Polycyclic Aromatic Hydrocarbones (PAHs), and Their Effects on Genes

Inhibition of the WNT/β-catenin pathway by fine particulate matter in haze: Roles of metals and polycyclic aromatic hydrocarbons

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Abstract

Air pollution might have a great impact on pulmonary health, but biological evidence in response to particulate matter less than 2.5 μm in size (PM2.5) has been lacking. Physicochemical characterization of haze PM2.5 collected from Beijing, Xian and Hong Kong was performed. Biological pathways were identified by proteomic profiling in mouse lungs, suggesting that WNT/β-catenin is important in the response to haze PM2.5. Suppression of β-catenin levels, activation of caspase-3 and alveolar destruction, as well as IL-6, TNF-α and IFN-γ production, were observed in the lungs. The inhibition of β-catenin, TCF4 and cyclin D1 was observed in vitro in response to haze PM2.5. The inhibition of WNT/β-catenin signaling, apoptosis-related results (caspase-3 and alveolar destruction), and inflammation, particularly including caspase-3 and alveolar destruction, were more highly associated with polycyclic aromatic hydrocarbons in haze PM2.5. In conclusion, decreased WNT/β-catenin expression modulated by haze PM2.5 could be involved in alveolar destruction and inflammation during haze episodes.

Activation of aryl hydrocarbon receptor promotes invasion of clear cell renal cell carcinoma and is associated with poor prognosis and cigarette smoke
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Although exposure to environmental pollutants is one of the risk factors for renal cell carcinoma (RCC), its relationship with carcinogenesis and the progression of RCC remains unknown.
The present study was designed to elucidate the role of the aryl hydrocarbon receptor (AhR), a major mediator of carcinogenesis caused by environmental pollutants, in the progression of RCC.
The expression of AhR was investigated in 120 patients
with RCC using immunohistochemistry, and its relationship with clinicopathological parameters and pr ognoses was statistically analyzed. RCC cell lines were exposed to indirubin or 2,3,7,8-tetrachlorodibenzopdioxin (TCDD), AhR ligands, to activate the AhR pathway, or were transfected with small interfering RNA (siRNA) for AhR. The expression of the AhR target genes CYP1A1 and C YP1B1, matrix metalloproteinases (MMPs),
and invasion through MatrigelTM were then examined. AhR was predominantly expressed in the nucle i of highgrade clear cell RCC (ccRCC) and tumor-
infiltrating lymphocytes (TILs), and its expression levels in cancer cells and TILs correlated with the pathological tumor stage and histological
grade. A multivariate Cox analysis revealed that the strong expression of AhR in cancer cells was a sig nificant and independent predictor of disease specific survival. AhR ligands up-regulated the expression of AhR and CYPs and promoted invasion by up-regulating MMPs. Furthermore, siRNA for AhR down-regulated CYPs, and inhibited cancer cell invasion together with the down-regulation of MMPs. These results suggest that
AhR regulates the invasion of ccRCC and may be involved in tumor immunity. Therefore, inhibiting th e activation of AhR may represent a potentially attractive therapeutic target for ccRCC patients.

Shorter telomere length in peripheral blood lymphocytes of workers exposed to polycyclic aromatic hydrocarbons Carcinogenesis vol.31 no.2 pp.216–221, 2010

Shorter telomere length (TL) in peripheral blood lymphocytes (PBLs) is predictive of lung cancer risk. Polycyclic aromatic hydrocarbons (PAHs) are established lung carcinogens that cause chromosome instability. Whether PAH exposure and its molecular effects are linked with shorter TL has never been evaluated. In the present study, we investigated the effect of chronic exposure to PAHs on TL measured in PBLs of Polish male non-current smoking coke-oven workers and matched controls. PAH exposure and molecular effects were characterized using measures of internal dose (urinary 1-pyrenol), effective dose [anti-benzo[a]pyrene diolepoxide (anti-BPDE)–DNA adduct], genetic instability (micro- nuclei, MN) and DNA methylation [p53 promoter and Alu and long interspersed nuclear element-1 (LINE-1) repetitive elements, as surrogate measures of global methylation] in PBLs. TL was measured by real-time polymerase chain reaction. Cokeoven workers were heavily exposed to PAHs (79% exceeded the uri- nary 1-pyrenol biological exposure index) and exhibited lower TL (P 5 0.038) than controls, as well as higher levels of genetic and chromosomal alterations [i.e. anti-BPDE–DNA adduct and MN (P < 0.0001)] and epigenetic changes [i.e. p53 gene-specific promoter and global methylation (P £ 0.001)]. TL decreased with longer duration of work as coke-oven worker (P 5 0.039) and in all subjects with higher levels of anti-BPDE–DNA adduct (P 5 0.042), p53 hypomethylation (P 5 0.005) and MN (P 5 0.009). In multivariate analysis, years of work in cokery (P 5 0.008) and p53 hypomethylation (P 5 0.001) were the principal determinants of shorter TL. Our results indicate that shorter TL is associated with chronic PAH exposure. The interrelations with other genetic and epigenetic mechanisms in our data suggest that shorter TL could be a central event in PAH carcinogenesis.

