Environmental Health Perspectives
Vol. 98, pp. 39–43, 1992

Perinatal and Multigenerational Effect of Carcinogens: Possible Contribution to Determination of Cancer Susceptibility

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Perinatal exposure to carcinogens may contribute to the determination of susceptibility to cancer in two situations: *a*) exposure *in utero* of embryonal or fetal somatic cells to carcinogens, and *b*) prezygotic exposure of the germ cells of one or both parents to carcinogens. Epidemiological as well as experimental studies demonstrate that exposure to carcinogens *in utero* increases the occurrence of cancer postnatally. Studies with experimental animals suggest that prezygotic exposure of germ cells to carcinogens can result in an increased incidence of cancer not only in immediate but also in subsequent generations. Although several studies suggest a transgeneration effect of carcinogens in human populations, the evidence cannot yet be considered conclusive. In particular, while some hypotheses can be advanced, the mechanism(s) by which increased susceptibility or predisposition to cancer may be transmitted via the germ cells has not yet been clarified. In conjunction with exposure both *in utero* and prezygotically, it is important to consider postnatal exposure to possible tumor-promoting agents. Results from experimental animals suggest that oncogenes can be activated transplacentally, and human studies indicate that tumor-suppressor gene inactivation may be involved in the transgenerational effect of carcinogens.

Introduction

It is clear that multiple genetic events are involved in carcinogenesis, as exemplified in human colon carcinogenesis (*1*). The multistage nature of cancer implies that cells that contain one or few genetic mutations may behave like normal cells; several other genetic insults are required to confer the tumor phenotype. It can thus be suggested that one or more genetic insults may occur in germ cells or in somatic cells *in utero*, which may not be expressed until further genetic events occur in postnatal life (*2*).

While the concept of multistage carcinogenesis and the multifactorial origins of cancer are well recognized, we still tend to evaluate carcinogenic risk as if most cancers were related causally to a single agent or a single exposure. This has also been the case in studies of the prezygotic or intrauterine effects of carcinogens. Recent studies suggest, in addition, that postnatal exposure to tumor-promoting agents plays a crucial role in producing tumors in animals that were exposed to carcinogens *in utero* or the male parents of which were exposed prior to mating. Prenatal carcinogenic events thus play an important role in determining postnatal susceptibility to carcinogens.

Molecular biological studies have shown that specific tumor-suppressor genes can be mutated in germ cells and transmitted to offspring. For example, *Rb* and *p53* genes were found to be mutated in hereditary retinoblastoma and Li-Fraumeni syndrome, respectively (*3,4*). In animal studies it has been established that mice that have transgenic activated oncogenes are prone to cancer (*5*). While such information supports the idea of transgenerational transmission of carcinogenic risk, it is not clear whether exogenous agents such as environmental carcinogens are responsible for these risks. We review here available data on this subject and discuss the possible importance of postnatal exposure to carcinogens and the molecular mechanisms of prenatal carcinogenic events.

Transplacental Initiation and Postnatal Promotion in Experimental Animals

Transplacental carcinogenic effects of a chemical were reported as early as 1947. Larsen (*6*) showed that administration of urethane to pregnant strain A mice resulted in the accelerated appearance of more pulmonary tumors in offspring. Since then, the prenatal carcinogenic effects of a large number of chemicals of quite different chemical structures have been demonstrated in several species (*7*).

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The first attempt to amplify the effect of exposure *in utero* to a carcinogen by postnatal exposure to another carcinogen was made by Goerttler et al. (*8*). After exposure *in utero* to 7,12-dimethylbenz[*a*]anthracene (DMBA), exposed offspring were painted with a tumor promoting agent, 12-*O*-tetradecanoylphorbol 13-acetate (TPA); an increased number of skin tumors was induced. These results were confirmed with other strains of mice (*9,10*). The transplacental initiation–postnatal promotion protocol has also been used in rats and patas monkeys (*11,12*). In rats, the incidence of follicular thyroid tumors in offspring that had been treated *in utero* with *N*-methyl-*N*-nitrosourea was increased after postnatal promotion by phenobarbital (*11*). Rice et al. (*12*) showed in monkeys that liver tumors could be initiated transplacentally by *N*-nitrosodiethylamine and promoted postnatally by phenobarbital.

