Virus and Polycyclic Aromatic Hydrocarbon-induced Carcinogenesis

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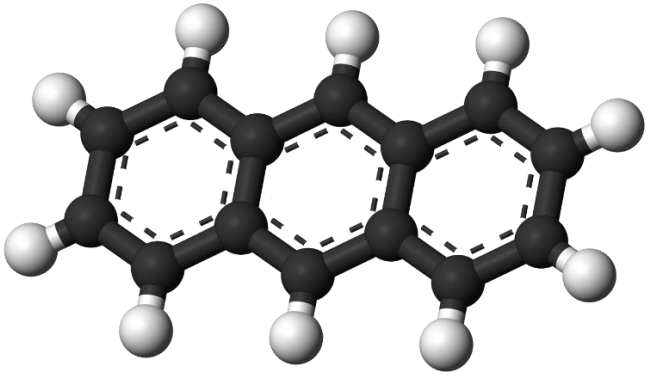
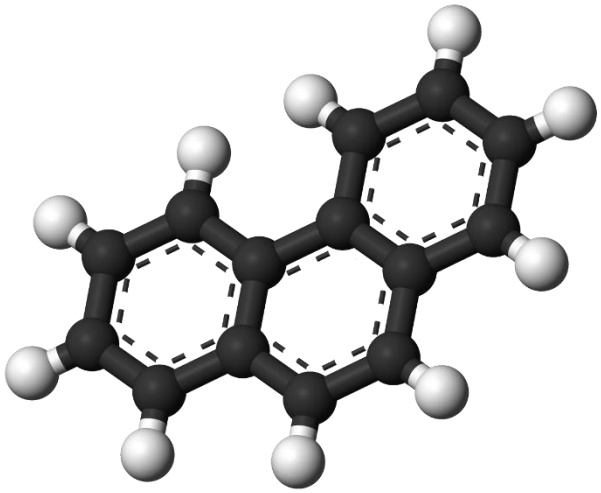
Polycyclic Aromatic Hydrocarbons (PAHs)

- PAHs are a class of organic compounds containing 3 or more fused benzene rings.
  - Consist of carbon and hydrogen only.



Anthracene



Phenanthrene

  - Behave as lipophilic and chemically inert compounds.

Exposure levels

- PAH exposure occurs on a regular basis for most people.
  - Air: 5 - 200,000 ng/m^3
    - Cigarette smoking: 20 – 40 ng/cigarette
  - Water: ~ 0.002 ppb in drinking water
  - Soil: < 2,000 µg/kg near cities
  - Foodstuffs: 2 – 20 µg/kg in grilled food

Biological fate

Absorption	Distribution	Metabolism	Excretion
• Ingestion • Inhalation • Dermal contact	• Enter the lymph • Circulate in the blood • Metabolized in the liver and kidney • Accumulate in breast milk and adipose tissue	• Via CYP enzymes • Primarily in the liver and kidney • Also in the adrenal glands, testes, thyroid, lungs, skin, sebaceous glands, and small intestines	• Feces • Urine

Pathogenic changes

- Toxicity: Carcinogenic, mutagenic, and teratogenic
  - Benzo[a]pyrene (B[a]P), the first chemically identified carcinogen, is the most extensively studied PAH.
- Genetic Susceptibility:
  - High level of CYP1A1 inducibility
  - Glutathione transferase deficiencies
- Oncogene activation: the *ras* oncogene

Carcinogenicity studies on PAHs

Epidemiologic Evidence

- Increased incidences of skin, lung, bladder, and gastrointestinal cancers in PAH-exposed workers.
  - The earliest human PAH-related epidemiologic study was reported in 1936 by investigators in Japan and England who studied lung cancer mortality among workers in coal carbonization and gasification processes.
  - Subsequent U.S. studies among coke oven workers confirmed an excess of lung cancer mortality, with the suggestion of excessive genitourinary system cancer mortality.
  - Later experimental studies showed that PAHs in soot were probably responsible for the increased incidence of scrotal cancer noted by Percival Pott among London chimney sweeps in his 1775 treatise.
- Only provide qualitative evidence because of the presence of PAH mixtures.

