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Transplacental Transfer of Genotoxins and Transplacental Carcinogenesis

by Herman Autrup

A number of chemical compounds induce cancer in the offspring of animals treated with these compounds. The fetus is sensitive to the toxic and teratogenic effects of chemicals in the early embryonic stages, whereas it is sensitive to carcinogenic effects during late fetal stages. Carcinogens may be direct acting or may require metabolic oxidation such as those in tobacco smoke. Activation can occur *in utero*. Animal experiments indicate that tumors can be initiated *in utero*, commonly by activation of cellular proto-oncogenes, and that promotion can occur after birth by postnatal treatment with tumor promoters. This may have important implications for humans. The initial peak of cancer incidence during the first 5 years of life may be due to prenatal exposure of either parent to mutagens, but the role of paternal exposure in relation to childhood cancer is controversial. There is an increased risk of cancer in children whose fathers work in heavy industry or whose mothers work in medical or dental services. The exact etiological agents have not been unequivocally identified. Information on human transplacental exposure to carcinogens and genotoxins is limited and based on measurement of maternal plasma concentrations or analysis of cord blood. Transplacental transfer of carcinogens in smoke and smoke-related damage to fetal tissue have been demonstrated. The mycotoxin aflatoxin B_1 or its metabolites have been detected in cord blood, as have metabolites of pesticides and polychlorinated biphenyls. New biomarkers may provide important information on the transplacental transfer of genotoxic compounds. Recent developments in the field of molecular biology such as polymerase chain reaction may disclose relevant biological changes occurring *in utero* as a consequence of exposure to environmental compounds.

Introduction

More than 600 compounds, mixtures of compounds, or chemical processes have been evaluated for their carcinogenic effect in humans by the International Agency for Research on Cancer, but there was clear evidence for human carcinogenic risk associated with exposure to only 50 of these (*1*). Some of these compounds have teratogenic or transplacental carcinogenic activity in experimental animals and therefore may be considered to be potentially hazardous to pregnant women. Animal experiments indicate that the fetus is sensitive to the toxic and teratogenic effects of radiation and chemicals at early embryological stages, but it is resistant to tumor induction. In contrast, chemicals have been found to induce tumors at high incidence rates when given during late fetal stages.

Epidemiological data on transplacental carcinogenesis are limited (Table 1), the first human example being the induction of vaginal adenocarcinoma following maternal exposure to diethylstilbestrol during the first trimester (*2*). This tumor does not occur during childhood, but there is an increased risk of its development later in life, albeit extremely low (*3*).

The initial peak of cancer incidence is during the first 5 years of life, and this may be explained by prenatal exposure of either parent to mutagenic agents. A number of epidemiological studies have been conducted to evaluate potential associations between the occupational activity of parent and the risk of cancer in their offspring, but no clear associations have been established (*4,5*). Children of mothers employed in medical and dental care were noted to have an elevated risk of renal cancer and osteogenic and soft-tissue sarcomas, whereas children of female nurses had an elevated risk for cancers at all sites (*5*). The handling of drugs and exposure to anesthetic agents were suggested to be potential risk factors, but the etiological agents responsible for the cancers were not identified. Significantly increased risk was also observed in children of fathers employed in heavy industry such as smiths and machinists, but the previous suggestions that exposure to hydrocarbons and lead was a risk factor could not be supported by the Danish study (*5*).

Prenatal events can contribute to the occurrence of cancer as a consequence of direct exposure of embryonic or fetal cells to the carcinogenic agents, or exposure of the cell itself at a prezygotic stage. The role of paternal exposure to carcinogens as a risk factor for childhood

Steno Institute of Public Health, Department of Environmental and Occupational Medicine, University of Aarhus, Universitetsparken, Building 180, Aarhus c, Denmark.

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Table 1. Epidemiological studies of perinatal carcinogenesis.

