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Benzo[a]pyrene and Human Embryo

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1. Introduction

Benzo[a]pyrene (B[a]P) is a typical compound of the polycyclic aromatic hydrocarbons (PAHs), compounds that are usually generated through the combustion of fossil fuels, wood, and other organic materials and are found in significant amounts in diesel exhaust, cigarette smoke, charcoal-broiled foods, and industrial waste-by-products (Boström et al, 2000). B[a]P is readily absorbed following inhalation, oral, and dermal routes of administration (Knafla et al, 2006). B[a]P absorption activates the aryl hydrocarbon receptor (AhR), which forms an active transcription factor heterodimer with the AhR nuclear translocator (ARNT), and induces the expression of a group of genes called the Ah gene battery, including the cytochrome P450 1A1 (CYP1A1), CYP1A2, and CYP1B1 genes (Shimizu et al, 2000; Nebert et al, 2000).
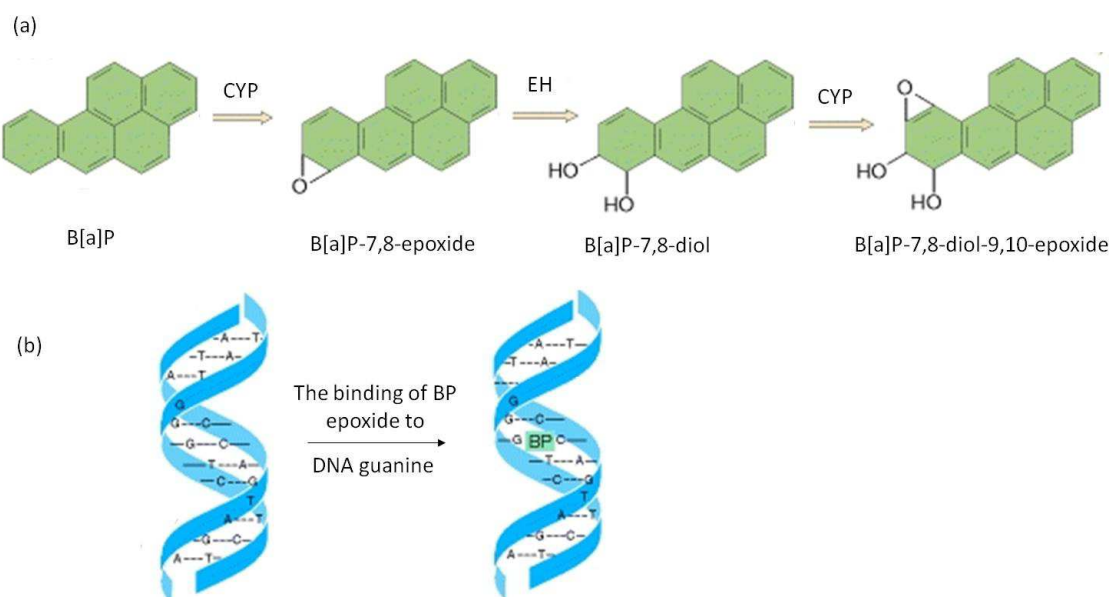

Fig. 1. The metabolic conversion of benzo[a]pyrene into a mutagen. (a) Benzo[a]pyrene goes through several steps as it is made more water soluble prior to excretion. (b) One of the intermediates in this process, B[a]P-7,8-diol-9,10-epoxide, is capable of reacting with guanine in DNA. This reaction leads to a distortion of the DNA molecule and mutations.

Several P450 enzymes are involved in key steps in the oxidation of B[a]P, and CYP1A1 has been demonstrated to be the most active in this oxidation in mammals (Chung et al, 2007). CYP1A1 activates B[a]P to B[a]P-7,8-epoxide, which through hydration by epoxide hydrolase (EH) is metabolized to (+/-)-B[a]P-trans-7,8-dihydrodiol (DHD). B[a]P-7,8-DHD may then serve as a substrate for a second CYP-dependent oxidation reaction, generating the ultimate carcinogenic metabolite r-7,t-8- dihydrodiol-t-9,10-oxy-7,8,9,10-tetrahydrobenzo[a]pyrene (BPDE-I) (Fig 1a). In the nucleus, the diol- epoxides may covalently bind to DNA, mainly forming deoxyguanoside-DNA adducts, which may result in misreplication and mutagenesis (Kaina, 2003) (Fig 1b).