Experimental Studies

- *In vivo* models
  - 2-year bioassay in rodents
  - 6-month transgenic mouse model
  - Neonatal mouse model
  - Enhanced 13-week bioassay
- *In vitro* models
  - Genotoxicity or cytogenetics assays
  - Cell transformation assays

In vivo models

- Standard approach: 2-year bioassay in rodents

Carcinogenesis. 1998 Jan;19(1):117-24.

A comparison of the tumors induced by coal tar and benzo[a]pyrene in a 2-year bioassay.

Culp SJ[1], Gaylor DW, Sheldon WG, Goldstein LS, Beland FA.

Author information

Abstract

The tumorigenicity of two coal tar mixtures was compared to that of benzo[a]pyrene after 2 years of feeding. Mixture 1, a composite of coal tar from seven coal gasification plant waste sites, was fed to female B6C3F1 mice (48 mice per group) for 2 years at doses of 0.0, 0.01, 0.03, 0.1, 0.3, 0.6 and 1.0%. Mixture 2, which was composed of coal tar from two of the seven waste sites and another site having a high benzo[a]pyrene content, was fed at doses of 0.0, 0.03, 0.1 and 0.3%. Additional groups of mice were fed 0, 5, 25 and 100 ppm benzo[a]pyrene. The coal tar diets induced a dose-related increase in hepatocellular adenomas and carcinomas, alveolar/bronchiolar adenomas and carcinomas, forestomach squamous epithelial papillomas and carcinomas, small intestine adenocarcinomas, histiocytic sarcomas, hemangiosarcomas in multiple organs and sarcomas. Benzo[a]pyrene treatment resulted in an increased incidence of papillomas and/or carcinomas of the forestomach, esophagus and tongue. A comparison of the results indicated that the benzo[a]pyrene in the coal tar diets could be responsible for the forestomach tumors. In contrast, the lung and liver tumors appeared to be due to other genotoxic components contained within the coal tar mixture, while the small intestine tumors resulted from chemically-induced cell proliferation that occurred at high doses of coal tar.

PMID: 9472702 [PubMed - indexed for MEDLINE] Free full text

Alternative assays

- 6-month transgenic mouse models:

  With an activated/overexpressed oncogene or an inactivated tumor suppressor gene → much more susceptible to carcinogens than a normal mouse → a more rapid induction of tumorigenesis.

  - Tg.AC model: Ha-*ras* proto-oncogene
  - rasH2 model: Ha-*ras* proto-oncogene
  - $p53^{+/-}$ model: *p53* tumor suppressor gene
  - $Xpa^{-/-}$ model: Xeroderma pigmentosum complementation group A gene

- Tg.AC model
  - The Tg.AC transgenic mouse has a v-Ha-ras gene with activating mutations fused to a zeta-globin promoter.
  - Dermal application of genotoxic or nongenotoxic carcinogens in Tg.AC mice results in the production of papillomas.
  - Many false positive results, few recommend its continued use.
- rasH2 model
  - The rasH2 mouse contains multiple copies of the human c-Ha-ras proto-oncogene as well as its native murine Ha-ras gene.
  - The rasH2 model has a very low incidence of spontaneous tumors, responds to both genotoxic and nongenotoxic carcinogens. In addition, it is considered neither insensitive nor prone to false positive results.
  - Most often used as a replacement for the 2-year bioassay.

- $p53^{+/-}$ model
  - The heterozygous $p53^{+/-}$ transgenic mouse contains a single functional p53 allele in each cell, has a low spontaneous tumor incidence, and responds primarily to genotoxic carcinogens.
  - Concerned may be relatively insensitive compared to other assays.
- $Xpa^{-/-}$ model
  - The $Xpa^{-/-}$ mouse has an almost complete deficiency in DNA nucleotide excision repair, and is susceptible to genotoxic carcinogens given dermally and orally.

- $Xpa^{-/-}/p53^{+/-}$ double knockout model
  - The $Xpa^{-/-}$ mouse is crossed with $p53^{+/-}$ mouse to generate the double knockout mice $Xpa^{-/-}/p53^{+/-}$.
  - A further enhance sensitivity towards genotoxic carcinogens due to the diminished cell cycle arrest and/or reduced apoptotic response.

Carcinogenesis. 2003 Mar;24(3):613-9.