Exposure/occupation[a]	Tumor site	Risk	Reference
Medical and dental care (F)	Renal	2.5*	(5)
Nurse (F)	All	1.4*	(5)
Medical/dental/veterinary pharmaceutical (M or F)	All	1.4*	(5)
Pharmacist (M)	Leukemia	19.7*	(6)
Smiths (M)	All	1.6*	(5)
Machinists (M)	All	1.5*	(5)
Smoking (M)	Leukemia	2.1*	(41)
> 10 cigarettes (M and F)	Hematopoietic	1.6*	(41)
Hydrocarbons (M)	Acute leukemia	2.5*	(6)

[a]F = father's occupation; M = mother's occupation.
*$p < 0.05$.

cancer is quite controversial and has not been substantiated in animal experiments. Treatment of male rats with ethylnitrosourea, a direct-acting carcinogen, up to 5 weeks before mating resulted in decreased fecundity but no increase in tumor incidence in the offspring (*6*). Among the most common tumors in infancy and childhood are the embryonic tumors such as those of kidney and retina, and these show a pattern of development that is consistent with a two-mutational-event sequence. The first mutation can either be inherited or may be acquired in a somatic cell, whereas the second event occurs in the target somatic cell. Carcinogenic mutations generally involve deactivation of suppressor genes. However, the nature and causes of the inactivating somatic mutations or chromosomal deletions have not been identified. The rapid development in molecular biology and the identification of a number of tumor-suppressor genes and their deactivation may soon provide new information.

Transplacental Carcinogenesis

Carcinogenesis is a multistage process where normal growth, differentiation, and development have gone out of control. Carcinogenesis is driven by spontaneous and carcinogen-induced genetic and epigenetic events. Operationally, the process has been divided into initiation, promotion, and progression. Tumor initiation involves a direct effect of the carcinogens on DNA, resulting in mutations. The biological consequence of some of those mutations may involve altered growth, resistance to cytotoxicity, and dysregulation of terminal differentiation. The promotion stage involves a clonal expansion of those cells with the changed properties. A number of animal experiments have demonstrated that the initiation can take place *in utero* with later promotion by treatment of the offspring. The postnatal exposure to tumor promoters will result in tumor formation at sites where no tumor would occur without the application of these promotors. Skin tumors developed in the descendants of pregnant mice treated with 7,12-dimethylbenz[*a*]anthracene (*7*) followed by postnatal treatment with 13-tetradecanoylphorbol acetate (TPA), similar to the classical skin tumor model where both treatment schedules are performed postnatally. Thyroid follicular tumors developed in rats after prenatal treatment with the direct-acting carcinogens *N*-alkylnitrosoureas and postnatal administrations of barbiturates (*8*). The initiation process is considered irreversible, in contrast to the promotional events. When Patas monkeys were treated transplacentally with the liver carcinogen diethylnitrosoamine (DEN), no hepatic tumors developed. However, treatment of the offsprings with the liver tumor promotor phenobarbital, starting at 4 years of age, resulted in the rapid appearance of hepatocellular carcinoma (*9*). Extrapolation of this information to the human situation may have some important implications. Intrauterine exposure to carcinogens may initiate some cells, but this will result in tumor formation if there is exposure to tumor promoters later in life.

Carcinogen Metabolism and DNA Repair

Carcinogens present in the environment could be activated to their biologically active form in the maternal liver, in placenta, or in fetal tissues. The initiation process involves the interaction of the ultimate form of the carcinogen with the DNA to form carcinogen–DNA adduct. Upon replication, or by a faulty DNA repair mechanism, this damage is transformed into a mutational event such as point mutations. Due to the high rate of replication and lack of DNA repair enzymes, animal experiments have shown that some fetal tissues are highly susceptible to carcinogenic agents and that this susceptibility is dependent on the gestational period (*10*). The formation of the active metabolites will most likely take place *in utero* by the embryo or fetus, but active metabolites may be formed in maternal tissue and can be transferred transplacentally. Formation of the biologically active metabolites can be mediated by the cytochrome P-450 mixed-function oxidase complex, and these enzyme activities have been demonstrated in human fetal liver from week 12 of gestation (*11,12*) as well as in extrahepatic tissues (*12,13*). The cytochrome P-450IA family of genes, which is involved in the activation of aromatic amines and polycyclic aromatic hydrocarbons (PAH) to their ultimate carcinogenic forms, is transcriptionally activated by PAHs and polyhalogenated dioxins and furans. This process is mediated by the Ah receptor that binds the toxins with high affinity, and the ligand-receptor complex is subsequently transferred to the nucleus where it binds to the xenobiotic-responsive elements. Animal experiments show that cytochrome P-450IA genes are inducible in fetal rat liver by a PAH, and that the level of induction is dependent on the amount of the Ah receptor. The receptor could be induced by barbiturate and PAH (*14*), and the concomitant exposure to dioxin and barbiturate had a synergistic effect on the induction. Transplacental transfer in man of PAHs found in cigarette smoke and other environmental toxins that either induce or bind to the Ah receptor, e.g., dioxins, may induce the cytochrome P-450IA activities in fetal tissues and hence modify response of the organism to a toxic insult.

