNA expression. TLR4 siRNA significantly blocked cadmium-activated phosphorylation of ERK1/2 MAPK and p38 MAPK (Fig. 3). In primary normal nasal epithelial cells, similar results are obtained (Fig. 4).

DISCUSSION

Cadmium-induced inflammatory reaction have reported that cadmium increases release of matrix metalloproteinase 9, interleukin (IL)-1β, IL-6, IL-8, macrophage inflammatory protein-2, and tumor necrosis factor-α in the respiratory tract of animal. These inflammatory mediators induce production of mucus in chronic inflammatory airway diseases such as COPD. Mucins, which are highly glycosylated proteins, are the major components of mucus. MUC4, MUC5AC, MUC5B, and MUC16 are the predominant mucins in chronic inflammatory airway diseases. In particular, MUC8 is upregulated in inflammatory conditions of nasosinus mucosa, such as chronic sinusitis and nasal polyps. Pro-inflammatory cytokine such as IL-1β lead to overexpression of MUC8 in human airway epithelial cells. However, the exact physiological function of MUC8 in respiratory disease remain poorly defined. Recent studies in airway epithelial cells have reported on TLR-mediated MUC5B and MUC8 expression: dephosphin attenuates LPS-induced MUC8 and MUC5B expression through TLR4-mediated signaling pathway and Staphylococcus aureus enterotoxin induces MUC5B expression in airway epithelial cells through TLR2-mediated signaling pathway in human airway epithelial cells. These findings suggest that activation of TLR is implicated in initiating or facilitating inflammation associated with expression of mucin in inflammatory airway diseases. Therefore, it could be hypothesized that cadmium might play a role in expression of mucin genes via TLR in human airway epithelial cells.

The results of this study suggest for the first time that cadmium induces MUC8 expression via TLR4-mediated ERK1/2 and p38 MAPK signaling pathway in human airway epithelial cells. These results provide important information indicating that cadmium may play a role in regulation of mucus-secrection through TLR-mediated MAPK signaling pathways in human airway epithelial cells.

CONCLUSIONS

The results of this study suggest for the first time that cadmium induces MUC8 expression via TLR4-mediated ERK1/2 and p38 MAPK signaling pathway in human airway epithelial cells. These results provide important information indicating that cadmium may play a role in regulation of mucus-secrection through TLR-mediated MAPK signaling pathways in human airway epithelial cells.