Combined oral benzo[a]pyrene and inhalatory ozone exposure have no effect on lung tumor development in DNA repair-deficient Xpa mice.

Hoogervorst EM[1], de Vries A, Beems RB, van Oostrom CT, Wester PW, Vos JG, Bruins W, Roodbergen M, Cassee FR, Vijg J, van Schooten FJ, van Steeg H.

Author information

Abstract

There is considerable concern about an enhanced risk of lung tumor development upon exposure of humans to polycyclic aromatic hydrocarbons (PAHs), like benzo[a] pyrene (B[a]P), in combination with induced lung cell proliferation by toxic agents like ozone. We studied this issue in wild-type (WT) C57BL/6 mice, the cancer prone nucleotide excision repair-deficient Xeroderma pigmentosum complementation group A mice (Xpa-/-) and the even more sensitive Xpa-/-/p53+/- mice. The mice were treated with B[a]P through the diet at a dose of 75 p.p.m., in combination with intermittent ozone exposures (0.8 p.p.m.). First, a dose-range finding study with WT and Xpa-/- mice was conducted to determine the optimal ozone concentration giving high cell proliferation and low toxic side effects. We show by BrdU incorporation that cell proliferation in the lung was induced by ozone, with an optimal concentration of 0.8 p.p.m., which was subsequently used in the (sub)chronic studies. In the subchronic study, in which lacZ mutant frequency and BPDE-DNA adduct formation were measured, the mice were treated for 13 weeks with B[a]P and/or ozone, whereas in the chronic study this treatment protocol was followed by a 6 month period on control feed and filtered air. As expected, oral B[a]P exposure appeared to be highly carcinogenic to Xpa-/- and Xpa-/-/p53+/- mice and to a lesser extent to WT mice. A high incidence of forestomach tumors and some tumors of the esophagus were found. In the lung, a clear genotoxic effect of B[a]P was found as shown by the presence of BPDE-DNA adducts. However, these DNA adducts in combination with induction of cell proliferation did not result in increased lacZ mutations, nor in lung tumor formation not even in the highly sensitive Xpa-/- and Xpa-/-/p53+/- mice. The implication of these findings for tumor risk assessment will be discussed.

PMID: 12663525 [PubMed - indexed for MEDLINE] Free full text

Alternative assays

- Neonatal mouse model

Carcinogenesis. 2007 Oct;28(10):2236-43. Epub 2007 May 23.

Potent carcinogenicity of cigarette smoke in mice exposed early in life.

Balansky R[1], Ganchev G, Iltcheva M, Steele VE, D'Agostini F, De Flora S.

