Abstract

Polycyclic aromatic hydrocarbons (PAH) represent a large group of organic compounds occuring as pollutants in ambient air. Besides their genotoxic effect, some of them are known to be complete carcinogens and act via nongenotoxic and tumor promoting mechanism. Although effects of many individual compounds are well-documented, human exposure to polycyclic aromatic hydrocarbons in ambient air occurs through complex mixtures and only few studies describe the behavior of PAH in real complex mixtures.

The first part of the thesis is dealing with the global gene expression changes in human embryonic lung fibroblasts (HEL) as a consequence of the effect of complex mixtures containing PAH extracted from the respirable airborne particles $PM_{2.5}$. These particles were collected in 4 localities in the Czech republic (Ostrava – Bartovice, Ostrava – Poruba, Karviná, Třeboň) differing in the level of the air pollution. Gene expression changes induced by three subtoxic concentrations of organic extracts (EOM – extractable organic matter) from each locality after 24 hour incubation were examined by microarray analysis. Pathway analysis using the Kyoto Encyclopedia of Genes and Genomes (KEGG) database was applied to interpret gene expression data. In each locality we identified several deregulated signaling pathways and most contributing genes. Most of deregulated pathways were dependent on activation of the arylhydrocarbon receptor (AhR). Among others, strongest deregulation by EOMs from all 4 localities exhibited AhR-dependent Metabolism of xenobiotics by cytochromes P450 and CYP1B1 as a gene with the most pronounced contribution to the pathway deregulation. The transcriptomic data did not differ substantially among the localities, suggesting that the air pollution originating mainly from various sources may have similar biological effect.

The second part of the thesis is focused on the effect of PAU on the specific cancer disease – prostate cancer. We used prostatic androgen-sensitive cancer cells (LNCaP) to investigate the mechanism of their survival with damaged DNA and further events leading to tumor promotion and progression. After the treatment of cells by strong mutagenes, benzo[a]pyrene (B[a]P) and dibenzo[a,l]pyrene (DB[a,l]P), induction of cytochromes P450 was observed indicating the metabolic activation of PAH. Despite a significant amount of DNA adducts, neither apoptosis, cell-cycle arrest, double-strand breaks nor DNA repair were induced. The accumulation of DNA damage and the inability to activate DNA damage response may lead to the development of the aggressive cancer phenotype. To explore global changes in gene expression in LNCaP cells, microarray analysis was applied. We compared gene expression profiles of cells treated with B[a]P and nongenotoxic AhR activator 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Results of the comparison showed significant overlap of deregulated genes. Over the 64% of significantly up-regulated and 47% of significantly down-regulated genes were similarly affected by both B[a]P and TCDD. Pathway analysis indicated suppresed expression of genes associated with the regulation and progression of the cell cycle suggesting a key role of activated AhR in nongenotoxic effect of B[a]P in the LNCaP cell line.

This thesis demonstrates that various applications of transcriptomics in the toxicology may be useful for numerous mechanistic studies. Microarray analysis to helps understand effects of complex mixtures containing many PAH as well as the detailed mechanism of action of individual compounds, for example in specific cancer disease and explain a prominent role of AhR activation by PAH.