2. Effects of benzo[a]pyrene on reproduction

Adverse reproductive effects were observed in several studies with B[a]P. Exposure of male and female zebrafish to B[a]P impaired reproduction in zebrafish (Hoffmann and Oris, 2006). Intraperitoneal administration of B[a]P to rat embryos has resulted in stillbirths, resorptions, and malformations; decreases in follicular growth and corpora lutea; and in testicular changes (Luijten et al, 2008). Subcutaneous injections of B[a]P produced increased resorptions in rats and direct embryonal injection led to decreased fetal survival in mice (Pereraa et al, 2005). In utero exposure to B[a]P has produced adverse reproductive effects in mice (Legraverend, et al, 1984). Dietary administration of doses as low as 10 mg/kg during gestation caused reduced fertility and reproductive capacity in offspring (Mackenzie and Angevine, 1981) and treatment by gavage with 120 mg/kg/day during gestation caused stillbirths and malformations (Legraverend et al, 1984).

2.1 Benzo[a]pyrene and male fertility

Spermatogenesis is carefully controlled to produce mature spermatozoa from spermatogonial stem cells in three major stages – the mitotic stage, the meiotic stage and the maturation stage (Verhofstad et al, 2010). Germ cells are susceptible for the induction of mutations during mitotic and meiotic divisions, because cell turnover is a prerequisite for fixation of DNA damage into mutations (Somers et al, 2002). Changes in the DNA sequence can be induced by exposure to chemicals during life, but may also be inherited via mutations in the spermatogonial stem cells, in that way increasing the risk of developing abnormalities or diseases in the offspring (Vilarino-Guell et al, 2003). B[a]P related DNA damages were observed at all stages of spermatogenesis (Zenzes et al, 1999), which were associated with significantly decreased sperm counts (Verhofstad et al, 2009).

Although B[a]P has been studied with respect to sperm DNA adducts (Kao et al, 1998) and apoptosis (Whitfield et al, 2002), few studies have evaluated its possible effect on sperm motion characteristics. Because the motion characteristics, hyperactivation status, and acrosomal reaction of spermatozoa indicate functional status and fertilizing potential (Cheo et al, 1997), it is worthwhile to note whether B[a]P has any effect on these parameters (Fig 2). A study of adult male F-344 rats showed that subchronic exposure to inhaled B[a]P contributed to reduced testicular and epididymal function (NTP, 2000). Moreover, some studies have proved that escalating hypermotility of spermatozoa occurs with increasing concentrations of B[a]P as a result of premature capacitation (Zenzes, 2000). B[a]P treatment can significantly decrease the percentage of halo formation, and the hyperactivation status

attained due to B[a]P treatment induces false acrosomal reactions in the spermatozoa (Yauk et al, 2008).
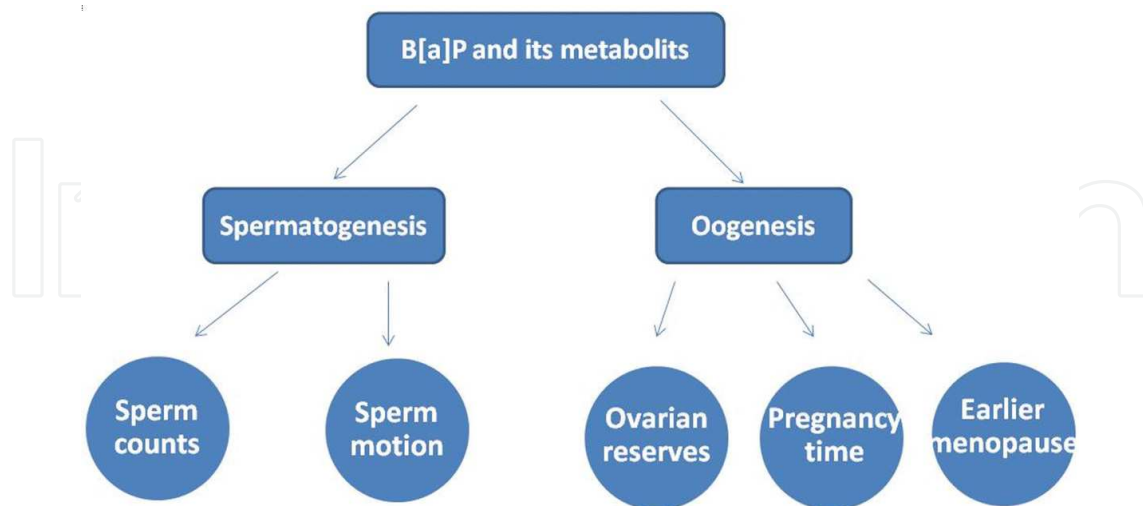

Fig. 2. Influence of benzo[a]pyrene on male and female fertility.