Author information

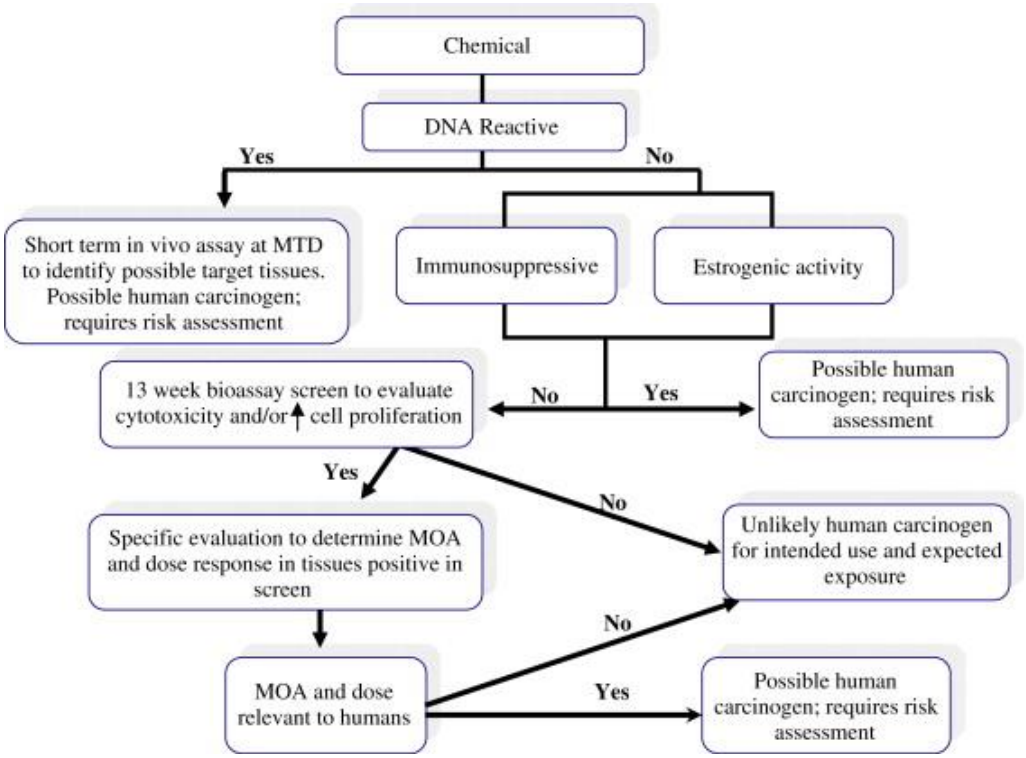
Abstract

In spite of the dominant role of cigarette smoke (CS) in cancer epidemiology, all studies performed during the past 60 years have shown that this complex mixture is either negative or weakly tumorigenic in experimental animals. We implemented studies aimed at evaluating whether exposure of mice early in life may enhance susceptibility to CS carcinogenicity. A total of 98 newborn Swiss albino mice were either untreated (controls) or received a subcutaneous injection of benzo(a)pyrene [B(a)P] (positive control) or were exposed whole-body to mainstream cigarette smoke (MCS) for 120 days, starting within 12 h after birth. Complete necropsy and histopathological analyses were performed at periodical intervals. In contrast with the lack of lung tumors in controls, MCS-exposed mice developed microscopically detectable tumors, starting only 75 days after birth and reaching an overall incidence of 78.3% after 181-230 days. The mean lung tumor multiplicities were 6.1 and 13.6 tumors per mouse in males and females, respectively, showing a significant intergender difference. Most tumors were microadenomas or adenomas, but 18.4% of the mice additionally had malignant lung cancer. MCS also induced bronchial and alveolar epithelial hyperplasia, and blood vessel proliferation. Furthermore, malignant tumors, some of which may have a metastatic origin, were detected in the urinary tract and liver of MCS-exposed mice. A somewhat different spectrum of tumors was observed in B(a)P-treated mice. In conclusion, MCS is a potent and broad spectrum carcinogen in mice when exposure starts early in life, covering stages of life corresponding to neonatal, childhood and adolescence periods in humans. This animal model will be useful to explore the mechanisms involved in CS-induced carcinogenesis and to investigate the protective effects of dietary agents and chemopreventive drugs.

PMID: 17522065 [PubMed - indexed for MEDLINE] Free full text

Alternative assays

- Enhanced 13-week bioassay



Routes of exposure

- Skin application
- Subcutaneous injection
- Oral administration
- Intraperitoneal injection
- Inhalation
- Intrapulmonary injection
- Intratracheal administration
- Buccal pouch application
- Subcutaneous tracheal grafts transplantation
- Intramammilary administration
- Intracolonic instillation
- Intravaginal application
- Intrafetal injection

Summary of reports of malignant tumors clearly induced in experimental animals by B[a]P

Organ site/ species	Lung	Trachea	Larynx	Forestomach	Liver	Lymphoid tissue (lymphoma)	Sarcoma (injection site)	Skin	Mammary gland
Mouse	x			x	x	x	x	x	
Rat	x						x		x
Hamster	x	x	x	x			x		

- Strong evidence
  - lung and skin cancers
- Possible associations
  - laryngeal, esophageal, gastrointestinal, pancreatic, cervical, colorectal, prostate and bladder cancers

<IARC Monographs – 100F>

In vitro models

- Traditional genotoxicity or cytogenetics assays
  - Significant irrelevant positive rate, follow-up animal testing is needed to confirm such effects.
  - Do not detect non-genotoxic carcinogens.
- Cell transformation assays (CTAs)
  - The only possible in vitro alternative to animal testing for carcinogenesis studies.
  - Can be used for both genotoxic and non-genotoxic compounds.
  - Common models
    - Syrian hamster embryo cells
    - C3H/10T1/2 Cl 8 mouse embryo cells
    - Balb/c 3T3 cells

- Cell transformation assays (CTAs)
  - Transgenic human cell lines
    - Human bronchial epithelial cells immortalized by SV40 large T antigen with an oncogenic allele of H-Ras (HBER) or c-Myc (HBEM)
    - Hepatocyte-like cells derived from the differentiation of human embryonic stem cells (hES-Hep)

Toxicol Appl Pharmacol. 2008 Nov 1;232(3):478-86. doi: 10.1016/j.taap.2008.08.009. Epub 2008 Aug 22.