Polymorphism in the DNA Repair Gene XPD, Polycyclic Aromatic Hydrocarbon-DNA Adducts, Cigarette Smoking, and Breast Cancer Risk

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DNA repair is essential to an individual's ability to respond to damage caused by environmental carcinogens. Alterations in DNA repair genes may affect cancer risk by influencing individual susceptibility to environmental exposures. XPD, a gene involved in nucleotide excision repair, may influence individual DNA repair capacity particularly of bulky adducts. Using a population-based breast cancer case-control study that was specifically conducted to examine markers of environmental exposures, such as polycyclic aromatic hydrocarbons (PAH), on Long Island, NY, we examined whether XPD genotype modified the associations among PAH-DNA adducts, cigarette smoking, and breast cancer risk. Specifically, we examined the XPD polymorphism at exon 23, position 751 in 1,053 breast cancer cases and 1,102 population-based controls. The presence of at least one variant allele (Lys/Gln or Gln/Gln) was associated with a 20% increase in risk of breast cancer [odds ratio (OR), 1.21; 95% confidence in- terval (95% CI), 1.01-1.44]. The increase in risk for homozygosity of the variant allele (Gln/Gln) seemed limited to those with PAH-DNA adduct levels above the median (OR, 1.61; 95% CI, 0.99-2.63 for adducts above the median versus OR, 1.05; 95% CI, 0.64-1.74 for adducts below the median), although the multiplicative interaction was not statistically significant. The increase in risk for homozygosity of the variant allele (Gln/Gln) was **only** seen among current smokers (OR, 1.97; 95% CI, 1.02-3.81 for current smokers versus OR, 0.87; 95% CI, 0.57-1.32 for never smokers); the multiplicative interaction was statistically significant. Overall, this study suggests that those individuals with this polymorphism in the XPD gene may face an increased risk of breast cancer from PAH-DNA adducts and cigarette smoking.

Aromatic hydrocarbon receptor-driven Bax gene expression is required for premature ovarian failure caused by biohazardous environmental chemicals Nature Genetics 28, 355 360 (2001)

Polycyclic aromatic hydrocarbons (PAHs) are toxic chemicals released into the environment by fossil fuel combustion. Moreover, a primary route of human exposure to PAHs is tobacco smoke. Oocyte destruction and ovarian failure occur in PAH-treated mice, and cigarette smoking causes early menopause in women. In many cells, PAHs activate the aromatic hydrocarbon receptor (Ahr), a member of the PerArnt-Sim family of transcription factors. The Ahr is also activated by dioxin, one of the most intensively studied environmental contaminants. Here we show that an exposure of mice to PAHs induces the expression of Bax in oocytes, followed by apoptosis. Ovarian damage caused by PAHs is prevented by Ahr or Bax inactivation. Oocytes microinjected with a Bax promoter–reporter construct show Ahr-dependent transcriptional activation after PAH, but not dioxin, treatment, consistent with findings that dioxin is not cytotoxic to oocytes. This difference in the action of PAHs versus dioxin is conveyed by a single base pair flanking each Ahr response element in the Bax promoter. Oocytes in human ovarian biopsies grafted into immunodeficient mice also accumulate Bax and undergo apoptosis after PAH exposure in vivo. Thus, Ahr-driven Bax transcription is a novel and evolutionarily conserved cell-death signaling pathway responsible for environmental toxicant induced ovarian failure.