2.2 Benzo[a]pyrene and female fertility

Ovarian function can be compromised by exposure to toxic chemicals (Younglai et al, 2007). In addition, the ovary itself can be affected resulting in disturbances in oocyte maturation and/or destruction of the oocyte. The mechanism of B[a]P-mediated ovotoxicity may be indirect (Fig 2), since oocytes at all stages of development are surrounded by follicular cells (Hombach-Klonisch et al, 2005). A loss in integrity of this follicular wall by B[a]P may compromise its ability to maintain oocyte viability (El Nemr et al, 1998). Extensive damages of ovarian follicles would also impair steroid hormone production which, in turn, affects the endocrine balance and results in ovarian failure (Shiverick and Salafa, 1999). The carcinogenic metabolite (BPDE-I) is a diol epoxide derivative of B[a]P which binds predominantly to the 2-amino group of DNA guanosine and forms adducts. In ovarian tissue, BPDE-DNA adducts were detected in oocytes and luteal cells in ovaries of adult women who were exposed to cigarette smoke from smoking themselves or from second-hand smoke (Wright et al, 2006).

B[a]P was reported to cross the placenta in mice, rats, and guinea pigs following maternal injection, dermal, or inhalation exposure to B[a]P (Karttunena et al, 2010). Evidence from human studies indicates that BPDE–DNA adducts have been found in the placentas of smoking mothers (Motejlek et al, 2006). In addition, prolonged time to pregnancy, earlier mean age of menopause, altered ovarian steroidogenesis, and depleted ovarian reserves, have all been observed in women who smoke compared to non-smokers (Younglai et al, 2005). Inhalation exposure of pregnant rats or mice to B[a]P resulted in decreased numbers of live pups at birth (Archibong et al, 2002; Wu et al, 2003). Injection of B[a]P to pregnant rats resulted in decreased fetal weight and increased fetal death (Bui et al, 2003). Administration of B[a]P by ingestion to pregnant rats resulted in an increased number of stillborn pups (Perera et al, 2004). Injection of pregnant mice with B[a]P also resulted in measurable changes in some enzymes in lungs (pyruvate kinase and lactic acid dehydrogenase) of exposed fetuses (Parman and Wells, 2002).

3. Mechanisms of benzo[a]pyrene on reproductive toxicity

3.1 Oxidative stress and damage

B[a]P has been proved to be able to enhance the generation of reactive oxygen species (ROS) by inducing cytochrome P450 enzymes and free radicals produced by B (a) P metabolism (Ji and Shen, 2009). Numerous studies demonstrated that B[a]P can induce oxidative DNA damage and the formation of teratogenic ROS, and B[a]P have been postulated, at least in part, to be involved in the underlying mechanisms in the teratogenicity of B[a]P (Wells et al, 2009). Most ROS are too unstable to travel beyond the cell, which are capable of damaging every molecule present inside the cell: carbohydrates, proteins, lipids and the DNA (Kovacic and Somanathan, 2006). Teratogenicity likely depends to a large extent upon a balance between the pathogenic pathways of xenobiotic bioactivation, oxidative macromolecular damage and signal transduction on one hand, and on the other, the protective pathways of maternal elimination, embryonic detoxification of xenobiotic reactive intermediates and reactive oxygen species, and embryonic pathways for the detection and repair of oxidative DNA damage (Jeng et al, 2005). Accordingly, embryopathic risk is theoretically determined by the balance between the pathogenic and embryoprotective pathways. The risk of ROS-mediated teratogenesis can be enhanced by either genetic or environmental determinants that increase embryonic xenobiotic bioactivation or decrease one or more of the antioxidants, so the teratologically relevant processes of embryopathic xenobiotic bioactivation and reactive intermediate detoxification, ROS formation and their associated protective pathways involving antioxidants and antioxidative enzymes, and pathways for the repair of oxidative DNA damage, all lie exclusively within the embryo.

3.2 Apoptosis and cell cycle

B[a]P has been shown to induce apoptosis and necrosis in various cell types (Ko et al, 2004; Patil et al, 2009). There are two major mitochondria-dependent pathways involved in apoptosis. One is mediated by Bax, a proapoptotic member of the Bcl-2 family. After receiving death signals, Bax is activated and inserts into the mitochondrial membrane, causing cytochrome c release, which triggers downstream apoptotic pathway, including apoptosome formation, caspase cascade activation, and nuclear degradation (Teijido and Dejean, 2010). B[a]P has been shown to activate apoptotic pathways in a number of studies using mammalian cell lines (Jiang et al, 2011). Other study with B[a]P in JEG-3 (human trophoblastic) cells found no evidence of apoptosis based on analysis of cell cycle phase distribution, DNA fragmentation, or Bax or Bcl-2 levels, which may due to concentration or cell type specific (Drukteinis et al, 2005).