Development of human cell models for assessing the carcinogenic potential of chemicals.

Pang Y[1], Li W, Ma R, Ji W, Wang Q, Li D, Xiao Y, Wei Q, Lai Y, Yang P, Chen L, Tang S, Lin Y, Zhuang Z, Zheng Y, Chen W.

⊕ Author information

Abstract

To develop human cell models for assessing the carcinogenic potential of chemicals, we established transgenic human cell lines and tested the sensitivity of known carcinogens using a cell transformation assay. A retroviral vector encoding an oncogenic allele of H-Ras (HBER) or c-Myc (HBEM) was introduced into human bronchial epithelial cells (HBE) immortalized by SV40 large T (LT) antigen, leading to increased cell proliferation but failing to confer a transformed phenotype characterized by
When these pre-transformed cells were treated with nickel sulf
by 19 wk in HBER cells or 16 wk in HBEM cells compared to
HBER cells or 9 wk in HBEM cells when cells were treated wit
TPA, NiSO4 or BPDE-induced cell transformation compared to
specificity is one of important factors determining the effectiver
compared the efficiency of three different metabolic conditions
prospective system used for metabolic activation of pro-carcino
transformation model can be applied to the assessment of pot

PMID: 18778725 [PubMed - indexed for MEDLINE]

Toxicol Sci. 2011 Dec;124(2):278-90. doi: 10.1093/toxsci/kfr225. Epub 2011 Aug 27.

Human embryonic stem cell derived hepatocyte-like cells as a tool for in vitro hazard assessment of chemical carcinogenicity.

Yildirimman R[1], Brolén G, Vilardell M, Eriksson G, Synnergren J, Gmuender H, Kamburov A, Ingelman-Sundberg M, Castell J, Lahoz A, Kleinjans J, van Delft J, Björquist P, Herwig R.

⊕ Author information

Abstract

Hepatocyte-like cells derived from the differentiation of human embryonic stem cells (hES-Hep) have potential to provide a human relevant in vitro test system in which to evaluate the carcinogenic hazard of chemicals. In this study, we have investigated this potential using a panel of 15 chemicals classified as noncarcinogens, genotoxic carcinogens, and nongenotoxic carcinogens and measured whole-genome transcriptome responses with gene expression microarrays. We applied an ANOVA model that identified 592 genes highly discriminative for the panel of chemicals. Supervised classification with these genes achieved a cross-validation accuracy of > 95%. Moreover, the expression of the response genes in hES-Hep was strongly correlated with that in human primary hepatocytes cultured in vitro. In order to infer mechanistic information on the consequences of chemical exposure in hES-Hep, we developed a computational method that measures the responses of biochemical pathways to the panel of treatments and showed that these responses were discriminative for the three toxicity classes and linked to carcinogenesis through p53, mitogen-activated protein kinases, and apoptosis pathway modules. It could further be shown that the discrimination of toxicity classes was improved when analyzing the microarray data at the pathway level. In summary, our results demonstrate, for the first time, the potential of human embryonic stem cell--derived hepatic cells as an in vitro model for hazard assessment of chemical carcinogenesis, although it should be noted that more compounds are needed to test the robustness of the assay.

