Cadmium, cobalt and lead cause stress response, cell cycle deregulation and increased steroid as well as xenobiotic metabolism in primary normal human bronchial epithelial cells which is coordinated by at least nine transcription factors.

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Abstract

Workers occupationally exposed to cadmium, cobalt and lead have been reported to have increased levels of DNA damage. To analyze whether in vivo relevant concentrations of heavy metals cause systematic alterations in RNA expression patterns, we performed a gene array study using primary normal human bronchial epithelial cells. Cells were incubated with 15 microg/l Cd(II), 25 microg/l Co(II) and 550 microg/l Pb(II) either with individual substances or in combination. Differentially expressed genes were filtered out and used to identify enriched GO categories as well as KEGG pathways and to identify transcription factors whose binding sites are enriched in a

given set of promoters. Interestingly, combined exposure to Cd(II), Co(II) and Pb(II) caused a coordinated response of at least seven stress response-related transcription factors, namely Oct-1, HIC1, TGIF, CREB, ATF4, SRF and YY1. A stress response was further corroborated by up regulation of genes involved in glutathione metabolism. A second major response to heavy metal exposure was deregulation of the cell cycle as evidenced by down regulation of the transcription factors ELK-1 and the Ets transcription factor GABP, as well as deregulation of genes involved in purine and pyrimidine metabolism. A third and surprising response was up regulation of genes involved in steroid metabolism, whereby promoter analysis identified up regulation of SRY that is known to play a role in sex determination. A forth response was up regulation of xenobiotic metabolising enzymes, particularly of dihydrodiol dehydrogenases 1 and 2 (AKR1C1, AKR1C2). Incubations with individual heavy metals showed that the response of AKR1C1 and AKR1C2 was predominantly caused by lead. In conclusion, we have shown that in vivo relevant concentrations of Cd(II), Co(II) and Pb(II) cause a complex and coordinated response in normal human bronchial epithelial cells. This study gives an overview of the most responsive genes.

Beteiligte Forschungseinheiten

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