Cell cycle regulation has been increasingly recognized as one of the important mechanisms required for the teratogenicity of B[a]P during the past several years. As reported, B[a]P induces cell cycle arrest in MCF-7 (human breast carcinoma) and HELF (human embryo lung fibroblasts) cells, and altered expression of genes that affect cell cycle regulation (Khan and Dipple, 2000; Gao et al, 2005). Moreover, cell cycle phases showed an accumulation of cells in the G1 and G2 phase after B[a]P exposure (Vaziri et al, 1997; Zhu et al, 2005). It has also been shown that BPDE, the metabolite of B[a]P, can induce a G2/M accumulation (Wang et al, 2003). In line with these findings, G1-S arrest was observed in testis of B[a]P exposed male mice(Verhofstad et al, 2010). B[a]P produces growth inhibition involving

G2/M arrest in JEG-3 trophoblastic cells (Drukteinis et al, 2005). Expression of G2/M phase genes showed a trend towards a higher induction of these genes in testis of mice after B[a]P exposure.

We and other have demonstrated that B[a]P could stimulate cell proliferation through certain signaling pathways (Jiao et al, 2008; Gao et al, 2007; Tannheimer et al, 1998). In addition, B[a]P-induced cell proliferation is accompanied by increased G1/S transition (Gao et al, 2006; Jia et al, 2006). Cyclin D1 serves as a key sensor and integrator of extracellular signals of cells in early to mid-G1 phase, involved in regulation of cell proliferation and differentiation (Neumeister et al, 2003). Cyclin D1 in complex with its partner, cyclin-dependent kinase 4 (CDK4), phosphorylates the product of the retinoblastoma gene, the retinoblastoma protein (pRb), a well known tumor suppressor. The phosphorylated pRb releases the E2F family that plays an integral role in cell cycle progression by inducing the expression of gene required for S phase entry (Wang et al, 2004). In a previous study, we found that B[a]P exposure also induces cyclin D1 overexpression in HELFs (Du et al, 2006; Ye et al, 2008). Exposure of HELF cells to B[a]P obviously induced cyclin D1 transcription in a dose- and time-dependent manners (Jiao et al, 2008). Cyclin D1/CDK4-E2F-1/4 pathways are also involved in the cell cycle changes in B[a]P-treated HELFs, but these pathways have different patterns in response to low dose and high dose B[a]P treatment: in cells treated with 2 μmol/L B[a]P, cyclin D1 positively regulates the expression of E2F-1, whereas CDK4 negatively regulates the expression of E2F-4; in cells treated with 100 μmol/L B[a]P, both cyclin D1 and CDK4 negatively regulate the expression of E2F-4 (Ye et al, 2008). All the above studies have demonstrated that cell cycle changes are involved in the teratogenicity of B[a]P.

3.3 Aberrant signaling pathways

Oxidative and genotoxic stress induced by B[a]P, activate checkpoint mechanisms for cell cycle control and apoptosis involving the p53 pathway and p21[CIP1] in mammalian cells (Pääjärvi et al, 2008). The importance of DNA damage detection is supported by the enhanced teratogenicity of B[a]P in p53 knockout mice (Nicol et al, 1995). We noted that primary sensors of DNA damage and stress appear to be the phosphotidyl-inostitol-3-(PI-3) kinases such as DNA-dependent protein kinase (DNA-PK), ATM (ataxia-telangiec-tasiamutated), and/or ATR(ATM related), with activation of p53 involving phosphorylation on serine 15 (Laposa et al, 2004; Bhuller and Wells, 2006).We previously found that PI-3K pathway was implicated in activator factor 1 (AP-1) transactivation induced by B[a]P (Gao, et al., 2007). C-Jun, a primary member components of AP-1 families, have been proved to be required for B[a]P-induced cell cycle alternation (Jiao et al, 2008). The conventional position of the c-Jun protein in the signaling transduction cascades is close to mitogen activated protein kinase (MAPK) family (Kennedy and Davis, 2003). Two subgroups of the MAPK family, extracellular signaling regulated kinase (ERK) and c-Jun NH2-terminal kinase (JNK), have been demonstrated to be able to activate c-Jun activation in B[a]P-treated HELF (Jiao et al, 2007). Other evidence shows that NF-κB signaling pathway might be involved during in the teratogenicity of B[a]P (Li et al, 2004).