PMID: 21873647 [PubMed - indexed for MEDLINE] PMCID: PMC3216410 Free PMC Article

Carcinogenic PAHs listed by IARC

- **Group 1 (carcinogenic)**
  - B[a]P
- **Group 2A (probably carcinogenic)**
  - Cyclopenta[cd]pyrene, dibenz[a,h]anthracene and dibenzo[a,l]pyrene
- **Group 2B (possibly carcinogenic)**
  - Benz[j]aceanthrylene, benz[a]anthracene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, benzo[c]phenanthrene, chrysene, dibenzo[a,h]pyrene, dibenzo[a,i]-pyrene, indeno[1,2,3-cd]pyrene and 5-methylchrysene

*__Group 1__: carcinogenic (sufficient evidence of carcinogenicity in humans, or less than sufficient evidence in humans and sufficient evidence in experimental animals)

__Group 2A__: probably carcinogenic (limited evidence in humans and sufficient evidence in experimental animals)

__Group 2B__: possibly carcinogenic (limited evidence in humans and less than sufficient evidence in experimental animals)

Carcinogenic mechanisms

- Diol epoxide mechanism
  - Mutations in proto-oncogenes (ras) and tumor-suppressor genes (p53)
- Radical cation mechanism
  - Apurinic sites and mutations in H-ras
- Ortho-quinone formation
  - Mutations in p53 tumor-suppressor gene
- Aryl hydrocarbon receptor mechanisms
- Immunological mechanisms

Interaction of Virus and PAHs in Carcinogenesis

Epstein-Barr Virus & PAHs

Toxicology. 1999 Mar 1;133(1):35-42.

Evaluation of the effect of smokeless tobacco purified products and extracts on latent Epstein-Barr virus.

Jenson HB[1], Heard P, Moyer MP.

⊕ Author information

Abstract

Numerous chemical tumor promoters induce latent Epstein Barr virus (EBV) to active replication. The effect of smokeless tobacco purified products N-nitrosonornicotine (NNN), 4-(N-methyl-N-nitrosamine)-1-3-pyridinyl)-1-butanone (NNK), benzo(a)pyrene (BaP), and smokeless tobacco extracts (dry snuff, moist snuff, and loose leaf tobacco) was tested for induction of latent EBV in Raji cells using fluorescence-activated cell sorter flow cytometry detection of the restricted component of EBV early antigen (EA-R). Concentrations of smokeless tobacco purified products or preparations were used that have carcinogenic effects in animal cell lines. There was no discernible effect for the 6-7-day duration of treatment on viability of Raji cells, or on induction of latent EBV in Raji cells. Results were comparable using paraformaldehyde- or acetone-fixed cells. There does not appear to be an in vitro effect of smokeless tobacco constituents on EBV-infected lymphocytes that may contribute to development of oral cancers.

PMID: 10413192 [PubMed - indexed for MEDLINE]

Hepatitis B Virus & PAHs

- Hepatitis B Virus may be the cause of up to 80% of all cases of hepatocellular carcinoma.
- Epidemiologic studies from Taiwan and mainland China revealed a significant positive correlation between PAH exposure and the risk of hepatocellular carcinoma.

Int J Cancer. 2002 May 1;99(1):14-21.

Polycyclic aromatic hydrocarbon-DNA adducts in liver tissues of hepatocellular carcinoma patients and controls.

Chen SY[1], Wang LY, Lunn RM, Tsai WY, Lee PH, Lee CS, Ahsan H, Zhang YJ, Chen CJ, Santella RM.

Author information

Abstract

HCC is a common cancer and HBV and A
smoking also contributes to the developme
present in both mainstream and sidestrea
electrophilic reactants (diol epoxides), whi
enzymes, including GSTM and GSTP. To
tissue by relative staining intensity with an
genotyped for polymorphism in several ger
patients with histologically confirmed HCC
0.01) between adducts in tumor and adjac
HBsAg in the group with the highest tertile
344) than in the group with the lowest terti
associations between adduct levels and ci
observed (OR = 20.3, 95% CI = 5.0-81.8)
intensity of tumor and nontumor tissue > 3
4-ABP- and AFB(1)-DNA adducts had bee
and AFB(1) had a significantly higher HCC
results suggest that PAHs may play a role
and exposure to 4-ABP and AFB(1).

PMID: 11948486 [PubMed - indexed for MEDLINE]

Cancer Lett. 2007 Jul 8;252(1):104-14. Epub 2007 Jan 23.

Polycyclic aromatic hydrocarbon- and aflatoxin-albumin adducts, hepatitis B virus infection and hepatocellular carcinoma in Taiwan.