In humans, diethylstilbestrol and X-rays are known to be transplacental carcinogens (*13,14*); however, there is no epidemiological evidence that postnatal exposure to other factors enhances tumor incidence in individuals exposed transplacentally to known carcinogens.

Oncogene Activation by Transplacental Carcinogenesis

Certain cellular proto-oncogenes are expressed in fetal tissues at levels different from those in their adult counterparts (*15*). Thus, it is possible that the vulnerability of oncogenes to the actions of external agents is different in fetuses and adults. In order to examine this possibility, we induced mouse skin tumors by the protocol of transplacental initiation by DMBA and postnatal treatment with TPA and then analyzed their oncogenes (*10*). No tumor was induced if the offspring were not painted with TPA postnatally, suggesting the DMBA may act merely as an initiating agent on epidermal cells. In the skin papillomas and carcinomas, we found the DMBA-specific activation pattern of Ha-*ras* genes, namely A to T transversion at the 61st codon. This specific mutation was not observed when benzo[*a*]pyrene was used as the transplacental initiating agent. These results suggested that DMBA induces an oncogenic mutation in fetal cells that remains dormant until the cells encounter a tumor-promoting stimulus during the postnatal period. Thus, the consequence of exposure *in utero* to carcinogens may be genetic damage equivalent to an initiation event, which may become manifest only after postnatal exposure to tumor promoting agents.

Oncogene activation in transplacentally induced tumors has also been observed in other studies (*16,17*). For example, rat peripheral nervous system tumors induced transplacentally by *N*-ethyl-*N*-nitrosourea contained mutations of the *neu* oncogene (*16*). The mutations were invariably T to A transversions at the 2012th base. Mutation of the *neu* oncogene in the peripheral nervous system in transplacentally induced tumors was also observed using *N*-methyl-*N*-nitrosourea (*17*): Following transplacental exposure to this compound, mammary and kidney tumors were produced, and an Ha-*ras* G to A transition was found in mammary and a Ki-*ras* G to A transition in kidney tumor cells (*17*). These results are compatible with those of Loktionov et al. (*18*), who showed that transplacental exposure to DMBA induced skin, liver, and lung tumors which contained Ha-*ras* (skin and liver) or Ki-*ras* (lung) A to T mutations. It can therefore be suggested that administration of a single carcinogen transplacentally produces tumors in multiple tissues, with specific patterns of oncogene activation. It is also interesting to note that tumors induced by prenatal exposure contain similar oncogene activation patterns as those observed in tumors induced postnatally by the same carcinogens, suggesting that fetal and adult cellular proto-oncogenes can be activated by carcinogens in a similar manner.

Transgenerational Effect of Carcinogens

Various studies in experimental animals suggest that the effects of a carcinogen can be transmitted multigenerationally, either when exposure occurs *in utero* or when parents (mostly fathers) are exposed before mating (*2*). The studies conducted to date are summarized in Table 1. While most carcinogens are genotoxic, diethylstilbestrol, which is not known to induce gene mutations, has also been shown to be a transgenerational carcinogen in mice (*19*). In addition, female offspring of male descendants of diethylstilbestrol-treated mothers mated with untreated females have a high incidence of uterine sarcomas and of benign tumors of the ovary (*20*). The molecular mechanisms of germ-cell transmission of genetic damage may not be limited to mutation; mechanisms such as genomic imprinting may play an important role (*21*).

Transmission of tumor initiation through germ cells which can be expressed following postnatal exposure to promoting agents has been reported by several authors. A multigeneration effect of DMBA on skin initiation was found by Napalkov et al. (*9*) and confirmed by Loktionov et al. (*22*), only after the offspring were painted with the skin tumor promoting agent TPA. Two-generation transmission of skin tumor initiation was recently extended to X-rays (*23*). Similarly, Nomura (*24*) and Vorobotsova and Kitaev (*25*) found that large clusters of lung tumor nodules developed when the offspring of irradiated parents were treated postnatally with urethane.