For a long period of time the placenta was considered to be a barrier against the transfer of toxic compounds to the fetus. The placenta has well-developed metabolic defense mechanisms such as catalase and superoxide dismutase activities, which increase as gestation progresses, thereby lowering the concentration of lipoperoxides in the blood (*15*). Biotransformation *in utero* is not only important in

transplacental carcinogenesis, but also plays a role in the conversion of the toxins to their dysmorphogenic form (*16*). The amounts of the biologically active metabolites depend on the level of P-450 activity and detoxifying enzymes, and also on endogenous nonprotein thiols that can protect the fetus against reactive metabolites and active oxygen radicals. Very little is known about these protective mechanisms in human fetal tissues. The epoxide hydrolase activity, which is involved in the detoxification of biologically active epoxides is found at a much lower level in fetal than in adult liver (*17*).

Oncogenes

The detection of transforming cellular oncogenes in tumors from humans and animals provided the basis for the hypothesis that cellular oncogenes are the critical genes involved in carcinogenesis. The *ras* oncogene was one of the first oncogenes to be detected, and it has been extensively studied. Members of the *ras* gene family are activated in a large proportion of human tumors. However, the most dramatic illustration of the involvement of the *ras* oncogene comes from animal tumors induced by chemicals, where activation of *ras* has been reported at a high frequency in a number of tumors of epithelial origin. The *ras* gene family can be activated by point mutations, and carcinogen-specific mutations in *ras* genes can be found in tumors produced by different chemical agents (*18*). A single treatment with methylnitrosourea during late stages of embryonic development induces a wide variety of tumors involving cells such as those of neuroectodermal origin. Tumors derived from the peripheral nervous system, but not the central nervous system, contained activated *neu* oncogene, whereas the Ha-*ras* and Ki-*ras* oncogenes were activated in the mammary carcinomas and kidney mesenchymal tumors, respectively. The transplacentally activated *ras* oncogenes contained a G to A transformation in the second base of codon 12 (*19*), similar to the mutation seen in tumors initiated with the same carcinogen during adult life. Using the two-step mouse-skin carcinogenesis model, tumors developing after transplacental initiation with DMBA and postnatal promotion with TPA contained the Ha-*ras* oncogene activated at codon 61. The liver tumors induced by the same protocol did contain the same type of mutation (*20*).

Transplacental exposure of experimental animals to chemical carcinogens cause an increase in tumor incidence not only in the F_1 generation but also in the F_2 generation, suggesting possible damage to the germ cells (*20*). An increase in the incidence of lung cancer and malformations has been reported in the progeny of parents either of which had been treated with either X-rays or urethane before mating, implying an action of the carcinogen on the germ cells.

Transplacental Exposure to Genotoxins

The transfer of a chemical to the fetus at various stages of development can be studied in experimental animals. However, this type of information for humans is limited to the perinatal period and can be obtained by sampling cord blood. Assessment of exposure to the embryo and fetus can only be roughly based on maternal plasma concentrations.