Targeting of Lung Cancer Mutational Hotspots by Polycyclic Aromatic Hydrocarbons

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Background: Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous in combustion products of organic matter, including cigarette smoke. Metabolically activated diol epoxides of these compounds, including benzo[a]pyrene diol epoxide (B[a]PDE), have been suggested as causative agents in the development of lung cancer. We previously mapped the distribution of B[a]PDE adducts within the p53 tumor suppressor gene (also known as TP53), which is mutated in 60% of human lung cancers, and found that B[a]PDE adducts preferentially form at lung cancer mutational hotspots (codons 154, 157, 158, 245, 248, and 273). Other PAHs may be important in lung cancer as well. Methods: Here we have mapped the distribution of adducts induced by diol epoxides of additional PAHs: chrysene (CDE), 5-methylchrysene (5-MCDE), 6-methylchrysene (6-MCDE), benzo[c]phenanthrene (B[c]PDE), and benzo[g]chrysene (B[g]CDE) within exons 5, 7, and 8 of the p53 gene in human bronchial epithelial cells. Results: CDE exposure produced only low levels of adducts. Exposure of cells to the other activated PAHs resulted in DNA damage patterns similar to those previously observed with B[a]PDE but with some distinct differences. 5-MCDE, 6-MCDE, B[g]CDE, and B[c]PDE efficiently induced adducts at guanines within codons 154, 156, 157, 158, and 159 of exon 5, codons 237, 245 and 248 of exon 7, and codon 273 of exon 8, but the relative levels of adducts at each site varied for each compound. B[g]CDE, B[c]PDE, and 5-MCDE induced damage at codon 158 more selectively than 6-MCDE or B[a]PDE. The sites most strongly involved in PAH adduct formation were also the sites of highest mutation frequency (codons 157, 158, 245, 248, and 273). Conclusion: The data suggest that PAHs contribute to the mutational spectrum in human lung cancer.

A possible mechanism for atherosclerosis induced by polycyclic aromatic hydrocarbons

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Polycyclic aromatic hydrocarbons (PAHs), aryl hydrocarbon receptor (AHR) ligands, induce atherogenesis. Liver X receptor (LXR) a is known to be involved in the control of cholesterol homeostasis. Thus, the purpose of this study was to investigate the effects of 3-methlycholanthrene (MC), one of the PAHs, on LXRa-mediated signal transductions. We found that expression of mRNAs for ATP binding cassette A1, sterol regulatory element binding protein 1c (SREBP-1c), fatty acid synthase, and stearoyl-CoA desaturase was suppressed by treatment of HepG2 cells with MC. A luciferase reporter assay revealed that LXRa- and SREBP-1c-mediated transactivations were inhibited by MC via AHR. Based on these lines of evidence, we propose that down-regulation of the LXRa-regulated genes by PAHs is one of the causes responsible for atherosclerosis induced by PAHs.

Epigenetics of breast cancer: Polycyclic aromatic hydrocarbons as risk factors

Environmental and Molecular Mutagenesis, 2002

In the absence of a causal relationship between the incidence of sporadic breast cancer and occurrence of mutations in breast cancer susceptibility genes, efforts directed to investigating the contribution of environmental xenobiotics in the etiology of sporadic mammary neoplasia are warranted. Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous pollutants, which have been shown to induce DNA damage and disrupt cell cycle progression. In this report we discuss published data pointing to PAHs as a risk factor in carcinogenesis, and present findings generated in our laboratory suggesting that the mammary tumorigenicity of PAHs may be attributable, at least in part, to disruption of BRCA-1 expression by reactive PAH-metabolites. We report that benzo[a]pyrene (B[a]P), selected as a prototype PAH, disrupts BRCA-1 transcription in estrogen receptor (ER)-positive but not ER-negative breast cancer cells. The reduced potential for BRCA-1 expression in B[a]P-treated cells coincides with disruption of cell cycle kinetics and accumulation of p53. These effects are counteracted by the AhR-antagonist α-naphthoflavone (ANF), and in breast cancer cells expressing mutant p53 or the E6 human papilloma virus protein. We suggest that exposure to PAHs may be a predisposing factor in the etiology of sporadic breast cancer by disrupting the expression of BRCA-1.

Thanks For Your Attention