4. Future work

Evidence from molecular studies in vitro combined with results from complementary studies in embryo culture and in vivo suggest that B[a]P in animal models contribute to both

constitutive origins of teratogenesis as well as a broad spectrum of B[a]P and its metabolites-initiated adverse developmental outcomes, including structural birth defects, traditionally referred to as teratogenesis, as well as developmental deficits and cancer in later postnatal life.
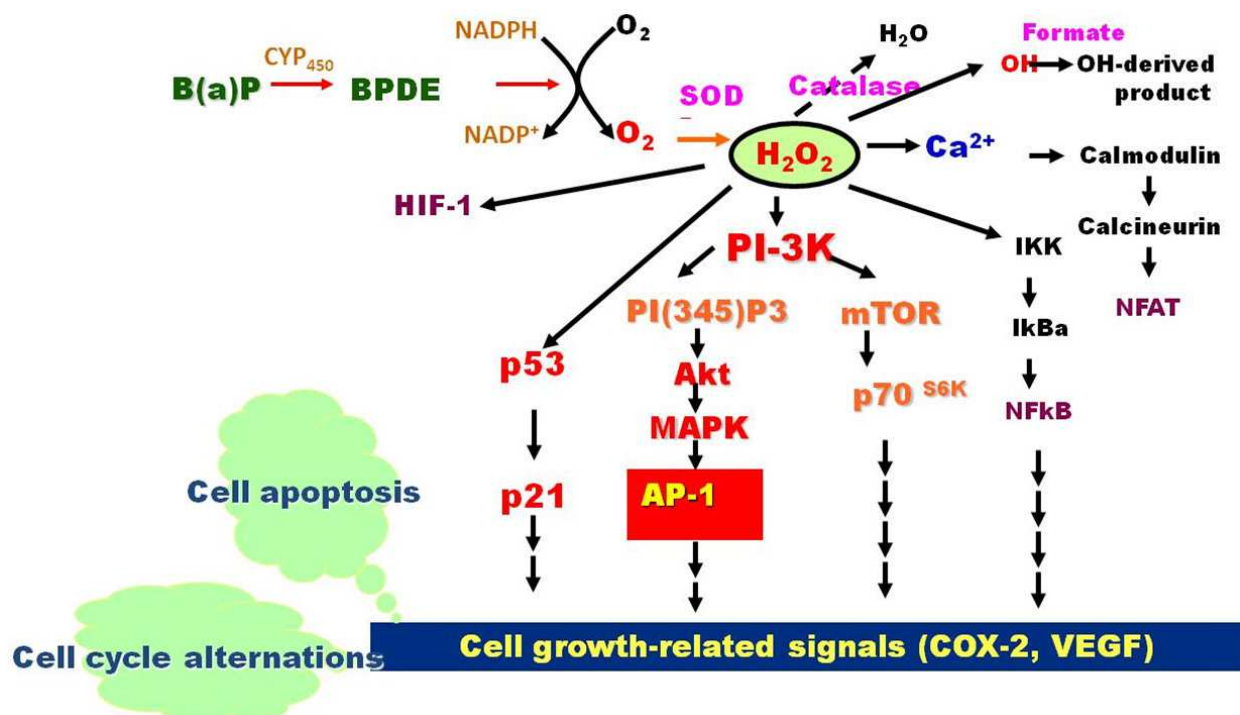

Fig. 3. Mechanism of benzo(a)pyrene-related reproduction toxicity.

At least some of probably mechanisms such as oxidative macromolecular damage, cell cycle alternation and signaling pathway aberrant activation, are involved in the the risk of teratogenesis of B[a]P (Fig 3). However, we still know relatively little about the full nature of B[a]P teratogenicity, particularly with regard to its signal transduction. It is likely that other important contributing signaling pathways remain to be discovered, and that more than one mechanism may contribute to the same adverse reproductive outcome. The results from animal studies provide a basis for similar evaluations in humans, for whom little information is available.

5. Acknowledgment

6. References

Archibong AE, Inyang F, Ramesh A, et al. (2002) Alteration of pregnancy related hormones and fetal survival in F-344 rats exposed by inhalation to benzo(a)pyrene. Reprod Toxicol 16: 801-808.
Bhuller Y & Wells PG. (2006) A developmental role for ataxia-telangiectasia mutated in protecting the embryo from spontaneous and phenytoin enhanced embryopathies in culture. Toxicol Sci. 93: 156-163.

Boström CE, Gerde P, Hanberg A, et al, (2002) Cancer risk assessment, indicators, and guidelines for polycyclic aromatic hydrocarbons in the ambient air. Environ Health Perspect 110: 451-488.

Bui QQ, Tran MB & West WL. (1986) A comparative study of the reproductive effects of methadone and benzo[a]pyrene in the pregnant and pseudopregnant rat. Toxicology 42: 195-204.

Cheo DL, Ruven HJ, Meira LB, et al. (1997) Characterization of defective nucleotide excision repair in XPC mutant mice. Mutat Res. 374: 1-9.

Chung JY, Kim JY, Kim YJ, et al. (2007) Cellular defense mechanisms against benzo[a]pyrene in testicular Leydig cells: implications of p53, aryl-hydrocarbon receptor, and cytochrome P450 1A1 status. Endocrinology. 148: 6134-6144.