Placental transfer has been observed for a number of different drugs. The ratio of the concentrations of fetal to maternal blood depends on the chemical structure of the drugs and ranges from 0.33 for cyclosporin A (*21*) to greater than 1 for chloroquine (*22*). The rate of transfer, however, is dependent on a variety of factors including molecular size and lipophilicity, degree of ionization and binding to blood components and placental tissue. It is generally assumed that protein-bound xenobiotic substances are less likely to pass the placental membrane, whereas the placenta does not protect against lipophilic compounds. The rate of transfer may also depend on the metabolism of the toxin in the placenta itself. The human placental mixed function oxidase (MFO) system is composed of several different P-450 isozymes. The basal level of these activities is very low, but can be induced by substances including constituents of cigarette smoke (*23–25*). The induction of P-450IA1 is mediated by the Ah receptor, and the level of induction is dependent on the affinity of the ligand for the receptor. It has been proposed that induction of IA1 activities could serve as a placental marker for exposure to polychlorinated dibenzofurans and polychlorinated biphenyls (*26*). A high level of MFO activity was detected in placentas from women in Yu-Cheng where people were accidentally exposed to rice contaminated with large quantities of dioxins (*27*).

The fetal exposure to organochloride pesticides and polychlorinated biphenyls has been evaluated in a number of studies by detection of the various metabolites in cord blood samples (*28*). The levels of these compounds in cord blood samples collected in industrialized nations, where the use of the compounds has been limited or banned, is lower than in samples collected in developing countries (*29*). These compounds are not carcinogenic as such, but many are potent promoters in experimental animals.

Several carcinogens and teratogens, such as PAHs and nitrosamines, are present in cigarette smoke. Different biochemical markers such as cotinine and thiocyanate are frequently used to assess passive exposure to smoking. The levels of these markers are identical in maternal and cord blood clearly indicating the compounds in cigarette smoke are passing from the mother to the fetus. However, no evidence of increased mutation frequency or sister chromatid exchanges (SCE) could be detected in cultured lymphocytes from cord blood (*30*). The studies on SCE in human lymphocytes of smokers and nonsmokers have yielded conflicting results. The effect of maternal exposure to cigarette smoke in the fetus has been studied in a number of animal studies. The number of SCE in fetal liver was increased following exposure to either mainstream or sidestream smoke, the sidestream being more active (*31*). This suggests that exposure to environmental tobacco smoke may represent a health hazard to the fetus. However, the available epidemiological data provide no conclusive evidence of an effect of maternal smoking during

pregnancy on the risk of cancer in children (*32*). An increased level of cadmium, another component of cigarette smoke, was seen in cord blood from smoking mothers compared to nonsmokers (*33*), indicating that many toxic components in cigarette smoke can pass the placental barrier.

Binding the active form of compounds to cellular DNA in fetal tissue would therefore be an indicator of fetal exposure to the genotoxin. Several sensitive methods have been developed to measure these reaction products (*34*), and umbilical cord tissues could serve as a good indicator for transplacental transfer of genotoxins. The ^{32}P-postlabeling technique has been applied to DNA isolated from fetal tissues from animals treated with different carcinogens. The level of adduct was generally higher in the maternal than in the fetal tissues, which may be indicative of maternal metabolism of the carcinogens. The organotropism of carcinogen–DNA adduct formation seen in maternal tissues was not observed in fetal tissues (*35*). The ^{32}P-postlabeling assay has been developed to detect bulky carcinogen–DNA adduct, and it is possible to detect one modified base in 10^8 bases. DNA isolated from the tissues is degraded into monophosphate nucleotides by a combination of nucleases, and ^{32}P is enzymatically transferred to the monophosphate nucleotides to form diphosphates which are separated by four-dimensional thin layer chromotography. A number of studies have demonstrated high levels of carcinogen-modified DNA in placenta from smokers (*36*), and in lung and liver DNA isolated from aborted fetuses (*37*). The presence of adduct in fetal tissues indicates the transplacental transfer of the carcinogens or their metabolites. In a recent study it was reported that the adduct level was significantly higher in umbilical artery and vein tissue from smokers than nonsmokers (Table 2). The presence of adduct in tissues from nonsmoking mothers suggests that passive smoking compounds or other general pollutants can pass the placental barrier (Hansen et al., manuscript submitted). The level of adduct was significantly higher in the maternal tissues than in the fetal tissues. The observation that the carcinogen–DNA adduct level was higher in the umbilical cord artery than in the vein suggests that fetal metabolism of the carcinogens takes place. One of the major carcinogenic components in cigarette smoke is benzo[*a*]pyrene. Using a combination of immunoaffinity chromatography linked with synchronous fluorescence spectrophotometry, the presence of benzo[*a*]pyrene diol epoxide adduct was detected in human placenta DNA, and the chemical identity was verified by GC–MS (*38*). Binding to hemoglobin is a good biomarker for the exposure to aromatic amines. 4-Aminobiphenyl adducts could be detected in both maternal and cord blood (Table 3).