Wu HC[1], Wang Q, Wang LW, Yang HI, Ahsan H, Tsai WY, Wang LY, Chen SY, Chen CJ, Santella RM.

Author information

Abstract

To determine the association between polycycl
nested within a community-based cohort was c
matched controls, were used to determine the
regression analysis was used to calculate odd
HCC. When compared to subjects in the lowes
2.4) and 2.0 (1.0-4.2: P(trend)=0.08) for subject
(0.6-6.1), 1.7 (0.6-4.9) and 2.1 (0.5-8.2; P(trend
3.5) and 2.9 (1.0-8.6; P(trend)=0.06), respectiv
AFB(1)-albumin adducts above the mean and c
low adducts and no viral infection. These result
among those with high aflatoxin exposure and
chronic HBV infection.

PMID: 17250958 [PubMed - indexed for MEDLINE] PMCI

J Expo Sci Environ Epidemiol. 2012 Nov;22(6):541-8. doi: 10.1038/jes.2011.29. Epub 2011 Sep 14.

Exposure to organochlorine pesticides is an independent risk factor of hepatocellular carcinoma: a case-control study.

Zhao B[1], Shen H, Liu F, Liu S, Niu J, Guo F, Sun X.

Author information

Abstract

Primary hepatocellular carcinoma (HCC) is highly prevalent in China. Although hepatitis B virus (HBV) and aflatoxin B1 (AFB1) are considered the major risk factors, among the high-risk cohorts only a small fraction develops liver cancer. Therefore, we investigated whether organochlorine pesticide exposure contributed to HCC risk in the Xiamen population. The questionnaire database was built from 346 HCC cases and 961 healthy controls during 2007-2009. The serum levels of α-, β-, γ-, δ-HCH, 1,1,1-trichloro-2,2-bis (p-chlorophenyl) ethane (p,p'-DDT), (1,1-dichloro-2,2-bis (p-chlorophenyl) ethylene (p,p'-DDE), 1,1,1-trichloro-2,2-bis (o-chlorophenyl) ethane and 1,1-dichloro-2,2-bis (p-chlorophenyl) ethane were measured by gas chromatography-tandem mass spectrometer, and statistical analysis was done using SPSS16. Significantly, we observed p,p'-DDT and p,p'-DDE, and at the first time β-HCH displayed quartile dose-dependent HCC risk trends; p,p'-DDT showed positive (i.e., synergistic) interactions with HBV, diabetes mellitus, AFB1 and polyaromatic hydrocarbon (PAH) exposure, but negative (i.e., antagonistic) interaction with heavy drinking; p,p'-DDE had positive interaction with PAH but negative interaction with HBV and p,p'-DDT; and β-HCH positively interacted with p,p'-DDT but negatively interacted with heavy drinking and diabetes. p,p'-DDT, p,p'-DDE and β-HCH were independent HCC risk factors. Because of their synergistic interactions with other factors, the high-level exposure combined with common AFB1 and HBV exposure in the investigated area may greatly enhance the risk of HCC.

PMID: 21915153 [PubMed - indexed for MEDLINE]

Hepatitis B Virus & PAHs

2000, Sohn *et al*.	The expression of HBV x protein resulted in enhanced cell susceptibility to cytotoxicity induced by B[a]P diol-epoxide.
2014, Chen *et al*.	Hepatitis B spliced protein could promote carcinogenic effects of B[a]P by interacting with microsomal epoxide hydrolase and enhancing its hydrolysis activity.

Mutat Res. 2000 Jun 30;460(1):17-28.

Retroviral expression of the hepatitis B virus x gene promotes liver cell susceptibility to carcinogen-induced site specific mutagenesis.

Sohn S[1], Jaitovitch-Groisman I, Benlimame N, Galipeau J, Batist G, Alaoui-Jamali MA.