Some evidence of transgenerational carcinogenesis in humans comes from an epidemiologic study of radiation workers near Sellafield in the United Kingdom (*26*). An increased rate of leukemia was seen among local residents under the age of 25 whose fathers were employed in the nuclear industry. A significant increase was observed in the children of fathers who had received 10 mSv or more of radiation in the 6 months prior to conceiving. These results are in contrast to the negative results found for atomic bomb survivors: no excess of leukemia was seen among the offspring of Japanese men who survived the atomic bomb blasts (*27*). Several reasons have been offered to explain the apparent discrepancy between the studies in Sellafield and in Hiroshima–Nagasaki. It is important to emphasize that only children born to survivors in Hiroshima–Nagasaki between 1946 and 1982 were studied, and very

Table 1. Multigenerational effects of carcinogens.[a]

Agent	Species (strain)	Treatment[b]	Tumors observed in subsequent generations[b]
MCA	Rat (Wistar)	Mother (before and shortly after mating)	Various sites
OATT	Mouse (C3HA)	Pregnant mother	Liver tumors
DMBA	Mouse (Swiss)	Pregnant mother	Mammary carcinomas, ovarian tumors, lung adenomas, etc.
DMBA	Mouse (MCA)	Pregnant mother	Lung adenomas, ovarian tumors, malignant lymphomas, etc.
MNU	Rat (BDIV)	Pregnant mother	Kidney tumors, neurogenic tumors, mammary tumors
ENU	Rat (BDVI)	Father before mating	Neurogenic tumors (in F_1)
X-rays, urethane, 4NQO	Mouse (ICR)	Mother or father before mating	Lung tumors, ovarian tumors, lymphocytic leukemia (in F_1, F_2, F_3)
DES	Mouse (CD-1)	Pregnant mother	Uterine adenocarcinomas, ovarian tumors
NDEA	Hamster	Pregnant mother	No evidence of increased risk in progeny
DMBA	Mouse (SHR)	Pregnant mother (TPA painted on F_0 and F_1)	Skin and various other tumors
X-rays	Mouse (SHR)	Father before mating (urethane treatment in F_1)	Multiple lung adenomas
		Father before mating (TPA treatment in F_1 and F_2)	Skin tumors
OAAT	Mouse (CBA)	Pregnant mother	Liver tumors
BP	Mouse (A)	Pregnant mother	Multiple lung adenomas in F_0, F_1, F_2, and F_3
ENU	Rat (BDIV)	Father before mating	No clear evidence of increased risk in progeny
DES	Mouse (CD-1)	Pregnant mother	Uterine sarcomas and benign ovarian tumors in F_1 females derived from treated male parents mated with untreated females

Abbreviations: MCA, 3-methylcholanthrene; OAAT, *o*-aminozaotoluene; DMBA, 7, 12-dimethylbenz[*a*]anthracene; MNU, *N*-methylnitrosourea; ENU, *N*-ethylnitrosourea; 4NQO, 4-nitroquinoline-1-oxide; NDEA, *N*-nitrosodiethylamine; DES, diethylstilbestrol; BP, benzo[*a*]pyrene; TPA, 12-*O*-tetradecanoylphorbol 13-acetate.

[a]Modified from Tomatis et al. (*2*), in which individual references are cited.

[b]F_0 generation exposed *in utero*.

few children were conceived during the first months following the atomic explosion. Since the report of Gardner et al. (*26*) suggests a high risk for childhood leukemia after paternal exposure during the 6 months before conception, the difference in the exposure period between Sellafield and Hiroshima–Nagasaki may have resulted in different multigenerational effects of radiation. It is also important to emphasize that Gardner et al. studied men who received chronic exposure to radiation, whereas the atomic bomb survivors received a single high dose. Assuming that radiation may act as an initiating agent in germ cells, it is also important to consider possible differences in postnatal exposures to tumor promoting agents: There may have been different postnatal risk factors in Hiroshima–Nagasaki and in Sellafield.

More than 30 studies have been published in which an association has been sought between childhood cancer and parental occupation (*27,28*). The sample sizes in the individual studies are generally too small for conclusions to be reached, and it is difficult to aggregate the studies because of different categorizations of exposures and occupations. While no clear-cut, positive association is found in any of the studies, some associations with specific occupational exposures appear more often than might be expected. These include exposures to motor vehicle exhaust, to fumes in welding, to paints, to pesticides, and in agriculture (*28,29*).