Table 2. Transplacental transfer of smoking-related carcinogens: relative adduct levels detected by ^{32}P-postlabeling.

Tissue	Smokers	Nonsmokers
All	42.8 ± 11.6	19.7 ± 4.2* (p = 0.021)
Maternal	62.6 ± 29.2† (p = 0.089)	29.2 ± 6.8‡ (p = 0.061)
Fetal	31.4 ± 12.4	14.7 ± 5.1* (p = 0.089)
Vein	23.5 ± 11	7.3 ± 2.3
Artery	39.4 ± 23	22.9 ± 10

*Significantly different from smokers.
†Significantly different from fetal tissue.
‡Significantly different from fetal tissue.

Table 3. Transplacental exposure to 4-aminobiphenyl in smokers: aromatic amine–hemoglobin adducts (*42*).

	Smokers	Nonsmokers
Fetal	92 ± 54 pg/g Hb	17 ± 33 pg/g Hb
Maternal	1.83 ± 1.08 pg/g Hb	22 ± 8 pg/g Hb
p	0.02	0.6
Maternal/fetal ratio	24	19

HB, hemoglobin.

Aflatoxin B_1, produced by *Aspergillus flavus* and *A. paraciticus*, is commonly found as a contaminant of many staple food commodities in the tropics. This compound is a potent human carcinogen, and exposure *in utero* has been suggested to play a role in the development of primary hepatocellular carcinomas in young children in Kenya. Analysis of cord blood samples from Africans (*39*) and Asians (*40*) showed the presence of aflatoxin B_1 and one of its metabolites, aflatoxin M_1. The relative frequency of aflatoxin-positive cord blood samples depended on geographical location and seasonal variation. A higher frequency of positive samples was seen in cord blood samples collected during the wet period compared to the cold, dry months. This seasonal variation in frequency and level of aflatoxin detection accords with an increase in aflatoxin contamination of foods during periods of high temperature and humidity. In Kenya, the mean birth weight of females born to aflatoxin-positive mothers was 255 g less than the mean birth weight of females born to aflatoxin-negative mothers (*39*).

Conclusion

We are living in a chemical world and are continuously exposed to a large number of chemical compounds that may adversely affect our health. Some of these compounds may be teratogenic, may initiate cancer that will develop later in adult life, or may result in delayed effects on descendants. Little information on human exposure to genotoxic agents is available, whereas a number of papers have described the effects of heavy metals. A number of new analytical techniques have been developed to assess human exposure to genotoxic compounds, and these could easily be applied to human fetal tissues or cord blood. As placental tissue is easily available, this tissue could serve as a surrogate tissue for the assessment of fetal exposure to genotoxic carcinogens.

Induction of cytochrome P-450 activity in the placenta may serve as an indirect measure of the exposure to compounds that are not in themselves genotoxic but may influence the carcinogenic process.

Developments in this area of molecular biology such as polymerase chain reaction (PCR) in combination with assays to detect mutations make it possible to study the activation of proto-oncogenes and cancer-suppressor genes in different fetal tissues. This could enable identifi-

cation of lesions that may have the potential of leading to the development of cancer and testing for such lesions could be performed following exposure to compounds with known tumor-promoting activity. Characterization of the type of mutation may suggest the identity of the chemical agent responsible for the mutation.

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