Author information

Abstract

Mutational inactivation of the tumor suppressor gene p53 is common in hepatocellular carcinomas (HC exon 7 of the p53 gene occurs in over 50% of HCC from endemic regions, where both chronic infection to carcinogens such as aflatoxin B1 (AFB1) prevail. In this study, we report the effect of the HBV x pro and AGG to AGT mutation in codon 249 of the p53 gene in the human liver cell line CCL13. Expressior function, results in enhanced cell susceptibility to cytotoxicity induced by the AFB1 active metabolite, epoxide. Under similar conditions, expression of HBx promotes apoptosis in a subset of cell populatior induces a low frequency of AGG to AGT mutation in codon 249 of the p53 gene, as determined by an a PCR) assay. However, expression of HBx enhances the frequency of AFB1-epoxide-induced AGG to A summary, this study demonstrates that expression of HBx enhances liver cell susceptibility to carcino alteration of the balance between DNA repair and apoptosis, two cellular defense mechanisms against

PMID: 10856831 [PubMed - indexed for MEDLINE]

BMC Cancer. 2014 Apr 23;14:282. doi: 10.1186/1471-2407-14-282.

Hepatitis B spliced protein (HBSP) promotes the carcinogenic effects of benzo [alpha] pyrene by interacting with microsomal epoxide hydrolase and enhancing its hydrolysis activity.

Chen JY, Chen WN, Jiao BY, Lin WS, Wu YL, Liu LL, Lin X[1].

Author information

Abstract

BACKGROUND: The risk of hepatocellular carcinoma (HCC) increases in chronic hepatitis B surface antigen (HBsAg) carriers who often have concomitant increase in the levels of benzo[alpha]pyrene-7,8-diol-9,10-epoxide(±) (BPDE)-DNA adduct in liver tissues, suggesting a possible co-carcinogenesis of Hepatitis B virus (HBV) and benzo[alpha]pyrene in HCC; however the exact mechanisms involved are unclear.

METHODS: The interaction between hepatitis B spliced protein (HBSP) and microsomal epoxide hydrolase (mEH) was confirmed using GST pull-down, co-immunoprecipitation and mammalian two-hybrid assay; the effects of HBSP on mEH-mediated B[alpha]P metabolism was examined by high performance liquid chromatography (HPLC); and the influences of HBSP on B[alpha]P carcinogenicity were evaluated by bromodeoxyuridine cell proliferation, anchorage-independent growth and tumor xenograft.

RESULTS: HBSP could interact with mEH in vitro and in vivo, and this interaction was mediated by the N terminal 47 amino acid residues of HBSP. HBSP could greatly enhance the hydrolysis activity of mEH in cell-free mouse liver microsomes, thus accelerating the metabolism of benzo[alpha]pyrene to produce more ultimate carcinnogen, BPDE, and this effect of HBSP requires the intact HBSP molecule. Expression of HBSP significantly increased the formation of BPDE-DNA adduct in benzo[alpha]pyrene-treated Huh-7 hepatoma cells, and this enhancement was blocked by knockdown of mEH. HBSP could enhance the cell proliferation, accelerate the G1/S transition, and promote cell transformation and tumorigenesis of B[alpha]P-treated Huh-7 hepatoma cells.

CONCLUSIONS: Our results demonstrated that HBSP could promote carcinogenic effects of B[alpha]P by interacting with mEH and enhancing its hydrolysis activity.

PMID: 24758376 [PubMed - in process] PMCID: PMC4002904 Free PMC Article

Human Papillomavirus & PAHs

1940s, Rous	The combination of cottontail rabbit papillomavirus and coal tar greatly increased the rate at which carcinomas developed.
1995, Sizemore *et al*.	Normal and HPV immortalized ectocervical epithelial cells had different response to B[a]P.
2008, Alam *et al*.	B[a]P enhanced HPV synthesis.
2012, Trushin *et al*.	High-risk HPV infection substantially increased the overall metabolism of B[a]P.
2013, Viarisio *et al*.	Cutaneous HPV strongly cooperates with 7,12-dimethylbenz[a]anthracene (DMBA) in skin carcinogenesis.

Summary

- PAHs are a class of organic compounds consisting of 3 or more fused benzene rings.
- The most significant endpoint of PAH toxicity is cancer.
- The 2-year bioassay is the standard approach to study PAH carcinogenicity *in vivo;* the cell transformation assay is regarded as its only possible *in vitro* alternative.
- It is suggested that no *in vitro* effect of PAHs on EBV-infected lymphocytes contributes to development of oral cancers.
- HBV might promote carcinogenic effects of PAHs.
- HPV could cooperate with PAHs in carcinogenesis.

The End.