Drukteinis JS, Medrano T, Ablordeppey E A, et al. (2005) Benzo[a]pyrene, but not 2,3,7,8-TCDD, Induces G2/M cell cycle arrest, p21CIP1 and p53 phosphorylation in human choriocarcinoma JEG-3 cells: a distinct signaling Pathway. Placenta, 26 Suppl A:S87-95.

Du H, Tang N, Liu B, et al. (2006) Benzo(a)pyrene-induced cell cycle progression is through ERKs/cyclin D1 pathway and requires the activation of JNKs and p38 mapk in human diploid lung fibroblasts. Mol Cell Biochem. 287: 78-89.

El Nemr A, Al Shawaf T, Sabatini L, et al. (1998) Effect of smoking on ovarian reserve and ovarian stimulation in in-vitro fertilization and embryo transfer. Hum Reprod . 13: 2192-2198.

Gao A, Liu B, Shi X, et al. (2006) Vitamin C inhibits benzo(a)pyrene-induced cell cycle changes partly via cyclin D1/E2F pathway in human embryo lung fibroblasts. Biomed. Environ. Science. 19: 239-244.

Gao A, Liu B, Shi X, et al. (2007) Phosphatidylinositol-3 kinase/Akt/p70S6K/AP-1 signaling pathway mediated benzo(a)pyrene-induced cell cycle alternation via cell cycle regulatory proteins in human embryo lung fibroblasts. Toxicol. Lett. 170: 30-41.

Guo N, Faller D V & Vaziri C. (2002) Carcinogen-induced S-phase arrest is Chk1 mediated and caffeine sensitive. Cell Growth Differ. 13: 77-86.

Hoffmann JL & Oris JT. (2006) Altered gene expression: A mechanism for reproductive toxicity in zebrafish exposed to benzo[a]pyrene. Aquat Toxicol. 78: 332-40.

Hombach-Klonisch S, Pocar P, Kietz S, et al. (2005) Molecular actions of polyhalogenated arylhydrocarbons (PAHs) in female reproduction. Current Medicinal Chemistry. 12: 599-616.

Jeng W, Wong AW, Ting-A-Kee R, et al. (2005). Methamphetamine- enhanced embryonic oxidative DNA damage and neurodevelopmental de?cits. Free Radic Biol Med 39: 317-326.

Ji HF & Shen L. (2009) Mechanisms of reactive oxygen species photogeneration by benzo[a]pyrene: A DFT study. J Mol Structure: THEOCHEM. 893: 6-8.

Jia X, Liu B, Shi X, et al. (2006) Inhibition of Benzo(a)pyrene-induced cell cycle progression by all-trans retinoic acid partly through cyclin D1/E2F-1 pathway in human embryo lung fibroblasts. Cell Biology International. 30: 183-189.

Jiang Y, Zhou X, Chen X, et al. (2011) Benzo(a)pyrene-induced mitochondrial dysfunction and cell death in p53-null Hep3B cells. Mutat Res. [Epub ahead of print]

Jiao S, Liu B, Gao A,et al. (2008) Benzo(a)pyrene-caused increased G1-S transition requires the activation of c-Jun through p53-dependent PI-3K/Akt/ERK pathway in human embryo lung fibroblasts.Toxicol Lett. 178: 167-175.

Jiao S, Liu B, Shi X, et al. (2006) JNK and ERK signaling pathways regulate Benzo(a)pyrene-induced c-Jun activation in human embryo lung fibroblasts. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. 25: 385-388.

Kaina B. (2003) DNA damage-triggered apoptosis: critical role of DNA repair, double-strand breaks, cell proliferation and signaling. Biochem Pharmacol 66: 1547-1554.

Kao SH, Chao HT & Wei YH. (1998) Multiple deletions of mitochondrial DNA are associated with the decline of motility and fertility of human spermatozoa. Mol Hum Reprod. 4: 657-666.

Karttunena V, Myllynenb P, Prochazkac G, et al. (2010) Placental transfer and DNA binding of benzo(a)pyrene in human placental perfusion. Toxicol Lett. 197: 75-81.

Kennedy Nj and Davis RJ. (2003) Role of JNK in tumor development. Cell Cycle 2:199-201.

Khan Q A & Dipple A (2000). Diverse chemical carcinogens fail to induce G1 arrest in MCF-7 cells. Carcinogenesis. 21:1611-1618.

Knafla A, Phillipps KA, Brecher RW, et al. (2006) Development of a dermal cancer slope factor for benzo[a]pyrene. Regul Toxico. Pharmaco. 45: 159-168.

Ko CB, Kim SJ, Park C, et al. (2004) Benzo(a)pyrene-induced apoptotic death of mouse hepatoma Hepa1c1c7 cells via activation of intrinsic caspase and mito- chondrial dysfunction. Toxicology. 199: 35-46.