Molecular Mechanisms in Transgenerational Carcinogenesis

The results of animal experiments show that carcinogens can induce heritable mutations and chromosomal translocations in germ cells (*30*). What kind of genes are altered in germ cells in order to bring about transgenerational carcinogenesis? While both cellular oncogenes and tumor suppressor genes may be critical targets of carcinogens in somatic cells, recessive tumor suppressor genes may be the preferred targets in germ cells. The presence of mutated oncogenes in germ cells may not be compatible with the normal process of development. A recent study by Loktionov et al. (*22*) indirectly supports this notion. When mice exposed to DMBA *in utero* were painted with TPA postnatally, a high incidence of skin tumors was seen, and most of the tumors contained an A to T transversion at the 61st codon of Ha-*ras*—the mutation often found in DMBA-induced tumors. When mice exposed *in utero* (F_0) were mated and their offspring (F_1) painted with TPA, the increased frequency of skin papillomas persisted, confirming the transgeneration "initiating" effect of DMBA. Tumors produced in the F_1 generation, however, did not contain the A to T mutation at the 61st codon of Ha-*ras*, suggesting that this mutation is not responsible for transgenerational carcinogenesis.

Transmission of mutant tumor-suppressor genes through germ cells has been shown to occur in humans. It has been proposed that the Li-Fraumeni syndrome is due to a germinal mutation of the recessive *p53* gene (*4*) and that the hereditary form of retinoblastoma is due to a point mutation of the retinoblastoma gene (*3*). Since many environmental carcinogens are known to induce mutations, the transgenerational effects of carcinogens may involve germ-line mutations of tumor-suppressor genes. Recent studies suggest that three-quarters of bilateral retinoblastomas are due to *de novo* mutation in germ cells (*31*).

De novo germ-cell mutation of *p53* gene was also reported in people who developed multiple tumors but did not express the characteristics of the Li-Fraumeni syndrome (S. H. Friend, personal communication). These results indicate that germ-cell mutations may continue to occur, and the question remains as to which carcinogens are responsible for them.

The molecular mechanisms of transgenerational carcinogenesis may involve genetic events other than classical mutations. Prody et al. (*32*) found amplification of the cholinesterase gene in two generations of a family subjected to prolonged exposure to organophosphorus insecticides. Since the extent of amplification was similar in the two generations, the gene amplification could have been transmitted via the germ line. Genomic imprinting, the mechanisms of which are largely unknown, may also influence transgenerational carcinogenesis. DNA methylation has been associated with genomic imprinting (*33*). Agents that alter DNA methylation in germ cells may induce heritable changes. It has been suggested, however, that the DNA methylation pattern is completely erased in primordial germ cells (*34*). Thus, if heritable change is associated with DNA methylation of germ cells, other genes that govern DNA methylation must be responsible.

Conclusion

In this review, we have emphasized the importance of prenatal exposure to carcinogens in at least some aspects of genetic predisposition to cancer. While the familial clustering of cancer cases may be an indicator of an inherited predisposition to cancer, cases involving new germ-cell mutations are difficult to detect. Exposure to carcinogens *in utero* or preconceptually plays an important role in determining susceptibility to postnatal exposure to carcinogens. Prezygotic exposure to a carcinogen may be at the origin of a so-called "initiating" event that is one of many in the sequence of events leading to neoplasia. The manifestation of such prenatal events depends on postnatal exposures (*10*).

It is possible that multiple mutations may accumulate within a few generations and result in an increased risk for cancer in the descendants. It is equally possible that germ cells with multiple mutations do not function as proper gametes and are not viable. Damage to germ cells is not limited to mutations; other changes such as gene amplification and DNA hypomethylation should also be considered.

In spite of its potential importance, multigenerational transmission of carcinogenic risk has not yet been studied extensively. In humans, there is no carcinogenic agent that has been shown unequivocally to be a transgenerational carcinogen. In the past, the necessity of analyzing many samples and of following multiple generations over a long time hindered progress in this research area. These limitations can now be circumvented, at least partially, by the use of the tools of molecular biology. Further studies in molecular biology should help in identifying environmental carcinogens that may cause transgenerational carcinogenesis and the molecular mechanisms involved.

This manuscript was presented at the Conference on Biomonitoring and Susceptibility Markers in Human Cancer: Applications in Molecular Epidemiology and Risk Assessment that was held in Kailua-Kona, Hawaii, 26 October–1 November 1991.

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