Kovacic P & Somanathan R. (2006). Mechanisms of teratogenesis: electron transfer, reactive oxygen species and antioxidants. Birth Defects Research Part C: Embryo Today Reviews. 78: 308-325.

Laposa RR, Henderson JT, Xu E, et al. (2004) Atm-null mice exhibit enhanced radiation-induced birth defects and a hybrid form of embryonic programmed cell death indicating a teratological suppressor function for ATM. FASEB J 18: 896-898.

Legraverend C, Guenthner TM and Nebert DW. (1984) Importance of the route of administration for genetic differences in benzo[a]pyrene-induced in utero toxicity and teratogenicity. Teratology. 29: 35-47.

Li J, Chen H, Ke Q, et al. (2004) Differential effects of polycyclic aromatic hydrocarbons on transactivation of AP-1 and NF-kappaB in mouse epidermal cl41 cells. Mol Carcinog 40: 104-115.

Luijten M, Verhoef A, Westerman A, et al. (2008) Application of a metabolizing system as an adjunct to the rat whole embryo culture. Toxicology in Vitro. 22: 1332-1336.

MacKenzie, KM & Angevine DM. (1981) Infertility in mice exposed in uteroto benzo[a]pyrene. Biol. Reprod. 24: 183-191.

Motejlek K, Palluch F, Neulen J, et al. (2006) Smoking impairs angiogenesis during maturation of human oocytes. Fertil Steril. 86:186-191.

National Toxicology Program (NTP, 2000). Toxicology and Carcinogenesis Studies of Naphthalene (CAS No. 91-20-3) in F344/N Rats (Inhalation Studies). TR-500.

Nebert DW, Roe AL, Dieter MZ, et al.2000. Role of the aromatic hydrocarbon receptor and [Ah] gene battery in the oxidative stress response, cell cycle control, and apoptosis. Biochem Pharmacol, 59: 65-85.

Neumeister P, Pixley FJ, Xiong Y, et al. (2003) Cyclin D1 governs adhesion and motility of macrophages. Mol Biol Cell 14: 2005-2015.

Nicol CJ, Harrison ML, Laposa RR, et al. (1995) A teratologic suppressor role for p53 in benzo[a]pyrene-treated transgenic p53-deficient mice. Nat Genet 10:181-187.

Pääjärvi G, Jernström B, Seidel A, et al. (2008) Anti-diol epoxide of benzo[a]pyrene induces transient Mdm2 and p53 Ser15 phosphorylation, while anti-diol epoxide of

dibenzo[a,l]pyrene induces a nontransient p53 Ser15 phosphorylation. Mol Carcinog. 47: 301-309.

Parman, T & Wells, PG. (2002) Embryonic prostaglandin H synthase-2 (PHS-2) expression and benzo[a]pyrene teratogenicity in PHS-2 knock-out mice. FASEB J. 16: 1001-1009.

Patil AJ, Gramajo AL, Sharma A, et al. (2009) Effects of benzo(e)pyrene on the retinal neurosensory cells and human microvascular endothelial cells in vitro. Curr. Eye Res. 34: 672-682.

Perera FP, Rauh V, Whyatt RM, et al. (2004) Molecular evidence of an interaction between prenatal environmental exposures and birth outcomes in a multiethnic population. Environ.Health Perspect. 112: 626-630.

Pereraa FP, Rauha V, Whyatt RM, et al. (2005) A summary of recent findings on birth outcomes and developmental effects of renatal ETS, PAH, and pesticide exposures. NeuroToxicology. 26: 573-587.

Pickford D & Morris LD. (1999) Effects of endocrine-disrupting contaminants on amphibian oogenesis: methoxychlor inhibits progesterone-induced maturation of xenopus laevis oocytes in vitro. Environ Health Perspect. 107: 285-292.

Research article

Shimizu, Y, Nakatsuru, Y, Ichinose, M, et al. (2000) Benz[a]pyrene carcinogenicity is lost in mice lacking the arylhydrocarbon receptor. Proc Natl Acad Sci USA 97: 779-782.

Shiverick KT & Salafa C. (1999) Cigarette smoking and pregnancy I: ovarian, uterine and placental effects. Placenta. 20: 265-272.

Somers CM, Yauk CL, White PA, et al. (2002) Air pollution induces heritable DNA mutations. Proc Natl Acad Sci USA. 99:15904-15907.

Tannheimer SL. Ethier SP, Caldwell KK, et al. (1998) Polycyclic aromatic hydrocarbon-induced alterations in tyrosine phosphorylation and insulin-like growth factor signaling pathways in the MCF-10A human mammary epithelial cell line. Carcinogenesis. 19: 1291-1297.

Teijido O & Dejean L. (2010) Upregulation of Bcl2 inhibits apoptosis-driven BAX insertion but favors BAX relocalization in mitochondria, FEBS Lett. 584: 3305-3310.

Vaziri C & Faller DV. (1997) A benzo[a]pyrene-induced cell cycle checkpoint resulting in p53-independent G1 arrest in 3T3 fibroblasts. J Biol Chem. 272: 2762-2769.

Verhofstad N, Pennings J L, van Oostrom CT, et al. (2010) Benzo(a)pyrene induces similar gene expression changes in testis of DNA repair proficient and deficient mice. BMC Genomics. 11:333-344.

Verhofstad N, van Oostrom CT, van Benthem J, et al. (2009) DNA adduct kinetics in reproductive tissues of DNA repair proficient and deficient male mice after oral exposure to benzo(a)pyrene. Environ Mol Mutagen. 51: 123-129.

Vilarino-Guell C, Smith AG and Dubrova YE. (2003) Germline mutation induction at mouse repeat DNA loci by chemical mutagens. Mutat Res. 526: 63-73.

Wang A, Gu J, Kremer K J, et al. (2003) Response of human mammary epithelial cells to DNA damage induced by BPDE: involvement of novel regulatory pathways. Carcinogenesis 24:225-234.

Wang C, Li Z, Fu M, et al. (2004) Signal transduction mediated by cyclin D1: from mitogens to cell proliferation: a molecular target with therapeutic potential. Cancer Treat Res. 119: 217-237.

Wells PG, McCallum GP, Chen CS, et al. (2009) Oxidative stress in developmental origins of disease: teratogenesis, neurodevelopmental de?cits, and cancer. Toxicol Sci. 108: 4-18.

Whitfield ML, Sherlock G, Saldanha AJ, et al. (2002) Identification of genes periodically expressed in the human cell cycle and their expression in tumors. Mol Biol Cell. 13: 1977-2000.

Wright KP, Trimarchi JR, Allsworth J, et al. (2006) The effect of female tobacco smoking on IVF outcomes. Hum Reprod. 21: 1930-1934.

Wu J, Ramesh A, Nayyar T, et al. (2003) Assessment of metabolites and AhR and CYP1A1 mRNA expression subsequent to prenatal exposure to inhaled benzo(a)pyrene. Int J Dev Neurosci. 21: 333-346.

Yauk C, Polyzos A, Rowan-Carroll A, et al. (2008) Germ-line mutations, DNA damage, and global hypermethylation in mice exposed to particulate air pollution in an urban/industrial location. Proc Natl Acad Sci USA. 105: 605-610.

Ye M, Liu B, Shi X, et al. (2008) Different patterns of Cyclin D1/CDK4-E2F-1/4 pathways in human embryo lung fibroblasts treated by benzo[a]pyrene at different doses. Biomed Environ Sci. 21: 30-36.

Younglai EV, Holloway AC & Foster WG. (2005) Environmental and occupational factors affecting fertility and IVF success. Hum Reprod Update. 11: 43-57.

Younglai EV, Wu YJ & Foster WG. (2007) Reproductive Toxicology of Environmental Toxicants: Emerging Issues and Concerns. Current Pharmaceutical Design. 13:, 3005-3019.

Zenzes MT, Bielecki R & Reed TE. (1999) Detection of benzo(a)pyrene diol epoxide-DNA adducts in sperm of men exposed to cigarette smoke. Fertil Steri. 72:330-335.

Zenzes MT. (2000) Smoking and reproduction: Gene damage to human gametes and embryos. Hum Reprod Update. 6: 122-131.

Zhu H, Smith C, Ansah C, et al. (2005) Responses of genes involved in cell cycle control to diverse DNA damaging chemicals in human lung adenocarcinoma A549 cells. Cancer Cell Int 5: 28.
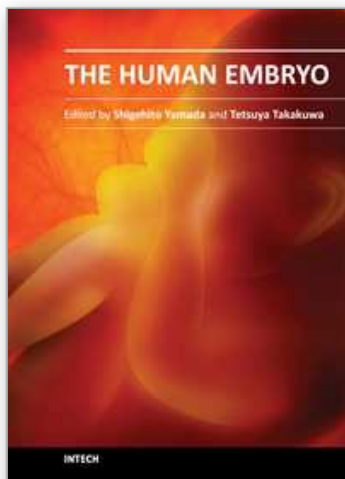
The Human Embryo

Edited by Dr. Shigehito Yamada

Human embryology is now rapidly moving to a new phase due to recent innovation and advances of life science including ES and iPS technology. This new era also directs a difficult challenge for scientists in terms of technological and ethical issues for future human embryology. However, human embryology is difficult to research due to ethics involved in the collection of human materials. This book traces the early history and provides knowledge on demonstration of principles from ancient to the most recent embryo studies amidst the unresolved scientific and ethical issues. We hope this book will help the readers to understand human embryo development better.

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